NOVARTIS

# Secukinumab (AIN457)

ADVISORY COMMITTEE BRIEFING MATERIAL:
AVAILABLE FOR PUBLIC RELEASE

## Prepared by Novartis Pharmaceuticals Corporation for the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

| | |
|---|---|
| Document type: | Advisory Committee Meeting Briefing Book |
| Document status: | Final |
| Release date: | September 12, 2014 |

# 1 Executive summary

## Introduction

This document summarizes the efficacy and safety data demonstrating that secukinumab, a first in class, targeted therapy, is highly efficacious with a good safety profile for patients with moderate to severe psoriasis. Statistically significant and clinically meaningful results will be presented. Collectively, the results of four double-blind, placebo-controlled trials consistently demonstrate that secukinumab is a highly efficacious treatment and that the 300 mg dose provides the greatest benefit to patients. Safety in psoriasis has been characterized with over 2700 patient years of experience and demonstrated a good profile, comparable to that of etanercept, supporting this product's utility as a new treatment option for patients with moderate to severe psoriasis.

## Disease and unmet medical need

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population (Griffiths and Barker 2007, Menter et al 2008). It is a complex disorder, characterized by inflammation, increased keratinocyte hyperproliferation, and altered epidermal differentiation (Nestle et al 2009). Psoriasis has significant negative impact on the global well-being of patients and people living with them (Martinez-Garcia et al 2014). Patients with moderate to severe disease represent approximately 15% to 25% of plaque psoriasis patients and generally require systemic therapy, as outlined in several international and regional treatment guidelines (Menter et al 2008, Pathirana et al 2009, American Academy of Dermatology 2013).

Although there are multiple agents approved for the treatment of psoriasis, many of the patients still do not achieve optimal efficacy when one considers clinically meaningful measures such as clear or almost clear skin (and demonstrated by PASI 90) with as few as 21% achieving this with etanercept (Langley et al 2014). Other limitations are slow onset, diminishing efficacy over time and drug-specific major safety concerns (Chastek et al 2013, Levin et al 2013). Thus, there remains a significant unmet patient need for new agents with unique mechanisms that can provide a rapid onset of effect, improved and sustained skin clearance, and a safety profile that allows for chronic use.

## Product

Secukinumab is a first in class fully human monoclonal antibody which selectively binds and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a key role in the pathogenesis of plaque psoriasis. At the therapeutic concentrations used in psoriasis, secukinumab fully neutralizes the activity of IL-17A, does not neutralize IL-17F, leaves other functions of Th17 cells intact, and does not directly influence the Th1 pathway. This new mechanism of action leads to the normalization of skin histology, including achievement of clear to almost clear skin for the majority of patients. This specificity offers the potential for fewer off target effects when compared to other available current treatment options.

The product exists as both a lyophilized formulation (LYO) for reconstitution and a liquid formulation that is delivered via either a pre-filled syringe (PFS) or autoinjector/Pen (AI). Both formulations and all delivery systems were evaluated in the clinical program.

## Clinical Program, Indication and Recommended Dose

The secukinumab clinical program is the largest registration clinical database for moderate to severe plaque psoriasis that has been submitted for review. This development program incorporated specific FDA advice and complied with CHMP guidelines for evaluation of treatments for psoriasis. It well characterizes the efficacy and safety of the product with blinded, comparative data through one year.

The proposed indication is:

*Secukinumab is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

The patient population studied in the psoriasis program is reflective of the proposed target population of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Inclusion criteria were typical to define moderate to severe psoriasis. Other criteria were generally less restrictive by allowing patients with a history of treated latent tuberculosis, or a history of cardiac disorders to participate in the clinical program.

The Phase II and III psoriasis registration program was comprised of ten studies (and one Phase II extension study). Four Phase II dose-ranging studies defined the dose regimens to carry forward to Phase III. Six Phase III studies, including four core studies with very similar designs (A2302, A2303, A2308 and A2309) (Table 1-1), characterized the safety and efficacy.

The four core studies were all double-blind, randomized, placebo-controlled trials and evaluated two dose regimens using either 150 mg or 300 mg of secukinumab compared with placebo. A2303 also included the active comparator etanercept. The larger two studies (A2302 and A2303) utilized the lyophilized product (LYO) that was reconstituted and administered in office. A2308 utilized the pre-filled syringe (PFS) and A2309 used the autoinjector (AI/Pen). In these two latter studies, study medication was self-administered. The other two studies (A2304 and A2307) evaluated alternate dosing regimens.

**Table 1-1 Psoriasis clinical program overview**

| Study | Phase 2 – 4 dose-ranging trials | N |
|---|---|---|
| A2102* | Proof of Concept – single iv dose (3mg/kg i.v.) | 36 |
| A2220 | Dose-ranging (25-150 mg s.c.) | 120 |
| A2212 | High Dose ranging i.v. (3-10 mg/kg i.v.) | 100 |
| A2211** | Dose regimen finding (150 mg using different schedules) | 404 |
| | **Phase 3 – Four Core DB, randomized, placebo, controlled studies** | |
| A2302 | 150, 300 mg s.c. vs. placebo [LYO] | 738 |
| A2303 | 150, 300 mg s.c. vs. placebo and vs. etanercept [LYO] | 1306 |
| A2308 | 150, 300 mg s.c. vs. placebo using pre-filled syringe | 177 |
| A2309 | 150, 300 mg s.c. vs. placebo using autoinjector | 182 |
| | **Phase 3 – Additional Studies – Alternate treatment regimens** | |
| A2304 | 'Treatment as needed' vs. 'Fixed interval' [LYO] | 965 |
| A2307 | Higher doses for partial responders [LYO] | 43 |

*A2102 is not part of the safety pool for all psoriasis trials (Pool B)

**A2211E1 is an extension study to A2211 and is not listed above but is included in safety pool B

These studies demonstrated that secukinumab is a highly efficacious treatment with the most pronounced benefits seen with the 300 mg dose, particularly at the more difficult to achieve measures of clear or almost clear skin (PASI 90, PASI 100, IGA mod 2011 0/1), both at early and later timepoints. The superior efficacy of secukinumab versus placebo was consistent in all subgroups of body weight, age, race, disease severity, and previous exposure or failure to systemic psoriasis therapy (including anti-TNFα inadequate responders (IR) and biologic IR patients). The 300 mg dose was associated with higher and faster response rates across weight groups and all other subgroups examined compared to 150 mg. In addition, responses were better maintained with 300 mg dose when compared to the 150 mg dose.

Based on these data, the recommended dose and regimen is:

*300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3 followed by monthly maintenance dosing starting at week 4.*

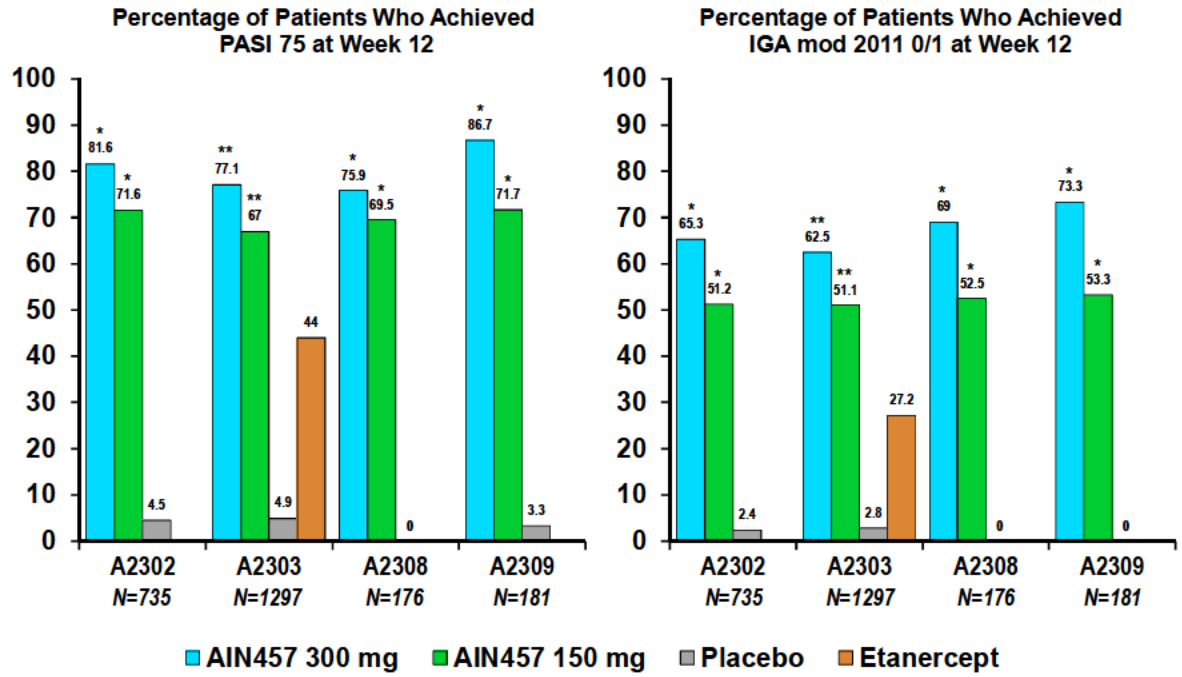
## Efficacy

Four double-blind, randomized, placebo-controlled core Phase III studies consistently demonstrated that secukinumab provided clinically meaningful, statistically significant improvement based on the co-primary endpoints of Psoriasis Area and Severity Index 75 response (PASI 75) and Investigator Global Assessment for clear to almost clear skin (IGA mod 2011 0/1) at week 12 ($p<0.0001$). IGA mod 2011 is a five point scale and the IGA mod 2011 0/1 response definition closely correlates to a PASI 90 response, both of these assess clear to almost clear skin. Efficacy was dose-dependent with consistently better responses achieved with the 300 mg over the 150 mg regimen in each of the 4 studies for the co-primary endpoints (Figure 1-1). The majority of patients attained clear to almost clear skin as evidenced by both PASI 90 (54.2% - 60.3%) and IGA mod 2011 0/1 response (62.5% - 73.3%) at Week 12 in each of the placebo-controlled studies with the 300 mg regimen (Figure 5-8).

On these more stringent endpoints of clear to almost-clear skin by IGA mod 2011 0/1 or PASI 90, the response rate for the 300 mg dose was approximately 10 - 20% higher than 150 mg in each of the four studies.

The differences in responses were sustained and greater at the week 52 endpoint. The difference in efficacy between doses was also statistically significant in other pre-specified efficacy analyses in these studies. In A2303, both secukinumab doses (300 mg and 150 mg) were statistically superior ($p<0.0001$) at Week 12 in achieving IGA mod 2011 0/1 and PASI 75 response to the active comparator, etanercept.

**Figure 1-1 Co-primary endpoint across four core studies**

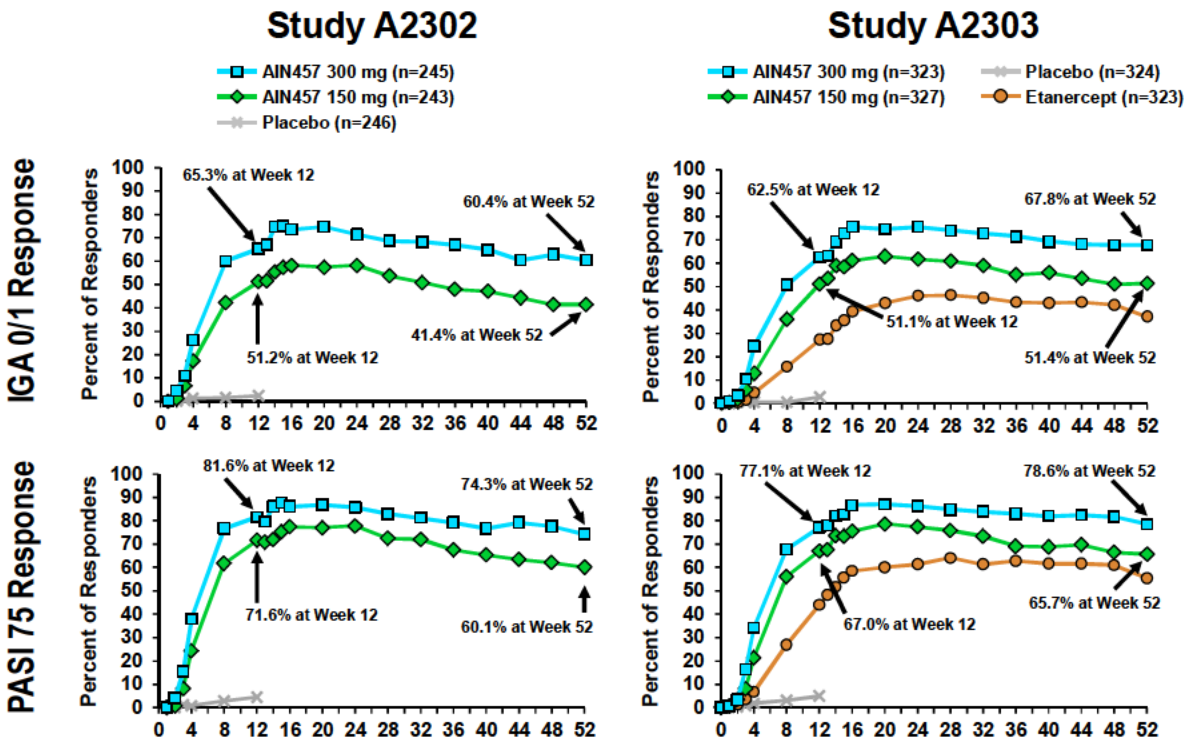



* $p < 0.0001$ versus placebo. Treatment comparisons for studies A2302 and A2303 were based on Cochran-Mantel-Haenszel testing and for studies A2308 and A2309 on Fisher's exact test.

** $p < 0.0001$ versus etanercept

Over time, a peak effect was seen around week 16 (Figure 1-2, Figure 5-13), with a high level of response maintained over at least 52 weeks with the 300mg dose (74.3-78.6% for PASI 75 and 60.4-67.8% IGA mod 2011 0/1) as shown from the two larger Phase III trials (A2302 and A2303). In A2303, efficacy was also compared with etanercept through 52-weeks (Figure 1-2, Figure 5-13). These response rates for 300 mg were approximately 16-20% better than 150 mg and 26-32% better than etanercept for the higher efficacy measures (e.g. PASI 90, IGA mod 2011 0/1 & PASI 100 responses) after 52 weeks of treatment (Table 1-2).

**Figure 1-2** **IGA mod 2011 0/1 and PASI 75 response rates over 52-weeks of treatment in studies A2302 and A2303 (non-responder imputation)**




Etanercept: Starting Dose: 50 mg twice weekly for 12 weeks Maintenance Dose: 50 mg once weekly
n = number of evaluable patients

**Table 1-2** **PASI 75, PASI 90, PASI 100, and IGA mod 2011 0/1 response rates at week 52 in studies A2302 and A2303 (non-responder imputation)**

| | A2302 | | A2303 | | |
|---|---|---|---|---|---|
| **Criterion** | **AIN457 300 mg % (n/m)** | **AIN457 150 mg % (n/m)** | **AIN457 300 mg % (n/m)** | **AIN457 150 mg % (n/m)** | **Etanercept % (n/m)** |
| IGA mod 2011 0/1 | 60.4% (148/245) | 41.4% (101/243) | 67.8% (219/323) | 51.4% (168/327) | 37.2% (120/323) |
| PASI 75 | 74.3% (182/254) | 60.1% (146/244) | 78.6% (254/323) | 65.7% (215/327) | 55.4% (179/323) |
| PASI 90 | 60.0% (147/245) | 36.2% (88/244) | 65.0% (210/323) | 45.0% (147/327) | 33.4% (108/323) |
| PASI 100 | 39.2% (96/245) | 20.2% (49/244) | 36.2% (117/323) | 19.9% (65/327) | 9.9% (32/323) |

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index
n=number of patients with response, m=number of patients evaluable.

Secukinumab 300 mg also provided a clinically meaningful improvement in the ability to maintain completely clear skin (PASI 100) after 52-weeks (36.2-39.2%). Using this most

stringent criterion, secukinumab 300 mg is almost twice as effective as 150 mg (36.2-39.2% vs. 19.9-20.2%) and almost four times as effective as etanercept (36.2-39.2% vs. 9.9%).

Patient reported outcome data were consistent with the PASI and IGA mod 2011 data that shows the advantage with secukinumab 300 mg over 150 mg. Secukinumab 300 mg also resulted in a substantially higher proportion of patients in both individual studies and in the pooled analysis (58.9%) with DLQI 0/1 response (0 or 1 response = "no effect at all on patient's life") compared with 150 mg (50.1% in pooled analysis) at Week 12, with an even greater benefit seen at Week 52 (68.5% for 300 mg vs. 53.8% for 150 mg), representing a consistent and sustained therapeutic gain by approximately 15% with the 300 mg over the 150 mg group.

Additionally, secukinumab 300 mg had a rapid onset of efficacy with an approximate 40% reduction of baseline symptoms (as measured using the PASI score) at Week 2 and 50% reduction by Week 3. In contrast, it took 4 weeks for secukinumab 150mg and 8 weeks for etanercept to reach a 50% reduction of symptoms. PsA patients (approximately 20% of the population) also benefited from secukinumab treatment both in terms of skin improvement and physical function (HAQ-DI), with the greatest benefit observed with secukinumab 300 mg.

The 300 mg dose was associated with higher response rates across the two weight strata outlined in the protocol (< 90 kg or ≥ 90 kg) shown in Table 1-3. Likewise, in additional exposure response analyses, requested by FDA, 300 mg was associated with clinically relevant improvements compared with 150 mg across all endpoints (IGA mod 2011 0/1, PASI 75 / 90 / 100) across all weight subgroup analyses assessed (including < 70 kg, 70-90 kg, and ≥ 90 kg (Section 5.4.6); tertile analyses and quartile analyses for body weight).

**Table 1-3 PASI 75, PASI 90, PASI 100, and IGA mod 2011 0/1 response rates at Week 12 by Weight Strata – Pooled Data**

| Weight Category | <90 kg | | | ≥90 kg | | |
|---|---|---|---|---|---|---|
| **Criterion** | **AIN457 300 mg % (n/m)** | **AIN457 150 mg % (n/m)** | **Difference*** | **AIN457 300 mg % (n/m)** | **AIN457 150 mg % (n/m)** | **Difference*** |
| IGA 0/1 | 70.3 % (296/421) | 56.0 % (233/416) | 14.3 % | 56.6 % (150/265) | 44.5 % (122/274) | 12.1 % |
| PASI 75 | 83.6 % (352/421) | 74.2 % (308/415) | 9.4 % | 72.8 % (193/265) | 61.7 % (169/274) | 11.1 % |
| PASI 90 | 64.6 % (272/421) | 47.2 % (196/415) | 17.4 % | 43.8 % (116/265) | 31.8 % (87/274) | 12.0 % |
| PASI 100 | 34.0 % (143/421) | 16.4 % (68/415) | 17.6 % | 17.4 % (46/265) | 9.1 % (25/274) | 8.3 % |

n=number of patients with response, m=number of patients evaluable

*Arithmetic difference between 300 mg response and 150 mg response

Similarly 300 mg performed better in all other subgroups examined (Section 5.4.9).

Efficacy was consistent with both formulations tested (lyophilisate vs. liquid), all delivery forms [lyophilisate in a vial (A2302 and A2303), pre-filled syringe (A2308) or autoinjector/pen (A2309)] and with physician (A2302 and A2303) or patient self-administration (A2308 and A2309).

## Safety

A large safety database provides the foundation to initially characterize several potential risks of concern for any biologic with immunomodulatory effects. The overall program across multiple investigational indications includes a total of 5,044 patients in 34 patient studies with a total of 3,588 patient years of exposure. The psoriasis program included 10 Phase II/III clinical trials and studied a total of 3,993 psoriasis patients of whom 3,430 received secukinumab (Pool B). The overall secukinumab exposure in psoriasis patients was 2,725 patient-years.

Safety pools were created to allow direct randomized comparisons of secukinumab with placebo and active comparator for the initial placebo-controlled 12 week period (Pool A including the four core, placebo-controlled Phase III studies) and a larger psoriasis pool (including all 10 Phase II/III psoriasis studies) providing longer duration of exposure for up to 52 weeks (Pool B, entire treatment duration). Selected rare events were investigated using all patients treated with secukinumab across all indications under investigation (Pool C). The data pooling plan was agreed with FDA prior to the Biologic License Application (BLA) submission.

Overall, secukinumab at both doses demonstrated comparable safety to etanercept over 52 weeks of treatment and was similar to placebo after adjustment for the shorter placebo duration of exposure. Secukinumab showed an initial imbalance vs. placebo in total AEs which was driven by mainly non-serious upper respiratory tract infections. This difference was observed only in the first 12 weeks of treatment and did not translate into a higher risk of serious infections or a higher risk of infection over 52 weeks of treatment. There was no difference between secukinumab doses in the overall rate of all infections or in upper respiratory tract infections. Secukinumab at both doses was comparable to etanercept in total AEs and infection AEs in the first 12 weeks and over the entire 52-week treatment period.

Preclinical data (Ishigame et al 2009, Kagami et al 2010) and observations in humans with genetic defects affecting the Th17 pathway (Puel et al 2011; Gaffen et al 2011) suggest that blockade of IL-17 might lead to an increased risk for fungal infections. IL-17 is considered relevant to the mucosal defense to *Candida* (Cypowyj et al 2012), typically resulting in oropharyngeal forms of *Candida* infections.

*Candida* infections were more frequent with secukinumab 300 mg (1.2% in the initial 12-week controlled period) while the 150 mg dose (0.4%) was comparable to placebo (0.3%) and etanercept (0.3%). The small imbalance between the secukinumab doses was limited to non-serious, localized mucosal or cutaneous candidiasis, primarily oral candidiasis. There were no reports of chronic or systemic candidiasis in any treatment group. *Candida* infections were responsive to standard treatment and did not necessitate discontinuation of study medication. These observations are consistent with the implied role of interleukin 17 (IL-17) in host

defense against mucosal *Candida* infections. Serious opportunistic infections have not been reported on secukinumab.

No reactivation of latent tuberculosis or viral hepatitis was observed in any psoriasis trial.

There was no imbalance in malignancy AEs among all secukinumab, placebo and etanercept-treated patients or between the secukinumab doses in the psoriasis trials. During the placebo-controlled portion of the psoriasis studies, the overall incidence of malignancies was similar between each of the secukinumab dose groups (0.1% and 0.4% for 300 mg and 150 mg, respectively) and placebo (0.4%). Over the entire treatment period in the psoriasis trials, the exposure adjusted rate of malignancies per 100 patient years was 0.77 and 0.97 for secukinumab 300 mg and 150 mg compared with 0.68 for etanercept and 1.49 for placebo. There was also no difference in the incidence of malignancy AEs between secukinumab and placebo over 52 weeks across all indications (Pool C). In the psoriasis population (pool B), there were 4 cases of malignant melanoma reported (2 malignant melanoma and 2 malignant melanoma in situ). All patients had one or more of the following risk factors: prior exposure to phototherapy, TNFα antagonists or methotrexate or pre-existing melanocytic nevus. No increase in the ratio of squamous cell carcinoma to basal cell carcinoma was observed.

The incidence of major adverse cardiovascular events (MACE) adjusted for exposure over 52 weeks was comparable to placebo and etanercept. Potential major adverse cardiovascular event (MACE) [including cardiovascular death, myocardial infarction, or stroke] cases, over the entire treatment period were reported for similar proportion of patients on secukinumab and etanercept: 6 (0.4%) with 300 mg, 5 (0.4%) with 150 mg, and 1 (0.3%) for etanercept. There was one MACE event also reported for placebo. After adjusting for exposure over the 52 week period, the exposure adjusted incidence was comparable for secukinumab, placebo, and etanercept (0.44 for secukinumab 150 mg, 0.51 for secukinumab 300 mg, 0.50 for placebo, and 0.34 for etanercept per 100 patient years). All cases had prior or active cardiovascular disease or other risk factors. These findings were supported by an independent cardiovascular/cerebrovascular adjudication committee review of individual case data from the psoriasis program and across all indications.

Treatment-emergent anti-drug antibodies (ADA) were detected in a total of 10 patients (0.4%) of which 3/10 were neutralizing antibodies. ADA in secukinumab-treated patients were not associated with clinically relevant AEs, loss of efficacy or abnormal serum concentrations of secukinumab. There was no evidence of a dose response (300 mg: 3/1410 = 0.2%; 150 mg: 7/1395 = 0.5%). Emergence of anti-secukinumab antibodies was not associated with injection site reactions or serious or severe hypersensitivity adverse events.

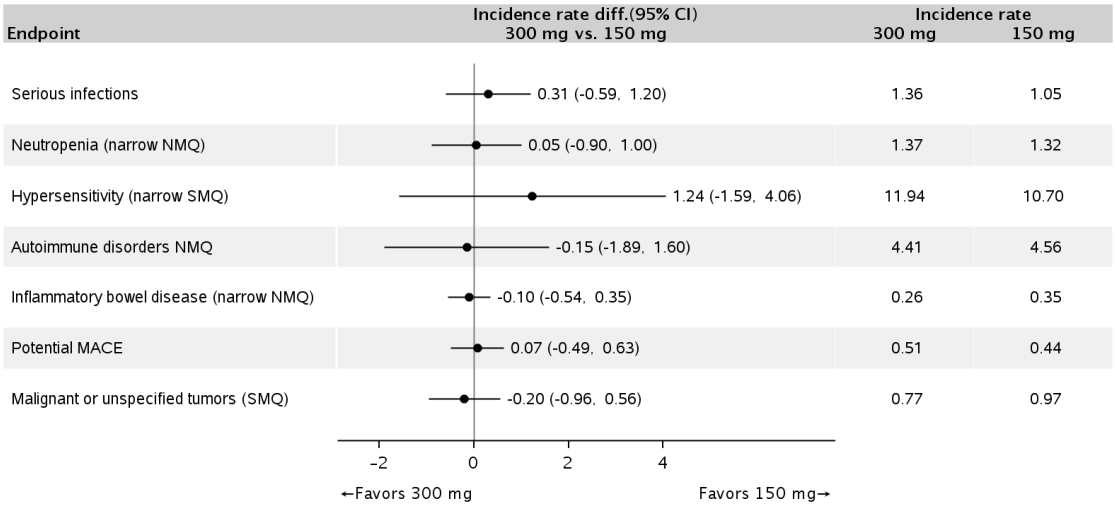
Risk minimization activities have been proposed for secukinumab to enhance our understanding of the potential safety issues and minimize risk. The plan includes both passive and enhanced pharmacovigilance surveillance and labeling.

## Conclusion

Secukinumab is a highly efficacious treatment for patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The 300 mg regimen is the optimal clinical dose for the following reasons:

- Consistently higher efficacy is achieved with the 300 mg regimen in each of the 4 studies for the co-primary endpoints at week 12.
- The response rate for the recommended dose of 300 mg dose was approximately 10-20% higher than 150 mg in each of the four studies on the more stringent endpoints of clear to almost-clear skin by IGA mod 2011 0/1 or PASI 90 at week 12.
- After 52 weeks of treatment, response rates for 300 mg (data from A2302 and A2303) were approximately 16-20% better than 150 mg secukinumab and 26-32% better than etanercept for the higher clearance efficacy measures (including PASI 90, IGA mod 2011 0/1 & PASI 100 responses).
- Maintenance of PASI 75 response was best with secukinumab 300 mg. The cumulative probability (Kaplan-Meier estimates) of loss of a Week 12 PASI 75 response by Week 52 was three times higher with etanercept (39.2%) and twice higher with secukinumab 150 mg (25.8%) compared with secukinumab 300 mg (12.9%).
- Incidence rates for the adverse events of interest for an immunomodulatory biologic including serious infections, autoimmune disorders, major adverse cardiovascular events (MACE) and malignancies were similar for the two doses (Figure 1-3) and similar to rates on etanercept and placebo.
- The rates of serious infections, malignancies and serious cardiovascular event were low with secukinumab. No dose dependency with secukinumab in any of these events was observed. However, superficial *Candida* infections occurred at a slightly higher frequency (<1% greater) with 300 mg vs 150 mg vs placebo (1.2% vs 0.4% vs. 0.3%). These infections were mild to moderate in severity and were clinically manageable/treatable with standard therapy without discontinuation. There were no cases of disseminated candidiasis or chronic mucocutaneous candidiasis. This observation of mucosal candidiasis is consistent with the implied role of IL-17 on skin and fungal infections, but less severe that what is observed in patients who have an inborn IL17A deficiency.

**Figure 1-3 Exposure-adjusted incidence and incidence rate difference (per 100 patient years) of key risk AEs - Entire treatment period (52 weeks) - (Pool B: all psoriasis studies – Safety set)**




These data demonstrate that secukinumab 300 mg allows a majority of patients with moderate to severe psoriasis to attain and maintain clear to almost clear skin. The safety profile allows chronic use for long term maintenance that is required for this population. The greatest therapeutic benefit in achieving sustained clear to almost clear skin and normal quality of life is achieved with 300 mg, with minimal additional safety risk compared with the 150 mg dose. This new, novel mechanistic approach to the treatment of psoriasis represents an improvement in the currently available therapeutic options for physicians and patients with psoriasis.

## Table of contents

## List of tables

## List of figures

## List of abbreviations

| | |
|---|---|
| ADA | anti-drug antibodies |
| ADR | adverse drug reaction |
| AE | adverse event |
| AI | autoinjector/pen |
| AIN457 | secukinumab |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BMI | body mass index |
| BSA | body surface area |
| CCV | cardiovascular/cerebrovascular |
| CCV-AC | Cardiovascular and Cerebrovascular Safety Adjudication Committee |
| CHD | coronary heart disease |
| CNS | central nervous system |
| CI | confidence interval |
| CL | clearance |
| Cmax | maximum serum concentration after a single dose |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLQI | Dermatology Life Quality Index |
| dPGA | dynamic Physician's Global Assessment |
| ECG | electrocardiogram |
| EQ-5D | EuroQOL 5-Dimension Health Questionnaire© |
| FAS | Full Analysis Set |
| FDA | United States Food and Drug Administration |
| FI | fixed interval dosing |
| GGT | gamma-glutamyltransferase |
| HAQ-DI | Health Assessment Questionnaire©-Disability Index |
| HBV | hepatitis B virus |
| HLT | high level term |

| | |
|---|---|
| HRQoL | health-related quality of life |
| hsCRP | high sensitivity C-reactive protein |
| ICH | International Conference on Harmonization |
| IFU | Instructions for Use |
| IGA | Investigator's Global Assessment |
| IGA mod 2009 | IGA scale used in part of the Phase II program, 6-point scale |
| IGA mod 2011 | IGA scale used in the Phase III program, 5-point scale |
| IgG | Immunoglobulin G |
| IL-17 | interleukin 17 |
| IQR | interquartile range |
| IR | incidence rate |
| ISF | interstitial fluid |
| i.v. | intravenous(ly) |
| LLN | lower limit of normal |
| LOCF | last observation carried forward |
| LTBI | latent tuberculosis |
| LYO | Lyophilisate in vial |
| mAb | monoclonal antibody |
| MACE | major adverse cardiovascular event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMP | metalloproteinases |
| NK | natural killer |
| NMQ | Novartis MedDRA Query |
| PASI | Psoriasis Area and Severity Index |
| PBO | placebo |
| PD | pharmacodynamics |
| p.e. | primary endpoint |
| PFS | pre-filled syringe |
| PGA | Physician's Global Assessment |
| PGIC | Patient Global Impression of Change |
| PhV | pharmacovigilence |
| PK | pharmacokinetics |

| | |
|---|---|
| PRO | patient-reported outcome |
| PsA | psoriatic arthritis |
| PT | preferred term |
| q4w | dosing once every four weeks |
| q8w | dosing once every eight weeks |
| q12w | dosing once every 12 weeks |
| QTc | corrected QT interval |
| QTcB | corrected QT interval as per Bazett's formula |
| QTcF | corrected QT interval as per Fridericia's formula |
| R | randomization |
| SAE | serious adverse event |
| s.c. | subcutaneous(ly) |
| SIAQ | self-injection assessment questionnaire |
| SMQ | Standardized MedDRA Query |
| SOC | system organ class |
| SoR | start of relapse (synonymous with treatment as needed) |
| ss | steady state |
| TB | tuberculosis |
| TBL | total bilirubin |
| TDAR | T cell dependent antibody responses |
| Th17 | T helper 17 cell |
| TNFα | tumor necrosis factor alpha |
| TNFα-IR | tumor necrosis factor alpha inadequate responder |
| ULN | upper limit of normal |
| Vd | volume of distribution |
| WBC | white blood cell |

# 2 Product development rationale

## 2.1 Moderate to severe psoriasis

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population (Griffiths and Barker 2007, Menter et al 2008). It is a complex disorder, characterized by inflammation, keratinocyte hyperproliferation, and altered epidermal differentiation (Nestle et al 2009). Psoriasis has significant negative impact on the global well-being of patients and people living with them (Martinez-Garcia et al 2014). Most (80-90%) of psoriasis patients have chronic plaque psoriasis, characterized by recurrent exacerbations and remissions of thickened, erythematous, scaly patches of skin that can occur anywhere on the body (Griffiths and Barker 2007, Menter et al 2008). Approximately 15% to 25% of these patients have moderate to severe disease requiring systemic therapy, as outlined in various international and regional treatment guidelines. This subset of moderate to severe patients is the target population for secukinumab.

Several oral drugs (including acitretin, cyclosporin, and methotrexate), and more recently several biologics, including TNF-α antagonists (adalimumab, etanercept, infliximab) and anti-IL12/IL23 (ustekinumab), have been approved for the treatment of psoriasis. Many patients have received substantial benefit from these therapies; however, achieving clear to almost clear skin (Gelfand et al 2012) remains the treatment goal for both patients and practitioners alike. Additionally, speed of onset, long term sustainability of treatment effect and minimization of drug-specific safety concerns (e.g., serious infections including tuberculosis (TB), malignancies including lymphoma, immunogenicity and demyelinating neurologic events) (Menter et al 2011, Menter et al 2008) remain areas where treatments could be improved.

## 2.2 Description of molecule and mechanism of action

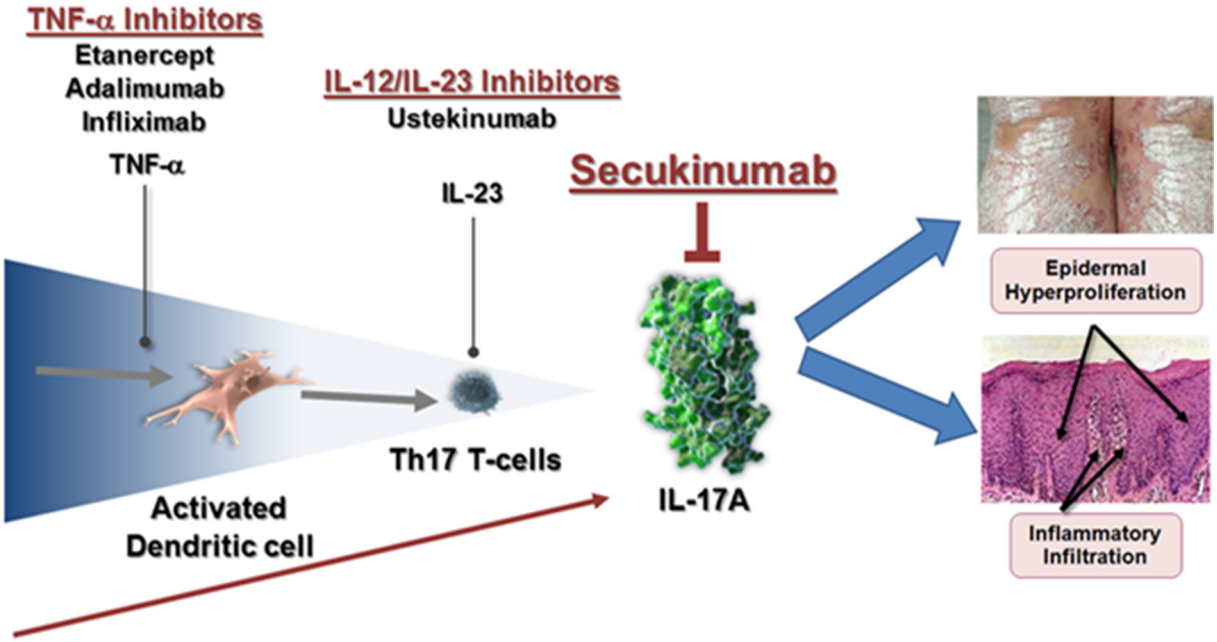
Secukinumab (also referred to in this document as AIN457) is unique from other approved therapies for psoriasis as it is a first in class recombinant high-affinity, fully human monoclonal antibody of the IgG1/kappa isotype that selectively targets IL-17A. Interleukin-17A (IL-17A; also known as IL-17) is a soluble pro-inflammatory cytokine which acts on a variety of cell types, including epithelial cells (such as keratinocytes), dendritic cells, macrophages, fibroblasts, osteoblasts, endothelial cells (Miossec and Kolls 2012) and astrocytes (Ma et al 2010; Meares et al 2012) and causes the release of pro-inflammatory cytokines, chemokines, antimicrobial peptides and mediators of tissue destruction (Fossiez et al1998; Onishi and Gaffen 2010; Miossec and Kolls 2012). It is a key cytokine that induces psoriasis by pleotropic effects on immune cells, fibroblasts and in particular keratinocytes by inducing various inflammatory mediators including cytokines (e.g. IL-6, TNF), chemokines (e.g. CXCL-1, CXCL-2, CCL-20 and CXCL-8/IL-8), matrix metalloproteinases (MMPs) and antimicrobial peptides (e.g. beta-defensin , S100 proteins and LL-37).

In the psoriatic skin, IL-17A is thought to be produced by e.g. infiltrating Th17 cells, neutrophils and mast cells. Upon activation of keratinocytes by IL-17A along with other inflammatory cytokines that synergize with IL-17A, this then leads to the further recruitment

and activation of neutrophils, lymphocytes and myeloid cells, eventually leading to a sustained local cutaneous inflammation that drives the psoriatic epidermal changes mediated by keratinocytes including increase in epidermal thickness (acanthosis), increase in outer stratum corneum (hyperkeratosis) and retention of nuclei in the cornified layer (parakeratosis) (Martin 2013).

Secukinumab interferes in this pathologic process by selectively binding to IL-17A and thereby preventing IL-17A interaction with the IL-17 receptor expressed on e.g. keratinocytes (Figure 2-1). By its mechanism of action, secukinumab prevents and reverses key pathologic processes in psoriasis leading to normalization of skin histology.

**Figure 2-1 Secukinumab mechanism of action and selective target through inhibition of IL-17A**




## 2.3 Description of product

Three product presentations were used in the clinical program and are currently under review for psoriasis:

- A lyophilisate (LYO) powder for solution which requires reconstitution with Sterile Water for Injection.
- Liquid in a pre-filled syringe (PFS) (150 mg strengths of Solution for injection) assembled with plunger rod and safety device for subcutaneous administration.
- Liquid in pre-filled syringe assembled in an auto-injector (AI/Pen) (150 mg strength of Solution for injection) for subcutaneous administration.

The only differences between the lyophilized and solution products are slight differences in stabilizing excipients and buffer concentration levels.

Extensive analytical studies support the physico-chemical comparability between the LYO and the liquid formulation.

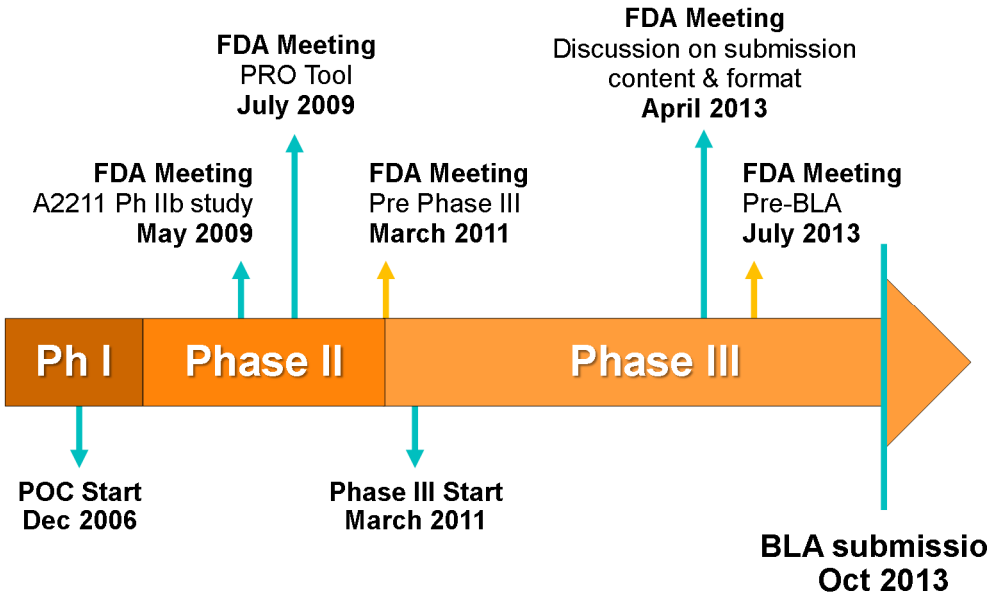
The LYO formulation was developed first and used subcutaneously in the two larger core studies (A2302 and A2303). This formulation requires reconstitution with Sterile Water for Injection and was administered subcutaneously in the healthcare provider office at the scheduled visits. Subsequently a liquid formulation that could be used in a more conveniently administered pre-filled syringe (PFS) and which is suitable for self-administration became available. This form was further improved by using the syringe enclosed within an easy to use Autoinjector (AI/Pen), also for self-administration. The human pharmacokinetic profiles between the two forms (LYO and Liquid in PFS) showed no difference in the time concentration profile (see Section 4.6).

Per FDA feedback, separate clinical efficacy and safety studies with the PFS and AI, as well as human factor studies, were performed. These two additional core Phase III placebo-controlled studies, one with PFS (A2308) and one with the AI (A2309) had safety and efficacy results that were essentially the same as those in the larger core studies (A2302 and A2303) which utilized the LYO formulation. The human factors study demonstrated ease of use for the PFS and AI/Pen. These studies, collectively demonstrated that patients could safely and conveniently self-administer the product.

## 2.4 Regulatory history

The secukinumab development program was designed in consultation with FDA, EU and Japanese Health Authorities and was based on applicable FDA and ICH regulatory guidelines.

There were multiple consultations with FDA on the program throughout the development program and the major meetings are shown in the timeline below.




After the successful proof-of-concept study (single dose i.v.) A2102, the Phase II program included three dose ranging / regimen finding studies (See Table 5-2). Data from Phase II studies A2212 and A2211 lead to the conduct of Study A2220 to assess a range of s.c. doses to address both FDA and EU health authority feedback.

Based on specific feedback from the FDA, two additional Phase III studies (A2308 and A2309) were added to the program to obtain clinical data with secukinumab delivered via PFS and with the AI/Pen respectively. Both trials were randomized, double-blind, placebo controlled safety and efficacy studies which also included usability and an assessment of any hazards of self-administration in psoriasis patients.

Per the FDA recommendation, the co-primary endpoint for the Investigator Global Assessment (IGA mod 2011) utilized a 5 point instead of the 6 point Physician Global Assessment (PGA) scale used in prior biologics programs. The rationale for moving to a five point scale was a) difficulties in differentiating between disease severity levels, including associated descriptors, and b) the preference for response criteria that, in addition to attaining a score of 0/1, also requires at least a two point reduction. Improvement by at least two points on a 5 point scale is considered more clinically meaningful than on a 6 point scale.

Additionally, the descriptors on the lower end (score of 1 for almost clear) of the five point scale were more stringent than for the "minimal' category (also score of 1) on the six point scale used in prior programs. These differences in global assessment scoring have led to a more conservative response definition with the IGA mod 2011. While achieving a score of 0/1 on the prior 6 point Physician/Investigator Global Assessment (PGA/IGA) scales correlated well with a PASI 75 response, the same score on the IGA mod 2011 correlates best with a greater PASI 90 response rate (Langley et al 2013).

The Phase III program is larger and more comprehensive than prior psoriasis biologics programs. It includes the following standard elements:

- Two double-blind placebo-controlled Phase III studies (there were 4 core double-blind placebo-controlled Phase III studies in the secukinumab program)
- Assessment of both short-term initial dosing and longer-term maintenance dosing
- Assessment of an adequate safety population to allow for extrapolation into the clinical setting (secukinumab program is the largest submitted in terms of number of patients treated and exposure)
- Specific monitoring appropriate for a new biologic agent, e.g. immunogenicity, rates of rebound/relapse, infections and malignancy, in a large patient population
- Additionally, the secukinumab Phase III program includes assessments beyond previous similar psoriasis programs:
    - Evaluation of efficacy in psoriasis patients who failed biologic/TNF-α antagonist treatment or were previously exposed to biologic/TNF- α antagonist
    - Long-term double-blind comparison (52 weeks) vs. biologic standard of care (etanercept)
    - Usability assessments (ability to follow Instructions for Use and Hazards) and subject satisfaction in self-administration of the PFS and AI/Pen.

Thus the clinical development program is robust, providing substantial evidence of both safety and efficacy with direct, randomized, comparative data against both placebo and an active control.

# 3 Nonclinical safety

The nonclinical program supported the clinical development program and there were no significant findings. Two antibodies were used to characterize the safety profile of secukinumab and anti-IL17A therapy: secukinumab itself and a mouse anti-mouse IL-17A surrogate antibody BZN035. The cynomolgus monkey was selected as a relevant species for evaluation of toxicity since secukinumab is able to neutralize cynomolgus, rhesus, and marmoset monkey IL-17A but not the rodent IL-17A.

The comprehensive toxicology program is shown in Table 3-1. This program is conducted in accordance with appropriate International Conference on Harmonization (ICH) guidelines and is consistent with standard programs that have been conducted for other monoclonal antibodies.

**Table 3-1 Toxicology program**

| Study type and duration | Route of administration | Doses / Concentrations | Species |
|---|---|---|---|
| *Safety pharmacology* | iv | 0, 10, 30, 100 mg/kg/w | Cynomolgus monkey |
| *Single–dose toxicity* | sc | 0, 15, 150 mg/kg | Cynomolgus monkey |
| *Repeat-dose toxicity* | | | |
| 3 months | sc | 0, 15, 50, 150 mg/kg/w | Cynomolgus monkey |
| 1 month | iv | 0, 10, 30, 100 mg/kg/w | Cynomolgus monkey |
| 1 month | iv | 0, 15, 50, 150 mg/kg/w | Cynomolgus monkey |
| 6 month | iv | 0, 15, 50, 150 mg/kg/w | Cynomolgus monkey |
| *Reproductive toxicity* | | | |
| Fertility & early embryonic development (surrogate Ab) | sc | 0, 15, 50, 150 mg/kg/w | Mice |
| Embryo-fetal development | sc | 0, 15, 50, 150 mg/kg/w | Cynomolgus monkey |
| Peri- and postnatal development (surrogate Ab) | sc | 0, 15, 50, 150 mg/kg/w | Mice |
| *Special toxicity studies* | | | |
| Blood compatibility (hemolysis) | *in vitro* | 2.5, 1.25 and 0.62 mg/mL | Cynomolgus monkey/ human |
| Antibody-dependent cellular cytotoxicity | *in vitro* | 10 µg/mL | Human |
| Tissue crossreactivity | *in vitro* | 1, 20, 50, and 230 µg/mL | Cynomolgus monkey/ human |
| Tissue crossreactivity | *in vitro* | 1, 20, 50, and 230 µg/mL | Cynomolgus monkey/ human |

i.v.: intravenous, s.c.: subcutaneous, surrogate Ab: murine anti-IL-17A murine antibody, w: week

Based on binding affinity and potency data, it is expected that at the concentrations achieved in the cynomolgus monkey toxicology studies at 150 mg/kg, complete pharmacological suppression of IL- 17A bioactivity should be achieved.

A surrogate anti-mouse antibody (BZN035) was used in reproductive toxicity studies, including a fertility and early embryonic development and pre- and post-natal development toxicity study in mice. Binding of BZN035 to mouse IL-17A was comparable to binding of secukinumab to human IL-17A and similarly, neutralization of the bioactivity of IL-17A with BZN035 was comparable to secukinumab. Systemic exposure to BZN035 in mice also showed systemic exposure above the exposure to secukinumab in human.

A summary of the preclinical data revealed:

- No adverse effects of secukinumab in a safety pharmacology study (cardiac, respiratory or central nervous system).
- No hypersensitivity reactions, immunotoxicity/immunosuppression, or treatment-related infections were observed in the conducted preclinical studies. A minimal non-adverse immunomodulatory activity (effects on lymphocyte subpopulations and T-cell dependent antibody response) was noted in the 13 and 26 week toxicity studies in cynomolgus monkeys. However, there were no secukinumab related macroscopic observations or adverse effects on organ weights at necropsy, no treatment-related histopathology findings nor altered distribution of T and B-lymphocytes in lymphoid tissues seen in young adult or adult monkeys.
- Postmortem, there were no secukinumab-related macroscopic observations or adverse effects on organ weights at necropsy, and there were no secukinumab-related histopathology findings. There were no tumors or pre-neoplastic changes observed in histopathology evaluations in any toxicity study in cynomolgus monkeys following secukinumab treatments.
- No secukinumab-related maternal toxicity or teratogenicity was observed in embryo fetal developmental toxicity evaluations. Treatment of mice with a murine anti-IL-17A murine antibody did not impact fertility and early embryonic as well as pre-and postnatal development parameters.
- No non-specific binding of secukinumab to normal human tissues was observed.

The exposures observed at the no effect level in the primate toxicity studies provide very large exposure multiples compared with projected human exposure with the proposed 300 mg regimen for the early weekly dosing (~ 50 fold) and with monthly chronic dosing (>100 fold).

In conclusion, the nonclinical data package confirmed the mechanism of action and the functional activity of this selective, fully human anti-IL-17A monoclonal antibody and characterized the nonclinical safety profile of the molecule. Secukinumab was well tolerated in safety pharmacology, general toxicology, and developmental and reproductive toxicology animal studies. These data are supportive of a positive benefit/risk ratio for the use of secukinumab in psoriasis.

# 4 Clinical pharmacology

## Summary

The proposed dose, form and regimen for secukinumab is 300 mg given subcutaneously by reconstituted lyophilized product or liquid in either the pre-filled syringe or auto-injector. Initial dosing begins at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. The purpose of this section is to summarize the expected PK profile with secukinumab using this dosing regimen and route of administration. The rationale for dose and regimen selection for Phase III and the proposed posology is covered in Section 5.3, Phase II Dose Selection.

Section 4.1 through Section 4.7 describe the key information gained from the clinical pharmacology studies on absorption (Section 4.1), distribution (Section 4.2), metabolism and excretion (Section 4.3), drug-drug interactions (Section 4.4), PK in special populations (Section 4.5), formulation comparisons (Section 4.6) and pharmacodynamics (Section 4.7). This information is intended to be presented in the USPI.

Collectively, the clinical pharmacology studies demonstrated that secukinumab displays PK properties typical of a human IgG1-type immunoglobulin interacting with a soluble cytokine target (i.e. IL-17A) without any sign of target-mediated disposition. As with other fully human immunoglobulin IgG-1 molecules, subcutaneous absorption was slow, clearance was low and half-life was long. There was no evidence of a time-dependent change in clearance.

## Clinical Pharmacology Studies

Secukinumab pharmacokinetics (PK) and pharmacodynamics markers were evaluated after both intravenous (i.v.) and subcutaneous (s.c.) administration in healthy volunteers and psoriasis patients (Table 4-1).

The first Phase II study in psoriasis (A2102, Table 4-1 below) established the safety and efficacy of a single i.v. infusion of secukinumab in 36 patients. Given that the ultimate desired market form was s.c. (rather than i.v.), the second Phase II study (A2103) established the absolute bioavailability of s.c. (given as diluted lyophilisate) compared i.v. using a cross-over design. A second early Phase II study (A2106) compared the bioequivalence of two s.c. presentations – LYO and PFS in a large number of healthy volunteers (n=150). Collectively, these three early studies established the PK and safety of a single dose of I.V, the relative bioavailability of s.c. to i.v. and the bioequivalence of two s.c. presentations – the LYO and liquid formulation in pre-filled syringe.

**Table 4-1 Clinical pharmacology studies in healthy volunteers for psoriasis program**

| Study and Purpose | Population | Treatment | Number of subjects enrolled |
|---|---|---|---|
| A1101<br>Ethnic sensitivity | Healthy Japanese Volunteers | -single 1, 3, 10 mg/kg i.v.<br>-single 150 or 300 mg s.c.<br>-placebo | 42 |
| A2102<br>Safety, effect & PK | Psoriasis Patients | -single 3 mg/kg i.v.<br>-single placebo i.v. | 36 |
| A2103<br>Bioavailability | Psoriasis Patients | -single 1 mg/kg i.v. → 150 mg s.c.<br>-single 150 mg s.c. → 1 mg/kg i.v. | 14 |
| A2104<br>Proof of Mechanism in ozone-induced airway neutrophilia | Healthy volunteers | -single 10 mg/kg i.v. dose<br>-placebo<br>-oral corticosteroids | 24 |
| A2106<br>Bioequivalence lyo/PFS | Healthy volunteers | -single 300 mg s.c. | 150 |
| A2224<br>Vaccine study | Healthy volunteers | -single 150 mg s.c.<br>-no treatment control | 50 |
| A2225<br>Skin Concentrations & PD markers | Healthy volunteers and psoriasis patients | -single 300 mg s.c. | 16 |
| A2228<br>Safety, tolerability and PK of 30 minute i.v. infusion | Healthy volunteers | -single 10 mg/kg i.v.<br>-placebo | 12 |

Sparse PK sampling was conducted in Phase II studies (A2211 and A2220) and Phase III studies (A2302, A2308 and A2309) and provided the basis for PK modeling and simulation and allowed good estimations of exposure parameters with chronic dosing for this diverse population (Section 5.3).

## 4.1 Absorption

Following a single subcutaneous dose (150 mg or 300 mg) in plaque psoriasis patients peak concentrations (Cmax) were reached between 5 and 6 days post-dose. With weekly dosing during the first month, maximum concentrations were achieved between 31 and 34 days. Peak concentrations at steady state (Cmax, ss) occur within 4-8 days after dosing.

Compared with exposure after a single dose, patients exhibited a 2 –fold increase in peak concentrations and AUC after repeated monthly dosing. Steady-state is reached after 20 weeks with monthly dosing.

Exposure (AUC and Cmax) was dose-proportional over a dose range from 0.3 - 10mg/kg given i.v. and from 25 mg to 300 mg given as s.c.

The average bioavailability with s.c. administration was 73%. These results are in line with the bioavailability estimates of other IgG1 human monoclonal antibodies (Wang et al 2008).

## 4.2 Distribution

The volume of distribution during the terminal phase (Vz) after a single i.v. administration ranged from 7.10 to 8.60 L, suggesting limited distribution to the peripheral compartments.

Concentrations of secukinumab, IL-17A, IL-17F and other downstream markers were measured using open flow microperfusion to assess distribution of secukinumab to the dermal interstitial fluid (ISF) (see also Section 4.7).

Local concentrations of secukinumab in the ISF were slightly higher in patients than in healthy volunteers (between 28-39% of serum concentrations and 23% of serum concentrations, respectively).

## 4.3 Metabolism and elimination

As a fully human IgG1 mAb, secukinumab is expected to be metabolized in the same manner as any endogenous immunoglobulin gamma via intracellular catabolism, following fluid-phase or receptor mediated endocytosis (Wang et al 2008) and degraded into small peptides and amino acids. The PK of secukinumab is consistent with this disposition pathway without any evidence for target-mediated disposition.

In both healthy volunteers and psoriasis patients, the mean elimination half-life for secukinumab ($T_{1/2}$) was ~27 days, which is typical for an endogenous IgG1 antibody.

Clearance was dose and time-independent as expected for a therapeutic IgG1 mAb interacting with a soluble target, such as IL-17A. Serum clearance was slow (CL=0.19 L/d with inter-patient variability of 32% CV) and the total volume of distribution was low (central compartment volume 3.61 L with 30% CV, and peripheral compartment volume of 2.87 L with 18% CV) in a 'typical' psoriasis patient weighing 90 kg. Demographic factors (gender, age, race, and disease severity) did not have a clinically meaningful impact on systemic exposure after adjusting for bodyweight.

## 4.4 Drug interactions

The potential for drug interactions between secukinumab, a monoclonal IgG1 antibody and small drug molecules is low, given the main route of elimination is via intracellular catabolism. CYP inhibitors and inducers are unlikely to affect secukinumab exposure-response relationships, given hepatic metabolizing enzymes such as CYPs and UGTs are not presumed to be involved with mAb elimination.

*Methotrexate*

It is noted that decreased clearances were reported for infliximab and adalimumab when co-administered with methotrexate. In contrast to these results, PK results in a dose finding study with secukinumab in rheumatoid arthritis patients indicated that methotrexate does not have an impact on the disposition of secukinumab.

*Vaccinations*

Healthy volunteers were treated with secukinumab and given either a subunit meningococcal or inactivated (killed) influenza vaccines to assess the impact of secukinumab on vaccination responses (Study A2204). This study demonstrated that a single dose of secukinumab 150 mg s.c. did not have an impact on the ability to mount protective antibody titers against either T cell dependent (influenza) or T cell independent (meningococcal) antigens. Therefore, patients receiving secukinumab may receive concurrent inactivated or non-live vaccinations.

Live vaccines should not be given concomitantly with secukinumab.

## 4.5 Special populations

*Geriatric*

Based on population pharmacokinetic analysis (n=71 patients ≥ 65 years of age), clearance in geriatric patients and patients less than 65 years of age was similar.

*Pediatric*

Pediatric studies have not been conducted to date.

*Renal Impairment*

Because secukinumab is a human IgG immunoglobulin with a large molecular size (~150 kDa), and intact immunoglobulin is filtered by the kidney only to a very small degree, only very small amounts of antibody are expected to be excreted in the urine. Renal impairment is not likely to influence urinary excretion and the overall PK profile. Consistent with other programs for monoclonal antibodies, formal studies to examine the impact of impaired renal function have not been conducted.

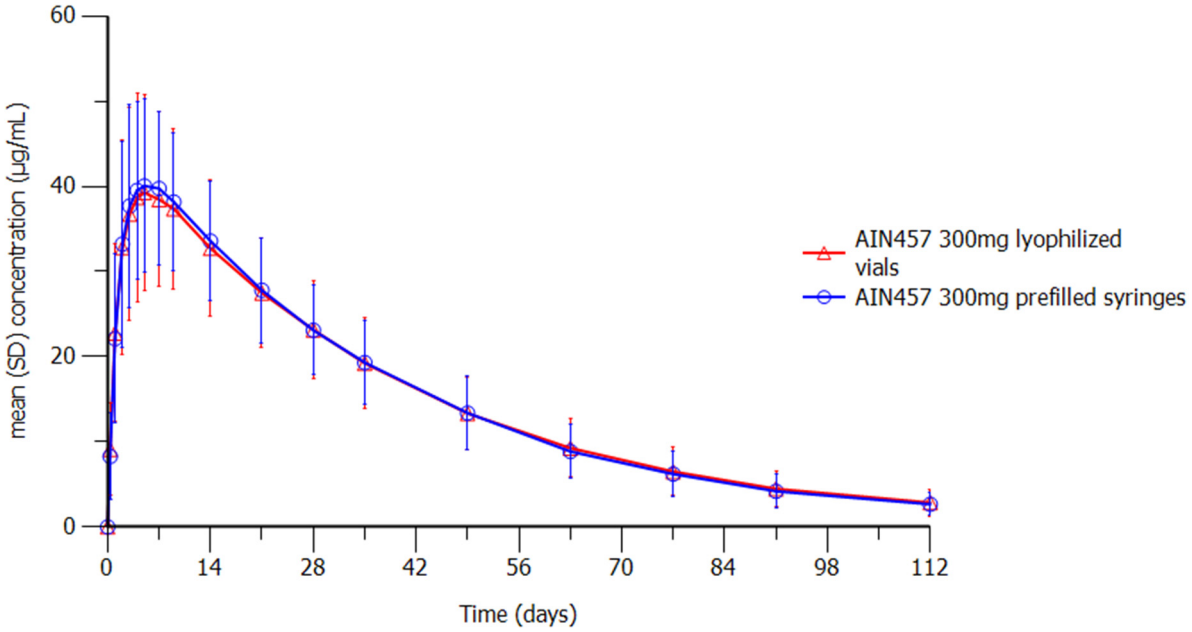
*Hepatic Impairment*

Hepatic impairment would not be expected to influence metabolism or excretion of human IgG. No formal studies were conducted to examine the impact of impaired hepatic function.

## 4.6 Formulation comparison of pharmacokinetics

Bioequivalence between the liquid formulation in the PFS and LYO was demonstrated in a parallel-design study with 2 x 75 (n=150) healthy volunteers after the administration of 300 mg secukinumab s.c. (study A2106). As expected, the concentration-time profiles were virtually overlapping over 112 days (approximately 4 half-lives), see Figure 4-1 below.

**Figure 4-1 Arithmetic mean (SD) concentration-time profiles by formulation (lyophilizate and PFS) (Study A2106)**




This large pharmacokinetic study established that there are no differences in pharmacokinetics of the LYO or liquid formulations. A comparably large pharmacokinetic study was not conducted for the AI/Pen because the formulation and internal 'bulk' syringe used in the AI/PEN is the same used in the pre-filled syringe.

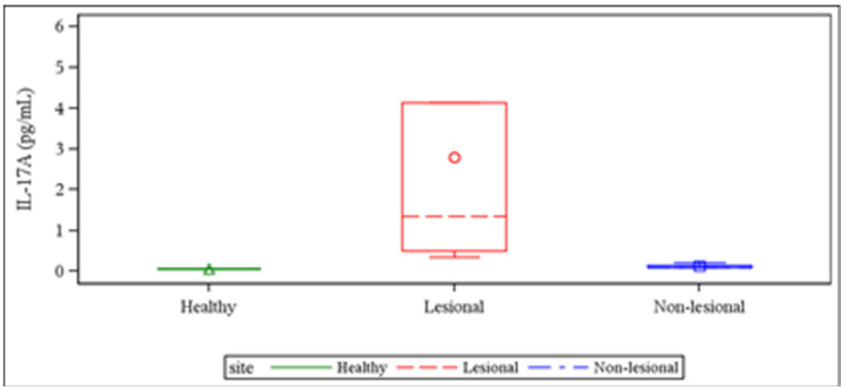
## 4.7 Pharmacodynamics

The pharmacodynamic effect of secukinumab in binding to IL-17A, and therefore inhibiting IL-17A signaling, is in the reduction of the inflammatory processes of psoriasis, with an associated therapeutic benefit on lesional skin (defined as skin that has active psoriasis).

The ability of secukinumab to bind and capture circulating IL-17A has formally been validated based on measurement of total serum IL-17A. Total IL-17A is defined as free IL-17A plus IL-17A complexed with secukinumab after exposure to secukinumab. Because the complex of secukinumab and IL-17A has a slower clearance than free IL-17A, total IL-17A serum levels after secukinumab exposure increase up to a plateau, followed by a gradual decrease after the end of the treatment period.

Quantification of IL-17A protein in interstitial fluid of lesional and non-lesional skin of psoriasis patients, and normal skin of healthy volunteers using open flow microperfusion sampling (Study A2225), showed significantly higher concentrations of baseline IL-17A in lesional skin in psoriasis patients compared to non-lesional skin in psoriasis patients and normal skin of healthy volunteers (Figure 4-2). Inhibition of IL-17A is likely to lead to therapeutic improvements in the lesional skin of psoriasis patients.

**Figure 4-2 Baseline free IL-17A levels in diluted dermal ISF from psoriasis patients and healthy volunteers (Study A2225)**




Line in the box: median, symbol in the box: arithmetic mean, low end of the box: 25th percentile, high end of the box: 75th percentile, low end of whisker: the lowest data value within 1.5 IQR of the lower quartile, high end of whisker: the highest value within 1.5 IQR of the upper quartile, IQR: the interquartile range (the difference between the third and first quartiles, the middle 50%);Triangle indicates 'Healthy', Circle indicates 'Lesional', Square indicates 'Non-lesional'

From studies A2102 and A2212, clinical improvements were paralleled by cellular and histological changes in psoriatic skin after a single dose of secukinumab 3 mg/kg i.v., including reduced epithelial thickness and parakeratosis, decreased Ki67 positive keratinocyte counts (a measure of keratinocyte proliferation), early decreases of skin-residing innate immune cell populations (e.g. myeloperoxidase-positive neutrophils) and decreases in CD3+ T cell numbers. These changes were paralleled by clinical PASI improvements.

# 5 Clinical development program

The secukinumab clinical development program was a large program designed to assess the benefits and risks of a new biologic product with a unique mechanism of action in the target indication of moderate to severe plaque psoriasis. The proposed indication is for the "*Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy*." In addition to double-blind, placebo-controlled trials, the program included a direct, randomized comparison with an approved biologic standard of care as is generally required for Europe. In this 52-week double-blind, active and placebo controlled comparative study (A2303), secukinumab demonstrated superior efficacy to etanercept with a comparable risk profile.

A total of 5,044 patients have been studied in 34 studies in the overall secukinumab program across all indications, including psoriasis (Pool C). The psoriasis program included 10 Phase II/III clinical trials and studied a total of 3,993 patients of whom 3,430 received secukinumab with a total of 2,725 patient-years of exposure (Pool B).

Four Phase II studies contributed to selection of the dosing regimens (Table 5-2) to carry forward into Phase III. Four core Phase III studies and two non-core Phase III studies (Table 5-3) established safety and efficacy of all product forms, as well as investigated alternate treatment paradigms ('treatment as needed' and higher dosing for partial responders).

## 5.1 Patient population

The criteria defining moderate to severe psoriasis are similar to other Phase III programs with inclusion criteria (PASI ≥ 12, IGA mod 2011 ≥ 3 and a total BSA ≥ 10%) reflecting published guidelines in Europe (CHMP/EWP/2454/02 2004) and discussions with Health Authorities, globally, including FDA. Other criteria were generally less restrictive by allowing patients with a history of treated latent tuberculosis, or a history of cardiac disorders to participate in the clinical program.

## 5.2 Efficacy measures

In both Phase II and Phase III studies, standard efficacy endpoints were used, incorporating both physician and patient-reported outcomes. The co-primary efficacy variables of all four core Phase III studies (A2302, A2303, A2308, A2309) were Psoriasis Area and Severity Index (PASI 75) response and Investigator's Global Assessment (IGA) mod 2011 0/1 response at Week 12.

Secondary variables in Phase III included PASI 90, PASI 100, maintenance of response based on PASI 75 and IGA mod 2011 0/1, patient reported outcome tools and health-related quality of life instruments, including the Dermatology Life Quality Index (DLQI), the EuroQOL 5-Dimension Health Questionnaire© (EQ-5D©), Health Assessment Questionnaire©-Disability Index (HAQ-DI), Psoriasis Symptom Diary©, and Patient Global Impression of Change (PGIC).

The IGA scoring system is widely used in the psoriasis indication, although there are many variants of this scale and no universally accepted scale exists. During Phase II, FDA advice on the descriptors utilized in the Novartis IGA scale used at the time (referred to as IGA mod 2007) was incorporated into the IGA mod 2009 rating scale, which contained 6 points.

For the Phase III program, the scale was condensed into a 5-point scale (IGA mod 2011) by collapsing the two highest points on the 6-point scale ("very severe" and "severe") into a single point ("severe") (Table 5-1). This modification was made in line with FDA feedback and supported by the lack of differentiation through the "very severe" point on the original 6-point scale, and the low prevalence of this patient type (Rich et al 2013). Improvement by at least two points on a 5 point scale is considered more clinically meaningful than on a 6 point scale. Additionally, the descriptors for a score of 1 (almost clear) were more stringent than previously used IGA/PGA 6 point scales.

**Table 5-1 The IGA mod 2011 rating 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. |

Note: Involvement of nails is not part of the assessment.

## 5.3 Phase II dose selection

The major purpose of this section is to summarize 1) the rationale for selection of the 150 mg and 300 mg s.c. doses for investigation in the Phase III trials, 2) the rationale for the loading regimen and 3) the scientific evidence supporting the 300 mg dose for all patients (rather than dosing by weight).

The comprehensive Phase II program includes four studies used for dose selection with 665 patients. These 4 studies included a proof of concept study with i.v. dosing followed by three dose-ranging and regimen-finding studies. The design of these 4 studies is summarized in Table 5-2. They were all conducted in the target population of patients with moderate to severe psoriasis who are poorly controlled by topical and/or phototherapy and may have failed to respond to or are intolerant to previous systemic therapy and/or ultraviolet (UV) therapy. Collectively, these four studies provided the clinical data, in conjunction with modeling and simulation, that 1) demonstrated that initial loading dosing was needed to provide rapid and strong improvement in psoriasis, 2) identified the initial s.c. loading regimen that best approximated the trough concentration achieved with high i.v. dosing while minimizing peak exposure, and 3) identified the 150 and 300 mg s.c. doses as those most promising to deliver desired patient benefit with acceptable risk.

**Table 5-2 Summary of studies used for dose selection**

| Study | Description | N | Treatments | Key Efficacy | Key Conclusions |
|---|---|---|---|---|---|
| **A2102** | Single dose (i.v.) in target population | 36 | 3 mg/kg secukinumab<br>PBO | PASI, dPGA | Secukinumab demonstrated efficacy in psoriasis (proof of concept). |
| **A2220** | Low dose-ranging (s.c.) in target population | 125 | 25, 75, or 150 mg secukinumab ('monthly') at R, Wks 4, 8<br>PBO at R, Wks 4, 8 | PASI 75, IGA mod 2009 (Wk 12) | Doses below 150 mg do not offer acceptable efficacy. |
| **A2212** | High dose ranging (i.v.) in target population | 100 | 1 x 3 mg/kg secukinumab<br>1 x 10 mg/kg secukinumab<br>3 x 10 mg/kg secukinumab<br>3 x PBO | PASI 75, IGA mod 2007 (Wk 12) | Doses above 150 mg might offer improved efficacy. |
| **A2211** | Dose regimen finding (s.c.) in target population | 404 | First 12 week period:<br>1 x 150 mg secukinumab ('single dose')<br>3 x 150 mg secukinumab at R, Wks 4, 8 ('monthly')<br>4 x 150 mg secukinumab at R, Wks 1, 2, 4 ('early')<br>5 x PBO at R, Wks 1, 2, 4, 8<br>Maintenance in responders:<br>Fixed Interval (every 12 weeks): 150 mg secukinumab at Wk 12, 24, PBO at relapse<br>Start of relapse: 150 mg secukinumab, PBO at Wk 12, & Wk 24 (if did not experience start of relapse)<br>Treatment in partial or non-responders:<br>Open label: 150 mg s.c. q4w secukinumab until Wk 32 | PASI 75, IGA mod 2009 (Wk 12) | An initial increased frequency induction regimen is beneficial.<br>Maintenance treatment should be given monthly (every four weeks).<br>Re-treatment at start of relapse might be beneficial for some patients. |

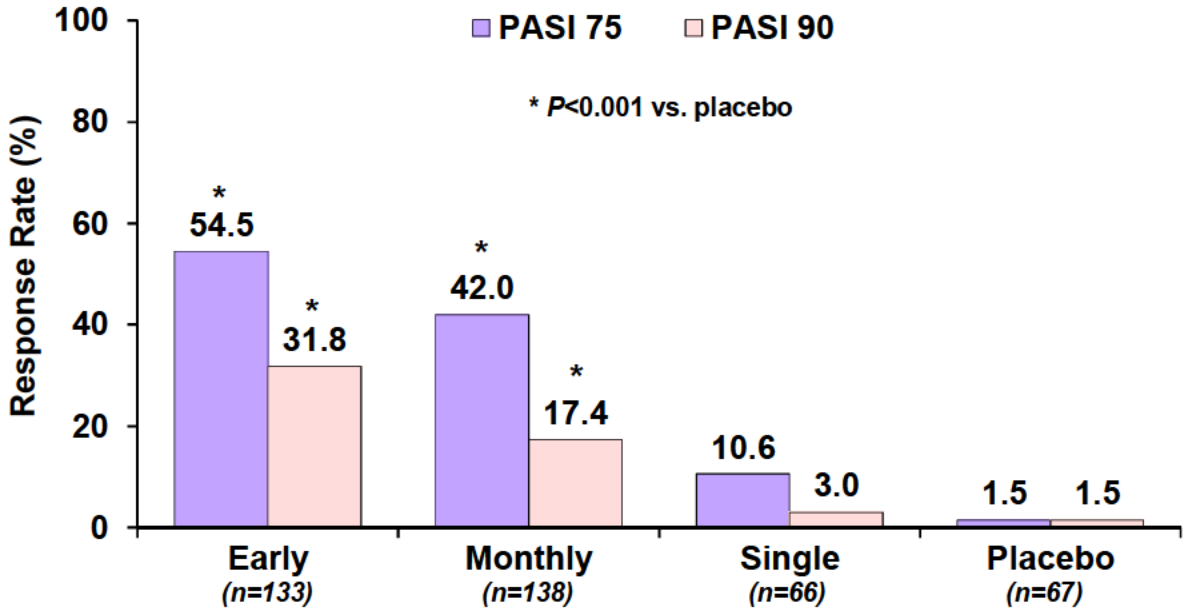
IGA = Investigator Global Assessment; PASI = Psoriasis Area and Severity Index; PBO = placebo; R = Randomization (baseline); Wks = weeks; dPGA = dynamic Physician's Global Assessment

Based on the data from these studies, doses of 150 mg and 300 mg s.c. administered, initially at Weeks 0, 1, 2, 3, 4 followed by every 4 weeks, were selected for study in Phase III. The Phase II studies included 665 randomized patients. Supportive safety data from Phase II studies in other indications contributed to the dose selection for Phase III.

Proof of concept was established with a single i.v. dose of 3 mg/kg in study A2102. Two subsequent studies evaluated different low doses (study A2220, s.c. administration, N=125), and different high doses (study A2212, i.v. administration, N=100). A third study assessed regimen finding using the same 150 mg 'monthly' dose (used in A2220) but also assessing 'early' loading (A2211, s.c. administration, N=404).

Twelve week results from the large s.c. regimen finding study (A2211) are shown in Figure 5-1. The highest PASI 75 response rates, which were statistically significant compared to placebo, were achieved with the higher cumulative doses (150 mg x 3 and 150 mg x 4). The more frequent regimen ('early' with 4 doses given over the first month) provided numerically higher responses than the less frequent regimen (3 doses given in monthly intervals): PASI 75 responses of 54.5% vs 42% and PASI 90 responses of 32% vs 17%, respectively.

**Figure 5-1 PASI 75 and PASI 90 responders after 12 weeks of treatment (A2211)**

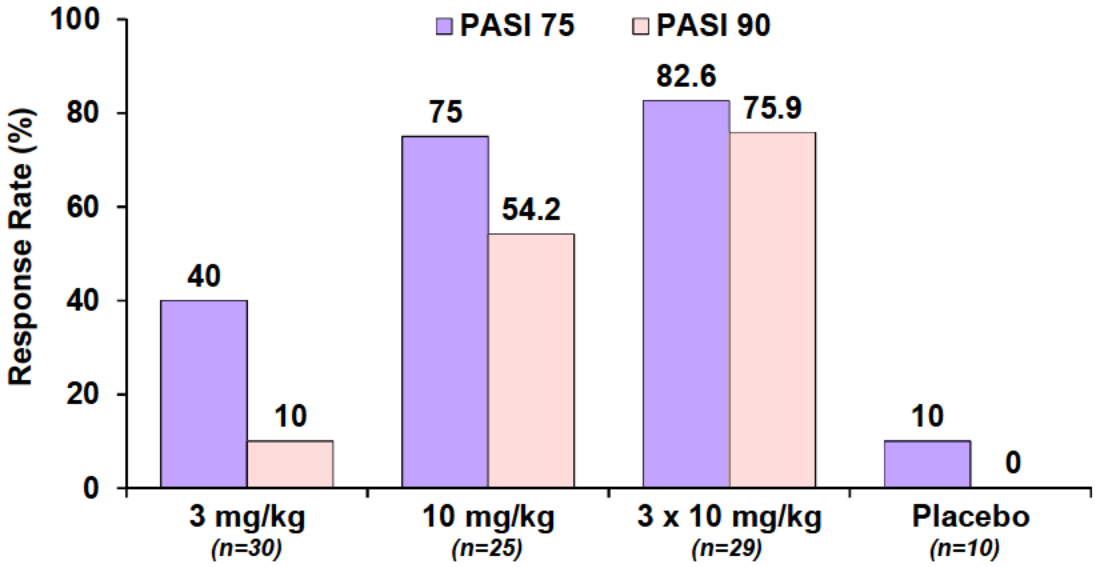



'Early' loading at weeks 0, 1, 2, 4; 'Monthly' injections at weeks 0, 4 and 8; 'Single' one injection at week 0
* p< 0.001 vs. placebo

Study A2212 used intravenous administration to explore response to higher exposure levels. It compared 3 i.v. dose regimens with placebo: single doses of 3 or 10 mg/kg or repeated doses of 10 mg/kg (given at Randomization, Week 2, and Week 4). Week 12 results for PASI 75 & 90 are shown in Figure 5-2. This study showed that higher PASI 75 response rates (83%, compared to 55% in A2211) could be achieved with the higher exposure achieved with 10 mg/kg administered intravenously repeatedly over the first 4 weeks of treatment (Weeks 0, 2, and 4). This is consistent with the finding from A2211 that multiple s.c. doses over the first month produced better responses than less frequent loading doses.

Response rates of PASI 75, PASI 90 and IGA mod 2007 0/1 consistently showed dose-related efficacy. There were a higher proportion of responders in the 10 mg/kg i.v., rather than the 3 mg/kg i.v., single dose cohort and an even higher proportion seen with the 3-times 10 mg/kg i.v. dosing.

**Figure 5-2 PASI 75 and PASI 90 responders after 12 weeks of treatment (A2212)**




Following input from the FDA, study A2220 evaluated s.c. dose-ranging to assess the lower range of the potential dose spectrum. This study evaluated 25 mg given as a single dose and 25 mg, 75 mg and 150 mg doses given once every four weeks.

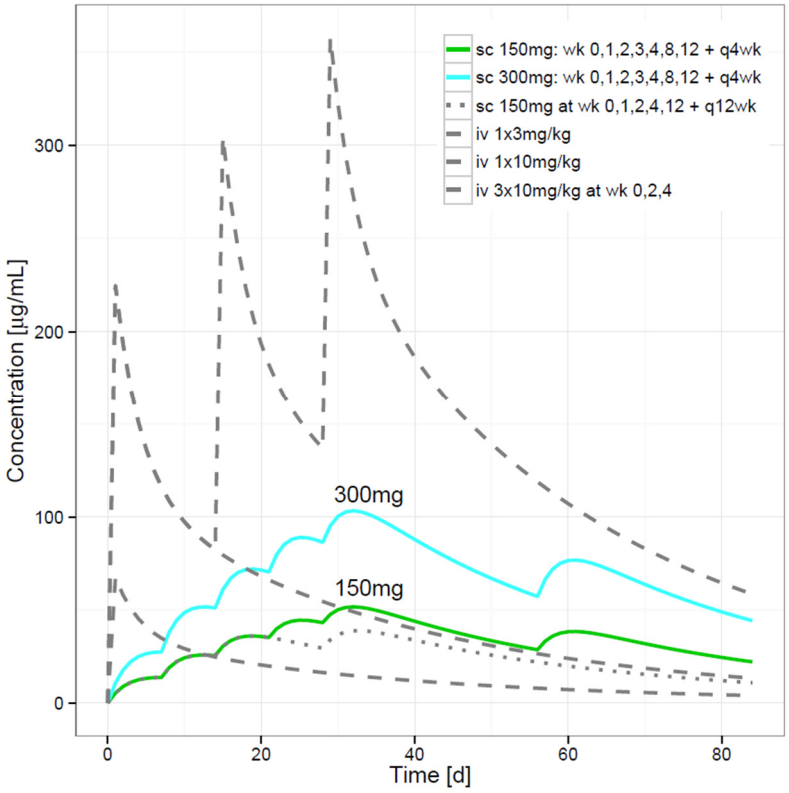
Efficacy was dose-related with both the 75 and 150 mg doses resulting in significantly more PASI 75 responders than placebo. The 25 mg dose was not effective. For higher levels of efficacy (PASI 90 and IGA 0/1), only the 150 mg dose was significantly greater than placebo.

Results achieved with the 75 mg dose were not considered efficacious enough compared to currently available treatment options. Thus, 150 mg administered subcutaneously was viewed as the lowest dose for achieving adequate overall efficacy in Phase III studies. Thus this study identified the low end of the dose range to be studied in Phase III.

The 300 mg s.c. dose selected for Phase III was based on understanding exposure-response using PK simulation from the Phase II studies. Peak efficacy was observed with 3 x 10 mg/kg i.v. doses over 1 month in study A2212. This efficacy could be achieved without apparent associated safety risks. Therefore, the goal was to identify a subcutaneous dose and regimen that would be close to the trough concentrations of i.v. dosing, while avoiding high peak exposures, and provide superior benefit without undue safety risk.

Pharmacokinetic simulations using data from the larger 150 mg subcutaneous regimen study (A2211) and the intravenous dose ranging study (A2212) showed that exposure with a 300 mg dose, initially given weekly, then every four weeks, provided exposure in between that of the 'floor' (150 mg s.c.) and the 'ceiling' (3 x 10 mg/kg) targets (Figure 5-3). Based on these considerations, the regimen of weekly s.c. injections of 150 or 300 mg at Weeks 0, 1, 2, 3, followed by monthly maintenance dosing starting at Week 4, was selected for confirmation in Phase III.

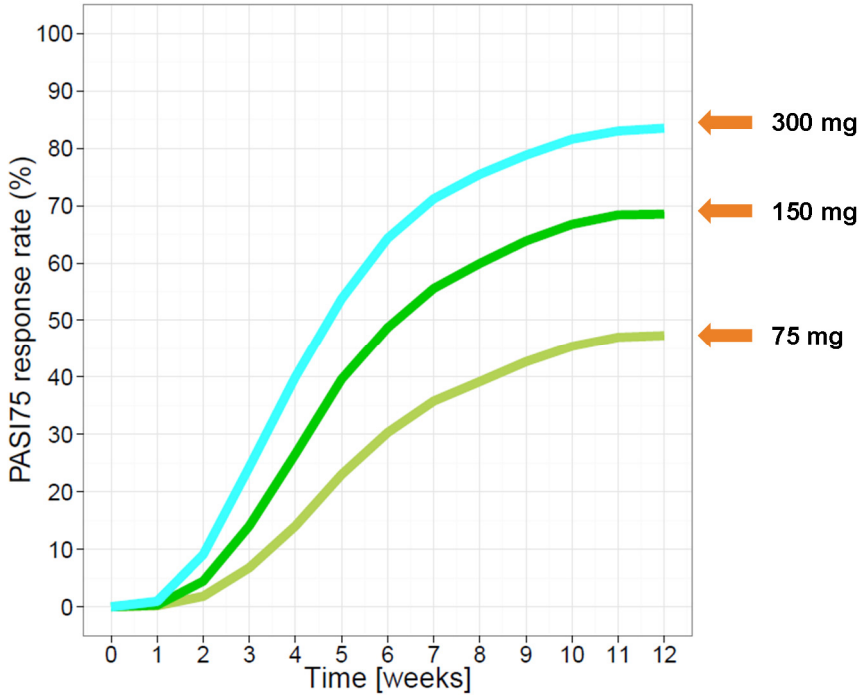
**Figure 5-3 Simulated exposures for different secukinumab dosing regimens**




The relationship between dose and regimen, plasma concentration, and response (PASI 75) was also modeled using a population-PK/PD approach. This allowed the response for the proposed subcutaneous dosing regimen to be simulated (Figure 5-4) for 75 mg, 150 mg and 300 mg, respectively. The PASI 75 response rate was predicted to be too low with 75 mg (only approximately 50% PASI at 12 weeks) relative to currently available therapeutic options. Both the 150 mg and 300 mg doses were predicted to provide substantially better efficacy than 75 mg, with greatest benefit suggested for the 300 mg dose.

In summary, a combination of dose-ranging and regimen-finding studies in conjunction with modeling and simulation was the basis for selection of the two doses studied in Phase III.

**Figure 5-4 Simulated PASI 75 response rates for dosing regimens**




Simulated PASI 75 response rates for 75, 150 mg and 300 mg s.c. over time with maintenance dosing given at Week 12 and every 4 weeks afterwards (dosing at Weeks 0, 1, 2, 3, 4, 8).

Based on these data, initial doses of 150 mg or 300 mg given at weeks 0, 1, 2 and 3 followed by monthly maintenance, starting at Week 4, were selected for Phase III studies. The Phase III results are described in Section 5.4.

## 5.4 Phase III efficacy

The large, core Phase III program with Studies A2302, A2303, A2308, and A2309 subsequently confirmed Phase II PASI 75 modeling predictions. While both the 150 and 300 mg doses were demonstrated to be efficacious, a clinically meaningful, higher response (PASI 75, 90, 100 and IGA mod 2011 0/1) was observed with 300 mg compared to the 150 mg regimen at 12 weeks.

The 4 randomized, double-blind, placebo-controlled Phase III psoriasis studies (Table 5-3) had almost identical study designs (Studies A2302, A2303, A2308, A2309). Study A2303 also included an active-controlled arm with the biologic TNF-α antagonist etanercept. This common study design framework is presented in Section 5.4.1. The focus will be on the results from the two large 52 week studies (A2302 and A2303). Section 5.4.2 describes the baseline demographic and disease characteristics and Section 5.4.3 summarizes efficacy outcomes. The co-primary outcomes from the two smaller double-blind, placebo-controlled trials (A2308 and A2309) will be presented in juxtaposition to the two larger studies. Collectively, the results from all 4 double-blind, placebo-controlled trials consistently demonstrate that secukinumab is a highly efficacious treatment and that the 300 mg dose provides the greatest benefit to patients.

Of the four core placebo-controlled Phase III studies, two (A2302 and A2303) used the LYO formulation. The other two utilized the liquid formulation, either in the PFS (A2308) or in the AI/Pen (A2309). All were designed to demonstrate the safety and efficacy of two secukinumab doses (150 mg, 300 mg) after 12 weeks of therapy, and to show efficacy and safety after a further 40 weeks of dosing, for a total treatment period of 52 weeks. A2308 and A2309 Week 12 primary endpoint data are provided and are ongoing.

The other two Phase III studies (Study A2304 and Study A2307) were designed to evaluate additional questions regarding regimen. Study A2304 compared 2 different maintenance regimens: fixed interval (FI) dosing throughout the maintenance period or "Treatment as needed" (i.e. initiation of dosing only at "Start of relapse" SoR) after an initial 12 week treatment period. This study provides support for the proposed monthly interval dosing. Study A2307 evaluated whether using higher doses for patients achieving only a partial response (i.e. PASI 50 responders without a PASI 75 response) in the initial 12 week period of Study A2304 would achieve a PASI 75 response.

Long term efficacy and safety over a 52 week treatment period is available from the three large Phase III studies (A2302, A2303, A2304) and 1 supportive ongoing Phase II extension trial (A2211E1). In addition, A2308, A2309 and additional extension studies (A2302E1 and A2304E1) are ongoing, utilizing monthly dosing with either 150 or 300 mg (planned for up to 4-5 years total exposure on secukinumab).

**Table 5-3 Summary of Phase III controlled, randomized, blinded trials**

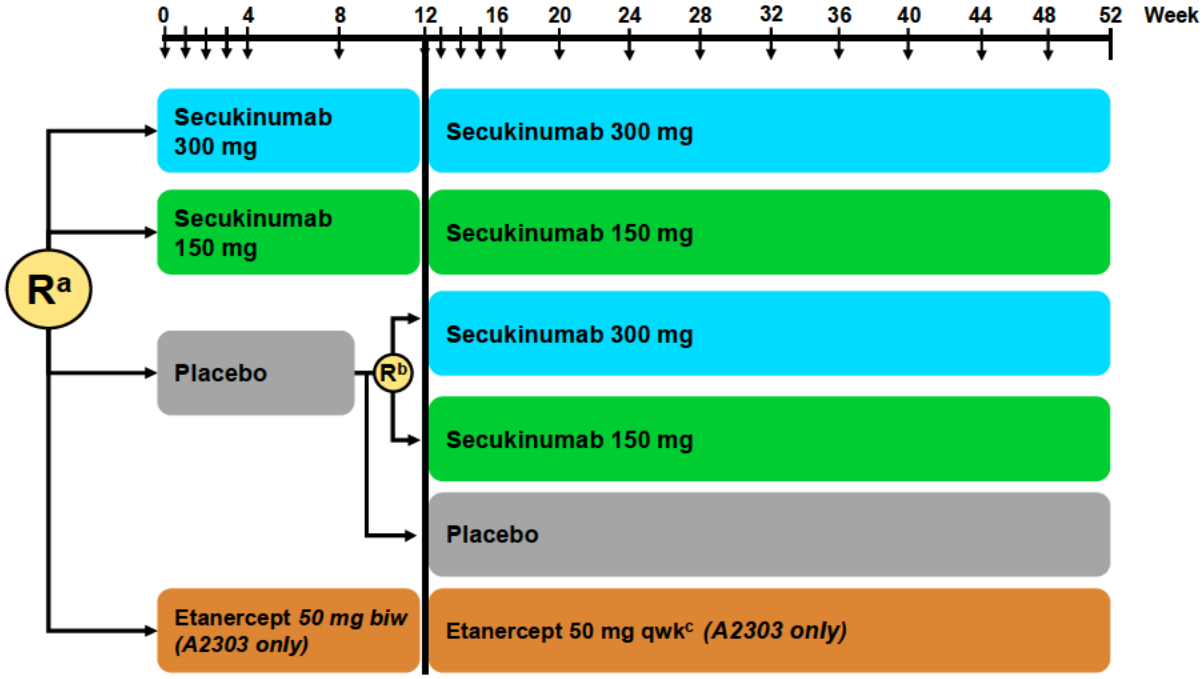
| Study | Description | N | Treatments | Primary variable |
|---|---|---|---|---|
| **Placebo controlled** | | | | |
| **A2302** *(52 Wk)* | Efficacy/safety (s.c.) in target population | 738† | 150 , 300 mg secukinumab, PBO[a] (*lyo*), at R, Wks 1, 2, 3, 4, then q4w until Wk 48 | PASI 75, IGA mod 2011 0/1 response (Wk 12) |
| **A2308** *(p.e. 12 Wk)* | Efficacy/safety (s.c.) in target population | 177 | 150, 300 mg secukinumab, PBO[a] (*self administration with PFS*) at R, Wks 1, 2, 3, 4, then q4w until Wk 48 | PASI 75, IGA mod 2011 0/1 response (Wk 12) |
| **A2309** *(p.e.12 Wk)* | Efficacy/safety (s.c.) in target population | 182 | 150 mg or 300 mg secukinumab, PBO[a] (*self administration* with *AI/pen*) at R, Wks 1, 2, 3, 4, then q4w until Wk 48 | PASI 75, IGA mod 2011 0/1 response (Wk 12) |
| **Placebo and active controlled** | | | | |
| **A2303** *(52 Wk)* | Efficacy/safety (s.c.) in target population | 1306‡ | 150 mg or 300 mg secukinumab, PBO[a] (*lyo*), at R, Wks 1, 2, 3, 4, then q4w until Wk 48<br>Etanercept 50 mg twice per week to Wk 12, then qw to Wk 51 | PASI 75, IGA mod 2011 0/1 response (Wk 12) (also assessed superiority to etanercept in a pre-specified hierarchical analysis) |
| **Maintenance regimen comparison** | | | | |
| **A2304** *(52 Wk)* | Maintenance of efficacy/ safety (s.c.) in target population | 965 | 150, 300 mg secukinumab (lyo) at R, Wks 1, 2, 3, 4, then q4w until Wk 12[b]<br>For PASI 75 responders:<br>*Fixed Interval:* at same dose q4w to Wk 48<br>*"Treatment as needed" at Start of relapse[c]:* PBO to relapse, then secukinumab at same dose q4w till PASI 75 then PBO to relapse or Wk 48 | PASI 75 (Wk 52 for all treated at Wk 40) (Wk 40 if on start of relapse dosing & not relapsed at Wk 40) |
| **A2307** *(40 Wk)* | Efficacy/safety in partial responders at Wk 12 in A2304 | 43 | 10 mg/kg i.v. secukinumab (R, Wks 2, 4), or 300 mg s.c. secukinumab (R, Wk 4), then 300 mg s.c. q4w to Wk 36 | PASI 75, IGA mod 2011 0/1 response at Wk 8 |

p.e. = 12 week primary endpoint analysis of an up to 216-week study (including the initial 12 week period, Maintenance, Optional Extension, and Follow-up periods)
AIN = AIN457, PBO = placebo, Lyo = lyophilisate in vial, PASI = Psoriasis Area and Severity Index, IGA = Investigator Global Assessment; R = randomization, qw = once weekly dosing
a = PASI 75 nonresponders on PBO were re-randomized 1:1 to 150 or 300 mg AIN457 and treated from Wk 12 onwards
b = PASI 75 nonresponders discontinued study treatment. Those with partial response (≥ 50% but <75% PASI reduction) were offered further treatment in Study A2307
c = start of relapse is a loss of ≥ 20% of the maximum PASI improvement gained in the study AND a loss of PASI 75 response
† Note one randomized patient was excluded from the efficacy and safety analyses due to having not signed an Informed consent to participate in Study A2302. Therefore N for analysis = 737 patients.
‡ Note one randomized patient was excluded from the efficacy and safety analyses due to a lab test that was performed before informed consent was provided and two further patients were excluded from the safety population because they did not take any dose of study medication during the initial12 week period, therefore N=1305 for efficacy and N=1303 for safety analyses.

### 5.4.1 Study design for the core placebo controlled studies

Four double-blind, placebo-controlled Phase III trials (A2302, A2308, A2309 and A2303) were of similar design and all examined efficacy of a 12-week initial dosing regimen of 150 and 300 mg doses once weekly (Weeks 0, 1, 2, 3 and 4) followed by maintenance dose every 4 weeks. All were double-blinded, placebo-controlled and one (A2303) also included the active control, etanercept. All four used essentially the same design as shown for A2303 in Figure 5-5. The only differences are that the etanercept arm was unique to A2303, and hence this study had slightly different exclusion criteria (e.g., exclusion of patients with previous exposure to etanercept). Results from the two larger, long term studies will be highlighted. Summaries of efficacy across all 4 placebo-controlled trials are also presented, showing consistency of results.

**Figure 5-5 Study design A2303**




[a] R, randomization at Week 0 to secukinumab (150 mg or 300 mg), etanercept 50 mg (Study A2303 only), or placebo with dosing at Weeks 0, 1, 2, 3, and 4, followed by maintenance dosing every 4 weeks

[b] Re-randomization of placebo patients that did not achieve PASI-75 response to secukinumab 150 mg or 300 mg administered at Weeks 12, 13, 14, 15, followed by dosing every 4 weeks maintenance dosing starting at Week 16

[c] Etanercept treatment qwk from Week 12 (A2303 only)

### 5.4.2 Baseline demographics and disease characteristics

Baseline demographics and disease characteristics were generally consistent across the four double-blind, placebo-controlled studies and were balanced across the treatment groups, these studies represent the target population. Key baseline demographics and disease characteristics for the two large randomized controlled studies (A2302 and A2303) are summarized in Table 5-4 and Table 5-5, respectively. A predominance of male subjects participated, as has been observed in clinical studies of other biologics (Leonardi et al 2003; Lebwohl et al 2003;

Menter et al 2008). Approximately 40% of patients had severe psoriasis by IGA mod 2011 and approximately 50% had failed prior systemic therapy. Patients could have failed a prior systemic therapy including methotrexate, retinoids, acitretin and/or biologics (see also Section 5.4.10).

**Table 5-4 Key Baseline Demographics - A2302 and A2303**

| | A2302 (N=738) | | | A2303 (N=1306) | | | |
|---|---|---|---|---|---|---|---|
| | 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 |
| Mean Age (years) | 44.9 | 44.9 | 45.4 | 44.5 | 45.4 | 44.1 | 43.8 |
| Male (%) | 69.0 | 68.6 | 69.4 | 68.5 | 72.2 | 72.7 | 71.2 |
| Caucasian (%) | 69.8 | 69.8 | 71.0 | 68.5 | 67.0 | 66.9 | 67.2 |
| Asian (%) | 21.2 | 22.0 | 18.5 | 22.3 | 22.0 | 22.1 | 22.7 |
| Black (%) | 1.6 | 2.0 | 4.0 | 0.6 | 0.9 | 0.9 | 0.0 |
| Mean weight (kg) | 88.8 | 87.1 | 89.7 | 83.0 | 83.6 | 82.0 | 84.6 |
| Cardiac Disorders (%) | 3.7 | 6.1 | 4.8 | 3.7 | 3.1 | 3.7 | 2.1 |
| Latent TB (%) | 4.1 | 5.7 | 3.2 | 6.4 | 7.0 | 3.7 | 5.2 |

**Table 5-5 Key Baseline Disease characteristics – A2302 and A2303**

| | A2302 (N=738) | | | A2303 (N=1306) | | | |
|---|---|---|---|---|---|---|---|
| | 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 |
| **Psoriasis duration, y*** | 17.4 | 17.5 | 17.3 | 15.8 | 17.3 | 16.6 | 16.4 |
| **Baseline PASI score*** | 22.5 | 22.3 | 21.4 | 23.9 | 23.7 | 24.1 | 23.2 |
| **BSA involvement, %*** | 32.8 | 33.3 | 29.7 | 34.3 | 34.5 | 35.2 | 33.6 |
| **IGA score+, %** | | | | | | | |
| **3 = moderate** | 62.9 | 65.7 | 60.9 | 62.1 | 63.0 | 62.0 | 59.8 |
| **4 = severe** | 37.1 | 34.3 | 39.1 | 37.9 | 37.0 | 38.0 | 40.2 |
| **PsA present, %** | 23.3 | 18.8 | 27.4 | 15.3 | 15 | 15 | 13.5 |

* Mean value; + Static 5-point IGA mod 2011 scale

BSA = body surface area; IGA = Investigator Global Assessment

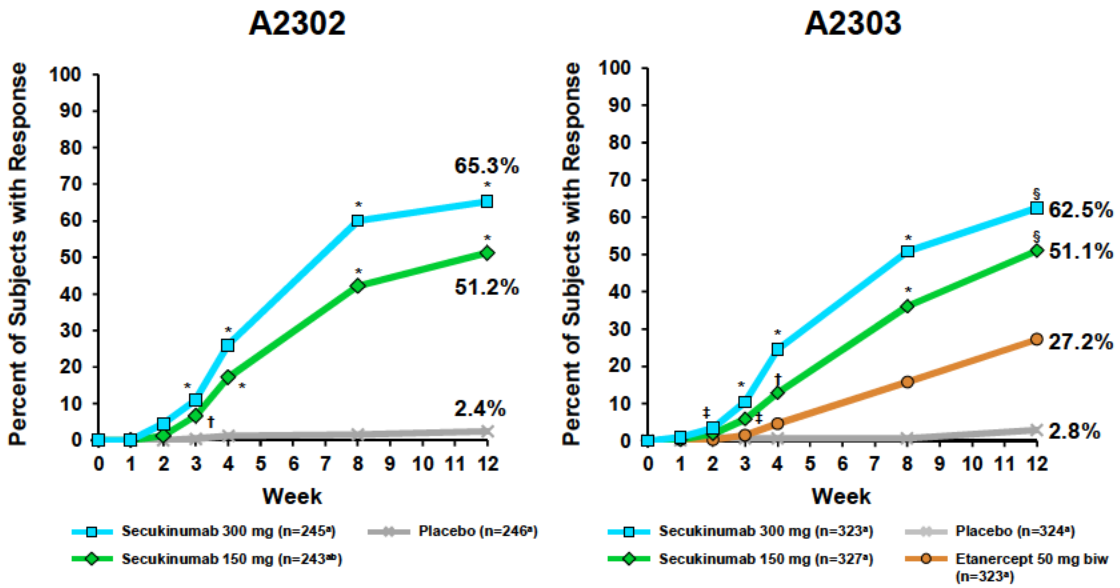
### 5.4.3 PASI and IGA results

Results from the two largest studies (A2302 with placebo control, A2303 with placebo and etanercept control) will be presented first followed by a summary of efficacy across all 4 placebo-controlled trials.

All 4 core, placebo-controlled studies (A2302, A2303, A2308, A2309) included co-primary efficacy variables of PASI 75 response and IGA mod 2011 0/1 response, both at Week 12. Although superiority of secukinumab to placebo ($p<0.0001$) was demonstrated for the co-primary efficacy criteria of PASI 75 and IGA mod 2011 0/1 at 12 weeks with both tested dose regimens, the 300 mg regimen provided optimal efficacy with 10-20% higher proportions of

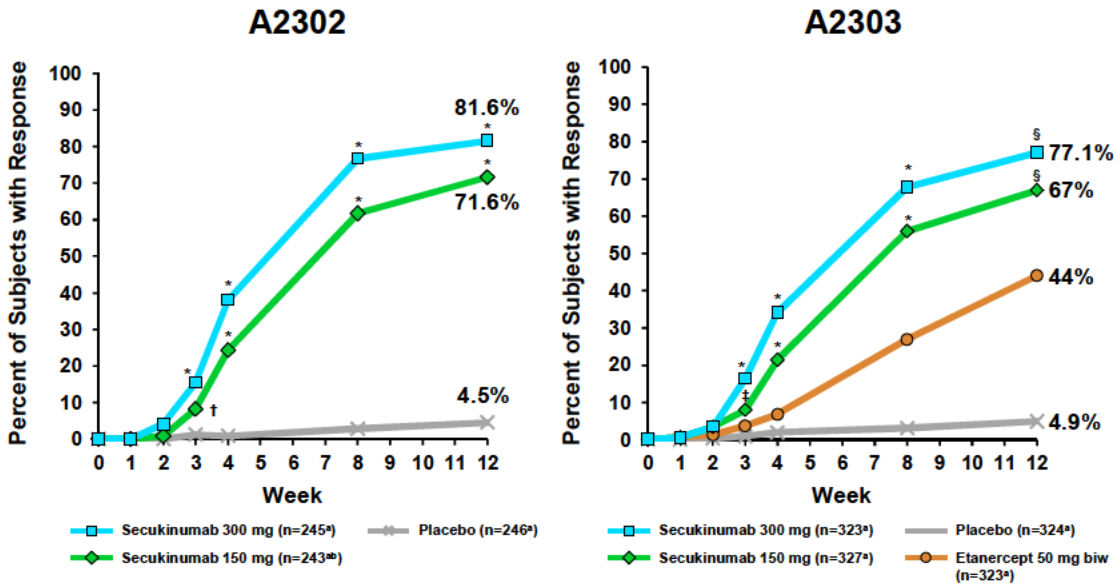
patients achieving IGA mod 2011 0/1 (Figure 5-6), PASI 75 response (Figure 5-7), PASI 90 (Figure 5-8) and PASI 100 (Figure 5-9). Results were highly consistent across all 4 core placebo-controlled trials (Figure 5-10).

**Figure 5-6 Co-primary endpoint - IGA mod 2011 0/1**



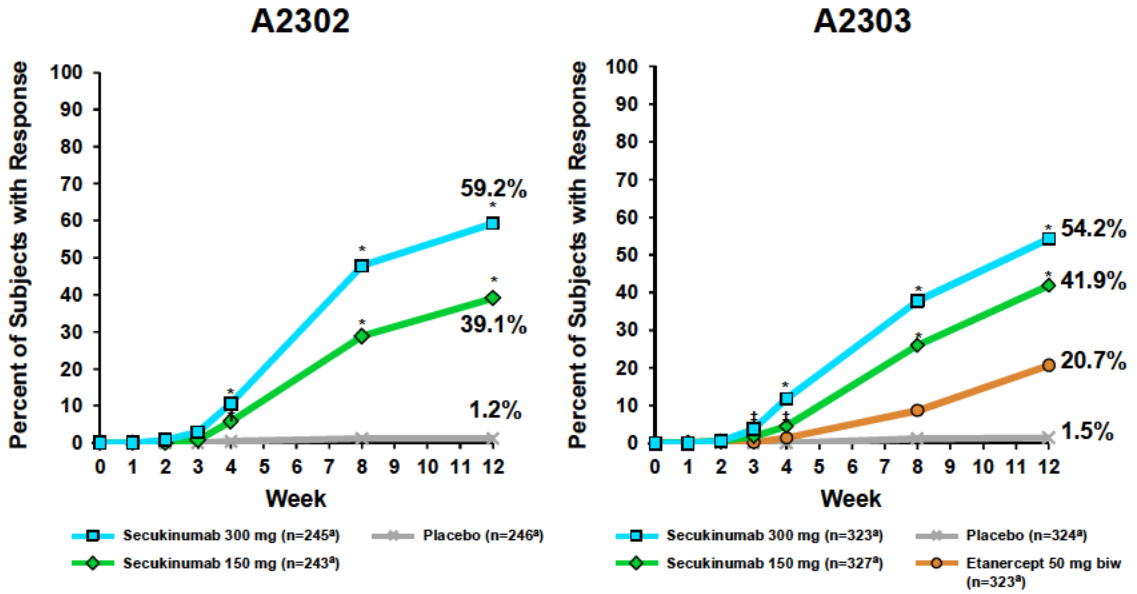

*$P < 0.0001$; †$P < 0.001$; ‡$P < 0.05$ §$P = 0.025$ for comparisons of secukinumab vs. etanercept. Only $P$ values for response rates at Week 12 were adjusted for multiplicity.
[a]Number of evaluable subjects. [b]Number of subjects evaluable for IGA 0/1 response in secukinumab 150 mg group was 244.

**Figure 5-7 Co-primary endpoint - PASI 75**



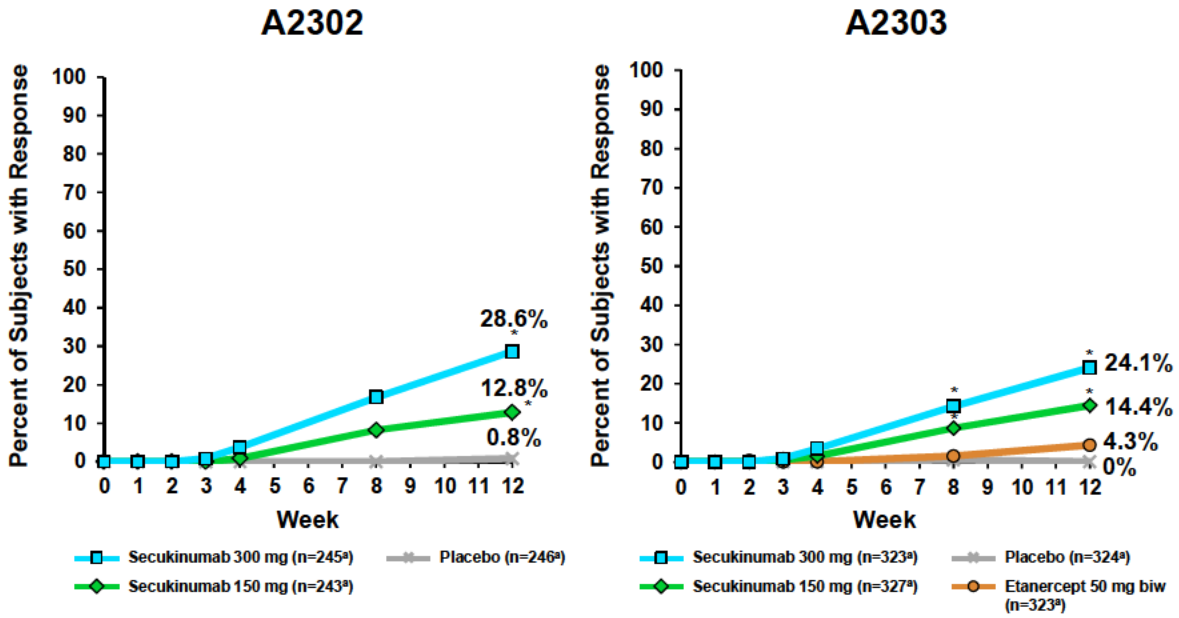

*$P < 0.0001$; †$P < 0.001$; ‡$P < 0.05$ §$P = 0.025$ for comparisons of secukinumab vs. etanercept. Only $P$ values for response rates at Week 12 were adjusted for multiplicity.
[a]Number of evaluable subjects. [b]Number of subjects evaluable for IGA 0/1 response in secukinumab 150 mg group was 244.

**Figure 5-8 Pre-specified secondary endpoint - PASI 90**




*$P < 0.0001$; †$P < 0.001$ for comparisons of secukinumab vs. placebo. Only $P$ values for PASI 90 response rates at Week 12 versus placebo were adjusted for multiplicity. ‡$P < 0.05$ for comparisons of secukinumab vs. etanercept.
[a]Number of evaluable subjects.

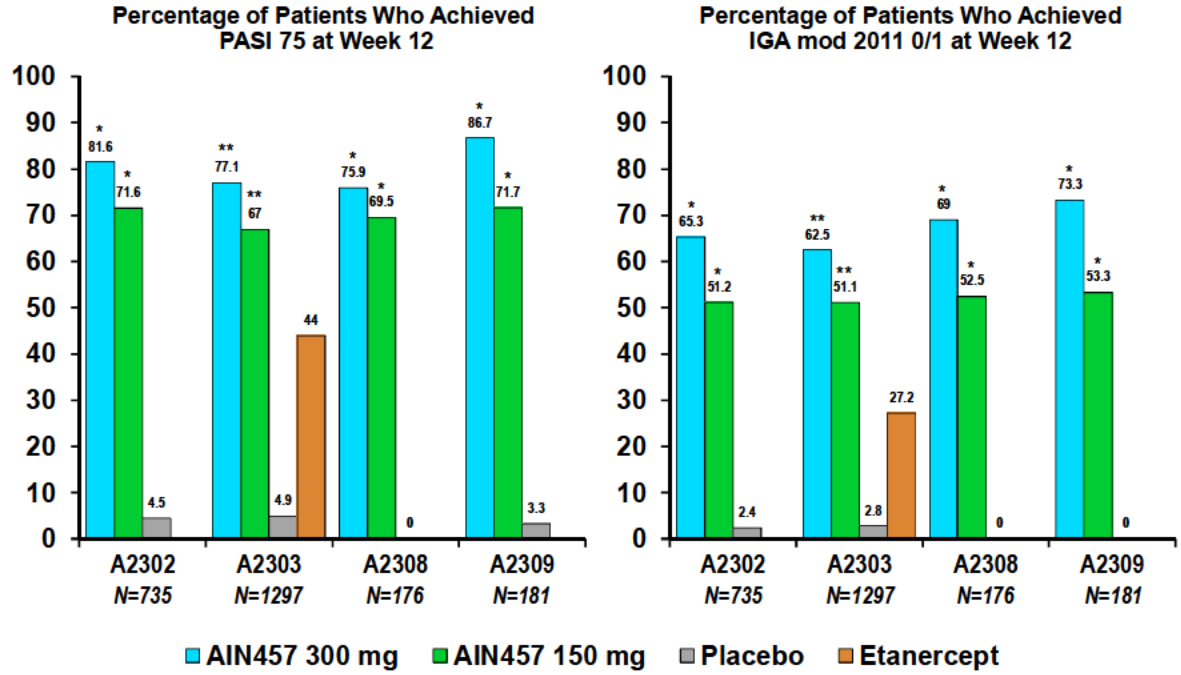
**Figure 5-9 Pre-specified secondary endpoint - PASI 100**




*P < 0.0001; [a]Number of evaluable subjects.

Figure 5-10 shows the consistency of the co-primary outcomes across all 4 core placebo controlled studies:

**Figure 5-10 Co-primary endpoint across all 4 core placebo-controlled studies**




* p < 0.0001 versus placebo. Treatment comparisons for studies A2302 and A2303 were based on Cochran-Mantel-Haenszel testing and for studies A2308 and A2309 on Fisher's exact test.

** p <0.0001 versus etanercept

Compared to the threshold of what was seen as "adequate response" as defined by PASI 75, newer psoriasis therapies have demonstrated even higher levels of efficacy by being able to achieve PASI 90 (90% reduction) or PASI 100 (100% clearance) (Griffiths et al 2010, Leonardi et al 2012, Papp et al 2012). PASI 75 has been the standard measurement for clinically meaningful efficacy for chronic plaque psoriasis. Dermatology clinical research is exploring PASI 90 (equivalent to 'clear' or 'almost clear' skin) as the new target for therapies capable of reaching this higher threshold, with the ultimate goal of complete clearance of skin symptoms (Mrowietz et al 2011a, Mrowietz et al 2011b). PASI 90 response correlates with improved health-related quality of life (HRQoL) compared to PASI 75. A higher percentage of patients who reach PASI 90 report no HRQoL impairment compared with a smaller percentage of those who only attain PASI 75 (Revicki et al 2008, Revicki et al 2013, Torii et al 2012).

The 300 mg dose had consistently 10 – 20% higher response rates compared with the 150 mg dose on all endpoints measured (PASI 75, PASI 90, PASI 100, IGA mod 2011 0/1) and this was observed across all 4 studies (Table 5-6). The absolute difference in response rates between the 300 mg and 150 mg dose groups generally increased with more stringent thresholds of PASI measure (PASI 90 and PASI 100) or with IGA mod 2011 0/1 denoting clear to almost clear skin (Figure 5-11).

**Table 5-6 Key 12 week efficacy data in the 4 core trials – physician reported primary outcomes**

| | AIN457 300 mg | AIN457 150 mg | Placebo | Etanercept |
|---|---|---|---|---|
| **PASI 75 - % achieving response** | | | | |
| A2302 | 81.6 | 71.6 | 4.5 | - |
| A2303 | 77.1 | 67 | 4.9 | 44.0 |
| A2308 | 75.9 | 69.5 | 0.0 | - |
| A2309 | 86.7 | 71.7 | 3.3 | - |
| **PASI 90 - % achieving response** | | | | |
| A2302 | 59.2 | 39.1 | 1.2 | - |
| A2303 | 54.2 | 41.9 | 1.5 | 20.7 |
| A2308 | 60.3 | 45.8 | 0.0 | - |
| A2309 | 55 | 40 | 0.0 | - |
| **PASI 100 - % achieving response** | | | | |
| A2302 | 28.6 | 12.8 | 0.8 | - |
| A2303 | 24.1 | 14.4 | 0.0 | 4.3 |
| A2308 | 43.1 | 8.5 | 0.0 | - |
| A2309 | 26.7 | 16.7 | 0.0 | - |
| **IGA mod 2011 0/1 - % achieving response** | | | | |
| A2302 | 65.3 | 51.2 | 2.4 | - |
| A2303 | 62.5 | 51.1 | 2.8 | 27.2 |
| A2308 | 69 | 52.5 | 0.0 | - |
| A2309 | 73.3 | 53.3 | 0.0 | - |
| **IGA mod 2011 0 - % achieving response** | | | | |
| A2302 | 32.2 | 16.4 | 0.8 | - |
| A2303 | 28.2 | 15.3 | 0.3 | 5.3 |
| A2308 | 44.8 | 10.2 | 0.0 | - |
| A2309 | 30 | 18.3 | 0.0 | - |

**Statistical significance** (statistical comparisons were not performed for IGA mod 2011 0)**:**

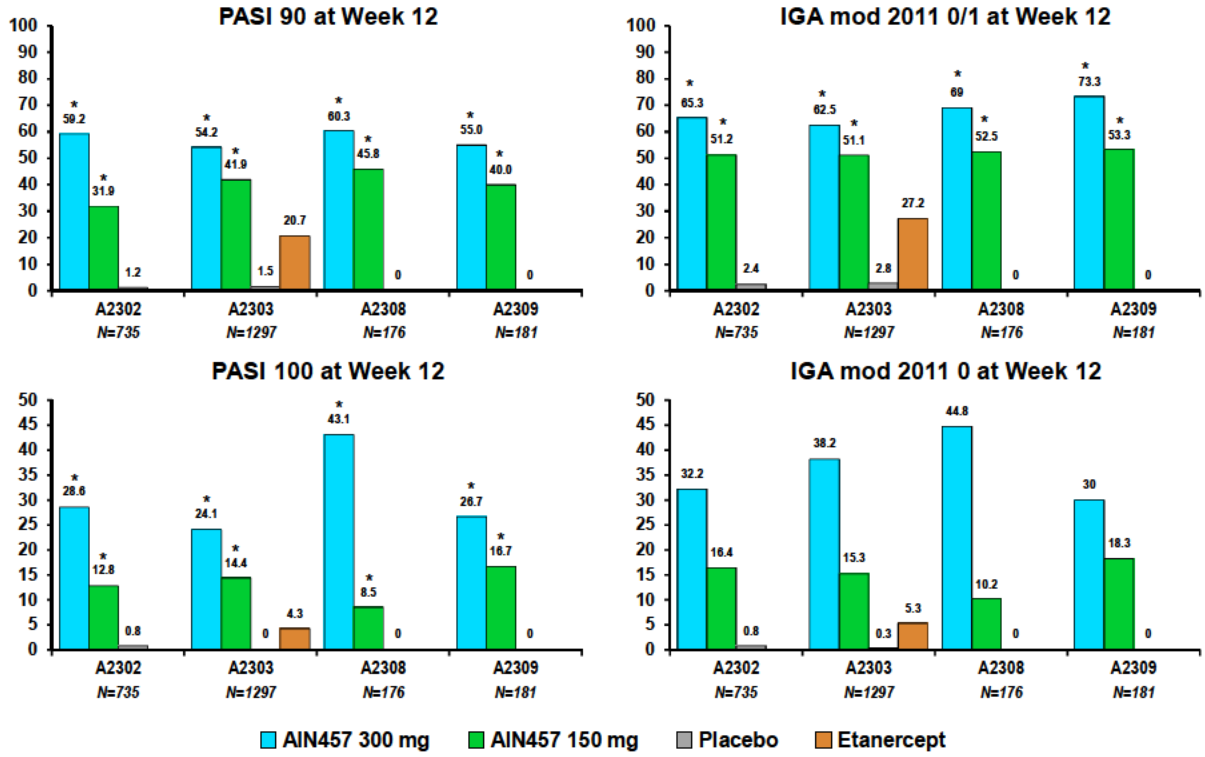
300 mg or 150 mg, vs. placebo: all comparisons were significant (P<0.0001).

300 mg vs. 150 mg: all comparisons were significant (P< 0.01) in the larger studies (A2302 and A2303).

300 mg or 150 mg, vs. etanercept (in Study A2303): comparisons between secukinumab and etanercept for PASI 75 and IGA mod 2011 0/1 were part of testing strategy with adjusted p-values of 0.025, unadjusted P<0.0001; comparisons for PASI 90 were not part of testing strategy and p values were not adjusted (P<0.0001).

*Note that for IGA mod 2011 0 values presented included LOCF, whereas all other endpoints were based on non-responder imputation. Treatment comparisons for studies A2302 and A2303 were based Cochran-Mantel-Haenszel testing and for studies A2308 and A2309 on Fisher's exact test.*

**Figure 5-11 Percentage of patients who achieved PASI 90, PASI 100, IGA 0/1 and IGA 0 at week 12**




Note that for IGA mod 2011 0 values presented included LOCF, whereas all other endpoints were based on non-responder imputation. Statistical comparisons were not performed for IGA 0.

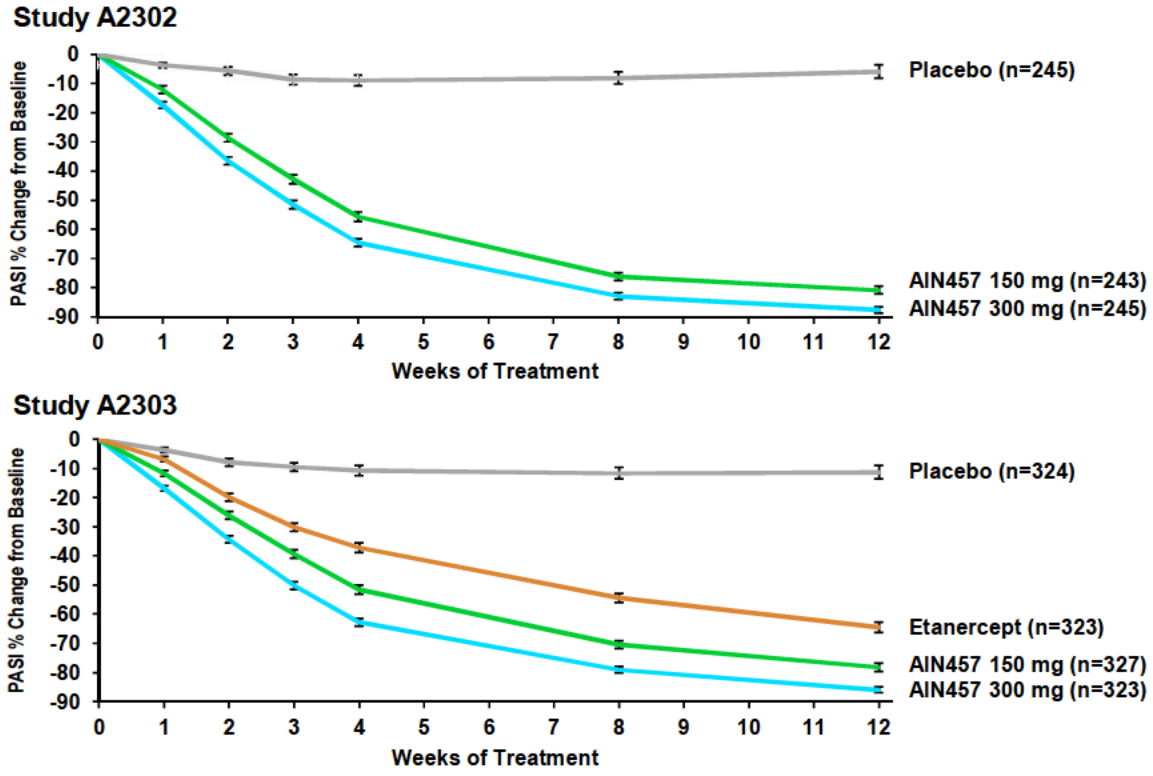
* $p < 0.0001$ versus placebo. Treatment comparisons for studies A2302 and A2303 were based on Cochran-Mantel-Haenszel testing and for studies A2308 and A2309 on Fisher's exact test.

Efficacy was consistent across the different formulations, forms and delivery methods of secukinumab. There were no clinically significant differences in efficacy between the LYO (A2302 and A2303) and liquid formulations (A2308 and A2309), forms (PFS in Study A2308 or AI/Pen in A2309), or delivery method (injection administered by site staff in A2302 and A2303 vs. self-administration using PFS or AI/Pen in studies A2308 and A2309, respectively).

### 5.4.4 Onset of response

Early onset of effect is a patient benefit based on patient feedback (Seston et al 2007). Early onset was observed with secukinumab at both dose levels, compared with etanercept or placebo in Studies A2302 and A2303 (Figure 5-12). The reduction in mean PASI score for the secukinumab 300 mg dose was consistently higher at each time point through Week 12. Secukinumab 300 mg had a rapid onset of efficacy with an approximate 40% reduction of mean PASI score at Week 2 and 50% reduction by Week 3. In contrast, it took 4 weeks for secukinumab 150mg and 8 weeks for etanercept to reach a 50% reduction of mean PASI score. The speed of onset of response was similar in the smaller trials A2308 and A2309.

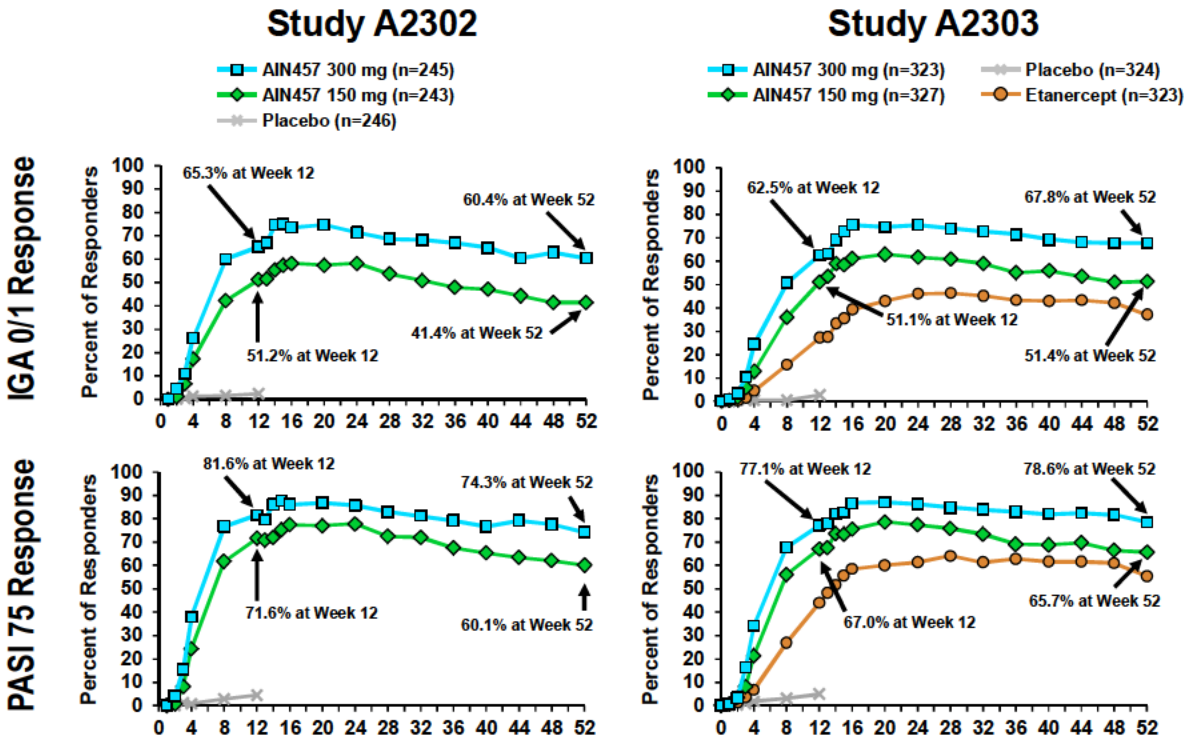
**Figure 5-12 Mean percentage change from baseline PASI score over time (mean +/- SE) LOCF in Study A2302 and Study A2303– Initial 12 week period**




## 5.4.5 Efficacy data over time

Regardless of the threshold of response (PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1), the increases in response rates shown for both secukinumab doses over the first 12 weeks of treatment continued to increase to approximately 16 weeks and were maintained for the remaining 52 weeks of study treatment. This is important to patients with moderate to severe psoriasis as they require long-term symptom control. PASI 75 and PASI 90 responses for the 2 largest Phase III trials (A2302 and A2303) over 52 weeks are shown in Figure 5-13. It is worthwhile noting that these graphs and analyses utilize a conservative statistical methodology of non-responder imputation that imputes non-response for any missing data (including discontinued patients or patients that failed to return for scheduled evaluation).

**Figure 5-13** **IGA mod 2011 0/1 and PASI 75 response rates over 52 weeks of treatment in studies A2302 and A2303 (non-responder imputation)**




n = number of evaluable patients

In all cases, clear separation of the doses is shown, with the greatest benefit for the secukinumab 300 mg dose.

The benefit for the secukinumab 300 mg dose over 150 mg dose increases over time and is greatest at week 52. For each PASI and IGA measure, the 300 mg dose showed a higher level of response at 52 weeks compared to the 150 mg dose and compared to etanercept. Moreover, response rates for 300 mg were approximately 16-20% better than 150 mg and 26-32% better than etanercept for the higher efficacy measures (e.g. PASI 90, IGA mod 2011 0/1 & PASI 100 responses) after 52 weeks of treatment.

In both Studies A2302 and A2303, the majority of secukinumab-treated patients who achieved a response at week 12 were able to maintain the response at week 52. In particular, patients receiving the 300 mg dose were more likely to maintain their response than patients receiving the 150 mg dose.

Based on the combined data from studies A2302 and A2303, the cumulative probability (Kaplan-Meier estimates) of loss of PASI 75 response is lowest with 300 mg (12.9%) at 40 weeks of maintenance (Week 52). The 150 mg dose has a loss rate almost twice as high (24.7%) and etanercept almost three times as high (33.8%). A lower loss of response at Week 52 in Week 12 IGA mod 2011 0/1 responders was also shown for the secukinumab 300 mg dose (25.8%), with 150 mg having a loss rate approximately one and a half times higher (39.2%). Again, these rates are based on a conservative non-responder imputation analysis

and not based on observed data (last observation carried forward-LOCF) which is commonly reported in publications.

Loss of response is a major reason for patient dissatisfaction with current therapies. The demonstrated high retention of response with IGA mod 2011 0/1 representing clear to almost clear skin over 52 weeks with secukinumab 300 mg is important to patients with moderate to severe psoriasis as they require long-term symptom control.

### 5.4.6 Body weight analysis

The 300 mg dose provides the greatest benefit regardless of baseline weight.

Higher response rates across the two weight strata, outlined in the protocol (< 90 kg or ≥ 90 kg), were observed with 300 mg (Table 5-7) at the primary endpoint timepoint.

**Table 5-7 Week 12 Response Rates by Weight Strata, A2302 and A2303, non-responder imputation**

| Weight Category | <90 kg | | ≥90 kg | |
|---|---|---|---|---|
| **Criterion** | **AIN 457 300 mg n/m (%)** | **AIN457 150 mg n/m (%)** | **AIN457 300 mg n/m (%)** | **AIN457 150 mg n/m (%)** |
| PASI 75 | 297/ 359 (82.7) | 261/ 355 (73.5) | 152/ 209 (72.7) | 132/ 215 (61.4) |
| PASI 90 | 226/ 359 (63.0) | 164/ 355 (46.2) | 94/ 209 (45.0) | 68/ 215 (31.6) |
| PASI 100 | 112/ 359 (31.2) | 58/ 355 (16.3) | 36/ 209 (17.2) | 20/ 215 (9.3) |
| IGA 0/1 | 243/ 359 (67.7) | 194/ 356 (54.5) | 119/ 209 (56.9) | 98/ 215 (45.6) |

n = number of subjects with response, m = number of subjects evaluable

Likewise, in additional exposure response analyses, requested by FDA, 300 mg was associated with clinically relevant improvements compared with 150 mg across all endpoints (IGA mod 2011 0/1, PASI 75 / 90 / 100).

Specifically, FDA requested weight subgroup analyses for < 70 kg, 70-90 kg, and ≥ 90 kg for the following efficacy endpoints: PASI 75, PASI 90, PASI 100, and IGA 0/1 response rate at Week 12 (timing of primary endpoint) (Table 5-8) and Week 16 (approximate time of peak response based on the observed data). These analyses focused on the two larger placebo controlled studies (A2302 and A2303) since, for these studies, data beyond Week 12 were available.

In almost all of the parameters, improved responses with 300 mg were in the double digits higher (8-18%) than with 150 mg. The magnitude of the differences between the two secukinumab doses was generally larger in the comparison of response rates based on the higher thresholds of PASI 90, PASI 100, or IGA 0/1.

Tertile analyses and quartile analyses for body weight and predicted exposures were also performed (data not shown). All of the analyses showed that the 300 mg regimen was consistently more beneficial across all weight subgroups evaluated.

**Table 5-8 Week 12 Response Rates by Weight Subgroups, A2302 and A2303, non-responder imputation**

| Weight Category | <70 kg | | | 70 kg to <90 kg | | | ≥90 kg | | |
|---|---|---|---|---|---|---|---|---|---|
| Response criterion | AIN457 300 mg n=145 (%) | AIN457 150 mg n=140 (%) | Diff*. (%) | AIN457 300 mg n=214 (%) | AIN457 150 mg n=215 (%) | Diff*. (%) | AIN457 300 mg n=209 (%) | AIN457 150 mg n=215 (%) | Diff* (%) |
| PASI 75 | 82.1 | 72.1 | 10.0 | 83.2 | 74.4 | 8.8 | 72.7 | 61.4 | 11.3 |
| PASI 90 | 67.6 | 52.9 | 14.7 | 59.8 | 41.9 | 17.9 | 45.0 | 31.6 | 13.4 |
| PASI 100 | 34.5 | 20.0 | 14.5 | 29.0 | 14.0 | 15.0 | 17.2 | 9.3 | 7.9 |
| IGA 0/1 | 69.7 | 57.1 | 12.6 | 66.4 | 52.8 | 13.6 | 56.9 | 45.6 | 11.2 |

*Arithmetic Difference between 300 mg response and 150 mg response

### 5.4.7 Patient reported outcomes

In addition to physical improvements to the skin, improvement in patients' quality of life is an important potential benefit of psoriasis treatment. It is reported by 88% of patients that psoriasis affects their emotional well-being and 82% state that it interferes with their enjoyment of life (Armstrong et al 2012). Therefore, in addition to physical measures of symptom relief, improvements in patient reported outcome measures, including health related quality of life, were measured in the clinical development program. As discussed earlier, PASI 90 response correlates better than PASI 75 with improved health-related quality of life (HRQoL) (Basra et al 2007, Revicki et al 2008, Torii et al 2012, Revicki et al 2013). Results of the quality of life and patient reported outcome data confirmed the clinical meaningfulness of the increased efficacy of 300 mg secukinumab on PASI 75, PASI 90, and PASI 100 results. Several different instruments (including DLQI, EQ-5D, Psoriasis Symptom Diary©, etc.) were used to measure impact on patients in the secukinumab program. In this briefing book we will focus on DLQI as summarized in the following section.

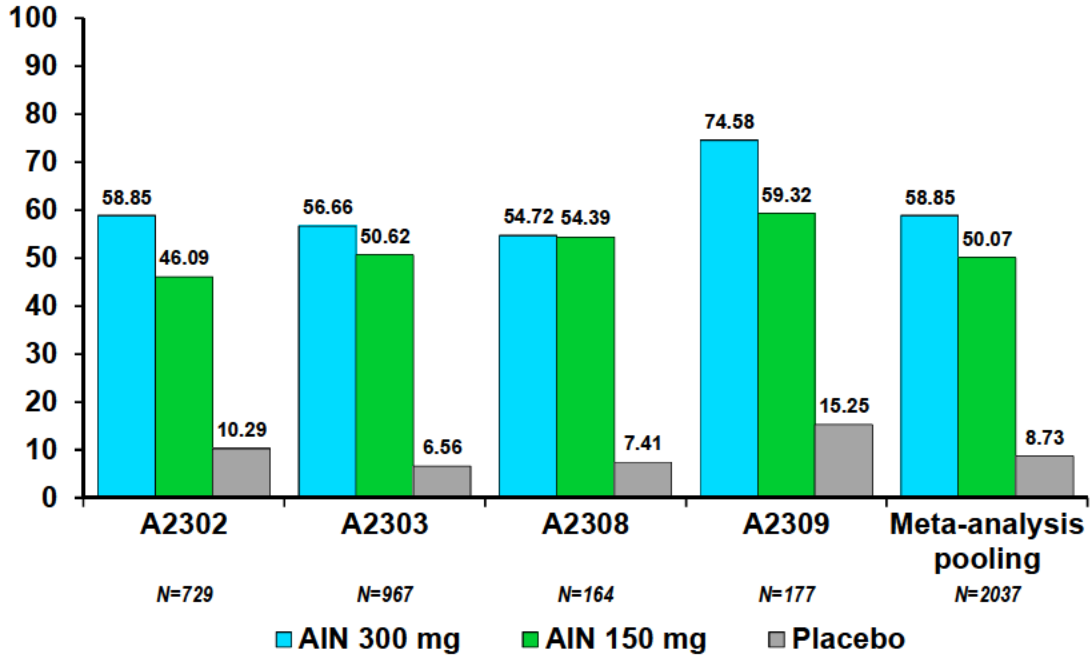
#### Dermatology Life Quality Index (DLQI) Results

The DLQI measures functional disability of adult patients with dermatological disorders (Finlay and Khan 1994). Widely used (tested across > 30 different skin conditions and available in > 80 languages, Basra et al 2008, Anon 2013), it is a self-administered assessment of 6 domains: daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. These domains are measured over the previous one week. DLQI total scores range from 0 to 30 (sum of 10 questions, each ranging from 0 (not at all) to 3 (very much) with higher scores indicating greater impairment in health-related quality of life.

The rate of DLQI 0 or 1 response (indicating no or little impairment in health-related quality of life) based on total score at Week 12 was greater with secukinumab treatment compared to placebo ($p<0.0001$ for all comparisons), with higher response rates for the 300 mg dose than

for the 150 mg dose. This effect was generally observed in each of the placebo-controlled trials and confirmed in the pooled analysis of these 4 studies (58.9% for 300 mg dose, 50.1% for 150 mg dose, 8.7% for placebo, Figure 5-14).

**Figure 5-14 DLQI 0/1 at Week 12 by Study and Pooled**




More importantly, secukinumab 300 mg resulted in a substantially higher proportion of patients with DLQI 0/1 response (i.e. "no effect at all on patient's life") at Week 52 (68.5% for 300 mg vs. 53.8% for 150 mg), representing a difference of approximately 15% between the 300 mg and 150 mg groups (Table 5-9). This magnitude of difference in the DLQI response is similar to the difference in PASI 90 responses between doses. The proportion of patients with DLQI 0/1 response at Week 52 was 46.9% with etanercept in study A2303 representing a difference of approximately 22% versus the secukinumab 300 mg dose.

**Table 5-9 PASI 90, IGA mod 2011 0/1 and DLQI response rates at Week 52 (non-responder imputation) – 52-week efficacy (pooled FAS of Studies A2302, A2303 and A2304)**

| | PASI 90 | | IGA mod 2011 0/1 | | DLQI 0/1 | |
|---|---|---|---|---|---|---|
| | % achieving response | Difference vs. 300 mg | % achieving response | Difference vs. 300 mg | % achieving response | Difference vs. 300 mg |
| **AIN457 300 mg** | 62.0 | - | 63.1 | - | 68.5% | - |
| **AIN457 150 mg** | 42.4 | 19.6% | 47.2 | 15.9% | 53.8% | 14.7% |
| **Etanercept** | 33.4 | 28.6% | 37.2 | 25.9% | 46.9% | 21.6% |

### 5.4.8 Individualized maintenance regimen trials

#### 5.4.8.1 Fixed Interval (FI) vs. 'Start on Relapse' (SoR)

A trial (A2304) comparing two different maintenance dosing regimens of secukinumab (a continuous dosing vs an 'intermittent' dosing), further demonstrated the clinical benefits, when maintenance treatment is given monthly. After initial doses at Baseline and Weeks 1, 2 and 3, 4 and 8, study A2304 compared the maintenance of response with two secukinumab dosing regimens starting at week 12: fixed interval (FI) or "Treatment as needed" upon start of relapse (SoR). A2304 was a non-inferiority study with a non-inferiority margin of 15%.

Patients were randomized to either the secukinumab 150 mg or 300 mg arm. At Week 12, PASI 75 responders were re-randomized to FI dosing on the same dose once every four weeks (q4w) to Week 48, whereas patients on SoR received placebo until they lost response. Loss of response was defined as loss of PASI 75 response and loss of $\geq$ 20 % of the maximum PASI gain during the study. When response was lost, patients received the same dose regimen as during the first 12 weeks of treatment, q4w, until they regained PASI 75 (and then restarted placebo) or to Week 48. Details of the study are provided in Table 5-3.

The primary endpoint of this study, maintenance of response, was not met. Treatment in the "Treatment as needed" arm failed to meet the pre-specified non-inferiority margin (-15%). This result indicates that continued treatment with secukinumab on a fixed interval (every 4 weeks) provides better disease control over time than intermittent treatment at time of relapse.

Consistently across efficacy measures, patients at the 300 mg secukinumab dose level showed higher response rates and increased maintenance of response over the 150 mg secukinumab dose level, and patients in the FI groups showed increased maintenance of response over SoR groups.

The difference in the proportion of patients maintaining response (per protocol defined primary endpoint) for 300 mg SoR vs. FI was -10.34% (lower bound of the CI of -19.37%) and for 150 mg SoR vs FI, the difference was -9.61% (lower bound of the CI of -20.10%). The proportion of patients in the 300 mg SoR group who were able to maintain response was lower compared to the 300 mg FI group (67.7% vs. 78.2%, respectively). A similar observation was made between the 150 mg SoR group and the 150 mg FI group (52.4% vs. 62.1%, respectively).

However, after assessing some of the more standard secondary endpoints at Week 52, the proportion of patients with PASI 75 response was substantially higher in the 300 mg FI and 150 mg FI groups (78.2% vs. 62.1%, respectively) compared to the 300 mg SoR and 150 mg SoR groups (41.0% vs. 35.0%, respectively). Further, at Week 52, the proportion of patients with PASI 90 response was numerically higher in the 300 mg FI and 150 mg FI groups (59.7% vs. 45.8%, respectively) compared to the 300 mg SoR and 150 mg SoR groups (13.8% vs. 11.2%, respectively). Lastly, at Week 52, the proportion of patients with PASI 100 response was numerically higher in the 300 mg FI and 150 mg FI groups (36.6% vs. 21.2%, respectively) compared to the 300 mg SoR and 150 mg SoR groups (5.1% vs. 2.4%, respectively).

These results clearly demonstrated that dosing every four weeks was a better treatment strategy for maintaining response compared with intermittent dosing, waiting for 'start' of relapse.

#### 5.4.8.2 Higher dosing for partial responders

Patients who achieved only a partial response in Study A2304 (i.e., patients achieving at least a PASI 50 but not PASI 75 response after 12 weeks of treatment at either 150 mg or 300 mg every 4 weeks) were offered treatment continuation in study A2307. In A2307, patients received secukinumab 10 mg/kg i.v. (at randomization, Weeks 2 and 4) or secukinumab 300 mg s.c. (at randomization and Week 4), followed by 300 mg s.c. every 4 weeks for all patients from Week 8 onwards. Due to a higher than anticipated response rate in Study A2304, only 43 patients were enrolled in this trial such that statistical comparisons of dosing regimens in this trial were not adequately powered. Numerically, a higher proportion of patients in the 10 mg/kg i.v. group had achieved PASI 75 at Week 8 compared with the 300 mg s.c. group (90.5% vs. 66.7% p=0.0649). By Week 40, there were numerically more PASI 75 responders in the group that had started with the high i.v. dosing arm (61.9 % vs. 47.6%). In both dose groups, a proportion of partial responders became full PASI 90 responders. This data also needs to be treated with caution in that the peak response is normally seen after 16 weeks of treatment with secukinumab. These data suggest that higher secukinumab exposures or a longer exposure to 300 mg can improve response rates in initial partial responders.

### 5.4.9 Patient subgroups

Numerically superior efficacy of secukinumab versus placebo and versus etanercept was consistently observed in all assessed subgroups. Similarly, secukinumab 300 mg resulted in consistently higher response rates versus 150 mg. Subgroup analyses were performed for PASI 75, PASI 90, and IGA mod 2011 0/1 response at Week 12. Subgroups analyzed included those with specific demographic traits, disease characteristics, such as concomitant psoriatic arthritis (PsA) or other background features at baseline, such as prior treatment status and prior response to those treatments.

#### 5.4.9.1 Age, Gender, Race, Region Subgroups

Subgroup analyses for age (<65 and ≥65 years), gender, race and region (US and Europe) are shown in Table 5-10. In all of the subgroups, the 300 mg dose resulted in a higher proportion of patients achieving efficacy for each of the parameters. There were 13 or fewer black patients per group, with more than 60% responding (PASI 75 and IGA mod 2011 0/1) with either secukinumab regimen compared with only 1/13 achieving PASI 75 and none achieving IGA mod 2011 0/1 or PASI 90 responses in the placebo group. Despite these small numbers in this particular subgroup, based on the data available it can be concluded that secukinumab is effective in treating psoriasis across race groups.

**Table 5-10 IGA mod 2011 0/1, PASI 75, and PASI 90 response at Week 12 by age, gender, race and region (non-responder imputation) – (A2302, A2303, A2308 and A2309 pooled)**

| Demographic variable | Criterion | AIN457 300 mg N=691 | | AIN457 150 mg N=692 | | Placebo N=692 | | Etanercept N=326 | |
|---|---|---|---|---|---|---|---|---|---|
| | | n/m | (%) | n/m | (%) | n/m | (%) | n/m | (%) |
| **Age** | | | | | | | | | |
| Age <65 | IGA 0/1 | 418/639 | (65.4) | 323/632 | (51.1) | 15/647 | (2.3) | 83/305 | (27.2) |
| | PASI 75 | 513/639 | (80.3) | 434/631 | (68.8) | 28/647 | (4.3) | 133/305 | (43.6) |
| | PASI 90 | 364/639 | (57.0) | 260/631 | (41.2) | 8/647 | (1.2) | 62/305 | (20.3) |
| Age ≥65 | IGA 0/1 | 28/ 47 | (59.6) | 32/ 58 | (55.2) | 0/ 43 | (0.0) | 5/18 | (27.8) |
| | PASI 75 | 32/ 47 | (68.1) | 43/ 58 | (74.1) | 1/43 | (2.3) | 9/18 | (50.0) |
| | PASI 90 | 24/ 47 | (51.1) | 23/ 58 | (39.7) | 0/ 43 | (0.0) | 5/18 | (27.8) |
| **Gender** | | | | | | | | | |
| Male | IGA 0/1 | 308/474 | (65.0) | 231/484 | (47.7) | 8/483 | (1.7) | 63/229 | (27.5) |
| | PASI 75 | 377/474 | (79.5) | 329/483 | (68.1) | 18/483 | (3.7) | 102/229 | (44.5) |
| | PASI 90 | 260/474 | (54.9) | 182/483 | (37.7) | 4/483 | (0.8) | 47/229) | (20.5) |
| Female | IGA 0/1 | 138/212 | (65.1) | 124/206 | (60.2) | 7/207 | (3.4) | 25/ 94 | (26.6) |
| | PASI 75 | 168/212 | (79.2) | 148/206 | (71.8) | 11/207 | (5.3) | 40/ 94 | (42.6) |
| | PASI 90 | 128/212 | (60.4) | 101/206 | (49.0) | 4/207 | (1.9) | 20/ 94 | (21.3) |
| **Race** | | | | | | | | | |
| Caucasian | IGA 0/1 | 329/500 | (65.8) | 260/497 | (52.3) | 8/508 | (1.6) | 60/218 | (27.5) |
| | PASI 75 | 399/500 | (79.8) | 346/496 | (69.8) | 16/508 | (3.1) | 98/218 | (45.0) |
| | PASI 90 | 275/500 | (55.0) | 203/496 | (40.9) | 4/508 | (0.8) | 45/218 | (20.6) |
| Asian | IGA 0/1 | 70/129 | (54.3) | 59/129 | (45.7) | 3/120 | (2.5) | 13/ 73 | (17.8) |
| | PASI 75 | 97/129 | (75.2) | 87/129 | (67.4) | 8/120 | (6.7) | 20/ 73 | (27.4) |
| | PASI 90 | 70/129 | (54.3) | 51/129 | (39.5) | 1/120 | (0.8) | 10/73 | (13.7) |
| Black | IGA 0/1 | 6/9 | (66.7) | 8/13 | (61.5) | 0/13 | (0.0) | - | - |
| | PASI 75 | 6/9 | (66.7) | 8/13 | (61.5) | 1/13 | (7.7) | - | - |
| | PASI 90 | 5/9 | (55.6) | 3/13 | (23.1) | 0/13 | (0.0) | - | - |
| **Region** | | | | | | | | | |
| US | IGA 0/1 | 94/145 | (64.8) | 69/140 | (49.3) | 1/154 | (0.6) | 4/15 | (26.7) |
| | PASI 75 | 109/145 | (75.2) | 90/139 | (64.7) | 4/154 | (2.6) | 6/15 | (40.0) |
| | PASI 90 | 81/145 | ( 55.9) | 44/139 | (31.7) | 0/154 | (0.0) | 3/ 15 | (20.0) |
| Europe | IGA 0/1 | 195/297 | (65.7) | 179/304 | (58.9) | 6/298 | (2.0) | 51/180 | (28.3) |
| | PASI 75 | 241/297 | (81.1) | 224/304 | (73.7) | 10/298 | (3.4) | 82/180 | (45.6) |
| | PASI 90 | 157/297 | ( 52.9) | 141/304 | (46.4) | 3/298 | (1.0) | 40/180 | (22.2) |
| Rest of World | IGA 0/1 | 157/244 | (64.3) | 107/246 | (43.5) | 8/238 | (3.4) | 33/128 | (25.8) |
| | PASI 75 | 187/244 | (76.6) | 156/246 | (62.6) | 14/238 | (5.9) | 54/128 | (42.2) |
| | PASI 90 | 150/244 | (61.5) | 98/246 | (39.8) | 5/238 | (2.1) | 24/128 | (18.8) |

N = number of patients included in efficacy analysis (Full Analysis Set), n = number of subjects with response, m = number of subjects evaluable

### 5.4.10 Response by Previous Therapy

Consistent with the overall results, the 300 mg dose was consistently better compared with 150 mg, placebo and etanercept in all subgroups of patients regardless of prior treatment status.

Secukinumab provided a substantial treatment effect compared to placebo regardless of previous systemic therapy status ($p<0.0001$ for all comparisons).

The majority of patients had received prior systemic therapies and a subset of these had received treatment with a biologic, including TNFα antagonists. In patients previously exposed to systemic therapy, response rates for IGA mod 2011 0/1, PASI 75 and PASI 90 were higher in the 300 mg group than the 150 mg group, including patients that had previously been exposed to and failed systemic therapy ($p<0.05$), see Table 5-11.

**Table 5-11 IGA mod 2011 0/1, PASI 75, and PASI 90 response at Week 12 by previous systemic therapy (A2302, A2303, A2308 and A2309, non-responder imputation)**

| **Not previously exposed to systemic therapy** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Response criterion** | **AIN457 300 mg N=252** | | **AIN457 150 mg N=245** | | **Placebo N=272** | | **Etanercept N=112** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 173/252 | (69.5) | 139/245 | (57.0) | 7/272 | (2.6) | 30/112 | (26.8) |
| PASI 75 | 205/252 | (82.3) | 173/245 | (70.9) | 12/272 | (4.4) | 50/112 | (44.6) |
| PASI 90 | 145/252 | (58.2) | 100/245 | (41.0) | 4/272 | (1.5) | 23/112 | (20.5) |
| **Previously exposed to systemic therapy** | | | | | | | | |
| **Response criterion** | **AIN457 300 mg N=438** | | **AIN457 150 mg N=447** | | **Placebo N=420** | | **Etanercept N=214** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 272/436 | (62.4) | 216/446 | (48.4) | 8/419 | (1.9) | 58/211 | (27.5) |
| PASI 75 | 339/436 | (77.8) | 304/445 | (68.3) | 17/419 | (4.1) | 92/211 | (43.6) |
| PASI 90 | 242/436 | (55.5) | 183/445 | (41.1) | 4/419 | (1.0) | 44/211 | (20.9) |
| **Previously exposed to and failed systemic therapy** | | | | | | | | |
| **Response criterion** | **AIN457 300 mg N=325** | | **AIN457 150 mg N=343** | | **Placebo N=317** | | **Etanercept N=166** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 193/324 | (59.6) | 157/342 | (45.9) | 8/316 | (2.5) | 42/163 | (25.8) |
| PASI 75 | 248/324 | (76.5) | 219/342 | (64.0) | 17/316 | (5.4) | 67/163 | (41.1) |
| PASI 90 | 172/324 | (53.1) | 130/342 | (38.0) | 4/316 | (1.3) | 33/163 | (20.2) |

n = number of subjects with response, m = number of subjects evaluable

The general trends for PASI 75, PASI 90 and IGA mod 2011 0/1 responses at Week 12 observed in the subgroups of previous exposure with biologic therapies (including TNFα antagonist) as well as prior biologic failures were consistent with those in the overall population (Table 5-12). Secukinumab was more efficacious compared to placebo regardless of previous biologic therapy status ($p<0.002$ for all comparisons). In patients previously exposed to systemic biological therapy and those not previously exposed, response rates for

IGA mod 2011 0/1 and PASI 75 were higher in the 300 mg group than the 150 mg group ($p<0.02$ for all comparisons).

**Table 5-12 IGA mod 2011 0/1, PASI 75, and PASI 90 response at Week 12 by previous biologic therapy (A2302, A2303, A2308 and A2309, non-responder imputation)**

| **Previously exposed to biologic therapy** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Response criterion** | **AIN457 300 mg N=146** | | **AIN457 150 mg N=161** | | **Placebo N=147** | | **Etanercept N=45** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 84/146 | (57.5) | 63/160 | (39.4) | 1/147 | (0.7) | 12/45 | (26.7) |
| PASI 75 | 108/146 | (74.0) | 96/160 | (60.0) | 4/147 | (2.7) | 24/45 | (53.3) |
| PASI 90 | 74/146 | (50.7) | 47/160 | (29.4) | 1/147 | (0.7) | 8/45 | (17.8) |
| **Previously exposed to and failed biologic therapy** | | | | | | | | |
| **Response criterion** | **AIN457 300 mg N=50** | | **AIN457 150 mg N=69** | | **Placebo N=56** | | **Etanercept N=16** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 26/50 | (52.0) | 24/69 | (34.8) | 1/56 | (1.8) | 4/16 | (25.0) |
| PASI 75 | 33/50 | (66.0) | 33/69 | (47.8) | 4/56 | (7.1) | 6/16 | (37.5) |
| PASI 90 | 21/50 | (42.0) | 19/69 | (27.5) | 1/56 | (1.8) | 2/16 | (12.5) |
| **Previously exposed to TNFα antagonists** | | | | | | | | |
| **Response criterion** | **AIN457 300 mg N=81** | | **AIN457 150 mg N=93** | | **Placebo N=89** | | **Etanercept N=21** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 47/81 | (58.0) | 34/92 | (37.0) | 1/89 | (1.1) | 9/21 | (42.9) |
| PASI 75 | 57/81 | (70.4) | 54/92 | (58.7) | 4/89 | (4.5) | 11/21 | (52.4) |
| PASI 90 | 39/81 | (48.1) | 24/92 | (26.1) | 1/89 | (1.1) | 4/21 | (19.0) |
| **Previously exposed to and failed TNFα antagonists** | | | | | | | | |
| **Response criterion** | **AIN457 300 mg N=37** | | **AIN457 150 mg N=49** | | **Placebo N=41** | | **Etanercept N=10** | |
| | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** | **n/m** | **(%)** |
| IGA 0/1 | 20/37 | (54.1) | 19/49 | (38.8) | 1/41 | (2.4) | 3/10 | (30.0) |
| PASI 75 | 25/37 | (67.6) | 25/49 | (51.0) | 4/41 | (9.8) | 3/10 | (30.0) |
| PASI 90 | 16/37 | (43.2) | 16/49 | (32.7) | 1/41 | (2.4) | 1/10 | (10.0) |

n = number of subjects with response, m = number of subjects evaluable

### 5.4.11 Tolerance or withdrawal effects

Across the Phase III studies, secukinumab showed sustained response rates up to 52 weeks of treatment as assessed using PASI and IGA mod 2011 response rates (Section 5.4.5). The immunogenicity data did not suggest that patients developed tolerance with loss of therapeutic effect or altered PK profiles (Section 5.5.12). This was also true in the study exploring the "Treatment as needed" maintenance regimen (A2304). Patients in this study stopped treatment for a median time of 24 weeks on 300 mg (SoR) and re-started based on recurrence of symptoms. A higher rate of immunogenicity was not observed in these patients.

Rebound was defined, per protocol, as an increase in PASI score to > 125% of baseline, or the occurrence of new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory

psoriasis within 8 weeks after the last dose of study treatment. Assessments of rebound were based on discontinued patients with post-treatment assessment for rebound 8 weeks after the last injection in A2302, A2303, A2304, A2308 and A2309 (n=100 on 300 mg, n=123 on 150 mg, n=41 on etanercept and n=27 on placebo).

Rebound events among the subset of patients who prematurely discontinued in the Phase III studies were reported most frequently with etanercept (17.1%), followed by secukinumab 150 mg (12.2%), 300 mg (7.0%) and placebo (3.7%). Few patients had increased PASI scores > 125% from baseline (2.0%, 0.8% and 2.4% for 300 mg, 150 mg and etanercept, respectively).

### 5.4.12 Efficacy conclusions

Secukinumab, when administered weekly for 4 weeks as a loading regimen followed by monthly injections at week 4, has been shown to be a highly efficacious treatment for moderate to severe plaque psoriasis. The 300 mg dose delivered the most clinically meaningful benefit to patients: the fastest onset, highest response rate (both early at Week 12 and later at Week 52), and was the most likely to achieve clear to almost clear skin. In addition, the higher 300 mg dose demonstrated the highest maintenance of response over time and was the most likely to achieve minimal impairment to a patient's quality of life. The results were consistent across four randomized, double-blind placebo-controlled Phase III trials.

All pre-specified endpoints of the key Phase III studies, adjusted for multiple testing, demonstrated superiority of both secukinumab doses over placebo and etanercept, for both co-primary endpoints, PASI 75 and IGA mod 2011 0/1, at Week 12 (all comparisons, $p<0.0001$).

Secukinumab 300 mg had a rapid onset of efficacy with an approximate 40% reduction of baseline symptoms (as measured using the PASI score) at Week 2 and 50% reduction by Week 3. It took 4 weeks for secukinumab 150mg and 8 weeks for etanercept to reach a 50% reduction of symptoms. Therefore, secukinumab, especially 300 mg, was associated with an early onset in the improvement of signs and symptoms of psoriasis, and these results were sustained over 52 weeks. For each of the thresholds of response (PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1), the increases in response rates shown for both secukinumab doses over the first 12 weeks of treatment continued to increase to approximately 16 weeks by almost 10% and then plateaued. The 300 mg dose demonstrated better maintenance of response for the co-primary endpoints as well as the more stringent endpoints of skin clearance i.e. PASI 90 and IGA 0/1.

Efficacy has also been demonstrated in all analyzed subgroups, including anti-TNFα inadequate responders (TNFα-IR).

The greater benefit of 300 mg compared to 150 mg was evident for all endpoints across all core studies, in all subgroups of patients, and for all time points between Week 12 and week 52. In particular:

- Achievement of clear to almost clear skin as reflected by PASI 90 and IGA mod 2011 0/1 response was achieved by 10-20% more patients with secukinumab 300 mg compared with the 150 mg group across the four core studies. These response rates for 300 mg were approximately 16-20% better than 150 mg and 26-32% better than etanercept for the

higher efficacy measures (e.g. PASI 90, IGA mod 2011 0/1 & PASI 100 responses) after 52 weeks of treatment

- This translated to a higher likelihood to achieve the benefit of "no effect at all on patient's life" from a quality of life perspective, at 12 weeks, 9% more patients achieved this DLQI 0/1 response. At 52 weeks, 15% more patients on 300 mg achieved this high threshold response.
- The superior efficacy of secukinumab versus placebo in PASI 75, IGA mod 2011 0/1, and PASI 90 responses at Week 12 was consistent in all subgroups of body weight, age, race, disease severity, and previous exposure or failure of systemic psoriasis therapy (including anti-TNFα-IR and other biologic IR patients). The 300 mg dose demonstrated higher response rates across weight groups (including lower body weight) and all other subgroups examined when compared to the 150 mg dose, placebo and etanercept. No subgroup was identified where the 150 mg would be the recommended dose.
- Early onset of efficacy was observed in the 300 mg secukinumab dose group, with 50% improvement in mean PASI scores achieved after 3 weeks vs. 4 weeks for 150 mg and 8 weeks for etanercept.
- Efficacy results were consistent with both formulations tested (lyophilisate vs. liquid), all delivery forms (lyophilisate in a vial, pre-filled syringe, or autoinjector/pen), and both types of administration (injection performed by site staff vs. self-injection). See Appendix 1 for further data to support self-administration.
- Rebound events among the subset of patients who prematurely discontinued in the Phase III studies were generally low and reported most frequently with etanercept (17.1%), followed by secukinumab 150 mg (12.2%), 300 mg (7.0%) and placebo (3.7%). Few patients had increased PASI scores > 125% from baseline (2.0%, 0.8% and 2.4% for 300 mg, 150 mg and etanercept, respectively).

## 5.5 Safety

### 5.5.1 Safety populations and extent of exposure

Five thousand forty-four patients have been studied in 34 clinical trials across multiple indications. In the psoriasis program, 3,430 patients have been treated with secukinumab in 10 Phase II or Phase III studies. Patient exposure to secukinumab at any dose in moderate to severe psoriasis includes >2,700 patient-years of exposure with over 1,600 psoriasis patients treated with any dose of secukinumab for at least 52 weeks.

Three separate data pools were created for the safety assessment (Table 5-13):

Pool A (N=1,382 secukinumab treated patients) consisted of the four core placebo-controlled Phase III trials. These trials allow direct randomized comparisons of secukinumab 300 mg s.c. and 150 mg s.c., placebo and active comparator etanercept (in 1 study) for the first 12 weeks of treatment.

Pool B (N=3,430 secukinumab treated patients) included patients from 10 Phase II or III randomized, double-blind psoriasis trials. These data provide for longer duration of exposure and include a broad range of doses, given either as s.c. or i.v. injections up to 52 weeks. This larger pool, includes higher doses and exposures (2,725 patient-years), and increases the

chances of observing new or less common events than seen in the 4 core studies. Treatment durations for different treatment and dose groups in this pool varied considerably, therefore the rate of AEs are reported adjusting for the time of observation (i.e., per 100 patient-years of follow-up).

Pool C (N=4,498 secukinumab treated patients) included all patients treated with secukinumab across all 34 clinical studies, regardless of indication, for which data were available at time of filing. Pool C includes studies in diseases other than psoriasis and therefore represents a very heterogeneous population. Consequently as the largest dataset and broadest range of exposures of patients, this dataset was only used to evaluate signals for rare events, such as MACE and malignancies.

This pooling methodology was discussed and agreed with FDA, European and Canadian Health Authorities.

**Table 5-13 Pooled studies included in the safety analyses**

| Pool | Trials included in data pool | Analysis periods and treatment groups |
|---|---|---|
| **Pool A** | **Core, placebo-controlled psoriasis trials; N=2399 (12 weeks)** | |
| (Ph III, vs. PBO) Psoriasis | 4 pivotal, placebo-controlled, randomized, double-blind, Phase III trials: A2302, A2303, A2308, A2309 | AIN457 150 mg (N=692)<br>AIN457 300 mg (N=690)<br>Placebo (N=694)<br>Etanercept (N=323) |
| **Pool B** | **All psoriasis trials (randomized, double-blind); N=3993 (12 weeks and 52 weeks)** | |
| (Ph II & III) Psoriasis | 10 randomized, blinded, Phase II and III trials: A2211, A2211E1, A2212, A2220, A2302, A2303, A2304, A2307, A2308, A2309 | 12 weeks:<br>AIN457 150 mg (N=1174)<br>AIN457 300 mg (N=1173)<br>Any AIN457 dose (N=2877) §<br>Placebo (N=793)<br>Etanercept (N=323)<br>52 weeks:<br>Any AIN457 150 mg (N=1395)<br>Any AIN457 300 mg (N=1410)<br>Any AIN457 dose (N=3430) §<br>Placebo (N=793)<br>Etanercept (N=323) |
| **Pool C** | **All secukinumab trials; N=5044 (52 weeks)** | |
| (Ph I, II & III) All indications | 34 secukinumab trials in various diseases (excluding healthy volunteers): A2101, A2102, A2103, A2202, A2202E1, A2204, A2206, A2206E1, A2208*, A2209, A2209E1, A2211, A2211E1, A2212, A2220, A2223, A2225#, A2302, A2303, A2304, A2307, A2308, A2309, B2201, C2301, C2301E1, C2302, C2302E1, C2303, C2303E1, CPJMR009 2202, F2201, F2206, F2208 | Any secukinumab dose (N=4498)<br>Placebo (N=1158) |

* = all cohorts, except cohort 4 were included
# = excluding the data from healthy volunteers
§ includes other doses in addition to 150 mg and 300 mg secukinumab
N=number of patients in the data pool or treatment group based on the Safety set

Patient exposure in each of the three safety pools for secukinumab is summarized in Table 5-14. Pool A provides safety data in 1,382 patients treated with at least one dose of secukinumab in the core, placebo-controlled Phase III trials in psoriasis. Pool B constitutes

the largest pool of patient-level safety data in psoriasis, with 3,430 secukinumab treated patients comprising 76% of the total extent of exposure to secukinumab.

**Table 5-14 Exposure to secukinumab across Pools A, B and C**

| Exposure (Weeks) | Pool A | | | | Pool B | | | | | Pool C |
|---|---|---|---|---|---|---|---|---|---|---|
| | 300 mg N=690 | 150 mg N=692 | Placebo N=694 | ETN N=323 | 300 mg N=1410 | 150 mg N=1395 | Any dose N=3430 | Placebo N=793 | ETN N=323 | Any dose N=4498 |
| ≥ 4 | 686 | 684 | 683 | 320 | 1403 | 1384 | 3407 | 779 | 320 | 4453 |
| ≥ 12 | 538 | 528 | 502 | 253 | 1348 | 1333 | 3261 | 577 | 306 | 4207 |
| ≥ 28 | - | - | - | - | 1186 | 1155 | 2721 | 33 | 290 | 3091 |
| ≥ 52 | - | - | - | - | 732 | 698 | 1641 | 26 | 241 | 1900 |
| Patient-years | 157.5 | 157.2 | 155.4 | 73.0 | 1177.5 | 1142.0 | 2724.6 | 201.3 | 293.5 | 3588.1 |

ETN=Etanercept
Exposure is cumulative starting from first dose.
Any dose for Pool B includes all secukinumab treated patients up to 3x10mg/kg i.v.
Patient-years exposure was calculated as a sum of individual patient durations in days divided by 365.25.

For Pool A, patient exposure was balanced across treatment groups during the initial 12 week dosing period. There were over twice as many patients in the secukinumab (N=690, 692) and placebo treatment groups (N=694) compared to etanercept (N=323) since only one of four core studies included an etanercept arm. All groups had a median duration of exposure of 84 days with ≥ 96% of patients exposed for at least 8 weeks.

For Pool B, the median duration of treatment exposure was similar for the 300 mg, 150 mg and etanercept groups (364 days, 364 days and 365 days, respectively). Based on the study design which allowed non-responding placebo patients to be randomized to secukinumab (150 mg or 300 mg), there are only a small number of placebo patients continuing beyond 12 weeks (4.8%). With most placebo patients moving into a secukinumab dose group, the number of secukinumab exposed patients is considerably larger than either etanercept or placebo (1,410 and 1,395 for secukinumab 300 mg and 150 mg vs. 793 for placebo, 323 for etanercept).

Pool C which included safety data from 34 studies across multiple indications had a median exposure of 357 days for secukinumab and 84 days for placebo.

Rates of AEs (including clinically important laboratory abnormalities) are summarized for the target population using Pools A (absolute incidence) and B (exposure adjusted incidence). Exposure adjusted rates of AEs are provided for Pool B to correct for differences in numbers and duration of patient exposure. Additional analyses were performed for AEs of special interest:

- Potential risks of immune-modulating biologics approved or assessed in psoriasis: infections including opportunistic infections, neutropenia, cardiovascular events including major adverse cardiovascular event (MACE) and cardiovascular and cerebrovascular (CCV) event and malignancies
- Potential risks of foreign proteins: hypersensitivity, administration or immune reactions, and autoimmune disorders
- Potential risk of compounds targeting the IL-17 pathway: Crohn's disease
- Routine risks: hepatotoxicity, QTc prolongation

An analysis was performed for the data pool of the core placebo-controlled psoriasis studies (Pool A) for the following clinical events: all infections, serious infections, serious opportunistic infections, malignances, hypersensitivity, and MACE. Pool A was also used to summarize the rates of the events which occurred during the initial 12 weeks of treatment in comparison to placebo and etanercept. Pool B was used to summarize and evaluate exposure adjusted incidences. Pool C was used to summarize exposure-adjusted incidences with 95% confidence intervals for the more rare events, such as MACE and malignances, over the entire treatment period as it contained the largest exposure to any dose (including high i.v. exposures) of secukinumab.

Data within this briefing book relate to the safety database submitted as a part of the BLA. As with any ongoing program safety information and individual new cases of potential interest are received, evaluated, and submitted to the FDA as per regulatory requirements on an ongoing basis.

### 5.5.2 Baseline demographics and comorbidities

The demographics and disease characteristics of the data from all psoriasis studies shown in Table 5-15 are very similar to those described earlier for the two large core studies (A2302 and A2303) (Table 5-4 and Table 5-5). Both datasets represent the target population.

**Table 5-15 Demographics and baseline characteristics – Pool B All psoriasis trials (Initial treatment assignment)**

| | AIN457 300 mg N=1173 | AIN457 150 mg N=1174 | Any AIN457 dose* N=2877 | Placebo N=793 | Etanercept N=323 | Total N=3993 |
|---|---|---|---|---|---|---|
| Mean Age (years) | 45.6 | 45.2 | 45.2 | 44.6 | 43.8 | 45.0 |
| Sex: Male (%) | 68.9 | 67.2 | 69.8 | 69.6 | 70.9 | 69.9 |
| Race (%) | | | | | | |
| Caucasian | 72.2 | 72.2 | 75.1 | 74.8 | 66.9 | 74.4 |
| Asian | 21.4 | 21.0 | 19.4 | 16.9 | 22.9 | 19.2 |
| Black | 1.9 | 1.5 | 1.4 | 1.9 | 0.0 | 1.4 |
| Mean Weight (kg) | 86.0 | 86.1 | 87.2 | 87.1 | 84.5 | 87.0 |
| Cardiac Disorders (%) | 3.8 | 3.8 | 4.6 | 4.8 | 2.2 | 4.5 |
| Latent TB (%) | 3.50 | 4.26 | 3.20 | 3.0 | 5.3 | 3.3 |

*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

### 5.5.3 Patient disposition

The majority (95%) of patients who entered the four core placebo-controlled psoriasis studies completed the 12 week placebo-controlled period (Table 5-16). The rate of discontinuations was higher in the placebo and etanercept groups compared to either secukinumab dose group. This difference was driven by more discontinuations due to lack of efficacy, subject/guardian decision and lost to follow-up in the placebo and etanercept groups. Discontinuations due to an AE were identical for the secukinumab groups and placebo. Other reasons for discontinuation were infrequent (≤0.5% overall) and showed no meaningful differences between the treatment groups.

**Table 5-16 Patient disposition – Initial 12 week period (Pool A: Core placebo-controlled psoriasis trials – Safety set)**

| Disposition/Reason | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) | Total N=2399 n (%) |
|---|---|---|---|---|---|
| Entered | 690 (100.0) | 692 (100.0) | 694 (100.0) | 323 (100.0) | 2399 (100.0) |
| Completed initial 12 week – placebo-controlled portion | 666 (96.5) | 661 (95.5) | 648 (93.4) | 303 (93.8) | 2278 (95.0) |
| Discontinued initial 12 week period | 24 (3.5) | 31 (4.5) | 46 (6.6) | 20 (6.2) | 121 (5.0) |
| Adverse event | 8 (1.2) | 8 (1.2) | 8 (1.2) | 6 (1.9) | 30 (1.3) |
| Lack of efficacy | 1 (0.1) | 1 (0.1) | 10 (1.4) | 2 (0.6) | 14 (0.6) |
| Lost to follow-up | 2 (0.3) | 1 (0.1) | 4 (0.6) | 3 (0.9) | 10 (0.4) |
| Physician decision | 1 (0.1) | 3 (0.4) | 2 (0.3) | 0 (0.0) | 6 (0.3) |
| Pregnancy | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Protocol deviation | 6 (0.9) | 3 (0.4) | 1 (0.1) | 3 (0.9) | 13 (0.5) |
| Technical problems | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.3) | 2 (0.1) |
| Subject/guardian decision | 5 (0.7) | 15 (2.2) | 20 (2.9) | 5 (1.5) | 45 (1.9) |
| Death | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

### 5.5.4 Overall adverse events, serious adverse events and discontinuations

An overview of the absolute and exposure adjusted incidences for any adverse event, serious adverse event and adverse event causing discontinuation for the four core placebo controlled studies during the initial 12 weeks (Pool A) and for the entire treatment period for all 10 psoriasis studies (Pool B), respectively are summarized in Table 5-17.

Overall adverse events were balanced for all treatment groups [secukinumab 300 mg (56.2%), 150 mg (59.5%), and etanercept (57.6%)] in the initial 12 week placebo-controlled period. SAE reports were slightly higher with secukinumab 300 mg (2.0%), 150 mg (2.0%), and placebo (1.7%) than etanercept (0.9%). Over the entire 52 week period, the exposure adjusted incidences of SAEs with secukinumab 300 mg or 150 mg were comparable to placebo and etanercept. Adverse events leading to discontinuations were comparable across all groups for both periods.

**Table 5-17 Overall Adverse Events, Serious Adverse Events and Discontinuations**

| **Placebo-controlled period (12 weeks) (Pool A)** | | | | |
|---|---|---|---|---|
| | **AIN457 300 mg** | **AIN457 150 mg** | **Placebo** | **Etanercept** |
| | N=690 | N=692 | N=694 | N=323 |
| | n (%) | n (%) | n (%) | n (%) |
| Any AE | 388 (56.2) | 412 (59.5) | 340 (49.0) | 186 (57.6) |
| Any SAE | 14 (2.0) | 14 (2.0) | 12 (1.7) | 3 (0.9) |
| Any AE causing discontinuation | 9 (1.3) | 8 (1.2) | 9 (1.3) | 6 (1.9) |
| **Entire treatment period – exposure adjusted (52 weeks) (Pool B)** | | | | |
| | **Any AIN457 300 mg** | **Any AIN457 150 mg** | **Placebo** | **Etanercept** |
| | N=1410 | N=1395 | N=793 | N=323 |
| | n (IR) | n (IR) | n (IR) | n (IR) |
| Any AE | 1091 (236.10) | 1066 (239.90) | 413 (351.79) | 253 (243.44) |
| Any SAE | 85 (7.42) | 76 (6.80) | 15 (7.54) | 20 (7.01) |
| | n (%) | n (%) | n (%) | n (%) |
| Any AE causing discontinuation | 46 (3.26) | 43 (3.08) | 11 (1.4) | 12 (3.7) |

IR=Exposure adjusted incidence rate per 100 patient-years

### 5.5.5 Common adverse clinical events

AEs were evaluated by primary system organ class (SOC) and by preferred term (PT) and according to severity (mild, moderate and severe) and causality (possibly related or not related) by Investigator's assessment. They were classified as common AEs (those occurring at an incidence $\geq$ 2% in Pool A), serious AEs (SAEs) including deaths, AEs causing discontinuation or interruption from study treatment or dose adjustment and AEs requiring concomitant medication.

Absolute incidence of AEs in the initial 12 week period is presented for the core placebo-controlled studies (Pool A). This has the advantage of a direct, randomized, contemporaneous placebo control for the same duration.

The comparison of absolute incidence rates vs. placebo for all psoriasis Phase II and Phase III studies over the entire treatment period (Pool B) is limited by study design in which only a small number of placebo responder patients continued on placebo treatment after Week 12. The incidence of AEs for Pool B was therefore summarized using exposure adjusted incidence rates (IR) per 100 patient-years of exposure (calculated as the number of patients with AEs divided by the patient- years in the treatment group × 100). Because of its larger size and inclusion of longer treatment durations, Pool B was used to search for rare AEs in the target psoriasis population:

a) It is the largest dataset of psoriasis patients (total of 3,993 patients of whom 3,430 received secukinumab) and includes 76% of the total patient years exposed to secukinumab in any indication, and

b) It represents the intended indication and dosing regimens.

#### 5.5.5.1 Common adverse events

Common AEs according to primary System Organ Class (SOC) for the initial 12 weeks in the core placebo-controlled psoriasis studies (Pool A) are summarized in Table 5-18. The overall incidence of AEs in the two secukinumab pool and etanercept arm was higher (~58%) than those treated with placebo (~49%). For secukinumab, this small imbalance was primarily driven by the most frequently occurring SOC of infections and infestations. For etanercept, this difference was driven by a higher incidence from two SOCs: general disorders and administration site conditions, as well as infections and infestations.

Common AEs, by preferred term in the initial 12 week dosing period for Pool A, are shown in Table 5-19. All three active treatment groups (secukinumab 150 and 300 mg and etanercept) reported a comparable incidence of AEs overall (56-60%) compared with placebo (49%). There were no clinically meaningful differences between treatment groups for most preferred terms. No clear dose dependency with secukinumab was observed with differences between the secukinumab 300 mg and 150 mg dose groups being generally less than 2%.

The rates of nasopharyngitis, upper respiratory tract infection, and diarrhea in both secukinumab dose groups were comparable to etanercept and all were higher than the placebo group.

Etanercept had the highest incidence of headache, arthralgia, back pain and injection site erythema. Psoriasis was reported as an AE more frequently in the placebo group than the secukinumab and etanercept groups. No other specific AEs among most frequent terms showed a dose-response trend.

Exposure adjusted rates of AEs over 52 weeks for all psoriasis patients (Pool B) are shown in Table 5-20. The overall exposure-adjusted incidence of AEs per 100 patient-years was similar for the 300 mg and 150 mg secukinumab and etanercept groups (236.1, 239.9 and 243.4, respectively) and lower than the placebo (351.8) group acknowledging limitations with placebo comparisons over the 52 week period.

The general pattern of AE profile over the entire treatment period was similar to the initial 12 weeks.

**Table 5-18 AEs by primary system organ class – (Pool A: Core placebo-controlled psoriasis trials 12 weeks)**

| Primary system organ class | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Any AIN457 dose N=1382 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **-Any AE** | 388 (56.2) | 412 (59.5) | 800 (57.89) | 340 (49.0) | 186 (57.6) |
| Infections and infestations | 194 (28.1) | 203 (29.3) | 397 (28.73) | 131 (18.9) | 79 (24.5) |
| Gastrointestinal disorders | 86 (12.5) | 76 (11.0) | 162 (11.72) | 64 (9.2) | 32 (9.9) |
| Skin and subcutaneous tissue disorders | 81 (11.7) | 79 (11.4) | 160 (11.58) | 63 (9.1) | 34 (10.5) |
| Nervous system disorders | 68 (9.9) | 59 (8.5) | 127 (9.19) | 50 (7.2) | 29 (9.0) |
| Musculoskeletal and connective tissue disorders | 56 (8.1) | 70 (10.1) | 126 (9.12) | 61 (8.8) | 27 (8.4) |
| Respiratory, thoracic and mediastinal disorders | 55 (8.0) | 40 (5.8) | 95 (6.87) | 39 (5.6) | 16 (5.0) |
| General disorders and administration site conditions | 45 (6.5) | 47 (6.8) | 92 (6.66) | 41 (5.9) | 58 (18.0) |
| Injury, poisoning and procedural complications | 39 (5.7) | 35 (5.1) | 74 (5.35) | 30 (4.3) | 14 (4.3) |
| Metabolism and nutrition disorders | 21 (3.0) | 30 (4.3) | 51 (3.69) | 22 (3.2) | 12 (3.7) |
| Vascular disorders | 9 (1.3) | 28 (4.0) | 37 (2.68) | 16 (2.3) | 7 (2.2) |
| Eye disorders | 22 (3.2) | 12 (1.7) | 34 (2.46) | 8 (1.2) | 1 (0.3) |
| Blood and lymphatic system disorders | 13 (1.9) | 17 (2.5) | 30 (2.17) | 7 (1.0) | 8 (2.5) |
| Investigations | 13 (1.9) | 16 (2.3) | 29 (2.10) | 12 (1.7) | 12 (3.7) |
| Psychiatric disorders | 15 (2.2) | 12 (1.7) | 27 (1.95) | 15 (2.2) | 6 (1.9) |
| Reproductive system and breast disorders | 13 (1.9) | 7 (1.0) | 20 (1.45) | 3 (0.4) | 2 (0.6) |
| Renal and urinary disorders | 7 (1.0) | 8 (1.2) | 15 (1.09) | 2 (0.3) | 5 (1.5) |
| Ear and labyrinth disorders | 7 (1.0) | 7 (1.0) | 14 (1.01) | 4 (0.6) | 2 (0.6) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 6 (0.9) | 8 (1.2) | 14 (1.01) | 6 (0.9) | 4 (1.2) |
| Cardiac disorders | 4 (0.6) | 8 (1.2) | 12 (0.87) | 12 (1.7) | 7 (2.2) |
| Immune system disorders | 2 (0.3) | 8 (1.2) | 10 (0.72) | 1 (0.1) | 4 (1.2) |
| Hepatobiliary disorders | 4 (0.6) | 2 (0.3) | 6 (0.43) | 4 (0.6) | 2 (0.6) |
| Congenital, familial and genetic disorders | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 0 (0.0) |
| Endocrine disorders | 0 (0.0) | 1 (0.1) | 1 (0.07) | 0 (0.0) | 0 (0.0) |
| Social circumstances | 0 (0.0) | 1 (0.1) | 1 (0.07) | 2 (0.3) | 0 (0.0) |

Treatment-emergent AEs are summarized. Primary system organ classes are sorted in descending order of frequency in Any AIN457 group.

**Table 5-19 Most frequent (≥ 2.0% in any group) AEs by preferred term – (Pool A: Core placebo-controlled psoriasis trials 12 weeks)**

| Preferred term (PT) | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Any AIN457 dose N=1382 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **-Any AE** | 388 (56.2) | 412 (59.5) | 800 (57.89) | 340 (49.0) | 186 (57.6) |
| Nasopharyngitis | 79 (11.4) | 85 (12.3) | 164 (11.87) | 60 (8.6) | 36 (11.1) |
| Headache | 45 (6.5) | 38 (5.5) | 83 (6.01) | 36 (5.2) | 23 (7.1) |
| Diarrhea | 28 (4.1) | 18 (2.6) | 46 (3.33) | 10 (1.4) | 11 (3.4) |
| Pruritus | 23 (3.3) | 21 (3.0) | 44 (3.18) | 18 (2.6) | 8 (2.5) |
| Upper respiratory tract infection | 17 (2.5) | 22 (3.2) | 39 (2.82) | 5 (0.7) | 7 (2.2) |
| Oropharyngeal pain | 15 (2.2) | 17 (2.5) | 32 (2.32) | 12 (1.7) | 4 (1.2) |
| Arthralgia | 9 (1.3) | 20 (2.9) | 29 (2.10) | 17 (2.4) | 12 (3.7) |
| Hypertension | 7 (1.0) | 22 (3.2) | 29 (2.10) | 12 (1.7) | 5 (1.5) |
| Cough | 19 (2.8) | 9 (1.3) | 28 (2.03) | 9 (1.3) | 4 (1.2) |
| Back pain | 14 (2.0) | 12 (1.7) | 26 (1.88) | 10 (1.4) | 9 (2.8) |
| Nausea | 14 (2.0) | 12 (1.7) | 26 (1.88) | 14 (2.0) | 4 (1.2) |
| Fatigue | 10 (1.4) | 14 (2.0) | 24 (1.74) | 7 (1.0) | 5 (1.5) |
| Psoriasis | 4 (0.6) | 10 (1.4) | 14 (1.01) | 20 (2.9) | 2 (0.6) |
| Pyrexia | 10 (1.4) | 4 (0.6) | 14 (1.01) | 6 (0.9) | 7 (2.2) |
| Injection site erythema | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 16 (5.0) |

Treatment-emergent AEs are summarized.
Preferred terms are sorted in descending order of frequency in any AIN457 group.

**Table 5-20 Exposure-adjusted incidence of the most frequent (≥3.0 per 100 patient-years in any group) AEs by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

| Preferred term | Any AIN457 300 mg N=1410 n (IR) | Any AIN457 150 mg N=1395 n (IR) | Any AIN457 dose* N=3430 n (IR) | Placebo N=793 n (IR) | Etanercept N=323 n (IR) |
|---|---|---|---|---|---|
| **-Any AE** | 1091 (236.10) | 1066 (239.90) | 2637 (252.86) | 413 (351.79) | 253 (243.44) |
| Nasopharyngitis | 281 (27.35) | 267 (26.92) | 687 (29.30) | 73 (38.74) | 86 (35.70) |
| Headache | 115 (10.46) | 111 (10.35) | 280 (10.99) | 43 (22.22) | 40 (15.16) |
| Upper respiratory tract infection | 91 (8.09) | 92 (8.44) | 228 (8.76) | 13 (6.53) | 18 (6.35) |
| Arthralgia | 68 (5.95) | 69 (6.23) | 174 (6.60) | 18 (9.12) | 23 (8.24) |
| Hypertension | 67 (5.85) | 68 (6.17) | 165 (6.25) | 13 (6.52) | 14 (4.91) |
| Diarrhea | 79 (6.99) | 63 (5.70) | 163 (6.19) | 13 (6.56) | 22 (7.86) |
| Back pain | 62 (5.40) | 52 (4.67) | 146 (5.50) | 11 (5.52) | 26 (9.35) |
| Pruritus | 54 (4.73) | 66 (6.01) | 135 (5.12) | 21 (10.65) | 16 (5.68) |
| Cough | 70 (6.14) | 44 (3.93) | 133 (5.01) | 13 (6.55) | 12 (4.17) |
| Psoriasis | 31 (2.66) | 22 (1.94) | 123 (4.59) | 28 (14.22) | 7 (2.41) |
| Oropharyngeal pain | 55 (4.80) | 40 (3.57) | 113 (4.25) | 13 (6.52) | 10 (3.47) |
| Bronchitis | 49 (4.24) | 35 (3.11) | 99 (3.70) | 7 (3.50) | 9 (3.11) |
| Influenza | 47 (4.06) | 36 (3.20) | 91 (3.39) | 7 (3.50) | 11 (3.80) |
| Folliculitis | 34 (2.93) | 33 (2.94) | 79 (2.94) | 7 (3.50) | 8 (2.77) |
| Pharyngitis | 43 (3.73) | 29 (2.58) | 79 (2.95) | 1 (0.50) | 6 (2.07) |
| Fatigue | 29 (2.50) | 30 (2.68) | 78 (2.91) | 10 (5.02) | 6 (2.08) |
| Gastroenteritis | 36 (3.10) | 32 (2.84) | 72 (2.68) | 7 (3.50) | 8 (2.76) |
| Pyrexia | 30 (2.57) | 26 (2.30) | 71 (2.63) | 7 (3.50) | 15 (5.30) |
| Pain in extremity | 30 (2.58) | 27 (2.40) | 69 (2.57) | 9 (4.50) | 4 (1.37) |
| Toothache | 24 (2.06) | 32 (2.84) | 68 (2.53) | 13 (6.54) | 7 (2.42) |
| Nausea | 24 (2.06) | 30 (2.68) | 67 (2.50) | 17 (8.57) | 7 (2.43) |
| Eczema | 37 (3.19) | 23 (2.04) | 66 (2.45) | 1 (0.50) | 2 (0.68) |
| Influenza like illness | 22 (1.89) | 27 (2.39) | 59 (2.19) | 4 (2.00) | 9 (3.11) |
| Abdominal pain upper | 21 (1.80) | 20 (1.77) | 57 (2.12) | 7 (3.49) | 3 (1.03) |
| Vomiting | 25 (2.16) | 13 (1.14) | 54 (2.01) | 6 (3.00) | 9 (3.13) |
| Myalgia | 22 (1.89) | 18 (1.59) | 53 (1.96) | 9 (4.51) | 9 (3.12) |
| Hypercholesterolemia | 16 (1.37) | 22 (1.95) | 51 (1.89) | 10 (5.04) | 7 (2.42) |
| Edema peripheral | 15 (1.28) | 20 (1.77) | 49 (1.82) | 9 (4.51) | 6 (2.07) |
| Urinary tract infection | 23 (1.97) | 15 (1.32) | 48 (1.78) | 3 (1.49) | 10 (3.49) |
| Oral herpes | 23 (1.98) | 17 (1.50) | 47 (1.74) | 3 (1.49) | 9 (3.11) |
| Abdominal pain | 11 (0.94) | 21 (1.86) | 39 (1.44) | 7 (3.51) | 8 (2.78) |
| Anxiety | 11 (0.94) | 8 (0.70) | 30 (1.11) | 7 (3.50) | 4 (1.37) |
| Dizziness | 13 (1.11) | 9 (0.79) | 28 (1.03) | 7 (3.50) | 5 (1.73) |
| Injection site erythema | 2 (0.17) | 2 (0.18) | 5 (0.18) | 0 (0.00) | 17 (6.05) |

Preferred terms are sorted in descending order of IR in Any AIN457 dose column.
IR=incidence rate per 100 patient-years.
For patients with event, exposure time is censored at time of first event.
*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

The majority of individual AEs were reported with comparable or lower exposure-adjusted rates for secukinumab compared with the placebo and etanercept groups. Nasopharyngitis and

headache, the two most common AEs, showed lower exposure-adjusted rates with either active treatment than with placebo.

Some infection AEs, such as upper respiratory tract infection, viral upper respiratory tract infection, oral candidiasis and otitis externa, occurred more frequently per 100 patient-years in the any secukinumab dose group compared with the placebo and etanercept groups. These infection events also showed higher exposure-adjusted rates with 300 mg vs. 150 mg secukinumab, but the difference in rates for each event was less than 1 event per 100 patient-years (Section 5.5.9.1). Urinary tract infection was more frequent with etanercept than secukinumab.

The higher total rate of treatment-related AEs with etanercept vs. secukinumab and placebo was driven by general disorders and administration site conditions, particularly injection site erythema (5% for etanercept vs. 0.07% for any secukinumab dose and 0% for placebo) (Table 5-19).

### 5.5.5.2 Common adverse events over time

The most frequently occurring AEs (at least 3% total observed in the respective treatment group) showed the same pattern across all active treatment groups, with rates decreasing in the first 6 months and stabilizing thereafter (Table 5-21). Few patients remained on placebo treatment after 3 months as most switched to secukinumab and therefore were not available for comparisons, beyond the already described initial 12 weeks. Results for Month 13 or later are difficult to interpret due to the small number of patients at that time.

Taken together, the results indicate that total AEs and specific events did not worsen with increasing duration of exposure.

**Table 5-21 Most frequent AEs (≥3% total observed in each group) by 3-month intervals and preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

| Day of onset | Total | To Month 3 | Month 4 to 6 | Month 7 to 9 | Month 10 to 12 | Month 13 or later |
|---|---|---|---|---|---|---|
| **Any AIN457 300 mg** | | | | | | |
| No. patients evaluated | 1410 | 1410 | 1330 | 1208 | 1049 | 142 |
| Nasopharyngitis | 281 (19.93) | 141 (10.00) | 56 (4.21) | 40 (3.31) | 41 (3.91) | 3 (2.1) |
| Headache | 115 (8.16) | 79 (5.60) | 18 (1.35) | 11 (0.91) | 7 (0.67) | 0 (0.0) |
| Upper respiratory tract infection | 91 (6.45) | 43 (3.05) | 24 (1.80) | 10 (0.83) | 13 (1.24) | 1 (0.7) |
| Diarrhea | 79 (5.60) | 41 (2.91) | 20 (1.50) | 12 (0.99) | 6 (0.57) | 0 (0.0) |
| Cough | 70 (4.96) | 34 (2.41) | 15 (1.13) | 10 (0.83) | 9 (0.86) | 2 (1.4) |
| Arthralgia | 68 (4.82) | 22 (1.56) | 18 (1.35) | 21 (1.74) | 7 (0.67) | 0 (0.0) |
| Hypertension | 67 (4.75) | 21 (1.49) | 18 (1.35) | 14 (1.16) | 13 (1.24) | 1 (0.7) |
| Back pain | 62 (4.40) | 22 (1.56) | 18 (1.35) | 13 (1.08) | 8 (0.76) | 1 (0.7) |
| Oropharyngeal pain | 55 (3.90) | 28 (1.99) | 13 (0.98) | 10 (0.83) | 4 (0.38) | 0 (0.0) |
| Pruritus | 54 (3.83) | 41 (2.91) | 7 (0.53) | 2 (0.17) | 3 (0.29) | 1 (0.7) |
| Bronchitis | 49 (3.48) | 14 (0.99) | 12 (0.90) | 16 (1.32) | 6 (0.57) | 1 (0.7) |
| Influenza | 47 (3.33) | 15 (1.06) | 5 (0.38) | 11 (0.91) | 14 (1.33) | 2 (1.4) |
| Pharyngitis | 43 (3.05) | 20 (1.42) | 10 (0.75) | 10 (0.83) | 3 (0.29) | 0 (0.0) |

| Day of onset | Total | To Month 3 | Month 4 to 6 | Month 7 to 9 | Month 10 to 12 | Month 13 or later |
|---|---|---|---|---|---|---|
| **Any AIN457 150 mg** | | | | | | |
| No. patients evaluated | 1395 | 1395 | 1307 | 1167 | 985 | 136 |
| Nasopharyngitis | 267 (19.14) | 151 (10.82) | 48 (3.67) | 32 (2.74) | 34 (3.5) | 2 (1.5) |
| Headache | 111 (7.96) | 70 (5.02) | 24 (1.84) | 11 (0.94) | 6 (0.6) | 0 (0.0) |
| Upper respiratory tract infection | 92 (6.59) | 44 (3.15) | 17 (1.30) | 23 (1.97) | 7 (0.7) | 1 (0.7) |
| Arthralgia | 69 (4.95) | 33 (2.37) | 17 (1.30) | 7 (0.60) | 11 (1.1) | 1 (0.7) |
| Hypertension | 68 (4.87) | 39 (2.80) | 11 (0.84) | 10 (0.86) | 6 (0.6) | 2 (1.5) |
| Pruritus | 66 (4.73) | 43 (3.08) | 11 (0.84) | 7 (0.60) | 5 (0.5) | 0 (0.0) |
| Diarrhea | 63 (4.52) | 31 (2.22) | 20 (1.53) | 7 (0.60) | 5 (0.5) | 0 (0.0) |
| Back pain | 52 (3.73) | 24 (1.72) | 12 (0.92) | 7 (0.60) | 7 (0.7) | 2 (1.5) |
| Cough | 44 (3.15) | 20 (1.43) | 9 (0.69) | 8 (0.69) | 7 (0.7) | 0 (0.0) |
| **Any AIN457 dose** | | | | | | |
| No. patients evaluated | 3430 | 3430 | 3038 | 2740 | 2291 | 291 |
| Nasopharyngitis | 687 (20.03) | 387 (11.28) | 121 (3.98) | 82 (2.99) | 90 (3.93) | 7 (2.4) |
| Headache | 280 (8.16) | 186 (5.42) | 50 (1.65) | 28 (1.02) | 16 (0.70) | 0 (0.0) |
| Upper respiratory tract infection | 228 (6.65) | 112 (3.27) | 53 (1.74) | 38 (1.39) | 21 (0.92) | 4 (1.4) |
| Arthralgia | 174 (5.07) | 69 (2.01) | 41 (1.35) | 35 (1.28) | 27 (1.18) | 2 (0.7) |
| Hypertension | 165 (4.81) | 74 (2.16) | 40 (1.32) | 28 (1.02) | 19 (0.83) | 4 (1.4) |
| Diarrhea | 163 (4.75) | 81 (2.36) | 45 (1.48) | 22 (0.80) | 15 (0.65) | 0 (0.0) |
| Back pain | 146 (4.26) | 58 (1.69) | 37 (1.22) | 29 (1.06) | 19 (0.83) | 3 (1.0) |
| Pruritus | 135 (3.94) | 96 (2.80) | 20 (0.66) | 9 (0.33) | 9 (0.39) | 1 (0.3) |
| Cough | 133 (3.88) | 65 (1.90) | 29 (0.95) | 18 (0.66) | 19 (0.83) | 2 (0.7) |
| Psoriasis | 123 (3.59) | 54 (1.57) | 23 (0.76) | 20 (0.73) | 19 (0.83) | 7 (2.4) |
| Oropharyngeal pain | 113 (3.29) | 56 (1.63) | 28 (0.92) | 16 (0.58) | 13 (0.57) | 0 (0.0) |
| **Etanercept** | | | | | | |
| No. patients evaluated | 323 | 323 | 301 | 288 | 275 | 150 |
| Nasopharyngitis | 86 (26.6) | 41 (12.7) | 21 (7.0) | 9 (3.1) | 13 (4.7) | 2 (1.3) |
| Headache | 40 (12.4) | 25 (7.7) | 8 (2.7) | 5 (1.7) | 2 (0.7) | 0 (0.0) |
| Back pain | 26 (8.0) | 9 (2.8) | 9 (3.0) | 4 (1.4) | 4 (1.5) | 0 (0.0) |
| Arthralgia | 23 (7.1) | 12 (3.7) | 5 (1.7) | 1 (0.3) | 5 (1.8) | 0 (0.0) |
| Diarrhea | 22 (6.8) | 12 (3.7) | 5 (1.7) | 3 (1.0) | 2 (0.7) | 0 (0.0) |
| Upper respiratory tract infection | 18 (5.6) | 7 (2.2) | 5 (1.7) | 1 (0.3) | 4 (1.5) | 1 (0.7) |
| Injection site erythema | 17 (5.3) | 16 (5.0) | 1 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pruritus | 16 (5.0) | 9 (2.8) | 5 (1.7) | 1 (0.3) | 1 (0.4) | 0 (0.0) |
| Pyrexia | 15 (4.6) | 7 (2.2) | 7 (2.3) | 1 (0.3) | 0 (0.0) | 0 (0.0) |
| Hypertension | 14 (4.3) | 6 (1.9) | 4 (1.3) | 1 (0.3) | 3 (1.1) | 0 (0.0) |
| Cough | 12 (3.7) | 4 (1.2) | 4 (1.3) | 2 (0.7) | 1 (0.4) | 1 (0.7) |
| Influenza | 11 (3.4) | 2 (0.6) | 2 (0.7) | 4 (1.4) | 2 (0.7) | 1 (0.7) |
| Oropharyngeal pain | 10 (3.1) | 4 (1.2) | 2 (0.7) | 2 (0.7) | 1 (0.4) | 1 (0.7) |
| Urinary tract infection | 10 (3.1) | 6 (1.9) | 1 (0.3) | 1 (0.3) | 2 (0.7) | 0 (0.0) |

Preferred terms are sorted in descending order of frequency in the Total column of each treatment group.
Number of patients evaluated was the number of patients at risk of experiencing AE.
Occurrence of same AE in multiple intervals was counted only in the interval when the AE started.
Few patients remained on placebo treatment after 3 months, as most switched to secukinumab and therefore were not available for comparisons, beyond the already described initial 12 weeks.

#### 5.5.5.3 Analysis of adverse effect dose-response information

Across the psoriasis trials, at the System Organ Class (SOC) level, there was no clear or consistent dose response seen for secukinumab 300 mg vs. 150 mg. For the most part, this was also the case when AEs were examined by the Preferred Term (PT) level.

Infections related to *Candida* were infrequent in both doses but did appear to show a dose response (1.2% with 300 mg vs. 0.4% with 150 mg) during the placebo controlled period (Table 5-27). This difference was also observed in exposure adjusted incidence with the larger Pool B for the entire treatment period (incidence per 100 patient years of 3.55 with 300 mg vs. 1.85 with 150 mg) (Table 5-28). Based on the implied role of IL-17 in mucosal defense against *Candida*, an imbalance relative to dose and placebo would not be unexpected. The imbalance between doses was limited to non-serious, localized mucosal or cutaneous candidiasis, consistent with the mechanism of action, with no reports of chronic or systemic disease in any treatment group.

### 5.5.6 Deaths

Seven deaths have been reported in the psoriasis program: six in the original submission and one additional death included in the four month safety update (data cut off was November 30, 2013) submitted to FDA. Two of the seven never received secukinumab (1 suicide during screening before any study drug administered and 1 MI in a placebo patient who never received secukinumab).

Of the remaining five, three occurred within 32 days (within approximately one half-life) of the last dose; 1 occurred approximately 4 months (112 days or approximately four half-lives) after the last dose and 1 occurred over a year after the last dose.

An overview of all seven deaths from the psoriasis studies is provided in Table 5-22 and a brief description of each is provided below.

**Table 5-22 Deaths in all Phase I to III psoriasis trials**

| Study/Age/sex/race Treatment | Cause of death (Preferred term) | Risk factors | Day of death (study period) | Days from last dose* | Investigator Assessment |
|---|---|---|---|---|---|
| **Secukinumab 300 mg** | | | | | |
| AIN457A2302/27/M/As Placebo-AIN457 300 mg | Unknown cause | Alcoholic liver disease, QTc prolonged | Day 285 (Post-study) | 112 | Not suspected |
| AIN457A2308/54/F/Ca AIN457 300 mg | Alcohol intoxication | Hypertension | Day 305 | 13 | Not suspected |
| **Secukinumab 150 mg** | | | | | |
| AIN457A2304/66/M/As AIN457 150 mg SoR | Cerebral hemorrhage (hemorrhagic stroke) | High fasting glucose (2xULN) High hsCRP (11xULN) | Day 319 (Maintenance) | 12 | Not suspected |
| AIN457A2211E1§/57/M/Ca AIN457 150 mg q4w | Intestinal ischemia, Hyperkalemia and renal failure | Hypertension, diabetes mellitus, dyslipidemia | Day 1041 (Extension) | 32 | Not suspected |
| AIN457A2211E1§/64/M/Ca AIN457 150mg q12w | Disseminated aspergillosis infection post liver transplant | History of liver cirrhosis, 2 liver transplants within 5 days, use of infliximab | Day 436 (Post-study) | 370 | Not suspected |
| **Placebo** | | | | | |
| AIN457A2220/53/M/Ca Placebo | Myocardial infarction (myocardial infarction) | Coronary bypass surgery, myocardial infarction and hypertension | Day 102 (Follow-up) | 43 | Not suspected |
| **Screening/No treatment** | | | | | |
| AIN457A2303/35/M/Ca No treatment | Committed suicide (Complete suicide) | None reported | Screening period | Not applicable | Not suspected |

Patient identifiers remain confidential.
M = male, F = female, As=Asian, Ca = Caucasian; hsCRP=high sensitivity C-reactive protein; ULN=upper limit of normal
* Day of onset=onset day of SAE leading to death or day of death
§ Death was reported to Argus safety database after database lock for interim analysis of Study A2211E1.

Patient from study A2302, a 27-year-old male with a 2-year history of alcoholic liver disease, received his first dose of the study medication (placebo) on (b) (6) (Day 1) and then switched to secukinumab 300 mg maintenance treatment on (b) (6) (Day 86). His last dose of study medication was on (b) (6) (Day 174). The patient discontinued study medication due to alcoholic liver disease. He died on (b) (6) (112 days after the last dose of study medication) due to unknown causes. The investigator did not know if an

autopsy was performed and did not suspect a relationship between the death and study medication.

Patient from study A2304 was a 66-year-old male patient with severe psoriasis in the 150 mg (treatment at start of relapse) group. The Investigator considered the event most likely to be due to a hemorrhagic stroke, although no autopsy was performed. The SAE was cerebral hemorrhage at Day 319, after the patient experienced vomiting, headache and loss of consciousness on Day 295 (12 days after the last dose of study medication). No relevant past medical history nor active medical condition were reported for the patient, although the patient did have risk factors including high fasting glucose (2xULN) and high hsCRP (11xULN) at baseline. The investigator did not consider the death to be related to study treatment. This death was adjudicated and confirmed as meeting the criteria of MACE. MACE events are discussed in Section 5.5.9.4.1.

Patient from study A2211E1 was a 57-year-old male patient on secukinumab 150 mg monthly treatment with cardiac arrest. The patient had a medical history of arterial hypertension, diabetes mellitus, and dyslipidemia. The concomitant medications included Alteis Duo, fluvastatin and metformin. Thirty-two days after the last dose of study medication (Day 1010), the patient complained of lower abdominal pain and had not eaten or drunk for 5 days prior to being hospitalized. On the same day of hospitalization, the patient experienced cardiac arrest and died subsequently. No autopsy was performed. The cause of death was reported by the investigator and treating physician as hyperkalemia (blood potassium 8.9), renal failure (creatinine 240mg/l and GFR function test 2ml/min) and intestinal ischemia.

Patient from study A2211E1, a 64-year-old male with a history of increased hepatic enzyme, thrombocytopenia, hyperbilirubinema and hypertension, received his first dose of 150 mg secukinumab during the core study on (b) (6) (Day 1). On (b) (6) (Day 255) he entered the extension study, received one dose of 150 mg secukinumab on the same day and then discontinued study treatment due to hepatic cirrhosis, an SAE which had started on 27-Apr-2010 during the core study. The patient started treatment with spironolactone on 05-Aug-2010 for edema, ascites and liver cirrhosis, and then azathioprine on 28-Aug-2010 for hepatitis. On 30-Aug-2010, the patient started treatment with infliximab for psoriasis but the infliximab was discontinued that same day. On 12-Sep-2010, the patient was diagnosed with decompensated liver cirrhosis and underwent liver transplantation twice ( (b) (6) and (b) (6) ). The patient was diagnosed with disseminated aspergillosis infection on 12-Jul-2011 and died from this infection on (b) (6) 436 days after the last dose of the study medication. It should be noted that this patient had discontinued secukinumab one year prior to the diagnosis of aspergillosis, a complication following liver transplantation. Prior therapy with azathioprine could be another confounding factor.

Patient from study A2308, a 54-year-old female with hypertension but no reported history of alcohol abuse, was randomized to placebo and started treatment on 10-Oct-2012. The study treatment code was blinded after Week 12, and the patient received the most recent dose on 15-Aug-2013. On (b) (6) the patient died of alcohol intoxication. The patient's post-mortem autopsy fluid contained ethanol (5.0 g/L). The cause of death as per the autopsy report was self-poisoning with alcohol leading to left ventricle insufficiency. The investigator did not suspect a relationship between the event and study medication.

Patient from study A2220 was a 53-year-old male patient who had a history of myocardial infarction (Oct 2002) and coronary artery bypass surgery ([(b) (6)] The patient received his first dose of the study medication (placebo) on [(b) (6)] (Day 1) and his last dose of the study medication on [(b) (6)] (Day 58). At the end of the treatment phase on [(b) (6)] (43 days after the last dose of the study medication), the patient died of myocardial infarction. No autopsy was performed. The investigator did not suspect a relationship between the event and study medication.

Patient from Study A2303 died during the screening phase (complete suicide) and did not receive any study medication.

### 5.5.7 Serious adverse events

Exposure-adjusted rates of SAEs by primary SOC for the entire treatment period of Pool B are summarized in Table 5-23. No clinically meaningful differences in the exposure-adjusted rates of total SAEs were observed across the treatment groups or between the secukinumab dose groups. The general pattern of SAEs over the entire treatment period was comparable to the initial 12-week period.

**Table 5-23 Exposure-adjusted incidence of SAEs by system organ class (SOC) – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

| Primary system organ class | Any AIN457 300 mg N=1410 n (IR) | Any AIN457 150 mg N=1395 n (IR) | Any AIN457 dose* N=3430 n (IR) | Placebo N=793 n (IR) | Etanercept N=323 n (IR) |
|---|---|---|---|---|---|
| **- Any SAE** | 85 (7.42) | 76 (6.80) | 207 (7.80) | 15 (7.54) | 20 (7.01) |
| Infections and infestations | 16 (1.36) | 12 (1.05) | 40 (1.47) | 2 (0.99) | 4 (1.37) |
| Cardiac disorders | 7 (0.60) | 13 (1.14) | 25 (0.92) | 0 (0.00) | 3 (1.03) |
| Injury, poisoning and procedural complications | 15 (1.28) | 3 (0.26) | 23 (0.85) | 3 (1.49) | 3 (1.03) |
| Gastrointestinal disorders | 7 (0.60) | 9 (0.79) | 21 (0.77) | 0 (0.00) | 0 (0.00) |
| Nervous system disorders | 6 (0.51) | 11 (0.97) | 18 (0.66) | 1 (0.50) | 2 (0.68) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 5 (0.43) | 6 (0.53) | 17 (0.63) | 1 (0.50) | 0 (0.00) |
| Skin and subcutaneous tissue disorders | 6 (0.51) | 5 (0.44) | 16 (0.59) | 5 (2.49) | 1 (0.34) |
| Musculoskeletal and connective tissue disorders | 7 (0.60) | 5 (0.44) | 15 (0.55) | 0 (0.00) | 4 (1.37) |
| Hepatobiliary disorders | 5 (0.43) | 5 (0.44) | 11 (0.40) | 0 (0.00) | 1 (0.34) |
| Psychiatric disorders | 4 (0.34) | 6 (0.53) | 11 (0.40) | 2 (0.99) | 0 (0.00) |
| Vascular disorders | 5 (0.42) | 5 (0.44) | 11 (0.40) | 0 (0.00) | 0 (0.00) |
| Respiratory, thoracic and mediastinal disorders | 2 (0.17) | 7 (0.61) | 10 (0.37) | 0 (0.00) | 1 (0.34) |
| Renal and urinary disorders | 5 (0.43) | 3 (0.26) | 9 (0.33) | 0 (0.00) | 1 (0.34) |
| Metabolism and nutrition disorders | 3 (0.25) | 4 (0.35) | 7 (0.26) | 0 (0.00) | 0 (0.00) |

| Primary system organ class | Any AIN457 300 mg N=1410 n (IR) | Any AIN457 150 mg N=1395 n (IR) | Any AIN457 dose* N=3430 n (IR) | Placebo N=793 n (IR) | Etanercept N=323 n (IR) |
|---|---|---|---|---|---|
| General disorders and administration site conditions | 1 (0.08) | 3 (0.26) | 4 (0.15) | 1 (0.50) | 0 (0.00) |
| Reproductive system and breast disorders | 3 (0.26) | 1 (0.09) | 4 (0.15) | 0 (0.00) | 0 (0.00) |
| Ear and labyrinth disorders | 1 (0.08) | 1 (0.09) | 2 (0.07) | 0 (0.00) | 0 (0.00) |
| Endocrine disorders | 0 (0.00) | 2 (0.18) | 2 (0.07) | 0 (0.00) | 1 (0.34) |
| Eye disorders | 0 (0.00) | 0 (0.00) | 1 (0.04) | 0 (0.00) | 0 (0.00) |
| Congenital, familial and genetic disorders | 1 (0.08) | 0 (0.00) | 1 (0.04) | 0 (0.00) | 0 (0.00) |
| Blood and lymphatic system disorders | 0 (0.00) | 1 (0.09) | 1 (0.04) | 0 (0.00) | 0 (0.00) |
| Investigations | 0 (0.00) | 1 (0.09) | 1 (0.04) | 0 (0.00) | 0 (0.00) |
| Social circumstances | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.50) | 0 (0.00) |

Treatment-emergent SAEs are summarized in this table.
Primary system organ classes are sorted in descending order of IR in Any AIN457 dose column.
IR=incidence rate per 100 patient years.
For patients with event, exposure time is censored at time of first event.
*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

During the initial 12 week dosing period of Pool A, the incidence of SAE was low across all treatment groups and comparable between secukinumab groups and placebo. No dose dependence with secukinumab was observed (Table 5-24).

Two patients on 150 mg secukinumab experienced pulmonary edema; both cases were associated with confounding circumstances and relevant medical history: one patient with active hypertension entered the study with preceding signs of erythroderma due to the prior required wash out period. Starting at Day 12, the patient was diagnosed with erythrodermic psoriasis and also developed dyspnea, cardiac failure and pulmonary edema. The patient discontinued study treatment due to the events, all of which resolved with appropriate treatment. It is known that erythrodermic psoriasis can result from withdrawal of medication and can lead to hyperdynamic status and cardiac failure (Jha et al 2005). The second patient also had active medical conditions including 7-year history of hypertension, aortic valve stenosis, cardiac failure, cardiomegaly, 3-year history of coronary artery disease, 2-year history of atrial fibrillation and dysuria, and was diagnosed with congestive cardiac failure, pulmonary edema, pneumonia and ascites at Day 25, which resolved with treatment. The patient withdrew consent and was discontinued from the study.

No similar cases of pulmonary edema were reported with secukinumab 300mg and in the broader psoriasis population (Pool B) over the entire 52 week treatment period.

**Table 5-24 Most frequent (≥2 patients in total) SAEs by preferred term – Initial 12 week period (Pool A: Core placebo-controlled psoriasis trials – Safety set)**

| Preferred term | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Any AIN457 dose N=1382 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **-Any SAE** | 14 (2.0) | 14 (2.0) | 28 (2.03) | 12 (1.7) | 3 (0.9) |
| Pulmonary edema | 0 (0.0) | 2 (0.3) | 2 (0.14) | 0 (0.0) | 0 (0.0) |
| Cellulitis | 0 (0.0) | 0 (0.0) | 0 (0.00) | 2 (0.3) | 0 (0.0) |
| Psoriasis | 0 (0.0) | 0 (0.0) | 0 (0.00) | 3 (0.4) | 0 (0.0) |

Preferred terms are sorted in descending order of frequency in the any AIN457 group.
Three overdoses, one for each AIN457 patient and one for placebo were all additional injections of placebo and therefore not true overdoses.

Exposure-adjusted rates of SAEs by primary preferred term for the entire treatment period of Pool B showed no clinically meaningful differences across the treatment groups or between the secukinumab dose groups (Table 5-25). No dose response was apparent for any specific SAE. Serious cases of cellulitis and psoriasis were more common with placebo vs. any secukinumab dose and etanercept. Transient ischemic attack and myocardial infarction were more common with etanercept vs. the two secukinumab doses and placebo and rates of angina pectoris and coronary artery disease were also low, despite the baseline imbalance with more secukinumab patients with cardiovascular risk factors (Table 5-33).

The event rates (Table 5-25) observed are too low to allow any meaningful conclusions regarding relative rates between groups. For example, a single case in the etanercept arm shows the highest rate, although it was only one patient. Thus, it can appear to result in quadruple the incidence compared with a single case in either of the secukinumab arms. A single case difference (2 vs. 1) in either of the secukinumab arms can appear to double the incidence between the groups.

**Table 5-25 Exposure adjusted incidence of the most frequent (≥0.15 per 100 patient years in the any secukinumab group) treatment-emergent SAEs by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

| Preferred Term | AIN457 300 mg N=1410 n (IR) (95%CI) | AIN457 150 mg N=1395 n (IR) (95%CI) | Any AIN457 dose* N=3430 n (IR) (95%CI) | Placebo N=793 n (IR) (95%CI) | Etanercept N=323 n (IR) (95%CI) |
|---|---|---|---|---|---|
| Any SAE | 85 (7.42) (5.92, 9.17) | 76 (6.80) (5.36, 8.52) | 207 (7.80) (6.77, 8.94) | 15 (7.54) (4.22, 12.44) | 20 (7.01) (4.28, 10.82) |
| Pneumonia | 3 (0.25) (0.05, 0.74) | 3 (0.26) (0.05, 0.77) | 6 (0.22) (0.08, 0.48) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Angina pectoris | 1 (0.08) (0.00, 0.47) | 2 (0.18) (0.02, 0.63) | 5 (0.18) (0.06, 0.43) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Cellulitis | 1 (0.08) (0.00, 0.47) | 2 (0.18) (0.02, 0.63) | 5 (0.18) (0.06, 0.43) | 2 (0.99) (0.12, 3.59) | 1 (0.34) (0.01, 1.90) |
| Abscess bacterial | 0 (0.00) (0.00, 0.31) | 3 (0.26) (0.05, 0.77) | 4 (0.15) (0.04, 0.38) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Appendicitis | 2 (0.17) (0.02, 0.61) | 1 (0.09) (0.00, 0.49) | 4 (0.15) (0.04, 0.38) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Coronary artery disease | 1 (0.08) (0.00, 0.47) | 1 (0.09) (0.00, 0.49) | 4 (0.15) (0.04, 0.38) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Hypertensive crisis | 2 (0.17) (0.02, 0.61) | 1 (0.09) (0.00, 0.49) | 4 (0.15) (0.04, 0.38) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Psoriasis | 1 (0.08) (0.00, 0.47) | 1 (0.09) (0.00, 0.49) | 4 (0.15) (0.04, 0.38) | 4 (1.99) (0.54, 5.09) | 1 (0.34) (0.01, 1.90) |
| Sciatica | 2 (0.17) (0.02, 0.61) | 2 (0.18) (0.02, 0.63) | 4 (0.15) (0.04, 0.38) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |

Preferred terms are sorted in descending order of frequency in the any AIN457 dose.IR=incidence rate per 100 patient years.
*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

### 5.5.8 Adverse events causing discontinuation

AEs causing discontinuation of study medication were reported for few patients during the first 12 weeks (≤2 patients in any group in Pools A) and overall incidences were comparable between the secukinumab, placebo and etanercept groups (1.3%, 1.2%, 1.3% and 1.9% for 300, 150, placebo and etanercept). There was no difference between the secukinumab dose groups.

Over the entire treatment period for Pool B the absolute incidences of AEs causing discontinuation was comparable between any secukinumab dose and etanercept (3.4% vs. 3.7%) (Table 5-26).

**Table 5-26 Most frequent (≥0.20% in any group) AEs causing discontinuation by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

| Preferred term | Any AIN457 300 mg N=1410 n (%) | Any AIN457 150 mg N=1395 n (%) | Any AIN457 dose* N=3430 n (%) | Placebo N=793 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **-Any AE causing discontinuation** | 46 (3.26) | 43 (3.08) | 118 (3.44) | 11 (1.4) | 12 (3.7) |
| Psoriasis | 2 (0.14) | 2 (0.14) | 8 (0.23) | 6 (0.8) | 2 (0.6) |
| Psoriatic arthropathy | 0 (0.00) | 4 (0.29) | 6 (0.17) | 0 (0.0) | 0 (0.0) |
| Thrombocytopenia | 1 (0.07) | 3 (0.22) | 4 (0.12) | 0 (0.0) | 0 (0.0) |
| Colitis ulcerative | 1 (0.07) | 2 (0.14) | 3 (0.09) | 0 (0.0) | 1 (0.3) |
| Gamma-glutamyltransferase increased | 0 (0.00) | 3 (0.22) | 3 (0.09) | 0 (0.0) | 0 (0.0) |
| Hepatic enzyme increased | 2 (0.14) | 1 (0.07) | 3 (0.09) | 0 (0.0) | 1 (0.3) |
| Neutropenia | 1 (0.07) | 1 (0.07) | 2 (0.06) | 0 (0.0) | 2 (0.6) |
| Interstitial lung disease | 1 (0.07) | 0 (0.00) | 1 (0.03) | 0 (0.0) | 1 (0.3) |
| Arteriosclerosis coronary artery | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.0) | 1 (0.3) |
| Injection site edema | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.0) | 1 (0.3) |
| Injection site rash | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.0) | 1 (0.3) |
| Myocardial infarction | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.0) | 1 (0.3) |
| Transient ischemic attack | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.0) | 1 (0.3) |
| VIIth nerve paralysis | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.0) | 1 (0.3) |

Preferred terms are sorted in descending order of frequency in any AIN457 group.
*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

### 5.5.9 AEs of special interest

AEs of special interest are summarized in this section. These AEs correspond to risks prespecified for secukinumab and other potential risks seen with other immunomodulating biologics used for psoriasis and they include:

- Potential risks of immunomodulating biologics approved or assessed in psoriasis (infections including opportunistic infections, neutropenia, malignancies, cardiovascular risks)
- Potential risks of foreign proteins: hypersensitivity, administration or immune reactions, and autoimmune disorders
- Potential risk of compounds targeting the IL-17 pathway: Crohn's disease

#### 5.5.9.1 Infections

A potential risk of infection should be considered with any immune-modulating biologic. In particular, there have been reports of increased susceptibility for infections with *Candida* in individuals who have genetic defects in IL-17 signaling (Gaffen et al 2011) and IL-17A is considered central to the mucosal defense to *Candida* (Cypowji et al 2012). These typically result in chronic mucocutaneous forms of *Candida* infections rather than more invasive or systemic disease (Gaffen et al 2011). Moreover, IL-17 is reported to have a role in the immune response to cutaneous staphylococcal infections as evidenced by an increased

susceptibility to these infections in individuals with defects in the generation of Th17 cells (Miller and Cho 2011).

The incidence of infections and infestations for secukinumab, at either dose, in the first 12 weeks of treatment, especially upper respiratory tract infections, was higher relative to placebo and comparable to etanercept. After adjusting for exposure over the entire 52-week treatment period, the secukinumab incidences were comparable to placebo and etanercept. There were no serious opportunistic infections, and no observed cases of reactivation of latent tuberculosis or viral hepatitis infection, and no imbalance in serious infections.

There was a slight increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action. All were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. In the entire treatment period among all psoriasis patients, there were two (0.1%) staphylococcal infections requiring antibiotic treatment occurring in patients treated with 150 mg of secukinumab and one (0.07%) observed with 300 mg of secukinumab. None were serious.

No cases of disseminated or CNS herpes were reported. An imbalance in tinea pedis for both secukinumab doses vs. placebo and etanercept was observed in the initial 12 week period (Pool A), but after adjusting for exposure in the entire treatment period (Pool B) both secukinumab doses were comparable to etanercept which were all greater than placebo. These differences in infection events are consistent with the implied role of IL-17 on fungal infections.

Upper respiratory tract infections, such as nasopharyngitis and upper respiratory tract infection, were the most common infections and were more frequent with secukinumab and etanercept vs. placebo (17.0%, 18.6% and 15.2%, respectively, for 300 mg, 150 mg and etanercept vs. 10.4% for placebo) during the initial 12 weeks. These remained the most frequent for the entire treatment period; however, the exposure adjusted incidences were lower or comparable to the exposure adjusted incidence with placebo (Table 5-20).

Nearly all of the infections occurring in the initial 12 weeks were non-serious and responded to conventional therapy. Very few required discontinuation or interruption of study treatment and these were reported with similar frequency across all treatment groups (0.9%, 0.7%, 1.0%, and 0.9% for 300 mg secukinumab, 150 mg secukinumab, placebo, and etanercept, respectively). The most common AEs causing discontinuation or interruption by preferred term were nasopharyngitis (0.1%, 0.3%, 0.4%, and 0.6%, for 300 mg, 150 mg, placebo and etanercept, respectively) and cellulitis (0.3% for placebo; 0% for both secukinumab doses, and etanercept). SAEs infections were reported in 1 (0.1%) patient in each of the secukinumab dose groups (anal abscess for 300 mg; pneumonia for 150 mg) and 2 (0.3%) patients in the placebo group (both, cellulitis) (Table 5-27). No patient on etanercept experienced a serious infection during this period.

Over the entire treatment period the exposure adjusted incidences of infections with secukinumab were comparable to placebo and etanercept (91.06, 85.29, 101.89 and 93.68 for 300 mg and 150 mg secukinumab, placebo and etanercept, respectively). These results indicate no increase in infections with secukinumab relative to placebo and etanercept over 52 weeks of treatment (Table 5-28). The majority of infections were upper respiratory tract infections, which occurred with comparable frequency per 100 patient-years across the

treatment groups (45.4, 45.0, 52.0 and 50.5, respectively, for any 300 mg, any 150 mg, placebo, and etanercept). Urinary tract infection was more frequent with etanercept than any dose of secukinumab (3.49 and 1.78 respectively) (Table 5-20). The exposure adjusted incidence rate of infection SAEs over the entire treatment period was also comparable between secukinumab doses, etanercept and placebo, regardless of type of infections.

#### 5.5.9.1.1 *Candida* Infections

The incidence during both the initial 12 weeks (Pool A) and during the entire treatment period (Pool B) of *Candida* infections was generally low for all groups. *Candida* infections were reported most frequently in the 300 mg group, followed by the 150 mg dose group, then etanercept and placebo (Table 5-27 and Table 5-28).

All *Candida* infections on secukinumab and placebo, summarized in Table 5-27 and Table 5-28, were mild or moderate in severity, while there was one case of gastrointestinal candidiasis on etanercept that was severe. The majority of the *Candida* infections in both secukinumab dose groups consisted of oral candidiasis and vulvovaginal candidiasis.

**Table 5-27 Infections overall and *Candida* infections – Initial 12 week period (Pool A: Core placebo-controlled psoriasis trials – Safety set)**

| Level 1<br>Level 2<br>Preferred term | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Any AIN457 dose N=1382 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **Based on all AEs** | | | | | |
| Infections and infestations (SOC)* | 195 (28.3) | 203 (29.3) | 398 (28.80) | 134 (19.3) | 83 (25.7) |
| Candida infections (HLT) | 8 (1.2) | 3 (0.4) | 11 (0.80) | 2 (0.3) | 1 (0.3) |
| Oral candidiasis (PT) | 4 (0.6) | 1 (0.1) | 5 (0.36) | 1 (0.1) | 0 (0.0) |
| Vulvovaginal candidiasis (PT) | 1 (0.1) | 2 (0.3) | 3 (0.22) | 1 (0.1) | 0 (0.0) |
| Balanitis candida (PT) | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 0 (0.0) |
| Candidiasis (PT) | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 0 (0.0) |
| Esophageal candidiasis (PT) | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 0 (0.0) |
| Gastrointestinal candidiasis (PT) | 0 (0.0) | 0 (0.0) | 0 (0.00) | 0 (0.0) | 1 (0.3) |
| **Based on SAEs** | | | | | |
| Infections and infestations (SOC)* | 1 (0.1) | 1 (0.1) | 2 (0.14) | 2 (0.3) | 0 (0.0) |
| Candida infections (HLT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Risk levels are not mutually exclusive
HLT=high level term; PT=preferred term; SOC=system organ class
* Primary and secondary infections and infestations SOC

Preferred terms are sorted within risk level in descending order of frequency of the Any AIN457 dose column

**Table 5-28 Exposure-adjusted incidence of *Candida* infections – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

| Level 1<br>Level 2<br>Preferred term | Any AIN457 300 mg N=1410 n (IR) | Any AIN457 150 mg N=1395 n (IR) | Any AIN457 dose** N=3430 n (IR) | Placebo N=793 n (IR) | Etanercept N=323 n (IR) |
|---|---|---|---|---|---|
| **Based on all AEs** | | | | | |
| Infections and infestations (SOC) | 704 (91.06) | 653 (85.29) | 1640 (91.36) | 173 (101.89) | 172 (93.68) |
| Candida infections (HLT) | 41 (3.55) | 21 (1.85) | 69 (2.56) | 2 (1.00) | 4 (1.37) |
| Oral candidiasis (PT) | 22 (1.89) | 8 (0.70) | 32 (1.18) | 1 (0.50) | 0 (0.00) |
| Vulvovaginal candidiasis (PT) | 10 (0.85) | 4 (0.35) | 14 (0.51) | 1 (0.50) | 0 (0.00) |
| Candidiasis (PT) | 5 (0.43) | 4 (0.35) | 9 (0.33) | 0 (0.00) | 0 (0.00) |
| Skin candida (PT) | 1 (0.08) | 1 (0.09) | 5 (0.18) | 0 (0.00) | 1 (0.34) |
| Intertrigo candida | 1 (0.08) | 2 (0.18) | 4 (0.15) | 0 (0.00) | 1 (0.34) |
| Esophageal candidiasis (PT) | 3 (0.26) | 1 (0.09) | 4 (0.15) | 0 (0.00) | 0 (0.00) |
| Axillary candidiasis (PT) | 0 (0.00) | 1 (0.09) | 1 (0.04) | 0 (0.00) | 0 (0.00) |
| Balanitis candida (PT) | 1 (0.08) | 0 (0.00) | 1 (0.04) | 0 (0.00) | 0 (0.00) |
| Genital candidiasis (PT) | 0 (0.00) | 0 (0.00) | 1 (0.04) | 0 (0.00) | 1 (0.34) |
| Gastrointestinal candidiasis (PT) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.34) |
| Orophayngeal candidiasis (PT) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.34) |
| **Based on SAEs** | | | | | |
| Infections and infestations (SOC)* | 16 (1.36) | 12 (1.05) | 40 (1.47) | 2 (0.99) | 4 (1.37) |
| Candida infections (HLT) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |

Risk levels are not mutually exclusive
HLT=high level term; PT=preferred term; SOC=system organ class
* Primary and secondary infections and infestations SOC
**ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.
Preferred terms are sorted in descending order of frequency in the any AIN457 column
IR=incidence rate per 100 patient-years. For patients with event, exposure time is censored at time of first event.

Esophageal candidiasis has been reported in 5 patients, four in the clinical trial program (3 on 300 mg and 1 on 150 mg) and 1 additional case on 300 mg in the 4 month safety update. The diagnosis of esophageal candidiasis was made by endoscopy in one patient and not reported for the remaining four patients. Two of these cases were mild (both in the 300 mg dose group) and two were moderate (one each in the 150 mg and 300 mg dose groups) in severity. It is notable that one patient had a history of duodenal ulcer, active gastroesophageal reflux disease and esophagitis at baseline. The onset of symptoms in all cases started after 2-3 months of receiving secukinumab and were managed successfully with standard topical or oral antifungal treatment. None resulted in any interruption or discontinuation of study treatment.

The fifth case on 300 mg reported in the 4 month safety update was coded as serious due to hospitalization for unexplained weight loss, although the esophageal candidiasis itself was considered not severe by the attending physician. This patient was diabetic and reported pain with food intake resulting in hospitalization for weight loss 161 days after starting study medication. It is notable that on examination the patient was found to have pre-existing oral candida infection. As with the other cases, this patient was successfully managed with

standard antifungal treatment (in this case Ampho-moronal lozenges) and the subject did not require discontinuation and completely recovered.

#### 5.5.9.1.2 Opportunistic infections

A search for possible opportunistic infections in the original BLA yielded five candidiasis cases (four esophageal candidiasis cases on secukinumab, previously described, and 1 case of gastrointestinal candidiasis in an etanercept patient) and 1 case of cytomegalovirus gastroenteritis in a placebo patient. None of these infections were serious and, the exposure adjusted incidences rate over the entire 52-week treatment period across all the dose groups are comparable (0.26, 0.09, 0.50 and 0.34 per 100 patient-years for 300 mg, 150 mg, placebo and etanercept).

#### 5.5.9.1.3 Other infections

There was an increase of additional mucocutaneous, non-serious infections (tinea pedis and herpes with secukinumab and etanercept, respectively) compared with placebo. Exposure adjusted incidence rate of herpes viral infections was highest for etanercept at 3.81 per 100 patient-years vs. 3.28, 2.93 and 2.49, respectively for secukinumab 300 mg, 150 mg and placebo. Tinea pedis occurred with comparable exposure-adjusted rates between secukinumab and etanercept groups (2.0, 1.8, and 1.4, respectively for 300 mg, 150 mg and etanercept) and were not reported in the placebo group (which was generally only 12 weeks in duration). All of these infections were non-serious, generally mild to moderate in severity, responsive to treatment and did not require treatment discontinuation from secukinumab.

In the Phase III studies (A2302, A2303, A2304, A2308 and A2309), there were a total of 132 patients (27 with prior history, and 105 diagnosed at screening) with either a past medical history of tuberculosis (TB) or who tested positive for latent tuberculosis (LTBI) at screening and subsequently treated with secukinumab. None of these patients reverted to active TB during treatment with secukinumab suggesting a low risk for reactivation. Three patients with LTBI who were diagnosed at screening were started on anti-TB medications within 7 days of randomization. None of these patients had a reactivation of TB (Table 5-29).

**Table 5-29 Patients with latent tuberculosis**

| Study | Treatment | Preferred term | Started anti-TB med | Study drug related | Action taken | SAE / Discontinuation |
|---|---|---|---|---|---|---|
| A2304 | AIN457 150 mg SoR | Latent tuberculosis | Day 1 | No | Myrin plus (Day1-61)<br>Rifinah (Day 61-173) | No/No |
| A2303 | Etanercept | Latent tuberculosis | Day 7 | No | Rifinah (Day 7-49)<br>Isoniazid (Day49-56 EoS) | No/No |
| A2303 | Etanercept | Latent tuberculosis | Day 1 | No | Isoniazid (1-395) | No/No |

Patient identifiers remain confidential.
EoS=end of study; SoR=start of relapse

There were two cases of hepatitis B in the secukinumab 150 mg group reported in patients who both had negative viral screening at baseline. The viral markers in both patients were

consistent with acute infection. These findings indicate that the hepatitis B infection was newly acquired during the study. There were no cases of hepatitis B infection in the secukinumab 300 mg group. Both patients received treatment and were reported as having recovered.

Because hepatitis B is a highly infectious virus with established risk factors for acquisition, the observation of newly acquired HBV in one dose group suggests an imbalance in the risk factors for HBV acquisition rather than an increased susceptibility to hepatitis B per se. This is consistent with the observation that there were no cases of hepatitis B in the secukinumab 300 mg group and that both patients had an unremarkable clinical course and responded to regular treatment.

#### 5.5.9.2 Neutropenia

Reductions in peripheral neutrophil counts are a possible pharmacodynamic effect of systemic IL-17A blockade, based on roles of IL17A in innate immunity and neutrophil biology (Stark et al 2005, Medzhitov 2007, Weaver et al 2007).

In the psoriasis program, neutropenia was more frequently observed with secukinumab and etanercept than with placebo, but most cases were mild (limited to CTC Grade 1-2), transient and reversible. Of the few secukinumab cases meeting CTCAE Grade 3 criteria (< 1000/mm$^3$) 15/18 cases had no temporal relationship to infections. The remaining 3 cases had non-serious infections (rhinitis, upper respiratory tract infection, and cystitis) which did not cause study treatment discontinuation. The single CTCAE Grade 4 neutropenia was reported with etanercept.

Table 5-30 summarizes the incidences of newly occurring or worsening CTCAE grades of neutropenia occurring in the initial 12 week placebo-controlled period and over the entire treatment period.

The total incidence at any grade was highest with etanercept in both the initial 12 week placebo-controlled period (12.9%) and the entire treatment period (23.4%) compared with any secukinumab dose (9.0 % for initial 12 weeks in Pool A and 13.1% for entire treatment period in Pool B). The total incidence for the placebo group was lower (2.7%).

In total, there were 18 secukinumab psoriasis patients with Grade 3 neutropenia (Table 5-30). These patients were assessed in detail regarding neutrophil counts over time and infection risk. There was neither an apparent dose relationship nor time pattern for the occurrences.

For 14/18 (78%), the neutropenia was transient and reversible, lasting 1-2 visits and decreasing to a lower grade or to normal range at the next subsequent visit. Among the remaining four secukinumab patients, two recorded a Grade 3 value at the last assessment only and follow-up values were not available. One patient (from study A2303) on 300 mg secukinumab entered the study with Grade 1 neutropenia and developed Grade 3 neutropenia starting at Day 8 which persisted and led to study treatment discontinuation, but no infection AEs were reported for this patient. The remaining patient (placebo non-responder) developed Grade 3 neutropenia while on placebo treatment and the abnormality recurred after switching to 300 mg secukinumab.

Eight of the 18 patients with Grade 3 neutropenia also reported to have an infection, mostly mild to moderate and mainly upper respiratory tract infections. Three of these patients had an infection near the time (± 1-2 weeks) of the Grade 3 neutropenia event. The infections temporally associated with the Grade 3 neutropenia event in those 3 patients were all non-serious AEs (upper respiratory tract infection, rhinitis, and cystitis) and 2/3 resolved while on secukinumab treatment, with one rhinitis reported as ongoing at the time of database lock. The case of upper respiratory tract infection was reported 16 days after the patient's neutrophil count had returned to normal. No opportunistic infections were reported.

The exposure-adjusted rate per 100 patient-years over the entire treatment period for the adverse events of neutropenia, as reported by Investigators, was higher for etanercept than for secukinumab and placebo (1.4 for etanercept vs. 0.6 for any 300 mg, 0.8 for any 150 mg and 0 for placebo). Neutropenia reported as an AE led to study treatment discontinuation in 1 patient on each of the secukinumab doses (0.07% each for 300 mg and 150 mg) and 2 (0.6%) patients on etanercept vs. 0 patients on placebo over the entire treatment period.

**Table 5-30 Neutropenia: number (%) with newly occurring or worsening CTCAE grades – Pool A Initial 12 weeks and Pool B entire treatment period**

| Neutrophils (/mm$^3$) | AIN457 300 mg n/m (%) | AIN457 150 mg n/m (%) | Any AIN457 dose* n/m (%) | Placebo** n/m (%) | Etanercept n/m (%) |
|---|---|---|---|---|---|
| | **Pool A Initial 12 Weeks** | | | | |
| | **N=690** | **N=692** | **N=1382** | **N=694** | **N=323** |
| **< LLN – 1500/mm$^3$** | 51/677 (7.5) | 47/678 (6.9) | 98/1355 (7.23) | 16/682 (2.3) | 29/310 (9.4) |
| **< 1500 – 1000/mm$^3$** | 11/685 (1.6) | 12/686 (1.7) | 23/1371 (1.68) | 2/688 (0.3) | 10/317 (3.2) |
| **< 1000 – 500/mm$^3$** | 1/685 (0.1) | 0/687 (0.0) | 1/1372 (0.07) | 1/688 (0.1) | 0/318 (0.0) |
| **< 500/mm$^3$** | 0/685 (0.0) | 0/688 (0.0) | 0/1373 (0.00) | 0/690 (0.0) | 1/318 (0.3) |
| **Total % incidence** | 9.2 | 8.6 | 9.0 | 2.7 | 12.9 |
| | **Pool B Entire Treatment Period** | | | | |
| | **N=1410** | **N=1395** | **N=3430** | **-** | **N=323** |
| **< LLN – 1500/mm$^3$** | 145/1385 (10.5) | 153/1368 (11.2) | 340/3369 (10.1) | - | 53/310 (17.1) |
| **< 1500 – 1000/mm$^3$** | 34/1402 (2.4) | 38/1384 (2.8) | 85/3409 (2.5) | - | 19/317 (6.0) |
| **< 1000 – 500/mm$^3$** | 10/1403 (0.7) | 8/1385 (0.6) | 18/3411 (0.5) | - | 0/318 (0.0) |
| **< 500/mm$^3$** | 0/1404 (0.0) | 0/1387 (0.0) | 0/3414 (0.0) | - | 1/318 (0.3) |
| **Total % incidence** | 13.6 | 14.6 | 13.1 | | 23.4 |

LLN=lower limit of normal; n=Number of patients with most extreme value meeting the criterion post-baseline and that is newly occurring or worsening compared to baseline; m=Number of patients with evaluable criterion who were better than the criterion at baseline

*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

**Few placebo patients continued after 12 weeks

### 5.5.9.3 Malignancies

While an increased risk of solid malignancies including liver cancer, and esophagus and oral cavity cancer, has been reported in patients with psoriasis compared to the general population (Boffetta et al 2011), neutralization of IL-17A is not expected to affect key anti-tumor immune defense mechanisms (Th1-type responses, CTLs and NK cells). This is supported by the fact that secukinumab had no effect on immune function parameters (T cell dependent antibody responses (TDAR) or NK cell function) and did not induce signs of

lymphoproliferative disease at dose levels of up to 150 mg/kg within chronic monkey toxicology studies (see Section 3).

The overall incidence of malignant or unspecified tumors was similar between the secukinumab dose groups and placebo (0.1% for 300 mg and 0.4% for 150 mg vs. 0.4% for placebo), with no events reported for the etanercept group in Pool A. Exposure adjusted incidences for the entire treatment period showed a higher rate of malignancies per 100 patient-years for the placebo group compared with the active treatment groups (1.49 for placebo vs. 0.96 for any secukinumab dose and 0.68 for etanercept). There was no dose dependency (0.77 for any 300 mg vs. 0.97 for any 150 mg) (Table 5-31). The number of non-skin tumors was low, mostly in single event and no clusters were observed across treatment groups.

Among skin tumors, basal cell carcinoma was the most frequent type of tumor with secukinumab groups (0.37 per 100 patient-years), which was comparable with placebo (0.50) vs. no case in etanercept. No dose dependency in basal cell carcinoma with secukinumab was observed. Four cases of malignant melanoma (2 malignant melanoma, 2 malignant melanoma in situ) were reported with secukinumab compared with no cases in etanercept and placebo. All patients had one or more of the following risk factors: prior exposure to phototherapy, TNFα antagonists or methotrexate or pre-existing melanocytic nevus.

No increase in the ratio of squamous cell carcinoma to basal cell carcinoma was observed.

**Table 5-31 Exposure-adjusted incidence of the most frequent AEs (reported by ≥2 patients in any group) of malignant or unspecified tumors – Entire treatment period (Pool B: all psoriasis studies – Safety set)**

| | Any AIN457 300 mg N=1410 n (IR) (95%CI) | Any AIN457 150 mg N=1395 n (IR) (95%CI) | Any AIN457 dose* N=3430 n (IR) (95%CI) | Placebo N=793 n (IR) (95%CI) | Etanercept N=323 n (IR) (95%CI) |
|---|---|---|---|---|---|
| Based on all AEs | | | | | |
| Malignant or unspecified tumors (SMQ) | 9 (0.77) (0.35, 1.46) | 11 (0.97) (0.48, 1.73) | 26 (0.96) (0.63, 1.40) | 3 (1.49) (0.31, 4.36) | 2 (0.68) (0.08, 2.47) |
| Basal cell carcinoma (PT) | 4 (0.34) (0.09, 0.87) | 5 (0.44) (0.14, 1.02) | 10 (0.37) (0.18, 0.68) | 1 (0.50) (0.01, 2.77) | 0 (0.00) (0.00, 1.26) |
| Malignant melanoma (PT) | 1 (0.08) (0.00, 0.47) | 0 (0.00) (0.00, 0.32) | 2 (0.07) (0.01, 0.27) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Malignant melanoma in situ (PT) | 1 (0.08) (0.00, 0.47) | 1 (0.09) (0.00, 0.49) | 2 (0.07) (0.01, 0.27) | 0 (0.00) (0.00, 1.83) | 0 (0.00) (0.00, 1.26) |
| Squamous cell carcinoma (PT) | 1 (0.08) (0.00, 0.47) | 1 (0.09) (0.00, 0.49) | 2 (0.07) (0.01, 0.27) | 2 (0.99) (0.12, 3.59) | 0 (0.00) (0.00, 1.26) |

PT=preferred term; SMQ=standardized MedDRA query
Preferred terms are sorted in descending order of frequency in the any AIN457 column.
IR=incidence rate per 100 patient-years. For patients with event, exposure time is censored at time of first event.
*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

Exposure-adjusted incidences in the broad Pool C across all indications and all secukinumab doses were similar to that observed in Pool B.

### 5.5.9.4 Cardiovascular assessment

#### 5.5.9.4.1 Major adverse cardiac events (MACE)

All potential MACE cases in the secukinumab program were reviewed and adjudicated by an independent Cardiovascular and Cerebrovascular Safety Adjudication Committee (CCV-AC) in a blinded manner on a program-wide basis. A summary of all cases in Pool B are provided in Table 5-32.

Patients with psoriasis have an increased risk of MACE (defined as myocardial infarction, stroke and cardiovascular death) beyond that attributable to the known cardiovascular risk factors (Gelfand et al 2006; Gelfand et al 2009; Mehta et al 2010). The incidence of MACE events in patients with psoriasis has been reported as 1.64 per 100 patient-years (range 1.43-1.89) in the literature (Mehta et al 2011). The observed exposure adjusted incidence of MACE was lower in the secukinumab clinical trials in psoriasis across all arms (range: 0.34-0.51 per 100 patient-years).

Potential MACE cases over the entire treatment period were reported for similar proportions of patients on secukinumab and etanercept: 6 (0.4%) for 300 mg, 5 (0.4%) for 150 mg and 1 (0.3%) for etanercept vs. 1 (0.1%) for placebo. These similar incidences between etanercept and secukinumab over essentially similar treatment durations are despite large baseline numerical imbalances in cardiovascular risk factors (Table 5-33), with higher numbers in the secukinumab groups than either placebo or etanercept groups.

After adjusting for exposure over the 52-week treatment period, secukinumab at both doses (IR=0.51 for 300 mg and 0.44 for 150 mg) was comparable to placebo and etanercept (IR=0.50 for placebo and 0.34 for etanercept). There was no dose dependence for secukinumab. The exposure-adjusted incidence of potential MACE AEs over the entire treatment period of all secukinumab trials (Pool C) was comparable between any secukinumab dose and placebo (0.42 vs. 0.59 per 100 patient-years). All cases had prior or active cardiovascular disease or relevant risk factor.

**Table 5-32 Overview of psoriasis patients with MACE – Entire treatment period (Pool B: all psoriasis trials – Safety set)**

| Study | Preferred term | SAE | Adjudication outcome | Medical history / Relevant risk factors |
|---|---|---|---|---|
| **Any AIN457 300 mg** | | | | |
| A2302 | Myocardial infarction | Yes | Myocardial infarction | Impaired glucose tolerance, dyslipidemia, obesity |
| A2304 | Acute myocardial infarction | Yes | Myocardial infarction | Prior stroke of unknown type, prior ischemic stroke, syncope, hypertension, hyperlipidemia, cardiac failure, congestive and atherosclerotic conditions including carotid artery stenosis and stable coronary artery disease, cardiac murmur, atrial fibrillation |
| A2308 | Acute myocardial infarction | Yes | Myocardial infarction | Dyslipidemia, hypertension, diabetes, obesity |
| A2308 | Cerebrovascular accident | Yes | Ischemic stroke | Stable coronary artery disease, prior myocardial infarction, coronary arterial stent insertion, percutaneous transluminal coronary angioplasty, prior transient ischemic attack |
| A2302 | Cerebrovascular accident | Yes | Ischemic stroke | The stroke was caused by a blood clot formed after a carotid artery dissection for a pseudoaneurysm |
| A2304 | Myocardial infarction | No | Not confirmed | Current smoker |
| **Any AIN457 150 mg** | | | | |
| A2302 | Ischemic stroke | Yes | Ischemic stroke | Stable coronary artery disease, dyslipidemia and uncomplicated diabetes |
| A2303 | Cerebrovascular accident | Yes | Ischemic stroke | Prior myocardial infarction, atrial f brillation, supraventricular tachycardia, hypertension, hyperlipidemia, stable coronary artery disease, atherosclerosis |
| A2303 | Myocardial infarction | Yes | Myocardial infarction | Uncomplicated diabetes, hypertension |
| A2304 | Hemorrhagic stroke | Yes | Stroke unspecified / Cardiovascular death | High blood levels of glucose and hsCRP at randomization |
| A2302 | Moyamoya disease | No | Not confirmed | Prior transient ischemic attack |
| A2211 | Myocardial infarction | No | Myocardial infarction | Current smoker (47 years) |
| **Placebo** | | | | |
| A2211 | Brain stem hemorrhage | No | Hemorrhagic stroke | Hypertension, current smoker |
| **Etanercept** | | | | |
| A2303 | Myocardial infarction | Yes | Myocardial infarction | Hypertension, depression |

Patient identifiers remain confidential.
* Alternative AIN457 150 mg regimen: loading dose at Weeks 1, 2, 3, and 5, followed by AIN457 150 mg q4w.

**Table 5-33 Medical history of cardiovascular risk factors in all phase III psoriasis studies (initial treatment assignment)**

| Medical history | AIN457 300 mg N=1173 % (n) | AIN457 150 mg N=1174 % (n) | Etanercept N=323 % (n) | Placebo N=694 % (n) |
|---|---|---|---|---|
| Hypertension* | 26.5% (311) | 29.8% (350) | 20.7% (67) | 21.9% (152) |
| Dyslipidemia/ hyperlipidemia* | 16.8% (197) | 16.0% (188) | 12.4% (40) | 13.8% (96) |
| Complicated diabetes* | 0.3% (4) | 0.3% (3) | 0.3% (1) | 0.3% (2) |
| Stable Coronary Artery Disease* | 2.2% (26) | 2.6% (31) | 0.9% (3) | 1.4% (10) |
| Myocardial infarction | 2.2% (26) | 1.4% (16) | 1.5% (5) | 1.7% (12) |
| Uncomplicated Diabetes Mellitus* | 9.0% (105) | 9.4% (110) | 8.0% (26) | 6.9% (48) |

*ongoing at the start of the study

### 5.5.9.4.2 Cardiovascular and cerebrovascular (CCV) events

Given the association between psoriasis and increased rates of cardiovascular disease and cardiovascular mortality, the evaluation of cardiovascular risk in patients with psoriasis was expanded to include events beyond myocardial infarction and stroke.

CCV events were identified using the following search terms:

- Myocardial infarction
- Central nervous system (CNS) hemorrhages and cerebrovascular conditions
- Cardiac failure
- Peripheral revascularization procedures (standard NMQ)
- Cardiac arrhythmia terms, non-specific (narrow SMQ)
- Ischemic cerebrovascular conditions (broad SMQ)
- Conduction defects (narrow SMQ)
- Other ischemic heart disease (narrow SMQ)
- Supraventricular tachyarrhythmias (narrow SMQ)
- Tachyarrhythmia terms, nonspecific (narrow SMQ)
- Ventricular tachyarrhythmias (narrow SMQ)

CCV events by NMQ were lower in the secukinumab dose groups (0.4% for 300 mg, 1.0% for 150 mg) compared with the placebo and etanercept groups (1.6% and 1.9%, respectively) in Pool A. Pool B exposure-adjusted incidences over 52 weeks (3.27 for 300 mg, 2.65 for 150 mg, 6.54 for placebo, 4.86 for etanercept per 100 patient-years). There was no difference in the total incidence of CCV SAEs per 100 patient-years (0.9 for 300 mg vs. 1.1 for 150 mg, with 0.5 for placebo and 1.0 for etanercept).

#### 5.5.9.4.3 QTc findings on ECG

Consistent with the targeted mechanism of action of secukinumab, no clinically significant effects on cardiac conduction were observed. Few patients experienced clinically relevant changes in ECGs or vital signs, and these events occurred at a comparable incidence for all treatment groups.

There were two secukinumab patients who had a QTcB>500 msec during the entire treatment period. Both had relatively high baseline QTcB/QTcF. The first, in the 300 mg group, was a 45-year old Asian male who entered the study with congestive cardiac failure and a baseline QTcB/QTcF reading of 489/479 msec. At Day 85 (Week 12) his QTcB/QTcF was 509/504 msec and remained >450 msec throughout the maintenance period up to Week 52. No AEs in the cardiac disorders SOC were reported for this patient.

The second patient who was in the 150 mg group was a 50-year-old Asian female with a history of ongoing hypertension. Her baseline QTcB/QTcF = 492/476 msec. At Day 85 (Week 12), her QTcB/QTcF was 504/481 msec, decreasing thereafter and remained >450 msec throughout the maintenance period (while the patient continued dosing) up to Week 52 (487/467 msec). The QTcB prolongation event was not reported as an AE and no AEs in the cardiac disorders SOC were reported for this patient.

Overall, the incidence of QTc prolongation was low and comparable across the treatment groups. No cases of Torsade de pointes/QT prolongation were reported as an AE in the entire treatment period of Pool B.

### 5.5.9.5 Administration and immune reactions

A search for administration or immune reactions, including administration site reactions, allergic reactions, anaphylaxis and anaphylactic reactions, immunogenicity, angioedema, severe cutaneous adverse reactions and autoimmune disorders was performed. The most frequent adverse events in the initial 12 week placebo controlled data are shown in Table 5-34.

Hypersensitivity AEs were reported in a higher proportion of patients in the secukinumab and etanercept dose groups compared with placebo. Urticaria was most frequently reported with secukinumab without an apparent dose relation in the initial 12 weeks. Cases of urticaria were non-serious, mostly mild to moderate in severity and not accompanied by other severe hypersensitivity-related adverse events. Injection site reactions, including erythema, pruritus, swelling and pain were most commonly reported with etanercept. Comparable proportions of secukinumab patients reported administration reactions as those with placebo.

**Table 5-34 Most frequent AEs (≥0.6% in any group) of administration and immune reactions – Initial 12 week period (Pool A: Core placebo-controlled psoriasis studies – Safety set)**

| Level 1<br>Preferred term | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Any AIN457 dose N=1382 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **Based on all AEs** | | | | | |
| Hypersensitivity (narrow SMQ) | 31 (4.5) | 31 (4.5) | 62 (4.49) | 9 (1.3) | 15 (4.6) |
| Urticaria (PT) | 4 (0.6) | 8 (1.2) | 12 (0.87) | 1 (0.1) | 2 (0.6) |
| Eczema (PT) | 6 (0.9) | 4 (0.6) | 10 (0.72) | 1 (0.1) | 1 (0.3) |
| Dermatitis contact (PT) | 4 (0.6) | 3 (0.4) | 7 (0.51) | 2 (0.3) | 2 (0.6) |
| Injection site urticaria (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.6) |
| Immune/administration reactions (NMQ) | 98 (14.2) | 85 (12.3) | 183 (13.24) | 82 (11.8) | 59 (18.3) |
| Pruritus (PT) | 23 (3.3) | 21 (3.0) | 44 (3.18) | 18 (2.6) | 8 (2.5) |
| Cough (PT) | 19 (2.8) | 9 (1.3) | 28 (2.03) | 9 (1.3) | 4 (1.2) |
| Psoriasis (PT) | 4 (0.6) | 10 (1.4) | 14 (1.01) | 20 (2.9) | 2 (0.6) |
| Urticaria (PT) | 4 (0.6) | 8 (1.2) | 12 (0.87) | 1 (0.1) | 2 (0.6) |
| Edema peripheral (PT) | 5 (0.7) | 7 (1.0) | 12 (0.87) | 8 (1.2) | 2 (0.6) |
| Pruritus generalized (PT) | 7 (1.0) | 4 (0.6) | 11 (0.80) | 2 (0.3) | 2 (0.6) |
| Dermatitis contact (PT) | 4 (0.6) | 3 (0.4) | 7 (0.51) | 2 (0.3) | 2 (0.6) |
| Conjunctivitis (PT) | 5 (0.7) | 2 (0.3) | 7 (0.51) | 1 (0.1) | 0 (0.0) |
| Erythema (PT) | 3 (0.4) | 3 (0.4) | 6 (0.43) | 3 (0.4) | 3 (0.9) |
| Injection site pain (PT) | 1 (0.1) | 4 (0.6) | 5 (0.36) | 1 (0.1) | 3 (0.9) |
| Psoriatic arthopathy (PT) | 2 (0.3) | 2 (0.3) | 4 (0.29) | 4 (0.6) | 0 (0.0) |
| Injection site erythema (PT) | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 16 (5.0) |
| Injection site rash (PT) | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 2 (0.6) |
| Injection site swelling (PT) | 1 (0.1) | 0 (0.0) | 1 (0.07) | 0 (0.0) | 4 (1.2) |
| Injection site urticaria (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.6) |
| Injection site infection (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.6) |
| Injection site reaction (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (1.9) |
| Injection site pruritus (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (1.5) |

NMQ=Novartis MedDRA query; PT=preferred term; SMQ=standardized MedDRA query
Preferred terms are sorted in descending order of frequency in the any AIN457 column

Most of the events mapping to the hypersensitivity and immune/administration reactions search were non-serious. The overall incidence of serious immune/administration reactions was higher in the placebo group compared to the active treatment groups (0.6% for placebo vs. 0.1%, 0.1% and 0%, respectively, for 300 mg, 150 mg and etanercept), mainly due to psoriasis SAEs in the placebo group (n=3, 0.4%) which were not reported in the active treatment groups (Table 5-35). The SAEs in the secukinumab dose groups were reported in not more than 1 (0.1%) patient each.

**Table 5-35 SAEs of administration and immune reactions – Initial 12 week period (Pool A: Core placebo-controlled psoriasis studies – Safety set)**

| Level 1<br>Preferred term | AIN457 300 mg N=690 n (%) | AIN457 150 mg N=692 n (%) | Any AIN457 dose N=1382 n (%) | Placebo N=694 n (%) | Etanercept N=323 n (%) |
|---|---|---|---|---|---|
| **Based on all SAEs** | | | | | |
| Hypersensitivity (narrow SMQ) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| Dermatitis exfoliative (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| Immune/administration reactions (NMQ) | 1 (0.1) | 1 (0.1) | 2 (0.14) | 4 (0.6) | 0 (0.0) |
| Dermatitis exfoliative (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) |
| Psoriasis (PT) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.4) | 0 (0.0) |

NMQ=Novartis MedDRA query; PT=preferred term; SMQ=standardized MedDRA query
Preferred terms are sorted in descending order of frequency in the any AIN457 column

During the placebo-controlled initial 12 week period, severe hypersensitivity events occurred at low and similar rates across the secukinumab and placebo groups, but were not reported in the etanercept group (0.4%, 0.3%, 0.4% and 0%, respectively, for 300 mg, 150 mg, placebo and etanercept). Severe immune/administration reactions occurred with comparable frequency among the secukinumab and placebo groups, which were higher than the etanercept group (1.6%, 1.3%, 2.2%, and 0.3%, respectively). Angioedemas occurred at similar rates for secukinumab and placebo.

Exposure-adjusted rates of the most frequently occurring AEs related to hypersensitivity and immune/administration reactions over the entire treatment period of all psoriasis trials (Pool B) are presented in Table 5-36. The profile observed in the entire treatment period was consistent with that noted for Pool A.

**Table 5-36 Exposure-adjusted incidence of the most frequent AEs (≥1.0 per 100 patient-years in any group) of hypersensitivity and immune/ administration reactions – Entire treatment period (Pool B: all psoriasis studies – Safety set)**

| Level 1<br>Preferred term | Any AIN457 300 mg N=1410 n (IR) | Any AIN457 150 mg N=1395 n (IR) | Any AIN457 dose* N=3430 n (IR) | Placebo N=793 n (IR) | Etanercept N=323 n (IR) |
|---|---|---|---|---|---|
| **Based on all AEs** | | | | | |
| Hypersensitivity (narrow SMQ) | 132 (11.94) | 115 (10.70) | 287 (11.17) | 9 (4.50) | 27 (9.73) |
| Eczema (PT) | 37 (3.19) | 23 (2.04) | 66 (2.45) | 1 (0.50) | 2 (0.68) |
| Urticaria (PT) | 20 (1.71) | 25 (2.22) | 50 (1.85) | 1 (0.50) | 3 (1.03) |
| Dermatitis contact (PT) | 23 (1.97) | 16 (1.41) | 47 (1.74) | 2 (0.99) | 5 (1.72) |
| Dermatitis (PT) | 14 (1.20) | 10 (0.88) | 28 (1.03) | 0 (0.00) | 3 (1.03) |
| Rhinitis allergic (PT) | 12 (1.03) | 10 (0.88) | 25 (0.92) | 0 (0.00) | 3 (1.03) |
| Immune/administration reactions (NMQ) | 318 (32.12) | 292 (30.16) | 782 (34.20) | 105 (57.65) | 95 (40.57) |
| Pruritus (PT) | 54 (4.73) | 66 (6.01) | 135 (5.12) | 21 (10.65) | 16 (5.68) |
| Cough (PT) | 70 (6.14) | 44 (3.93) | 133 (5.01) | 13 (6.55) | 12 (4.17) |
| Psoriasis (PT) | 31 (2.66) | 22 (1.94) | 123 (4.59) | 28 (14.22) | 7 (2.41) |
| Urticaria (PT) | 20 (1.71) | 25 (2.22) | 50 (1.85) | 1 (0.50) | 3 (1.03) |
| Edema peripheral (PT) | 15 (1.28) | 20 (1.77) | 49 (1.82) | 9 (4.51) | 6 (2.07) |
| Dermatitis contact (PT) | 23 (1.97) | 16 (1.41) | 47 (1.74) | 2 (0.99) | 5 (1.72) |
| Conjunctivitis (PT) | 23 (1.97) | 13 (1.14) | 44 (1.63) | 1 (0.50) | 3 (1.02) |
| Pruritus generalized (PT) | 15 (1.29) | 14 (1.24) | 41 (1.52) | 5 (2.50) | 3 (1.03) |
| Injection site pain (PT) | 12 (1.03) | 8 (0.70) | 25 (0.92) | 1 (0.50) | 4 (1.38) |
| Rhinitis allergic (PT) | 12 (1.03) | 10 (0.88) | 25 (0.92) | 0 (0.00) | 3 (1.03) |
| Seasonal allergy (PT) | 11 (0.94) | 6 (0.53) | 22 (0.81) | 1 (0.50) | 3 (1.03) |
| Erythema (PT) | 10 (0.85) | 7 (0.62) | 17 (0.63) | 3 (1.49) | 3 (1.03) |
| Injection site hematoma (PT) | 3 (0.26) | 2 (0.18) | 7 (0.26) | 2 (1.00) | 0 (0.00) |
| Injection site erythema (PT) | 2 (0.17) | 2 (0.18) | 5 (0.18) | 0 (0.00) | 17 (6.05) |
| Hypotension (PT) | 1 (0.08) | 2 (0.18) | 4 (0.15) | 2 (1.00) | 0 (0.00) |
| Injection site swelling (PT) | 1 (0.08) | 1 (0.09) | 4 (0.15) | 0 (0.00) | 4 (1.38) |
| Injection site reaction (PT) | 1 (0.09) | 1 (0.09) | 2 (0.07) | 0 (0.00) | 6 (2.08) |
| Injection site pruritus (PT) | 1 (0.08) | 1 (0.09) | 2 (0.07) | 0 (0.00) | 6 (2.08) |

NMQ=Novartis MedDRA query; PT=preferred term; SMQ=standardized MedDRA query
Preferred terms are sorted in descending order of frequency in the any AIN457 column
IR=incidence rate per 100 patient-years. For patients with event, exposure time is censored at time of first event.
*ANY AIN457 dose includes doses other than 150 and 300 mg in Pool B.

A higher incidence per 100 patient-years of hypersensitivity AEs was noted for secukinumab and etanercept compared with placebo (11.9 for any 300 mg, 10.7 for any 150 mg and 9.7 for etanercept vs. 4.5 for placebo). This difference vs. placebo was due, in part, to urticaria, an identified adverse reaction, as well as eczema, dermatitis, contact dermatitis and allergic rhinitis. No clear pattern of dose dependence was observed for secukinumab, although a slightly higher incidence of eczema adverse events were observed with 300 mg (3.2%) compared with 150 mg (2.0%) over the entire treatment period. In addition, the adverse event preferred terms (MedDRA) of eczema and dermatitis were not considered reflective of an

increased risk in a defined dermatologic process as these are non-specific terms that cover a diverse collection of skin diseases with different underlying pathophysiologies.

Of 54 cases of urticaria two, one with 300 mg secukinumab and one with placebo, were reported as severe. The severe case on 300 mg also led to discontinuation of study treatment; no other cases of urticaria caused discontinuation. The severe case on placebo was associated with angioedema and led to an interruption of dosing. Fifteen of 54 patients developed urticaria within 2 days of study treatment dosing [13/50 (26%) on secukinumab and 2/3 (67%) on etanercept], suggesting that the majority of the urticaria cases on secukinumab were not immediately linked to secukinumab administration. Three cases, two with secukinumab and the one with placebo described above, were accompanied by concurrent angioedema, with a time-to-onset of urticaria from 1 to 7 days from the most recent dose of study treatment. No action was taken with study treatment in the two secukinumab treated patients, who both continued dosing throughout the maintenance period with no recurrence of urticaria or angioedema. The limited number of angioedema events arising in those patients who experience urticaria and the absence of recurrence upon continued dosing with secukinumab suggest that these urticaria events are idiosyncratic and not associated with an overall serious drug allergy that might be associated with anaphylaxis. Angioedema overall was reported less frequently per 100 patient-years for secukinumab and etanercept compared with placebo (0.11 and 0 for any secukinumab dose and etanercept vs. 0.5 for placebo).

There were no investigational product related reports of anaphylactic reaction in the psoriasis program. There has been one anaphylactic reaction reported for a secukinumab patient during the administration of the first dose of 10 mg/kg i.v. secukinumab for ankylosing spondylitis. Signs and symptoms developed within an hour of infusion start on Day 1, including generalized hives, lip edema and shortness of breath that required treatment with high-dose intravenous corticosteroids. The patient recovered fully from this event the next day (Day 2). The occurrence of this event during the administration of secukinumab suggests a causal relationship between the anaphylactic reaction and study drug administration. In study A2304, which evaluated the regimen allowing patients to halt treatment until needed with relapse, there was no increase in hypersensitivity or immune/administration reactions in patients who were randomized to this 'Treatment as needed' maintenance dosing. The incidence per 100 patient-years of hypersensitivity AEs in these 'Treatment as needed' dosing groups was lower than that reported for the 4-week fixed interval dosing groups (300 mg SoR=9.5 and 150 mg SoR=8.5 vs. 300 mg FI=13.1 and 150 mg FI=11.4). Similar results were reported for immune/administration reactions (300 mg SoR=25.3 and 150 mg SoR=29.7 vs. 300 mg FI=33.2 and 150 mg FI=36.1).

The studies evaluating PFS and AI forms of secukinumab administration (Studies A2308 and A2309) showed no new or unexpected administration and immune reactions compared to the profile seen in studies using LYO (e.g. Studies A2302 and A2303).

#### 5.5.9.6 Autoimmune disorders

There was no increased risk of autoimmune disorders.

A broad search for autoimmune disorders, including nearly 250 terms, was performed within the clinical psoriasis program. The search yielded a higher overall incidence for placebo vs.

secukinumab and etanercept in all treatment periods of Pools A and B for AE's as well as SAE's. The higher incidence for placebo was primarily due to psoriasis reported as an AE/ SAE.

Other SAEs in the autoimmune disorders search, reported for secukinumab at any dose, included ulcerative colitis (n=3, IR=0.11), Crohn's disease (n=3, IR=0.11), granulomatosis with polyangiitis (n=1, IR=0.04), multiple sclerosis (n=1, IR=0.04) and pemphigus (n=1, IR=0.04). For etanercept, the 2 SAEs in the autoimmune disorders were interstitial lung disease (n=1, IR=0.34) and psoriatic arthropathy (n=1, IR=0.34)

No events of central nervous system (CNS) demyelination were identified. The single SAE of multiple sclerosis, reported for 1 secukinumab patient in the 150 mg group was in a patient with a long-standing history (16 years) of multiple sclerosis.

#### 5.5.9.7 Crohn's disease

Crohn's disease is considered to be an immune-mediated disease, like psoriasis, and is characterized by chronic intestinal inflammation. The incidence of Crohn's disease among psoriasis patients is about 4 times higher than that in control cohorts (Li et al 2013). The pathogenesis of both diseases is believed to be associated with IL-17-producing T cells (Skroza et al 2013). The therapeutic benefits of treating psoriasis and Crohn's disease with TNF-α antagonists reinforce the current understanding of a possible common pathophysiological pathway for both diseases. Therefore, compounds that target the IL-17 pathway have been studied for treating both psoriasis and Crohn's disease. However, the published data have been disappointing regarding the efficacy of targeting IL-17A for patients with Crohn's disease (Hueber et al 2012; Targan et al 2012).

The exposure-adjusted incidence of inflammatory bowel disease per 100 patient-years in Pool B over the entire treatment period was similar between 300 mg and 150 mg secukinumab and etanercept (0.26, 0.35 and 0.34, respectively).

A total of 3 cases of Crohn's disease were reported (all on 150 mg secukinumab). Two were considered flare of existing disease in patients with prior history of Crohn's disease and 1 was a new event occurring in a patient with symptoms at baseline suggestive of possible active undiagnosed Crohn's disease. All 3 events were SAEs. Of the 2 cases with flare, one resolved with treatment, one was ongoing at the time of reporting, and both led to discontinuation of secukinumab. The new event resolved with treatment and did not cause study drug discontinuation. No cases of Crohn's disease were reported for 300 mg secukinumab, placebo and etanercept.

These data do not suggest a causal relationship between secukinumab treatment and exacerbation of Crohn's disease. However, due to the potential involvement of the IL-17 pathway in the pathogenesis, it is not possible to rule out the potential of increased risk of an exacerbation of Crohn's disease. Because of this, exacerbation of Crohn's disease is included as a potential risk in the risk minimization activities for routine pharmacovigilence post-marketing.

### 5.5.10 Hematology

Newly occurring or worsening hematology parameters occurring during the first 12 weeks of the placebo controlled trials (Pool A) are shown in Table 5-37. See Appendix 2 for CTCAE laboratory parameters.

The majority of newly occurring or worsening hematology abnormalities were CTCAE Grade 1 or 2. For leukocytes, neutrophils and platelets, these were more frequently reported in the secukinumab and etanercept groups compared with placebo. These grade 1 or 2 abnormalities did not necessitate withholding or discontinuing therapy. There was no clinically meaningful difference between secukinumab and etanercept. Neutropenia is discussed in greater detail in Section 5.5.9.2.

**Table 5-37 Hematology: Number (%) of patients with newly occurring or worsening CTCAE grades – Initial 12 week period (Pool A: Core placebo-controlled psoriasis trials – Safety set)**

| Criterion | AIN457 300 mg N=690 n/m (%) | AIN457 150 mg N=692 n/m (%) | Any AIN457 dose N=1382 n/m (%) | Placebo N=694 n/m (%) | Etanercept N=323 n/m (%) |
|---|---|---|---|---|---|
| **Hemoglobin (g/dL)** | | | | | |
| < LLN – 10.0 g/dL | 23/655 (3.5) | 28/657 (4.3) | 51/1312 (3.89) | 40/659 (6.1) | 9/309 (2.9) |
| < 10.0 – 8.0 g/dL | 4/685 (0.6) | 3/686 (0.4) | 7/1371 (0.51) | 6/691 (0.9) | 0/318 (0.0) |
| **Leukocytes (/mm$^3$)** | | | | | |
| < LLN – 3000/mm$^3$ | 54/671 (8.0) | 45/672 (6.7) | 99/1343 (7.37) | 22/677 (3.2) | 18/305 (5.9) |
| < 3000 – 2000/mm$^3$ | 3/684 (0.4) | 3/686 (0.4) | 6/1370 (0.44) | 2/690 (0.3) | 7/317 (2.2) |
| < 2000 – 1000/mm$^3$ | 1/685 (0.1) | 0/688 (0.0) | 1/1373 (0.07) | 0/691 (0.0) | 0/318 (0.0) |
| **Lymphocytes (absolute) (/mm$^3$)** | | | | | |
| < LLN – 800/mm$^3$ | 30/651 (4.6) | 34/654 (5.2) | 64/1305 (4.90) | 50/658 (7.6) | 8/299 (2.7) |
| < 800 – 500/mm$^3$ | 11/675 (1.6) | 15/675 (2.2) | 26/1350 (1.93) | 9/685 (1.3) | 4/313 (1.3) |
| < 500 – 200/mm$^3$ | 0/685 (0.0) | 2/686 (0.3) | 2/1371 (0.15) | 1/690 (0.1) | 0/318 (0.0) |
| **Neutrophils (absolute) (/mm$^3$)** | | | | | |
| < LLN – 1500/mm$^3$ | 51/677 (7.5) | 47/678 (6.9) | 98/1355 (7.23) | 16/682 (2.3) | 29/310 (9.4) |
| < 1500 – 1000/mm$^3$ | 11/685 (1.6) | 12/686 (1.7) | 23/1371 (1.68) | 2/688 (0.3) | 10/317 (3.2) |
| < 1000 – 500/mm$^3$ | 1/685 (0.1) | 0/687 (0.0) | 1/1372 (0.07) | 1/688 (0.1) | 0/318 (0.0) |
| < 500/mm$^3$ | 0/685 (0.0) | 0/688 (0.0) | 0/1373 (0.00) | 0/690 (0.0) | 1/318 (0.3) |
| **Platelets (/mm$^3$)** | | | | | |
| < LLN – 75,000/mm$^3$ | 16/665 (2.4) | 27/672 (4.0) | 43/1337 (3.22) | 12/672 (1.8) | 12/312 (3.8) |
| < 75,000 – 50,000/mm$^3$ | 0/682 (0.0) | 2/686 (0.3) | 2/1368 (0.15) | 1/691 (0.1) | 1/317 (0.3) |
| < 50,000 – 25,000/mm$^3$ | 0/682 (0.0) | 1/686 (0.1) | 1/1368 (0.07) | 0/691 (0.0) | 0/317 (0.0) |

LLN=lower limit of normal
n=Number of patients with most extreme value meeting the criterion post-baseline and that is newly occurring or worsening compared to baseline
m=Number of patients with evaluable criterion who were better than the criterion at baseline

There is no clinical evidence of any general impact on bone marrow. Grade 1 or 2 abnormalities in hemoglobin and grade 1 abnormalities in absolute lymphocytes were more common with placebo than with secukinumab and etanercept.

None of the parameters, including neutrophils, suggest dose-related increases in CTCAE Grade 3 abnormalities with secukinumab. The only Grade 4 abnormality (neutropenia) occurred with an etanercept patient.

### 5.5.11 Clinical chemistry

Most newly occurring or worsening abnormalities in clinical chemistry parameters were CTCAE Grade 1 or 2. Over the entire period in psoriasis patients (Pool B), there was no dose response relationship apparent for the secukinumab groups. Patterns from the initial 12 week placebo controlled portion (Pool A) were similar to those observed for the entire treatment period. The incidence of abnormalities in liver function tests and lipids were generally comparable to those observed with etanercept. For serum creatinine, there was a slightly higher incidence of grade 1 abnormalities with secukinumab, which were transient and reversible.

#### 5.5.11.1 Liver function tests

There were no unconfounded Hy's law cases reflecting drug induced liver injury (DILI) with secukinumab. Laboratory Hy's Law criteria were met for three secukinumab patients in all psoriasis trials (Pool B); all with alternative causative etiologies (alcoholic hepatitis, cholecystitis, acetaminophen use) or showed normalized values upon continued exposure to secukinumab. The available safety data do not suggest the potential for severe drug-induced liver injury (DILI) from secukinumab treatment.

For liver function parameters in Pool A, the incidence of liver enzyme elevations was generally low and comparable among treatment groups. While a numerically higher proportion of elevations in ALT or AST >5×ULN was noted with 150 mg secukinumab vs. placebo, there was no dose response for secukinumab and rates were comparable to etanercept (0.3%, 0.9%, 0.3%, and 0.9%, respectively, for 300 mg, 150 mg, placebo, and etanercept).

Combined elevations in ALT or AST >3×ULN and TBL >2×ULN in Pool A were observed in 1 (0.1%) patient on 150 mg secukinumab and 1 (0.1%) placebo patient. No further cases were reported in Pool B.

In Pool A, combined abnormalities of ALT or AST >3×ULN with TBL >2×ULN and ALP <2×ULN (Hy's Law laboratory criteria) were reported in 1 (0.1%) patient on 150 mg secukinumab and 1 (0.1%) patient on placebo. Both cases were not reported as an AE nor were there any other clinical symptoms. The abnormal values normalized by the next visit for the placebo patient, while the patient on 150 mg had a long-standing history of excessive alcohol consumption (since year 2000), with elevations in ALT (Grade 1), AST (Grade 1), and GGT (Grade 2) at baseline and reported a 10-day course of acamprosate taken for alcohol withdrawal as a concomitant medication, prior to developing these combined liver enzyme elevations. One further secukinumab 150 mg patient met these criteria in Pool B over 52 weeks: elevations in ALT (>10×ULN), AST (>5×ULN), TBL (>2×ULN), and ALP (<2×ULN) occurred in this patient at Week 44 during the maintenance period and were reported by the investigator as non-serious AEs related to study treatment. Sixteen days prior, this patient had taken two different non-prescription cold preparations both containing acetaminophen for 5 days. By the next visit (Week 48) ALT, AST, TBL and ALP levels were all decreased and the patient received the next scheduled dose of secukinumab after a 1-week delay. All values had

returned to normal limits by Week 52 with continued treatment. A secukinumab 300 mg patient with SAEs of cholecystitis and hepatitis met these laboratory criteria based on local laboratory results: the hepatic enzyme elevations in this patient were temporally associated with the radiographically-confirmed concurrent cholecystitis and, therefore, did not represent drug-induced liver injury. The events resolved concurrently with treatment. Thus, the 3 secukinumab patients identified in the entire treatment period across all psoriasis trials (Pool B) as meeting Hy's Law laboratory criteria had alternative causative etiologies (alcoholic hepatitis, cholecystitis, acetaminophen use) or showed normalized values upon re-exposure to secukinumab, that indicate these were not true Hy's Law cases and do not reflect true DILI and are, therefore, not predictive of severe DILI cases developing in the post-marketing setting.

#### 5.5.11.2 Creatinine

In Pool A, Grade 1 (>ULN - 1.5 x ULN) elevations in creatinine were slightly more frequent with secukinumab 300 mg and 150 mg than with placebo or etanercept (5.9% and 5.2% vs. 4.0% and 2.9%), whilst Grade 2 (>1.5 - 3.0 x ULN) elevations showed no clinically meaningful differences between the treatment groups (0.3%, 0.3%, 0.1% and 0%, respectively, for 300 mg, 150 mg, placebo and etanercept). None led to treatment discontinuation. A similar pattern was seen for Pool B over 52 weeks.

### 5.5.12 Immunogenicity

Secukinumab-specific anti-drug antibodies (ADA) and neutralizing antibodies were assessed in all Phase III trials and in a long-term Phase II extension trial (A2211E1) using a sensitive, common assay procedure. Samples in Phase III studies were evaluated for ADA at baseline and immediately before dosing at Weeks 12, 24, and 52 (4 weeks after the last dose) using the Meso Scale Discovery (MSD) bridging assay, with a stepwise approach for screening, confirmation, and titration. All treatment groups were evaluated for secukinumab-specific ADA, including placebo and etanercept groups.

The sensitivity of the ADA assay was 4 ng/mL with a drug tolerance threshold of 53.8 µg/mL defined by a positive control antibody. Steady-state serum concentrations of secukinumab were generally below the quoted level of drug tolerance in nearly all Week 24 and 52 samples tested. Confirmed positive samples were analyzed for neutralizing antibodies. Correlations between ADA, PK and loss of efficacy were systematically assessed in Phase III studies with the proposed 4-week fixed interval dosing regimen, as other patients on irregular and less frequent dosing schedules were not considered assessable for loss of efficacy.

As expected with a sensitive assay procedure, ADA were detected in all treatment groups in the Phase III program, including non-specific ADA in some patients at baseline (45/3407 = 1.3%, 8 out of 45 were positive at a later time point as well). Of the 2842 patients who received any dose of secukinumab in the Phase III program (including the 37 patients who received two different regimens in studies 2304 and 2307), a total of 10 patients (0.4%) had treatment-emergent ADA (any 300 mg: 3/1410 = 0.2%; any 150 mg: 7/1395 = 0.5%), of which 3/10 were neutralizing antibodies.

Of the 10 patients with treatment-emergent ADA, 5 patients (50%) reverted to a seronegative state at a later timepoint with no detectable ADA. There was no evidence of a secukinumab

dose-response for ADA. No patient treated with the PFS or AI forms of secukinumab (Studies A2308 and A2309, respectively) developed treatment-emergent ADA (Table 5-38). There was no evidence of a significant increase in ADA frequency or titer over time, including in those patients who received doses less frequently.

**Table 5-38 Overview of formation of anti-drug antibodies (ADA)**

| | A2302 | A2303 [3] | A2304 | A2307 | A2308 | A2309 |
|---|---|---|---|---|---|---|
| **No. of samples/No. of subjects** | 2597/737 | 4757/1303 | 3558/965 | 110/43 | 349/177 | 362/182 |
| **Baseline ADA positive [2]** | 10 (1.3%) | 15 (1.1%) | 10 (1.0%) | 0 (0%) | 10 (5.6%) | 0 (0%) |
| **Treatment-emergent ADA positive [1]** | 2 (0.3%) | 4 (0.3%) | 4 (0.4%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Inconclusive status[4] (secukinumab levels > drug tolerance level at week 24, 52, and week 60)** | 6% | 7% | 3% | 3% week 40 only | n.a. [5,6] | n.a [5,7] |

[1] negative at baseline, positive after start of secukinumab treatment;
[2] includes patients who were either only positive at baseline or positive at baseline and post-baseline;
[3] 980 secukinumab-treated patients in A2303;
[4] Inconclusive status: steady-state serum concentrations of secukinumab were above level of drug tolerance of 53.8 µg/mL in Week 24 and 52 samples tested.
[5] not applicable, only baseline and week 12 data available at time point of reporting.
[6] 100% and 63% of patients of treated patients had post-treatment sample (week 12) below drug tolererance level at 150 and 300 mg doses, respectively;
[7] 70.4% of post-treatment samples (week 12) were below drug tolererance level.

Across all Phase III studies, treatment-emergent ADA were not associated with altered PK profiles in patients on 4-week fixed interval dosing, in whom PK profiles could be compared to the larger study population. Furthermore, the development of treatment-emergent ADA was not associated with a loss of PASI 75 response or a loss of efficacy defined conservatively as a 6-point increase from the minimum achieved PASI score. It is notable that of the three patients who tested positive for both treatment-emergent ADA and neutralizing antibodies (3/2842 = 0.1%), PK profiles were normal and therapeutic efficacy was maintained in the 2 patients who received 4-week fixed interval dosing, whereas the third patient on a SoR regimen could not be assessed for efficacy or change in PK. The development of ADA was not associated with any injection site reactions or administration reactions, including hypersensitivity events. No increase in immunogenicity or related adverse events (AEs) was detected in patients re-treated with secukinumab at the start of relapse.

In summary, positive ADA responses occurred at very low frequency (Table 5-38), were mostly transient and of low titer. Development of ADA was not dependent on the dose, frequency of dosing, or device. There was no correlation between ADA or neutralizing antibodies and alteration in PK profile or reduction in efficacy. There was no association between ADA and safety or tolerability.

## 5.5.13 Special patient populations

### 5.5.13.1 Subgroups by Demography and Baseline Disease

All AEs and SAEs were evaluated in demographic subgroups (age groups, gender, race, and region), baseline characteristics (body weight, body weight strata, baseline PASI, severity of psoriasis, 10 year CHD risk category, baseline IGA mod 2011 score and psoriatic arthritis at

baseline), previous therapies (systemic, biologic and non-biologic therapies). Overall, no discerning trends by subgroups were observed in the study population.

#### 5.5.13.1.1 Age

Most patients were < 65 years of age and AEs by age did not reveal any trends in total AEs or in the most frequently affected SOC of infections and infestations compared to the overall population. In older age groups (≥ 65 and ≥ 75 years), a higher incidence of infections and infestations was observed in the etanercept group.

#### 5.5.13.1.2 Gender

The incidence of total AEs was higher in females (61.5%) vs. males (56.3%) across all treatment groups, including placebo. The exposure adjusted incidences for both SOCs were comparable for secukinumab and etanercept for both males and females.

#### 5.5.13.1.3 Race

Caucasians and Asians constituted more than 90% of the population and the AE profile in the initial 12 week period by race was similar to that observed in the overall population. No black patients received etanercept. There were no race-related trends overall or in the most frequently affected SOC of infections and infestations compared to the overall population.

#### 5.5.13.1.4 Weight

AEs are summarized by body weight (< 70 kg, ≥ 70 - < 90 kg, ≥ 90 kg). The exposure-adjusted AE profile over the entire treatment period by weight was similar to that observed in the overall population of Pool B (Table 5-39). SAEs were generally single patient events; events occurring in more than one patient are presented by body weight in Table 5-40. The incidence per 100 patient-years of total AEs showed the same pattern as seen in the overall population, with higher rates in the placebo group compared with the any secukinumab dose and etanercept groups.

**Table 5-39 Exposure-adjusted incidence of adverse events by weight (≥ 3.0 per 100 patient-years) – Entire treatment period (Pool B: all psoriasis trials – Safety set)**

| Weight | < 70 kg | | 70 kg to < 90 kg | | ≥ 90 kg | |
|---|---|---|---|---|---|---|
| Secukinumab Dose | 300 mg N = 372 n (IR) | 150 mg N = 337 n (IR) | 300 mg N = 492 n (IR) | 150 mg N = 508 n (IR) | 300 mg N = 546 n (IR) | 150 mg N = 550 n (IR) |
| Any preferred term | 275 (207.0) | 264 (246.1) | 395 (254.2) | 382 (223.9) | 421 (242.2) | 420 (252.3) |
| Nasopharyngitis | 55 (19.7) | 64 (26.0) | 106 (29.2) | 88 (23.6) | 120 (31.2) | 115 (30.8) |
| Headache | 33 (11.3) | 25 (9.4) | 38 (9.7) | 42 (10.6) | 44 (10.6) | 44 (10.7) |
| Pruritus | 18 (6.0) | 28 (10.7) | 24 (5.9) | 21 (5.1) | 12 (2.8) | 17 (4.0) |
| Diarrhea | 27 (9.2) | 13 (4.7) | 28 (6.9) | 22 (5.4) | 24 (5.6) | 28 (6.6) |
| Upper respiratory tract infection | 19 (6.3) | 18 (6.6) | 32 (7.9) | 33 (8.2) | 40 (9.5) | 41 (9.9) |
| Arthralgia | 19 (6.3) | 10 (3.6) | 25 (6.1) | 23 (5.7) | 24 (5.5) | 36 (8.5) |
| Hypertension | 13 (4.3) | 15 (5.5) | 20 (4.9) | 24 (5.9) | 34 (8.0) | 29 (6.9) |
| Cough | 20 (6.7) | 10 (3.6) | 19 (4.6) | 15 (3.6) | 31 (7.3) | 19 (4.4) |
| Back pain | 15 (4.9) | 7 (2.5) | 19 (4.6) | 23 (5.7) | 28 (6.5) | 22 (5.2) |
| Eczema | 14 (4.6) | 11 (4.0) | 14 (3.4) | 6 (1.4) | - | - |
| Oropharyngeal pain | 15 (5.0) | 9 (3.2) | 21 (5.1) | 13 (3.2) | 19 (4.4) | 18 (4.2) |
| Psoriasis | 7 (2.3) | 6 (2.2) | 10 (2.4) | 6 (1.4) | 14 (3.2) | 10 (2.3) |
| Influenza | 13 (4.2) | 9 (3.3) | 18 (4.4) | 17 (4.1) | 16 (3.7) | 10 (2.3) |
| Pyrexia | 11 (3.6) | 10 (3.6) | 10 (2.4) | 10 (2.4) | 9 (2.0) | 6 (1.4) |
| Pharyngitis | 8 (2.6) | 11 (4.0) | 21 (5.2) | 9 (2.2) | 14 (3.2) | 9 (2.1) |
| Bronchitis | 9 (2.9) | 9 (3.2) | 13 (3.1) | 8 (1.9) | 27 (6.2) | 18 (4.2) |
| Rhinitis | 10 (3.3) | 7 (2.5) | 12 (2.9) | 8 (1.9) | 10 (2.3) | 8 (1.8) |
| Folliculitis | 7 (2.3) | 11 (4.0) | 18 (4.4) | 11 (2.7) | 9 (2.1) | 11 (2.5) |
| Urticaria | 6 (1.9) | 9 (3.3) | 11 (2.7) | 7 (1.7) | - | - |
| Dyslipidemia | 2 (0.6) | 9 (3.3) | - | - | - | - |
| Pain in extremity | 9 (2.9) | 5 (1.8) | 10 (2.4) | 7 (1.7) | 11 (2.5) | 15 (3.5) |
| Fatigue | 8 (2.6) | 5 (1.8) | 10 (2.4) | 12 (2.9) | 11 (2.5) | 13 (3.0) |
| Nausea | 8 (2.6) | 5 (1.8) | 7 (1.7) | 9 (2.2) | 9 (2.1) | 16 (3.7) |
| Gastroenteritis | 6 (1.9) | 6 (2.2) | 20 (4.9) | 12 (2.9) | 10 (2.3) | 14 (3.2) |
| Hypercholesterolemia | 4 (1.3) | 6 (2.2) | 6 (1.4) | 3 (0.7) | 6 (1.4) | 13 (3.0) |
| Viral Upper Respiratory Tract Infection | - | - | 13 (3.1) | 8 (1.9) | 14 (3.2) | 7 (1.6) |
| Sinusitis | 4 (1.3) | 6 (2.2) | 6 (1.4) | 8 (1.9) | 16 (3.7) | 9 (2.1) |
| Toothache | - | - | 10 (2.4) | 9 (2.2) | 10 (2.3) | 16 (3.7) |
| Edema peripheral | 3 (1.0) | 1 (0.4) | - | - | 9 (2.1) | 13 (3.0) |
| Gamma-glutamyltransferase increased | - | - | - | - | 11 (2.5) | 13 (3.0) |

IR=incidence rate per 100 patient-years. For patients with event, exposure time is censored at time of first event.

**Table 5-40 Exposure-adjusted incidence of SAEs by weight occurring in ≥ 1 patient in any group – Entire treatment period (Pool B: all psoriasis trials – Safety set)**

| Weight | < 70 kg | | 70 kg to < 90 kg | | ≥ 90 kg | |
|---|---|---|---|---|---|---|
| Secukinumab Dose | 300 mg N = 372 n (IR) | 150 mg N = 337 n (IR) | 300 mg N = 492 n (IR) | 150 mg N = 508 n (IR) | 300 mg N = 546 n (IR) | 150 mg N = 550 n (IR) |
| Any preferred term | 16 (5.2) | 23 (8.4) | 31 (7.6) | 25 (6.1) | 38 (8.8) | 28 (6.5) |
| Angina pectoris | - | - | - | - | 1 (0.2) | 2 (0.5) |
| Cellulitis | - | - | - | - | 1 (0.2) | 2 (0.5) |
| Pneumonia | 1 (0.3) | | | 1 (0.24) | 2 (0.5) | 2 (0.5) |
| Basal cell carcinoma | - | - | - | 1 (0.24) | 2 (0.5) | - |
| Hypertensive crisis | - | - | - | - | 2 (0.5) | 1 (0.2) |
| Cholelithiasis | - | - | - | 2 (0.5) | 1 (0.23) | - |
| Hypoaethesia | - | - | - | 2 (0.5) | - | - |
| Rib Fracture | - | - | 2 (0.5) | - | - | - |

## 5.6 Safety conclusions

In conclusion, secukinumab 300 mg and 150 mg have comparable safety profiles to each other and to the active comparator (etanercept) over 52 weeks. The risks identified in this extensive program show that secukinumab 300 mg is acceptable for use in adult patients with moderate to severe plaque psoriasis. The safety database includes over 5,000 patients studied, of whom, 3,430 psoriasis patients were treated with secukinumab covering 2,725 patient-years of exposure.

Secukinumab showed an imbalance vs. placebo in total AEs, which was driven by infections, mainly non-serious upper respiratory tract infections, but this difference was observed only in the first 12 weeks of treatment and did not translate into infection SAEs or into an imbalance over 52 weeks of treatment. There was also no difference between secukinumab 300 mg and 150 mg in the overall rate of infections or in upper respiratory tract infections. Secukinumab at both doses was comparable to etanercept in total AEs and infection AEs in the first 12 weeks and over the entire 52-week treatment period.

The incidence of *Candida* infections was more frequent with 300 mg, while 150 mg was comparable to placebo, and etanercept in both the initial 12 weeks (Pool A) (1.2%, 0.4%, 0.3% and 0.3% respectively) and during the entire treatment period (Pool B) (Incidence rate of 3.55, 1.85, 1.00 and 1.37 per 100 patient years, respectively). The imbalance between doses was limited to non-serious, localized mucosal or cutaneous candidiasis, with no reports of chronic or systemic disease in any treatment group. *Candida* infections were responsive to standard treatment and did not necessitate discontinuation of study medication. No serious opportunistic infections were reported. No reactivation of tuberculosis or viral hepatitis was observed in any psoriasis trial.

SAEs and discontinuations due to AEs were infrequent in the first 12 weeks of treatment and showed no differences among secukinumab, placebo and etanercept. Over the entire treatment period, the exposure adjusted incidence rate of SAEs remained comparable across treatment groups. Secukinumab was comparable to etanercept in AEs leading to discontinuation over 52 weeks, while few placebo patients remained after 3 months due to lack of response and were not available for comparison at later time points.

Neutropenia was comparable for secukinumab, both doses, and etanercept. Most cases were mild (limited to CTC Grade 1-2), transient and reversible. Neutropenia < $1000/mm^3$ (CTCAE Grade 3) was reported infrequently with secukinumab, with no dose dependence and no temporal relationship to infections in 15/18 patients. Events temporally associated with neutropenia in 3 patients were all non-serious infections (upper respiratory tract infection, rhinitis, and cystitis). Neutropenia < $500/mm^3$ (CTCAE Grade 4) was observed only on etanercept (1 patient) and was temporally associated with an infection.

There is no evidence that secukinumab confers an increased risk for malignancy. There was no clinically meaningful difference in malignancies among secukinumab, placebo and etanercept, or between the secukinumab doses, in psoriasis trials (Pools A and B) or between secukinumab and placebo over 52 weeks across all indications (Pool C). In the psoriasis population (Pool B), there were 4 cases of malignant melanoma reported (2 malignant melanoma and 2 malignant melanoma in situ). All patients had one or more of the following risk factors: prior exposure to phototherapy, TNFα antagonists or methotrexate or pre-existing melanocytic naevus. No increase in the ratio of squamous cell carcinoma to basal cell carcinoma was observed.

All MACE events were adjudicated by an external independent adjudication committee who were blinded to the treatment allocation. Despite allowing inclusion of patients with a prior history of myocardial infarction or chronic artery disease, the rate of MACE was low and was comparable for secukinumab to both placebo and etanercept in the initial 12 weeks of treatment in psoriasis trials. There was no increased risk over 52 weeks compared with placebo in Pool B of all psoriasis trials and in Pool C for secukinumab-treated patients.

Despite small imbalances in the incidence of mild hepatic transaminase elevations vs. placebo, secukinumab was not associated with a higher rate of combined elevations in hepatic transaminases and serum bilirubin. There was no dose response for secukinumab and rates were comparable to etanercept. Laboratory criteria for Hy's law were met in 4 patients (2 on 150 mg, 1 on 300 mg based on local lab data, and 1 on placebo); all cases had evidence of an established causative etiology or showed normalized values upon re-exposure to secukinumab.

The exposure-adjusted incidence of inflammatory bowel disease per 100 patient-years in Pool B over the entire treatment period was similar between any 300 mg and any 150 mg secukinumab and etanercept (0.26, 0.35 and 0.34, respectively). A total of 3 cases of Crohn's disease were reported (all on 150 mg), of which 2 were considered flare of existing disease in patients with prior history of Crohn's disease, and 1 was a new event occurring in a patient with symptoms at baseline suggestive of possible active undiagnosed Crohn's disease. No cases of Crohn's disease were reported for 300 mg secukinumab, placebo and etanercept. These data are not indicative of a relationship between secukinumab treatment and exacerbation or new onset of Crohn's disease. However, due to the potential involvement of

the IL-17 pathway in the pathogenesis, it is not possible to rule out the potential of increased risk of an exacerbation of Crohn's disease. Therefore inclusion of a warning in the prescribing information has been proposed to advise that caution should be exercised when prescribing to patients with active Crohn's disease and such patients should be followed closely. Exacerbation of Crohn's disease is also included as a potential risk for post-marketing risk minimization activities (see Section 6 Risk minimization activities).

The rate of hypersensitivity AEs was comparable between secukinumab and etanercept and lowest with placebo. The higher total rate of treatment-related AEs with etanercept vs. secukinumab and placebo was driven by general disorders and administration site conditions, particularly injection site erythema (5% for etanercept vs. 0.07% for any secukinumab dose and 0% for placebo).

Positive ADA responses occurred at very low frequency (Table 5-38), were mostly transient, and of low titer. Development of ADA was not dependent on the dose, frequency of dosing, or device. There was no correlation between ADA or neutralizing antibodies and alteration in PK profile or reduction in efficacy. There was no association between ADA and safety or tolerability.

An additional four months of data from ongoing studies, encompassing a total of approximately 1900 patient-years of additional exposure across 32 studies (including 800 patient-years in plaque psoriasis) has recently been submitted to the FDA as a 4 month Safety Update. After review of these data, the benefit risk profile and safety conclusions within the original BLA remain unchanged.

## 5.7 Benefits and risk conclusions

Secukinumab has been evaluated in an extensive clinical program for the treatment of patients with moderate to severe plaque psoriasis. As the first in class, new mode of action product, specifically neutralizing IL-17A, secukinumab provides an important addition to existing treatment options for this serious disease.

The 300 mg regimen is the optimal clinical dose for the following reasons:

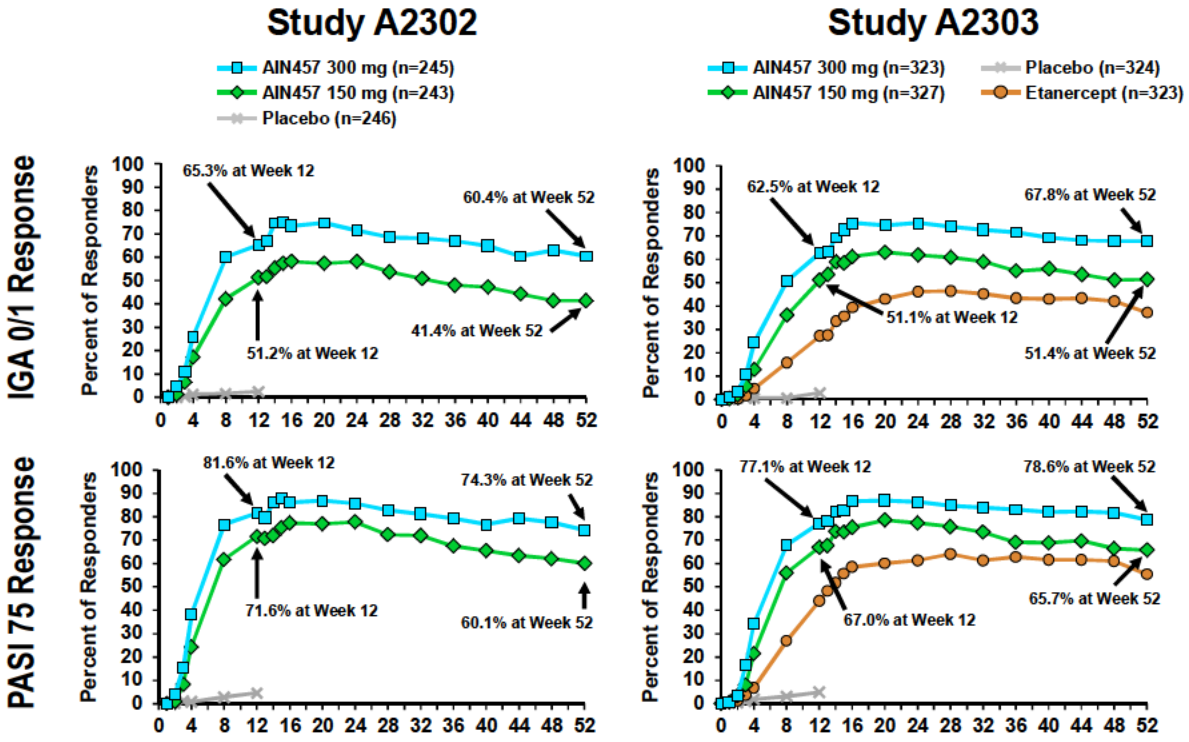
- Consistently higher efficacy is achieved with the 300 mg regimen in each of the 4 studies for the co-primary endpoints at week 12.
- The response rate for the recommended dose of 300 mg dose was approximately 10-20% higher than 150 mg in each of the four studies on the more stringent endpoints of clear to almost-clear skin by IGA mod 2011 0/1 or PASI 90 at week 12.
- After 52 weeks of treatment, response rates for 300 mg (data from A2302 and A2303) were approximately 16-20% better than 150 mg secukinumab and 26-32% better than etanercept for the higher clearance efficacy measures (including PASI 90, IGA mod 2011 0/1 & PASI 100 responses).
- Maintenance of PASI 75 response was best with secukinumab 300 mg. The cumulative probability (Kaplan-Meier estimates) of loss of a Week 12 PASI 75 response by Week 52 was three times higher with etanercept (39.2%) and twice higher with secukinumab 150 mg (25.8%) compared with secukinumab 300 mg (12.9%).

- Incidence rates for the adverse events of interest for an immunomodulatory biologic including serious infections, autoimmune disorders, major adverse cardiovascular events (MACE) and malignancies were similar for the two doses (Figure 5-16) and similar to rates on etanercept and placebo.

All four core Phase III studies met the co-primary endpoints (PASI 75 and IGA mod 2011 0/1) at Week 12 showing superiority of both doses compared to placebo, and in the study which included etanercept (A2303), superiority was demonstrated against this active comparator. More importantly, the difference in responses compared with either placebo or etanercept was greater with the more stringent criteria representing almost clear/clear skin (PASI 90, PASI 100 and IGA mod 2011 0/1) and was sustained over 52 weeks.

In A2302 and A2303, the proportion of patients treated with 300 mg secukinumab achieving PASI 90 (54.2-59.2%) or IGA 0/1 (62.5-65.3%) at Week 12 was more than double the response achieved with etanercept (20.7% PASI 90; 27.2% IGA 0/1) (Figure 5-6) and (Figure 5-8). After 52-weeks of treatment, approximately 60% of patients treated with 300 mg (60-68%) presented with almost clear or clear skin (IGA 0/1, PASI 90 or 100) (Figure 5-15, Table 1-2) compared to 36-51% of patients treated with 150 mg.

**Figure 5-15 IGA mod 2011 0/1 and PASI 75 response rates over 52 weeks of treatment in studies A2302 and A2303 (non-responder imputation)**




n = number of evaluable patients

Secukinumab 300 mg also provided a clinically meaningful improvement (36-39%) in achieving completely clear skin (PASI 100) after one year. Using this most stringent criterion, secukinumab 300 mg is approximately twice as effective as 150 mg (36-39% vs. 20%) and

almost four times as effective as etanercept (36-39% vs. 10%). In line with this degree of improvement in skin scores, secukinumab 300 mg offers patients the best chance to not only improve symptoms, but also to achieve normal quality of life (DLQI 0/1). Responses were better maintained with 300 mg secukinumab when compared to the 150 mg dose, as approximately 2/3 of patients (68.2%) were able to achieve this important goal after one year versus approximately 50% for both 150 mg secukinumab (52.9%) and etanercept (46.9%) (pooled 52 week data for A2302 and A2303).

The benefits of the 300 mg secukinumab dose were demonstrated across all subgroups studied, including weight (age, gender, race, region, baseline disease severity, exposure to previous systemic psoriasis therapy, and comorbid psoriatic arthritis) (Section 5.4.6 and Section 5.4.9). Furthermore, 300 mg secukinumab showed improvement in these subgroups, over the 150 mg dose, placebo, and etanercept.

Another attribute that is desirable is a rapid onset of action (Seston et al 2007). Secukinumab treatment was associated with an early onset in the improvement of signs and symptoms (Section 5.4.4). The most rapid response was observed with secukinumab 300 mg with over 50% reduction in PASI score by Week 3 vs. Week 4 for the 150 mg dose and around Week 8 for etanercept.

All three forms of product LYO powder (Studies A2302 and A2303) and liquid formulation in either PFS (A2308) or an AI/Pen (A2309) produced similar results in efficacy. These data provide clinical evidence supporting the physical/chemical characterization that demonstrates comparability of the formulations (powder or liquid) and subcutaneous delivery via either syringe or autoinjector.

A total of 5,044 patients have participated in clinical studies in various indications (plaque psoriasis and other autoimmune conditions). Of these, the majority (3,993) were patients with moderate to severe plaque psoriasis, of whom 3,430 received secukinumab. The total patient-years of exposure across all indications is 3,588 patient years and for psoriasis is 2,725 patient years.

In general, the overall safety profile as presented in Section 5.5 was similar for both the 300 mg and 150 mg doses and not dissimilar to etanercept (A2303). AEs of special interest corresponding to potential risks are discussed in Section 5.5.9.

Specific analyses were conducted on targeted AEs based on secukinumab mechanism of action and specific risks in the target patient population.

The exposure-adjusted incidence (rate per 100 patient-years) of these events is summarized for the entire treatment period (up to Week 52) for Pool B (all psoriasis studies) in Table 5-41.

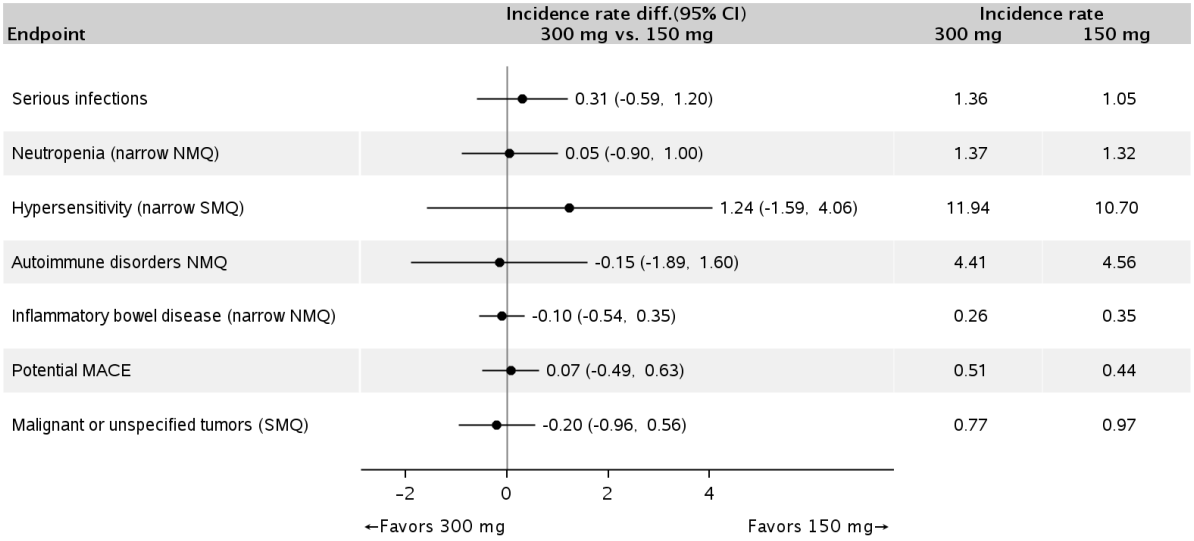
**Table 5-41 Exposure-adjusted incidence of key AEs of interest – Entire treatment period (52 weeks) (Pool B: all psoriasis studies – Safety set)**

| | AIN457 300 mg N=1410 (IR) (95%CI) | AIN457 150 mg N=1395 (IR) (95%CI) | Placebo N=793 (IR) (95%CI) | Etanercept N=323 (IR) (95%CI) |
|---|---|---|---|---|
| Infections and infestations SOC | 91.06 (84.46, 98.05) | 85.29 (78.88, 92.09) | 101.89 (87.27, 118.25) | 93.68 (80.20, 108.77) |
| Serious infections | 1.36 (0.78, 2.21) | 1.05 (0.55, 1.84) | 0.99 (0.12, 3.59) | 1.37 (0.37, 3.51) |
| Serious opportunistic infections | 0 (0.00, 0.31) | 0 (0.00, 0.32) | 0 (0.00, 1.83) | 0 (0.00, 1.26) |
| Neutropenia (narrow NMQ) | 1.37 (0.78, 2.23) | 1.32 (0.74, 2.18) | 0 (0.00, 1.83) | 1.71 (0.56, 4.00) |
| Hypersensitivity (narrow SMQ) | 11.94 (9.99, 14.15) | 10.70 (8.83, 12.84) | 4.50 (2.06, 8.55) | 9.73 (6.41, 14.15) |
| Immune/administration reactions (NMQ) | 32.12 (28.68, 35.85) | 30.16 (26.80, 33.83) | 57.65 (47.15, 69.79) | 40.57 (32.83, 49.60) |
| Autoimmune disorders NMQ (based on all AEs) | 4.41 (3.29, 5.80) | 4.56 (3.40, 6.00) | 16.84 (11.59, 23.64) | 3.45 (1.66, 6.35) |
| Inflammatory bowel disease (narrow NMQ) | 0.26 (0.05, 0.75) | 0.35 (0.10, 0.90) | 0 (0.00, 1.83) | 0.34 (0.01, 1.90) |
| Crohn's disease (PT) | 0 (0.00, 0.31) | 0.18 (0.02, 0.63) | 0 (0.00, 1.83) | 0 (0.00, 1.26) |
| Potential MACE (based on all AEs) | 0.51 (0.19, 1.11) | 0.44 (0.14, 1.02) | 0.50 (0.01, 2.77) | 0.34 (0.01, 1.90) |
| Malignant or unspecified tumors (SMQ) (based on all AEs) | 0.77 (0.35, 1.46) | 0.97 (0.48, 1.73) | 1.49 (0.31, 4.36) | 0.68 (0.08, 2.47) |

Secukinumab at both doses was comparable to etanercept in total AEs (56.2%, 59.5%, 49.0% and 57.6%) and infection AEs in the first 12 weeks (28.1%, 29.3%, 18.9% and 24.5% for 300 mg, 150 mg, placebo and etanercept) (Table 5-18) and over the 52-week treatment period (Table 5-41). There was a low rate of infection SAEs at 12 weeks (0.09%, 0.17%, 0.30% and 0% for 300 mg, 150 mg, placebo and etanercept) and this remained balanced across treatment groups over 52 weeks of treatment.

The risk differences, for the two doses of secukinumab, for the key AEs of interest are shown in Figure 5-16. For both doses, exposure adjusted incidences for key risks were similar.

**Figure 5-16 Exposure-adjusted incidence and incidence rate difference (per 100 patient years) of key AEs of interest - Entire treatment period (Pool B: all psoriasis studies– Safety set)**




The incidence during the initial 12 weeks (Pool A) and the incidence rates during the entire treatment period (Pool B) of *Candida* infections were generally low for all groups. *Candida* infections were reported most frequently in the 300 mg group, followed by the 150 mg dose group, then etanercept and placebo (Table 5-27 and Table 5-28). The imbalance between doses was limited to non-serious, localized mucosal or cutaneous candidiasis, consistent with the mechanism of action, with no reports of chronic or systemic disease in any treatment group. Esophageal candidiasis has been reported in 5 patients, four in the clinical trial program (3 on 300 mg and 1 on 150 mg) and 1 additional case on 300 mg in the 4 month safety update. All *Candida* infections were responsive to standard treatment and did not necessitate discontinuation.

Overall, the safety profile characterized for secukinumab 300 mg was comparable to etanercept and demonstrates that the safety risk is acceptable for chronic use of the treatment of psoriasis. Other than the small, incremental risk in *Candida* infections for the secukinumab 300 mg dose (limited to non-serious, localized mucosal or cutaneous candidiasis), the incidence of adverse events in general were not suggestive of a dose response compared to 150 mg.

Therefore, secukinumab is proposed for use in adult patients with moderate to severe plaque psoriasis, who are candidates for systemic therapy or phototherapy. The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4.

# 6 Risk minimization activities

The secukinumab program is a large program with controlled safety data through 52 weeks. However, as with any new therapy new events and/or characterization of identified or potential rare events only appear in the broader population exposed post-marketing. As part of the ongoing effort to assure patient safety, risk minimization activities post-approval have been proposed and are summarized in Table 6-1, Table 6-2, and Table 6-3.

**Table 6-1 Identified risks**

| Identified risks | Areas requiring confirmation or further investigation | Proposed routine and additional PhV activities | Objectives |
|---|---|---|---|
| Infections and infestations | Incidence, nature and outcomes for rare and clinically relevant infectious events | Routine pharmacovigilance | To assess:<br>• Reporting rate and change in severity and clinical characteristics of the events<br>• Risk factors<br>• Exposure and co-medications<br>• Role of neutropenia |
| Neutropenia | Incidence and clinical relevance under real live conditions | Routine pharmacovigilance | To assess:<br>• Reporting rate and change in severity<br>• Risk factors<br>• Exposure and co-medications<br>• Associated infectious events where applicable |
| Hypersensitivity | Incidence, nature and outcomes for rare and clinically relevant hypersensitivity events | Routine pharmacovigilance | To assess:<br>• Reporting rate and change in severity<br>• Clinical characteristics of the events<br>• Risk factors |

**Table 6-2 Potential risks**

| Potential risks | Areas requiring confirmation or further investigation | Proposed routine and additional PhV activities | Objectives |
|---|---|---|---|
| Malignant or unspecified tumors | Incidence and nature during long term exposure | Routine pharmacovigilance<br><br>Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients on secukinumab therapy, estimated sample size 2000, follow up period of 5 years | To assess:<br>• Reporting rate and change in severity in the postmarketing setting<br>• Incidence, compared to expected rates, can be further evaluated in the proposed registry<br>• Nature of the events<br>• Risk factors<br>Registry proposed to collect long-term information on malignancies in real-life population |
| Major Adverse Cardiovascular Events (MACE) | Incidence during long term exposure | Routine pharmacovigilance | To assess:<br>• Reporting rate and change in severity<br>• Characteristics of exposure |
| Immunogenicity | Incidence and clinical relevance during long-term exposure | Routine pharmacovigilance | To assess:<br>• Reporting rate and change in severity of accompanying events associated with immunogenicity<br>• Risk factors |
| Crohn's disease | Incidence and clinical relevance | Routine pharmacovigilance | To assess:<br>• Reporting rate and change in severity<br>• Nature and outcome of the events<br>• Risk factors |

## Table 6-3 Potential interactions and missing information

| | Areas requiring confirmation or further investigation | Proposed routine and additional PhV activities | Objectives |
|---|---|---|---|
| **Potential interactions** | | | |
| Interactions with Live Vaccines | Incidence of vaccine complications | Routine pharmacovigilance | To assess:<br>• Reporting rate and any accompanying events<br>• Nature of the events<br>• Risk factions |
| **Missing information** | | | |
| Fetal exposure in utero | Absence of fetal malformation<br>Incidence of spontaneous abortions | Routine pharmacovigilance | To assess outcome of pregnancies with fetal exposure |
| Long term safety data | Incidence and nature of malignancies and MACE during long term exposure | Routine pharmacovigilance<br>Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients on secukinumab therapy, estimated sample size 2000, follow up period of 5 years | To assess:<br>• Reporting rate and change in severity of adverse events<br>• Nature and outcome of the events<br>• Risk factors<br>Registry proposed to collect long-term information on malignancies in real-life population |
| Long term efficacy data | Maintenance of efficacy over time (exceeding 1 year) | Routine pharmacovigilance | To assess :<br>• Reporting rate for loss of efficacy<br>• Associated adverse events<br>• Risk factors |

# 7 References

[American Academy of Dermatology and AAD Association] Position Statement. (Internet) Available from: <http://www.aad.org/Forms/Policies/Uploads/PS/PS%20on%20Treatment%20of%20Psoriatic%20Patients.pdf> (Accessed 21 Aug 2014).

[Anon (2013)] Dermatology Life Quality Index (DLQI). Cardiff University, School of Medicine. (Internet) Available from: <http://www.dermatology.org.uk/quality/dlqi/quality-dlqi.html> (Accessed 18 Sep 2013).

[Armstrong AW, Schupp C, Wu J, et al (2012)] Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. PLoS One; 7(12):e52935. doi:10.1371/journal.pone.0052935.

[Basra MKA, Fenech R, Gatt RM, et al (2008)] The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol; 159:997-1035.

[Boffetta P, Gridley G, Lindeloef B (2001)] Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. J Invest Dermatol; 117:1531-37.

[Chastek B, Fox KM, Watson C, Kricorian G, Gandra SR (2013)] Psoriasis treatment patterns with etanercept and adalimumab in a United States health plan population. J Dermatolog Treat; 24:25-33.

[Cypowyj S, Picard C, Marodi L, et al (2012)] Immunity to infection in IL-17-deficient mice and humans. Eur J Immunol; 42:2246-2254.

[Fossiez F, Banchereau J, Murray R, et al (1998)] Interleukin-17. Int Rev Immunol; 16:541-551.]

[Finlay AY, Khan GK (1994)] Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. Clin Exp Dermatol; 19:210-16.

[Gaffen SL, Hernandez-Santos N, Peterson AC (2011)] IL-17 signaling in host defense against Candida albicans. Immunol Res; 50(2-3): 181-7.

[Gelfand JM, Wan J, Callis Duffin K, et al (2012)] Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol; 148(4):487-94.

[Gelfand JM, Dommasch ED, Shin DB, et al (2009)] The risk of stroke in patients with psoriasis. J Invest Dermatol; 129:2411-18.

[Gelfand JM, Neimann AL, Shin DB, et al (2006)] Risk of myocardial infarction in patients with psoriasis. JAMA; 296:1735-41.

[Griffiths CEM, Strober BE, van de Kerkhof P, et al (2010)] Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. New Engl J Med; 362:118-28.

[Griffiths CEM, Barker JNWN (2007)] Pathogenesis and clinical features of psoriasis. Lancet; 370:263-71.

[Hueber W, Sands BE, Lewitzky S, et al (2012)] Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut; 61:1693-1700.

[Kagami S, Rizzo HL, Lee JJ, et al (2010)] Circulating Th17, Th22 and Th1 cells are increased in psoriasis. J of Invest Dermatol; 130:1373-83.

[Jha PK, Das SR, Musleh GS, et al (2005)] Psoriasis-induced post-operative cardiac failure. Ann Thorac Surg; 79:1390–1.

[Langley RG, Elewski BE, Lebwohl M, et al (2014)] Secukinumab in plaque psoriasis – results of two phase 3 trials. NEJM; 371:326-338.

[Langley RGB, Feldmen SR, Nyirady J, et al (2013)] The 5 point investigator's global assessment (IGA) scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat, Early Online: 1-9.

[Lebwohl M, Christoperhs E, Langley R, Ortonne J, Roberts J, Griffiths C (2003)] An International, Randomized, Double-blind, Placebo-Controlled Phase 3 Trial of Intramuscular Alefacept in Patients With Chronic Plaque Psoriasis. Arch Dermatol;139(6):719-727.

[Leonardi C, Matheson R, Zachariae C, et al (2012)] Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. New Engl J Med; 366:1190-9.

[Leonardi CL, Powers JL, Matheson RT, et al (2003)] Etanercept as monotherapy in patients with psoriasis. N Engl J Med; 349: 2014-22.

[Levin EC, Gupta R, Brown G, Malakouti M, Koo J (2014)] Biologic fatigue in psoriasis. J Derm Treatment; 25:78-82.

[Li WQ, Han JL, Chan AT, et al (2013)] Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. Ann Rheum Dis; 72:1200-5.

[Ma X, Reynolds SL, Baker BJ, et al (2010)] IL-17 enhancement of the IL-6 signaling cascade in astrocytes. J Immunol; 184:4898-4906.

[Martin DA, Towne JE, Kricorian G, et al (2013)] The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. J Invest Dermatol; 133:17–26.

[Martínez-García E, Arias-Santiago S, Valenzuela-Salas IJ et al (2014)] Quality of life in persons living with psoriasis patients. Am Acad Dermatol.;71(2):302-7.

[Meares GP, Ma X, Qin H, et al (2012)] Regulation of CCL20 Expression in Astrocytes by IL-6 and IL-17. GLIA; 60:771-781.

[Medzhitov R (2007)] Recognition of micoorganisms and activation of the immune response. Nature; 449:819-26.

[Mehta NN, Yu Y, Pinnelas R, et al (2011)] Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med; 124(8):775.e1-775.e6.

[Mehta NN, Azfar RS, Shin DB, et al (2010)] Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J; 31:1000-6.

[Menter A, Korman NJ, Elmets CA et al (2011)] Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad

Dermatol; 65:137-74.

[Menter A, Gottlieb A, Feldman SR et al (2008)] Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol; 58:826–50.

[Miller LS, Cho JS (2011)] Immunity against Staphylococcus aureus cutaneous infections. Nat Rev Immunol; 11:505-18.

[Miossec P, Kolls JK (2012)] Targeting IL-17 and Th17 cells in chronic inflammation. Nat Rev Drug Discovery; 11:763-776.

[Mrowietz U, Kragballe K, Reich K, et al (2011a)] Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res; 303:1-10.

[Mrowietz U, Kragballe K, Nast A, et al (2011b)] Strategies for improving the quality of care in psoriasis with the use of treatment goals – a report on an implementation meeting. J Eur Acad Dermatol Venereol.; 25 (Suppl. 3):1-13.

[Nestle FO, Kaplan DH, Barker J (2009)] Mechanisms of disease: Psoriasis. N Engl J Med; 2652 361:496-509.

[Onishi RM, Gaffen SL (2010)] Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. Immunology; 129:311-21.

[Papp KA, Leonardi C, Menter A, et al (2012)] Brodalumab, an anti-interleukin 17-receptor antibody for psoriasis. New Engl J Med; 366(13):1181-9.

[Pathirana D, Ormerod AD, Saiag P, et al (2009)] European S3-Guidelines on the systemic treatment of psoriasis vulgaris. JEADV; 23 (Suppl. 2): 5 – 70.

[Puel A, Cypowyj S, Bustamante J, et al (2011)] Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science; 332:65-68.

[Revicki D, Chau D, Viswanathan HN, et al (2013)] Improvement in patient reported symptoms and health related quality of life associated with achieving Psoriasis Area and Severity Index 100 [abstract]. J Am Acad Dermatol; 68(4):AB202.

[Revicki DA, Willian MK, Menter A, et al (2008)] Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. Dermatology; 216:260-70.

[Rich P, Sigurgeirsson B, Thaci D, et al (2013)] Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. Br J Dermatol 168:402-11.

[Seston EM, Ashcroft DM, and Griffiths CEM (2007)] Balancing the benefits and risks of drug treatment: a stated-preference, discrete choice experiment with patients with psoriasis. Arch Dermatol; 143(9):1175-79.

[Skroza N, Proietti I, Pampena R, et al (2013)] Correlations between psoriasis and inflammatory bowel diseases. Biomed Res Int; 2013:983902. doi: 10.1155/2013/983902.

[Stark MA, Huo Y, Burcin TL, et al (2005)] Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. Immunity; 22:285-94.

[Targan SR, Feagan BG, Vermeire S, et al (2012)] A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AMG 827 in subjects with moderate to severe Crohn's disease. Gastroenterology; 143 (3):e26 Mo2083

[Torii H, Sato N, Yoshinari T, et al (2012)] Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: An analysis of Japanese clinical trials of infliximab. J Dermatol; 2687 39:253-59.

[Wang W, Wang EQ, Balthasar JP (2008)] Monoclonal antibody pharmacokinetics and pharmacodynamics. Clinical Pharmacology and Therapeutics; 84(5):548-58.

[Weaver CT, Hatton RD, Mangan PR, et al (2007)] IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol; 25:821-52.

# 8 Appendices

## Appendix 1: Usability Testing for Prefilled Syringe and Autoinjector

### Self-administration with prefilled syringe and autoinjector/pen

Two secukinumab formulations were used in the Phase III program: lyophilisate in a vial in studies A2302 and A2303 (injection prepared by an un-blinded pharmacist and administered by blinded study site personnel) and liquid formulation (self-injection using a pre-filled syringe [A2308] or an AI/Pen [A2309]).

Studies A2308 (PFS) and A2309 (AI/Pen) have demonstrated that PFS and autoinjector/pen delivery methods of secukinumab are safe, efficacious, and that the instructions for use are appropriate for subject usability. This is based upon the observer analysis of patient self-administration of i/ ability to follow key steps in the instructions for use (IFU), ii/ the absence of critical hazards observed, and iii/ patient feedback on the Self-Injection Administration Questionnaire (SIAQ) scale of subject satisfaction with the delivery form. This data is further supported by simulated use studies conducted within this patient population with both PFS and AI/Pen forms. Therefore, after proper training in subcutaneous injection techniques, patients may self-inject secukinumab (including 'at home' administration) using a pre-filled syringe or autoinjector/pen, if a physician determines that it is appropriate. The data indicate that patients were able to successfully administer self-injection following the utilized IFU, with no critical hazards observed, and patients found self-injection with PFS or AI acceptable.

### Usability of secukinumab administration with prefilled syringe

Potential use-related hazards were assessed using a check list completed by a staff site member observing the self-administration at Baseline and Week 1. Approximately 2,422 s.c. administrations with PFS were recorded up to Week 12. At randomization and Week 1, when the hazard assessment was performed, approximately 706 injections were recorded. There were no critical hazards observed, for example, no accidental needle sticks in a critical area, no immediate type allergic reactions, or no breakages of the device.

Patients were trained on self-injection during the Randomization visit when the first dose of study drug was administered. At Week 1, patients were able to refer to the IFU instructions and were supervised by site staff but did not receive further training. Self-administration of first injection of study drug was successfully performed at Week 1 by all patients. Successful self-administration was achieved when the patient performed all the required 6 critical steps (out of 18 steps) to effectively and safely deliver the correct dose from the prefilled syringe (PFS) at the correct injection site (Table 8-1).

**Table 8-1 Number (%) of patients with successful self-administration of study drug at Week 1 (non-responder imputation) (Safety set)**

| Treatment | N | n/m | % | (95% CI) | p-value |
|---|---|---|---|---|---|
| Total | 177 | 174/174 | 100.0 | (97.9, 100.0) | 1.0000 |
| AIN457 150 mg | 59 | 58/58 | 100.0 | (93.8, 100.0) | 0.9978 |
| AIN457 300 mg | 59 | 57/57 | 100.0 | (93.7, 100.0) | 0.9975 |
| Placebo | 59 | 59/59 | 100.0 | (93.9, 100.0) | 0.9980 |

Successful self-administration: successfully performed six critical steps as per the Instructions for Use (IFU).
n=number of patients with successful self-administration of study drug, m=number of patients evaluable.

Nearly all patients successfully completed all 18 steps of the Instructions for Use (IFU) required to administer secukinumab via a PFS. The only step with a slightly lower compliance rate (172/177; 97.2% at Baseline) was Step 18, pertaining to syringe disposal in a sharps container.

Patients completed the pre- and post- modules of the Self-Injection Assessment Questionnaire (SIAQ) which measures the overall patient experience with subcutaneous self-injection. The patient-reported scores on the principal domains of the SIAQ (scale 0 to 10) increased (improved) over time between the Randomization and Week 12 visits for all treatment groups. The absolute change from Baseline to Week 12 in the mean score for the total population was +0.83 for the "feelings about self-injection" domain, +1.14 for the "self-confidence" domain, and +1.52 for the "satisfaction with self-injection" domain. These results suggest that self-injection with PFS was acceptable to study participants.

### Usability of secukinumab administration with autoinjector/pen

Potential use-related hazards were assessed using a check list completed by a staff site member observing the self-administration at Baseline (following training) and Week 1 (representing a one week training delay). Approximately 2,488 s.c. administrations with AI were recorded up to Week 12. At randomization and Week 1, when the hazard assessment was performed, approximately 721 injections were recorded. There were no critical hazards observed, for example, no accidental needle sticks in a critical area, no immediate type allergic reactions, or no breakages of the device.

Patients were trained on self-injection during the Randomization visit when the first dose of study drug was administered. At Week 1, patients were able to refer to the IFU instructions and were supervised by site staff but did not receive further training.

Successful self-administration was achieved when the patient performed the required four critical steps (out of 14 steps) to effectively and safely deliver the correct dose from the AI at the correct injection site. Self-administration of the first autoinjection of study drug was successfully performed at Week 1 by all patients (Table 8-2).

**Table 8-2 Number (%) of patients with successful self-administration of study drug at Week 1 (non-responder imputation) (Safety set)**

| Treatment | N | n/m | % (95% CI) | p-value |
|---|---|---|---|---|
| Total | 182 | 178/178 | 100.0 (97.9, 100.0) | 1.0000 |
| AIN457 150 mg | 61 | 59/59 | 100.0 (93.9, 100.0) | 0.9980 |
| AIN457 300 mg | 60 | 59/59 | 100.0 (93.9, 100.0) | 0.9980 |
| Placebo | 61 | 60/60 | 100.0 (94.0, 100.0) | 0.9982 |

n=number of pateints with successful self-administration of study drug. M=number of patients evaluable.
Successful self-administration: successfully performed four critical steps as per the IFU.
p-value refers to exact binomial test for successful self-administration proportion $\geq$ 90%

Nearly all patients successfully completed the IFU 14 indicated steps required to administer secukinumab via AI. The only steps with a slightly lower compliance rate were Steps 1 and 14, pertaining to washing hands with soap and disposal of the AI into a sharps container.

Patients completed the pre- and post- modules of the SIAQ.

The patient-reported scores on the principal domains of the SIAQ (scale 0 to 10) increased (improved) over time between the Randomization and Week 12 visits for all treatment groups. The absolute change from Baseline to Week 12 in the mean score for the total population was +1.00 for the "feelings about self-injection" domain, +1.47 for the "self-confidence" domain, and +2.35 for the "satisfaction with self-injection" domain. These results suggest that self-injection with AI was acceptable to study participants, and particularly in secukinumab-treated patients who scored higher on all 3 domains compared with placebo-treated patients.

# Appendix 2: CTCAE Grades

**Table 8-3 CTCAE grades for laboratory parameters**

| CTCAE v4.0 Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Hematology** | | | | |
| Hemoglobin decreased (Anemia) | <LLN - 6.2 mmol/L | <6.2 - 4.9 mmol/L | <4.9 mmol/L | |
| Platelet count decreased | <LLN - 75.0 $x10^9$ /L | <75.0 - 50.0 $x10^9$ /L | <50.0 - 25.0 $x10^9$ /L | <25.0 $x10^9$ /L |
| WBC count decreased | <LLN - 3.0 $x10^9$ /L | <3.0 - 2.0 $x10^9$ /L | <2.0 - 1.0 $x10^9$ /L | <1.0 $x10^9$ /L |
| Neutrophil count decreased | <LLN - 1.5 $x10^9$ /L | <1.5 - 1.0 $x10^9$ /L | <1.0 - 0.5 $x10^9$ /L | <0.5 $x10^9$ /L |
| Lymphocyte count decreased | <LLN - 0.8 $x10^9$ /L | <0.8 - 0.5 $x10^9$ /L | <0.5 - 0.2 $x10^9$ /L | <0.2 $x10^9$ /L |
| **Clinical chemistry** | | | | |
| Creatinine increased | >1 - 1.5 x baseline; >ULN - 1.5 x ULN | >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN | >3.0 baseline; >3.0 - 6.0 x ULN | >6.0 x ULN |
| TBL increased | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 10.0 x ULN | >10.0 x ULN |
| GGT increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| ALT increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| AST increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| ALP increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Glucose increased (Hyperglycemia ) | >ULN - 8.9 mmol/L | >8.9 - 13.9 mmol/L | >13.9 - 27.8 mmol/L | >27.8 mmol/L |
| Glucose decreased (Hypoglycemia) | <LLN - 3.0 mmol/L | <3.0 - 2.2 mmol/L | <2.2 - 1.7 mmol/L | <1.7 mmol/L |
| Cholesterol high | >ULN - 7.75 mmol/L | >7.75 -10.34 mmol/L | >10.34 - 12.92 mmol/L | >12.92 mmol/L |
| Hypertriglyceridemia | 1.71 - 3.42 mmol/L | >3.42 - 5.7mmol/L | >5.7 - 11.4 mmol/L | >11.4 mmol/L |

LLN = lower limit of normal, ULN = upper limit of normal