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APPLICATION NUMBER:

125504Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125-504
Priority or Standard	S
Submit Date(s)	October, 22, 2013
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Division / Office	DDDP/ OND
Reviewer Name(s)	Amy Woitach
Review Completion Date	December 2, 2014
Established Name	Secukinumab
(Proposed) Trade Name	Cosentyx
Therapeutic Class	Biologic
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	powder for solution, solution for injection, 150 mg, 150 mg/mL
Dosing Regimen	
Indication(s)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

Intended Population(s)	Adults 18 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of Cosentyx (secukinumab) as indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. This reviewer is recommending approval of both the 150 mg dose and the 300 mg dose by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by maintenance dosing every 4 weeks starting at Week 4. BLA 125504 supports approval of three presentations: 150 mg/mL in a single-use prefilled SensoReady pen for injection, 150 mg/mL in a single-use prefilled syringe for injection, and 150 mg powder for solution in a single-use vial for injection.

1.2 Risk Benefit Assessment

The Applicant is seeking approval for a secukinumab dose of 300 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly dosing starting at Week 4.

Secukinumab (AIN457) 300 mg and 150 mg doses in lyophilisate in vial (LYO) were both demonstrated to be superior to placebo in the treatment of moderate to severe plaque psoriasis in two Phase 3 trials (2302 and 2303). The trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score ≥12, an Investigator's Global Assessment (IGA) score of at least 3, and body surface area (BSA) involvement ≥10% at baseline. Trial subjects randomized to receive secukinumab received injections once a week for the first 4 weeks and then once every 4 weeks through Week 52.

The overall study population in the psoriasis development program was representative of the target patient population of adult patients with moderate to severe plaque psoriasis. The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., ≥ 75% reduction in PASI score) at Week 12 and scoring IGA 0 or 1 at Week 12, with a secondary endpoint of PASI 90 response (i.e., ≥ 90% reduction in PASI score) at Week 12. Both secukinumab 300 mg and 150 mg were superior to placebo ($p<0.0001$) for the co-primary endpoints of PASI 75and IGA of 0 or 1, as well as the secondary endpoint of PASI 90 in each of the pivotal trials.

For the co-primary endpoints, secukinumab 300 mg showed a higher response (approximately 10%) than those of the 150 mg dose for the co-primary endpoints.

The number of individuals exposed to secukinumab in the BLA trials exceeds ICH guidelines, and is adequate for Agency evaluation of safety in subjects with psoriasis. Novartis reported that 3430 psoriasis subjects were exposed to at least one dose of secukinumab (1395 subjects on 150 mg and 1410 subjects on 300 mg). 2751 subjects treated for at least 6 months and 1641 subjects treated for at least 1 year. Investigators exposed reasonable numbers of subjects to the proposed dose (300 mg loading dose at weeks 0, 1, 2, 3, 4, 8) 690 subjects on 300 mg. An additional 692 subjects were exposed to a loading dose of 150 mg. The majority of the subjects continued maintenance dosing every 4 weeks until Week 48. Long term studies are ongoing.

The safety data from the secukinumab development program for psoriasis identified the profile of a biologic immunosuppressant therapy associated with inherent risks, such as serious infections and effects on leukocytes. The overall safety profile appears to be similar to other biologic products approved for the treatment of plaque psoriasis.

The 300 mg dose appears to be slightly more effective than the treatment effect observed in the 150 mg cohort. However, at the increased dose, systemic exposure is increased. This reviewer finds that the minimum therapeutically effective dose would be clinically optimal for a subset of patients given that the safety risks of this therapeutic biologic for long term use are not yet fully characterized. Doubling the dose and increasing systemic exposure (and the potential risks that higher exposure may convey over time) is not necessary for a significant number of patients to achieve success and for a subset of the study population, the risk/ benefit is more favorable for the 150mg dose than for the 300 mg dose.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Risk mitigation measures beyond professional labeling are not warranted for secukinumab at this time. Based on the known safety profile for the drug class and the risks associated with secukinumab from the clinical trials, the benefit-risk profile is acceptable and can be mitigated through the professional labeling.

A proposed REMS was voluntarily submitted by Novartis on October 22, 2013, as part of the original submission. The proposed REMS has the goal of communicating to healthcare professionals and pharmacists the risk of infections associated with secukinumab treatment and consists of a communication plan (CP) (Dear Healthcare Professional and Dear Pharmacist letters, and Letters to Professional Societies for prescribers and pharmacists), and a timetable for submission of assessments.

Medications infliximab, adalimumab, and etanercept, which had REMS programs that were most similar to that proposed for secukinumab (risk of infection), had their REMS released after the REMS CP requirements were complete and the REMS assessment

showed that healthcare professionals understood the key messages regarding ILs and risk of infection.

The Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for BLA 125504 concludes that there will be a baseline familiarity with the management of the risks associated with this medication. DRISK believes that the prescriber population will use the knowledge gained through the aforementioned REMS regarding the risk of infection and apply it to managing patients prescribed secukinumab. See Felicia Duffy's 10/7/14 review for details of the evaluation.

This reviewer concurs with DRISK's recommendation that a REMS for this product is not necessary at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The risk of malignancy in patients is a safety concern for immunosuppressive drugs in general. Because it is unlikely that short premarket trials would detect rare events with long latency such as malignancy, this reviewer recommends a post-marketing assessment of malignancy. The applicant is proposing to enroll subjects in a multicenter, longitudinal, observational disease registry to collect and analyze data on incidence and nature of malignancies. This reviewer finds this approach reasonable.

In addition to malignancy, registries for precedent products also followed for the occurrence of serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events and pregnancy exposure. However, it is this reviewer's opinion that these events can be assessed similarly through evaluation of data from long-term extension studies and reports of post-marketing events. Enhanced pharmacovigilance is recommended for the post-marketing phase for this product to further assess longer term safety outcomes.

If secukinumab is approved for treatment of plaque psoriasis, this reviewer recommends postmarketing requirements included:

- Long term safety studies which included the proposed disease registry and continuation of the ongoing long-term extension trials.
- Studies to achieve compliance with PREA

2 Introduction and Regulatory Background

2.1 Product Information

Secukinumab (AIN457) is a first in class recombinant high-affinity, fully human monoclonal anti-human antibody of the IgG1/kappa isotype that targets IL-17AThe applicant is evaluating secukinumab in various patient populations under the following INDs:

- IND 100418 (DDDP) for psoriasis

2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant proposes their product for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

In practice, a recommendation of systemic therapy or phototherapy is based on clinical judgment, and the decision to proceed is one made between the patient and physician. Some clinicians employ a BSA of ≥10 or involvement of palms and/or soles, in which disease severity may be challenging to adequately manage with topical therapies. The products in the table below could be considered as therapeutic options for the applicant's targeted population.

Table 1: Approved Systemic Therapies for Psoriasis

Small Molecule Therapies		
Product	**Class**	**Warnings/Precautions**
Acitretin	retinoid	teratogen; hepatotoxicity; hyperostosis; lipid effects
Methotrexate	folate antagonist	teratogen; liver fibrosis/cirrhosis; hematologic toxicity; interstitial pneumonitis; opportunistic infections
Cyclosporine	inhibits IL-2	hypertension; nephrotoxicity; serious infections; malignancy
Apremilast	phosphodiesterase 4 inhibitor	Depression; weight decrease; drug-drug interactions
Biologic Therapies		

Etanercept	TNFα-blocker	serious infections (including TB); malignancy; central nervous system demyelinating disorders; hematologic events (pancytopenia); reactivation of hepatitis B; autoimmunity
Adalimumab	TNFα-blocker	Serious infections (including TB); malignancy; reactivation of hepatitis B; demyelinating disease; hematologic reactions (pancytopenia); autoimmunity
Infliximab	TNFα-blocker	serious infections (including TB); malignancy; demyelinating disease; hepatotoxicity
Usetekinumab	interleukin-12 and -23 antagonist	serious infections; malignancy; reversible posterior leukoencephalopathy syndrome

Phototherapy

This therapy involves exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA. Phototherapy requires frequent office visits (e.g. three times per week) and carries an increased risk of squamous cell carcinoma (of the skin).

2.3 Availability of Proposed Active Ingredient in the United States

The product is not available in the United States. At the time of submission secukinumab is not marketed globally. The applicant is concurrently seeking global marketing authority.

On 20 November 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Cosentyx powder for solution for injection, solution for injection in pre-filled pen, solution for injection in pre-filled syringe intended for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

2.4 Important Safety Issues with Consideration to Related Drugs

Potential risks based on class of drug (anti-cytokine) and of the drug substance (foreign protein) were considered. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular/cerebrovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity.

Of note 2 biologics previously approved for the treatment of psoriasis have been voluntarily withdrawn from the market: Alefacept, an inhibitor of LFA-3/CD2 interaction which carried warnings for lymphopenia, serious infections, and malignancy; Efalizumab, which binds CD11a and was voluntary withdrawn based on the finding of an association with the use of efalizumab and an increased risk of progressive multifocal leukoencephalopathy (PML) approximately 5.5 years after approval. The

relevance of these products to secukinumab is unclear since neither product directly targeted IL-17.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant requested an End of Phase 2 meeting held on 3/2/11 which was granted as a guidance meeting because Phase 2 trials were ongoing. The package included summaries of Phase 1 and 2 studies as well as two pivotal Phase 3 protocol synopses (CAIN457A2302, CAIN457A2303) and other phase 3 studies (CAIN457A2304, CAIN457A2307) for which the Agency provided general comments. Despite Agency recommendations for further Phase 2 development, the sponsor has elected to move into Phase 3. The pivotal trials are being conducted with the lyophilized powder formulation and were not submitted for a special protocol assessment (SPA).
The above protocols and their protocol amendments in addition to protocols to evaluate the pre-filled syringe formulation (CAIN457A2308) and the autoinjector/ prefilled syringe configuration (CAIN457A2309) have been the subject of several Agency reviews and comments were conveyed.

The Agency has also held discussions with the applicant regarding a human factor study on the autoinjector and patient reported outcomes. The applicant submitted an initial Pediatric Study Plan to address PREA (see section 7.6.3 Pediatrics and Assessment of Effects on Growth).

2.6 Other Relevant Background Information

Study CAIN457A2303 used both EU-sourced Enbrel (etanercept) as an active comparator product to secukinumab, the primary drug under investigation. Because EU-sourced Enbrel is considered an investigative product in the US, this study was conducted under a separate IND (113,021). Within IND 113,021 exists a cross reference to IND 100,418 which currently contains all relevant information for the psoriasis indication for secukinumab.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical site of Drs. Papp and Szepietowski were selected for inspection because they were among the larger enrolling sites and study treatment exhibited somewhat greater efficacy than most other sites. OSI has determined that regarding both sites, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The clinical site of Dr. Bardur Sigurgeirsson was selected and inspected independently by the European Medicines Agency (EMA). The findings of the inspection are based on the Integrated Inspection Report shared by the EMA with FDA. Having reviewed EMA's inspection report on the conduct of Protocol CAIN457A2303 at Dr. Sigurgeirsson's site, OSI is in agreement that the data generated by this site appear acceptable in support of the respective indication.

3.2 Compliance with Good Clinical Practices

The applicant stated in the NDA submission that the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants. Written informed consent was obtained prior to the subject entering the studies. This reviewer did not find information to indicate that good clinical practices were not followed.

3.3 Financial Disclosures

See Clinical Investigator Financial Disclosure attachment. No potentially conflicting financial interests were identified based on information submitted by the applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Office of Biotechnology Products, OPS, CDER, recommends approval (see CMC reviews by Drs. Camilli and Kennett). The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that Cosentyx (secukinumab) be approved for human use (under conditions specified in the package insert). OBP also recommends the following Post-Marketing Commitments:

To re-evaluate secukinumab lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process for

- drug substance

- drug product (vial)
- drug product (prefilled syringe)

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Dr. Jill Merrill finds BLA 125504 is approvable from a pharmacology/toxicology perspective (see 8/7/14 review).

Secukinumab cross reacts with cynomolgus, rhesus and marmoset monkey IL-17A, but not with rodent IL-17A, making the cynomolgus monkey the most appropriate nonclinical species. Single-dose and repeat-dose toxicity and embryofetal development studies have been conducted with the cynomolgus monkey. A murine surrogate antibody against mouse IL-17A (BZN035) was developed and used for fertility and early embryonic development and peri- and postnatal development studies in mice. No treatment related effects on reproductive function, fertility or early embryo-fetal development were noted.

Repeat dose toxicity studies in monkeys indicated secukinumab was well tolerated at the injection site with no treatment-related pathology changes during the 26-week treatment and 13-week recovery period. Due to clinical chemistry effects and immunotoxicity (decreases in total lymphocytes, B cells and T cells) observed at the high dose, the NOAEL appears to be 50 mg/kg/week. Clinical dosing at 1/10th the NOAEL (300 mg/60 kg = 5 mg/kg) did not significantly decrease total lymphocytes.

4.4 Clinical Pharmacology

From a Clinical Pharmacology standpoint, the review team finds the BLA is acceptable for approval.

4.4.1 Mechanism of Action

Secukinumab binds to the proinflammatory cytokine interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in the normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis.

While the applicant purports that IL 17A is highly upregulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients, the clinical significance of this finding is

not clear, and this reviewer proposes [redacted] (b) (4)

4.4.2 Pharmacodynamics

The serum levels of total IL-17A (free and secukinumab-bound IL-17A) is low at baseline and increased following secukinumab treatment (at Week 4 and Week 12) in subjects with plaque psoriasis.

The applicant hypothesizes that the increase in total serum IL-17A concentrations is due to a slower clearance of IL-17A-secukinumab complex compared to free IL-17A. However, it is not clear to this reviewer what the implications of these differences in the dynamics of IL-17A would be clinically. Based on clinical trial data, this does not appear to impact the short-term efficacy or safety of secukinumab in the treatment of psoriasis. Whether there is an effect on long term safety or efficacy is unknown.

4.4.3 Pharmacokinetics (PK)

PK was evaluated in healthy subjects and in subjects with psoriasis in multiple secukinumab clinical trials. Secukinumab displayed PK properties typical of a human IgG immunoglobulin. The clearance and the volume of distribution values appear to be higher in subjects with psoriasis than in healthy subjects.

Pivotal trials evaluated the lyophilized (LYO) formulation. PK comparability of the proposed to-be-marketed presentations was demonstrated for only the prefilled syringe (PFS). The comparability between the PFS and the LYO was demonstrated by the PK results from the bioequivalence (BE) Study CAIN457A2106. The Applicant did not conduct a dedicated PK study to evaluate the comparability between the AI and the LYO. Results from the cross-study comparison of secukinumab trough concentrations in Phase 3 trials cannot support the PK comparability between the AI and the LYO. Secukinumab trough concentrations resulting from the AI administration appeared to be approximately 10%-30% higher across the two doses (150 mg and 300 mg) and two time-points (Week 4 and Week 12) in comparison to those resulting from the LYO administration. The cumulative distribution of the trough secukinumab concentration data at 12-weeks showed substantial overlap in exposures between observed exposures from the AI and other presentations.

Each of the presentations was evaluated in a small 52-week trial, for which 12 weeks of data is available. At the 150 mg dose, both PFS and AI showed similar efficacy results as LYO based on the IGA 0/1 and PASI 75 response rates at Week 12. However, at the 300 mg dose, AI appeared to have numerically higher response rates than LYO for both IGA 0/1 and PASI 75.

The Clinical Pharmacology review team recommends that the Applicant provides additional clinical experience with the AI presentation in the ongoing clinical study(ies) in lieu of a dedicated study comparing exposures between the AI and LYO presentations.

Reviewer comment: The PK differences between the AI and LYO presentations as seen by cross-study comparisons have been discussed between the clinical and clinical pharmacology teams. Given the limitations of cross-study comparisons and overlapping exposures, it is not clear to this reviewer if this represents a meaningful difference in exposure, and this has not been correlated to any demonstrated safety risk. The efficacy data for the 300 mg dose may support a difference in exposure; there does not appear to be a meaningful difference in safety based on cross-comparisons of LYO and AI at 12 weeks. However, given the short duration and the small number of subjects in the study evaluating the AI (trial 2309) the interpretation is limited. This reviewer does not conclude that a larger clinical trial evaluating the safety of the AI would provide substantially useful safety information and recommends monitoring for safety differences between the AI and LYO presentations in the ongoing LTE trials and in post-marketing.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The proposed indication is supported by the 52-week safety and efficacy data from the Phase 3 trials CAIN457A2302, CAIN457A2303, (hereafter referred to as 2302 and 2303, respectively) and 12-week safety and efficacy data from the Phase 3 trials CAIN457A2308, and CAIN457A 2309 (hereafter referred to as 2308 and 2309). An additional 6 Phase 2/3 trials have been conducted in psoriasis. Safety update reports were also provided in support of the current application.

Trials 2302, 2303, 2308 and 2309 were similarly designed to assess two secukinumab doses (150 mg and 300 mg). Trial 2303 included an active comparator arm with a non-US approved biologic (EU-approved Etanercept). Efficacy comparisons between secukinumab and the active comparator will not be discussed by this reviewer since without a demonstration of comparability between EU and US etanercept and without a confirmatory second study, comparability claims cannot be supported for labeling.

Three presentations of secukinumab: lyophilisate in vial (LYO), liquid in pre-filled syringe (PFS), and liquid in pen/autoinjector (AI) were evaluated. All psoriasis trials were conducted in patients with moderate to severe plaque psoriasis. Six phase 3 psoriasis trials were completed and summarized in the table below:

Table 2: Phase 3 studies in psoriasis

Study	Description	Formulation	N	Treatments
Placebo-controlled, active-controlled trials				
A2302 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Lyophilisate in vial	738	150 , 300 mg AIN, PBO[a] qw for 4 wk, then q4w to Wk 48
A2303 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled and active comparator (etanercept) comparison	Lyophilisate in vial	1306	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48 Etanercept 50 mg twice per week to Wk 12, then qw to Wk 51
A2308[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Pre-filled syringe	177	150, 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2309[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Autoinjector / pen	182	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2304 *(52 Wk)*	Maintenance of efficacy/safety (s.c.) in target population comparing maintenance regimens of continuous every 4 wk dosing vs. "Retreatment at start of relapse" – maintenance regimen comparison	Lyophilisate in vial	966	150, 300 mg AIN qw for 4 wk, then q4w until Wk 12[b,c] For PASI 75 responders: *Fixed Interval:* induction dose q4w to Wk 48 *Retreatment at start of relapse*[d]: PBO to relapse, then induction dose q4w till PASI 75 then PBO to relapse or Wk 48
A2307 *(40 Wk)*	Efficacy/safety of uptitration in partial responders at Wk 12 from A2304 – dose regimen comparison	Lyophilisate in vial	43	10 mg/kg i.v. or 300 mg s.c. AIN at randomization, Wk 2 and Wk 4, then 300 mg s.c. q4w to Wk 36

N=number of patients randomized
AIN = AIN457/secukinumab; LYO=lyophilisate in vial; PBO = placebo; PASI = Psoriasis Area and Severity Index
[a] = PASI 75 nonresponders on PBO were re-randomized 1:1 to 150 or 300 mg AIN and treated from Wk 12 onwards
[b] = PASI nonresponders discontinued study treatment
[c] = partial responders could enter Study A2307
[d] = start of relapse is a loss of ≥ 20% of the max. PASI gained in the study, with a loss of PASI 75 response
[e] = 12 weeks safety data of 52 week study
Source: [Tabular Listing of all Clinical Studies]

Four phase 2 trials were performed to support dose selection for phase III, only one of which included longer term maintenance therapy (150 mg SC q4w) per the following summary table:

Table 3: Phase 2 studies in psoriasis

Study	Description	Formulation	N	Treatments
A2102	Single dose (i.v.) in target population	Lyophilisate in vial	36	3 mg/kg AIN PBO
A2211	Multi-dose regimen finding (s.c.) in target population	Lyophilisate in vial	404	Induction 1 x 150 mg AIN 3 x 150 mg AIN at Wk 1, 5, 9 4 x 150 mg AIN at Wk 1, 2, 3, 5 5 x PBO at Wk 1, 2, 3, 5, 9 Maintenance in responders: *Fixed Interval:* 150 mg at Wk 13, 25 *Start of relapse:* 150 mg AIN, PBO at Wk 13, 25 Treatment in partial or non-responders: *Open label:* 150 mg s.c. q4w AIN until Wk 33
A2212	Multiple-loading dose regimen (i.v.) in target population	Lyophilisate in vial	100^	1 x 3 AIN at Day 1 1 x 10 mg/kg AIN at Day 1 3 x 10 mg/kg AIN at Day 1, 15, 29 3 x PBO at Day 1, 15 , 29
A2220	Dose-ranging (s.c.) in target population	Lyophilisate in vial	125	3 x 150 mg AIN at Wk 1, 5, 9 3 x 75 mg AIN at Wk 1, 5, 9 3 x 25 mg AIN at Wk 1, 5, 9 1 x 25 AIN at Wk 1 PBO at Wk 1, 5, 9
*A2204***	*Single dose (i.v.) in target population*	*Lyophilisate in vial*	*80*	*0.3, 1, or 3 mg/kg AIN* *PBO*

The Applicant is seeking approval for a secukinumab dose of 300 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly dosing starting at Week 4. Each 300 mg dose is given as 2 150 mg SC injections with one of the following proposed formulation and presentations:

- Injection: 150 mg/mL in a single-use prefilled SensoReady pen (AI, autoinjector)
- Injection: 150 mg/mL in a single-use prefilled syringe (PFS)
- Injection, powder for solution: 150 mg in a single-use vial (LYO)

5.2 Review Strategy

The results of the first 12 weeks of treatment were the primary source of efficacy data. The efficacy data from 12 to 52 weeks were reviewed primarily to support that any efficacy in the first 12 weeks was sustained to 52 weeks.

The safety review will primarily focus on safety data through Week 52 from Trials 2302 and 2303 and data through Week 12 from the Trials 2308 and 2309. Additional analyses were conducted on AEs of special interest based on safety issues seen in related drugs.

5.3 Discussion of Individual Studies/Clinical Trials

The 2 pivotal trials to support approval, 2302 and 2303, are described here.

Trial 2302
The study was designed to demonstrate efficacy after 12 weeks of secukinumab treatment compared to placebo administered subcutaneously, and to assess the safety, tolerability, and long-term efficacy up to 1 year in patients with moderate to severe chronic plaque psoriasis.

Trial 2303
This was a pivotal study to compare secukinumab to placebo with an anti-TNF biologic (EU approved etanercept) and to support EU registration of secukinumab. The study was designed to demonstrate efficacy after 12 weeks of treatment administered subcutaneously, and to assess the safety, tolerability, and long-term efficacy up to 1 year in patients with moderate to severe chronic plaque psoriasis.

2302 and 2303
Trials 2302 and 2303 were mostly identical in design except that Trial 2303 included an active biologic comparator arm (i.e., EU-sourced etanercept). Co-primary endpoints were PASI 75 and IGA 0 or 1 response at Week 12. Key secondary endpoints proposed were the following:

- The proportion of subjects with PASI 90 response at Week 12

- maintenance of PASI 75 after 52 weeks of treatment,
- maintenance of IGA 0 or 1 response after 52 weeks of treatment.

No maintenance comparisons of secukinumab could be made against the placebo arm because there was no placebo arm for the maintenance period.

Major inclusion criteria:

- ≥18 of age
- PASI score ≥12
- IGA score of at least 3
- BSA involvement ≥10%

Major exclusion criteria:

- Forms of psoriasis other than chronic plaque-type
- Pregnant or nursing (lactating) women
- Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy.
- Significant medical problems, including but not limited to the following: uncontrolled hypertension (≥160 systolic /95 diastolic mmHg), congestive heart failure [New York Heart Association status of class III or IV]
- Subjects with a serum creatinine level exceeding 176.8 µmol/L (2.0 mg/dL)
- Screening total WBC count <2,500/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL
- Chest X-ray or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening
- Active systemic infections during the last two weeks (exception: common cold) prior to randomization
- History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) at screening. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines.
- Known infection with HIV, hepatitis B or hepatitis C at screening or randomization
- History of lymphoproliferative disease or any known malignancy
- Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

Study Plan:
During the induction period (baseline to Week 8), subjects will receive a total of 12 weekly injections (2 injections of study treatment and/or placebo at baseline, Weeks 1, 2, 3, 4, and 8). During the Maintenance period (Week 12 to Week 48), subjects received a total of 26 injections (2 injections of study treatment and/or placebo at Week 12, 13,

14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48). While subjects were scheduled to be dosed once every four weeks from Weeks 12 to 48 for maintenance, during Weeks 13, 14, 15, subjects received a weekly dose of placebo to maintain blinding because non-responders from the placebo group that were re-randomized at Week 12 to either secukinumab 150 mg or 300 mg received weekly injections at Week 12, 13, 14, 15 followed by injections once every four weeks from Week 16 to Week 48.

For the maintenance period, only those subjects in the placebo group will be rerandomized depending on the PASI75 response at Week 12:

- PASI 75 responders at Week 12: continue on placebo
- PASI 75 nonresponders at Week 12: re-randomized 1:1 to 150 mg or 300 mg

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

6 Review of Efficacy

Efficacy Summary

Secukinumab (AIN457) 300 mg and 150 mg in lyophilisate in vial (LYO) were superior to placebo in the treatment of moderate to severe plaque psoriasis in two Phase 3 trials (2302 and 2303). The trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score ≥12, an Investigator's Global Assessment (IGA) score of at least 3, and body surface area (BSA) involvement ≥10% at baseline. Trial subjects randomized to receive secukinumab received injections once a week for the first 4 weeks and then once every 4 weeks through Week 52.

The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., ≥ 75% reduction in PASI score) at Week 12 and scoring IGA 0 or 1 at Week 12, with a secondary endpoint of PASI 90 response (i.e., ≥ 90% reduction in PASI score) at Week 12. Both secukinumab 300 mg and 150 mg were superior to placebo ($p<0.0001$) for the co-primary endpoints of PASI 75and IGA of 0 or 1, as well as the secondary endpoint of PASI 90 in each of the pivotal trials.

6.1 Indication

Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

6.1.1 Methods

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

In study 2303, the applicant included a non-US licensed active comparator (EU approved etanercept) study arm. At the beginning of application review, it was determined that the team would not consider data relating to the active comparator for labeling as these results were not replicated in a second trial.

6.1.2 Demographics

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

Table 4: Baseline Demographics for Trials 2302 and 2303

	Trial 2302			Trial 2303			
	AIN457 300mg N=245	**AIN457 150mg N=245**	**Placebo N=248**	**AIN457 300mg N=327**	**AIN457 150mg N=327**	**Placebo N=326**	**Etanercept N=326**
Gender							
Female	76 (31%)	77 (31%)	76 (31%)	103 (32%)	91 (28%)	89 (27%)	94 (29%)
Male	169 (69%)	168 (69%)	172 (69%)	224 (69%)	236 (72%)	237 (73%)	232 (71%)
Age							
Mean	45	45	45	45	45	44	44
SD	14	13	13	13	13	13	13
Range	19-76	18-83	19-80	20-79	18-79	18-82	18-79
Median	45	45	45	45	45	44	44
<65	228 (93%)	223 (91%)	229 (92%)	305 (93%)	304 (93%)	311 (95%)	308 (94%)
≥65	17 (7%)	22 (9%)	19 (8%)	22 (7%)	23 (7%)	15 (5%)	18 (6%)
Race							
Asian	52 (21%)	54 (22%)	46 (19%)	73 (22%)	72 (22%)	72 (22%)	74 (23%)
Black	4 (2%)	5 (2%)	10 (4%)	2 (1%)	3 (1%)	3 (1%)	0 (0%)
Caucasian	171 (70%)	171 (70%)	176 (71%)	224 (69%)	219 (67%)	217 (67%)	219 (67%)
Native American	7 (3%)	5 (2%)	3 (1%)	22 (7%)	28 (9%)	25 (8%)	27 (8%)
Pacific Islander	3 (1%)	1 (0.4%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.3%)
Other	6 (2%)	9 (4%)	13 (5%)	5 (2%)	5 (2%)	5 (2%)	4 (1%)
Unknown	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	1 (0.3%)
Weight							
Mean	88.8	87.1	89.7	83.0	83.6	82.0	84.6

SD	24.0	22.3	25.0	21.6	20.8	20.4	20.5
Range	48-186	48-159	43-192	45-219	42-163	42-148	42-176
Median	84	85	85	81	82	80	82
<90 kg	142 (58%)	141 (58%)	143 (58%)	220 (67%)	215 (66%)	217 (67%)	219 (67%)
≥ 90 kg	103 (42%)	104 (42%)	105 (42%)	107 (33%)	112 (34%)	109 (33%)	108 (33%)

Source: applicant's table

The predominant race in the trials is Caucasian which is consistent with the disease prevalence by race. The genetic components involved in psoriasis are complex and race is likely to be an indicator of genetic background. However, this reviewer has not been able to identify literature reports describing differential responses to previously approved psoriasis treatments based on race. Thus, it is reasonable to conclude that secukinumab would likely be effective across underrepresented races.

The baseline disease characteristics of IGA, PASI and BSA were generally balanced across treatment groups in Trials 2302 and 2303. Approximately 62% of subjects had a baseline IGA of 3 (moderate), and the rest of the subjects had a baseline IGA of 4 (severe). The mean PASI score was about 23 (the minimum for inclusion was a PASI score of 12). The table below shows the baseline disease severity for the pivotal trials.

Table 5: Baseline severity for Trials 2302 and 2303

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

Source: applicant's table

Subjects were required to have a baseline BSA involvement of at least 10% and averaged about 33% involvement. The disease severity appears to be consistent with intended indication of moderate to severe psoriasis.

6.1.3 Subject Disposition

Study 2302

Most randomized patients (700/738, 94.9%) completed the Induction period. Of the 700 patients who entered the maintenance period, 623 (89.0%) completed this period. The majority of patients originally randomized to placebo were re-randomized to secukinumab 150 mg or 300 mg starting at Week 12, as designated by the protocol if PASI 75 was not achieved at Week 12. The most common reasons for discontinuation of maintenance treatment among the 700 patients were adverse event (24/700, 3.4%), subject/guardian decision (17/700, 2.4%) and lack of efficacy (16/700, 2.3%).

Study 2303

Most randomized patients (1233/1306, 94.4%) completed the Induction period. Of the 1233 patients who entered the maintenance period, 1100 (89.2%) completed the maintenance period. The majority of patients originally randomized to placebo were re-randomized to secukinumab 150 mg or 300 mg starting at Week 12, as designated by the protocol if PASI 75 was not achieved at Week 12. The most common reasons for discontinuation of maintenance treatment among the 133 patients who discontinued were subject/guardian decision (44/1281, 3.4%), lack of efficacy (27/1281, 2.1%), and adverse event (21/1281, 1.6%).

For the pivotal studies, approximately 6% of subjects had missing data at the Week 12 visit, and per the protocol-specified primary imputation method, these subjects were treated as nonresponse for the efficacy analyses. With such low rates of missing data along with the large treatment effect, the impact of the imputation method on efficacy is minimal.

6.1.4 Analysis of Primary Endpoint(s)

The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., ≥ 75% reduction in PASI score) at Week 12 and scoring IGA 0 or 1 at Week 12, The table below summarizes the efficacy results for the co-primary endpoints for the two Phase 3 trials.

Table 6: Results of the Co-primary Efficacy Endpoints at Week 12

	Trial 2302			Trial 2303			
	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
Co-primary endpoints							
IGA of clear or almost clear	160 (65%)	125 (51%)	6 (2%)	202 (62%)	167 (51%)	9 (3%)	88 (27%)
PASI 75 Response	200 (82%)	174 (71%)	11 (4%)	249 (76%)	219 (67%)	16 (5%)	142 (44%)

Source: Agency reviewer table

Both secukinumab 300 mg and 150 mg were superior to placebo (p<0.0001) for the co-primary endpoints of PASI 75 response and IGA of 0 or 1 in each of the pivotal trials.

Reviewer comment: Although the 300 mg dose demonstrates better efficacy than the 150 mg when comparing study populations, a significant number of individual subjects achieve success at the lower dose. This reviewer finds that the minimum therapeutically effective dose would be optimal for a subset of patients given that the safety risks of this therapeutic biologic for long term use are not yet fully characterized. Ways to define the population who would benefit from the lower dose were explored and are presented in section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations below.

In addition to trials 2302 and 2303, two Phase 3 trials to support the safety and efficacy of secukinumab presentations prefilled syringe (2308) and autoinjector (2309) were conducted using the same co-primary endpoints. The table below shows the results of the co-primary endpoints at Week 12 for Trials 2308 and 2309.

Table 7: Co-primary Efficacy Endpoints at Week 12 using the Prefilled Syringe (Trial 2308) and Autoinjector (Trial 2309)

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

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

The results of the co-primary efficacy endpoints were statistically significant (p<0.0001). While the trials showed that the PFS and AI presentations were superior to placebo, the trials were not designed to address how the efficacies compare to those of the original LYO formulation of secukinumab. However, in comparing the efficacy results across trials, the response rates in Trials 2308 and 2309 were generally similar to those of trials 2302 and 2303.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoints proposed were the following:

- The proportion of subjects with PASI 90 response at Week 12
- maintenance of PASI 75 after 52 weeks of treatment,

- maintenance of IGA 0 or 1 response after 52 weeks of treatment.

No maintenance comparisons of secukinumab could be made against the placebo arm because there was no placebo arm for the maintenance period. Thus, only a comparison for PASI 90 is shown in the table below.

Table 8: Efficacy for secondary endpoint PASI 90 at Week 12

	Trial 2302			Trial 2303			
	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
Key secondary endpoint							
PASI 90 response	145 (59%)	95 (39%)	3 (1%)	175 (54%)	137 (42%)	5 (2%)	67 (21%)

Both secukinumab 300 mg and 150 mg were superior to placebo ($p<0.0001$) for the secondary endpoint of PASI 90 response in each of the pivotal trials.

Reviewer comment: The applicant proposes to include a labeling claim regarding PASI 90 stating the following:

> *In addition, PASI 90 response at week 12 was achieved with COSENTYX 300 mg and 150 mg compared to placebo in 59% (145/245) and 39% (95/245) versus 1% (3/248) of subjects, respectively (Trial 1) and 54% (175/327) and 42% (137/327) versus 2% (5/326) of subjects, respectively (Trial 2). Similar results were seen in Trials 3 and 4.*

Although PASI 90 claims have not been included in labeling for precedent psoriasis drugs, given that it is pre-specified, statistically significant and in this reviewer's opinion clinically meaningful, this reviewer recommends maintaining the applicant's proposal in labeling.

6.1.6 Other Endpoints

The sponsor developed a new 16-item patient-reported outcome (PRO) measure, the electronic Psoriasis Symptom Diary for the measurement of itching, pain and scaling in patients with chronic plaque psoriasis for use as secondary endpoint in phase 3 clinical trials. The 16 items of the diary evaluate signs and symptoms, patient-reported bother, and psoriasis-related daily impacts. The Study Endpoints team reviewed the applicant's patient-reported outcome measure. Dr. Yasmin Choudhry's review concludes that the sponsor has provided sufficient evidence to support the validity and reliability of these three items to support proposed labeling claim of improvements in itching, pain, and scaling provided that the clinical trial data are clinically meaningful and statistically robust as determined by the clinical and statistical review staff.

Patient reported outcomes (PRO) on itching, pain, and scaling were included as pre-specified secondary endpoints. However, not all centers had the Psoriasis Diary device available and subjects could elect not to use the device at sites where the device was available. As a result, approximately 40% of subjects from each trial participated in assessing the PRO responses on itching, pain, and scaling. Protocols did not call for minimum baseline itch, pain, scaling severities as inclusion criteria. As such, the level of itching, pain and scaling at baseline varied widely from no symptoms (i.e., score of 0) to severe symptoms (i.e., score of 10). The mean PRO scores for itching, pain, and scaling at baseline, as well as the mean score for each PRO by baseline IGA severity, and by IGA response (i.e., success or failure) at Week 12 are summarized in the biostatistical review.

Mean pain, itch and scaling scores at baseline generally correlated with IGA severity (i.e. higher for an IGA=4 than IGA=3).

In conclusion, for those subjects that reported the PROs, the improvement in the severity of psoriasis disease severity also led to the improvement in itching, pain, and scaling. This was even the case for the subjects who were of IGA failures, although the improvements were smaller in magnitude compared to those of the IGA successes. while the secukinumab 300 mg dose yielded higher IGA success rates compared to those of the 150 mg dose, the responses for itching, pain and scaling at Week 12 across the two secukinumab doses were similar. In addition, while the IGA as well as PASI 75 responses at Week 12 for the secukinumab doses were almost double the response as those for the etanercept, the itch responses at Week 12 for the secukinumab doses are only slightly higher in comparison to those for etanercept group.

The proposed PRO labeling claim is improvements in itching, pain, and scaling at Week 12 compared with placebo. The applicants proposed labeling is as follows:

> *(b) (4) improvements in signs and symptoms related to itching, pain, and scaling at week 12 compared to placebo (Studies 1 & 2) were (b) (4) using the (b) (4) Psoriasis Symptom Diary.*

Reviewer comment: The instrument to assess the PROs has been deemed valid. However, the robustness of this assessment from a statistical perspective is not ideal. The comparisons of the PRO endpoints were added to the testing strategy as secondary endpoints in the amended protocol. Only a subset of subjects participated in the PRO diary assessments.
Therefore,, it is not clear whether the findings from these endpoints are generalizable to the overall population because the subset assessed may not encompass a random sample of the total population.
The signs and symptoms of itching, pain and scaling are reasonably correlated with the disease. It is this reviewer's opinion that these are not clinically meaningful as they do not add information on the patient experience which can be the target of therapeutic

intervention with this biologic product. Thus, this reviewer finds the PRO elements do not warrant a labeling claim.

6.1.7 Subpopulations

The table below presents the IGA 0 or 1 success by gender, race, age, and weight strata at baseline for the pivotal trials. Efficacy responses were generally similar by subgroup analysis. Some lower responses were seen by race (Asian) and age (≥65) in trial 2303. However this is likely due to fewer numbers of subjects enrolled.

Table 9: IGA Success by Gender, Age, Race and Weight for Trials 2302 and 2303

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

Source: Agency reviewer's table

The IGA success by gender presented inconsistent findings across the pivotal trials for the female subjects by dose (higher response to 300 mg in trial 2302 and higher response to 150 mg in 2303). Subgroup analysis by gender/ dose in Trial 2304

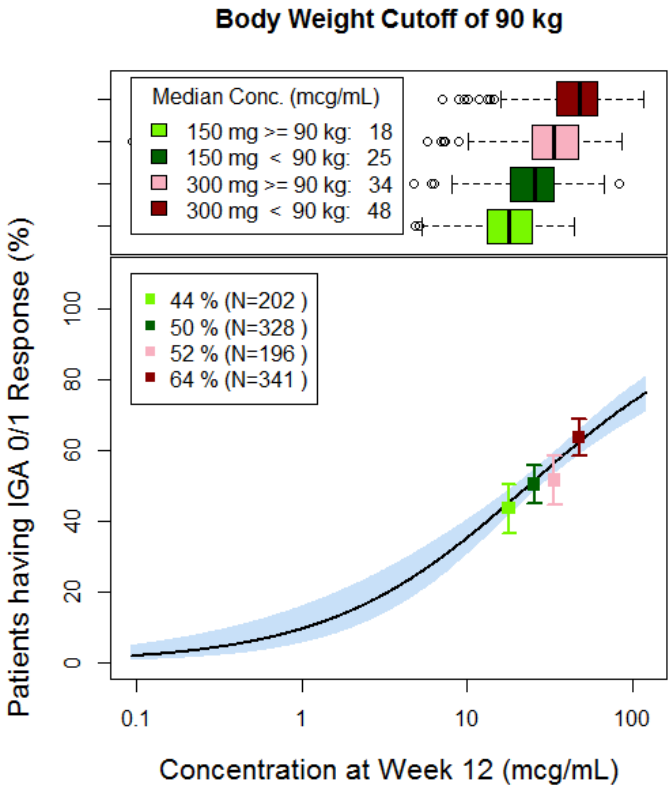
demonstrated higher IGA responses for both men and women with the secukinumab 300 mg dose.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy and safety of secukinumab evaluated in Phase 3 trials included two doses of secukinumab (150 mg or 300 mg). The efficacy results overall showed that both 150 mg and 300 mg doses of secukinumab are highly efficacious compared to placebo, however, a greater number of responders was shown in favor of the 300 mg dose compared to the 150 mg dose. See Table 6 above.

Bodyweight was identified as the major covariate significantly influencing secukinumab exposure. As shown in the clinical pharmacology review, multiple analyses support the role of higher secukinumab exposure as a significant factor in achieving a higher PASI 75 or IGA 0/1 response. Thus, bodyweight has an impact on efficacy response. Within each secukinumab dose group (150 mg or 300 mg), the trough concentrations of secukinumab and clinical response rates were generally higher in the lower body weight group as shown in the figure below.

Figure 1: Effect of body weight on exposure-response for IGA 0/1 at Week 12 in Trials 2302 and 2303



Source: Agency reviewer analysis

Mean serum concentration following 300 mg in patients with body weight < 90 kg (50.14 mcg/mL) is approximately 40% higher than that in patients with body weight ≥ 90 kg (36.14 mcg/mL). This difference in mean serum concentration between body weight group is slightly less pronounced following 150 mg (36%: < 90 kg (26.08 mcg/mL); ≥ 90 kg (19.20 mcg/mL).

When given the same 150 mg or 300 mg dose, the median trough secukinumab concentrations and the associated clinical response rates for PASI 75 and IGA 0/1 in subjects with bodyweight ≥90 kg in the 300 mg group were comparable to those in subjects with bodyweight <90 kg in the 150 mg group. Within each secukinumab dose of 150 mg or 300 mg, the clinical response rates were generally higher in the lower bodyweight group. Within each bodyweight subgroup, secukinumab dose of 300 mg showed consistently higher response rates when compared to the 150 dose regimen. See the table below.

Table 10: Week 12 response rates by body weight randomization strata in combined studies 2302 and 2303

Dose	150 mg			300 mg		
Body weight	**Overall**	**<90 kg**	**≥90 kg**	**Overall**	**<90 kg**	**≥90 kg**
PASI 75	68.9% (393/570)	73.5% (261/355)	61.4% (132/215)	79.0% (449/568)	82.7% (297/359)	72.7% (152/209)
IGA 0/1	51.1% (292/571)	54.5% (194/356)	45.6% (98/215)	63.7% (362/568)	67.7% (243/359)	56.9% (119/209)

Source: Table a65 Q4_1-1.1; Response to FDA IR, July 14, 2014

Reviewer comment: Subjects of lower bodyweight (<90 kg) were more likely to achieve success than higher bodyweight subjects at the 150 mg dose, yet this patient population saw an increase in response by increasing dose to 300 mg. Therefore, some (albeit a fewer number) of low bodyweight subjects appear to benefit from the higher dose. Although somewhat predictive of response, bodyweight does not appear to be the only factor.

It remains this reviewer's position that doubling the dose (and the potential risks that higher exposure may convey over time) is not necessary for a significant number of patients to achieve clinical success and there is value in prescribers understanding that option and the data behind this recommendation. Based on the conducted studies, it is difficult to define a population other than one based on weight for which the higher dose may be needed. It is not this reviewer's intent to limit access to those who would benefit from the 300 mg dose. However, it is very unlikely that the safety profile for secukinumab across a broader patient population has been fully characterized at this

juncture. Also, the effect of exposure on potential risks in a broader population is not known. For a subset of the study population, the risk/ benefit is more favorable for the 150mg dose than for the 300 mg dose.

Based on the correlation of bodyweight and efficacy the clinical pharmacology team is recommending the following PMC:

> To explore a higher dosing regimen for the subgroup of subjects with higher body weight We recommend that the Applicant explores a higher dose (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight (e.g., ≥90 kg) and evaluate the treatment effects and safety profiles in this subgroup to provide an option for those who cannot achieve the therapeutic goal at 300 mg dose. This recommendation is based on the lower observed clinical response rates (by approximately 10% with respect to both PASI 75 and IGA 0/1) in subjects with body weight ≥90 kg than those in subjects with body weight <90 kg at the recommended 300 mg dose where no safety concerns were observed. Simulations with the population PK model indicate that the secukinumab dose of 450 mg administered to subjects with body weight ≥90 kg would achieve a similar exposure as the recommended 300 mg dose in subjects with body weight <90 kg.

Reviewer comment: Because efficacy appears to correlate with exposure and body weight is a major determinant of exposure, it is reasonable to this reviewer that some patients of some higher body weight will benefit from a dose greater than 300 mg. Additionally, the exposure would not be expected to increase for these patients since it appears to correlate with bodyweight. This reviewer agrees with further evaluation to maximizing efficacy based on bodyweight. However, it is not clear to this reviewer as to which weight cut-off should be evaluated. Based on current data ≥90 kg may be a reasonable starting point that is supported by the exposure data from subjects <90 mg treated with the 300 mg dose. However, should additional dose-dependent safety risks arise, this weight cut-off may need to be raised. Trials that explore additional dose ranging information would be useful and this recommendation should be communicated to the applicant. However it is not clear to this reviewer that such a trial should be an obligation for the applicant until long term safety at the higher exposure (e.g. as seen in<90 mg patients treated with the 300 mg dose)is better characterized.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The table below shows the efficacy response at Week 52 for those subjects who were successes at Week 12. With continued treatment in the maintenance period (every 4 weeks), 76% and 63% of the subjects maintained their IGA success status at Week 52 for those that received secukinumab 300 mg and 150 mg, respectively. Similarly for the PASI 75 responses, 82% and 75% of the PASI 75 responders at Week 12 maintained

their PASI 75 responses at Week 52 for those that received the secukinumab 300 mg and 150 mg, respectively.

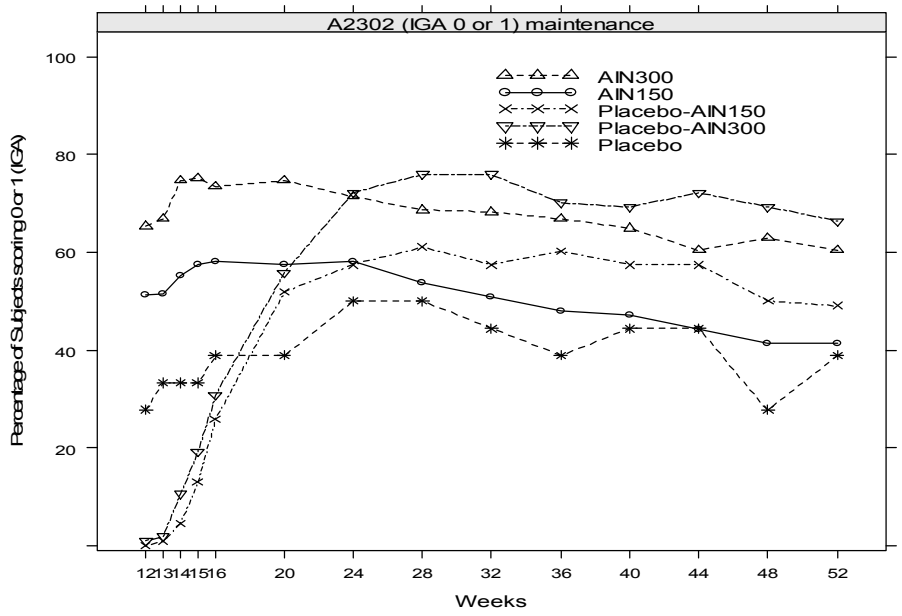
Table 11: Efficacy at Week 52 for Week 12 responders in trials 2302 and 2303

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

Source: Agency reviewer's table

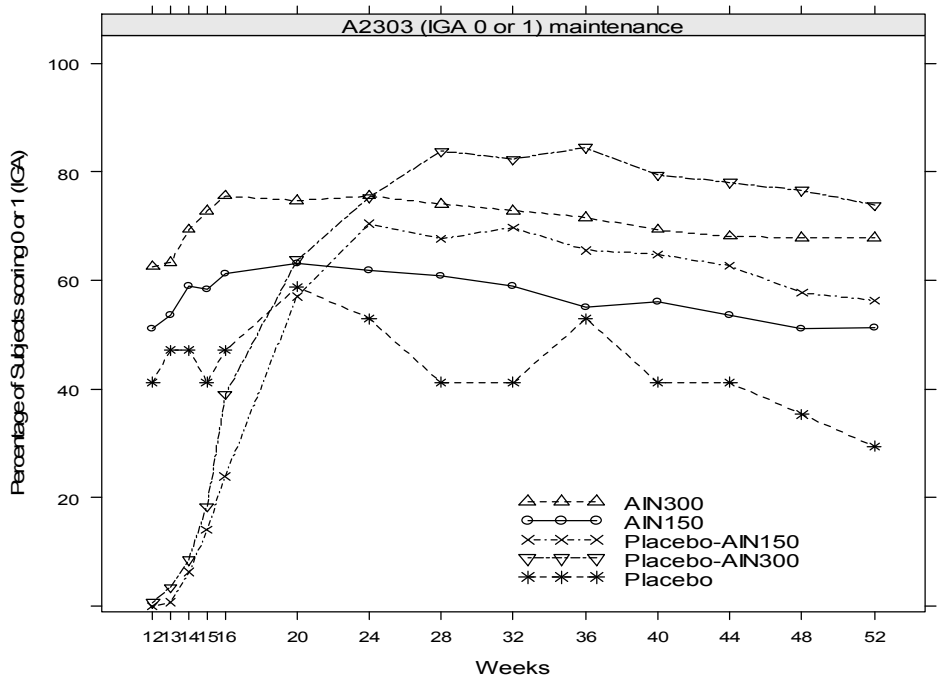
IGA 0 or 1 and PASI 75 responses in the maintenance period for the pivotal trials (2302 and 2303) were analyzed and presented in the biostatistical review. The figures below show the IGA responses over time.

Figure 2: IGA 0 or 1 responses for the Maintenance Period in Trial 2303



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

Figure 3: IGA 0 or 1 responses for the Maintenance Period in Trial 2303



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

A slight decline is noted in the response over time. It is not clear whether this is due to an actual loss of response or to missing data imputed as failures. The IGA and the PASI 75 responses were generally higher for the secukinumab 300 mg group compared to those of the secukinumab 150 mg group. Also noted is that subjects who were initially on placebo for the induction period had slightly higher response as compared to subjects on the same dose over the entire treatment period.

6.1.10 Additional Efficacy Issues/Analyses

Additional phase 3 trials included study 2304 that compared two maintenance regimens (i.e., retreatment at start of relapse (SoR) regimen versus the retreatment at fixed interval (FI) regimen) and 2307 that investigated uptitration in partial responders (i.e., PASI 50 but not PASI 75 responders).

2304

The primary objective of Trial 2304 was to demonstrate the non-inferiority of 150 mg and 300 mg of secukinumab administered at the start of relapse (SoR) versus the fixed interval (FI) regimens of 150 mg and 300 mg of secukinumab respectively with respect to PASI 75 response. In this multicenter, randomized, double-blind trial, a total of 843 subjects with moderate to severe chronic plaque-type psoriasis from about 133 global study sites were enrolled. Men or women who are ≥18 of age, PASI score ≥12, IGA score of at least 3, and BSA involvement ≥10% at baseline were randomized in a 1:1

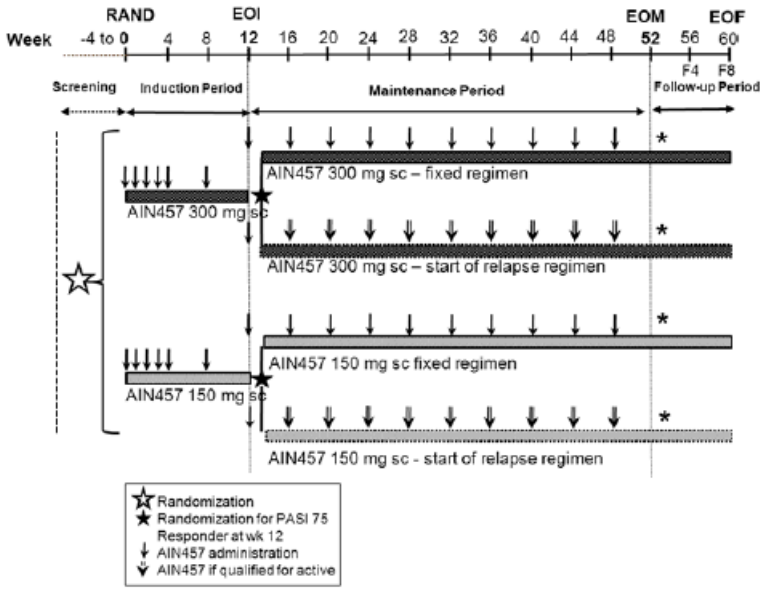
ratio to either secukinumab 300 mg or 150 mg. Randomized subjects were stratified by geographical region and body weight collected at baseline (<90 kg or ≥90 kg).

Subjects received treatment at randomization, Weeks 1, 2, 3, 4 and 8 with assessment at Week 12. Based on the Week 12 PASI 75 responses, these subjects were then re-randomized to one of the two maintenance treatment arms in a 1:1 ratio:

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

Subjects who finished the maintenance period entered the treatment-free follow-up period with visits on Weeks 56 and 60. The study design is shown below.

Figure 4: Study Design for Trial 2304



Source: Applicant figure

For the primary endpoint for Trial 2304 was defined as below:

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

The sponsor conducted non-inferiority testing of the retreatment at SoR regimen vs. the FI regimen using a non-inferiority margin (Δ) of 15%.

Of the 928 subjects who completed the induction period, a total of 843 (91%) of subjects were re-randomized to the maintenance period to either FI dosing or start of SoR dosing at their respective dose. Approximately 91% of subjects completed the 52-week maintenance period, and the discontinuation rate was highest for the 150 mg SoR arm (12%) compared to the other treatment arms (about 8%). The most common reason for discontinuation was subject/guardian decision (4%), and the rates were similar for 150 mg SoR and 150 mg FI, and also for 300 mg SoR and 300 mg FI arms. The discontinuation rate due to adverse events was highest for the 300 mg FI arm compared to the rest of the arms.

A comparison of the PASI 75 response rates of the retreatment at SoR regimen to the retreatment at FI regimen showed point estimates were about -10% different between the SoR and the FI regimens; however, the lower limit of the confidence interval was -20% which exceeded the prespecified -15% margin. Thus, the non-inferiority of the SoR regimen to the FI regimen was not achieved. The results are shown in the table below.

Table 12: Comparison of PASI 75 Response at Week 52 for Trial 2304

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

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

Reviewer comment: Precedent labelling for ustekinumab does contain information regarding randomized withdrawal outcomes. The applicant is not proposing labeling claims based on this trial [redacted] [b) (4)] *Although this reviewer finds that information on randomized withdrawal would be useful to prescribers in titrating therapy, without a demonstration of non-inferiority, it is unclear how this information could guide the use of secukinumab differently than current medical management of biologic therapy.*

2307

The primary objective of Trial 2307 was to demonstrate the efficacy of intravenous (i.v.) versus subcutaneous (s.c.) administration of secukinumab in moderate to severe plaque type psoriasis subjects who achieved a partial response after 12 weeks of treatment in Study 2304 with respect to both PASI75 and IGA 0 or 1 response at Week 8.

The sample size was small (43 subjects) due to a higher than anticipated induction response rate and the study was not powered to evaluate the effect of dose escalation. However, we conducted an exploratory subgroup analysis of partial responders receiving subcutaneous doses of 150 mg during the induction period. This analysis

showed that a substantial number of subjects had clinical benefits from dose escalation to either 300 mg sc or 10 mg/kg iv. This table below shows the Agency's analysis.

Table 13: Partial Responders to 150 mg may benefit from higher doses

Escalated Dose	Weight Group	N	PASI 75	IGA 0/1
300 mg sc	All	15	10 (67 %)	6 (40%)
	≥ 90 kg	9	5 (56%)	4 (44%)
	< 90 kg	6	5 (83%)	2 (33%)
10 mg/kg iv	All	14	12 (86%)	9 (64%)
	≥ 90 kg	7	7 (100%)	5 (71%)
	< 90 kg	7	5 (71%)	4 (57%)

Source: Agency reviewer table

For escalation to the 300 mg dose, a number of subjects (regardless of weight) had improved PASI and IGA scores. For uptitration to 10 mg/kg iv, clinical benefits were also seen and were greater in the subjects with weights >90 kg. The overall trial did not meet the required statistical significance for the coprimary endpoints, although there were trends in favor of the i.v. dose.

Reviewer comment: The utility of the study findings is limited due to the small sample size. Because of the small number of subjects, additional studies would be needed to support dose escalation in partial responders.

7 Review of Safety

Safety Summary

This review considers the safety data for Cosentyx (secukinumab) as presented in BLA 125504.The number of individuals exposed to secukinumab in the BLA trials exceeds ICH guidelines, and is adequate for Agency evaluation of safety in subjects with psoriasis. Novartis reported that 3430 psoriasis subjects were exposed to at least one dose of secukinumab (1395 subjects on 150 mg and 1410 subjects on 300 mg). 2751 subjects treated for at least 6 months and 1641 subjects treated for at least 1 year.

Investigators exposed reasonable numbers of subjects to the proposed dose (300 mg loading dose at weeks 0, 1, 2, 3, 4, 8) 690 subjects on 300 mg. An additional 692 subjects were exposed to a loading dose of 150 mg. The majority of the subjects continued maintenance dosing every 4 weeks until Week 48. Long term studies are ongoing.

There were no notable inconsistencies across the data sources (summaries, reports, data sets, etc.). The routine safety monitoring in the clinical trials seemed appropriate and capable of identifying major safety signals with secukinumab.

Deaths occurred infrequently in the clinical trials and the safety data did not suggest an increased mortality risk in subjects exposed to secukinumab. In reviewing the individual narratives for deaths in patients exposed to secukinumab, there did not appear to be treatment-related causes of death.

In general, this reviewer agrees with the applicant's safety assessments. The overall safety profile appears to be similar to other biologic products approved for the treatment of plaque psoriasis. Given the efficacy results described in the previous section, this reviewer concludes that the applicant has provided a positive risk benefit analysis for secukinumab in this application.

7.1 Methods

This section will primarily focus on review of the safety data through Week 52 from Trials 2302 and 2303 and data through Week 12 from the Trials 2308 and 2309. Data in individual trials 2302 and 2303, the largest trials was reviewed individually and as part of pooled data. As the trial designs were similar, the safety analysis was conducted by pooling the safety data at 12 weeks and 52 weeks. Follow-up safety data provided in the Safety Update Report was also reviewed. Primary safety analyses evaluated treatment-emergent adverse events (AEs), serious AEs (SAEs), severe and life-threatening AEs, AEs leading to discontinuation, deaths and laboratory abnormalities in the Phase 3 trials. Additional analyses of AEs of special interest were conducted. These were chosen based on AEs seen with similar precedent immunomodulatory products.

In study 2303, the applicant included a non-US licensed active comparator (EU approved etanercept) study arm. At the beginning of application review, it was determined that the team would not consider data relating to the active comparator for labeling as these results were not replicated in a second trial. This review will not describe safety comparisons between secukinumab and the non-US licensed active comparator in detail. This reviewer used the safety outcome from the active etanercept comparator to provide a general context for some of the AEs known to occur with the use of TNF-alpha inhibitors.

Safety comparisons between active and placebo arms were consistent through the primary endpoint time point of 12 weeks, but diverged in longer term extension assessments. There are differing sample sizes between the active and placebo arms as well as differing durations of therapy for many patients as time progressed over the 52 weeks of follow-up in long term extension trials. Placebo patients experienced high

efficacy failure rates and dropout rates, and could be placed on active therapy in extension trials. Thus, the numbers of placebo patients became quite small. Exposure-adjusted analysis was used to assess safety beyond 12 weeks.

Studies 2308 and 2309 were conducted as supportive studies which evaluated the PFS and AI presentations. The studies are small (subjects for 2308 and for 2309) and the safety data submitted was of 12 week duration. The safety of the PFS and AI will be based primarily on the results from the pivotal studies. Trials 2308 and 2309 are considered supportive.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

At the time of BLA submission, 5044 subjects were enrolled in 34 trials evaluating secukinumab for various diseases. 10 of these studies, which included 3993 subjects, were conducted in plaque psoriasis. The psoriasis phase III program was initiated in 2011, and is comprised of six phase III studies (2302, 2303, 2304, 2307, 2308, 2309). Trials assessed three presentations of secukinumab (lyophilisate in vial, liquid in pre-filled syringe, and liquid in pen/autoinjector). The four pivotal and 2 additional supportive phase 3 trials in patients with psoriasis are described in the table below.

Table 14: Summary of Phase 3 Trials in Psoriasis

Study	Description	Formulation	N	Treatments
Placebo-controlled, active-controlled trials				
A2302 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Lyophilisate in vial	738	150 , 300 mg AIN, PBO[a] qw for 4 wk, then q4w to Wk 48
A2303 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled and active comparator (etanercept) comparison	Lyophilisate in vial	1306	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48 Etanercept 50 mg twice per week to Wk 12, then qw to Wk 51
A2308[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Pre-filled syringe	177	150, 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2309[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Autoinjector / pen	182	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48

A2304 *(52 Wk)*	Maintenance of efficacy/safety (s.c.) in target population comparing maintenance regimens of continuous every 4 wk dosing vs. "Retreatment at start of relapse" – maintenance regimen comparison	Lyophilisate in vial	966	150, 300 mg AIN qw for 4 wk, then q4w until Wk 12[b,c] For PASI 75 responders: *Fixed Interval:* induction dose q4w to Wk 48 *Retreatment at start of relapse*[d]: PBO to relapse, then induction dose q4w till PASI 75 then PBO to relapse or Wk 48
A2307 *(40 Wk)*	Efficacy/safety of uptitration in partial responders at Wk 12 from A2304 – dose regimen comparison	Lyophilisate in vial	43	10 mg/kg i.v. or 300 mg s.c. AIN at randomization, Wk 2 and Wk 4, then 300 mg s.c. q4w to Wk 36

N=number of patients randomized
AIN = AIN457/secukinumab; LYO=lyophilisate in vial; PBO = placebo; PASI = Psoriasis Area and Severity Index
[a] = PASI 75 nonresponders on PBO were re-randomized 1:1 to 150 or 300 mg AIN and treated from Wk 12 onwards
[b] = PASI nonresponders discontinued study treatment
[c] = partial responders could enter Study A2307
[d] = start of relapse is a loss of ≥ 20% of the max. PASI gained in the study, with a loss of PASI 75 response
[e] = 12 weeks safety data of 52 week study
Source: Applicant SCS Table 1-1

Four Phase 2 trials were performed to support dose selection for Phase 3, only one of which included longer term maintenance therapy (150 mg SC q4w). Study (2204) was excluded from the analysis due to data quality concerns. Specifically, center 0001 enrolled 65/ 80 patients in the trial, but was found to have GCP violations that resulted in the site being closed. Deficiencies included failure to protect blinding, failure to administer study drug infusions as per protocol, and failure to maintain adequate records resulting in underreporting of AEs. The safety results of study 2204 were therefore considered separately and not included in the data pools for this review. The Phase 2 trials are shown in the table below.

Table 15: Summary of Phase 2 Trials in Psoriasis

Study	Description	Formulation	N	Treatments
A2102	Single dose (i.v.) in target population	Lyophilisate in vial	36	3 mg/kg AIN PBO
A2211	Multi-dose regimen finding (s.c.) in target population	Lyophilisate in vial	404	Induction 1 x 150 mg AIN 3 x 150 mg AIN at Wk 1, 5, 9 4 x 150 mg AIN at Wk 1, 2, 3, 5 5 x PBO at Wk 1, 2, 3, 5, 9 Maintenance in responders: *Fixed Interval:* 150 mg at Wk 13, 25 *Start of relapse:* 150 mg AIN, PBO at Wk 13, 25 Treatment in partial or non-responders: *Open label:* 150 mg s.c. q4w AIN until Wk 33
A2212	Multiple-loading dose regimen (i.v.) in target population	Lyophilisate in vial	100*	1 x 3 AIN at Day 1 1 x 10 mg/kg AIN at Day 1 3 x 10 mg/kg AIN at Day 1, 15, 29 3 x PBO at Day 1, 15 , 29
A2220	Dose-ranging (s.c.) in target population	Lyophilisate in vial	125	3 x 150 mg AIN at Wk 1, 5, 9 3 x 75 mg AIN at Wk 1, 5, 9 3 x 25 mg AIN at Wk 1, 5, 9 1 x 25 AIN at Wk 1 PBO at Wk 1, 5, 9
*A2204***	*Single dose (i.v.) in target population*	*Lyophilisate in vial*	*80*	*0.3, 1, or 3 mg/kg AIN* *PBO*

Source: Applicant SCS Table 1-2

7.1.2 Categorization of Adverse Events

The coding of adverse events in the BLA appeared adequate and allowed for accurate estimation of adverse event risks.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data was pooled for analysis. This reviewer focused primarily on 2 data pools provided by the applicant, pool A and pool B. Pool A consisted of the 4 randomized, placebo-controlled studies 2302, 2303, 2308, and 2309. Pool A provides short-term safety data with comparable numbers of subjects for secukinumab 150 mg, 300mg and placebo through week 12. This data pool included 1382 subjects who received any dose of secukinumab. Of those approximately half received 150mg (692 subjects) and half received 300 mg (690 subjects) and a similar number of subjects received placebo.

Another analysis provided pooled safety data from all 10 psoriasis trials (Pool B) which included a broader range of doses and/or dosing regimens. Various loading and maintenance doses, routes of administration, alternative dosing intervals and duration of treatment are included in this pooled analysis. Pool B provides safety data through week 52 with dosing ranges of 3 to 30 mg/kg (i.v.); 25 to 300 mg (s.c.). 3430 subjects received any dose of secukinumab. Of those, 2751 subjects were treated for at least 6 months and 1641 subjects treated for at least 1 year. Due to differing sample sizes

between the active and placebo arms and differing durations of therapy, treatment arms were compared using exposure-adjusted rates.

The applicant provided an additional pooled safety analysis (pool C) of all secukinumab trials which were conducted for various indications. The greater number of subjects in Pool C (N=5044) could increase the likelihood of detecting rare AEs. However, due to population differences, the interpretation of safety risk data in this pooled analysis is limited.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of individuals exposed to secukinumab in the BLA trials exceeds ICH guidelines. Novartis reported that 3430 psoriasis subjects were exposed to at least one dose of secukinumab (1395 subjects on 150 mg and 1410 subjects on 300 mg). 2751 subjects treated for at least 6 months and 1641 subjects treated for at least 1 year.

Investigators exposed reasonable numbers of subjects to the proposed dose (300 mg loading dose at weeks 0, 1, 2, 3, 4, 8), 690 subjects on 300 mg. An additional 692 subjects were exposed to a loading dose of 150 mg. The majority of the subjects continued maintenance dosing every 4 weeks until Week 48. Long term studies are ongoing.

Analysis of the number of injections of active treatment given to subjects in Pool B supports that a reasonable number of subjects were exposed to the 300 mg dose for nearly 1 year. The table below summarizes the distribution of injections by dose.

Table 16: Number of active injections – Entire treatment period (Pool B: All psoriasis trials – Safety set)

	Any AIN457 150 mg N=1395 n (%)	**Any AIN457 300 mg N=1410 n (%)**	**Any AIN457 dose N=3430 n (%)**	**Placebo N=793 n (%)**	**Etanercept N=323 n (%)**
Total number of injections					
n	1395	1410	3430	793	323
Mean	46.8	47.1	40.1	21.9	92.5
Median	32.0	32.0	32.0	12.0	102.0
Min – Max	2 - 114	2 - 111	1 - 114	1 - 103	3 - 112
Total number of active or placebo injections*					
n	1395	1410	3430	793	323
Mean	12.7	25.5	17.0	21.9	57.9
Median	14.0	30.0	16.0	12.0	64.0
Min - Max	1 - 17	2 - 33	1 - 33	1 - 103	1 - 74

*Total number of AIN457 injections for AIN457 150 mg, AIN457 300 mg and Any AIN457 dose groups; total number of placebo injections for the placebo group; total number of etanercept injections for the etanercept group.
Source SCS table 1-11

For 1 year of treatment per the proposed dosing the number of doses expected would be 16: an induction period of 6 doses (Weeks 0, 1, 2, 3, 4, and 8) and maintenance period of 10 doses (Week 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48). The median number of active injections was 14 (14 doses) for 150mg and 30 injections (15 doses) for 300 mg. This indicates that approximately 700 subjects received 1 year of treatment for each dose.

Demographics of the target population

For the overall secukinumab Phase 3 experience, a majority of the subjects were Caucasian (72%), males (70%) and the average age of participants was 44.8 years (with a range of 18-85 years). A summary of the demographic data is below.

Table 17: Demographics of subjects in studies 2302, 2303, 2308 and 2309 induction period

Demographic variable	**AIN457 150 mg N=692**	**AIN457 300 mg N=690**	**Placebo N=694**	**Etanercept N=323**	**Total N=2399**
Age group in years, n (%)	634 (91.6)	642 (93.0)	651 (93.8)	305 (94.4)	2232 (93.04)
< 65					
≥ 65	58 (8.4)	48 (7.0)	43 (6.2)	18 (5.6)	167 (6.96)
≥ 75	10 (1.4)	6 (0.9)	10 (1.4)	3 (0.9)	29 (1.21)
Age (years)					
n	692	690	694	323	2399
Mean	45.1	44.9	44.7	43.8	44.8

SD	13.38	13.32	12.79	12.99	13.14
Median	45.0	45.0	45.0	44.0	45.0
Min - Max	18 - 83	18 - 83	18 - 82	18 - 79	18 – 83
Sex, n (%)					
Female	207 (29.9)	214 (31.0)	208 (30.0)	94 (29.1)	723 (30.14)
Male	485 (70.1)	476 (69.0)	486 (70.0)	229 (70.9)	1676 (69.86)
Race, n (%)					
Caucasian	499 (72.1)	504 (73.0)	511 (73.6)	216 (66.9)	1730 (72.11)
Black	13 (1.9)	9 (1.3)	13 (1.9)	0 (0.0)	35 (1.46)
Asian	129 (18.6)	129 (18.7)	121 (17.4)	74 (22.9)	453 (18.88)
Native American	33 (4.8)	29 (4.2)	28 (4.0)	27 (8.4)	117 (4.88)
Pacific Islander	1 (0.1)	4 (0.6)	1 (0.1)	1 (0.3)	7 (0.29)
Unknown	1 (0.1)	2 (0.3)	2 (0.3)	1 (0.3)	6 (0.25)
Other	16 (2.3)	13 (1.9)	18 (2.6)	4 (1.2)	51 (2.13)
Weight (kg)					
n	692	690	694	323	2399
Mean	86.60	86.56	86.05	84.45	86.14
SD	23.150	23.226	22.590	20.542	22.673
Median	84.00	83.91	83.25	81.60	83.30
Min - Max	43.1 - 215.0	45.0 - 219.1	42.0 - 191.9	42.0 - 175.6	42.0 - 219.1
BMI (kg/m^2)					
n	692	687	693	321	2393
Mean	29.38	29.40	29.08	28.71	29.21
SD	7.031	6.891	6.929	5.942	6.824
Median	28.32	28.10	27.83	27.64	28.03
Min - Max	16.5 - 79.7	17.4 - 67.4	16.2 - 71.2	15.4 - 58.3	15.4 - 79.7

Source: sponsor table 1-17 summary of clinical safety

The Agency analyzed the baseline demographics for the pivotal trials (2302 and 2303). See 9/8/14 Biostatistical Review for Agency analysis. The percentages were similar to the pooled data. The baseline demographics were generally balanced across the treatment arms for the two pivotal trials (2302 and 2303). Subjects were predominantly male, Caucasian and Asian, with an age mean and median in the 5th decade of life. The mean weight was about 88 kg in Trial 2302 and 83 kg in Trial 2303.

7.2.2 Explorations for Dose Response

A range of doses and dosing regimens were explored in Phase 2 studies to explore dose-response. The Phase 2 efficacy data overall supported the selection of the 150 mg dose to be tested in Phase 3 and suggested that early induction doses could achieve a higher clinical response rate at Week 12. The selection of the 300 mg SC dosing regimen for Phase 3 trials was supported by model-based PK simulations.

The applicant evaluated 2 doses 150mg and 300 mg in the phase 3 studies. Since two doses were selected for further Phase 3 evaluation, it allowed for further assessment of dose-response in a much larger patient population. Safety data comparing both doses was available for approximately 700 subjects each for maximal duration of dose. Overall, a slightly higher proportion of subjects were exposed to the 150 mg dose because this dose was evaluated in Phase 2 studies (as represented in Pool B).

52 weeks exposure (with monthly dosing) is the maximal duration of dose studied at the time of application submission. This has been found to be an acceptable pre-market duration of treatment for approval of precedent biologics for the treatment of psoriasis. However, for a chronic disease in which the treatment controls symptoms, but is not curative, long-term safety information is needed and has been shown to provide additional useful safety information. The applicant has proposed to continue open-label extension studies to provide 4 years of additional long term data (A2302E1 and A2304E1) which utilizes the same dosing regimen as Phase 3. These studies are ongoing at the time of this submission. While the data these extension studies provide will not be optimal, this reviewer finds this approach most practical and thus a reasonable way to proceed.

7.2.3 Special Animal and/or In Vitro Testing

In the pivotal cynomolgus monkey study, AIN457 derived from CHO cells was administered intravenously (15, 50, 150 mg/kg/week; 4/sex/group) for 26 weeks followed by a 13-week recovery period (2/sex for control and high dose group only; study # 502618; IND 100418, entered in DARRTS 2-4-2010). AIN457 appeared to cause decreases in CD4+ T lymphocytes and increases in CD16+ lymphocytes at the high dose and decreased NK cell activity at the mid- and high-dose levels. Immunotoxicity was observed in one high-dose female that developed skin lesions (treated with antibiotics), splenic lymphocytic atrophy, decreased NK cell activity, and decreased T-cell dependent antigen response. Based on these data, the NOAEL appears to be 50 mg/kg/week with an $AUC_{0\text{-}168\ hr}$ of 316000 µg ●hr/mL.

Clinical dosing at $1/10^{th}$ the NOAEL (300 mg/60 kg = 5 mg/kg) did not significantly decrease total lymphocytes.

The pharmacology/toxicology team concluded that no treatment related effects on any of the neurological, cardiovascular or respiratory parameters were noted single intravenous doses of secukinumab up to 100 mg/kg in cynomolgus monkeys and no qualitative or quantitative electrocardiographic or neurological changes attributable to secukinumab administration in all repeated dose toxicity studies.

7.2.4 Routine Clinical Testing

Safety assessments consisted of:

- Monitoring of all spontaneous AEs and SAEs, with their severity and relationship to study drug, and pregnancies
- Hematology, blood chemistry and urine and regular assessments of vital signs, ECGs, physical condition, height and body weight
- Immunogenicity

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic pathway of secukinumab has not been characterized. It is assumed that as a human IgG1κ monoclonal antibody secukinumab is degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

In subjects with psoriasis, the mean half-life values of secukinumab ranged from 22 to 31 days and the mean apparent clearances values ranged from 0.14 to 0.22 L/day across several clinical trials. The apparent clearance appears to be higher in psoriasis patients than in healthy subjects. Body weight was a significant intrinsic factor for clearance. Secukinumab clearance increases with increasing body weight.

No formal studies were conducted in subjects with renal impairment. Secukinumab is a human IgG immunoglobulin with large molecular size of approximately150 kDa; therefore, non-degraded secukinumab is unlikely to be filtered by kidney or excreted in urine.

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

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential risks based on class of drug (anti-cytokine) and of the drug substance (foreign protein) were analyzed. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular/cerebrovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity. These AEs of special interest are described in section 7.3.5 Submission Specific Primary Safety Concerns.

7.3 Major Safety Results

7.3.1 Deaths

A total of 6 deaths were reported through 31-Jul-2013 across all psoriasis trials and the safety data did not suggest an increased mortality risk in psoriasis subjects exposed to secukinumab. There were no deaths reported in the 12 week pooled analysis of studies 2302, 2303, 2308 and 2309. The reported causes of death included the following: 1) cerebral hemorrhage; 2) intestinal ischemia; 3) disseminated aspergillosis infection; 4) unknown cause; 5) myocardial infarction; 6) suicide; 7) alcohol poisoning. The 6 deaths reported in the original application are described in the table below. One new death was reported in the safety update and is discussed in section 7.7 Additional Submissions / Safety Issues.

Table 18: Deaths in all psoriasis trials

PID Age/sex/race Treatment	Cause of death (Preferred term)	Risk factors	Day of death (study period)	No. days from last dose to onset*	Study drug related
Secukinumab on-treatment					
[AIN457A2304- 66/M/As AIN457 150 mg SoR	Cerebral (hemorrhagic stroke)	High fasting High hsCRP (11xULN)	Day 319	12	Not
Secukinumab off-treatment					
AIN457A2211E1-0084-00025§ 57/M/Ca AIN457 150 mg q4w	Intestinal ischemia, Hyperkalemia and renal failure	Hypertension, diabetes dyslipidemia	Day 1041 (Extension)	32	Not suspected
AIN457A2211E1-0039-00001§ 64/M/Ca AIN457 150 mg q12w	Disseminated aspergillosis Infection (Aspergillosis)	History of liver cirrhosis, 2 liver transplants within 5 days, use of infliximab	Day 436 (Post-study)	370	Not suspected**
Placebo to secukinumab off-treatment					
[AIN457A2302-3081008] 27/M/As Placebo-AIN457 300 mg	Unknown cause	Alcoholic liver disease, QTc prolonged	Day 285 (Post-study)	112	Not suspected
Placebo off treatment					
[AIN457A2220-0050-	Myocardial	Coronary bypass	Day 102	43	Not

00003] 53/M/Ca Placebo	infarction (myocardial infarction)	surgery, myocardial infarction and hypertension	(Follow-up)		suspected
No treatment					
[A2303-3305-5004] (35/M/Ca) No treatment	Committed suicide (Complete suicide)	None reported	Screening period	Not applicable	Not suspected

Source: Applicant's SCS Table 2-9

Four deaths were reported in subjects exposed to secukinumab; one death was reported on placebo; one of the deaths was a completed suicide that occurred during the screening period before any drug was administered. In each of these cases, the subject's death was judged unrelated to secukinumab by the investigator.

Reviewer comment: This reviewer finds the cases to be confounded and causality cannot be definitively attributed to the treatment. Subject AIN457A2211E1-0039-00001, who died from disseminated aspergillosis status-post liver transplant, developed autoimmune hepatitis on secukinumab treatment requiring the transplant. This AE report was reviewed (see review by A. Woitach in DARRTS 6/6/12) and this reviewer concluded that the individual case does not provide definitive causality for any of the reported events.

It is this reviewer's opinion that the cases reporting death do not appear to represent a treatment related safety signal at this juncture. Based on the deaths which occurred in trials, cardiovascular risks and autoimmune diseases should be monitored by post-marketing surveillance.

7.3.2 Nonfatal Serious Adverse Events (SAE's)

In the 12-week pooled analysis of Trials 2302, 2303, 2308 and 2309 (Pool A), the incidence of SAEs was low and comparable for both doses of secukinumab and placebo (2.0% for both 300 mg and 150 mg vs. 1.7% for placebo). Reported SAEs by MedDRA System Organ Class (SOC) are shown in the table below.

Table 19: SAEs by primary system organ class (Pool A)

Primary system organ class	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 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)
Injury, poisoning and procedural complications	3 (0.4)	3 (0.4)	6 (0.43)	3 (0.4)	0 (0.0)
Gastrointestinal disorders	3 (0.4)	1 (0.1)	4 (0.29)	0 (0.0)	0 (0.0)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4)	1 (0.1)	4 (0.29)	0 (0.0)	0 (0.0)
Cardiac disorders	2 (0.3)	1 (0.1)	3 (0.22)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.1)	2 (0.3)	3 (0.22)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	3 (0.4)	0 (0.0)	3 (0.22)	0 (0.0)	0 (0.0)
Infections and infestations	1 (0.1)	1 (0.1)	2 (0.14)	2 (0.3)	0 (0.0)
Metabolism and nutrition disorders	1 (0.1)	1 (0.1)	2 (0.14)	0 (0.0)	0 (0.0)
Psychiatric disorders	2 (0.3)	0 (0.0)	2 (0.14)	2 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.3)	0 (0.0)	2 (0.14)	4 (0.6)	0 (0.0)
General disorders and administration site conditions	1 (0.1)	0 (0.0)	1 (0.07)	1 (0.1)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.00)	1 (0.1)	0 (0.0)

Source: Applicant SCS Table 2-11

No SAE was reported in any SOC with greater than 1% frequency. Serious psychiatric disorders were reported with comparable frequency between 150 mg and placebo: 2 patients or 0.3% each in the 150 mg group (insomnia and suicide attempt) and the placebo group (major depression, panic attack, alcohol withdrawal syndrome). SAEs in selected risks, such as Cardiovascular and cerebrovascular (CCV) events and malignancies, showed small imbalances for secukinumab and will be discussed further in section *7.3.5 Submission Specific Primary Safety Concerns*.

The most frequent SAEs (occurring in ≥ 2 patients in secukinumab subjects) by preferred term in the induction period of Pool A studies were overdose and pulmonary edema. Overdose is discussed in section 7.6.4. Two subjects on 150 mg secukinumab experienced pulmonary edema.

- Patient [AIN457A2309-8001006], with a 52-year history of psoriasis, stable coronary artery disease, atrial fibrillation and dysuria, was diagnosed with congestive cardiac failure, pulmonary edema, pneumonia and ascites at Day 25. All events resolved with treatment. The patient withdrew consent and was discontinued from the study.

Reviewer comment: Given known pre-existing cardiac disease it is plausible that the event describes congestive heart failure. Dr. Preston Dunnmon, from FDA DCRP cardiology, finds it unlikely that this represents drug-induced congestive heart failure and this reviewer concurs.

- Patient [A2302-2011-2011004]
  Patient details: 65 years, male, Asian
  Treatment group: AIN457 150 mg
  SAE (cardiac failure, pulmonary edema),
  Discontinued due to AE (erythrodermic psoriasis)

  On Day 1 ((b) (6)), after a wash out period, the subject presented with redness, swelling and desquamation; symptoms which were on the verge of erythroderma. On Day 12 (b) (6)), the subject complained of increased dyspnea on exertion. His oxygen saturation (SpO2) was between 88% and 90% and was also diagnosed with erythrodermic psoriasis. The subject was diagnosed with cardiac failure and pulmonary edema by x-ray and computed chest tomography. Brain natriuretic peptide (BNP) was elevated at 544.2 and a cardiac ultrasonography on showed normal LV function. The edema was treated with furosemide and antibiotics. The erythrodermic psoriasis was treated with cyclosporine. The subject discontinued study treatment (last dose Day 7) due to the events, which resolved with treatment. The investigator suspected a relationship between the events cardiac failure, pulmonary edema, erythrodermic psoriasis and the study medication.

Reviewer comment: Dr. Preston Dunnmon, DCRP cardiology finds it unlikely that this case also represents drug-induced congestive heart failure and this reviewer concurs. It is possible that the hypoxia and pulmonary edema is related to erythrodermic psoriasis. Cases of generalized pustular and erythrodermic psoriasis have been reported to be complicated by acute respiratory distress syndrome (ARDS)[1]. The BNP elevation in the absence left ventricular dysfunction may suggest a non-cardiac cause of the edema such as ARDS[2]. Although the pulmonary edema may be related to erythrodermic psoriasis, it is unlikely that secukinumab caused the erythrodermic psoriasis. The wash out period off of treatment is more likely to be the cause.

Exposure-adjusted rates per 100 patient-years over the entire treatment period in all psoriasis trials were higher for 300 mg than 150 mg secukinumab (7.4 vs. 6.8). These arms had similar numbers of subjects treated for similar length of duration permitting a more direct comparison. However due to the differing sample sizes between the active and placebo arms as well as differing durations of therapy for many subjects as time progressed over the 52 weeks of follow-up in long term extension trials, a direct comparison between treatment and placebo cannot be made. The best approach, but not without limitations, is to analyze using exposure-adjusted rate. Using this analysis the rate for the 300 mg dose was comparable to placebo (7.4 vs. 7.5). This reviewer interprets this data to suggest that more serious adverse events may be likely to occur with the higher

dose of secukinumab. However, serious events related to treatment at either dose are not so frequent as to be greatly prominent over background events.

Overall, the exposure-adjusted rates for secukinumab treated subjects were low (≤0.22 per 100 patient-years) and the most frequent events by preferred term are shown in the table below.

Table 20: Exposure adjusted incidence of the most frequent (>=0.10 per 100patient years in any secukinumab group) SAEs by preferred term (Pool B entire treatment period)

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
-Any SAE	76 (6.80)	85 (7.42)	207 (7.80)	15 (7.54)	20 (7.01)
Pneumonia	3 (0.26)	3 (0.25)	6 (0.22)	0 (0.00)	0 (0.00)
Angina pectoris	2 (0.18)	1 (0.08)	5 (0.18)	0 (0.00)	0 (0.00)
Cellulitis	2 (0.18)	1 (0.08)	5 (0.18)	2 (0.99)	1 (0.34)
Abscess bacterial	3 (0.26)	0 (0.00)	4 (0.15)	0 (0.00)	0 (0.00)
Appendicitis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Coronary artery disease	1 (0.09)	1 (0.08)	4 (0.15)	0 (0.00)	0 (0.00)
Hypertensive crisis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Psoriasis	1 (0.09)	1 (0.08)	4 (0.15)	4 (1.99)	1 (0.34)
Sciatica	2 (0.18)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Angina unstable	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Arthralgia	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	1 (0.34)
Back pain	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Basal cell carcinoma	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cerebrovascular accident	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cholelithiasis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Colitis ulcerative	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Crohn's disease	2 (0.18)	0 (0.00)	3 (0.11)	0 (0.00)	0 (0.00)
Headache	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Nephrolithiasis	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Osteoarthritis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Pancreatitis	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Syncope	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Acute myocardial infarction	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Cholecystitis	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Concussion	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Hypoaesthesia	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Myocardial infarction	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	1 (0.34)
Overdose	1 (0.09)	1 (0.08)	2 (0.07)	1 (0.50)	0 (0.00)

Palpitations	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Pulmonary edema	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Rib fracture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Tendon rupture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Vomiting	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)

Infections, including pneumonia and bacterial abscess, were reported more frequently with secukinumab treatment, but not reported for either placebo or etanercept. The PT pneumonia was reported by the highest number of subjects 0.2% (6/3430). Also inflammatory bowel disease (Crohn's and ulcerative colitis) were reported as most frequent SAEs with secukinumab treatment, but not reported for either placebo or etanercept.

7.3.3 Dropouts and/or Discontinuations

The overall rate of AEs causing discontinuation of induction study treatment was low and comparable among the treatment groups. Two events caused discontinuation in more than one patient in total: erythrodermic psoriasis in 2 patients on 150 mg secukinumab and psoriasis in 5 patients on placebo. All other AEs leading to discontinuation were single occurrences. AEs causing discontinuation in the induction period of Pool A studies are summarized in the table below.

Table 21: AE Causing Discontinuation (Pool A)

Preferred term	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	Any AIN457 dose N=1382 n (%)	Placebo N=694 n (%)	Etanercept N=323 n (%)
-Any AE causing discontinuation	8 (1.2)	9 (1.3)	17 (1.23)	9 (1.3)	6 (1.9)
Erythrodermic psoriasis	2 (0.3)	0 (0.0)	2 (0.14)	0 (0.0)	0 (0.0)
Alopecia	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)	0 (0.0)
Bladder cancer	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)	0 (0.0)
Bursitis	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Colitis ulcerative	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	1 (0.3)
Crohn's disease	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)	0 (0.0)
Drug eruption	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Eczema nummular	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Pharyngitis bacterial	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)	0 (0.0)
Psoriatic arthropathy	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)	0 (0.0)
Transaminases increased	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Urticaria	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)

Cellulitis	0 (0.0)	0 (0.0)	0 (0.00)	1 (0.1)	0 (0.0)
Dermatitis exfoliative	0 (0.0)	0 (0.0)	0 (0.00)	1 (0.1)	0 (0.0)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	1 (0.3)
Herpes virus infection	0 (0.0)	0 (0.0)	0 (0.00)	1 (0.1)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.00)	1 (0.1)	0 (0.0)
Injection site edema	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	1 (0.3)
Injection site rash	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	1 (0.3)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	1 (0.3)
Psoriasis	0 (0.0)	0 (0.0)	0 (0.00)	5 (0.7)	0 (0.0)
Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	1 (0.3)

Source: Applicant's SCS table 2-17

Of the 2 subjects who discontinued due to erythrodermic psoriasis:

- Subject [AIN457A2302-2011004] presented at Day 1 with symptoms that were "on the verge of erythroderma" as reported by the investigator. The event was confounded by the preceding wash-out period.

- Subject [AIN457A2303-4104003] developed erythrodermic psoriasis on Day 8 when his PASI score was 45.6 (vs. a score of 31.6 at screening). The event was not suspected to be related to study medication.

AEs of erythrodermic psoriasis are described in more detail in Section 2.1.4.4.

One subject [AIN457A2302-3021003] discontinued 150 mg secukinumab due to thrombocytopenia. The subject's platelet count was low at Day 1 (127x109/L; reference range140-450) and the patient was diagnosed with persistent, but clinically not significant, thrombocytopenia at Day 4 (no lab results were available to confirm the AE). Study medication was discontinued (last dose given at Day 8) and the patient's platelet count increased to 141x109/L at Day 15. No bleeding disorders were reported.

The absolute incidence of AEs causing discontinuation was comparable between any secukinumab dose and etanercept (3.4% vs. 3.7%), and both rates were higher than placebo(1.4%). The small number of subjects receiving placebo treatment after Week 12 limits the interpretation. AEs by the most frequently occurring preferred terms which caused discontinuation over the entire treatment period of Pool B trials are presented in the table below.

Table 22: Most frequent (>=0.20% in any group) AEs causing discontinuation for entire treatment period (Pool B)

Preferred term	Any AIN457 150 mg N=1395 n (%)	Any AIN457 300 mg N=1410 n (%)	Any AIN457 dose N=3430 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
-Any AE causing discontinuation	43 (3.08)	46 (3.26)	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	4 (0.29)	0 (0.00)	6 (0.17)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (0.22)	1 (0.07)	4 (0.12)	0 (0.0)	0 (0.0)
Colitis ulcerative	2 (0.14)	1 (0.07)	3 (0.09)	0 (0.0)	1 (0.3)
Gamma-glutamyltransferase increased	3 (0.22)	0 (0.00)	3 (0.09)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	1 (0.07)	2 (0.14)	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	0 (0.00)	1 (0.07)	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)

Source: Applicant's SCS table 2-19

Thrombocytopenia led to discontinuation in 1 subject on any 300 mg and 3 subjects on any 150 mg, but was not reported for placebo and etanercept. For 3 of these cases, the reported AEs of thrombocytopenia were associated with decreased platelet counts at baseline or an active medical condition of thrombocytopenia at study entry; no lab results were available to confirm the remaining case. Crohn's disease and hepatic enzyme elevations (including gamma glutamyltransferase) will be discussed in section 7.3.5 Submission Specific Primary Safety Concerns below.

7.3.4 Significant Adverse Events

The overall incidence of AEs causing dose interruption over the entire treatment period was highest in the 300 mg dose; the 150 mg dose was similar to etanercept. Active treatment arms were all higher than placebo (5.3%, 4.4% and 4.6%, respectively, for any 300 mg, 150 mg and etanercept vs. 1.9% for placebo). AEs contributing to this imbalance were primarily infections which were more frequent for the 300 mg dose than 150 mg dose [45/1410 (3.2%) vs. 32/1395 (2.3%)]. Bronchitis, influenza, and pneumonia were the infection preferred terms which occurred more frequently (3-4 times) in the 300 mg than 150 mg dose of secukinumab.

AEs requiring concomitant medication reported in the induction period of the Pool A was higher in the secukinumab dose groups (40.6% for 300 mg vs. 42.6% for 150 mg) than the placebo and etanercept groups (34.3% and 38.1%, respectively). This difference was due mainly to infections and infestations (20.4% for 300 mg and 19.9% for 150 mg vs. 13.7% for placebo and 16.1% for etanercept). Eye disorders requiring concomitant medication were more frequently reported for the 300 mg secukinumab group (2.2%), while the rate was comparable between 150 mg secukinumab and placebo (0.9% vs. 0.4%) and lowest with etanercept (0%).

AEs requiring concomitant medication reported over the entire treatment period of Pool B was slightly higher in the secukinumab 300 mg than 150 mg (64.3% vs 62.9%) and both were higher than placebo (37.2%). SOCs contributing to the difference in active treatments vs. placebo included infections and infestations (40.8%, 35.8% and 41.5% for 300 mg, 150 mg and etanercept, respectively, vs. 15.9% for placebo), gastrointestinal disorders (11.0%, 10.5% and 14.6% vs. 4.5%), musculoskeletal and connective tissue disorders (11.2%, 11.0% and 14.6% vs. 5.2%) and skin and subcutaneous tissue disorders (11.4%, 11.8% and10.8% vs. 5.5%). Notable differences between the rates seen for 300 mg and 150 mg doses were primarily for preferred terms in the infections and infestations SOC which showed:

- 5 to 6 fold increases for 300 mg for erysipelas, bacterial pharyngitis, bacterial infection
- 2 to 3 fold increases for 300 mg urinary tract infections, bacterial sinusitis, otitis media/ otitis media bacterial, bacterial skin infections, impetigo, oral candidiasis, vulvovaginal candidiasis.

7.3.5 Submission Specific Primary Safety Concerns

Potential risks based on class of drug (anti-cytokine) and of the drug substance (foreign protein) were analyzed. Potential risks associated with immunomodulating biologic therapies may include infections, neutropenia, cardiovascular/cerebrovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity. These AEs of special interest are shown in the table below.

Table 23: Summary of AEs, SAEs and selected risks in the first 12 weeks and over 52 weeks of treatment

	Pool A – First 12 weeks				Pool B – Entire 52 weeks			
	AIN457 150 mg N=692 n (%)	**AIN457 300 mg N=690 n (%)**	**PBO N=694 n (%)**	**Etaner-cept N=323 n (%)**	**Any AIN457 150 mg N=1395 n (IR)**	**Any AIN457 300 mg N=1410 n (IR)**	**PBO N=793 n (IR)**	**Etaner-cept N=323 n (IR)**
Total AEs	412 (59.5)	388 (56.2)	340 (49.0)	186 (57.6)	1066 (239.90)	1091 (236.10)	413 (351.79)	253 (243.44)
Total SAEs	14 (2.0)	14 (2.0)	12 (1.7)	3 (0.9)	76 (6.80)	85 (7.42)	15 (7.54)	20 (7.01)
Selected risks based on AEs								
Infections and infestations (SOC)	203 (29.3)	195 (28.3)	134 (19.3)	83 (25.7)	653 (85.29)	704 (91.06)	173 (101.89)	172 (93.68)
URTIs (HLT)	129 (18.6)	117 (17.0)	72 (10.4)	49 (15.2)	408 (45.02)	426 (45.39)	96 (52.03)	113 (50.50)
Candida infections (HLT)	3 (0.4)	8 (1.2)	2 (0.3)	1 (0.3)	21 (1.85)	41 (3.55)	2 (1.00)	4 (1.37)
MACE (NMQ)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	5 (0.44)	6 (0.51)	1 (0.50)	1 (0.34)

CCV-related events (NMQ)	7 (1.0)	3 (0.4)	11 (1.6)	6 (1.9)	30 (2.65)	82 (3.04)	13 (6.54)	14 (4.86)
Malignant or unspecified tumors (SMQ)	3 (0.4)	1 (0.1)	3 (0.4)	0 (0.0)	11 (0.97)	9 (0.77)	3 (1.49)	2 (0.68)
Hypersensitivity (narrow SMQ)	31 (4.5)	31 (4.5)	9 (1.3)	15 (4.6)	115 (10.70)	132 (11.94)	9 (4.50)	27 (9.73)
Neutropenia (narrow NMQ)	2 (0.3)	4 (0.6)	0 (0.0)	2 (0.6)	15 (1.32)	16 (1.37)	0 (0.00)	5 (1.71)
Crohn's disease (PT)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)

IR=exposure-adjusted incidence rate per 100 patient-years
CCV=cardio-cerebrovascular; HLT=high level term; MACE=major adverse cardiovascular event; NMQ=Novartis MedDRA query; PBO=placebo; PT=preferred term; SMQ=standardized MedDRA query SOC=system organ class; URTIs=upper respiratory tract infections
Source: Applicant SCS [SCS-Appendix 1-Table 9.1-1.1, Table 9.2-2.1, Table 10.1-1.1, Table 10.2-2.1, Table 10.1 5.1, and Table 10.2-6.1]

Erythrodermic/ Pustular Psoriasis

A number of cases of erythrodermic psoriasis were reported over the entire treatment period in Pool B and the rates were higher for secukinumab (n=23, IR=0.85 for secukinumab; n=1, IR=0.50 for placebo; n=1, IR=0.34 for etanercept). The majority (17/23) of the cases on secukinumab were reported in Phase 2, whereas a comparable number was not confirmed in the larger Phase 3 trials, with 6 cases reported. Rates were higher in the 150 mg dose than the 300 mg dose of secukinumab. Rates were higher for secukinumab groups with 4-week fixed interval (FI) dosing (n=1, IR=0.13 for 300 mg; n=4, IR=0.53 for 150 mg) than start of relapse (SoR) maintenance dosing (n=0 for 300 mg SoR; n=1, IR=0.51 for 150 mg SoR). 4 out of the 6 cases were observed in the first 12 weeks of treatment. AEs of erythrodermic psoriasis were more frequently reported in patients with severe baseline disease than in patient with moderate baseline disease.

All but 2 cases were non-serious. The 2 SAEs of erythrodermic psoriasis occurred in the any secukinumab dose group in the Phase 2 trials. Both patients [AIN457A2211-0100-00009] and [AIN457A2211-0001-00007] presented with symptoms of erythrodermic psoriasis early after baseline (Days 5 and 8, respectively) and increased PASI scores (57.0 at Day 5 vs. 17.7 at screening for A2211-0100-00009 and 23.7 at Day 8 vs. 14.2 at screening for A2211-0001-00007). For both SAEs, the investigator did not suspect a relationship between the erythrodermic psoriasis and study medication.

AEs causing more frequent discontinuation with secukinumab relative to placebo included erythrodermic psoriasis. 2 subjects [AIN457A2302-2011004] and [AIN457A2303-4104003] discontinued Phase 3 studies due to erythrodermic psoriasis. The cases are described above in section 7.3.3.

Reviewer comment: Erythrodermic psoriasis is usually considered to be a generalized erythrodermal and inflammatory psoriasis. Erythrodermic psoriasis is considered a

severe disease, and can even be life-threatening. The majority of the reported AEs of erythrodermic psoriasis were unlikely to be true erythrodermic psoriasis because they were considered nonserious, did not lead to study treatment discontinuation, were of mild or moderate severity, and had low PASI scores, many of which were lower at the time of the event compared with baseline.

It is unclear why many more subjects reported this AE in the Phase 2 studies as compared to the Phase 3 studies. Many events occurred early in induction. It is possible that induction dosing in Phase 2, following the wash-out period, affected the initial response to treatment which resulted in a disease flare that was reported as erythrodermic psoriasis. Because of fewer cases in Phase 3, few serious cases, no cases described as life-threating and no evidence of causality, this reviewer finds that labeling is not needed regarding the reported cases.

Pustular psoriasis was reported in 10 patients on secukinumab and 1 placebo patient over the entire treatment period in Pool B. The exposure-adjusted incidence was higher in the 300mg secukinumab dose group as compared to the 150 mg dose group, but rates for both secukinumab cohorts were lower than the placebo group (n=4, IR=0.34 for any 300 mg; n=2, IR=0.18 for any 150 mg; and n=1, IR=0.50 for placebo).

All cases were non-serious, with the exception of one case on 150 mg SoR. This patient [AIN457A2304-6010023] experienced contact dermatitis on Day 193 and pustular psoriasis on Day 272 of the maintenance period. Both events resolved with treatment and did not cause study treatment discontinuation. The investigator did not suspect a relationship between the events of contact dermatitis and pustular psoriasis and study medication.

Reviewer comment: There are multiple causes of pustular psoriasis including infections, certain drugs and withdrawal of steroids, but often no cause is identified. Pustular psoriasis can be life-threatening especially if associated with systemic symptoms. There does not seem to be a causal relationship between secukinumab and pustular psoriasis and none of the cases reported appear to be of the severe form of the disease. No labeling is needed regarding the reported cases.

Infections

In pool A, with 12 weeks of treatment, infections were reported more frequently in secukinumab treated subjects. Common infections such as nasopharyngitis and upper respiratory tract infection were reported more frequently in the two secukinumab dose groups as compared to placebo. Serious infections were reported infrequently. SAEs in the infections and infestations SOC 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)

The imbalance for infections was also seen in Pool B. Over the 52 week treatment period slightly higher exposure-adjusted rates of SAEs were seen in secukinumab treated subjects. The exposure-adjusted rates of SAEs in the infections and infestations SOC were similar between the any 300 mg and etanercept groups (both, 1.4), which were higher than the 150 mg and placebo groups (1.1 and 1.0, respectively). The majority of infections were not severe and responded to therapy.

Observations in humans with genetic defects affecting the Th17 pathway and in individuals who have genetic defects in IL-17 signaling suggest that blockade of IL-17 increases the risk for fungal infections, particularly mucocutaneous candidiasis, as well as staphylococcal skin infections. These adverse events as well as some others related to infections demonstrated a dose-response event rate as shown in the table below.

Table 24 : Adverse Events related to infections reported in psoriasis studies which show a dose-response

Adverse Event	300 mg	150 mg	placebo
Candida infections	1.2%	0.4%	0.3%
Herpes viral infections	1.6%	0.9%	0.4%
Infections requiring antimicrobial treatment	12.2%	9.4%	7.2%
Otitis externa	0.7%	0.4%	0%
Otitis media	0.6%	0%	0.1%

Additional information on AEs related to infections which show a dose-response is provided in section 7.5.1 Dose Dependency for Adverse Events.

A higher rate of Candida infections with secukinumab, particularly the higher dose, was observed consistently at both 12 weeks and entire treatment periods. Infections related to Candida did appear to show a dose response as shown in section 7.5.1. All Candida infections on secukinumab were mild or moderate in severity. 4 cases of esophageal candidiasis were reported (1 on 150 mg and 3 on 300 mg). Two of these cases were mild and two were moderate in severity. All were managed successfully with antifungal treatment and did not result in any interruption or discontinuation of study treatment. There was 1 additional case of esophageal candidiasis reported in the safety update. There were no reported cases of reactivation of latent tuberculosis.

Herpes viral infections (HLT) occurred in a higher proportion of patients in the 300 mg group than the 150 mg group and were higher than placebo. No cases of disseminated or CNS herpes were reported. Cytomegaloviral infections (HLT) were reported in 3

patients (1 on 300 mg, 1 on another secukinumab dose, 1 on placebo), (0.07 vs. 0.50). None of these infections were serious.

Infections requiring oral or parenteral antimicrobial concomitant treatment were also more frequently reported in the 300 mg group than the 150 mg group.

Ear infections (HLT) were reported more frequently in the 300 mg group than in 150 mg group, which was comparable to placebo and etanercept. Events driving this imbalance were otitis externa and otitis media.

The applicant proposes labeling pertaining to infections in section 5 warnings and precautions and section 6.1 adverse reactions. This reviewer concurs with the applicant's proposal for section 5 and proposes the addition of other infections for which this reviewer finds them to be adverse reactions.

> Section 6.1 Clinical Trials Experience: Adverse reactions that occurred at rates less than 1% in the placebo-controlled period of Trials 1, 2, 3 and 4 through week 12 included:
>
> > Applicant proposed: sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, otitis externa, neutropenia
> > Additional terms recommended by reviewer: impetigo, otitis media, ulcerative colitis, increased liver transaminases

Also, it is this reviewer's recommendation to add the following warning regarding evaluation for tuberculosis:

> 5.2 Pre-treatment Evaluation for Tuberculosis
> Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX. Do not administer COSENTYX to patients with active TB infection. Initiate treatment of latent TB prior to administering COSENTYX. Consider anti-TB therapy prior to initiation of COSENTYX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving CONSENTYX should be monitored closely for signs and symptoms of active TB during and after treatment.

This language is found in precedent labels and reflects clinical trial design.

Hypersensitivity

The applicant provided search results using the hypersensitivity narrow SMQ and immune/administration reactions broad Novartis MedDRA Query. The Immune/administration reactions by broad NMQ is comprised of 3 SMQs of anaphylactic reactions, angioedema and severe cutaneous adverse reactions, and 5 HLGTs of administration site reactions, allergic conditions, autoimmune disorders, immune disorders NEC, and immunology and allergy investigations. This reviewer finds

the terms in the query reasonable to search for hypersensitivity, immune/administration reactions. In both the pooled 12 week analyses (pool A) and pooled data of all psoriasis studies (pool B) hypersensitivity AEs were reported in a higher proportion of subjects in the secukinumab dose groups compared with the placebo group. Percentages for pool A were 4.5% and 4.5% respectively, for 300 mg and 150 mg vs.1.3% for placebo. Percentages were similar in pool B. A higher incidence per 100 patient-years of hypersensitivity AEs was noted for secukinumab compared with placebo (11.9 for any 300 mg, 10.7 for any 150 mg and 4.5 for placebo).

The majority of hypersensitivity cases in pool B secukinumab-treated subjects were due to urticaria. One severe case of urticaria on 300 mg also led to discontinuation of study treatment; one severe case also occurred on placebo. The other 52 cases of urticaria in pool B were reported as mild to moderate and no other cases of urticaria caused discontinuation.

The applicant's reported analysis of angioedema in pool A using HLT were 0.6%, 0.1%, and 0.3% for 150 mg, 300 mg, and placebo. Eyelid edema occurred in 2 patients (on 150 mg), while all other preferred terms (such as laryngeal edema, swelling face, swollen tongue, angioedema and face edema) occurred in 1 patient each. This reviewer's analysis used angioedema narrow SMQ for each pivotal study confirmed that there does not appear to be a dose-relationship for secukinumab and the AE angioedema.

When looking at events in the entire treatment period of pool B, corrected for exposure-adjusted event rates, Angioedemas (HLT) were less frequent for secukinumab and etanercept compared to placebo (0.5, 0.5 and 0 for any 300 mg, any 150 mg and etanercept vs. 1.00 for placebo). The relationship of angioedema and secukinumab is unclear at this time. Angioedema associated with other symptoms of hypersensitivity suggesting a more serious reaction was reviewed and summarized below.

There were three cases of urticarial accompanied by concurrent angioedema, with a time-to-onset of urticaria from the most recent dose of study treatment of 1 day (AIN457A2211-0526-00008 on secukinumab), 5 days (AIN457A2309-6009008 on placebo) and 7 days (AIN457A2304-4034002 on secukinumab).

> Subject AIN457A2211-0526-00008, a 35 year old male, was treated with secukinumab induction: monthly (3 × 150 mg AIN457 s.c.); Maintenance: Open Label(150 mg AIN457 s.c. every 4 weeks). He received the first dose of the study medication on Day 1 (24 Sep 2009).On Day 169 (12 Feb 2010), during the induction period, the patient was diagnosed with sporadic angioedema. He was treated with levocetirizine hydrochloride; no other treatment was reported for this patient. The sporadic angioedema was ongoing at the time of reporting. Induction and maintenance periods were completed. The patient received the last dose of the study medication on Day 225 (06 May 2010) and entered the extension study

on (03 Jun 2010. The investigator did not suspect a relationship between the angioedema and the study medication.

Reviewer comment: The latency of onset of urticaria in patient AIN457A2304-4034002 indicates this was not an immediate hypersensitivity event. No action was taken with study treatment in patient AIN457A2211-0526-00008 on secukinumab. These cases do not appear to be consistent with an immediate hypersensitivity event.

In ongoing secukinumab studies across all indications serious anaphylactic reactions appear to be rare. One case was reported in the psoriasis studies. However, it does not appear to be related to study medication. This case was reported as a non-serious AE of anaphylaxis in subject (AIN457A2303-2129004) which was reported to be related to a food allergen (nuts) for which the patient had a pre-existing medical history. This reaction did not appear to be temporally related to dose administration and similar symptoms did not occur on rechallenge. One additional case has been reported in the ankylosing spondylitis program and symptoms are consistent with an immediate hypersensitivity reaction. The case is described below:

A 48 year old male subject [AIN457A2209-0486120] with a past medical history of hypertension and ankylosing spondylitis was administered the first dose of 10 mg/kg i.v. secukinumab in study A2209. Signs and symptoms developed within an hour of start of infusion, including generalized hives, lip, eyelid and tongue edema and shortness of breath that required treatment with high-dose intravenous corticosteroids and diphenhydramine. Vital signs (VS) were: blood pressure (BP) 114/76 mmHg, pulse 64 bpm, respirations 12bpm. The patient recovered fully from this event the next day. The subject did not receive secukinumab prior to this infusion, and did not have a past history of allergies, including allergic reactions to other drugs.

Reviewer comment: The occurrence of this anaphylactic event during the administration of secukinumab indicates a likely causal relationship between the anaphylactic reaction and study drug administration. This reviewer concurs with the applicant's proposal for including hypersensitivity reactions in section 5 and 6 of labeling and a contraindication to patients with a severe hypersensitivity reaction to the drug.

Autoimmune events

The applicant provided search results of autoimmune related adverse events using the Novartis MedDRA Query (NMQ) "Autoimmune Disorders". This NMQ includes a total of 246 preferred terms (PT) covering both systemic and organ-specific autoimmune disorders. This reviewer finds the terms in the query reasonable to search for autoimmune disorders. In both the pooled 12 week analyses (pool A) and pooled data of all psoriasis studies (pool B) autoimmune AEs were reported in a higher proportion of subjects in the placebo dose groups compared with the secukinumab group. Incidence in pool A was 1.0% and 2.0% for 300 mg and 150 mg, respectively, vs. 3.5% for

placebo. In pool B the exposure-adjusted incidence for both AEs/ SAEs was also lower in the active treatment groups relative to placebo. Exposure-adjusted incidence for SAEs of autoimmune disorders was 0.43 for any 300 mg, 0.44 for any 150 mg and. 1.99 for placebo.

However this analysis is confounded because the imbalance is driven by placebo-treated subjects reporting psoriasis more frequently, as would be expected. Psoriasis was more frequent with placebo (2.9%) than with the secukinumab doses (0.6% and 1.4% for 300 mg and 150 mg, respectively) in pool A. Also, SAEs of psoriasis occurred more frequently in the placebo group in pool B with an exposure-adjusted incidence of 1.99 for placebo vs. 0.08 for any 300 mg and 0.09 for any 150 mg. SAEs for autoimmune disorders not related to psoriasis were reported only in treatment arms. This reviewer evaluated autoimmune AEs after discounting potentially related events of psoriasis and arthropathy; a greater number of events were reported for secukinumab and are shown in the table below.

Table 25: Autoimmune Adverse Events by Preferred Term (Pool B entire treatment period)

Preferred Term (PT)	Secukinumab Any 150 N=1395	Secukinumab Any 300 N=1410	Secukinumab Any dose N=3430	Placebo N=793	Non-US approved Etanercept comparator N=323
Ulcerative colitis	2	2	4		1
Crohn's disease	2		3		
Basedow's (Grave's)	2		2		
Scleritis		1	1	1	
Pemphius		1	1		
Autoimmune thyroiditis		1	1		
Alopecia aereata		1	1		
Dermatitis herpetiformis		1	1		
Granulomatosis with polyangiitis		1	1		
Sjogrens	1		1		
Palpable purpura	1		1		
Vitiligo	1		1		
Multiple sclerosis	1		1		
Antinuclear antibody positive			1		
Autoimmune hepatitis			1		
Cholangitis sclerosing			1		
Pernicious anemia					1
Nodular vasculitis					1
Total	10	8	22	1	3

Source: Applicant SCS Appendix 1, Table 9.2-1.2

Other reported cases from safety updates include: Autoimmune hemolytic anemia, Crohn's disease, Thoracic myelitis, Idiopathic thrombocytopenia, and Ulcerative colitis.

Although the number of events for secukinumab-treated subjects was greater, the rate appears similar to the active comparator and TNF alpha inhibitors have been associated with the paradoxical development of autoimmune disease.

Inflammatory bowel disease will be discussed in the section below. Case narratives of the other autoimmune SAEs are as follows:

- The SAE of multiple sclerosis was reported in a patient [AIN457A2304-3024001] on 150 mg with a long-standing (16 years) history of multiple sclerosis. The patient received the last dose of study medication on Day 336 (27 Sep 2012). On Day (b) (6) the patient experienced worsening of hypoesthesia on both feet and legs, and trunk and was hospitalized. A CT scan of the head on Day 355 ((b) (6)) revealed signs of established multiple sclerosis. The hypoesthesia and CNS inflammation resolved with treatment. Treatment included baclofen, methylprednisolone and interferon beta-1A. The event central nervous system inflammation was considered resolved on Day 372 ((b) (6)). The patient was discharged from the hospital on Day (b) (6) . The investigator did not suspect the events (hypoesthesia, multiple sclerosis, CNS inflammation) to be related to study medication, but rather to the underlying multiple sclerosis.

- The SAE of granulomatosis with polyangiitis was reported in a 60 year old male[AIN457A2304- 5012002] with no relevant medical history, diagnosed after more than 10 months of 300 mg secukinumab dosing on a fixed-interval regimen and based on confirmatory tests that included biopsies of the left nasal septum, sinus CTs, positive cultures and a positive anti-neutrophil cytoplasmic antibody (ANCA) test, without evidence of lung involvement. The diagnosis of granulomatosis with polyangitis, or Wegener's granulomatosis, was established on Day 316 (26 Jul 2012). Study medication was temporarily interrupted, but the patient eventually completed the study and continued to be dosed in the extension study (AIN457A2304E1). The events of nasal vestibulitis and granulomatosis with polyangiitis were ongoing at the time of the end of trial 2304 and his enrollment on Day 393 (11 Oct 2012) into the extension trial 2304E1. At the time of reporting, the patient was continuing in the extension study and his most recent visit was on Day 600 (06 May 2013).

- The SAE of pemphigus was reported in patient [AIN457A2304-4041006], a 62 year old male, whose active medical conditions included hypertension treated with amlodipine, valsartan and nifedipine. The patient had 2 doses of 300 mg secukinumab prior to the SAE (initially presenting on Day 8, with the diagnosis

confirmed on Day 29) and then discontinued study treatment as a result of the event. On Day 29 (21 Feb 2012), positive autoantibody test (unspecified) and he was diagnosed with pemphigus. Treatment included antibiotics and steroids. On Day (b) (6), the patient was hospitalized for steroid pulse therapy. On Day (b) (6) he was discharged from hospital. The event pemphigus was ongoing at the time of reporting. The investigator suspected a relationship between the event pemphigus and the study medication.

Reviewer comment: Autoimmune diseases represent a heterogeneous family of chronic, disabling diseases with different natural histories and a wide spectrum of clinical symptoms. While many individual autoimmune diseases are rare, these disorders share underlying defects in the immune response which leads the body to target its own organs and tissues. Data on the overall incidence and prevalence of autoimmune disease is limited. This makes it difficult to predict the number of cases that one would expect in the study population. Other biologic therapies affecting molecular components of the immune system for the treatment of autoimmune disease have been associated with the paradoxical development of autoimmune processes. Anti-TNF agents carry warnings describing the various autoimmune diseases associated with use of the product.

Because the event rate of autoimmune adverse events is similar to that of Etanercept, this reviewer is concerned that the product may also be associated with paradoxical development of autoimmune disease. It is not clear to this reviewer how best to label the product to reflect this concern because the majority of the individual events only occur one time. Also, if secukinumab is found to be associated with inducing autoimmunity, it is not clear which patients would be at risk and thus steps to mitigate development of an autoimmune disease could be not be described in labeling.

The applicant is proposing a labeled warning for Crohn's disease, for which there is additional strength of evidence to support, see below. It is this reviewer's opinion that at this juncture, additional information should be collected on autoimmune AEs in long-term studies and post-marketing to better characterize the potential risk for associated autoimmune disease.

Inflammatory Bowel Disease

The applicant performed a search using the inflammatory bowel disease (IBD) narrow NMQ. This reviewer finds the search teams in the query to be acceptable. The search in Pool A yielded 3 cases of IBD in total, with an incidence across the treatment groups (0.1%, 0.1%, 0% and 0.3% for 300 mg, 150 mg, placebo and etanercept). Of these, the 2 cases on secukinumab were SAEs. Among 22 patients with a prior history of IBD (secukinumab 13 and placebo 9), Crohn's disease was reported in 1 patient on 150 mg compared with 0 patients on placebo. Among 1369 patients on secukinumab with no prior history of IBD, ulcerative colitis was reported in one patient on 300 mg. No patient

in the etanercept group had a prior history of IBD; a non-serious case of ulcerative colitis was reported in 1 patient on etanercept

The search in the psoriasis clinical database over the entire treatment period (Pool B) identified a total of 10 cases (secukinumab 9, etanercept 1) of IBD, yielding an exposure-adjusted incidence rate per 100 patient-years of 0.26 for 300 mg, 0.35 for 150 mg and 0.34 for etanercept. No cases were reported for placebo. Search results are shown in the table below.

Table 26: Exposure-adjusted incidence of inflammatory bowel disease (Pool B entire treatment period)

Level 1 Preferred term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Based on all AEs					
Inflammatory bowel disease (narrow NMQ)	4 (0.35)	3 (0.26)	9 (0.33)	0 (0.00)	1 (0.34)
Colitis ulcerative (PT)	2 (0.18)	2 (0.17)	4 (0.15)	0 (0.00)	1 (0.34)
Crohn's disease (PT)	2 (0.18)	0 (0.00)	3 (0.11)	0 (0.00)	0 (0.00)
Anal fistula (PT)	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	0 (0.00)
Cholangitis sclerosing (PT)	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)

Source: Applicant SCS table 2-42

Crohn's disease

Of the 3 cases of Crohn's disease PT reported for secukinumab (2 on 150 mg and 1 on an alternative 150 mg dose regimen), 2 were reported in patients with prior history of IBD [AIN457A2303-3524013] and [AIN457A2211E1-0080-00004] and 1 was a new event [AIN457A2304-3032001]. All 3 events were SAEs and lead to treatment discontinuation. Of the 2 exacerbation cases, one resolved with treatment and the other was ongoing at the time of reporting. The 2 cases which occurred in the Phase 3 studies are described below:

- Patient [AIN457A2304-3032001], a 31 year old female, experienced a non-serious adverse event of upper abdominal pain on Day 39 (12 Mar 2012), in the induction period of the study. The patient experienced post-prandial diarrhea, on Day (b) (6), in the maintenance period of the study, the patient experienced gastric/abdominal pain leading to hospitalization and on Day (b) (6) was diagnosed with Crohn's disease of moderate severity. The study medication was permanently discontinued and the patient received the last dose of study medication on Day (b) (6)). The events (Crohn's disease, abdominal pain, ileus) were considered resolved on Day

(b) (6) and the patient was discharged from the hospital on the same day. The investigator did not suspect a relationship between the events and the study medication.

- Patient [AIN457A2303-3524013], who had a 30-year history of recurrent Crohn's disease, experienced progression of Crohn's disease on Day 56 of the induction period. The event was reported as a SAE and study treatment was discontinued. The event was reported as recovering on Day 128 following treatment with oral amoxicillin/clavulanic acid. The event was considered to be related to study treatment by the investigator.

One case retrieved in the IBD search reports an anal fistula without other symptoms of inflammatory bowel disease.

- Patient [AIN457A2303-3220001], a 36 year old male with prior psoriasis therapies that included methotrexate and topical treatment and no relevant medical history received the first dose of the study medication on Day 1 (13 Mar 2012).The patient completed Week 12 visit (induction period) on Day 84 (04 Jun 2012) and switched from placebo to secukinumab 300 mg. On Day (b) (6), in the maintenance period of the study (induction period for secukinumab 300 mg), the patient was hospitalized due to pain in the anal area, was diagnosed with anal fistula and underwent a surgical procedure. Treatment included piperacillin with tazobactam. No action was taken with the study medication. On (b) (6), the patient was discharged from the hospital, and the event of anal fistula was considered resolved. The patient completed the maintenance period of the study on Day 367, having received the last dose of the study medication on Day 362. The investigator did not suspect a relationship between the event anal fistula and the study medication.

Reviewer comment: Fistulas are often found in patients with inflammatory bowel disease, particularly Crohn disease. The cumulative incidence of fistula formation in patients with Crohn's disease is 17–50%. Perianal activity often parallels abdominal disease activity, but it may occasionally be the primary site of active disease.

Because anal fistulas can also be associated with abscess, diverticulitis, foreign-body reactions, actinomycosis, chlamydia, lymphogranuloma venereum (LGV), syphilis, tuberculosis, radiation exposure, and HIV disease, there is not enough information to determine if this is the first presentation of Crohn's disease or if the fistula is due to some other etiology.

One additional case of Crohn's disease was identified in the psoriasis program, in patient AIN457A2308-6012005 on 300 mg in Study A2308 (Argus ID PHHO2013US005303), which occurred during the maintenance period and therefore

was not included in the data pools. The safety update identified in ongoing psoriasis trials 1 additional case of Crohn's disease that is an exacerbation after 315 days of secukinumab 150 mg.

Additional cases have been identified within the secukinumab development program: 3 from the ankylosing spondylitis program, 2 from the psoriatic arthritis program, 1 from the rheumatoid arthritis program and 1 from the uveitis program.

Reviewer comment: Crohn's disease is considered to be an immune-mediated disease, like psoriasis, and is characterized by chronic intestinal inflammation. The pathogenesis of both diseases is believed to be associated with IL-17-producing T cells. However, published data have not supported the efficacy of targeting IL-17A for patients with Crohn's disease. Worsening of the symptoms of active Crohn's disease was observed in patients receiving either active treatment or placebo in published clinical trials. (b) (4) *hus animal models and in vitro data are not fully predictive of the IL-17 human experience.*

Ulcerative colitis

A total of 5 cases of ulcerative colitis were reported in the entire treatment period Pool B. 4 on secukinumab (2 on 300 mg and 2 on 150 mg) and 1 on etanercept. 3 of the cases on secukinumab were SAEs and 3 lead to discontinuation.
1 case of ulcerative colitis was reported in a patient with prior history of IBD and 3 events (2 cases of ulcerative colitis and 1 case of sclerosing cholangitis) in patients with no prior history of IBD. The cases are described below.

- [AIN457A2302-5024008], a 64 year old female patient history of microscopic colitis and prior psoriasis therapies including methotrexate and etanercept received the first dose of secukinumab (300 mg) on Day 1 (20 Oct 2011). On Day 59, symptoms of abdominal pain and hematochezia recurred and subsequently she was diagnosed with ulcerative colitis. The patient did not carry a diagnosis of UC at baseline, however reported symptoms occurring 2 months prior to receiving study treatment. The treatment with the study medication was permanently discontinued due to the event ulcerative colitis and the patient received the last dose of the study medication on Day 57 (15 Dec 2011). The patient was discharged from the hospital on Day (b) (6)) and the event was ongoing at the time of reporting. The investigator reported that the event was not related to study treatment.

- Patient [A2303-3420-3420008], a 24 year old male patient with no relevant medical history received the first dose of secukinumab (300 mg) on Day 1

(27 Oct 2011). On Day 65 (30 Dec 2011) in the induction period of study, the patient presented with severe diarrhea. On Day 100 (03 Feb 2012) in the maintenance period of study, the patient presented again with diarrhea. On Day [redacted], the patient was hospitalized and was diagnosed with ulcerative colitis. Treatment with the study medication was interrupted temporarily due to the event ulcerative colitis. The patient completed the maintenance period of the study on Day 364 (24 Oct 2012), having received the last dose of the study medication on Day 358 (18 Oct 2012). At the time of reporting, he had completed the follow-up period on Day 420 (19 Dec 2012).The investigator suspected a relationship between the event colitis ulcerative and the study medication.

- Patient [A2302-2082-2082003] a 64 year old male with no relevant medical history and prior psoriasis therapies including topical treatments and phototherapy received the first dose of secukinumab (150 mg) on Day 1 (03 Aug 2011). On Day [redacted], in the maintenance period of the study, the patient experienced abdominal pain, fever and diarrhea which resulted in hospitalization on the same day. He was diagnosed with ulcerative colitis. The patient also presented with a first episode of intestinal bleeding (hemorrhage). His stool examination on Day 151 (31 Dec 2011), showed Candida albicans. The patient experienced a second episode of intestinal bleeding on Day [redacted] and was re-admitted to the hospital. The patient recovered from intestinal bleeding on Day [redacted]). The patient was discharged from the hospital on Day [redacted]. The study medication was permanently discontinued on Day 111 (21 Nov 2011). The events were improving at the time of this reporting. The investigator suspected a relationship between the event colitis ulcerative and the study medication.

- Patient A2304-5043002, a 31year old female with a history of 7 years of ulcerative colitis presented with a flare of ulcerative colitis after 191 days on treatment with secukinumab150mg. The patient was discontinued form the study and is recovering at the time of reporting.

- Patient AIN457A2211-0039001 had a diagnosis of sclerosing cholangitis on Day 184 [Study A2211-Listing 16.2.7-1.1], and reportedly had no other symptoms or signs suggestive of IBD.

  Reviewer comment: PSC is strongly associated with inflammatory bowel disease, mainly ulcerative colitis. Approximately 75-90% of patients with primary sclerosing cholangitis (PSC) have inflammatory bowel disease (IBD). Patients with PSC but without IBD are more likely to be women and to be older at diagnosis. There is not enough information to determine if this case is more likely to be associated with ulcerative colitis.

- The etanercept patient (AIN457A2303-2208011) was a 32 year-old male Caucasian who experienced ulcerative colitis on Day 65 during the induction period. The event was graded as severe and was not reported as an SAE. The investigator suspected a relationship between the event and study drug and the study drug was permanently discontinued.

The safety update identified in ongoing psoriasis trials 1 additional new case of ulcerative colitis after 518 days of secukinumab 300 mg. Also, 2 SAE cases of inflammatory bowel disease were reported in the ankylosing spondylitis program.

Reviewer comment: The applicant is proposing labeling for Crohn's disease in the warnings and precautions section. This reviewer agrees with including labeling based on clinical trial data and the biologic plausibility (clinical trials assessing treatment of Crohn's disease with anti-IL-17 demonstrated lack of efficacy/ worsening of symptoms). The proposed labeling expresses cautious use in patients with a history of Crohn's disease. Given that in all of the cases in which flares were reported, subjects permanently discontinued treatment and events were characterized as SAEs, this warning seems appropriate to this reviewer. Based on the cases to date, it is this reviewer's opinion that the strength of evidence does not suggest a contraindication for use in patients with a history of Crohn's disease.

It is this reviewer's opinion that the cases of ulcerative colitis seen in the studies are plausible adverse reactions. Patients with psoriasis may have an increased risk of UC and it is difficult to determine if the cases observed are greater than background in psoriasis patients. The best comparison is at 12 weeks in which 1 case was reported on secukinumab, 1 case on etanercept and none on placebo. The rates were: 0 (0.0), 1 (0.1), 1 (0.07), 0 (0.0), 1 (0.3) for 150 mg, 300 mg, any secukinumab, placebo, etanercept, respectively. Additional cases on secukinumab treatment were reported over the entire treatment period (Pool B). Although the number of subjects and durations of treatment prevent a direct comparison with placebo, there are some notable characteristics of the UC cases.

Half of the 4 cases reported in Pool B were new cases in patients without exposure to prior biologic therapy and one additional new-onset case was reported in the safety update. Also, the PT ulcerative colitis was a most frequent cause of discontinuation (>=0.2%) and a most frequent SAE (>= 0.10 per 100 patient years). Although the exposure adjusted rate of ulcerative colitis was higher in etanercept (0.15 for secukinumab, 0.34 for etanercept, 0.0 for placebo), no SAEs of ulcerative colitis were reported for etanercept. Etanercept is labelled for inflammatory bowel disease in the post-marketing section.

Neutropenia

Blood and lymphatic system disorders (SOC) were comparable between secukinumab and etanercept (1.9%, 2.5% and 2.5% for 300 mg, 150 mg and etanercept, respectively). Rates in all active treatment groups were greater than placebo (1.0%). The imbalance vs. placebo was primarily due to lymphadenopathy, eosinophilia, leukopenia, lymphocytosis and neutropenia.

Neutropenia was primarily assessed based on central laboratory assessments which are discussed in section 7.4.2 Laboratory Findings. AE analysis using terms in both narrow and broad queries served as an additional assessment.

The incidence of the preferred term neutropenia was higher in all active treatment groups compared to placebo in Pool A.

Neutropenia narrow NMQ for 300 mg, 150 mg, placebo, and etanercept, respectively

- 0.3%, 0.1%, 0.0%, and 0.6%

Neutropenia broad NMQ for 300 mg, 150 mg, placebo, and etanercept, respectively

- 0.6%, 0.3%, 0.0%, and 0.6%

Reviewer comment: The applicant is proposing to include neutropenia in labeling as an adverse reaction that occurred at rates less than 1%. This reviewer concurs with the proposal. The incidence of neutropenia AEs was higher on secukinumab than placebo and increases were dose dependent. Also, the PT neutropenia was a most frequent (>=0.10% in any group) AEs causing discontinuation. Neutropenia as assessed based on central laboratory assessments and was more frequently associated with secukinumab treatment in a dose-dependent manner. Most cases of neutropenia associated with secukinumab were transient and reversible and a few were associated with non-serious infections. Therefore, it is this reviewer's opinion that the labeling of neutropenia does not need to be elevated to the warnings and precautions section at this time.

There is biologic plausibility for the reductions in peripheral neutrophil counts. It may be due to a possible pharmacodynamic effect of systemic IL-17A blockade, based on the role of IL17A in innate immunity and neutrophil biology. Because neutropenic events were also reported with Phase 2 results of two other anti-IL17 therapies, brodalumab[3] and ixekizumab[4], there appears to be a class effect. Assessment for neutropenia should continue to be conducted in LTE studies and AE reports in post-marketing should be followed. However, because few serious cases occurred, this reviewer is not recommending labeling the product for neutrophil monitoring at specific intervals during treatment.

Major Adverse Cardiovascular Events (MACE)

Subjects with stable cardiovascular risk factors were not excluded from the phase 2/ 3 clinical trials that have been submitted to support this BLA. Major adverse cardiovascular events (MACE) [including cardiovascular death, myocardial infarction, or stroke] were confirmed by an independent cardiovascular/cerebrovascular (CCV) adjudication committee. In the first 12 weeks of treatment in psoriasis trials, the rate of MACE was low across all treatment arms. The 12 week induction period of Pool B trials identified 3 (0.3%) patients on 300 mg secukinumab and 1 (0.1%) patient on placebo reporting a MACE for adjudication. This represents 2 more cases (1 on 300 mg and 1 on placebo) in addition to the 2 cases identified in Pool A. No potential MACE cases were identified for adjudication in the 150 mg or etanercept. All 4 were confirmed MACE.

Cases on secukinumab:

- acute myocardial infarction [AIN457A2308-6004004]
- acute myocardial infarction [AIN457A2304-5037008]
- cerebrovascular accident [AIN457A2308-6017002]

Case on placebo:

- brain stem hemorrhage [AIN457A2211-0092001]

All 3 events in the secukinumab arm have the similar mechanism of ischemia; the event on placebo does not. Although the number of events is few, an imbalance in ischemic events, more frequent in secukinumab-treated subjects on the highest dose (300mg), was noted.

It is expected that few events would be identified in this short, 3 month assessment period. The longer assessment at 52 weeks identified additional MACE cases. However, direct comparisons cannot be made. There were differing sample sizes between the active and placebo arms as well as differing durations of therapy for many patients as time progressed over the 52 weeks of follow-up. Placebo patients experienced high efficacy failure rates and dropout rates, and could be placed on active therapy in extension trials. Thus, the numbers of placebo patients became quite small and analysis adjusting for exposure (per 100 patient years) over the 52-week treatment period was performed. After adjusting for exposure, secukinumab at both doses (IR=0.51 for any 300 mg and 0.44 for any 150 mg) was comparable to placebo and etanercept (IR=0.50 for placebo and 0.34 for etanercept).

MACE cases submitted with the original application and additional cases reported in the safety update are shown in the table below.

Table 27: Overview of plaque psoriasis cases of MACE on secukinumab treatment (Pool B entire treatment period)

Subject ID (ARGUS code) / Age / Sex / Ethnicity / Treatment	MACE (preferred term) / TTO (Days)	Relevant medical history or risk factors	Action taken regarding study drug / Outcome / Study drug relationship	Adjudication outcome

Secukinumab 150 mg s.c.				
A2302E1-5018-00022 (PHHO2013US013389)/63/ M/Caucasian	Acute myocardial infarction / 253	Current smoker Elevated LPA levels	Temporarily interrupted / Complete recovery / Not suspected	Confirmed
A2303-3229-00011 (PHHO2012IN013115)/53/M /Asian	Myocardial infarction / 268	Diabetes, hypertension	Temporarily interrupted / Complete recovery / Not suspected	Confirmed
A2302E1-3100-00024 /55/M/Native American	Asymptomatic myocardial infarction / 364	Diabetes mellitus, hypertension, hyperlipidemia	Continued / Complete recovery / Not suspected	Confirmed
A2211E1-0512-00008 (PHHO2013US010413)/61/ M/Asian	Acute myocardial infarction / 1085	Myocardial infarction, hypertension, coronary artery disease	Temporarily interrupted / Recovered with sequelae / Not suspected	Confirmed
A2302-1004-00017 (PHHO2012AR006097)/57/ M/Caucasian	Ischemic stroke / 77	Coronary artery disease, dyslipidemia and diabetes	Discontinued / Recovered with sequelae / Suspected	Confirmed
A2302-2006-00005/46/F/ Asian	Moyamoya disease / 172	Smoker, prior transient ischemic attack	Continued / Not recovered / Not suspected	Not confirmed
A2303-2238-00007 (PHHO2012DE012095)/62/ M/Caucasian	Cerebrovascular accident / 223	Ex-smoker, prior myocardial infarction, atrial fibrillation, supraventricular tachycardia, hypertension, hyperlipidemia, coronary artery disease, atherosclerosis, arteriosclerosis, left bundle branch block	Discontinued / Condition improving, / Not suspected	Confirmed
Secukinumab 150 mg s.c. at "start of relapse"				
A2304-7055-00004 (PHHO2012VN018168)/66/ M/Asian	Hemorrhagic stroke / 295	High blood levels of glucose and hsCRP at randomization	Fatal / Not suspected	Confirmed
Secukinumab 150 mg s.c. alternate regimen				
A2211-0507-00005/62/M/ Caucasian	Myocardial infarction / 262	Smoker (for 47 years), concurrent hyperlipidemia and diabetes	Continued / Recovered / Not suspected	Confirmed
Secukinumab 300 mg s.c.				
A2304-3021-00002 /51/M/ Asian	Myocardial infarction / 203	Smoker	Continued / Recovered / Not suspected	Not confirmed
A2304-5037-00008 (PHHO2012US006467)/89/F /Caucasian	Acute myocardial infarction / 14	Prior stroke of unknown type, prior ischemic stroke, syncope, hypertension, hyperlipidemia, congestive cardiac failure	Unknown / Not reported / Not suspected	Confirmed

		and atherosclerotic conditions including carotid artery stenosis and stable coronary artery disease, cardiac murmur, atrial f brillation		
A2308-6004-00004 (PHHO2012US012516)/60/ M/Caucasian	Acute myocardial infarction / 55	Dyslipidemia, hypertension, diabetes, obesity	Temporarily interrupted / Complete recovery / Not suspected	Confirmed
A2302-5032-00001 (PHHO2012US012744)/57/ M/Caucasian	Myocardial infarction / 274	Myocardial infarction Impaired glucose tolerance, dyslipidemia, obesity	Continued / Complete recovery / Not suspected	Confirmed
A2308-6017-00002 (PHHO2012US010254)/49/ M/Black	Cerebrovascular accident / 20	Stable coronary artery disease, prior myocardial infarction, coronary arterial stent insertion, percutaneous transluminal coronary angioplasty, prior transient ischemic attack, sickle cell trait	Temporarily interrupted / Recovered with sequelae / Not suspected	Confirmed
A2302-5038-00004 (PHHO2012US007228)/37/ M/Caucasian	Cerebrovascular accident / 112	The stroke was caused by a blood clot formed after a carotid artery dissection for a pseudo aneurysm	Discontinued / Condition improving / Not suspected	Confirmed
A2302E1-3135-00011 (PHHO2013HU014391)/69/ F/Caucasian	Ischemic stroke / 282	Diabetes mellitus, tachycardia, hypertension, postthyroidectomy	Discontinued / Complete recovery / Not suspected	Confirmed
Secukinumab 300 mg s.c. at "start of relapse"				
A2304E1-3024-00010 (PHHO2013DE009057)/63/ M/Caucasian	NSTEMI / 217	Exsmoker,hypertension	Continued / Complete recovery / Not suspected	Confirmed

Source: Applicant 9/3/14 Amendment

All cases were associated with either prior or active cardiovascular disease or risk factors at baseline.

The Agency's Division of Cardiovascular and Renal Products was consulted to provide context to the MACE reports and input on the cardiovascular safety. Refer to Dr. Preston Dunnmon's thorough 5/14/14 review evaluating the cardiovascular events in the psoriasis program.

Reviewer's comment: This review concurs with Dr. Preston Dunnmon's assessment that there is not a convincing signal for a CV safety concern based on current data. This reviewer does not think there is substantial evidence to recommend labeling of CV risk at this juncture. However, given the limitations of the 52 week assessment and the

potential risk for cardiac events based on drug class, this reviewer recommends assessment of CV in LTE studies and post-marketing reports.

Malignancy

In pooled 12 week analyses (Pool A) the overall incidence of malignant or unspecified tumors by SMQ based on AEs was similar between the secukinumab dose groups and placebo. For Pool A (0.1% for 300 mg, 0.4% for 150 mg and 0.4% for placebo). Pool A malignancy adverse events and SAEs are presented in the table below.

Table 28: Malignancies and Skin Tumors (Pool A)

Level 1 Preferred term	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	Any AIN457 dose N=1382 n (%)	Placebo N=694 n (%)
Based on all AEs				
Malignant or unspecified tumors (SMQ)	3 (0.4)	1 (0.1)	4 (0.29)	3 (0.4)
Basal cell carcinoma (PT)	1 (0.1)	0 (0.0)	1 (0.07)	1 (0.1)
Bladder cancer (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Malignant melanoma in situ (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Neoplasm malignant (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Neoplasm (PT)	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)
Squamous cell carcinoma (PT)	0 (0.0)	0 (0.0)	0 (0.00)	2 (0.3)
Skin tumors malignant and unspecified (NMQ) (broad)	2 (0.3)	0 (0.0)	2 (0.14)	3 (0.4)
Basal cell carcinoma (PT)	1 (0.1)	0 (0.0)	1 (0.07)	1 (0.1)
Malignant melanoma in situ (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Squamous cell carcinoma (PT)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.03)
Based on all SAEs				
Malignant or unspecified tumors (SMQ)	3 (0.4)	0 (0.0)	3 (0.22)	0 (0.0)
Basal cell carcinoma (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Bladder cancer (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Malignant melanoma in situ (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Skin tumors malignant and unspecified (NMQ) (broad)	2 (0.3)	0 (0.0)	2 (0.14)	0 (0.0)
Basal cell carcinoma (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)
Malignant melanoma in situ (PT)	1 (0.1)	0 (0.0)	1 (0.07)	0 (0.0)

In Pool A, SAEs in malignancies, showed imbalances for secukinumab and were reported only in the 150 mg group (n=3, 0.4%). These events included bladder cancer and 2 skin malignancies (BCC and malignant melanoma in situ).

The exposure-adjusted rates of AEs related to malignant or unspecified tumors over the entire treatment period of Pool B showed a higher incidence for the placebo group compared with the active treatment groups (1.49 for placebo vs. 0.77 for any 300 mg vs.

0.97 for any 150 mg). The most frequent events in Pool B by exposure-adjusted incidence are shown in the table below.

Table 29: Exposure-adjusted incidence of the most frequent (>=0.05 per 100 patient-years in any group) AEs of malignant or unspecified tumors (Pool B Entire treatment period)

Level 1 Preferred term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	AnyAIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Based on all AEs					
Malignant or unspecified tumors (SMQ)	11 (0.97)	9 (0.77)	26 (0.96)	3 (1.49)	2 (0.68)
Basal cell carcinoma (PT)	5 (0.44)	4 (0.34)	10 (0.37)	1 (0.50)	0 (0.00)
Bladder cancer (PT)	1 (0.09)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Malignant melanoma (PT)	0 (0.00)	1 (0.08)	2 (0.07)	0 (0.00)	0 (0.00)
Malignant melanoma in situ (PT)	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	0 (0.00)
Thyroid cancer (PT)	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Squamous cell carcinoma (PT)	1 (0.09)	1 (0.08)	2 (0.07)	2 (0.99)	0 (0.00)
Follicular thyroid cancer (PT)	1 (0.09)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Neoplasm (PT)	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Neoplasm malignant (PT)	1 (0.09)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Renal cancer (PT)	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	0 (0.00)
Squamous cell carcinoma of skin (PT)	1 (0.09)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Bowen's disease (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Skin tumors malignant and unspecified (NMQ) (broad)	8 (0.70)	7 (0.60)	17 (0.63)	3 (1.49)	1 (0.34)
Basal cell carcinoma (PT)	5 (0.44)	4 (0.34)	10 (0.37)	1 (0.50)	0 (0.00)
Squamous cell carcinoma (PT)	1 (0.09)	1 (0.08)	2 (0.07)	2 (0.99)	0 (0.00)
Malignant melanoma (PT)	0 (0.00)	1 (0.08)	2 (0.07)	0 (0.00)	0 (0.00)
Malignant melanoma in situ (PT)	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	0 (0.00)
Squamous cell carcinoma of skin (PT)	1 (0.09)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Bowen's disease (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)

There were 3 cases of thyroid cancer reported in the 150 mg treatment arm of 1395 subjects. No cases were reported in the 300 mg treatment arm. One case of thyroid cancer was reported in a 70-year-old patient [AIN457A2302-1004003] with an 8-month history of methotrexate use and an active condition of thyroid nodule at baseline (noted as suspected thyroid pathology by X-ray at screening). One case of follicular thyroid cancer was reported in a 29-year-old patient [AIN457A2302-5013005] with a 24 pack-year smoking history who was also coded as having a nonserious case of thyroid

cancer; therefore, this patient was counted twice for the same event in the summary of malignancy AEs.

Reviewer comment: The significance of the cases is unclear. The rate appears to be greater than expected based on background rates. The number of new cases of thyroid cancer was 12.9 per 100,000 men and women per year based on 2007-2011 cases in SEER database. This reviewer has been unable to find a biological plausible etiology for IL-17 associated thyroid cancer in the literature. Th17 lymphocytes and its main cytokine IL-17 are thought to be involved in the pathogenesis of autoimmune thyroid disease because elevated IL-17 levels have been found in serum samples collected from patients with autoimmune diseases including Hashimoto thyroiditis and intractable Grave's disease. The understanding of intrathyroid expression of IL-17RA and the role of IL-17 on thyroid is limited. Thyroid disease should be monitored in LTE studies and postmarketing reports.

There were 2 cases of bladder cancer reported in any secukinumab dose of 3430 subjects. One case of bladder cancer was reported in a 50-year-old patient [AIN457A2211-0042-00012] with a long-standing history of asymptomatic hematuria. The second case of bladder cancer occurred in a 71-year-old patient [AIN457A2302-5025022], with a 40 pack-year smoking history and 7-month history of etanercept, who presented with urinary frequency only 4 weeks after starting secukinumab.

Reviewer comment: Smoking tobacco is a risk factor for the development of bladder cancer and thus in one subject a plausible etiology. The significance of higher rate of cases is unclear. The rate appears to be greater than expected based on background rates. The number of new cases of bladder cancer was 20.5 per 100,000 men and women per year based on 2007-2011 cases in SEER database.

Both patients with malignant melanoma/malignant melanoma in situ SAEs [AIN457A2211-0030-00024] and [AIN457A2309-6001001] were smokers and had prior exposure to phototherapy.

There were no reports of lymphoma in any treatment group over 52 weeks of all psoriasis trials. However, the latency period for malignancy would be expected to be longer than 52 weeks.

There were 2 cases of malignant melanoma on secukinumab, both in patients who were smokers and had prior exposure to phototherapy.

Additional malignancies reported as SAEs were individual cases of colon cancer, renal cancer, pleomorphic adenoma, and testicular cancer.

Reviewer comment: At this juncture, there is no evidence that secukinumab confers an increased risk for malignancy. Confounding prior psoriasis therapies (phototherapy,

chemophototherapy, and biologic therapy) which carry a malignancy risk complicates interpretation. Premarketing trials are of relatively short duration and cannot reliably detect rare events with long latency such as malignancy; the applicant has proposed a malignancy registry in their risk management plan. This reviewer finds that post-marketing assessment of malignancy is a reasonable approach.

Hepatotoxicity

The risk of liver injury was monitored through monthly laboratory assessments and evaluation of hepatotoxicity-related AEs throughout the entire 52-week treatment period. Baseline viral screens excluded patients with active or latent infection with hepatitis B or hepatitis C.

A small imbalance in the incidence of mild hepatic transaminase elevations was seen for secukinumab as compared to placebo in Pool A.

ALT/AST elevations for 300 mg, 150 mg, placebo, and etanercept, respectively

- >3×ULN: 1.5%, 1.9%, 1.2%, and 1.9%
- >5×ULN: 0.3%, 0.9%, 0.3%, and 0.9%
- >8×ULN: 0%, 0.3%, 0%, and 0.3%

TBL elevations for 300 mg, 150 mg, placebo, and etanercept, respectively

- >2×ULN: 0.1%, 0.4%, 0.3%, and 0.3%
- >3×ULN: were only observed in the placebo and etanercept groups

As in Pool A, rates in Pool B for notable laboratory abnormalities in liver function tests in secukinumab groups that were numerically higher than in placebo were comparable to rates with etanercept. CTCAE Grade 4 abnormalities during the entire treatment period were noted for ALT (one patient in the any secukinumab 300 mg group) and GGT (two patients in the any secukinumab 150 mg group).

Notable cases associated with elevated transaminases are described below:

- 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 in Pool A. Neither case was reported as an AE or SAE. The patient on 150 mg secukinumab (AIN457A2303-2206017) had a long-standing history of excessive alcohol consumption with elevations in ALT (Grade 1), AST (Grade 1), and GGT (Grade 2) at baseline.

- For the single case of ALT >20×ULN that occurred during the maintenance period in a patient (A2304-7055012): hepatic enzyme elevations occurred on Day 310, with peak values at Day 366. No action was taken with study treatment and two additional secukinumab doses were received on Day 394 and Day 422.

Liver function tests normalizing at Day 422. Of note, bilirubin remained normal in this patient, except for one mild elevation to 26 µmol/L (normal range: 3-21 µmol/L) on Day 366.

- Over the entire treatment period across all psoriasis studies, one additional patient (A2304-5013011) in the 150 mg group was identified as meeting Hy's Law laboratory criteria. 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. By Week 52 (end of maintenance period), all hepatic enzyme levels had returned to within normal limits.

- One additional patient met Hy's Law laboratory criteria based on local laboratory results: patient [AIN457A2304-3065007] in the 300 mg group, who reported SAEs of cholecystitis and hepatitis. The hepatic enzyme elevations in this patient were temporally associated with concurrent cholecystitis and, therefore, did not represent drug-induced liver injury.

Reviewer comment: The 3 cases of secukinumab patients identified in the entire treatment period across all psoriasis trials who met Hy's Law laboratory criteria had plausible alternative causative etiologies (alcoholic hepatitis, cholecystitis, and acetaminophen use) for their hepatic enzyme elevations. Also, 2 patients were continued on treatment and hepatic enzyme levels decreased. It is this reviewer's opinion that these cases are unlikely to represent cases of drug induced liver injury (DILI).

Elevations in hepatic transaminases, as compared to placebo, were seen in all pooled analyses. Rates appear to be comparable to those seen with etanercept for which "elevated transaminases" is labeled. This reviewer recommends labeling the transaminase elevations which were seen in clinical trials.

A comprehensive search of all AEs covered under the drug-related hepatic disorders broad SMQ during the first 12 weeks of treatment (Pool A) revealed a higher proportion of AEs in the secukinumab dose groups vs. placebo (1.9% for 300 mg and 1.3% for 150 mg vs. 0.9% for placebo). There was no imbalance of severe events within this SMQ. Only 1 event was reported as an SAE, a case of ascites in the setting of cardiac failure [AIN457A2309-8001006] in the 150 mg group

The exposure-adjusted incidence rates over the entire treatment period for drug-related hepatic disorders (broad SMQ) were comparable between secukinumab and etanercept

groups, which were higher than placebo (5.4, 5.1 and 5.6 for any 300 mg, 150 mg and etanercept vs. 4.5 for placebo)

A small number of patients on secukinumab discontinued study treatment due to AEs related to liver enzyme elevations (3/1410, 0.2% for any 300 mg; 3/1395, 0.2% for any 150 mg; and 1/323 vs.0.3% for etanercept). A small number SAEs related to hepatic disorders were reported.

Reviewer comment: The role of IL-17A blockade in direct liver toxicity is not known. Evaluation of AEs related to hepatic disorders in the clinical trials did not identify a safety signal for liver toxicity at this juncture.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The absolute incidence of total AEs in the induction period of both Pools A and B was higher with secukinumab (300 mg, 150 mg, or any dose) compared to placebo. The imbalance in total AEs was mainly due to the most frequently occurring SOC of infections and infestations. Consistent with the results by SOC, the rates of nasopharyngitis and upper respiratory tract infection in the two secukinumab dose groups were higher than the placebo. Common AEs by preferred term in the induction period of Pool A trials are summarized by study in the table below.

Table 30: Most common Treatment-Emergent Adverse Events during the Induction Period (Pool A) of Pivotal Phase 3 Trials

Study 2302			
Adverse Events (preferred term)	**AIN457 300mg N=245**	**AIN457 150 mg N=245**	**Placebo N=247**
Any	135 (55%)	148 (60%)	116 (47%)
Nasopharyngitis	22 (9%)	23 (9%)	19 (8%)
Headache	12 (5%)	13 (5%)	7 (3%)
Upper respiratory tract infection	9 (4%)	10 (4%)	0 (0%)
Pruritus	9 (4%)	8 (3%)	5 (2%)
Oropharyngeal pain	4 (2%)	10 (4%)	3 (1%)
Fatigue	2 (1%)	8 (3%)	2 (1%)
Diarrhea	5 (2%)	4 (2%)	3 (1%)
Hypertension	0 (0%)	9 (4%)	3 (1%)
Arthralgia	2 (1%)	6 (2%)	7 (3%)
Influenza like illness	5 (2%)	3 (1%)	3 (1%)
Study 2303			

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

Source: excerpt from applicant's table

The incidences of the most common events were similar across all treatment arms (300 mg, 150mg, and placebo) and between studies. Pooled data of common AEs is shown in the table below.

Table 31: Most frequent (>=2.0% in any group) AEs by preferred term for induction period (Pool A)

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

Source: applicant SCS table 2-2

Reviewer comment: The most common AEs seen in the studies correspond with common ailments. It is unlikely that the majority of them are related to treatment. The profiles appear similar to other approved biologics for the treatment of plaque psoriasis. There is no apparent safety signal based on the common AE profile for secukinumab.

AEs which were classified by the investigator as possibly related and occurred > 1% included pruritus, nasopharyngitis, headache and fatigue. The applicant proposed the following table for labeling of adverse reactions:

Table 32: Proposed labeling of adverse reactions

Adverse Reactions	COSENTYX		Placebo (N=694) n (%)
	300 mg (N=691) n (%)	150 mg (N=692) n (%)	
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)
Rhinorrhea	8 (1.2)	2 (0.3)	1 (0.1)

Reviewer comment: To adjudicate AEs as being reasonably and plausibly related to the drug treatment, this reviewer looked at the totality of the data. AEs which occurred at a frequency of ≥1% for both pool A and pool B were evaluated to see if there is a pattern of events with long term use. The analysis by investigator assessment was not particularly useful in this assessment. This reviewer concurs with the applicant to included infections as adverse reactions because of biologic plausibility. Frequently reported cardiac terms (hypertension and hypercholestereima) were more closely evaluated with laboratory assessments and input from the Division of Cardio and Renal Products and did not appear related. Other AE terms frequently reported were common ailments, occurred as frequently/ nearly as frequently in the placebo arm and did have biologic plausibility. This reviewer concurs with the applicant's proposed labeling of adverse reactions.

7.4.2 Laboratory Findings

Criteria for clinically notable laboratory abnormalities were based on Common Terminology Criteria for Adverse Events (CTCAE) grades.

Hematology

As with the approved biologics targeting the immune system, secukinumab causes decreases in leukocytes. Decreases in total lymphocytes, B cell, and T cells were seen at higher doses in monkeys. However, the decrease in white blood cells seen in clinical trials appears to be neutrophil predominant and dose-dependent, but less frequent than etanercept. Lymphopenia was more frequently seen in secukinumab than in etanercept, but was less frequent than placebo in Pool A; shifts from normal grade to Grade 3-4 were observed in 2 patients on 150 mg secukinumab and 1 patient on

placebo for lymphocytes. In Pool B (over the entire treatment period) Grade 3 lymphopenia was more frequent in the secukinumab groups (0.4% for any 300 mg and 0.5% for any 150 mg) than with placebo (0.1%) and etanercept (0%).

AEs regarding neutropenia were discussed above under section 7.7.3. Newly occurring or worsening abnormalities in hematology parameters during the induction period of Pool A are shown in the table below:

Table 33: Hematology: number (%) of patients with newly occurring or worsening CTCAE grades – Induction period (Pool A)

Criterion	AIN457 150 mg N=692 n/m (%)	AIN457 300 mg N=690 n/m (%)	Any AIN457 dose N=1382 n/m (%)	Placebo N=694 n/m (%)	Etanercept N=323 n/m (%)
Hemoglobin (g/L)					
< LLN - 100 g/L	28/657 (4.3)	23/655 (3.5)	51/1312 (3.89)	40/659 (6.1)	9/309 (2.9)
< 100 - 80 g/L	3/686 (0.4)	4/685 (0.6)	7/1371 (0.51)	6/691 (0.9)	0/318 (0.0)
< 80 g/L	0/688 (0.0)	0/686 (0.0)	0/1374 (0.00)	0/692 (0.0)	0/320 (0.0)
Leukocytes (10E9/L)					
< LLN - 3.0 x 10E9/L	45/672 (6.7)	54/671 (8.0)	99/1343 (7.37)	22/677 (3.2)	18/305 (5.9)
< 3.0 - 2.0 x 10E9/L	3/686 (0.4)	3/684 (0.4)	6/1370 (0.44)	2/690 (0.3)	7/317 (2.2)
< 2.0 - 1.0 x 10E9/L	0/688 (0.0)	1/685 (0.1)	1/1373 (0.07)	0/691 (0.0)	0/318 (0.0)
< 1.0 x 10E9/L	0/688 (0.0)	0/685 (0.0)	0/1373 (0.00)	0/691 (0.0)	0/318 (0.0)
Lymphocytes (absolute) (10E9/L)					
< LLN - 0.8 x 10E9/L	34/654 (5.2)	30/651 (4.6)	64/1305 (4.90)	50/658 (7.6)	8/299 (2.7)
< 0.8 - 0.5 x 10E9/L	15/675 (2.2)	11/675 (1.6)	26/1350 (1.93)	9/685 (1.3)	4/313 (1.3)
< 0.5 - 0.2 x 10E9/L	2/686 (0.3)	0/685 (0.0)	2/1371 (0.15)	1/690 (0.1)	0/318 (0.0)
< 0.2 x 10E9/L	0/688 (0.0)	0/685 (0.0)	0/1373 (0.00)	0/690 (0.0)	0/318 (0.0)
Neutrophils (absolute) (10E9/L)					
< LLN - 1.5 x 10E9/L	47/678 (6.9)	51/677 (7.5)	98/1355 (7.23)	16/682 (2.3)	29/310 (9.4)
< 1.5 - 1.0 x 10E9/L	12/686 (1.7)	11/685 (1.6)	23/1371 (1.68)	2/688 (0.3)	10/317 (3.2)
< 1.0 - 0.5 x 10E9/L	0/687 (0.0)	1/685 (0.1)	1/1372 (0.07)	1/688 (0.1)	0/318 (0.0)
< 0.5 x 10E9/L	0/688 (0.0)	0/685 (0.0)	0/1373 (0.00)	0/690 (0.0)	1/318 (0.3)
Platelets (10E9/L)					
< LLN - 75 x 10E9/L	27/672 (4.0)	16/665 (2.4)	43/1337 (3.22)	12/672 (1.8)	12/312 (3.8)
< 75 - 50 x 10E9/L	2/686 (0.3)	0/682 (0.0)	2/1368 (0.15)	1/691 (0.1)	1/317 (0.3)
< 50 - 25 x 10E9/L	1/686 (0.1)	0/682 (0.0)	1/1368 (0.07)	0/691 (0.0)	0/317 (0.0)
< 25 x 10E9/L	0/686 (0.0)	0/682 (0.0)	0/1368 (0.00)	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
Source: Applicant SCS Table 3-4

Neutropenia (CTCAE Grades 1 and 2) was more frequently observed with secukinumab and etanercept than with placebo, but most cases were mild, transient and reversible.

CTCAE Grade 3 Neutropenia <1.0-0.5x109/L was reported in 18/3993 patients on secukinumab, over the entire treatment period in Pool B. The rate was highest in the 300 mg secukinumab dose groups (n=10, 0.7% for any 300 mg and n=8, 0.6% for any 150 mg) and for 1 placebo patient (0.1%). Most cases were transient and reversible. Of the 18 cases on secukinumab, 3 patients had mild or moderate, non-serious infections (rhinitis, upper respiratory tract infection and cystitis), which did not cause study treatment discontinuation, within 1-2 weeks of the Grade 3 neutropenia event. Patient [AIN457A2303-2125010] in the 300 mg group showed persistent Grade 3 neutropenia, which was reported as a mild, non-serious AE and led to study treatment discontinuation.

Grade 4 neutropenia was reported for 1 etanercept patient only.

The rate of Grade 2 leukopenia, lymphopenia and thrombocytopenia was higher in the secukinumab dose groups vs. placebo. Grade 3 abnormalities in lymphocytes and platelets were reported in a small number of patients, with no clinically meaningful differences between the secukinumab doses.

Chemistry

Novartis presented results for a number of blood chemistry tests including creatinine, glucose, cholesterol, triglycerides, ALT, AST, GGT, AP and bilirubin. For the majority of these tests, there did not appear to be meaningful differences in mean change from baseline or outliers (shift to low or high) when comparing secukinumab treated patients to placebo patients. Results for liver related lab tests are presented with hepatic events in section 7.7.3 above. Patients with newly occurring or worsening CTCAE grades in the first 12 weeks of treatment (Pool A) are shown in the table below.

Table 34: Clinical chemistry: number (%) of patients with newly occurring or worsening CTCAE grades (Pool A)

Criterion	AIN457 150 mg N=692 n/m (%)	AIN457 300 mg N=690 n/m (%)	Any AIN457 dose N=1382 n/m (%)	Placebo N=694 n/m (%)	Etanercept N=323 n/m (%)
ALT (U/L)					
> ULN - 3.0 x ULN	93/593 (15.7)	86/593 (14.5)	179/1186 (15.09)	69/596 (11.6)	50/265 (18.9)
> 3.0 - 5.0 x ULN	6/687 (0.9)	6/684 (0.9)	12/1371 (0.88)	6/690 (0.9)	5/316 (1.6)
> 5.0 - 20.0 x ULN	4/690 (0.6)	1/685 (0.1)	5/1375 (0.36)	1/692 (0.1)	3/321 (0.9)
> 20.0 x ULN	0/690 (0.0)	0/686 (0.0)	0/1376 (0.00)	0/692 (0.0)	0/321 (0.0)
AST (U/L)					
> ULN - 3.0 x ULN	66/645 (10.2)	63/647 (9.7)	129/1292 (9.98)	56/646 (8.7)	33/296 (11.1)
> 3.0 - 5.0 x ULN	2/689 (0.3)	4/684 (0.6)	6/1373 (0.44)	3/691 (0.4)	2/319 (0.6)
> 5.0 - 20.0 x ULN	5/690 (0.7)	1/685 (0.1)	6/1375 (0.44)	2/692 (0.3)	1/321 (0.3)

> 20.0 x ULN	0/690 (0.0)	0/685 (0.0)	0/1375 (0.00)	0/692 (0.0)	0/321 (0.0)
ALP (U/L)					
> ULN - 2.5 x ULN	11/655 (1.7)	19/662 (2.9)	30/1317 (2.28)	22/653 (3.4)	5/306 (1.6)
> 2.5 - 5.0 x ULN	0/690 (0.0)	0/686 (0.0)	0/1376 (0.00)	0/692 (0.0)	0/321 (0.0)
> 5.0 - 20.0 x ULN	0/690 (0.0)	0/686 (0.0)	0/1376 (0.00)	0/692 (0.0)	0/321 (0.0)
> 20.0 x ULN	0/690 (0.0)	0/686 (0.0)	0/1376 (0.00)	0/692 (0.0)	0/321 (0.0)
Bilirubin (umol/L)					
> ULN - 1.5 x ULN	19/680 (2.8)	29/674 (4.3)	48/1354 (3.55)	16/676 (2.4)	10/314 (3.2)
> 1.5 - 3.0 x ULN	4/688 (0.6)	5/685 (0.7)	9/1373 (0.66)	1/690 (0.1)	6/319 (1.9)
> 3.0 - 10.0 x ULN	0/690 (0.0)	0/686 (0.0)	0/1376 (0.00)	2/692 (0.3)	1/321 (0.3)
> 10.0 x ULN	0/690 (0.0)	0/686 (0.0)	0/1376 (0.00)	0/692 (0.0)	0/321 (0.0)
Cholesterol (mmol/L)					
> ULN - 7.75 mmol/L	71/369 (19.2)	71/405 (17.5)	142/774 (18.35)	62/358 (17.3)	22/168 (13.1)
> 7.75 - 10.34 mmol/L	8/635 (1.3)	4/627 (0.6)	12/1262 (0.95)	3/625 (0.5)	2/290 (0.7)
> 10.34 - 12.92 mmol/L	1/639 (0.2)	0/634 (0.0)	1/1273 (0.08)	0/633 (0.0)	0/295 (0.0)
> 12.92 mmol/L	0/639 (0.0)	0/635 (0.0)	0/1274 (0.00)	0/633 (0.0)	1/296 (0.3)
Creatinine (umol/L)					
> ULN - 1.5 x ULN	35/667 (5.2)	39/660 (5.9)	74/1327 (5.58)	27/670 (4.0)	9/314 (2.9)
> 1.5 - 3.0 x ULN	2/690 (0.3)	2/685 (0.3)	4/1375 (0.29)	1/691 (0.1)	0/321 (0.0)
> 3.0 - 6.0 x ULN	0/691 (0.0)	0/686 (0.0)	0/1377 (0.00)	0/692 (0.0)	0/321 (0.0)
> 6.0 x ULN	0/691 (0.0)	0/686 (0.0)	0/1377 (0.00)	0/692 (0.0)	0/321 (0.0)
GGT (U/L)					
> ULN - 2.5 x ULN	46/565 (8.1)	48/583 (8.2)	94/1148 (8.19)	47/564 (8.3)	26/255 (10.2)
> 2.5 - 5.0 x ULN	21/671 (3.1)	12/671 (1.8)	33/1342 (2.46)	10/673 (1.5)	8/314 (2.5)
> 5.0 - 20.0 x ULN	5/687 (0.7)	3/683 (0.4)	8/1370 (0.58)	2/688 (0.3)	3/320 (0.9)
> 20.0 x ULN	0/691 (0.0)	0/686 (0.0)	0/1377 (0.00)	0/692 (0.0)	0/321 (0.0)
Glucose, plasma, fasting decreased (mmol/L)					
< LLN - 3.0 mmol/L	4/520 (0.8)	4/527 (0.8)	8/1047 (0.76)	1/523 (0.2)	1/293 (0.3)
< 3.0 - 2.2 mmol/L	1/527 (0.2)	0/530 (0.0)	1/1057 (0.09)	1/526 (0.2)	1/294 (0.3)
< 2.2 - 1.7 mmol/L	0/527 (0.0)	0/531 (0.0)	0/1058 (0.00)	0/526 (0.0)	0/294 (0.0)

Criterion	AIN457 150 mg N=692 n/m (%)	AIN457 300 mg N=690 n/m (%)	Any AIN457 dose N=1382 n/m (%)	Placebo N=694 n/m (%)	Etanercept N=323 n/m (%)
< 1.7 mmol/L	0/527 (0.0)	0/531 (0.0)	0/1058 (0.00)	0/526 (0.0)	0/294 (0.0)
Glucose, plasma, fasting increased (mmol/L)					
> ULN - 8.9 mmol/L	17/473 (3.6)	22/468 (4.7)	39/941 (4.14)	19/476 (4.0)	7/260 (2.7)
> 8.9 - 13.9 mmol/L	6/501 (1.2)	6/510 (1.2)	12/1011 (1.19)	6/506 (1.2)	3/279 (1.1)
> 13.9 - 27.8 mmol/L	3/520 (0.6)	2/525 (0.4)	5/1045 (0.48)	8/521 (1.5)	2/292 (0.7)
> 27.8 mmol/L	0/527 (0.0)	0/532 (0.0)	0/1059 (0.00)	0/526 (0.0)	0/294 (0.0)
Triglycerides (mmol/L)					
>=1.71 - 3.42 mmol/L	77/400 (19.3)	59/415 (14.2)	136/815 (16.69)	55/383 (14.4)	24/185 (13.0)
> 3.42 - 5.7 mmol/L	29/603 (4.8)	23/606 (3.8)	52/1209 (4.30)	13/582 (2.2)	10/271 (3.7)

> 5.7 - 11.4 mmol/L	13/634 (2.1)	8/627 (1.3)	21/1261 (1.67)	8/623 (1.3)	2/290 (0.7)
> 11.4 mmol/L	2/638 (0.3)	1/633 (0.2)	3/1271 (0.24)	3/632 (0.5)	4/295 (1.4)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gammaglutamyltransferase;
LLN=lower limit of normal, ULN=upper 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
Source: Applicant SCS Table 3-6

Grade 1 elevations in creatinine were more frequent with 300 mg and 150 mg than with placebo or etanercept (5.9% for 300 mg and 5.2% for 150 mg vs. 4.0% for placebo and 2.9% for etanercept). There were few Grade 2 creatinine elevations and difference between the secukinumab and placebo appear to not be clinically meaningful. Most of the creatinine abnormalities were transient, lasting 1-2 visits, and reversible while on treatment. None of the creatinine abnormalities led to discontinuation of study treatment

During the induction period, small median increases were observed for the secukinumab dose groups, whereas the placebo and etanercept groups showed small median decreases in lipid parameters. LDL, cholesterol and triglyceride abnormalities were mostly ≥ ULN but < 1.5×ULN. The differences do not appear to be clinically meaningful.

7.4.3 Vital Signs

The applicant conducted analysis of vital signs was performed by defining criteria for notable vital sign abnormalities that were just above at the cutoffs for defining stage I blood pressure elevations and tachycardia, per the following table:

Table 35: Criteria for Notable Vital Sign Abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	≥ 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	≥ 90 mmHg or < 60 mmHg
Pulse (bpm)	> 100 bpm or < 60 bpm

Source: Applicant SCS Table 4-1

The results of this analysis demonstrated slightly higher percentages of subjects experiencing BP and pulse elevations on secukinumab as compared to placebo, but these were similar to the Etanercept group. Data from the induction period of Pool B, the presence of a consistent BP and/or pulse effect was not seen. Data from Pool A is shown in the table below:

Table 36: Pool A Subjects with Newly Occurring Notable Abnormalities in Vital Signs

Vital signs Category	AIN457 150 mg N=692 n/m (%)	AIN457 300 mg N=690 n/m (%)	Any AIN457 dose N=1382 n/m (%)	Placebo N=694 n/m (%)	Etanercept N=323 n/m (%)
Systolic BP (mmHg)					
High only	135/544 (24.8)	152/555 (27.4)	287/1099 (26.11)	143/567 (25.2)	77/271 (28.4)
Low only	4/689 (0.6)	4/686 (0.6)	8/1375 (0.58)	1/691 (0.1)	2/319 (0.6)
High and Low	0/544 (0.0)	0/555 (0.0)	0/1099 (0.00)	0/566 (0.0)	0/269 (0.0)
Diastolic BP (mmHg)					
High only	137/577 (23.7)	155/586 (26.5)	292/1163 (25.11)	128/582 (22.0)	72/271 (26.6)
Low only	22/681 (3.2)	25/680 (3.7)	47/1361 (3.45)	26/684 (3.8)	14/318 (4.4)
High and Low	1/569 (0.2)	3/580 (0.5)	4/1149 (0.35)	1/574 (0.2)	0/268 (0.0)
Pulse (bpm)					
High only	33/682 (4.8)	25/681 (3.7)	58/1363 (4.26)	27/688 (3.9)	9/314 (2.9)
Low only	59/643 (9.2)	72/638 (11.3)	131/1281 (10.23)	53/635 (8.3)	32/309 (10.4)
High and Low	1/635 (0.2)	0/635 (0.0)	1/1270 (0.08)	0/631 (0.0)	1/303 (0.3)

BP=blood pressure
All BP and pulse rate measurements were taken in sitting position. Systolic blood pressure (BP): high: >=140 mmHg, low: <90 mmHg; Diastolic blood pressure (BP): high: >=90 mmHg, low: <60 mmHg; Pulse rate: high: >100 bpm, low: <60 bpm
Newly occurring – patients not meeting criterion at baseline and meeting criterion post-baseline
n=number of patients who meet the designated criterion
m=number of patients at risk for an abnormality with a non-missing value at baseline and post-baseline
Source: Applicant SCS Table 4-2

It was noted that the common AE analysis shows an excess of AEs in the vascular disorder SOC which was primarily due to a higher rate of hypertension in the 150 mg arm of Pool A. Also, all four SAEs of hypertensive crisis that occurred in the entire treatment period of Pool B clustered in the secukinumab treatment arms.

Because the vital sign analysis was limited to assessing extreme shifts of blood pressure, an information request was sent to the applicant to provide shift tables between normal, stage I, and Stage II BPs, and K-M curves showing time to first BP above those cutoffs in order to confirm the lack of any extreme BP effect.

On 6/3/14 the applicant responded by providing shift-table analysis for Pool A and Pool B subjects. Summaries of the shift table analysis are in the tables below.

Table 37: Summary from Shift Table between Normal, Stage I, and Stage II Blood Pressure Measurements for Subjects in Pool A

Treatment Group	From normal / prehypertension to stage I	From normal / prehypertension to stage II	From stage I to stage II

150 mg	147 / 497 (29.6%)	10 / 497 (2.0%)	37 / 183 (20.2%)
300 mg	172 / 514 (33.5%)	8 / 514 (1.6%)	42 / 160 (26.3%)
Placebo	155 / 516 (30.0%)	12 / 516 (2.3%)	33 / 164 (20.1%)
Etanercept	77 / 248 (31.0%)	11 / 248 (4.4%)	14 / 66 (21.2%)

Source: Applicant 6/13/14 amendment table 1-3

Table 38: Summary from Shift Table between Normal, Stage I, and Stage II Blood Pressure Measurements for Subjects in Pool B for Entire Treatment Period

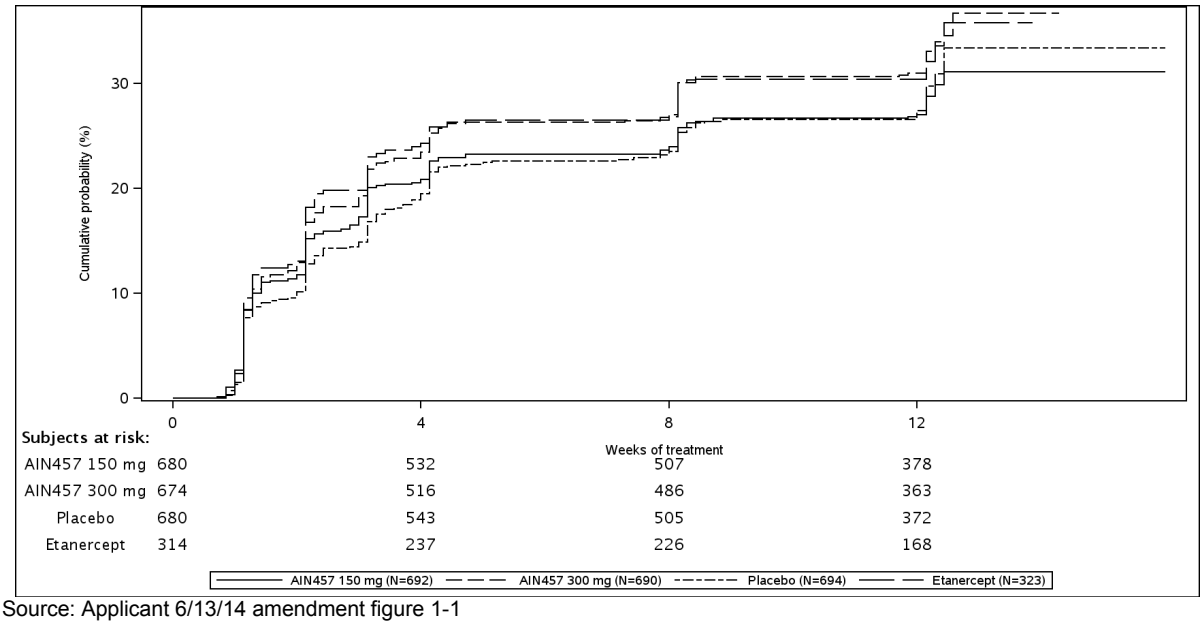
Treatment Group	From normal /prehypertension to stage I	From normal /prehypertension to stage II	From stage I to stage II
Any 150 mg	384 / 1009 (38.1%)	45 / 1009 (4.5%)	113 / 351 (32.2%)
Any 300 mg	439 /1028 (42.7%)	52 / 1028 (5.1%)	106 / 354 (29.9%)
Any AIN	997 / 2413 (41.3%)	134 / 2413 (5.6%)	276 / 829 (33.3%)
Placebo	176 / 573 (30.7%)	15 /573 (2.6%)	41 / 189 (21.7%)
Etanercept	97 / 248 (39.1%)	23 /248 (9.3%)	25 / 66 (37.9%)

Source: Applicant 6/13/14 amendment table 1-4

Shift table analysis demonstrates that there is a lack of a consistent trend across treatment groups, and trends seen with the secukinumab treatment group are similar to those of Etanercept.

Kaplan-Meier analysis shows that after 12 weeks, the cumulative rate for secukinumab 300 mg is 30.9% (95% CI: 27.6, 34.6),secukinumab 150 is 27.0% (95% CI: 23.8, 30.5), etanercept (50mg BIW) is 30.4% (95% CI: 25.6, 35.8) and for placebo 27.5% (95% CI: 24.3, 31.1) as shown in the figure below.

Figure 5: Cumulative probabilities for blood pressure measurements that meet JNC VII criteria that meet Stage I or Stage II hypertension



Source: Applicant 6/13/14 amendment figure 1-1

Kaplan-Meier analysis also shows that after 52 weeks, the cumulative rate for secukinumab 300 mg is 45.5% (95% CI: 42.8, 48.3),secukinumab 150 is 43.2% (95% CI: 40.4, 46.1), etanercept (50mg BIW) is 47.1% (95% CI: 41.7, 53.0) and for placebo 49.2% (95% CI: 39.2, 60.2).

Although rates are higher for the 300 mg group as compared with the 150 mg group, because the associated confidence intervals are overlapping, the rates are essentially comparable across all treatment groups. The Kaplan-Meier analysis at both 12 weeks and 52 weeks does not suggest any clinically meaningful difference in time to first BP elevation between the treatment groups.

7.4.4 Electrocardiograms (ECGs)

In clinical studies conducted with secukinumab, standard 12-lead ECGs were performed at selected visits. The following ECG variables were summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc) using Bazett (QTcB) and Fridericia (QTcF) corrections. Dr. Preston Dunnmon, cardiology concludes and this reviewer agrees that there is no evidence for important drug induced prolongation of the QT interval or PR interval in the categorical analyses of the induction periods for Pool A and Pool B, as shown in the tables below:

Table 39: Subjects with Notable Abnormal ECG Parameters (Pool A Induction Period)

	AIN457 150 mg N=692	AIN457 300 mg N=690	Any AIN457 dose N=1382	Placebo N=694	Etanercept N=323

Criterion	n/m (%)	n/m (%)	n/m (%)	n/m (%)	n/m (%)
QTcB > 500 msec	0/606 (0.0)	1/597 (0.2)	1/1203 (0.08)	0/600 (0.0)	0/266 (0.0)
QTcB > 480 msec	3/602 (0.5)	2/593 (0.3)	5/1195 (0.42)	6/598 (1.0)	0/264 (0.0)
QTcB > 450 msec	24/566 (4.2)	16/563 (2.8)	40/1129 (3.54)	30/555 (5.4)	10/253 (4.0)
QTcB changes from baseline > 30 msec	35/606 (5.8)	23/599 (3.8)	58/1205 (4.81)	34/600 (5.7)	16/266 (6.0)
QTcB changes from baseline > 60 msec	1/606 (0.2)	1/599 (0.2)	2/1205 (0.17)	3/600 (0.5)	0/266 (0.0)
QTcF > 500 msec	0/606 (0.0)	1/599 (0.2)	1/1205 (0.08)	0/600 (0.0)	0/266 (0.0)
QTcF > 480 msec	2/605 (0.3)	2/597 (0.3)	4/1202 (0.33)	2/599 (0.3)	0/265 (0.0)
QTcF > 450 msec	6/589 (1.0)	8/587 (1.4)	14/1176 (1.19)	13/587 (2.2)	6/261 (2.3)
QTcF changes from baseline > 30 msec	15/606 (2.5)	16/599 (2.7)	31/1205 (2.57)	22/600 (3.7)	9/266 (3.4)
QTcF changes from baseline > 60 msec	0/606 (0.0)	0/599 (0.0)	0/1205 (0.00)	0/600 (0.0)	0/266 (0.0)
PR > 250 msec	2/601 (0.3)	0/590 (0.0)	2/1191 (0.17)	0/597 (0.0)	1/265 (0.4)

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 did not meet the criterion at baseline
Source: Applicant's SCS Table 4-4

Table 40: Subjects with Notable Abnormal ECG Parameters (Pool B Induction Period)

Criterion	AIN457 150 mg N=1174 n/m (%)	AIN457 300 mg N=1173 n/m (%)	Any AIN457 dose N=2877 n/m (%)	Placebo N=793 n/m (%)	Etanercept N=323 n/m (%)
QTcB > 500 msec	1/1025 (0.10)	1/1033 (0.10)	2/2154 (0.09)	0/615 (0.0)	0/266 (0.0)
QTcB > 480 msec	4/1017 (0.39)	5/1021 (0.49)	10/2133 (0.47)	6/613 (1.0)	0/264 (0.0)
QTcB > 450 msec	49/946 (5.18)	29/963 (3.01)	80/2002 (4.00)	30/570 (5.3)	10/253 (4.0)
QTcB changes from baseline > 30 msec	50/1025 (4.88)	39/1035 (3.77)	96/2157 (4.45)	36/615 (5.9)	16/266 (6.0)
QTcB changes from baseline > 60 msec	3/1025 (0.29)	2/1035 (0.19)	5/2157 (0.23)	3/615 (0.5)	0/266 (0.0)
QTcF > 500 msec	0/1025 (0.00)	1/1035 (0.10)	1/2156 (0.05)	0/615 (0.0)	0/266 (0.0)
QTcF > 480 msec	3/1024 (0.29)	2/1032 (0.19)	5/2152 (0.23)	2/614 (0.3)	0/265 (0.0)
QTcF > 450 msec	12/1000 (1.20)	16/1011 (1.58)	30/2105 (1.43)	13/602 (2.2)	6/261 (2.3)
QTcF changes from baseline > 30 msec	26/1025 (2.54)	30/1035 (2.90)	66/2157 (3.06)	22/615 (3.6)	9/266 (3.4)
QTcF changes from baseline > 60 msec	0/1025 (0.00)	0/1035 (0.00)	0/2157 (0.00)	0/615 (0.0)	0/266 (0.0)
PR > 250 msec	2/1018 (0.20)	0/1022 (0.00)	3/2137 (0.14)	0/612 (0.0)	1/265 (0.4)

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 did not meet the criterion at baseline
Source: Applicant's SCS Table 4-5

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted because no special safety concern arose from non-clinical safety data obtained with secukinumab.

7.4.6 Immunogenicity

In the psoriasis Phase 3 trials, 0.4% (10/2842) of subjects developed secukinumab treatment-emergent anti-drug antibodies (ADA). Of the 10 subjects who developed ADAs, 3 subjects were classified as positive for neutralizing antibodies, 5 subjects were classified as negative for neutralizing antibodies, and the remaining 2 subjects were not characterized for neutralizing antibodies status.

Non-treatment emergent ADAs were also observed in the same psoriasis trials in which 1.7% (56/3364) of secukinumab naive subjects had positive ADA at baseline (n=47) or at a post-baseline time point without secukinumab exposure (n=9) in placebo subjects. Among the 56 subjects tested positive for ADA at baseline, 49 subjects did not have any positive ADA samples following the treatment with secukinumab.

Subjects with secukinumab treatment-emergent ADA were not associated with a loss of therapeutic efficacy which is defined as increase in PASI score by 6 points from minimum PASI score achieved on treatment. The development of treatment-emergent ADA was not associated with injection site reactions or other severe administration reactions including hypersensitivity events. Overall, no evidence of altered PK, efficacy or safety has been observed in subjects who developed secukinumab treatment-emergent ADA in psoriasis Phase 3 trials. However, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on the clinical efficacy and/or safety measures because of the small number of subjects with treatment-emergent ADA.

The neutralizing ADA assay appears to be insensitive and the presence of secukinumab in the clinical serum sample in subjects with higher levels would interfere with the assay. Novartis provided additional data which indicates that the assay may be more sensitive. Since the levels of ADA detected are relatively low, the Product Quality reviewer finds the assay acceptable. See Product Quality Review (immunogenicity section) by Tura Camilli, Ph.D., for more detailed information regarding the immunogenicity assay validation. The Clinical Pharmacology team also finds that is not essential at this time to develop an improved neutralizing ADA assay because the overall immunogenicity incidence is low for secukinumab in the psoriasis Phase 3 trials and there was no evidence of altered PK, efficacy or safety in the ADA positive subjects. See Clinical Pharmacology Review. This reviewer concurs with the Clinical Pharmacology team's assessment.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The applicant evaluated 2 doses (150mg and 300 mg) in the phase 3 studies. Since two doses were selected for further Phase 3 evaluation, it allows for further assessment of dose-response for both safety and efficacy in a much larger patient population. Differences in efficacy between the doses were noted with an overall increase in response for the 300 mg dose group. See section 6.1.4 Analysis of Primary Endpoint(s).

Safety data comparing both doses was available for approximately 700 subjects each for the maximal duration of dose of 52 weeks (induction dosing followed by monthly dosing). Additional data is also available for comparison between doses, but it is of a shorter duration of 12 weeks. Pooled analysis of 52-week safety data in the two pivotal Phase 3 trials showed an overall AE rate of 80.3% and 81.9%, respectively, for the 150 mg and 300 mg doses. Analyses for the majority of specific adverse events evaluated did not demonstrate differences between the 300 mg and 150 mg secukinumab cohorts. Dose-dependent differences were noted for neutropenia and infections. For neutropenia, small increases in rates for reported AEs and decreases in neutrophil counts on laboratory analysis were noted to be dose-dependent. The overall rate of reported AEs for infections and infestations was also dose-dependent. Differences, with higher rates in the 300 mg group, were seen for some types of upper respiratory tract infections (pneumonia, bacterial pharyngitis, and sinusitis) and mucosal/ skin infections (impetigo, candidiasis). Also, herpes viral infections occurred in a higher proportion of patients in the 300 mg group than the 150 mg group and were higher than placebo (1.6%, 0.9%, 0.4% for 300 mg, 150 mg and placebo); no cases of disseminated or CNS herpes were reported. Infections requiring oral or parenteral antimicrobial concomitant treatment were more frequently reported in the 300 mg group than the 150 mg group (12.2% for 300 mg, 9.4% for 150 mg and 7.2% for placebo.

In analyzing infections which were dose-related, a difference for candida infections was noted. These infections were more frequently reported at the 300 mg cohort and are consistent with mechanism of action. Animal models predict susceptibility to candidiasis with deficiencies in the IL-17 pathway. Of the various known human deficiencies in the IL-17 pathway, the majority are associated with chronic mucocutaneous candidiasis (CMC). Some may also be associated with staphylococcal skin infections and pulmonary infections[5].

To more closely examine the relationship between infections and exposure, particularly candidiasis, an exploratory safety analysis by exposure quartiles was performed. The analysis showed a trend of increasing AEs with increasing exposure only at 300 mg

dose. Across the exposure quartiles, the overall AE rates were 75.3%, 88.0%, 84.0% and 73.7% (in an increasing order of the exposure quartile), respectively, for the 150 mg dose and 72.8%, 80.8%, 83.3% and 87.6%, respectively for the 300 mg dose. See table below.

Table 41: Overall treatment emergent adverse events by Week 52 secukinumab trough serum concentration quartiles for the 150 mg dose in pooled analysis for 2302 and 2303

	AE rate by Secukinumab concentration quartile 150 mg dose group				
Concentration quartile	1st quartile	2nd quartile	3rd quartile	4th quartile	
Concentration range (n)	<11.6 mcg/mL (n=97)	≥11.6 to <15.9 mcg/mL (n=100)	≥15.9 to <22.1 mcg/mL (n=100)	≥22.1 to <94.9 mcg/mL (n=99)	Any concentration (n=396)
Any AEs	73 (75.3%)	88 (88.0%)	84 (84.0%)	73 (73.7%)	318 (80.3%)
Candida infection	1 (1.0%)	1 (1.0%)	4 (4.0%)	3 (3.0%)	9 (2.3%)

Source: Table 3-1, Table 3-3, Response to FDA information request, July 14, 2014.

Table 42: Overall treatment emergent adverse events by Week 52 secukinumab trough serum concentration quartiles for the 300 mg dose in pooled analysis for 2302 and 2303

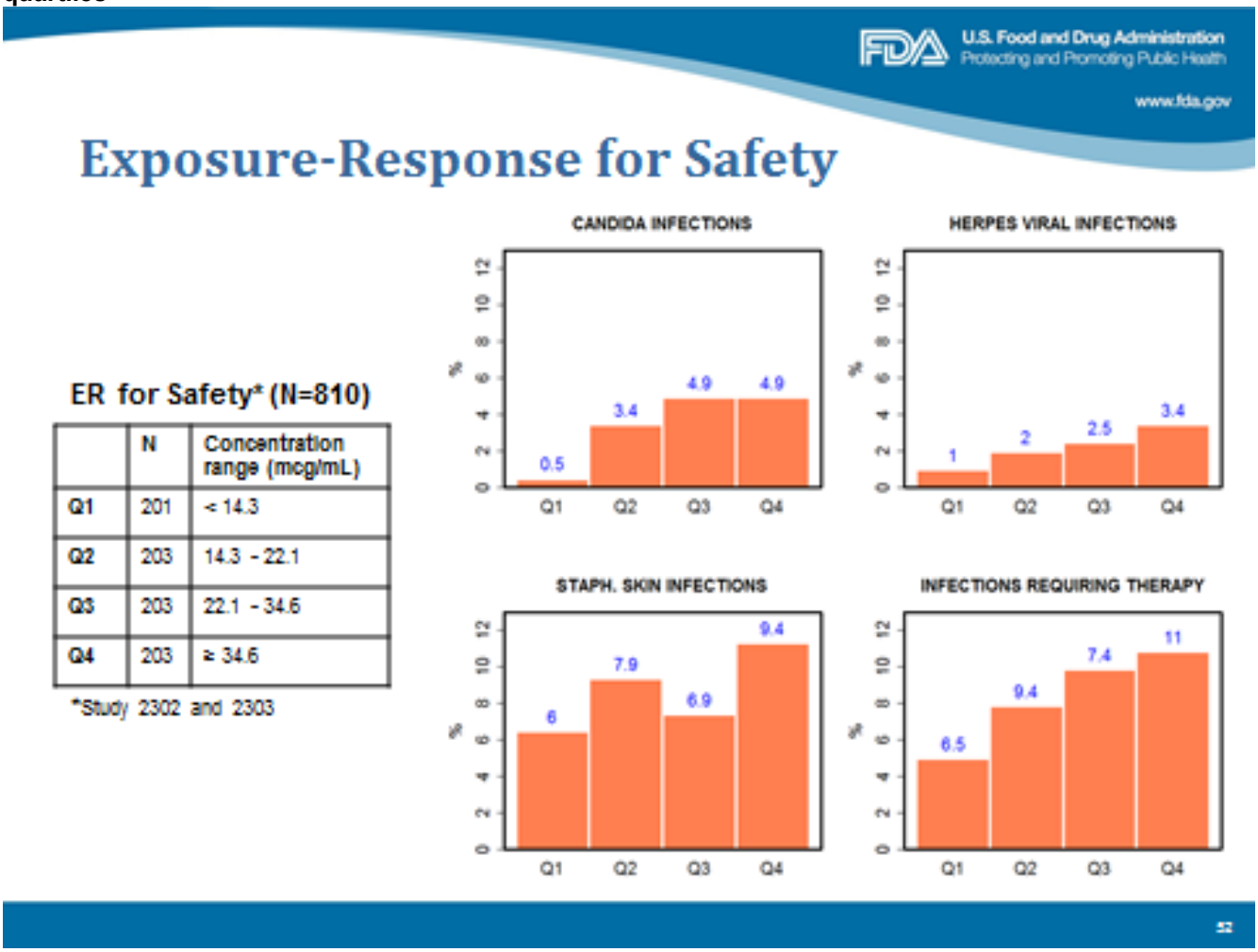
Concentration quartile	**AE rate by Secukinumab concentration quartiles 300 mg dose group**				Any concentration (n=414)
	1st quartile	2nd quartile	3rd quartile	4th quartile	
	<21.5 mcg/mL (n=103)	≥21.5 to <31.4 mcg/mL (n=104)	≥31.4 to <43.1 mcg/mL (n=102)	≥43.1 to <105 mcg/mL (n=105)	
Any AEs	75 (72.8%)	84 (80.8%)	88 (86.3%)	92 (87.6%)	339 (81.9%)
Candida infection	2 (1.9)	4 (3.8%)	7 (6.9%)	6 (5.7%)	19 (4.6%)

Source: Table 3-2, Table 3-4, Response to FDA information request, July 14, 2014.

The overall number of total events (n=9 for 150 mg and n=19 for 300 mg treatment groups) is small, the Phase 3 data showed a trend of association between exposure and candida infection.

The Agency conducted its own analyses with pooled data. Concentrations of secukinumab were divided into four quartiles in exposure response analysis. The concentrations at week 52 were utilized for the analysis. Adverse events that showed dose response relationship from the applicants report and AEs that are possibly related to the mechanism of drug action were evaluated and are show in the figure below.

Figure 6: Exposure-Response for safety by Week 52 secukinumab trough serum concentration quartiles



The profiles show that candida infections, herpes viral infections, staphylococcal skin infections, and all infections that required treatment increased as concentration of secukinumab increased. Again, due to small numbers, these represent a trend and are not statistically significant.

At the same dose the secukinumab serum concentrations were higher in subjects with a lower body weight than those in subjects with a higher body weight in the Phase 3 trials. Thus, weight is likely to have an impact exposure-response to safety.

The applicant provided an analysis of AEs for most frequently reported SOC by weight strata; this is presented in 7.5.3 Drug-Demographic Interactions. The table below comparing AEs for the SOC infection and infestations is an excerpt from this analysis.

Table 43: Exposure-adjusted incidence of adverse events by weight strata (Pool B entire treatment period) most frequent SOCs

	300 mg		150 mg	
	<90 kg N=864 N(IR)	**≥90 kg** N=546 N(IR)	**<90 kg** N=845 N(IR)	**≥90 kg** N=550 N(IR)
Any AE	670 (232.5)	421 (242.2)	646 (232.5)	420 (252.3)
Infections and infestations	422 (87.4)	279 (95.5)	381 (79.5)	264 (91.0)

IR=incidence rate per 100 patient-years
Source: Applicant SCS Table 5-5

For infections, the rate in the 300mg dose group was greater than in the 150 mg dose group for both weight strata. Within the 300mg group dose, subjects weighing <90 kg demonstrated higher rates of infections than subjects weighing >90 kg.

The Agency analyzed incidence rates by dose and weight group for AEs that showed dose response relationship from the applicants report and AEs that are possibly related to the mechanism of drug action were evaluated. The following set of table shows the results.

Table 44: Incidence rates by dose and weight group

Preferred term		**150 mg n (%)**		**300 mg n (%)**	
		≥ 90 kg (N=147)	**< 90 kg (N=249)**	**≥ 90 kg (N=143)**	**< 90 kg (N=271)**
Candida Overall		**2 (1.4%)**	**7 (2.8%)**	**3 (2.1%)**	**16 (5.9%)**
	Oral candidiasis	2 (1.4%)	2 (0.8%)	2 (1.4%)	10 (3.7%)
	Axillary candidiasis	0	1 (0.4%)	0	0
	Intertrigo candida	0	1 (0.4%)	0	0
	Esophageal candidiasis	0	1 (0.4%)	0	1 (0.4%)
	Skin candida	0	1 (0.4%)	0	1 (0.4%)
	Vulvovaginal candidiasis	0	1 (0.4%)	0	3 (1.1%)
	Balanitis candida	0	0	0	1 (0.4%)

	Candidiasis	0	0	1 (0.7%)	1 (0.4%)
HSV Overall		**1 (0.7%)**	**5 (2.0%)**	**2 (1.4%)**	**10 (3.7%)**
	Herpes simplex	0	2 (0.8%)	0	1 (0.4%)
	Herpes virus infection	0	1 (0.4%)	0	0
	Herpes zoster	0	1 (0.4%)	0	1 (0.4%)
	Oral herpes	1 (0.7%)	1 (0.4%)	2 (1.4%)	8 (3.0%)
Infections that required therapy Overall		**7 (4.8%)**	**16 (6.4%)**	**17 (11.9%)**	**28 (10.3%)**

Infection rates were higher with the 300 mg dose, and it was higher in lighter patients (<90 kg) for the same dose. As predicted by exposure, lighter patients who received 300 mg dose had higher rates of infection due to the higher concentrations. Exposure response analysis for safety demonstrates that adverse event rates for certain types of infections tend to increase as the concentration of secukinumab increases. The effect of body weight was also observed.

Reviewer comment: The applicant proposes a 300 mg dose for all patients regardless of weight, or other patient variables. Overall, with the exception of small differences between the doses for treatable infections and CTCAE grade 1/ 2 neutropenia, the safety analysis to date indicates no major dose-dependent safety issues. My review of the application suggests that both the 300 mg dose and the 150 mg dose of secukinumab are both reasonably safe for some duration of plaque psoriasis treatment. It is uncertain if these small differences in neutrophil count and infections will translate into more serious adverse reactions when secukinumab is used for a longer duration of treatment in a broader patient population. Also, it is not clear to this reviewer if the increased incidence in candida infections (which may severe as a "marker" for level of IL-17 inhibition) in patients with higher exposure suggests an increased risk for immunosuppression. If so, in is uncertain if the effects will only be limited to CMC. Additional long-term safety information is needed to make these determinations based on experience with other precedent biologic products.

7.5.2 Time Dependency for Adverse Events

AEs over the entire treatment period of all psoriasis studies are summarized by 3-month intervals in the table below.

Table 45: Summary of AEs/SAEs by 3-month intervals (Pool B entire treatment period)

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
All AEs	1066 (76.42)	794 (56.92)	479 (36.65)	393 (33.68)	288 (29.2)	34 (25.0)
Deaths	1 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Non-fatal SAEs	75 (5.38)	26 (1.86)	21 (1.61)	18 (1.54)	14 (1.4)	2 (1.5)
AEs causing treatment discontinuation	43 (3.08)	36 (2.58)	5 (0.38)	1 (0.09)	0 (0.0)	1 (0.7)
Any AIN457 300 mg						
No. patients evaluated	1410	1410	1330	1208	1049	142
All AEs	1091 (77.38)	784 (55.60)	527 (39.62)	472 (39.07)	326 (31.08)	41 (28.9)
Deaths	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)
Non-fatal SAEs	85 (6.03)	27 (1.91)	23 (1.73)	22 (1.82)	16 (1.53)	0 (0.0)
AEs causing treatment discontinuation	46 (3.26)	38 (2.70)	5 (0.38)	3 (0.25)	0 (0.00)	0 (0.0)
Any AIN457 dose						
No. patients evaluated	3430	3430	3038	2740	2291	291
All AEs	2637 (76.88)	1959 (57.11)	1203 (39.60)	1025 (37.41)	742 (32.39)	97 (33.3)
Deaths	1 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.0)
Non-fatal SAEs	206 (6.01)	73 (2.13)	54 (1.78)	52 (1.90)	33 (1.44)	3 (1.0)
AEs causing treatment discontinuation	118 (3.44)	98 (2.86)	12 (0.39)	6 (0.22)	1 (0.04)	1 (0.3)

Day of onset	Total	To Month 3	Month 4 to 6	Month 7 to 9	Month 10 to 12	Month 13 or later
Placebo						
No. patients evaluated	793	793	39	32	30	10
All AEs	413 (52.1)	402 (50.7)	16 (41.0)	10 (31.3)	8 (26.7)	1 (10.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAEs	15 (1.9)	13 (1.6)	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)
AEs causing treatment discontinuation	11 (1.4)	11 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Etanercept						
No. patients evaluated	323	323	301	288	275	150
All AEs	253 (78.3)	193 (59.8)	141 (46.8)	103 (35.8)	78 (28.4)	17 (11.3)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAEs	20 (6.2)	4 (1.2)	7 (2.3)	4 (1.4)	5 (1.8)	0 (0.0)
AEs causing treatment discontinuation	12 (3.7)	12 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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.
Source: Applicant SCS Table 2-7

All treatment groups show the same general pattern of a decrease in the proportion of patients reporting AEs/SAEs over time.

Reviewer comment: No safety signal is apparent over time. However, the limitation of this analysis is that there are fewer subjects at risk of experiencing an AE over time. It is this reviewer's opinion that the decrease in AEs seen over approximately 12 months is not substantial support that increasing exposure is without risk. Similar duration of treatment has supported the approval for other biologic therapies for the treatment of plaque psoriasis and this information seems reasonably reassuring to support approval of secukinumab.

7.5.3 Drug-Demographic Interactions

Gender

The incidence of total AEs was higher in females vs. males across all treatment groups in Pool A and in Pool B by analyzing exposure-adjusted AE profiles as shown in the table below.

Table 46: Exposure-adjusted incidence of adverse events by gender (Pool B entire treatment period) most frequent SOCs

Gender subgroup Primary system organ class	Any AIN457 150 mg n (IR)	Any AIN457 300 mg n (IR)	Any AIN457 dose n (IR)	Placebo n (IR)	Etanercept n (IR)
Male – N	958	974	2406	552	229
Any AE	702 (214.8)	750 (226.1)	1809 (236.6)	279 (338.7)	171 (209.9)
Infections and infestations	413 (75.5)	469 (84.3)	1084 (83.3)	112 (95.1)	116 (85.1)
Skin and subcutaneous tissue disorders	154 (22.1)	192 (27.1)	457 (27.5)	59 (46.4)	32 (17.0)
Gastrointestinal disorders	155 (22.2)	163 (22.4)	398 (23.5)	47 (36.7)	42 (22.8)
Female – N	437	436	1024	241	94
Any AE	364 (309.6)	341 (261.6)	828 (297.7)	134 (382.6)	82 (364.9)
Infections and infestations	232 (104.4)	232 (106.2)	544 (109.1)	58 (111.3)	54 (108.5)
Skin and subcutaneous tissue disorders	116 (40.8)	95 (31.4)	259 (39.0)	20 (33.3)	29 (45.2)
Gastrointestinal disorders	98 (32.7)	99 (33.3)	223 (32.7)	30 (51.7)	26 (39.2)

IR=incidence rate per 100 patient-years
Source: Applicant SCS Table 5-2

Total AEs and the SOC of infections and infestations showed the same pattern in both genders. There appeared to be no meaningful differences in AE risk for males versus females.

Age

The majority of patients in Pool B were < 65 years of age. There did not appear to be meaningful differences in AE risk when comparing secukinumab subjects <65 years old to those >=65 years old as shown in the table below.

Table 47: Exposure-adjusted incidence of adverse events by age (Pool B entire treatment period) most frequent SOCs

Age subgroup Primary system organ class	Any AIN457 150 mg n (IR)	Any AIN457 300 mg n (IR)	Any AIN457 dose n (IR)	Placebo n (IR)	Etanercept n (IR)
65 yr - N	1293	1311	3200	744	305
Any AE	991 (242.4)	1014 (237.5)	2462 (255.0)	389 (354.0)	238 (239.7)
Infections and infestations	604 (84.9)	659 (91.9)	1535 (91.9)	163 (102.1)	162 (91.3)
Skin and subcutaneous tissue disorders	253 (27.8)	258 (27.3)	659 (30.3)	77 (43.9)	56 (23.4)
Gastrointestinal disorders	234 (25.1)	248 (26.0)	583 (26.2)	74 (42.4)	63 (26.3)
≥ 65 yr - N	102	99	230	49	18
Any AE	75 (211.4)	77 (219.5)	175 (225.8)	24 (320.2)	15 (322.9)
Infections and infestations	41 (71.3)	42 (72.4)	93 (71.4)	7 (67.8)	8 (92.2)
Skin and subcutaneous tissue disorders	17 (24.4)	29 (44.6)	57 (38.0)	2 (17.1)	5 (36.6)
Gastrointestinal disorders	19 (28.6)	14 (20.0)	38 (24.3)	3 (26.4)	5 (46.7)
≥ 75 yr - N	15	15	32	10	3
Any AE	11 (245.1)	12 (313.5)	25 (295.5)	6 (437.4)	2 (177.7)
Infections and infestations	6 (84.5)	5 (64.7)	12 (78.4)	1 (44.2)	2 (177.7)
Skin and subcutaneous tissue disorders	5 (57.7)	2 (21.8)	8 (42.0)	2 (95.1)	0 (0.0)
Gastrointestinal disorders	2 (20.9)	4 (51.5)	6 (31.8)	0 (0.0)	0 (0.0)

IR=incidence rate per 100 patient-years
Source: Applicant SCS Table 5-1

Subjects over 75 years of age were not significantly represented in the study making it difficult to draw definitive conclusions. The trends in AEs seem similar to other age cohorts.

Race

The AE profile by race showed similar trends as those observed for the overall population of Pool A and entire treatment period of Pool B as shown in the table below.

Table 48: Exposure-adjusted incidence of adverse events by race (Pool B entire treatment period) most frequent SOCs

Race subgroup Primary system organ class	Any AIN457 150 mg n (IR)	Any AIN457 300 mg n (IR)	Any AIN457 dose n (IR)	Placebo n (IR)	Etanercept n (IR)
Caucasian-N	1001	1017	2558	593	216
-Any AE	757 (239.8)	795 (256.8)	1966 (265.4)	317 (383.6)	179 (291.4)
Infections and infestations	486 (92.8)	540 (103.6)	1274 (101.1)	140 (119.2)	131 (115.5)

Skin and subcutaneous tissue disorders	167 (23.7)	190 (26.3)	496 (28.9)	53 (39.7)	41 (24.4)
Gastrointestinal disorders	189 (27.3)	202 (28.5)	487 (28.5)	61 (47.0)	50 (30.2)
Black-N	27	20	51	15	0
-Any AE	21 (253.3)	13 (139.4)	37 (205.5)	5 (194.5)	-
Infections and infestations	6 (34.1)	2 (14.3)	9 (27.1)	2 (62.7)	-
Skin and subcutaneous tissue disorders	8 (50.7)	2 (14.0)	11 (34.3)	2 (53.4)	-
Gastrointestinal disorders	2 (10.0)	1 (6.9)	3 (8.2)	0 (0.0)	-
Asian-N	292	296	664	134	74
-Any AE	228 (226.2)	221 (187.8)	508 (213.6)	60 (249.0)	47 (140.9)
Infections and infestations	117 (63.4)	115 (58.1)	262 (62.4)	20 (58.9)	25 (48.3)
Skin and subcutaneous tissue disorders	81 (39.8)	75 (34.3)	175 (37.6)	18 (53.0)	15 (26.2)
Gastrointestinal disorders	41 (17.5)	42 (17.2)	93 (17.7)	9 (24.9)	11 (18.9)
Native American-N	47	44	92	28	27
-Any AE	39 (335.9)	32 (180.3)	72 (242.7)	13 (289.5)	22 (288.6)
Infections and infestations	22 (78.1)	23 (85.3)	46 (83.0)	1 (14.2)	9 (49.3)
Skin and subcutaneous tissue disorders	10 (28.9)	10 (28.6)	20 (28.6)	3 (44.0)	4 (17.8)
Gastrointestinal disorders	13 (40.5)	10 (29.0)	23 (34.3)	5 (74.1)	6 (28.2)
Pacific islander -N	2	5	7	2	1
-Any AE	1 (89.7)	4 (172.1)	5 (145.4)	2 (7305.0)	1 (652.2)
Infections and infestations	1 (72.0)	3 (93.2)	4 (86.8)	0 (0.0)	1 (652.2)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (118.6)	3 (69.9)	1 (405.8)	0 (0.0)
Gastrointestinal disorders	1 (89.7)	1 (26.0)	2 (40.3)	0 (0.0)	0 (0.0)
Other-N	22	24	50	19	4
-Any AE	17 (305.3)	22 (481.5)	42 (375.2)	15 (450.2)	3 (225.0)
Infections and infestations	10 (89.8)	14 (136.2)	26 (114.7)	6 (80.8)	3 (119.0)
Skin and subcutaneous tissue disorders	3 (18.8)	5 (31.9)	8 (23.6)	2 (23.5)	1 (32.1)
Gastrointestinal disorders	5 (36.2)	5 (29.2)	10 (30.2)	2 (23.0)	1 (30.6)

IR=incidence rate per 100 patient-years
Source: Applicant SCS Table 5-3

However, other than Caucasians (72.11%) and Asians (18.88%), few other races were significantly represented in the studies. Thus, no definitive conclusion based on safety in other races can be made.

Weight

The incidence per 100 patient-years of total AEs and AEs in the infections and infestations SOC showed higher rates in the placebo group compared with the any secukinumab dose and lower weight Etanercept subjects. To this reviewer the usefulness of comparison to placebo is not clear since the risk of infections with Etanercept has been well characterized. This reviewer finds this data useful in

comparing the safety profile of both doses of secukinumab by weight because these arms had similar numbers of subjects treated for similar length of duration permitting a more direct comparison. The table below shows the most frequent adverse events by weight strata.

Table 49: Exposure-adjusted incidence of adverse events by weight strata (Pool B entire treatment period) most frequent SOCs

Weight strata subgroup Primary system organ class	Any AIN457 150 mg n (IR)	Any AIN457 300 mg n (IR)	Any AIN457 dose n (IR)	Placebo n (IR)	Etanercept n (IR)
<**90 kg**-N	845	864	2022	472	217
-Any AE	646 (232.5)	670 (232.5)	1564 (244.8)	240 (333.3)	166 (222.3)
Infections and infestations	381 (79.5)	422 (87.4)	947 (86.4)	92 (88.4)	104 (77.4)
Skin and subcutaneous tissue disorders	183 (30. 9)	197 (32.1)	459 (33.2)	52 (45.6)	42 (24.9)
Gastrointestinal disorders	149 (24.1)	172 (27.3)	369 (25.8)	45 (39.4)	48 (28.9)
≥**90 kg** -N	550	546	1408	321	106
-Any AE	420 (252.3)	421 (242.2)	1073 (265.6)	173 (381.1)	87 (297.4)
Infections and infestations	264 (91.0)	279 (95.5)	681 (96.7)	78 (118.5)	66 (127.7)
Skin and subcutaneous tissue disorders	87 (22.4)	90 (22.7)	257 (27.1)	27 (36.9)	19 (22.6)
Gastrointestinal disorders	104 (27.5)	90 (22.8)	252 (26.6)	32 (44.5)	20 (23.8)

IR=incidence rate per 100 patient-years
Source: Applicant SCS Table 5-5

The incidence rate of AEs was comparable between the doses in the lower weight subjects and slightly lower than in the higher weight subjects where 150 mg rate was greater than the 300 mg rate. For infections, the rate in the 300mg dose group was greater than in the 150 mg dose group for both weight strata. Within the 300mg group dose, subjects weighing <90 kg demonstrated higher rates of infections than subjects weighing >90 kg.

7.5.4 Drug-Disease Interactions

There is a potential for psoriasis disease-drug-drug interaction (disease-DDI) based on the current understanding that psoriasis patients have elevated proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon disease improvement following biological treatment. The clinical pharmacology team is recommending that the Applicant conducts a clinical trial to determine the potential of secukinumab to alter the metabolism of CYP substrates in psoriasis patients (e.g., using a cocktail of relevant CYP probe drugs). This reviewer concurs with the request for a post-marketing commitment to assess disease-DDI. Labeling is also recommended to describe possible drug-drug interactions impacted by changes in CYP enzymes. See section 7.5.5 Drug-Drug Interactions below.

7.5.5 Drug-Drug Interactions

Drug-drug interaction (DDI) studies have not been conducted for secukinumab. The following language is recommended for the DDI section of the labeling.

> *The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, COSENTYX, an antagonist of IL-17A, could normalize the formation of CYP450 enzymes. A role for IL-17A in the regulation of CYP450 enzymes has not been reported. Upon initiation or discontinuation of COSENTYX in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate as needed.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The risk of malignancy in patients is a safety concern for immunosuppressive drugs in general. Long term use of secukinumab may lead to increased risk of tumor development in psoriasis patients, particularly in those who have been exposed to other therapies which could increase the risk of tumor development, such as UVB, photodynamic therapy, and other immunosuppressive agents.

Although animal data and clinical trial data did not suggest a risk, it is unlikely that short premarket trials would detect rare events with long latency such as malignancy. The applicant proposes to monitor malignancy in psoriasis patients administered secukinumab as a part of malignancy registry in their risk management plan. This reviewer finds that post-marketing assessment of malignancy is a reasonable approach.

Safety data on malignancy is discussed in detail in Section 7.3.5 above.

7.6.2 Human Reproduction and Pregnancy Data

Novartis did not study the use of secukinumab in pregnant women. The clinical trials in the psoriasis development program required that women have a negative pregnancy test prior to enrollment and required that women participating in clinical trials use contraception. Pregnancy was a reason for discontinuation from the trial. Despite these requirements, pregnancies were reported in the clinical trials. In pivotal trials 2302, 2303, 2308 and 2309, one subject discontinued the study in the induction phase due to pregnancy and 8 subjects discontinued the study during the maintenance phase. All

subjects received some dose of secukinumab. The applicant provided a summary of the outcome of all pregnancies across the entire secukinumab development program.

As of Jul 12, 2014 Novartis identified 58 pregnancies during secukinumab clinical trials, with 49 occurring in secukinumab exposed subjects (37 maternal exposure; 12 paternal exposure). The pregnancy outcomes are described in the table below:

Table 50: Pregnancy Outcome for all Secukinumab Trials

	Secukinumab	Placebo	No Treatment	Blinded
Maternal Exposure				
• Normal baby	9	1	1	0
• Abortion (n=spontaneous)	22 (10)	1 (0)	0	1 (0)
• Unknown: lost to follow-up or future due date	6	0	0	1
• Premature	0	0	0	0
Paternal Exposure				
• Normal baby	8	0	0	3
• Abortion (n=spontaneous)	2 (2)	0	0	0
• Unknown: lost to follow-up or future due date	1	0	0	1
• Premature	1	0	0	0
Total	49	2	1	6

Source: Applicant Advisory Committee Meeting documents

Reviewer comment: Animal studies do not indicate harmful effects for secukinumab with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. Human evidence from the literature, based on collective evidence from pregnancies in inflammatory arthritis and IBD, suggests that exposure to anti-TNF therapies at the time of conception or during the first trimester does not result in an increased risk of adverse pregnancy and fetal outcomes. Monoclonal antibodies have been shown to cross the placenta during the second and third trimester. These antibodies may be functional in the fetus, as demonstrated by lymphopenia reported at birth in children exposed to rituximab in utero.(reference)

Because animal reproduction studies are not always predictive of human response and secukinumab has not been studied in pregnancy, labeling should state that secukinumab should be used during pregnancy only if the benefits clearly outweigh the potential risks.

7.6.3 Pediatrics and Assessment of Effects on Growth

An approval of secukinumab in adult patients would trigger PREA as a new active ingredient. The requirements needed to address PREA were discussed with the applicant at a guidance meeting on March 2, 2011. The Agency found the general approach of waiver/ deferral of pediatric subjects to be reasonable. Because the development plan for secukinumab predates the requirements under the Food and Drug Administration Safety and Innovation Act (FDASIA), the applicant was not required to submit an initial Pediatric Study Plan (iPSP) within 60 days of an EOP2 meeting. However, Novartis submitted an iPSP for secukinumab on February 11, 2013. This plan was reviewed and discussed at PeRC on February 27, 2013. PeRC and DDDP determined that it was premature to agree with the proposed deferred studies as outlined and the plan should be replaced with a broader plan which would address the informational needs for safety and efficacy in pediatric patients. Written comments regarding the iPSP were sent to the applicant on April 5, 2013. The applicant decided not to follow the process for pediatric plans under FSASIA and submit a plan to address PREA with the BLA submission.

The applicant is requesting a waiver for pediatric patients under 6 years of age based on studies not being feasible to conduct as there are too few children under the age of 6 with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This reviewer concurs with the waiver based on the estimates described in the available, albeit limited, literature. Studies show that the prevalence of psoriasis in pediatric patients is low and that the rate increases in the older age cohorts. The limitations of the studies are that the type and severity of psoriasis captured in the data is not defined. Therefore, the subset of pediatric patients under the age of 6 with moderate to severe plaque psoriasis available to study would likely be limited. Also in support of the waiver the sponsor cites the unknown impact of secukinumab on the developing innate immune system in this age group and concomitant live vaccinations which are often administrated in this age group.

For pediatric patients 6 to 17 years of age, the applicant is requesting a deferral until after 12 months of treatment data in adults from phase 3 trials is available and PK modeling is assessed to guide dosing. They have proposed the submission of the final study report as December 31, 2018 and have submitted a protocol for a 288 pediatric subject study. This reviewer does not concur with the applicant's proposed timeline for the pediatric studies. At this juncture the safety for this monoclonal antibody which affects the immune system is not sufficiently characterized to permit evaluation of risk or rare adverse events or for adverse events with long latency periods (e.g. malignancies). It is the recommendation of this reviewer to delay the initiation of pediatric studies until the adult long-term safety is better characterized.

Granting a waiver in the 0-6 year 11 month pediatric cohort and deferral for a period of several years post-approval in the 6-17 year cohort is consistent with the approach the

Division has taken for biologics approved for the treatment of psoriasis. To date no biologic treatment has been approved in the U.S. for use in patients with plaque psoriasis less than 18 years of age. However, some TNF inhibitor products, which have been approved for use in pediatric autoimmune diseases, are used off-label to treat pediatric patients with psoriasis.

The pediatric plan was discussed at the Pediatric Review committee on July 16, 2014. The committee agreed with the Division to grant a partial waiver in patients ages birth to less than 6 years because studies are impossible or highly impractical and to the deferral because additional safety or effectiveness data is needed. There was some disagreement about the length of time to complete the studies. Some PeRC members noted that the safety concern should be addressed with proper controlled studies in children rather than waiting on adult long-term safety data if the current data do not identify a specific pediatric safety concern. Some PeRC members agreed that a long deferral to complete pediatric studies would be acceptable to collect long-term adult safety information but that labeling should reflect that the product is not recommended to be used in pediatric patients if this approach is used.

*Reviewer comment: It is the recommendation of this reviewer to delay the initiation of pediatric studies until the adult long-term safety is better characterized. However, this reviewer does not concur with PeRC to label Cosentyx **not** for use in pediatric patients. It is this reviewer's opinion that secukinumab should not be used broadly in the pediatric population until safety in adults in further evaluated in long-term studies and postmarketing experience. Contraindicating use in pediatric patients, however, may deter off-labelled use in pediatric patients deemed appropriate by the clinician. This reviewer recommends the following: Safety and effectiveness of Cosentyx in pediatric patients have not been evaluated.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Novartis did not identify reports of secukinumab overdose in clinical studies. Overdose (preferred term) was reported as an SAE in 3 subjects (2 on secukinumab and 1 on placebo). However, the extra doses taken were placebo injections and thus were not overdoses of active drug. Single doses of secukinumab up to 30 mg/kg (i.e. approximately 2000 – 3000 mg) have been administered intravenously in clinical studies in other autoimmune indications, and doses up to 3 x 10 mg/kg i.v. have been administered in psoriasis studies. Acute toxicity was not seen with these treatments.

As expected, the safety profile of secukinumab did not suggest rewarding effects or abuse related behaviors related to treatment.

Complete withdrawal was not fully assessed as many subjects continue on treatment for long term safety assessment. In study 2304 comparing a fixed interval (FI) and a start-of-relapse (SoR) maintenance dosing regimen, no clear withdrawal or rebound effects

were seen. The AE profile was comparable between subjects in both arms. The incidence of worsening forms of psoriasis, such as erythrodermic psoriasis and pustular psoriasis, was low overall and comparable between the FI and SoR dosing regimens (described in Section 7.3.5).

7.7 Additional Submissions / Safety Issues

The cut-off date for safety data included in the original submission was July 31, 2013. The applicant submitted a 120-Day safety update summarizing new safety information available from 32 ongoing clinical trials in plaque psoriasis and 9 other indications, as well as relevant follow-up information on previously reported SAEs. The update encompasses deaths and non-fatal serious adverse events (SAEs) reported to the Novartis ARGUS database between 01-Aug-2013 and 30-Nov-2013 (inclusive). The applicant reports that that update includes 700 newly enrolled patients (including 20 in plaque psoriasis) and a total of 5300 ongoing patients (including 2500 in plaque psoriasis).

Clinical studies for plaque psoriasis contributing reports (through November 30, 2013) to the safety update are in the table below. If studies were included in the summary of clinical safety (SCS), the cutoff for inclusion in the SCS submission is shown.

Table 51: Psoriasis clinical studies with secukinumab contributing new or updated safety data in the reporting period (01-Aug-2013 to 30-Nov-2013)

Indications	Studies	Studies included in SCS pooling
Phase II	A2223, A2211E1	A2211E1 (up to 21-Jan-2013)
Phase III	A2302, A2303, A2304, A2307	Up to end of maintenance period (Week 52 for A2302, A2303, A2304; Week 40 for A2307)
	A2308, A2309	Up to end of induction period (Week 12)
	A2302E1, A2304E1, AGB01	---

Source: Applicant 2/8/14 amendment table 1-1

One new death and 61 new non-fatal SAEs were reported in the safety update. The new SAEs were from studies A2302E1 (29 cases), A2304E1 (19 cases), A2309 (9 cases), A2211E1 (3 cases) and A2308 (2cases). No new SAEs were reported for placebo. However, there are few ongoing placebo subjects during the 120-Day SU reporting interval (7 placebo patients in Study A2223 as of 31-Jul-2013). There are few placebo subjects in studies A2302 and A2303 but remain blinded.

The death was that of a 54-year-old female with hypertension but no history of alcohol abuse. 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

subject was enrolled in study A2308 and was treated with placebo for the first 12 weeks. The subject's study treatment after re-randomization remains blinded.

Reviewer comment: The level of ethanol is consistent with fatal outcomes. The information is not sufficient to assess causality.

120 day safety update/ product specific safety issues

- **Infection:** 13 subjects had new serious infections during the reporting interval
  - 2 psoriasis subjects on 150 mg dose reported tonsillitis and anal abscess
  - 6 psoriasis subjects on 300 mg dose reported urinary tract infection, staphylococcal sepsis, gastrointestinal infection, tonsillitis, sepsis
  - 5 psoriasis subjects receiving blinded secukinumab dose reported tonsillitis, esophageal candidiasis, erysipelas, pneumonia

One opportunistic infection (esophageal candidiasis) and 2 cases of sepsis were reported. These cases are described below.

- Patient A2302E1-2235-2235010, a 57-year-old (93 kg) male with a history of diabetes mellitus, arterial hypertension, appendectomy, intestinal polyps (benign), hepatic steatosis and sigmoid diverticulosis, was randomized to secukinumab 300 mg in the core study A2303 and received the first dose on 05-Mar-2012. He started extension treatment on 08-Mar-2013 and received the most recent dose on 23-Aug-2013. The patient reported progressive weight loss of 16 kg over 8 months. On (b) (6), he was hospitalized for work-up to exclude a malignant process. The patient's blood glucose level at the time of admission was 91 mg/dL. Physical examination of mucous membranes showed pronounced oral candidiasis. The patient responded well to treatment with amphotericin (ampho-moronal lozenge) and was considered completed recovered on 09-Oct-2013. The investigator suspected the event to be related to study medication, and also cited the progression of concomitant disease (diabetes mellitus) as a possible contributing factor.

- Patient [A2302E1-3135-3135008 (PHHO2013HU014087), a 56-year-old female with a history of hypertension, diabetes mellitus, benign ovarian tumor and allergic rhinitis, was randomized to placebo in the core study A2303 on 30-Dec-2011 and switched to secukinumab 300 mg on 20-Mar-2012. The patient started extension treatment on 27-Dec-2012 and received the most recent dose on 01-Oct-2013. On (b) (6), the patient was hospitalized for sepsis. The patient was treated with ceftriaxone and clarithromycin. On 19-Oct-2013, the patient completely recovered from the sepsis. The investigator did not suspect the event to be related to study medication.

- Patient A2304E1-3020-3020004 (PHHO2013DE010029), a 37-year-old male with a history of alcohol abuse and smoking, was randomized to secukinumab 300 mg start of relapse (SoR) dosing regimen and received the first dose on 26-Oct-2011 in the core study A2304. There was no history of liver or biliary disorders, and the patient's lipase values were within normal limits prior to the event. On an unspecified date in 2012, the patient's gammaglutamyltransferase (GGT) values were >100-200 U/L (normal range: <55). The patient received the most recent dose of study medication on 03-Jul-2013 in the extension study A2304E1. Laboratory tests on 04-Jul-2013 showed elevated but stable liver enzyme values. A few days prior to 20-Jul-2013, the patient began experiencing recurrent upper abdominal pain. On (b) (6), the patient was hospitalized and diagnosed with acute exudative pancreatitis. The hospital course was complicated with worsening lung function requiring intensive care and ventilation. Abnormal cytology suggested myelodysplastic disease or myeloproliferative neuroplasia. Hospital course was also complicated with staphylococcal sepsis diagnosed on (b) (6). The patient was treated with ciprofloxacin. On (b) (6), the patient completely recovered from the staphylococcal sepsis, upper abdominal pain and delirium. On (b) (6), the patient completely recovered from the pancreatitis and was discharged from hospital. The investigator suspected a relationship between the staphylococcal sepsis and study medication. The other events (pancreatitis, deterioration of lung function, upper abdominal pain and delirium) were suspected to be related to the progression of concomitant disease (alcohol abuse).

Reviewer comment: Oropharyngeal candidiasis, or thrush, is a common local infection seen in infants, older adults who wear dentures, patients treated with antibiotics, chemotherapy, or radiation therapy to the head and neck, and those with cellular immune deficiency states, such as AIDS. Candida *esophagitis is more commonly seen in immunocompromised patients. It tends to occur later in the natural history of HIV infection and almost invariably at lower $CD4^+$ T-cell counts. Because of the mechanism of secukinumab and the known relationship of IL-17 blockade and mucocutaneous candidiasis, it is not clear if this case of esophageal candidiasis, treated with amphotericin B lozenges, is suggestive of a degree of immunosuppression that could potentially lead to serious complications. However, no cases of disseminated candidiasis have been reported in the clinical trials. The product will be labeled for risk of Candida infections.*

Both cases of sepsis occurred on 300 mg of secukinumab. It is possible that the cases may be related to immunosuppression due to secukinumab treatment. Other factors could have contributed to the increase risk for severe infection. In one case, a risk factor included the concomitant disease diabetes and in the other case, a prolonged

hospital course and possible hematological disease may have contributed. The product will be labeled to warn of risk for infections. There is not enough information to determine whether there are factors (e.g. at risk patient population) that can be used to mitigate the risk for infection.

- **Hypersensitivity:**
  - 2 cases (contact dermatitis/ skin reaction) were identified in a search using the hypersensitivity narrow SMQ. Both cases remain blinded.
- **Autoimmune events:**
  - The applicant reports a total of 7 cases retrieved from a search of the autoimmune disorders NMQ in plaque psoriasis studies. 5 cases describe psoriasis
  - 1 psoriasis subjects on 150 mg dose reported autoimmune hemolytic anemia
  - 1 psoriasis subjects on 300 mg dose reported idiopathic thrombocytopenia

Patient A2304E1-5037-5037009 was a 72-year-old, 109kg, male with a history chronic obstructive pulmonary disease (COPD), chronic kidney disease/chronic renal insufficiency with stage 3 proteinuria, hypertension, GERD, splenomegaly, elevated liver function tests, hepatic steatosis, coronary artery disease and chronic anemia. He was randomized to secukinumab 150 mg fixed-time dosing interval in Study A2304 and received the first dose on 15-Feb-2012 with the most recent and last dose on 11-Jun-2013. On 19-Aug-2013, the patient complained of fatigue, malaise and dyspnea on exertion and was scheduled for an outpatient blood transfusion on (b) (6). He was found to have warm antibodies and diagnosed with autoimmune hemolytic anemia by a hematologist. Laboratory tests showed elevated creatinine, elevated total bilirubin, decreased iron, decreased hemoglobin (6 g/dL), and elevated LDH and ferritin. The patient received steroid treatment (prednisone) along with paracetamol, budesonide, formoterol fumarate, diphenhydramine, furosemide, ondansetron, and folate sodium. The patient was discontinued from study medication. On (b) (6), the patient completely recovered from the event and was discharged from hospital. The investigator suspected the event to be related to study medication.

Patient A2302E1-3002-3002001 was a 53-year-old, 93 kg male with a history of arterial hypertension. He was randomized to secukinumab 300 mg in the core study A2302 and received the first dose on 29-Aug-2011, continued treatment in the extension study and received the most recent dose on 11-Sep-2013. On the same day, he was diagnosed with idiopathic thrombocytopenia with a platelet count of 46×10^9/L (normal range: 150-450). On 16-Oct-2013, blood tests showed antinuclear antibodies (ANA) >1:200 (normal range: <1:40). The investigator reported that the event was related to study medication and valsartan, although valsartan was thought to exacerbate but not initiate the thrombocytopenia.

Reviewer comment: It is not clear from the information available whether the event was related to secukinumab treatment. The temporal relationship suggests a possible relationship. There is no information as to whether the platelet count recovered when the medication is discontinued. Other biologics have been reported to be associated with both thrombocytopenia and autoimmune disorders. This reviewer recommends monitoring for both thrombocytopenia and autoimmune disorders in post-marketing surveillance with secukinumab.

- **Inflammatory Bowel Disease:** 2 SAE cases of inflammatory bowel disease (which included the Crohn's disease as one of the search terms) occurring in the ankylosing spondylitis program. No new SAEs in the inflammatory bowel disease NMQ, which includes Crohn's disease, were reported in the plaque psoriasis studies.

- **Neutropenia**: no neutropenia SAE was reported
- **Major Adverse Cardiovascular Events (MACE):** Four potential cases of MACE in plaque psoriasis studies were identified and referred for adjudication by the CCV-AC. There were three acute myocardial infarctions and one stroke. All were confirmed by the event committee. Three are known to be on AIN457, and for the other case, treatment is blinded. Mace events provided in the safety update were reviewed by Dr. Preston Dunnmon, cardiology. This reviewer concurs with Dr. Dunnmon's assessment that these cases are difficult to interpret due to the fact that there are very few placebo patients left.

- **Malignancy:** Three new malignancies in plaque psoriasis studies were reported.
    - 2 psoriasis subjects on 150 mg dose reported malignant melanoma carcinoma (time to onset 1350 days), endometrial adenocarcinoma carcinoma (time to onset 553 days)
    - 4 psoriasis subjects on 300 mg dose reported basal cell carcinoma (time to onset 280 days)

Reviewer comment: Although events are collected in support of long-term safety because there is no longer a placebo reference arm, the relationship of event to secukinumab is not clear and assessments of causality are unable to be made at this juncture.

Additional safety information submitted on 8/25/14 included safety data of all ongoing studies across indications from December 1, 2013 and July 12, 2014. No new safety signal was identified. A summary of the cases in the psoriasis population is described below:

- **Infection:** there have been an additional 22 new, unblinded cases of serious infections reported (21 secukinumab; 1 placebo)

  - 8 psoriasis subjects on 150 mg dose reported diverticulitis, pneumonia, peritosillar abscess, influenza, epididymitis, appendicitis, myelitis requiring appropriate antimicrobial therapy and in some cases surgery
  - 4 psoriasis subjects on 300 mg dose reported appendicitis, erysipelas, clostridium colitis
  - Overall, the pattern of blinded infection SAEs is consistent with events previously reported.
- **Hypersensitivity:**
  - there were no new unblinded cases of hypersensitivity to secukinumab
  - 2 blinded cases were reported in ongoing RA, active comparator (abatacept) study including one anaphylatoid reaction that occurred with the second IV infusion. The subject experienced flushing, flank pain, feeling of tongue swelling, BP elevation and required hospitalization.
- **Autoimmune events:** Of the 23 cases retrieved by the search, 8 cases were unblinded
  - The applicant reports that 5 of the cases are due to exacerbations of the underlying diseases in the treated indications.
  - 2 cases involve inflammatory bowel disease which includes 1 case of Crohn's disease and 1 case of ulcerative colitis discussed below
  - 1 case of thoracic myelitis of probable autoimmune etiology in a 52 year old, 87 kg subject on 150 mg of secukinumab for 477 days
- **Inflammatory Bowel Disease:**
  - 1 case of Crohn's disease (exacerbation after 315 days of secukinumab 150 mg)
  - 1 new case of ulcerative colitis (new onset after 518 days of secukinumab 300 mg)
- **Neutropenia**: 1 case of neutropenia was reported from in clinical study CAIN457A2313 in nail psoriasis. The case remains blinded and may be confounded with a pre-existing hematological disorder.
- **Major Adverse Cardiovascular Events (MACE):** Updated information on MACE across all indications was provided in this safety update and a 9/3/14 response to an information request regarding the update. The cases reported in psoriasis subjects were described in section 7.3.5. The additional reports do not support evidence of a signal for major adverse cardiovascular (CV) events at this juncture.
- **Malignancy:** thirteen new cases of malignancy SAEs were received
  - 11 were from the psoriasis program, 1 from psoriatic arthritis and 1from rheumatoid arthritis
  - 2 psoriasis subjects on 150 mg dose reported prostate cancer, Bowen's disease, basal cell carcinoma
  - 5 psoriasis subjects on 300 mg dose reported Bowen's disease, prostate cancer, basal cell carcinoma, B-cell lymphoma, bladder cancer
  - 4 blinded psoriasis subjects report basal cell carcinoma, colon cancer, lung adenocarcinoma

8 Postmarket Experience

To date secukinumab has not been marketed anywhere in the world and no postmarketing information is available.

9 Appendices

9.1 Literature Review/References

1. Arch Dermatol. 1997 Jun;133(6):747-50. Pustular and erythrodermic psoriasis complicated by acute respiratory distress syndrome. Sadeh JS1, Rudikoff D, Gordon ML, Bowden J, Goldman BD, Lebwohl M.
2. Swiss Med Wkly. 2003 Sep 26;133(37-38):515-8. Elevation of B-type natriuretic peptide levels in acute respiratory distress syndrome. Maeder M1, Ammann P, Rickli H, Diethelm M.
3. N Engl J Med; 366:1181-9. (2012). Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. Papp KA, Leonardi C, Menter A
4. N Engl J Med; 366:1190-9. (2012). Anti-interleukin-17 monoclonal antibody izekizumab in chronic plaque psoriasis. Lenoardi C, Matheson R, Zachariae C et al
5. Clin. Infect. Dis. 26, 259-274 (1998). Oropharyngeal and esophageal candidiasis in immunocompromised patients: treatment issues. Darouiche RO

9.2 Labeling Recommendations

Labeling recommendations are contained within the body of the document. Below is a summary of these recommendations along with the relevant section referenced:

Dosage and Administration: recommend label for use of both 150 mg and 300 mg doses (section 6.1.8)

Contraindications: recommend label for hypersensitivity reaction (section 7.3.5)

Warnings and Precautions: recommend label for pre-treatment evaluation for dose dependent infections and tuberculosis (section 7.3.5)

Adverse Reactions: recommend additional ARs based on safety review (section 7.3.5)

Drug Interactions: recommend alternative language for vaccinations based on the input of CBER colleagues.

Dr. Doran Fink, CBER/OVRR/DVRPA reviewed an open label, single dose study (2224) to evaluate whether exposure to Cosentyx affected antibody responses elicited by meningococcal and influenza vaccines. The review concludes that antibody responses do not provide definitive evidence of vaccine effectiveness and language regarding vaccination should describe the study in the proper context.

Clinical Trials: recommend removal of (b) (4)

Labeling negotiations are ongoing at the time of this review.

9.3 Advisory Committee Meeting

A Dermatologic and Ophthalmologic Drugs Advisory Committee meeting was convened on October 20, 2014 to discuss this BLA. The following section summarizes the Committee's discussion on the topics and voting questions:
Question to the Committee:

1. VOTE: Considering potential risks and benefits, do the available data support approval of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy?

Background Information for Consideration (Issue 1): As the question states, we are asking the Committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, does not mean that one must agree with all of the proposed dosing recommendations or that one must define all labeling recommendations. Questions 2 and 3 that follow the general approval question/vote will give the Committee a chance to provide opinions on more granular issues. If you do not believe the available data support approval, please consider what additional studies should be recommended.

Vote: Yes: 7 No: 0 Abstain: 0

Committee Discussion: *The committee unanimously agreed that based on the potential risks and benefits, the available data support the approval of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The committee agreed that the efficacy data was strong and that the benefit is clear. The committee noted that post-marketing studies will be needed to determine the safety of long term use of secukinumab, but with the data that is currently available, there seems to be a positive risk/benefit. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Please comment on the strength of evidence for use of secukinumab at a dose strength of 300 mg. Discuss alternative dosing concepts based on the background provided.

Background Information for Consideration (Issue 2): The Phase 3 efficacy results showed that both 150 mg and 300 mg doses of secukinumab achieved significantly higher response rates compared to the placebo and the 300 mg dose achieved a higher response rate compared to the 150 mg dose. At the same dose, secukinumab serum concentrations were higher in subjects with a body weight < 90kg than those in subjects with a body weight ≥ 90 kg, and the clinical response rates were approximately 10% higher in the lower body weight group at both 150 mg and 300 mg doses. A limited number of observed adverse events, mostly infections, demonstrated an increasing trend with higher exposure.

Committee Discussion: *The majority of the committee agreed that the recommended dose should be the 300 mg dose based on the efficacy data. Some committee members noted that the 150 mg should also be available for patients that have exceptionally low body weight, but would be at the discretion of the physician to determine the dose. Please see the transcript for details of the committee discussion.*

3. DISCUSSION: What is your view on further exploring the 450 mg dose in patients who weigh ≥90kg? If you believe that it would be acceptable to explore a higher dose, when/how should this be evaluated?

Background Information for Consideration (Issue 3): The available clinical data suggest that response rates in patients weighing ≥90 kg administered 300 mg secukinumab could be further increased with a higher secukinumab dose. However, no safety or efficacy data are currently available for secukinumab doses above 300 mg sc.

Committee Discussion: *The majority of the committee agreed that the 450 mg dose in patients weighing >90 kg should be considered. Some committee members noted that the 450 mg dose may be of benefit for patients who are non-responders to the 300 mg dose, thus a post-market study of the 450 mg dose in slow or non-responders should be done Please see the transcript for details of the committee discussion.*

4. DISCUSSION: Please comment on postmarketing studies/trials that are needed to further define the safety of secukinumab, including, but not limited to the need for long-term studies to evaluate malignancy and other potential risks.

Committee Discussion: *The majority of the committee agreed with the sponsor's suggested post-marketing plan. One committee member noted that the sponsor's post-marketing study is designed to evaluate cardiac events and does not address long term risks such as malignancies or autoimmune diseases. The committee member recommended that additional studies with large databases needs to be evaluated in*

addition to the sponsor's suggested post-marketing plan to address long term risks. Another committee member noted that if there is an extension study, although this is not a randomized trial, it should be done in a blinded fashion to assess adverse events. Please see the transcript for details of the committee discussion.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY S WOITACH
12/05/2014

DAVID L KETTL
12/09/2014

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

DCRP Consult BLA 125504

DATE: Desired Completion date: 27 Feb 2014
Date of initial review: 29 Apr 2014
Completion date: 17 Apr 2014

FROM: Preston M. Dunnmon, M.D., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Matthew White, RPM, DDDP, x64997
Amy Woitach, Clinical Reviewer, DDDP, x64078
David Kettl, Clinical TL, DDDP, x62105

SPONSOR: Novartis

NAME OF DRUG: Cosentyx (secukinumab - anti-IL17A antagonist antibody), formerly AIN457

FORMULATION: Secukinumab is supplied as 150 mg secukinumab in 1 mL of sterile solution in a single-use prefilled syringe (also referred to as PFS), a single-use prefilled pen (also referred to as AI, pen, or SensoReady pen) for self/home administration; and as 150 mg secukinumab as a powder for solution (requiring reconstitution for injection) in a single-use glass vial (also referred to as 'Lyo in vial') for use by health care professionals only.

DOSE: 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. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.

DEVELOPMENT INDICATION: for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

DOCUMENTS AVAILABLE FOR REVIEW: BLA 125504

Background

Secukinumab is a first-in-class, fully human, monoclonal IgG1κ anti-IL17A antagonist antibody for the treatment of moderate to severe psoriasis. The sponsor states the following:

> *IL-17A is a naturally occurring cytokine that is involved in inflammatory and immune responses. IL-17A also plays a key role in the pathogenesis of plaque psoriasis. IL-17A is upregulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients. Secukinumab works by binding to IL-17A and in this way inhibiting its interaction with the IL-17 receptor. As a result, secukinumab indirectly inhibits the release of proinflammatory cytokines, chemokines, and mediators of tissue damage, and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Treatment with secukinumab reduces erythema, induration, and desquamation present in plaque psoriasis lesions, as well as itch and pain caused by these skin symptoms.*

The psoriasis phase III program was initiated in 2011, and is comprised of five pivotal phase III studies (2302, 2303, 2304, 2308, 2309), and one supportive study (2307), and assesses three forms of secukinumab (lyophilisate in vial, liquid in pre-filled syringe, and liquid in pen/autoinjector). There were four phase II trials in patients with psoriasis. The sponsor notes a total of more than 3,400 psoriasis patients have been treated with secukinumab in controlled and uncontrolled clinical studies, and a total of approximately 4,500 patients have been treated with secukinumab in controlled and uncontrolled clinical studies in various indications (plaque psoriasis and other immune mediated conditions). From these datasets, the sponsor concludes that the safety of secukinumab is similar to or improved over current standard biologic treatments.

Subjects with stable cardiovascular risk factors were not excluded from the phase II and phase III clinical trials that have been submitted to support this BLA. The applicant has provided 2 types of analyses of cardiovascular events described in the summary of clinical safety (section 2.1.5.2):

1) Major adverse cardiovascular events (MACE) identified using Novartis MedDRA Query (NMQ) search terms (see Appendix 1 of this review) and adjudicated by a cardiovascular and cerebrovascular safety adjudication committee
2) Cardiovascular and cerebrovascular (CCV) events using an expanded SMQ-based search definition set.

The review Division noted a small imbalance in ischemic events (more frequent in secukinumab-treated subjects). However, the overall number of MACE and CCV events was low. The applicant compares incidences (12 wk) of secukinumab vs. placebo vs. entanercept and incidences (52+ wk) in dose-adjusted exposure (per 100 patient years) of secukinumab vs. placebo vs. entanercept. Additional cases of MACE have been recently included in the 120 day safety update (2/20/14).

The review Division requests DCRPs opinion with respect to the following:

- Is the Applicant's search and analyses adequate for assessing the cardiovascular safety for this product?
- Is dose-adjusted exposure analysis preferred for the 52+ wk comparison vs. incidence of events?
- Please provide your assessment of cardiovascular safety and advise on whether you would recommend labeling or additional data/analysis to better assess/describe cardiovascular safety.

Rationale for CV Safety Concerns

The sponsor's rationale for being concerned about a potential for CV harm, and the methodology to be used to collect data to address this concern was stated as follows:

> *Whether and how anti-inflammatory therapies modulate CV risks has become a focus of attention for regulators as well as for the scientific community. A recent publication of rare but numerically greater incidence of major adverse cardiovascular events (MACE) in patients receiving anti IL-12/23 antibodies for the treatment of plaque psoriasis compared to patients on placebo (Ryan 2011) provides a rationale for monitoring and evaluating the potential risk of MACE in the secukinumab clinical development program.*

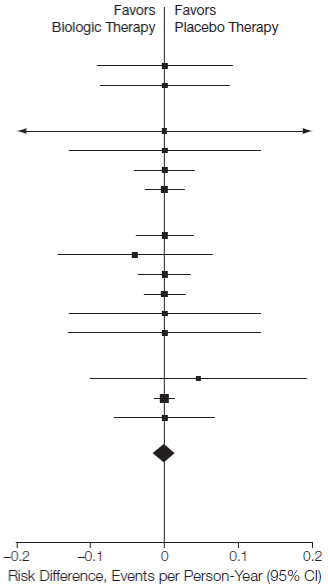
IL-17 is an IL-23 induced cytokine in atherosclerotic plaque inflammation[1]. Meta-analyses of MACE events from RCTs using anti-TNF-alpha agents (e.g. etanercept) and from RCTs using anti-IL-12/23 agents (e.g. briakinumab) were performed (Ryan, 2011). Though no significant drug effect of MACE was demonstrated in these meta-analyses, the authors were concerned about the numerically higher number of MACE events that occurred with the anti-IL-12/23 agents. The results of those two meta-analyses are shown in the following two figures from the Ryan publication:

[1] Ryan C et al. Chronic Plaque Psoriasis and Cardiovascular Events. JAMA, August 24/31, 2011; 306(8):864-871.

Figure 3. Risk Difference of MACEs in Patients Treated With Anti–TNF-α Agents Compared With Placebo in RCTs

Source	Biologic Therapy Events, No.	Biologic Therapy Person-Years	Placebo Events, No.	Placebo Person-Years	Weight, %	Risk Difference, Events per Person-Year (95% CI)
Etanercept						
Menter et al,[14] 2010	0	32	0	16	3.4	0.00 (–0.09 to 0.09)
Strober et al,[15] 2010	0	32	0	17	3.4	0.00 (–0.09 to 0.09)
Infliximab						
Chaudhari et al,[20] 2001	0	4	0	2	0.4	0.00 (–0.50 to 0.50)
Gottlieb et al,[21] 2004	0	38	0	10	2.4	0.00 (–0.13 to 0.13)
Reich et al,[22] 2005	0	139	0	35	8.6	0.00 (–0.04 to 0.04)
Menter et al,[23] 2007	0	168	0	56	12.9	0.00 (–0.03 to 0.03)
Etanercept						
Leonardi et al,[24] 2003	0	112	0	38	8.7	0.00 (–0.04 to 0.04)
Gottlieb et al,[25] 2003	0	26	1	25	3.9	–0.04 (–0.14 to 0.06)
Papp et al,[26] 2005	0	90	0	44	9.0	0.00 (–0.03 to 0.03)
Tyring et al,[27] 2006	0	72	0	71	10.9	0.00 (–0.03 to 0.03)
Van de Kerkhof et al,[28] 2008	0	22	0	11	2.2	0.00 (–0.13 to 0.13)
Bagel et al,[29] 2010	0	14	0	14	2.1	0.00 (–0.13-0.13)
Adalimumab						
Gordon et al,[30] 2006	1	22	0	12	2.4	0.04 (–0.10 to 0.19)
Menter et al,[31] 2008	0	250	0	122	25.1	0.00 (–0.01 to 0.01)
Asahina et al,[32] 2010	0	57	0	21	4.7	0.00 (–0.07 to 0.07)
Overall		1078		494	100.0	–0.0005 (–0.01 to 0.009)
Total events	1		1			

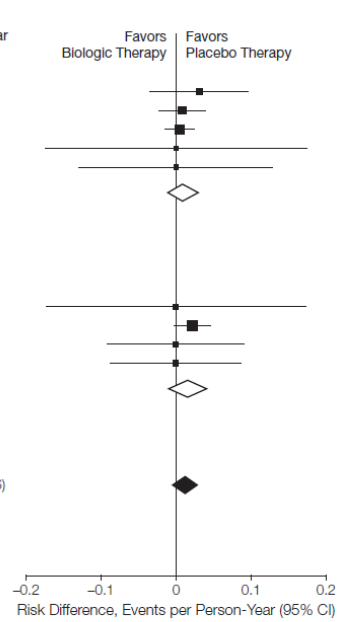
Heterogeneity: $\chi^2 = 0.96$, $df = 14$; $P > .99$; $I^2 = 0\%$
Test for overall effect: $z = 0.07$ $P = .94$
Test for subgroup differences: $\chi^2 = .07$; $P = .94$



Mantel-Haenszel fixed-effects method used to calculate risk difference, person-years of events. CI indicates confidence interval; MACE, major adverse cardiovascular event; RCTs, randomized controlled trials; TNF, tumor necrosis factor.

Figure 2. Risk Difference of MACEs in Patients Treated With Anti–IL-12/23 Agents Compared With Placebo in RCTs

Source	Biologic Therapy Events, No.	Biologic Therapy Person-Years	Placebo Events, No.	Placebo Person-Years	Weight, %	Risk Difference, Events per Person-Year (95% CI)
Ustekinumab						
Krueger et al,[6] 2007	3	97	0	25	8.4	0.03 (–0.03 to 0.09)
Leonardi et al,[7] 2008	1	117	0	59	16.6	0.01 (–0.02 to 0.04)
Papp et al,[8] 2008	1	189	0	94	26.5	0.01 (–0.01 to 0.02)
Igarashi et al,[10] 2010	0	29	0	7	2.4	0.00 (–0.17 to 0.17)
Youn et al,[11] 2010	0	14	0	14	3.0	0.00 (–0.13 to 0.13)
Subtotal (95% CI)		446		199	56.9	0.01 (–0.01 to 0.03)
Total events	5		0			
Heterogeneity: $\chi^2 = 0.65$, $df = 4$; $P = .96$; $I^2 = 0\%$						
Test for overall effect: $z = 0.96$; $P = .34$						
Briakinumab						
Kimball et al,[12] 2008	0	35	0	7	2.5	0.00 (–0.17 to 0.17)
Gordon et al,[13] 2010	5	226	0	111	31.5	0.02 (–0.002 to 0.04)
Menter et al,[14] 2010	0	32	0	16	4.5	0.00 (–0.09 to 0.09)
Stober et al,[15] 2010	0	32	0	17	4.7	0.00 (–0.09 to 0.09)
Subtotal (95% CI)		325		151	43.1	0.02 (–0.01 to 0.04)
Total events	5		0			
Heterogeneity: $\chi^2 = 0.54$, $df = 3$; $P = .91$; $I^2 = 0\%$						
Test for overall effect: $z = 1.27$; $P = 0.20$						
Overall		771		350	100.0	0.012 (–0.001 to 0.026)
Total events	10		0			
Heterogeneity: $\chi^2 = 1.79$, $df = 8$; $P = .99$; $I^2 = 0\%$						
Test for overall effect: $z = 1.58$ $P = .12$						
Test for subgroup differences: $\chi^2 = 0.17$; $df = 1$; $P = .68$; $I^2 = 0\%$						



Mantel-Haenszel fixed-effects method used to calculate risk difference, person-years of events. MACE indicates major adverse cardiovascular event; IL, interleukin; RCTs randomized controlled trials; CI, confidence interval.

Identification of MACE and CCV events of interest

Serious adverse events (CV-SAEs) related to MACE that were reported by investigators during the secukinumab (AIN457) clinical trials were retrospectively identified via a computerized search of the clinical trial database as well as the safety database, using customized Novartis MedDRA queries (NMQs). The preferred terms included in the principle NMQ definition set are shown in Appendix 1 of this review. This definition set was sufficiently comprehensive to serve its intended purpose. In addition, the sponsor scanned for additional CCV SAEs using a more broad set of SMQs (definitions given in the text of this review).

Reviewer's comment: post-hoc adjudication of CV events based on adverse event reporting from trials with no CV endpoints does not correct for ascertainment that is likely to be incomplete (though not necessarily biased). However, stroke, MI, and death outcomes are unlikely to have gone unnoticed.

The CCV-Adjudication Committee (CCV-AC)

The sponsor modeled its approach for quantifying MACE/CCV events risk from the 2009 FDA briefing document for Saxagliptin. Accordingly, the CCV-AC was chartered to independently and blindly review, evaluate and categorize cardio- and cerebrovascular events including, but may not be limited to, MACE (a composite of myocardial infarction, stroke and cardiovascular death) that may be observed during the secukinumab (AIN457) clinical development program. The CCV-AC membership was as follows:

Expert	Institution	City, Country	Field
(b) (4)			

Definitions for MI, stroke, and CV death that were used by the CCV-AC are listed in Appendix 2 of this Review. The CCV-AC adjudication form is shown in Appendix 3 of this review.

Nonclinical Safety Findings (from sponsor's nonclinical overview and tox summary)

The sponsor states that therapeutic monoclonal antibodies that are cytokine modulators have been identified for harboring DDI potential. It has been reported that cytokine levels are associated with the expression, stability, and activity of certain cytochrome P450 (CYP450) enzymes in several in vitro and limited in vivo studies. Due to the limited number of co-medications in secukinumab-treated psoriasis patients and the down regulation of IL-6 after secukinumab treatment, it is concluded that for the general psoriasis patient population, the clinical impact of secukinumab-induced DDI is minimal; therefore dedicated DDI studies were not considered necessary.

The sponsor also notes that the cardiovascular, CNS and respiratory safety of secukinumab was assessed in a specific telemetry safety pharmacology study in cynomolgus monkeys. No biologically relevant effects on the cardiovascular, CNS or respiratory functions attributable to secukinumab were observed. No unexpected binding to cardiac or cardiovascular, CNS or respiratory tissues was identified in any of the cross reactivity studies using cynomolgus monkey and human tissues. In addition, *In vitro* blood compatibility and antibody-dependent cellular cytotoxicity analyses did not show any adverse reactions.

Clinical Trials -- Integrated Safety Data Structure

All psoriasis trials were conducted in patients with moderate to severe plaque psoriasis. Six phase III psoriasis trials were completed and summarized in the table below:

Table 1-1 Summary of phase III studies in psoriasis

Study	Description	Formulation	N	Treatments
Placebo-controlled, active-controlled trials				
A2302 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Lyophilisate in vial	738	150 , 300 mg AIN, PBO[a] qw for 4 wk, then q4w to Wk 48
A2303 *(52 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled and active comparator (etanercept) comparison	Lyophilisate in vial	1306	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48 Etanercept 50 mg twice per week to Wk 12, then qw to Wk 51
A2308[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Pre-filled syringe	177	150, 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2309[e] *(12 Wk)*	Efficacy/safety (s.c.) in target population – placebo-controlled	Autoinjector / pen	182	150 mg or 300 mg AIN, PBO[a] qw for 4 wk, then q4w until Wk 48
A2304 *(52 Wk)*	Maintenance of efficacy/safety (s.c.) in target population comparing maintenance regimens of continuous every 4 wk dosing vs. "Retreatment at start of relapse" – maintenance regimen comparison	Lyophilisate in vial	966	150, 300 mg AIN qw for 4 wk, then q4w until Wk 12[b,c] For PASI 75 responders: *Fixed Interval:* induction dose q4w to Wk 48 *Retreatment at start of relapse*[d]: PBO to relapse, then induction dose q4w till PASI 75 then PBO to relapse or Wk 48
A2307 *(40 Wk)*	Efficacy/safety of uptitration in partial responders at Wk 12 from A2304 – dose regimen comparison	Lyophilisate in vial	43	10 mg/kg i.v. or 300 mg s.c. AIN at randomization, Wk 2 and Wk 4, then 300 mg s.c. q4w to Wk 36

N=number of patients randomized
AIN = AIN457/secukinumab; LYO=lyophilisate in vial; PBO = placebo; PASI = Psoriasis Area and Severity Index
[a] = PASI 75 nonresponders on PBO were re-randomized 1:1 to 150 or 300 mg AIN and treated from Wk 12 onwards
[b] = PASI nonresponders discontinued study treatment
[c] = partial responders could enter Study A2307
[d] = start of relapse is a loss of ≥ 20% of the max. PASI gained in the study, with a loss of PASI 75 response
[e] = 12 weeks safety data of 52 week study
Source: [Tabular Listing of all Clinical Studies]

Four phase II trials were performed to support dose selection for phase III, only one of which included longer term maintenance therapy (150 mg SC q4w) per the following summary table:

Table 1-2 Summary of phase II studies in psoriasis

Study	Description	Formulation	N	Treatments
A2102	Single dose (i.v.) in target population	Lyophilisate in vial	36	3 mg/kg AIN PBO
A2211	Multi-dose regimen finding (s.c.) in target population	Lyophilisate in vial	404	Induction 1 x 150 mg AIN 3 x 150 mg AIN at Wk 1, 5, 9 4 x 150 mg AIN at Wk 1, 2, 3, 5 5 x PBO at Wk 1, 2, 3, 5, 9 Maintenance in responders: *Fixed Interval:* 150 mg at Wk 13, 25 *Start of relapse:* 150 mg AIN, PBO at Wk 13, 25 Treatment in partial or non-responders: *Open label:* 150 mg s.c. q4w AIN until Wk 33
A2212	Multiple-loading dose regimen (i.v.) in target population	Lyophilisate in vial	100*	1 x 3 AIN at Day 1 1 x 10 mg/kg AIN at Day 1 3 x 10 mg/kg AIN at Day 1, 15, 29 3 x PBO at Day 1, 15 , 29
A2220	Dose-ranging (s.c.) in target population	Lyophilisate in vial	125	3 x 150 mg AIN at Wk 1, 5, 9 3 x 75 mg AIN at Wk 1, 5, 9 3 x 25 mg AIN at Wk 1, 5, 9 1 x 25 AIN at Wk 1 PBO at Wk 1, 5, 9
*A2204***	*Single dose (i.v.) in target population*	*Lyophilisate in vial*	*80*	*0.3, 1, or 3 mg/kg AIN* *PBO*

An additional phase II study (2212) was conducted but excluded from the analysis due to data quality concerns. Specifically, center 0001 enrolled 65/ 80 patients in the trial, but was found to have GCP violations that resulted in the site being closed. Deficiencies included failure to protect blinding, failure to administer study drug infusions as per protocol, and failure to maintain adequate records resulting in underreporting of AEs. The safety results of study 2204 were therefore considered separately and not included in the data pools.

Safety data up to 52 weeks are provided by 2 placebo-controlled trials (Study A2302 and Study A2303, the latter incorporating an active comparator control), and 1 maintenance regimen comparison trial (Study A2304). Further longer term data (>1 year) are provided by an ongoing, uncontrolled, extension study (Study A2211E1). The main features of these trials are summarized in Table 1-3 below (from the Summary of Clinical Safety (SCS)):

Table 1-3 Summary of trials in psoriasis providing longer term safety data

Study	Description	N	Treatments
Reported studies*			
A2302 (52 Wk)	Efficacy/safety (s.c.) in target population – placebo-controlled	738	150 , 300 mg AIN, PBO[a] qw for 4 wks, then q4w to Wk 48
A2303 (52 Wk)	Efficacy/safety (s.c.) in target population - placebo-controlled and active comparator (etanercept) comparison	1306	150 mg or 300 mg AIN, PBO[a] qw for 4 wks, then q4w until Wk 48 Etanercept 50 mg twice per week to Wk 12, then qw to Wk 51
A2304 (52 Wk)	Maintenance of efficacy/safety (s.c.) in target population comparing maintenance regimens of continuous every 4 wk dosing vs. "Retreatment as needed" – maintenance regimen comparison	966	150, 300 mg AIN qw for 4 wks, then q4w until Wk 12[b,c] For PASI 75 responders: Fixed Interval: induction dose q4w to Wk 48 Start of relapse[d]: PBO to start of relapse, then induction dose q4w till PASI 75 then PBO to Wk 48
A2211E1 (data cut-off: 21-Jan-2013 ; >52 weeks up to 175 weeks**)	Long-term safety (s.c.) in target population – placebo-controlled	275	Maintenance in responders: Fixed Interval: 150 mg AIN at Wk 1, then q12w Start of relapse: 150 mg AIN at start of relapse PBO: at Wk 1 and then q12w Treatment in partial or non-responders: Open Label: 150 mg AIN at Wk 1 and then q4w
Ongoing, not yet reported studies			
A2302E1 (104 Wk)	Randomized withdrawal study assessing maintenance of efficacy/safety (s.c.) in 52-week PASI 75 responders or partial responders from A2302 and A2303	1144	150 mg or 300 mg AIN, PBO (pre-filled syringe) q4w Wk 52 to Wk 152 or until first relapse At first visit with relapse: loading dose qw for 3 wks, then q4w
A2304E1 (104 Wk)	Maintenance of efficacy/safety (s.c.) in target population comparing maintenance regimens of continuous every 4 wk dosing vs. "Retreatment as needed" – maintenance regimen comparison	675	150 mg or 300 mg AIN, PBO (pre-filled syringe) Patients from A2304: fixed-time regimen q4w Wk 52 to Wk 152; or PBO until first relapse, then 150 mg or 300 mg AIN Patients from A2307: 300 mg q4w Wk 52 to Wk 152

* An additional phase III study, Study A2307, provides cumulative safety data up to 52 weeks for 21 patients treated with 300 mg secukinumab sc qw for 4 weeks and up to 40 weeks for 22 patients treated with secukinumab 10 mg/kg i.v.
** Safety data from Study A2211E1 up to 175 weeks of exposure was included in Pool C of all secukinumab trials
[a] = PASI 75 nonresponders on PBO were re-randomized 1:1 to 150 mg or 300 mg IAN and treated from Wk 12-48
[b] = PASI nonresponders discontinued study treatment
[c] = partial responders could enter Study A2307
[d] = start of relapse is a loss of ≥ 20% of the max. PASI gained in the study, with a loss of PASI 75 response
AIN = AIN457, PBO = placebo, PASI = Psoriasis Area and Severity Index, IGA = Investigator's Global Assessment
Source: [Tabular Listing of all Clinical Studies]

Clinical trials with secukinumab in non-psoriasis indications are summarized in the following table. The trials of healthy subjects are listed but not included in data pooling (from the SCS):

Table 1-4 Overview of clinical trials in other indications

Source of data	Details	Studies included in pooling
Psoriatic arthritis		
(Ph II & III)	2 completed trials [A2206, A2206E1]	A2206 and A2206E1
	2 ongoing trials [F2306, F2312]	--
Palmoplantar psoriasis		
(Ph III)	1 ongoing trial [A2312]	--
Nail psoriasis		
(Ph III)	1 ongoing trial [A2313]	--
Rheumatoid arthritis		
(Ph II & III)	2 completed trials [A2101, F2201]	A2101 and F2201
	6 ongoing trials [F2206, F2208, F2302, F2309, F2309E1, F2311]	F2206 and F2208
Ankylosing spondylitis		
(Ph II & III)	2 completed trials [A2209, A2209E1]	A2209 and A2209E1
	2 ongoing trials [F2305, F2310]	--
Multiple sclerosis		
(Ph II)	1 completed trial [B2201]	B2201
	2 ongoing trial [B2201E1, B2203]	--
Crohn's disease		
(Ph II)	2 completed trials [A2202, A2202E1]	A2202 and A2202E1
Asthma		
(Ph II)	1 ongoing trial [D2204]	--
Ophthalmology		
(Ph II & III)	1 ph II trials in uveitis [A2208]	A2208
	6 ph III trials in uveitis [C2301, C2301E1, C2302, C2302E1, C2303, C2303E1]	C2301, C2301E1, C2302, C2302E1, C2303 and C2303E1
	1 PoC trial in dry eye syndrome [CPJMR0092202]	CPJMR0092202
Polymyalgia rheumatic		
(Ph II)	1 ongoing PoC trial [CPJMR0012201]	--
Healthy volunteers		
(Ph I & II)	7 phase I & II trials [A1101, A2104, A2106, A2224, A2228; Sandoz 101, Sandoz 102, Sandoz 105]	--

Ph = phase, PoC = proof of concept
Source: [Tabular Listing of all Clinical Studies]; [Statistical Overview]

Accordingly, three data pools have been defined for the purposes of the sponsor's safety analysis:

- Pool A – Pivotal, placebo-controlled psoriasis trials (12 weeks)
- Pool B – all blinded and controlled psoriasis trials (12 weeks and 52 weeks)
- Pool C – all secukinumab trials, all indications, any dose, controlled or open-label (52 weeks)

The final structure of the integration is shown in the table below (from the SCS):

Table 1-5 Trials used in pooled safety datasets

Pool	Trials included in data pool	Analysis periods and treatment groups
Pool A	**Pivotal, 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; 157 pt-yr) AIN457 300 mg (N=690; 158 pt-yr) Placebo (N=694; 155 pt-yr) Etanercept (N=323; 73 pt-yr)
Pool B	**All psoriasis trials (randomized, double-blind); N=3993 (12 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: AIN457 150 mg (N=1174; 268 pt-yr) AIN457 300 mg (N=1173; 268 pt-yr) Any AIN457 dose (N=2877; 655 pt-yr) § Placebo (N=793; 176 pt-yr) Etanercept (N=323; 73 pt-yr) 52 weeks: Any AIN457 150 mg (N=1395; 1142 pt-yr) Any AIN457 300 mg (N=1410; 1178 pt-yr) Any AIN457 dose (N=3430; 2725 pt-yr) § Placebo (N=793; 201 pt-yr) Etanercept (N=323; 294 pt-yr)
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; 3588 pt-yr) § Placebo (N=1158; 339 pt-yr)

* Total number of patients treated with secukinumab and/or placebo; some patients received placebo before switching to secukinumab
** = all cohorts, except cohort 4 were included
# = excluding the data from healthy volunteers
§ includes other doses, dose regimens and i.v. administration in addition to fixed interval 150 mg and 300 mg s.c. secukinumab
N=number of patients in the data pool or treatment group based on the Safety set; pt-yr=patient-years of exposure
Source: [Statistical Overview]; [SCS-Appendix 1-Table 7.1-1.1, Table 7.2-1.1, Table 7.2-1.2 and Table 7.3-1.1]

The evaluation of CV safety will focus on pools A and B, though the uncontrolled occurrence of CCV outcomes will be noted for Pool C.

Reviewers comment: None of the four pivotal trials included in Pool A incorporated a MACE or CCV outcome event as a primary or secondary endpoint. Adjudication by the CCV-AC was done retrospectively, assessing cardiovascular and cerebrovascular adverse events across the entire program via NMQ queries of adverse event and clinical databases. With respect to dropouts, the sponsor imputed "no-response" values into the efficacy dataset for dropouts, and attempted post-withdrawal safety follow-up for four weeks after premature discontinuation.

Analysis Periods

- Induction period: Day 1 until Week 12 visit for all assessments

- Maintenance period:
  - Week 12 visit until the last visit of the maintenance period. For Studies A2302, A2303 and A2304, it includes the Week 52 visit, unless the patient entered the extension study. For patients entering the extension study at Week 52, the Week 52 assessments performed before start of extension treatment were included.
  - There is no maintenance period for Studies A2212 and A2220.
  - Patients in Study A2307 rolled over from Study 2304 (where they received induction treatment for 12 weeks) and therefore the maintenance period in A2307 is defined as randomization to the Week 40 visit.

- Entire treatment period:
  - Day 1 until the last visit of the treatment period. For Studies A2302, A2303 and A2304, it includes the Week 52 visit, unless the patient entered the extension study (as defined above for the maintenance period). For all other studies, the end of the entire treatment period is defined as the visit scheduled 4 weeks after the last dose of study treatment. If no visits were scheduled 4 weeks after last dose, all safety assessments and reported events up to 4 weeks (28 days) after last dose were included. The overall duration of the entire treatment period was at least 12 weeks.
  - For patients in Study A2307, the entire treatment period included 12-week data from Study A2304 and 40-week data from Study A2307.
  - For patients originally randomized to placebo and then re-randomized to secukinumab (Studies A2302, A2303, A2211), there were two entire treatment periods: on placebo before switching and on secukinumab after switching.
  - The follow-up period for Studies A2302, A2303, A2304 and A2307 are not included in the CSRs and the SCS provided in this submission. Data for the follow-up period, Weeks 52 to 60, will be described in separate study reports.

Sponsor's Planned MACE Analysis

MACE events were analyzed by meta-analysis for the data pools of the pivotal placebo-controlled psoriasis studies (Pool A). The absolute rate difference for all studies assuming a fixed-effect model was estimated by means of the Mantel-Haenszel method of Greenland and Robins (Greenland and Robins 1985). As it turned out, there were so few MACE events that only the absolute number and incidence of these events was displayed (see table 2-25 on page 35 of this consult).

Exposure

Pool A (pivotal placebo-controlled trials, induction period)

All treatment groups in Pool A had similar durations of exposure to study treatment in the induction period. The median duration of exposure was 84 days and ≥ 96% of patients were exposed for at least 8 weeks. However, total exposure to the entanercept active control arm was just under half the exposure in the AIN457 arms due to fewer patients being exposed in that arm, as seen in the table below (from the SCS). For those patients who came earlier than Day 85 for the Week 12 visit, they were not included in the "≥12 weeks" row for the induction period.

Table 1-7 Duration of exposure to study treatment - Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)

Duration of exposure	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	Any AIN457 dose N=1382 n (%)	Placebo N=694 n (%)	Etanercept N=323 n (%)
Any exposure	692 (100.0)	690 (100.0)	1382 (100.00)	694 (100.0)	323 (100.0)
≥ 1 week	692 (100.0)	688 (99.7)	1380 (99.86)	694 (100.0)	323 (100.0)
≥ 2 weeks	688 (99.4)	687 (99.6)	1375 (99.49)	691 (99.6)	321 (99.4)
≥ 3 weeks	684 (98.8)	687 (99.6)	1371 (99.20)	687 (99.0)	321 (99.4)
≥ 4 weeks	684 (98.8)	686 (99.4)	1370 (99.13)	683 (98.4)	320 (99.1)
≥ 8 weeks	677 (97.8)	677 (98.1)	1354 (97.97)	668 (96.3)	314 (97.2)
≥ 12 weeks	528 (76.3)	538 (78.0)	1066 (77.13)	502 (72.3)	253 (78.3)
Days					
n	692	690	1382	694	323
Mean	83.0	83.4	83.2	81.8	82.6
SD	10.95	8.58	9.83	11.48	9.45
Median	84.0	84.0	84.0	84.0	84.0
Min - Max	8 - 223	1 - 152	1 - 223	8 - 124	9 – 96
Patient years	157.2	157.5	314.6	155.4	73.0

Duration of exposure to study treatment is defined as end of treatment period – start date of study treatment + 1.
Exposure in patient-years is calculated as a sum of individual patient durations in days divided by 365.25.
Source: [SCS-Appendix 1-Table 7.1-1.1]

Pool B (all psoriasis trials, induction period and entire treatment period) and Pool C

All treatment groups in Pool B had similar durations of exposure to study treatment in the induction period. The median duration of exposure was 84 days and ≥95% of patients were exposed for at least 8 weeks. However, total exposure was substantially less in the placebo and entanercept arms due to substantially fewer patients in these arms, as shown in the table below:

Table 1-9 Duration of exposure to study treatment – Induction period (Pool B: All psoriasis trials – Safety set)

Duration of exposure	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
Any exposure	1174 (100.00)	1173 (100.00)	2877 (100.00)	793 (100.0)	323 (100.0)
>= 1 week	1174 (100.00)	1171 (99.83)	2874 (99.90)	792 (99.9)	323 (100.0)
>= 2 weeks	1168 (99.49)	1170 (99.74)	2864 (99.55)	789 (99.5)	321 (99.4)
>= 3 weeks	1164 (99.15)	1167 (99.49)	2857 (99.30)	783 (98.7)	321 (99.4)
>= 4 weeks	1163 (99.06)	1166 (99.40)	2854 (99.20)	779 (98.2)	320 (99.1)
>= 8 weeks	1151 (98.04)	1150 (98.04)	2815 (97.84)	754 (95.1)	314 (97.2)
>= 12 weeks	924 (78.71)	919 (78.35)	2279 (79.21)	571 (72.0)	253 (78.3)
Days					
n	1174	1173	2877	793	323
Mean	83.3	83.3	83.2	81.2	82.6
SD	10.09	8.74	9.87	13.06	9.45
Median	84.0	84.0	84.0	84.0	84.0
Min - Max	8 - 223	1 - 152	1 - 223	1 - 127	9 - 96
Patient-years	267.7	267.5	655.4	176.2	73.0

Duration of exposure to study treatment is defined as end of treatment period – start date of study treatment + 1.
Exposure in patient-years is calculated as a sum of individual patient durations in days divided by 365.25.
Source: [SCS-Appendix 1-Table 7.2-1.1]

The exposure differential for placebo became much more pronounced for the entire treatment analysis period due to the high number of patients failing placebo treatment and rolling over to active drug, as can be seen in exposure table for Pool B (entire treatment period) below:

Table 1-10 Duration of exposure to study treatment – Entire treatment period (Pool B: All psoriasis trials – Safety set)

Duration of exposure	Any AIN457 150 mg N=1395 n (%)	Any AIN457 300 mg N=1410 n (%)	Any AIN457 dose N=3430 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
Any exposure	1395 (100.00)	1410 (100.00)	3430 (100.00)	793 (100.0)	323 (100.0)
>= 1 week	1395 (100.00)	1408 (99.86)	3427 (99.91)	792 (99.9)	323 (100.0)
>= 2 weeks	1389 (99.57)	1407 (99.79)	3417 (99.62)	789 (99.5)	321 (99.4)
>= 3 weeks	1385 (99.28)	1404 (99.57)	3410 (99.42)	783 (98.7)	321 (99.4)
>= 4 weeks	1384 (99.21)	1403 (99.50)	3407 (99.33)	779 (98.2)	320 (99.1)
>= 8 weeks	1371 (98.28)	1382 (98.01)	3360 (97.96)	754 (95.1)	314 (97.2)
>= 12 weeks	1333 (95.56)	1348 (95.60)	3261 (95.07)	577 (72.8)	306 (94.7)
>= 16 weeks	1194 (85.59)	1227(87.02)	2834 (82.62)	38 (4.8)	300 (92.9)
>= 20 weeks	1183 (84.80)	1206 (85.53)	2789 (81.31)	35 (4.4)	297 (92.0)
>= 24 weeks	1165 (83.51)	1193 (84.61)	2751 (80.20)	34 (4.3)	292 (90.4)
>= 28 weeks	1155 (82.80)	1186 (84.11)	2721 (79.33)	33 (4.2)	290 (89.8)
>= 32 weeks	1139 (81.65)	1179 (83.62)	2692 (78.48)	32 (4.0)	284 (87.9)
>= 36 weeks	1114 (79.86)	1168(82.84)	2642 (77.03)	31 (3.9)	281 (87.0)
>= 40 weeks	1061 (76.06)	1106 (78.44)	2466 (71.90)	31 (3.9)	276 (85.4)
>= 44 weeks	876 (62.80)	932 (66.10)	2066 (60.23)	31 (3.9)	274 (84.8)
>= 48 weeks	861 (61.72)	922 (65.39)	2029 (59.15)	30 (3.8)	270 (83.6)
>= 52 weeks	698 (50.04)	732 (51.91)	1641 (47.84)	26 (3.3)	241 (74.6)
Days					
n	1395	1410	3430	793	323
Mean	299.0	305.0	290.1	92.7	331.9
SD	103.89	101.67	110.53	57.05	89.70
Median	364.0	364.0	363.0	84.0	365.0
Min - Max	8 - 453	1 - 432	1 - 453	1 - 377	9 - 406
Patient-years	1142.0	1177.5	2724.6	201.3	293.5

The exposure differential between AIN457 (any dose) and placebo for the entire treatment period of Pool C (all trials, all indications), was even more imbalanced, as seen in the table below:

Table 1-12 Duration of exposure to study treatment – Entire treatment period (Pool C: All secukinumab trials) (Safety set)

Duration of exposure	Any AIN457 dose N=4498	Placebo N=1158
Any exposure	4498 (100.00)	1158(100.00)
>= 1 week	4493 (99.89)	1157(99.91)
>= 2 weeks	4480 (99.60)	1151(99.40)
>= 3 weeks	4468(99.33)	1145(98.88)
>= 4 weeks	4453 (99.00)	1138(98.27)
>= 8 weeks	4376(97.29)	1102(95.16)
>= 12 weeks	4207(93.53)	908(78.41)
>= 16 weeks	3327(73.97)	201(17.36)
>= 20 weeks	3259(72.45)	180(15.54)
>= 24 weeks	3202(71.19)	134(11.57)
>= 28 weeks	3091(68.72)	88(7.60)
>= 32 weeks	3034(67.45)	82(7.08)
>= 36 weeks	2941(65.38)	77(6.65)
>= 40 weeks	2751(61.16)	65(5.61)
>= 44 weeks	2354(52.33)	51(4.40)
>= 48 weeks	2296(51.04)	43(3.71)
>= 52 weeks	1900(42.24)	33(2.85)
Days		
n	4498	1158
Mean	291.4	106.8
SD	191.90	71.98
Median	357.0	84.0
Min - Max	1 - 1224	1 - 752
Patient- years	3588.1	338.7

Duration of exposure to study treatment is defined as end of treatment period – start date of study treatment + 1.
Exposure in patient years is calculated as a sum of individual patient durations in days divided by 365.25.
Source: [SCS-Appendix 1-Table 7.3-1.1]

Of note, Pool B constitutes the largest pool of safety data in psoriasis, with 3430 patients treated with at least one dose of secukinumab, with 2725 patient-years of exposure comprising 76% of the total exposure. Therefore, the psoriasis studies in Pool B constitute the majority of the unblinded safety data for the program, with smaller exposure contributions from completed studies in other indications contributing to Pool C.

Reviewer's note: Given these time-driven exposure imbalances, which are understandable given the nature of the disease the lack of effectiveness of placebo, I agree with the sponsor's use of exposure-corrected adverse event rates for the extended follow-up analyses of Pool B and Pool C.

Patient Dispositions

For Pool A (pivotal placebo-controlled psoriasis trials), greater than 95% of patients treated with AIN457 during induction completed the induction period. There were no deaths and similar percentages of patients discontinued drug due to adverse events across the treatment arms, as seen in the table below (from the SCS). Withdrawals for lack of efficacy were numerically lower for the AIN457 treatment arms than for Placebo or for the Etanercept active comparator, as seen in the disposition summary table below:

Table 1-14 Patient disposition – Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)

Disposition/Reason	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 n (%)	Placebo N=694 n (%)	Etanercept N=323 n (%)	Total N=2399 n (%)
Entered induction period	692 (100.0)	690 (100.0)	694 (100.0)	323 (100.0)	2399 (100.00)
Completed Induction period	661 (95.5)	666 (96.5)	648 (93.4)	303 (93.8)	2278 (94.96)
Discontinued Induction	31 (4.5)	24 (3.5)	46 (6.6)	20 (6.2)	121 (5.04)
Adverse event	8 (1.2)	8 (1.2)	8 (1.2)	6 (1.9)	30 (1.25)
Lack of efficacy	1 (0.1)	1 (0.1)	10 (1.4)	2 (0.6)	14 (0.58)
Lost to follow-up	1 (0.1)	2 (0.3)	4 (0.6)	3 (0.9)	10 (0.42)
Non-compliance with study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)
Physician decision	3 (0.4)	1 (0.1)	2 (0.3)	0 (0.0)	6 (0.25)
Pregnancy	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.04)
Protocol deviation	3 (0.4)	6 (0.9)	1 (0.1)	3 (0.9)	13 (0.54)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)
Technical problems	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	2 (0.08)
Subject/guardian decision	15 (2.2)	5 (0.7)	20 (2.9)	5 (1.5)	45 (1.88)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)

Source: [SCS-Appendix 1-Table 6.1-1.1]

The disposition data for the induction period of Pool B (all psoriasis trials) were similar.

For the maintenance period of Pool B (all psoriasis trials), a numerically higher percentage of patients on AIN457 remained on therapy as compared to placebo and Etanercept (88% vs 81% vs 87%, respectively), with adverse event-driven withdrawal being similar for the AIN457 and placebo groups, as seen in the table below (from the SCS). There was one death in an AIN457 treatment group in Pool B, which will be discussed below in the MACE analysis.

Table 1-16 Patient disposition – Maintenance period (Pool B: All psoriasis trials – Safety set)

Disposition /Reason	AIN457 150 mg N=748 n (%)	AIN457 300 mg N=772 n (%)	Any AIN457 dose N=2853 n (%)	Placebo N=37 n (%)	Etanercept N=303 n (%)	Total N=3193 n (%)
Entered	748 (100.0)	772 (100.0)	2853 (100.00)	37 (100.0)	303 (100.0)	3193 (100.00)
Completed Maintenance	663 (88.6)	708 (91.7)	2516 (88.19)	30 (81.1)	263 (86.8)	2809 (87.97)
Discontinued Maintenance	85 (11.4)	64 (8.3)	337 (11.81)	7 (18.9)	40 (13.2)	384 (12.03)
Adverse event	16 (2.1)	20 (2.6)	74 (2.59)	1 (2.7)	5 (1.7)	80 (2.51)
Lack of efficacy	22 (2.9)	6 (0.8)	75 (2.63)	1 (2.7)	10 (3.3)	86 (2.69)
Lost to follow-up	6 (0.8)	4 (0.5)	35 (1.23)	0 (0.0)	5 (1.7)	40 (1.25)
Non-compliance with study treatment	3 (0.4)	1 (0.1)	8 (0.28)	0 (0.0)	2 (0.7)	10 (0.31)
Physician decision	0 (0.0)	2 (0.3)	2 (0.07)	0 (0.0)	1 (0.3)	3 (0.09)
Pregnancy	1 (0.1)	4 (0.5)	8 (0.28)	0 (0.0)	0 (0.0)	8 (0.25)
Protocol deviation	10 (1.3)	7 (0.9)	29 (1.02)	0 (0.0)	2 (0.7)	31 (0.97)
No longer requires treatment	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.00)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	1 (0.3)	1 (0.03)
Technical problems	0 (0.0)	0 (0.0)	2 (0.07)	0 (0.0)	0 (0.0)	2 (0.06)
Subject/guardian decision	27 (3.6)	20 (2.6)	103 (3.61)	5 (13.5)	14 (4.6)	122 (3.82)
Death*	0 (0.0)	0 (0.0)	1 (0.04)	0 (0.0)	0 (0.0)	1 (0.03)

* One death reported in a patient on an alternative 150 mg dosing regimen in [Study A2220-Section 2.1.2.1]
Source: [SCS-Appendix 1-Table 6.2-1.2]

Demographics and Baseline CV Risk

The sponsor notes that exclusion criteria were less restrictive in the AIN457 phase II/III trials than may have been the case with other biologics being developed for the treatment of psoriasis. Germaine to this consult, there were no exclusions of patients with active, ongoing cardiovascular or cerebrovascular diseases, unless the conditions were severe, progressive, or uncontrolled, such as uncontrolled hypertension or significant congestive heart failure (NYHA class III or class IV).

For Pool A (pivotal placebo-controlled psoriasis trials), the subject mean age was approximately 45 years, and 70% were male. Mean BMIs across study arms were approximately 29 kg/m^2. With respect to smoking history in Pool A overall, 35.0% were current smokers, 19.9% were former smokers, and 45.1% had never smoked. The three most commonly reported cardiovascular risk factors were hypertension, dyslipidemia/hyperlipidemia and uncomplicated diabetes. Most of the reported prior cardiovascular conditions were ongoing at the time of enrollment. Small percentage imbalances in cardiovascular risk factors were seen for both secukinumab dose groups compared with placebo and, to a lesser extent, etanercept, but given the different sample sizes this translated into larger imbalances in the absolute number of patients at risk in the secukinumab dose groups. These included hypertension (25.8% for 300 mg and 28.3% for 150 mg vs. 22.3% for placebo and 20.7% for etanercept), dyslipidemia/hyperlipidemia (18.4% and 17.6% vs. 14.3% and 13.0%), uncomplicated

diabetes (9.1% and 9.1% vs. 7.5% and 8.4%) and stable coronary artery disease (2.5% and 2.5% vs. 1.4% and 0.9%). In addition, the 300 mg group showed higher rates of prior myocardial infarction (2.6% for 300 mg vs. 1.0%, 1.7% and 1.8%, respectively, for 150 mg, placebo and etanercept) and atrial fibrillation (1.6% for 300 mg vs. 0.7%, 0.6% and 0.3%, respectively, for 150 mg, placebo and etanercept). As would be expected, similar trends were seen in the Pool B demographics since Pool A is a subset of Pool B.

Common Adverse Events

Common AEs according to primary SOC in the induction period of the pivotal placebo-controlled psoriasis studies (Pool A) are summarized in Table 2-1 below (from SCS). Findings relevant to CCV safety include:

- Blood and lymphatic system disorders (SOC) were similar between secukinumab and etanercept (1.9%, 2.5% and 2.5% for 300 mg, 150 mg and etanercept, respectively), though rates in all active treatment groups were greater than placebo (1.0%). The imbalance vs. placebo was primarily due to lymphadenopathy, eosinophilia, leukopenia, lymphocytosis and neutropenia, although the rates of these events in the 300 mg secukinumab dose group were generally low (0.1-0.7%) and similar to etanercept (0-0.9%).

- Renal disorders were reported with a comparable rate for 300 mg and 150 mg secukinumab and etanercept (1.0%, 1.2% and 1.5%, respectively), which were higher than placebo (0.3%). As all events in any active treatment groups were single occurrences, there was no predominant term driving the imbalance vs. placebo.

- A higher rate of vascular disorders was observed with 150 mg secukinumab (4.0%) than with 300 mg (1.3%), which was lower than placebo and etanercept (2.3% and 2.2%, respectively). This difference was primarily due to a higher rate of hypertension in the 150 mg group (3.2%) compared to the 300 mg, placebo and etanercept groups (1.0%, 1.7% and 1.5%, respectively). Both secukinumab dose groups also reported a higher rate of hypertension at baseline (25.8% for 300 mg and 28.3% for 150 mg vs. 22.3% for placebo and 20.7% for etanercept).

- PTs in the cardiac disorders SOC were reported more frequently for placebo and etanercept (1.7% and 2.2%, respectively) than for either secukinumab dose (0.6% for 300 mg and 1.2% for 150 mg), despite higher rates of prior cardiovascular disease or risk factors for such reported at baseline. AEs contributing to this difference vs. were related to conduction disorders, such as left bundle branch block.

Common AEs for the Pool A induction period are summarized by SOC in the table below:

Table 2-1 AEs by primary system organ class – Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)

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

The general profile of AEs in the induction period was similar between Pools A and B, with no increase in the rate of total AEs or any SOC and no new involvement of SOCs in the larger psoriasis data Pool B than seen in the pivotal placebo-controlled trial Pool A.

The general profile of AEs over the entire treatment period was similar to the induction period, with no new involvement of SOCs over 52 weeks of treatment than seen in the first 12 weeks of treatment. However, in the exposure-adjusted analysis Pool B (all blinded and controlled psoriasis trials) for the entire treatment period, hypertension AEs occurred at a lower rate on any dose of AIN457 than occurred with placebo, as seen in the table below:

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

Deaths - psoriasis

A total of 16 deaths have been reported up to 31-Jul-2013 across all secukinumab trials: 6 in psoriasis clinical trials and 10 in other indications. A summary table of reported 6 deaths in psoriasis studies through the 31 July 2013 SCS cutoff is as follows (from SCS):

Table 2-9 Deaths in all Phase I to III psoriasis trials

PID Age/sex/race Treatment	Cause of death (Preferred term)	Risk factors	Day of death (study period)	No. days from last dose to onset*	Study drug related
Secukinumab on-treatment					
[AIN457A2304-7055004] 66/M/As AIN457 150 mg SoR	Cerebral hemorrhage (hemorrhagic stroke)	High fasting glucose (2xULN) High hsCRP (11xULN)	Day 319 (Maintenance)	12	Not suspected
Secukinumab off-treatment					
AIN457A2211E1-0084-00025§ 57/M/Ca AIN457 150 mg q4w	Intestinal ischemia, Hyperkalemia and renal failure	Hypertension, diabetes mellitus, dyslipidemia	Day 1041 (Extension)	32	Not suspected
AIN457A2211E1-0039-00001§ 64/M/Ca AIN457 150 mg q12w	Disseminated aspergillosis infection (Aspergillosis)	History of liver cirrhosis, 2 liver transplants within 5 days, use of infliximab	Day 436 (Post-study)	370	Not suspected**
Placebo to secukinumab off-treatment					
[AIN457A2302-3081008] 27/M/As Placebo-AIN457 300 mg	Unknown cause	Alcoholic liver disease, QTc prolonged	Day 285 (Post-study)	112	Not suspected
Placebo off-treatment					
[AIN457A2220-0050-00003] 53/M/Ca Placebo	Myocardial infarction (myocardial infarction)	Coronary bypass surgery, myocardial infarction and hypertension	Day 102 (Follow-up)	43	Not suspected
No treatment					
[A2303-3305-5004] (35/M/Ca) No treatment	Committed suicide (Complete suicide)	None reported	Screening period	Not applicable	Not suspected

PID = patient identification, 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
** Suspected per transplant surgeon involved although the investigator did not suspect a causal relation
§ Death was reported to Argus safety database after database lock for interim analysis of Study A2211E1.
Source: [SCS Appendix 1-Listing 15.2-1]; [Study A2220-Section 14.3.3]; [Study A2302-Section 14.3.3] ; [Study A2303-Section 14.3.3]; [SCS-Appendix 2]

Of the 6 deaths in psoriasis patients, none occurred during the induction periods of Pool A or Pool B. One of the six deaths was a completed suicide that occurred during the

screening period before any drug was administered. Of the remaining 5 deaths, all of which occurred during the post-induction period, there was/were:

- 1 on-treatment death for 150 mg secukinumab SoR (Start of Relapse, AIN457A2304-7055004), yielding a calculated incidence of on-treatment death in the Pool B entire treatment period of 0.03% (1/3430) for secukinumab vs. 0% (0/793) for placebo and 0% (0/323) for etanercept.
- 2 off-treatment deaths for 150 mg secukinumab
- 1 patient who switched from placebo to secukinumab 300 mg maintenance treatment died 3 weeks post-study
- 1 off-treatment death for a placebo patient.

Details of these six deaths are as follows:

- Patient [AIN457A2304-7055004]: a 66-year-old male patient in the 150 mg SoR secukinumab group, experienced vomiting, headache and loss of consciousness on Day 295 (12 days after the last dose of study medication), and was diagnosed with stroke (no confirmation by computed tomography (CT) scan or magnetic resonance imaging (MRI)). The patient died at Day 319; no autopsy was performed. The patient entered the study with approximately a 5-year history of psoriasis without PsA history. Prior to being randomized, his fasting blood glucose was 14.2 mmol/L (2.2-fold the upper limit of normal [ULN]) and his high sensitivity C-reactive protein (hsCRP) was 34.49 mg/L (11.5-fold the ULN), indicating an increased baseline risk of cardiovascular events. The investigator did not consider the death to be related to study treatment, and stated that the likely cause of death was hemorrhagic stroke. This death was adjudicated and confirmed as meeting the criteria of MACE.

- Patient [AIN457A2211E1-0084-0025] (Argus ID: PHHO2013FR009983): a 57-year-old male patient on secukinumab 150 mg monthly treatment. The patient had a medical history of arterial hypertension, diabetes mellitus, and dyslipidemia. 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 glomerular filtration rate (GFR) function test 2ml/min) and intestinal ischemia.

- Patient [AIN457A2211E1-0039-00001] (Argus ID: PHHO2012DE001274), 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 26-Oct-2009 (Day 1). On 7-Jul-2010 (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 (see narrative [AIN457A2211-0039-00001]). The patient started spironolactone for ascites on

03-Jul-2010 and then azathioprine for hepatitis on 28-Aug-2010. 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) . The patient was diagnosed with disseminated aspergillosis infection on 12-Jul-2011 and died from this infection on (b) (6) , (b) (6) 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 [AIN457A2302-3081008], a 27-year-old male with a 2-year history of alcoholic liver disease, received his first dose of the study medication (placebo) on 5-Jan-2012 (Day 1) and then switched to secukinumab 300 mg maintenance treatment on 30-Mar-2012 (Day 86). His last dose of study medication was on 26-Jun-2012 (Day 174). The patient discontinued study medication due to alcoholic liver disease. He died on (b) (6) ((b) (6) 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 [AIN457A2220-0050-00003] was a 53-year-old male patient who had a history of myocardial infarction (Oct 2002) and coronary artery bypass surgery (Dec 2002). The patient received his first dose of the study medication (placebo) on 02-Jun-2012 (Day 1) and his last dose of the study medication on 29-Jul-2012 (Day 58). At the end of the treatment phase on (b) (6) ((b) (6) 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 [AIN457A2303-3305004] died during the screening phase (complete suicide) and did not receive any study medication.

Reviewer's note – only one of these deaths appears to be a cardiovascular death (patient 7055004, who is thought to have suffered a hemorrhagic stroke). This event was adjudicated as a MACE event.

Deaths – other indications

10 deaths have been reported from non-psoriasis development programs up to the 31-Jul-2013 SCS cutoff: 6 from rheumatoid arthritis, 2 from ankylosing spondylitis, 1 from psoriatic arthropathy and 1 from uveitis studies. Eight deaths occurred on treatment and 2 off treatment. Seven cases (Argus PIDs: PHHO2012DE008210, PHHO2012DE017673,

PHHO2012RU015037, PHHO2012RU017835, PHHO2013AT001457, PHHO2013DE000828 and PHHO2013HU009637) remained blinded at the time of the data cutoff. The reported causes of death for these 7 cases were pulmonary embolism (1 case), complete suicide (1), lung carcinoma cell stage IV (1), gastric adenocarcinoma (1), acute myocardial infarction (1), intracranial venous sinus thrombosis (1), and cerebrovascular insufficiency/cerebral artery embolism/cardiopulmonary failure (1). None of these 7 deaths were considered by the investigator to be related to study medication. The other 3 deaths are summarized in the table below:

Table 2-10 Deaths in other indications

PID (Argus ID) Age/sex/race Dose (Indication)	Cause of death (Preferred term)	Risk factors	Day of death	No. days from last dose to onset*	Study drug related
On-treatment					
[AIN457C2303-0308-00005] (PHHO2010TR08607) 42/M/Ca AIN457 300 mg q4w (Uveitis)	Pulmonary thromboembolism (Pulmonary embolism)	Mitral valve disease, Behcet's disease, total femur prosthesis surgery	Day 128	15	Not suspected
AIN457F2302-1136003 (PHHO2012JP005952) 69/F/Ukn AIN457 150 mg (Rheumatoid arthritis)	Myocardial infarction (Myocardial infarction)	Hypertension, arteriosclerosis coronary artery; rheumatoid arthritis	(b) (6)	4	Suspected
Off-treatment					
[AIN457F2201-0309-00006] (PHHO2011RU07176) 63/F/Ca AIN457 25 mg (Rheumatoid arthritis)	Acute left ventricular failure (Acute left ventricular failure)	Hypertension, coronary artery disease	Day 422	166	Not suspected

PID = patient identification, M = male, F = female, Ca = Caucasian; UKn = unknown
*Day of onset=onset day of SAE leading to death or day of death
Source: [Study AIN457F2201-Section 14.3.3], [Study AIN457C2303-Section 14.3.3], [SCS-Appendix 2]

Details of these three deaths are as follows:

- Patient [AIN457C2303-0308-00005], a 42-year-old male with uveitis related to Behcet's disease, started the first dose of 300 mg secukinumab on 1-Feb-2010 (Day 1) and took the last dose on 24-May-2010 (Day 113). On 3-Jun-2010, the patient had a tonic-clonic seizure and a cranial MRI venography showed left transverse sinus thrombosis. The patient was treated with Clexan and antiepileptic (phenytoin and topiramate). On (b) (6) ((b) (6) days after the last dose of the study medication), the patient died of pulmonary embolism. The patient had a medical history of mitral valve disease, Behcet's disease and total femur prosthesis surgery 3 months prior to death. His concomitant medications included anticoagulant (Fragmin), anti-inflammatory drugs (Parol and Majezik) and digoxin.

- Patient AIN457F2302-1136003 (Argus ID: PHHO2012JP005952), a 69-year-old female with rheumatoid arthritis, started 150 mg secukinumab on 1-Nov-2011. Four days after the last dose of study medication on [redacted], the patient complained of malaise and was later found unconscious in a bathtub and subsequently died in the hospital. The diagnosis was myocardial infarction. The investigator could not rule out a causal relationship between the sudden death and study medication, and also commented that the patient had hypertension and possible presence of coronary artery stenosis prior to receiving the study medication. In addition, the patient had a long history of rheumatoid arthritis and increased risk of myocardial infarction.

- Patient [AIN457F2201-0309-00006], a 63-year-old female with rheumatoid arthritis, received the first dose of 25 mg secukinumab on 8-Dec-2009 and the last dose on 10-Nov-2010 (Day 338). On [redacted] days since the last dose of the study medication), the patient experienced cerebral infarction and was treated with magnesium, cytoflavin, dexonum, morphine, heparin, enalapril, indapamide and glycine. On [redacted] ([redacted] days since the last dose of the study medication), the patient died of acute left ventricular failure. The patient had a history of hypertension, coronary artery disease and atherosclerosis of carotids, and her concomitant medications included methotrexate, methylprednisolone and Nimesulide. The investigator considered the events were due to the progression of concomitant diseases (coronary artery disease and atherosclerosis of carotids).

CCV SAEs

SAEs by SOC for Pool A (induction period, safety set) are summarized in the following SCS table:

Table 2-11 SAEs by primary system organ class – Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)

Primary system organ class	AIN457 150 mg N=692 n (%)	AIN457 300 mg N=690 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)
Injury, poisoning and procedural complications	3 (0.4)	3 (0.4)	6 (0.43)	3 (0.4)	0 (0.0)
Gastrointestinal disorders	3 (0.4)	1 (0.1)	4 (0.29)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4)	1 (0.1)	4 (0.29)	0 (0.0)	0 (0.0)
Cardiac disorders	2 (0.3)	1 (0.1)	3 (0.22)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.1)	2 (0.3)	3 (0.22)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	3 (0.4)	0 (0.0)	3 (0.22)	0 (0.0)	0 (0.0)
Infections and infestations	1 (0.1)	1 (0.1)	2 (0.14)	2 (0.3)	0 (0.0)
Metabolism and nutrition disorders	1 (0.1)	1 (0.1)	2 (0.14)	0 (0.0)	0 (0.0)
Psychiatric disorders	2 (0.3)	0 (0.0)	2 (0.14)	2 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.3)	0 (0.0)	2 (0.14)	4 (0.6)	0 (0.0)
General disorders and administration site conditions	1 (0.1)	0 (0.0)	1 (0.07)	1 (0.1)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	0 (0.0)	1 (0.1)	1 (0.07)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.00)	1 (0.1)	0 (0.0)

Treatment-emergent SAEs are summarized.
Primary system organ classes are sorted in descending order of frequency in any AIN457 group.
Source: [SCS-Appendix 1-Table 10.1-5.1]

SAEs in the SOC of cardiac disorders were reported in 1 (0.1%) in the 300 mg group (acute myocardial infarction) and 2 (0.3%) patients in the 150 mg group (cardiac failure and congestive cardiac failure) but none for placebo or etanercept. One patient on placebo experienced the SAE of TIA. One patient on 300 mg AIN457 experienced the SAE of "fluid overload". Two patients on 150 mg AIN457 experienced pulmonary edema with details as follows:

- [AIN457A2302-20110004]- not adjudicated
  - Prior history of hypertension
  - Starting at Day 12, the patient developed dyspnea with an oxygen saturation (SpO2) between 88% and 90% He was also diagnosed with erythrodermic psoriasis and treated with cyclosporine
  - On Day 13 (06 Dec 2011), the patient's breathing difficulty became aggravated and pneumonia was suspected. His temperature was at 38° C, SpO2 was 76%. On Day 14 (07 Dec 2011), his PO2 was decreased to 36.6 Torr (mmHg), and PCO2 was at 29.5 Torr (mmHg). On Day (b) (6) ((b) (6)), the patient presented with bloody sputum which resulted in

hospitalization. The patient was diagnosed with cardiac failure and pulmonary edema by x-ray and computed chest tomography. On Day [redacted], the brain natriuretic peptide (BNP) was at 544.2 (units not reported). A cardiac ultrasonography on showed a mild tricuspid regurgitation, a right pressure gradient of 36 mmHg, a main pulmonary artery acceleration time (AT)/ejection time (ET) ratio of 0.35, good LV contraction, no pericardial effusion, no right sided cardiomegaly, no LV septal displacement. On Day [redacted], an electrocardiogram showed a heart rate of 79 bpm, a PR interval at 150 ms, a QRS duration of 88 ms, a QT/QTc interval 400/435ms. On Day [redacted] an echocardiography showed a circumferential pericardial effusion, no tamponed, and a good LV contraction. Treatment for the events included furosemide, Bi-level positive airway pressure (BiPAP), dextrose in Ringer's lactate, sivelestat, ranitidine, carperitide, pazufloxacin, heparin, and minocycline. The event pulmonary edema was considered resolved on Day [redacted], and the event erythrodermic psoriasis was considered resolved on Day [redacted]. The event heart failure was considered resolved on Day [redacted].

- Subject discontinued study treatment due to the events, which resolved with treatment.

- [AIN457A2309-8001006] – not adjudicated
  - 72 y/o male, current smoker, with h/o stable coronary artery disease and atrial fibrillation
  - On Day 25 (04 Jan 2013), in the induction period, the patient was diagnosed with congestive cardiac failure (NYHA class III). On Day [redacted], he experienced dyspnea and on the same day was hospitalized and diagnosed with pulmonary edema, pneumonia and ascites.
  - At the time of these events, the patient was also noted to have aortic valve stenosis, atrial fibrillation and flutter, cardiomegaly and post thrombotic syndrome. An EKG on the same day
  - [redacted] showed atrial fibrillation. On Day [redacted], ultrasonography revealed a pleural effusion (500 ml) and a CT scan on Day [redacted] confirmed pulmonary edema. On the same day [redacted], thoracentesis with ultrasonography was performed. Other treatment included digoxin, isosorbide mononitrate, spironolactone, acetylsalicylic acid, torasemide and human albumin for the congestive cardiac failure and cefuroxime for the pneumonia.
  - The congestive cardiac failure, ascites, cardiomegaly, pulmonary edema, pneumonia and post thrombotic syndrome were all considered resolved on Day [redacted] and the patient was discharged from the hospital on the same day.
  - The investigator did not suspect a relationship between the events and the study medication.
  - The patient withdrew consent and was discontinued from the study.

Similar trends were seen for the induction period of Pool B, as shown in the table below:

Table 2-13 SAEs by primary system organ class – Induction period (Pool B: All psoriasis trials – Safety set)

Primary system organ class	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
-Any SAE	22 (1.87)	23 (1.96)	62 (2.16)	13 (1.6)	3 (0.9)
Injury, poisoning and procedural complications	3 (0.26)	5 (0.43)	11 (0.38)	3 (0.4)	0 (0.0)
Cardiac disorders	4 (0.34)	2 (0.17)	10 (0.35)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (0.34)	2 (0.17)	8 (0.28)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.26)	3 (0.26)	7 (0.24)	0 (0.0)	0 (0.0)
Infections and infestations	2 (0.17)	1 (0.09)	6 (0.21)	2 (0.3)	0 (0.0)
Nervous system disorders	1 (0.09)	3 (0.26)	5 (0.17)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	4 (0.34)	0 (0.00)	5 (0.17)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.17)	1 (0.09)	5 (0.17)	5 (0.6)	0 (0.0)
Hepatobiliary disorders	1 (0.09)	2 (0.17)	3 (0.10)	0 (0.0)	1 (0.3)
Psychiatric disorders	3 (0.26)	0 (0.00)	3 (0.10)	2 (0.3)	0 (0.0)
Vascular disorders	2 (0.17)	0 (0.00)	3 (0.10)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (0.17)	0 (0.00)	2 (0.07)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	1 (0.09)	1 (0.09)	2 (0.07)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.0)	1 (0.3)
Investigations	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.00)	1 (0.09)	1 (0.03)	0 (0.0)	0 (0.0)

Table 2-14 Most frequent SAEs (>=0.10% in any group) by preferred term – Induction period (Pool B: All psoriasis trials – Safety set)

Preferred term	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
-Any SAE	22 (1.87)	23 (1.96)	62 (2.16)	13 (1.6)	3 (0.9)
Angina pectoris	1 (0.09)	0 (0.00)	3 (0.10)	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.0)	0 (0.0)
Overdose	1 (0.09)	1 (0.09)	2 (0.07)	1 (0.1)	0 (0.0)
Pulmonary edema	2 (0.17)	0 (0.00)	2 (0.07)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	1 (0.09)	0 (0.00)	1 (0.03)	1 (0.1)	0 (0.0)
Panic attack	1 (0.09)	0 (0.00)	1 (0.03)	1 (0.1)	0 (0.0)
Psoriasis	0 (0.00)	0 (0.00)	1 (0.03)	4 (0.5)	0 (0.0)
Transient ischemic attack	0 (0.00)	0 (0.00)	1 (0.03)	0 (0.0)	1 (0.3)
Abstains from alcohol	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Alcohol poisoning	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Alcohol withdrawal syndrome	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Calculus urethral	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Cellulitis	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.3)	0 (0.0)
Cholecystitis acute	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Dermatitis exfoliative	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Major depression	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Tendon injury	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)

Likewise, similar trends were seen in the exposure-adjusted data for the entire treatment period of Pool B, as seen in the Table below:

Table 2-15 Exposure-adjusted incidence of SAEs by primary system organ class – Entire treatment period (Pool B: All psoriasis trials – Safety set)

Primary system organ class	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
- Any SAE	76 (6.80)	85 (7.42)	207 (7.80)	15 (7.54)	20 (7.01)
Infections and infestations	12 (1.05)	16 (1.36)	40 (1.47)	2 (0.99)	4 (1.37)
Cardiac disorders	13 (1.14)	7 (0.60)	25 (0.92)	0 (0.00)	3 (1.03)
Injury, poisoning and procedural complications	3 (0.26)	15 (1.28)	23 (0.85)	3 (1.49)	3 (1.03)
Gastrointestinal disorders	9 (0.79)	7 (0.60)	21 (0.77)	0 (0.00)	0 (0.00)
Nervous system disorders	11 (0.97)	6 (0.51)	18 (0.66)	1 (0.50)	2 (0.68)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (0.53)	5 (0.43)	17 (0.63)	1 (0.50)	0 (0.00)
Skin and subcutaneous tissue disorders	5 (0.44)	6 (0.51)	16 (0.59)	5 (2.49)	1 (0.34)
Musculoskeletal and connective tissue disorders	5 (0.44)	7 (0.60)	15 (0.55)	0 (0.00)	4 (1.37)
Hepatobiliary disorders	5 (0.44)	5 (0.43)	11 (0.40)	0 (0.00)	1 (0.34)
Psychiatric disorders	6 (0.53)	4 (0.34)	11 (0.40)	2 (0.99)	0 (0.00)
Vascular disorders	5 (0.44)	5 (0.42)	11 (0.40)	0 (0.00)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	7 (0.61)	2 (0.17)	10 (0.37)	0 (0.00)	1 (0.34)
Renal and urinary disorders	3 (0.26)	5 (0.43)	9 (0.33)	0 (0.00)	1 (0.34)
Metabolism and nutrition disorders	4 (0.35)	3 (0.25)	7 (0.26)	0 (0.00)	0 (0.00)
General disorders and administration site conditions	3 (0.26)	1 (0.08)	4 (0.15)	1 (0.50)	0 (0.00)
Reproductive system and breast disorders	1 (0.09)	3 (0.26)	4 (0.15)	0 (0.00)	0 (0.00)
Ear and labyrinth disorders	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	0 (0.00)
Endocrine disorders	2 (0.18)	0 (0.00)	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	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	0 (0.00)
Blood and lymphatic system disorders	1 (0.09)	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Investigations	1 (0.09)	0 (0.00)	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)

Of note, for the entire treatment period of Pool B, there were 4 hypertensive crises and 3 syncopal events, all of which occurred with AIN457 therapy, as shown in the table below for SAE preferred terms (PTs) from the entire treatment period for Pool B:

Table 2-16 **Exposure adjusted incidence of the most frequent (>=0.10 per 100 patient years in any group) SAEs by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
-Any SAE	76 (6.80)	85 (7.42)	207 (7.80)	15 (7.54)	20 (7.01)
Pneumonia	3 (0.26)	3 (0.25)	6 (0.22)	0 (0.00)	0 (0.00)
Angina pectoris	2 (0.18)	1 (0.08)	5 (0.18)	0 (0.00)	0 (0.00)
Cellulitis	2 (0.18)	1 (0.08)	5 (0.18)	2 (0.99)	1 (0.34)
Abscess bacterial	3 (0.26)	0 (0.00)	4 (0.15)	0 (0.00)	0 (0.00)
Appendicitis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Coronary artery disease	1 (0.09)	1 (0.08)	4 (0.15)	0 (0.00)	0 (0.00)
Hypertensive crisis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Psoriasis	1 (0.09)	1 (0.08)	4 (0.15)	4 (1.99)	1 (0.34)
Sciatica	2 (0.18)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Angina unstable	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Arthralgia	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	1 (0.34)
Back pain	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Basal cell carcinoma	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cerebrovascular accident	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cholelithiasis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Colitis ulcerative	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Crohn's disease	2 (0.18)	0 (0.00)	3 (0.11)	0 (0.00)	0 (0.00)
Headache	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Nephrolithiasis	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Osteoarthritis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Pancreatitis	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Syncope	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Acute myocardial infarction	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Cholecystitis	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Concussion	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)

Hypoaesthesia	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Myocardial infarction	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	1 (0.34)
Overdose	1 (0.09)	1 (0.08)	2 (0.07)	1 (0.50)	0 (0.00)
Palpitations	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Pulmonary edema	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Rib fracture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Tendon rupture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Vomiting	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Acute tonsillitis	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.34)
Alcohol withdrawal syndrome	0 (0.00)	1 (0.08)	1 (0.04)	1 (0.50)	0 (0.00)
Arteriosclerosis coronary artery	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Bursitis	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Cholecystitis acute	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Ligament rupture	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Non-cardiac chest pain	1 (0.09)	0 (0.00)	1 (0.04)	1 (0.50)	0 (0.00)
Panic attack	1 (0.09)	0 (0.00)	1 (0.04)	1 (0.50)	0 (0.00)
Radius fracture	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Transient ischemic attack	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.50)	2 (0.68)
Abstains from alcohol	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Alcohol poisoning	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Benign neoplasm of skin	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Calculus urethral	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Cardiac arrest	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Clavicle fracture	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Dermatitis exfoliative	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Diverticulitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Interstitial lung disease	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Major depression	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Mitral valve incompetence	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Osteonecrosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Psoriatic arthropathy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Rotator cuff syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Tendon injury	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Thyrotoxic crisis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Urinary tract infection	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Viith nerve paralysis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)

MACE

Pool A (induction period)

- two adjudicated MACE events (1 MI, 1 CVA, both reported as SAEs)
- both in the 300 mg AIN457 group
- No MACE reported for placebo or entanercept.
- MACE incidence 0.3% for the 300 mg Dose

Pool B (induction period)

- 4 adjudicated MACE events (3 in the 300 mg AIN457 group, one in placebo

    - MACE cases in the 300 mg group consisted of acute myocardial infarction [AIN457A2308-6004004] and [AIN457A2304-5037008] and cerebrovascular accident [AIN457A2308-6017002]
    - Placebo MACE case - brain stem hemorrhage (patient AIN457A2211-0092001)
- No MACE reported for placebo or entanercept.
- MACE incidence 3 (0.3%) patients on 300 mg secukinumab and 1 (0.1%) patient on placebo.

Pool B (entire treatment period)

- Potential MACE cases over the entire treatment period were reported for similar proportions of patients on secukinumab and etanercept, which were higher than placebo: 6 (0.4%) for any 300 mg, 5 (0.4%) for any 150 mg and 1 (0.3%) for etanercept vs. 1 (0.1%) for placebo
- Potential MACE PTs included the following:
    - In the any 150 mg group, the 5 events were myocardial infarction, cerebrovascular accident, hemorrhagic stroke, ischemic stroke and Moyamoya disease.
    - In the any 300 mg group, the 6 events were myocardial infarction (n=2), acute myocardial infarction (n=2) and cerebrovascular accident (n=2).
    - In the placebo group, one patient had brain stem hemorrhage
    - In the etanercept group, one patient experienced myocardial infarction.
- The majority of potential MACE were reported as SAEs, except for 1 case in the any 300 mg group (myocardial infarction), 1 case in the any 150 mg group (moyamoya disease), and 1 case in the placebo group (brain stem hemorrhage).
- Five of the 6 cases in the any 300 mg group and the single case on placebo did not cause discontinuation. The discontinuation rate due to MACE was 0.1% (n=1) in the any 300 mg group (cerebrovascular accident), 0.2% (n=3) in the any 150 mg group (cerebrovascular accident, hemorrhagic stroke, ischemic stroke), and 0.3% (n=1) in the etanercept group (myocardial infarction)
- After adjusting for exposure over the 52 weeks, the incidence per 100 patient-years of potential MACE AEs was similar across the treatment groups (0.51, 0.44, 0.50 and 0.34, respectively, for any 300 mg, any 150 mg, placebo and etanercept)
- All but 2 cases (moyamoya disease in the any 150 mg group and myocardial infarction in the any 300 mg group) were confirmed as meeting the criteria of MACE.
- The incidence of adjudication-confirmed MACE was low and comparable between the secukinumab dose groups. There were 5 (0.4%) cases for any 300 mg on 1178 patient-years of exposure, 4 (0.3%) cases for any 150 mg on 1142 patient-years of exposure, 1 (0.1%) case for placebo on 201 patient-years of exposure, and 1 (0.3%) for etanercept on 293.5 patient- years of exposure
- The following table summarizes the Pool B adjudication results for MACE events during the entire treatment period:

Table 2-25 MACE adjudication results – Entire treatment period (Pool B: All psoriasis trials – Safety set)

MACE category Adjudication outcome	Any AIN457 150 mg N=1395 n (%)	Any AIN457 300 mg N=1410 n (%)	Any AIN457 dose N=3430 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
Myocardial infarction					
Yes	1 (0.07)	3 (0.21)	5 (0.15)*	0 (0.0)	1 (0.3)
Indeterminate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)
Stroke					
Yes	3 (0.22)	2 (0.14)	5 (0.15)	1 (0.1)	0 (0.0)
Indeterminate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)
Cardiovascular death					
Cardiovascular	1 (0.07)**	0 (0.00)	1 (0.03)**	0 (0.0)	0 (0.0)
Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)
Total no. MACE (Yes)#	4 (0.29)	5 (0.35)	10 (0.29)*	1 (0.1)	1 (0.3)

* Includes one patient AIN457A2211-0507005 treated with an alternate AIN457 150 mg regimen (early induction at Weeks 1, 2, 3 and 5, followed by AIN457 150 mg q4w).
** Death due to stroke
# Total MACE (Yes) is the sum of patients in the Myocardial infarction (Yes) and Stroke (Yes) rows; the cardiovascular death is also counted in the Stroke (Yes) row.
Source: [SCS-Appendix 1-Table 9.2-14.1]; [SCS-Appendix 5-CCV-AC Charter –Section 7.2]

Pool C (all trials, entire treatment period)

- The exposure-adjusted incidence of potential MACE AEs over the entire treatment period of all secukinumab trials (Pool C) was similar between the any secukinumab dose group and placebo (n=15, IR=0.42 for any secukinumab dose vs. n=2, IR=0.59 for placebo)
- Similar rates of MACE SAEs were also observed between the any secukinumab dose group and in Pool C (n=13, IR=0.36 for any secukinumab dose vs. n=1, IR=0.30 for placebo)

Reviewer's comment: The sponsor states the following:

> *There were additional cases identified for adjudication (see [SCS-Appendix 1-Listing 21.3-1]) but these were not considered in the pooled analysis because the event was either not treatment emergent or occurred during the follow-up period, was not reported to the clinical trial database by the designated data reporting cut-off date for pooling, or did not meet the definition of MACE as per NMQ criteria.*

Going to the listing cited above, the following listing was given for cases that were adjudicated but not included in the pooled analyses:

Listing 21.3-1 (Page 1 of 1)
Adjudicated MACE events: myocardial infarctions and strokes
(All secukinumab studies - Safety set)

Study/ Subject Identifier	Reported Term	MI or Stroke criteria met	Start Date	MI classification or Type of stroke	Was the reported term agreed?/ Specified term if No	Myocardial infarction or stroke	Adjudication committee decision
A2102/ 10055501	Myocardial Infarction	No	2007-05-14		No/CHF	MYOCARDIAL INFARCTION	CONSENSUS
A2206E1/ 00237132	Actue Myocardial Infarction	Indeterminate	2012-02-15			MYOCARDIAL INFARCTION	CONSENSUS
C2302/ 0652002	MI	No	2011-01-06		No/Myocarditis with VF arrest	MYOCARDIAL INFARCTION	CONSENSUS
F2201/ 0013017	Myocardial Infarction	Indeterminate	2010-10-10			MYOCARDIAL INFARCTION	CONSENSUS
F2201/ 0301006	Cerebrovascular accident/Lacunar infarction	Yes	2010-08-12	ISCHEMIC		STROKE	CONSENSUS
F2201/ 0309006	Cerebral infarction	Yes	2011-04-18	UNKNOWN		STROKE	CONSENSUS
F2201/ 0520003	Myocardial Infarction	Yes	2010-01-25	TYPE 1: SPONTANEOUS MI		MYOCARDIAL INFARCTION	CONSENSUS
F2206/ 0151010	Myocardial Infarction	Yes	2012-10-16	TYPE 1: SPONTANEOUS MI		MYOCARDIAL INFARCTION	CONSENSUS
F2206/ 0151020	Myocardial Infarction	Yes	2012-06-15	TYPE 1: SPONTANEOUS MI		MYOCARDIAL INFARCTION	CONSENSUS

For the last five entries (two strokes and three MIs), it is unclear what the rationale was for not including these cases in the pooled analyses, or what dose of drug was taken in each case.

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 by the sponsor to include events beyond myocardial infarction and stroke. Events identified by this expanded search were called CCV events. The NMQ definition set for this search included PTs from the following MedDRA SMQs:

- Myocardial infarction (broad SMQ)
- Central nervous system (CNS) hemorrhages and cerebrovascular conditions (broad SMQ)
- Cardiac failure (narrow SMQ)
- 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).

No new MACE events were identified using these expanded search terms for electronic queries of safety and clinical databases. The incidence of CCV AEs and SAEs for the induction period of Pool B is shown below, with a lower overall incidence of CCV events

in the AIN457 arms as compared to placebo and etanercept, and similar trends as were seen for the original MACE analysis for this cohort:

Table 2-29 Cardio-cerebrovascular-related events – Induction period (Pool B: all psoriasis studies – Safety set)

Level 1 Preferred term	AIN457 150 mg N=1174 n (%)	AIN457 300 mg N=1173 n (%)	Any AIN457 dose N=2877 n (%)	Placebo N=793 n (%)	Etanercept N=323 n (%)
Based on all AEs					
Cardio-cerebrovascular-related events (NMQ)	11 (0.94)	9 (0.77)	28 (0.97)	12 (1.5)	6 (1.9)
Atrioventricular block first degree (PT)	2 (0.17)	3 (0.26)	5 (0.17)	5 (0.6)	0 (0.0)
Angina pectoris (PT)	1 (0.09)	0 (0.00)	4 (0.14)	1 (0.1)	0 (0.0)
Coronary artery disease (PT)	0 (0.00)	0 (0.00)	4 (0.14)	0 (0.0)	0 (0.0)
Pulmonary edema (PT)	2 (0.17)	0 (0.00)	2 (0.07)	0 (0.0)	0 (0.0)
Cardiac failure congestive (PT)	1 (0.09)	0 (0.00)	2 (0.07)	0 (0.0)	0 (0.0)
Transient ischemic attack (PT)	1 (0.09)	0 (0.00)	2 (0.07)	0 (0.0)	1 (0.3)
Acute myocardial infarction (PT)	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles (PT)	1 (0.09)	1 (0.09)	2 (0.07)	0 (0.0)	0 (0.0)
Ventricular extrasystoles (PT)	1 (0.09)	1 (0.09)	2 (0.07)	0 (0.0)	0 (0.0)
Bundle branch block right (PT)	1 (0.09)	1 (0.09)	2 (0.07)	1 (0.1)	0 (0.0)
Cardiac failure (PT)	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Cerebrovascular accident (PT)	0 (0.00)	1 (0.09)	1 (0.03)	0 (0.0)	0 (0.0)
Myocardial ischemia (PT)	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Bundle branch block left (PT)	0 (0.00)	1 (0.09)	1 (0.03)	3 (0.4)	2 (0.6)
Atrial fibrillation (PT)	0 (0.00)	1 (0.09)	1 (0.03)	1 (0.1)	1 (0.3)
Peripheral arterial occlusive disease (PT)	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Arrhythmia (PT)	0 (0.00)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Angina unstable (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Dysarthria (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	1 (0.3)
Extrasystoles (PT)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Brain stem hemorrhage (PT)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Conduction disorder (PT)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	0 (0.0)
Based on SAEs					
Cardio-cerebrovascular-related events (NMQ)	3 (0.26)	3 (0.26)	11 (0.38)	0 (0.0)	1 (0.3)
Angina pectoris (PT)	1 (0.09)	0 (0.00)	3 (0.10)	0 (0.0)	0 (0.0)
Pulmonary edema (PT)	2 (0.17)	0 (0.00)	2 (0.07)	0 (0.0)	0 (0.0)
Acute myocardial infarction (PT)	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.0)	0 (0.0)
Coronary artery disease (PT)	0 (0.00)	0 (0.00)	2 (0.07)	0 (0.0)	0 (0.0)
Cardiac failure congestive (PT)	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Cardiac failure (PT)	1 (0.09)	0 (0.00)	1 (0.03)	0 (0.0)	0 (0.0)
Cerebrovascular accident (PT)	0 (0.00)	1 (0.09)	1 (0.03)	0 (0.0)	0 (0.0)
Transient ischemic attack (PT)	0 (0.00)	0 (0.00)	1 (0.03)	0 (0.0)	1 (0.3)
Atrial fibrillation (PT)	0 (0.00)	1 (0.09)	1 (0.03)	0 (0.0)	0 (0.0)

Exposure adjusted analysis of Pool B for the entire treatment period demonstrated similar trends in the incidence rates of these events, as shown in the table below:

Table 2-30 Exposure-adjusted incidence of most frequent (>=0.10 per 100 patient-years in any group) cardio-cerebrovascular-related events – Entire treatment period (Pool B: all psoriasis studies – Safety set)

Level 1 Preferred term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
Based on all AEs					
Cardio-cerebrovascular-related events (NMQ)	30 (2.65)	38 (3.27)	82 (3.04)	13 (6.54)	14 (4.86)
Atrioventricular block first degree (PT)	4 (0.35)	9 (0.77)	15 (0.55)	5 (2.49)	1 (0.34)
Coronary artery disease (PT)	2 (0.18)	2 (0.17)	8 (0.29)	0 (0.00)	0 (0.00)
Angina pectoris (PT)	3 (0.26)	2 (0.17)	8 (0.29)	1 (0.50)	1 (0.34)
Atrial fibrillation (PT)	3 (0.26)	3 (0.25)	7 (0.26)	1 (0.50)	1 (0.34)
Bundle branch block right (PT)	0 (0.00)	4 (0.34)	5 (0.18)	1 (0.50)	0 (0.00)
Sinus bradycardia (PT)	1 (0.09)	4 (0.34)	5 (0.18)	0 (0.00)	0 (0.00)
Bundle branch block left (PT)	0 (0.00)	4 (0.34)	4 (0.15)	3 (1.50)	3 (1.03)
Cardiac failure congestive (PT)	2 (0.18)	0 (0.00)	3 (0.11)	0 (0.00)	0 (0.00)
Myocardial infarction (PT)	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	1 (0.34)
Supraventricular extrasystoles (PT)	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	1 (0.34)
Ventricular extrasystoles (PT)	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	2 (0.68)
Cerebrovascular accident (PT)	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Arrhythmia (PT)	1 (0.09)	0 (0.00)	3 (0.11)	0 (0.00)	1 (0.34)
Angina unstable (PT)	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	1 (0.34)
Pulmonary edema (PT)	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Transient ischemic attack (PT)	1 (0.09)	0 (0.00)	2 (0.07)	1 (0.50)	2 (0.68)
Acute myocardial infarction (PT)	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Myocardial ischemia (PT)	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Arteriosclerosis coronary artery (PT)	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Conduction disorder (PT)	0 (0.00)	1 (0.08)	1 (0.04)	1 (0.50)	1 (0.34)
Dysarthria (PT)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Extrasystoles (PT)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Brain stem hemorrhage (PT)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Based on SAEs					
Cardio-cerebrovascular-related events (NMQ)	13 (1.14)	10 (0.85)	29 (1.07)	1 (0.50)	3 (1.02)
Angina pectoris (PT)	2 (0.18)	1 (0.08)	5 (0.18)	0 (0.00)	0 (0.00)
Coronary artery disease (PT)	1 (0.09)	1 (0.08)	4 (0.15)	0 (0.00)	0 (0.00)
Cerebrovascular accident (PT)	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Angina unstable (PT)	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Pulmonary edema (PT)	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Acute myocardial infarction (PT)	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Myocardial infarction (PT)	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	1 (0.34)
Transient ischemic attack (PT)	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.50)	2 (0.68)
Arteriosclerosis coronary artery (PT)	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)

Vital Signs

A fairly rudimentary analysis of vital signs was performed by defining criteria for notable vital sign abnormalities that were just above at the cutoffs for defining stage I blood pressure elevations and tachycardia, per the following table:

Table 4-1 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	≥ 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	≥ 90 mmHg or < 60 mmHg
Pulse (bpm)	> 100 bpm or < 60 bpm

The results of this analysis demonstrated slightly higher percentages of patients experiencing BP and pulse elevations on AIN457 therapy as compared to placebo, but these were similar to the Etanercept group of patients, as seen in the table below:

Table 4-2 Vital signs: number (%) of patients with newly occurring notable abnormalities – Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)

Vital signs Category	AIN457 150 mg N=692 n/m (%)	AIN457 300 mg N=690 n/m (%)	Any AIN457 dose N=1382 n/m (%)	Placebo N=694 n/m (%)	Etanercept N=323 n/m (%)
Systolic BP (mmHg)					
High only	135/544 (24.8)	152/555 (27.4)	287/1099 (26.11)	143/567 (25.2)	77/271 (28.4)
Low only	4/689 (0.6)	4/686 (0.6)	8/1375 (0.58)	1/691 (0.1)	2/319 (0.6)
High and Low	0/544 (0.0)	0/555 (0.0)	0/1099 (0.00)	0/566 (0.0)	0/269 (0.0)
Diastolic BP (mmHg)					
High only	137/577 (23.7)	155/586 (26.5)	292/1163 (25.11)	128/582 (22.0)	72/271 (26.6)
Low only	22/681 (3.2)	25/680 (3.7)	47/1361 (3.45)	26/684 (3.8)	14/318 (4.4)
High and Low	1/569 (0.2)	3/580 (0.5)	4/1149 (0.35)	1/574 (0.2)	0/268 (0.0)
Pulse (bpm)					
High only	33/682 (4.8)	25/681 (3.7)	58/1363 (4.26)	27/688 (3.9)	9/314 (2.9)
Low only	59/643 (9.2)	72/638 (11.3)	131/1281 (10.23)	53/635 (8.3)	32/309 (10.4)
High and Low	1/635 (0.2)	0/635 (0.0)	1/1270 (0.08)	0/631 (0.0)	1/303 (0.3)

BP=blood pressure
All BP and pulse rate measurements were taken in sitting position. Systolic blood pressure (BP): high: >=140 mmHg, low: <90 mmHg; Diastolic blood pressure (BP): high: >=90 mmHg, low: <60 mmHg; Pulse rate: high: >100 bpm, low: <60 bpm
Newly occurring – patients not meeting criterion at baseline and meeting criterion post-baseline
n=number of patients who meet the designated criterion
m=number of patients at risk for an abnormality with a non-missing value at baseline and post-baseline
Source: [SCS-Appendix 1-Table 12.1-1.1]

However, in the larger experience with the induction period of Pool B, the presence of a consistent BP and/or pulse effect was unimpressive:

Table 4-3 Vital signs: number (%) of patients with newly occurring notable abnormalities – Induction period (Pool B: All psoriasis trials – Safety set)

Vital signs Category	AIN457 150 mg N=1174 n/m (%)	AIN457 300 mg N=1173 n/m (%)	Any AIN457 dose N=2877 n/m (%)	Placebo N=793 n/m (%)	Etanercept N=323 n/m (%)
Systolic BP (mmHg)					
High only	225/928 (24.25)	246/934 (26.34)	586/2206 (26.56)	169/633 (26.7)	77/271 (28.4)
Low only	7/1169 (0.60)	5/1168 (0.43)	15/2775 (0.54)	1/778 (0.1)	2/319 (0.6)
High and Low	0/927 (0.00)	0/933 (0.00)	0/2203 (0.00)	0/631 (0.0)	0/269 (0.0)
Diastolic BP (mmHg)					
High only	224/983 (22.79)	256/988 (25.91)	587/2326 (25.24)	147/652 (22.5)	72/271 (26.6)
Low only	42/1153 (3.64)	39/1160 (3.36)	102/2744 (3.72)	29/770 (3.8)	14/318 (4.4)
High and Low	2/966 (0.21)	3/979 (0.31)	6/2292 (0.26)	1/642 (0.2)	0/268 (0.0)
Pulse (bpm)					
High only	50/1154 (4.33)	43/1154 (3.73)	105/2739 (3.83)	35/773 (4.5)	9/314 (2.9)
Low only	98/1102 (8.89)	100/1107 (9.03)	261/2615 (9.98)	57/716 (8.0)	32/309 (10.4)
High and Low	1/1085 (0.09)	0/1094 (0.00)	1/2578 (0.04)	0/709 (0.0)	1/303 (0.3)

BP=blood pressure
All BP and pulse rate measurements were taken in sitting position. Systolic blood pressure (BP): high: >=140 mmHg, low: <90 mmHg; Diastolic blood pressure (BP): high: >=90 mmHg, low: <60 mmHg; Pulse rate: high: >100 bpm, low: <60 bpm
Newly occurring – patients not meeting criterion at baseline and meeting criterion post-baseline
n=number of patients who meet the designated criterion
m=number of patients at risk for an abnormality with a non-missing value at baseline and post-baseline
Source: [SCS-Appendix 1-Table 12.2-1.1]

Electrocardiographic findings

TQT – not done

ECG Data Analysis

In clinical studies of secukinumab, standard 12-lead ECGs were performed at selected visits. The following ECG variables were summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc) using Bazett (QTcB) and Fridericia (QTcF) corrections. There is no evidence for important drug-induced prolongation of the QT interval or PR interval in the categorical analyses of the induction periods for Pool A and Pool B, as shown in the tables below:

Table 4-4 **Number (%) of patients with notably abnormal ECG parameters after baseline – Induction period (Pool A: Pivotal placebo-controlled psoriasis trials – Safety set)**

Criterion	AIN457 150 mg N=692 n/m (%)	AIN457 300 mg N=690 n/m (%)	Any AIN457 dose N=1382 n/m (%)	Placebo N=694 n/m (%)	Etanercept N=323 n/m (%)
QTcB > 500 msec	0/606 (0.0)	1/597 (0.2)	1/1203 (0.08)	0/600 (0.0)	0/266 (0.0)
QTcB > 480 msec	3/602 (0.5)	2/593 (0.3)	5/1195 (0.42)	6/598 (1.0)	0/264 (0.0)
QTcB > 450 msec	24/566 (4.2)	16/563 (2.8)	40/1129 (3.54)	30/555 (5.4)	10/253 (4.0)
QTcB changes from baseline > 30 msec	35/606 (5.8)	23/599 (3.8)	58/1205 (4.81)	34/600 (5.7)	16/266 (6.0)
QTcB changes from baseline > 60 msec	1/606 (0.2)	1/599 (0.2)	2/1205 (0.17)	3/600 (0.5)	0/266 (0.0)
QTcF > 500 msec	0/606 (0.0)	1/599 (0.2)	1/1205 (0.08)	0/600 (0.0)	0/266 (0.0)
QTcF > 480 msec	2/605 (0.3)	2/597 (0.3)	4/1202 (0.33)	2/599 (0.3)	0/265 (0.0)
QTcF > 450 msec	6/589 (1.0)	8/587 (1.4)	14/1176 (1.19)	13/587 (2.2)	6/261 (2.3)
QTcF changes from baseline > 30 msec	15/606 (2.5)	16/599 (2.7)	31/1205 (2.57)	22/600 (3.7)	9/266 (3.4)
QTcF changes from baseline > 60 msec	0/606 (0.0)	0/599 (0.0)	0/1205 (0.00)	0/600 (0.0)	0/266 (0.0)
PR > 250 msec	2/601 (0.3)	0/590 (0.0)	2/1191 (0.17)	0/597 (0.0)	1/265 (0.4)

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 did not meet the criterion at baseline
Source: [SCS-Appendix 1-Table 13.1-1.1]

Table 4-5 **Number (%) of patients with notably abnormal ECG parameters after baseline – Induction period (Pool B: All psoriasis trials – Safety set)**

Criterion	AIN457 150 mg N=1174 n/m (%)	AIN457 300 mg N=1173 n/m (%)	Any AIN457 dose N=2877 n/m (%)	Placebo N=793 n/m (%)	Etanercept N=323 n/m (%)
QTcB > 500 msec	1/1025 (0.10)	1/1033 (0.10)	2/2154 (0.09)	0/615 (0.0)	0/266 (0.0)
QTcB > 480 msec	4/1017 (0.39)	5/1021 (0.49)	10/2133 (0.47)	6/613 (1.0)	0/264 (0.0)
QTcB > 450 msec	49/946 (5.18)	29/963 (3.01)	80/2002 (4.00)	30/570 (5.3)	10/253 (4.0)
QTcB changes from baseline > 30 msec	50/1025 (4.88)	39/1035 (3.77)	96/2157 (4.45)	36/615 (5.9)	16/266 (6.0)
QTcB changes from baseline > 60 msec	3/1025 (0.29)	2/1035 (0.19)	5/2157 (0.23)	3/615 (0.5)	0/266 (0.0)
QTcF > 500 msec	0/1025 (0.00)	1/1035 (0.10)	1/2156 (0.05)	0/615 (0.0)	0/266 (0.0)
QTcF > 480 msec	3/1024 (0.29)	2/1032 (0.19)	5/2152 (0.23)	2/614 (0.3)	0/265 (0.0)
QTcF > 450 msec	12/1000 (1.20)	16/1011 (1.58)	30/2105 (1.43)	13/602 (2.2)	6/261 (2.3)
QTcF changes from baseline > 30 msec	26/1025 (2.54)	30/1035 (2.90)	66/2157 (3.06)	22/615 (3.6)	9/266 (3.4)
QTcF changes from baseline > 60 msec	0/1025 (0.00)	0/1035 (0.00)	0/2157 (0.00)	0/615 (0.0)	0/266 (0.0)
PR > 250 msec	2/1018 (0.20)	0/1022 (0.00)	3/2137 (0.14)	0/612 (0.0)	1/265 (0.4)

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 did not meet the criterion at baseline
Source: [SCS-Appendix 1-Table 13.2-1.1]

120 Day Safety Update

Four potential cases of MACE in plaque psoriasis studies were identified and referred for adjudication by the CCV-AC. There were three acute myocardial infarctions and one stroke. All were confirmed by the event committee. Three are known to be on AIN457, and for the other case, treatment is blinded. A summary of those events and the final adjudication determinations are shown in the following table:

Table 2-4 Overview of new MACE in plaque psoriasis studies

Study-center-patient (ARGUS code) Age/Sex/Race Treatment	SAE preferred term	SAE onset date / Time to onset*	Medical history or risk factors	Adjudication decision (Event type)	Outcome / Study drug relationship
A2211E1-0512-00008 [PHHO2013US010413] 61/M/Asian AIN457 150 mg	Acute myocardial infarction	04-Aug-2013 / 1085 days	Myocardial infarction, hypertension, coronary artery disease	Confirmed (Myocardial infarction)	Recovered with sequelae / Not suspected
A2309-4008-4008001 [PHHO2013US012153] 49/M/Caucasian Treatment blinded**	Myocardial infarction	23-Aug-2013 / 284 days	Hyperlipidemia, ruptured papillary heart muscle	Confirmed (Myocardial infarction)	Complete recovery / Not suspected
A2302E1-3135-3135011 [PHHO2013HU014391] 69/F/Caucasian AIN457 dose blinded	Ischemic stroke	10-Oct-2013 / 282 days	Diabetes mellitus, tachycardia, hypertension, thyroidectomy	Confirmed (Stroke)	Complete recovery / Not suspected
A2302E1-5018-5018022 [PHHO2013US013389] 63/M/Caucasian AIN457 dose blinded	Myocardial infarction	11-Oct-2013 / 253 days	Elevated LDL and total cholesterol #, current smoker, heavy exercise one week prior to onset	Confirmed (Myocardial infarction)	Complete recovery / Not suspected

* Time to onset = date from first dose of study medication to date of SAE onset as per ARGUS case report
** Patient was randomized to placebo at study start; treatment code remains blinded after Week 12.
# Elevated LDL and total cholesterol values at randomization in the core study A2302
Source: [SU-Appendix 2]; [SU-Appendix 3]

Reviewer's comment – this is somewhat difficult to interpret due to the fact that there are very few placebo patients left. The sponsor states that, "…no new SAEs were reported for placebo, as there were few ongoing placebo patients during the 120-Day SU reporting interval (7 placebo patients in Study A2223 as of 31-Jul-2013). The only other studies with placebo patients were A2302 and A2303; however, both studies completed the last patient last visit prior to the 120-Day SU reporting interval (30-Apr-2013 for A2302 and 08-Jun-2013 for A2303) and no new SAE reports from these 2 studies were expected for this SU. Treatment codes remained blinded after Week 12 for patients initially randomized to placebo in Studies A2308 and A2309."

Assessments

1. Is the Applicant's search and analyses adequate for assessing the cardiovascular safety for this product?

There are two elements to this question that need to be addressed separately. First is whether the trials were capable of generating adequate CCV safety data from which to draw conclusions. Second is whether the analytical assessment on the data that was generated was appropriate.

As far as the as ability of the datasets to address CCV safety, there are some limitations. To start with, the induction period of Pool A (placebo-controlled psoriasis trials) has about 700 patients in the 150 mg, 300mg, and placebo arms in trials of 12 weeks duration. The active treatment arms of the induction period for Pool B (all controlled psoriasis trials, 12 weeks duration) are a little larger, starting with 1174, 1173, and 793 patients in the 150 mg, 300 mg, and placebo arms respectively. While these sample sizes may have been inadequate to show statistically significant differences in MACE events between the groups, this was at least in part the result of the fact that MACE events occurred so infrequently in this fairly young population of psoriasis patients. Furthermore, it should be noted that the patient exposure years for the entire treatment period of pool B were 1142, 1178, and 201 for the 150mg, 300mg, and placebo-treated patients, respectively. Thus, the active drug exposure in this sponsor's psoriasis development program far exceeded the 771 patient exposure years for the anti-IL12/23 agents in the Ryan-2011 meta-analysis.

Another potential limitation was the high and asymmetrical number of dropouts. The entire treatment period for Pool B is the best data that is available to assess CV safety in the psoriasis population with respect to sample size and duration of exposure, but the dropout rate from the 52 week analysis was exceptional, with only about half the patients remaining in the active treatment arms at week 52, and fully 96.7% of the placebo patients having dropped out or switched to other therapies. These premature drops were not followed for safety outcomes until the end of the studies.

The analytical approach likewise had some limitations. None of these studies had a prespecified safety or efficacy endpoint measuring CV outcomes – this entire analysis is based on retrospective electronic NMQ/SMQ scanning of the datasets for specific sets of Preferred Term adverse event occurrences and death. Thus, incomplete ascertainment of CCV events may have occurred. However, it is unlikely that an important loss of MI, stroke, and death events occurred while patients were participating in the trials – the potential for lack of ascertainment of these types of events would have been reasonably expected to have been confined to the dropouts.

These things being said, we do think that the sponsor has done a very good job (as probably a good of job as can be done) defining patient pools to maximize exposure. Furthermore, the data was assessed with two different definition sets for CV adverse outcomes which produced similar results across three differently defined assessment periods. The inclusion of the etanercept control, albeit small (323 subjects), served as a benchmark for the safety of therapy with a biologic in this condition, though once again, the limited sample size, exposure times, and very small number of CCV events limit the conclusions that can be made regarding comparative cardiac safety between AIN457 and etanercept.

2. **Is dose-adjusted exposure analysis preferred for the 52+ wk comparison vs. incidence of events?**

   Yes. There were differing sample sizes between the active and placebo arms as well as differing durations of therapy for many patients as time progressed over the 52 weeks of follow-up. Placebo patients experienced high efficacy failure rates and dropout rates, and could be placed on active therapy in extension trials. Thus, the numbers of placebo patients became quite small. In this circumstance, the exposure-adjusted analyses of event rates are preferred.

3. **Please provide your assessment of cardiovascular safety and advise on whether you would recommend labeling or additional data/ analysis to better assess/describe cardiovascular safety.**

   In the context of the 2011 Ryan meta-analysis (which did not show a statistically significant harmful effect), the clustering of CCV SAEs in the active AIN457 treatment arms of the entire treatment period of Pool B was carefully examined, and that table is reproduced below for convenience:

Table 2-16 **Exposure adjusted incidence of the most frequent (>=0.10 per 100 patient years in any group) SAEs by preferred term – Entire treatment period (Pool B: All psoriasis trials – Safety set)**

Preferred Term	Any AIN457 150 mg N=1395 n (IR)	Any AIN457 300 mg N=1410 n (IR)	Any AIN457 dose N=3430 n (IR)	Placebo N=793 n (IR)	Etanercept N=323 n (IR)
-Any SAE	76 (6.80)	85 (7.42)	207 (7.80)	15 (7.54)	20 (7.01)
Pneumonia	3 (0.26)	3 (0.25)	6 (0.22)	0 (0.00)	0 (0.00)
Angina pectoris	2 (0.18)	1 (0.08)	5 (0.18)	0 (0.00)	0 (0.00)
Cellulitis	2 (0.18)	1 (0.08)	5 (0.18)	2 (0.99)	1 (0.34)
Abscess bacterial	3 (0.26)	0 (0.00)	4 (0.15)	0 (0.00)	0 (0.00)
Appendicitis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Coronary artery disease	1 (0.09)	1 (0.08)	4 (0.15)	0 (0.00)	0 (0.00)
Hypertensive crisis	1 (0.09)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Psoriasis	1 (0.09)	1 (0.08)	4 (0.15)	4 (1.99)	1 (0.34)
Sciatica	2 (0.18)	2 (0.17)	4 (0.15)	0 (0.00)	0 (0.00)
Angina unstable	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Arthralgia	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	1 (0.34)
Back pain	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Basal cell carcinoma	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cerebrovascular accident	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Cholelithiasis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Colitis ulcerative	1 (0.09)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Crohn's disease	2 (0.18)	0 (0.00)	3 (0.11)	0 (0.00)	0 (0.00)
Headache	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Nephrolithiasis	0 (0.00)	2 (0.17)	3 (0.11)	0 (0.00)	0 (0.00)
Osteoarthritis	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Pancreatitis	1 (0.09)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Syncope	2 (0.18)	1 (0.08)	3 (0.11)	0 (0.00)	0 (0.00)
Acute myocardial infarction	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Cholecystitis	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Concussion	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)

Hypoaesthesia	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Myocardial infarction	1 (0.09)	1 (0.08)	2 (0.07)	0 (0.00)	1 (0.34)
Overdose	1 (0.09)	1 (0.08)	2 (0.07)	1 (0.50)	0 (0.00)
Palpitations	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Pulmonary edema	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Rib fracture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Tendon rupture	0 (0.00)	2 (0.17)	2 (0.07)	0 (0.00)	0 (0.00)
Vomiting	2 (0.18)	0 (0.00)	2 (0.07)	0 (0.00)	0 (0.00)
Acute tonsillitis	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.34)
Alcohol withdrawal syndrome	0 (0.00)	1 (0.08)	1 (0.04)	1 (0.50)	0 (0.00)
Arteriosclerosis coronary artery	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Bursitis	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Cholecystitis acute	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Ligament rupture	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Non-cardiac chest pain	1 (0.09)	0 (0.00)	1 (0.04)	1 (0.50)	0 (0.00)
Panic attack	1 (0.09)	0 (0.00)	1 (0.04)	1 (0.50)	0 (0.00)
Radius fracture	0 (0.00)	1 (0.08)	1 (0.04)	0 (0.00)	1 (0.34)
Transient ischemic attack	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.50)	2 (0.68)
Abstains from alcohol	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Alcohol poisoning	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Benign neoplasm of skin	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Calculus urethral	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Cardiac arrest	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Clavicle fracture	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Dermatitis exfoliative	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Diverticulitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Interstitial lung disease	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Major depression	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Mitral valve incompetence	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Osteonecrosis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Psoriatic arthropathy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Rotator cuff syndrome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Tendon injury	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.50)	0 (0.00)
Thyrotoxic crisis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Urinary tract infection	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)
Viith nerve paralysis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)

It can be seen that non-MACE CCV events in the entire treatment period of Pool B occurred infrequently (1 or 2 occurrences at most) in the 150 and 300 mg active treatment arms, with some of these events occurring in the placebo and/or Etanercept arms as well. While the expression of the rates of these events in terms of patient years of exposure helps put their incidence into context with the placebo comparator, it does not correct for the near complete dropout of placebo patients during extended follow-up, which limits the number of patients available in the placebo arms to have events. Thus, there is not a convincing signal here for a CV safety concern, and we think that the CV safety of this product can be adequately described in labeling.

Additional DCRP Comments

- The sponsor states that the follow-up period for Studies A2302, A2303, A2304 and A2307 are not included in the CSRs and the SCS provided in this submission, and that data for the follow-up period, Weeks 52 to 60, will be described in separate study reports. When will those follow-up reports be submitted for review?

- This sponsor's vital sign analysis is limited with respect to assessing extreme shifts of blood pressure in the smaller number of potentially vulnerable patients. We note that the common AE analysis shows an excess of AEs in the vascular disorder SOC which was primarily due to a higher rate of hypertension in the 150 mg arm of Pool A. Furthermore, all four SAEs of hypertensive crisis that occurred in the entire treatment period of Pool B clustered in the AIN 457 treatment arms. Just to confirm the lack of any extreme BP effect in a small number of patients, shift tables between normal, stage I, and Stage II BPs, and K-M curves showing time to first BP above those cutoffs would be helpful.

- It is unclear what occurred with the two episodes of pulmonary edema that were reported within 30 days of starting study drug (see details of clinical courses, pages 27-28 of this review). Both of these subjects became very ill (one profoundly hypoxic, the other developed ascites). Both resolved when study drug was discontinued. There is no known mechanism by which a human antibody could cause such an effect. It is noted that one of these patients had preserved LV systolic function by echo and was treated with antibiotics (raising the possibility that this was pneumonia). The other patient had atrial fibrillation at baseline and developed ascites (suggesting pre-existing cardiac disease). It is unlikely that these cases represented drug-induced congestive heart failure (though we would be glad to review any other information that may be available regarding these two subjects).

  Of note, the sponsor reports that the two SAEs in the cardiac disorders SOC of Pool A on 150 mg AIN457 were these two cases. Furthermore, in the expanded SMQ search for CCV events, only two cases of cardiac failure or congestive cardiac failure were identified, and these were the same two patients as described above.

Appendix 1
Preferred terms used in MACE NMQs (from sponsor's CCV-AC Charter Appendix 1)

7.1 [Appendix 1] Pre-specified adverse events MedDRA terms related to MACE (MI, stroke and CV death)

Preferred terms for myocardial infarction	Preferred terms for stroke		Preferred terms for cardiovascular death
Acute myocardial infarction	Basal ganglia haemorrhage	Haemorrhage intracranial	Preferred terms with a fatal outcome that belong to SOC Cardiac disorders or SOC Vascular disorders
Coronary artery embolism	Basal ganglia infarction	Haemorrhagic cerebral infarction	
Coronary artery thrombosis	Basal ganglia stroke	Haemorrhagic stroke	
Myocardial infarction	Basilar artery thrombosis	Haemorrhagic transformation stroke	Preferred term "Death"
Papillary muscle infarction	Brain injury	Intracranial haematoma	
Post procedural myocardial infarction	Brain stem haemorrhage	Intraventricular haemorrhage	
Silent myocardial infarction	Brain stem infarction	Ischaemic cerebral infarction	
	Brain stem stroke	Ischaemic stroke	
	Brain stem thrombosis	Lacunar infarction	
	Carotid arterial embolus	Lateral medullary syndrome	
	Carotid artery thrombosis	Moyamoya disease	
	Central nervous system haemorrhage	Post procedural stroke	
	Cerebellar artery thrombosis	Putamen haemorrhage	
	Cerebellar embolism	Stroke in evolution	
	Cerebellar haematoma	Thalamic infarction	
	Cerebellar haemorrhage	Thalamus haemorrhage	
	Cerebellar infarction	Thrombotic cerebral infarction	
	Cerebral artery embolism	Thrombotic stroke	
	Cerebral artery thrombosis	Wallenberg syndrome	
	Cerebral haematoma		
	Cerebral haemorrhage		
	Cerebral infarction		
	Cerebral thrombosis		
	Cerebral venous thrombosis		
	Cerebrovascular accident		
	Embolic cerebral infarction		
	Embolic stroke		

Appendix 2
MACE Event Definitions for CCV-AC (from sponsor's CCV-AC Appendix-2)

7.2 [Appendix 2] Definitions of MACE categories for the Committee

The categorization of MACE-related cardiovascular and cerebrovascular events:

- Myocardial infarction
- Stroke (ischemic/hemorrhagic)
- Cardiovascular death

The above events will be categorised as detailed below:

With the exception of ECG-detected myocardial infarction, when an adverse event is submitted to the Committee that specifically states a coronary, cerebrovascular, or cardiovascular death event, the Committee will assign one of the following categories to the reported event.

- No: Information available, including clinical symptoms and ancillary testing, is unlikely or definitely not consistent with the diagnosis of one of the MACE.
- Yes: Clinical symptoms and ancillary testing (lab/ECG/radiography) are definitely or probably consistent with the diagnosis of one of the MACE.
- Unknown/indeterminate: There is insufficient information currently available to adjudicate this event.

Further clarification: Adjudicators will adhere to the MACE definitions outlined in the Charter. However, they will have flexibility to determine if the reported event is probably MACE, even if those criteria are not strictly met with the available information. If this is the determination, they will check "Yes".

Definitions of categories for adjudication:

7.2.1 Definition of Myocardial Infarction

Acute Myocardial Infarction: the term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI.

Spontaneous MI: Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
  - ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points:

BLA 125504

7 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
05/01/2014

THOMAS A MARCINIAK
05/01/2014

NORMAN L STOCKBRIDGE
05/01/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125-504 **Applicant:** Novartis Pharmaceuticals Corporation **Stamp Date:** October 24, 2013

Drug Name: Cosentyx (secukinumab) powder for solution, solution for injection **NDA Type:** S

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			Two doses (150mg and 300mg) were studied in one phase 2 study and the two pivotal safety and efficacy studies. Additionally, maintenance dosing was evaluated comparing a fixed dose regimen and treatment on start of

	Content Parameter	Yes	No	NA	Comment
					relapse.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: A randomized, double-blind, placebo controlled multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, and to assess the safety, tolerability and longterm efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis. (ERASURE) (2302) Indication: Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy Pivotal Study #2: A randomized, double-blind, double-dummy, placebo controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, compared to placebo and etanercept, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis. (FIXTURE) (2303) Indication: Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	X			Two pivotal safety and efficacy studies appear adequate for review.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Pivotal studies were conducted globally. Study 2302 in Argentina, Canada, Colombia, Estonia, Iceland, Israel, Japan, Latvia, Lithuania, Mexico, Taiwan, United States; Study 2303 in Argentina, Australia, Belgium, Canada, Colombia, Egypt, Finland, France, Germany, Guatemala, Hungary,

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	Content Parameter	Yes	No	NA	Comment
					Iceland, India, Italy, Republic of Korea, Philippines, Poland, Romania, Singapore, Spain, Sweden, United Kingdom, United States This will be a review issue.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		X		The Division had requested the following which was not provided: A summary of reported adverse events for autoimmune diseases. Include both systemic (e.g. lupus, vasculitis, sarcoidosis, antiphospholipid syndrome and inflammatory myopathies) and organ-specific (e.g. interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis, psoriasis, inflammatory bowel disease and autoimmune hepatitis) autoimmune processes.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			No TQT study was conducted as is consistent for large molecules and agreed to by the Agency
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

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	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Study2302: Treatment-emergent adverse events (AEs) were coded using MedDRA version 15.1 Study2303: Treatment-emergent adverse events (AEs) were coded using MedDRA version 16.0
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant is seeking agreement on the design of the deferred psoriasis study with secukinumab for ages 6 to less than 18 years of age and a waiver for the treatment of psoriasis in pediatric patients with secukinumab who are less than 6 years of age
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the		X		

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A; Application is fileable from a clinical perspective

Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

Provide a summary of reported adverse events for autoimmune diseases or provide the location of this information in the current submission. Include both systemic (e.g. lupus, vasculitis, sarcoidosis, antiphospholipid syndrome and inflammatory myopathies) and organ-specific (e.g. interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis, psoriasis, inflammatory bowel disease and autoimmune hepatitis) autoimmune processes.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY S WOITACH
12/06/2013

DAVID L KETTL
12/06/2013