

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125504Orig1s001

Trade Name: COSENTYX

Generic or Proper Name: secukinumab

Sponsor: Novartis

Approval Date: 01/15/2016

Indication: COSENTYX is a human interleukin-17A antagonist indicated for the treatment of:

- moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
- adults with active psoriatic arthritis (PsA)
- adults with active ankylosing spondylitis (AS).

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125504Orig1s001

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



BLA 125504/S-001and S-002

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
One Health Plaza
Building 125/2nd Floor
East Hanover, NJ 07936-1080

Attention: Kristine Ogozalek, MS
Drug Regulatory Affairs, Integrated Hospital Care

Dear Ms. Ogozalek:

Please refer to your supplemental Biologics License Applications (sBLA) dated March 18 and 23, 2015, received March 18 and 23, 2015, submitted under section 351(a) of the Public Health Service Act for Cosentyx (secukinumab).

These Prior Approval supplemental biologics applications provide for the following two new indications: Psoriatic Arthritis (PsA)(S-001) and Ankylosing Spondylitis (AS)(S-002).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below/indicated in the enclosed labeling.

1. Remove the % sign from the cell in the bottom row, far right column of table 4.
2. Add a space between week and 16 in the last row, far left column of table 5 and table 7.

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for these applications because necessary studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Laura Musse, Regulatory Health Project Manager, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

SARAH K YIM
01/15/2016
Signing for Badrul Chowdhury, M.D., Ph.D.

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COSENTYX safely and effectively. See full prescribing information for COSENTYX.

COSENTYX® (secukinumab) injection, for subcutaneous use
COSENTYX® (secukinumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2, 1.3)	X/201X
Dosage and Administration (2.1, 2.2, 2.3, 2.4)	X/201X
Warnings and Precautions (5.1, 5.3)	X/201X

INDICATIONS AND USAGE

COSENTYX is a human interleukin-17A antagonist indicated for the treatment of:

- moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. (1.1)
- adults with active psoriatic arthritis (PsA). (1.2)
- adults with active ankylosing spondylitis (AS). (1.3)

DOSAGE AND ADMINISTRATION

Plaque Psoriasis

- Recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable. (2.1)

Psoriatic Arthritis

- For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosage and administration for plaque psoriasis (2.1)
- For other psoriatic arthritis patients administer with or without a loading dosage. The recommended dosage:
 - With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
 - Without a loading dosage is 150 mg every 4 weeks
 - If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg. (2.2)

Ankylosing Spondylitis

- Administer with or without a loading dosage. The recommended dosage:
 - With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
 - Without a loading dosage is 150 mg every 4 weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

- **Injection:** 150 mg/mL solution in a single-use Sensoready® pen (3)
- **Injection:** 150 mg/mL solution in a single-use prefilled syringe (3)
- **For Injection:** 150 mg, lyophilized powder in a single-use vial for reconstitution for healthcare professional use only (3)

CONTRAINDICATIONS

Serious hypersensitivity reaction to secukinumab or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- **Infections:** Serious infections have occurred. Caution should be exercised when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue COSENTYX until the infection resolves. (5.1)
- **Tuberculosis (TB):** Prior to initiating treatment with COSENTYX, evaluate for TB. (5.2)
- **Inflammatory Bowel Disease:** Cases of inflammatory bowel disease were observed in clinical trials. Caution should be exercised when prescribing COSENTYX to patients with inflammatory bowel disease. (5.3)
- **Hypersensitivity Reactions:** If an anaphylactic reaction or other serious allergic reaction occurs, discontinue COSENTYX immediately and initiate appropriate therapy. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (>1%) are nasopharyngitis, diarrhea, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Live Vaccines:** Live vaccines should not be given with COSENTYX. (5.6, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: January/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

COSENTYX[®] is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

1.2 Psoriatic Arthritis

COSENTYX is indicated for the treatment of adult patients with active psoriatic arthritis.

1.3 Ankylosing Spondylitis

COSENTYX is indicated for the treatment of adult patients with active ankylosing spondylitis.

2 DOSAGE AND ADMINISTRATION

2.1 Plaque Psoriasis

The recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. Each 300 mg dosage is given as 2 subcutaneous injections of 150 mg.

For some patients, a dosage of 150 mg may be acceptable.

2.2 Psoriatic Arthritis

For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis [*see Dosage and Administration (2.1)*].

For other psoriatic arthritis patients, administer COSENTYX with or without a loading dosage by subcutaneous injection. The recommended dosage:

- With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
- Without a loading dosage is 150 mg every 4 weeks
- If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg.

COSENTYX may be administered with or without methotrexate.

2.3 Ankylosing Spondylitis

Administer COSENTYX with or without a loading dosage by subcutaneous injection. The recommended dosage:

- With a loading dosage is 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
- Without a loading dosage is 150 mg every 4 weeks.

2.4 Assessment Prior to Initiation of COSENTYX

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX [*see Warnings and Precautions (5.2)*].

2.5 Important Administration Instructions

There are three presentations for COSENTYX (i.e., Sensoready pen, prefilled syringe, and lyophilized powder in vial for reconstitution). The COSENTYX “Instructions for Use” for each presentation contains more detailed instructions on the preparation and administration of COSENTYX [*see Instructions for Use*].

COSENTYX is intended for use under the guidance and supervision of a physician. Patients may self-inject after proper training in subcutaneous injection technique using the Sensoready pen or prefilled syringe and when deemed appropriate. The lyophilized powder for reconstitution is for healthcare provider use only. Administer each injection at a different anatomic location (such as upper arms, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, indurated, or affected by psoriasis. Administration of COSENTYX in the upper, outer arm may be performed by a caregiver or healthcare provider.

2.6 Preparation for Use of COSENTYX Sensoready[®] Pen and Prefilled Syringe

Before injection, remove COSENTYX Sensoready pen or COSENTYX prefilled syringe from the refrigerator and allow COSENTYX to reach room temperature (15 to 30 minutes) without removing the needle cap.

The removable cap of the COSENTYX Sensoready pen and the COSENTYX prefilled syringe contains natural rubber latex and should not be handled by latex-sensitive individuals [see *Warnings and Precautions* (5.5)].

Inspect COSENTYX visually for particulate matter and discoloration prior to administration. COSENTYX injection is a clear to slightly opalescent, colorless to slightly yellow solution. Do not use if the liquid contains visible particles, is discolored or cloudy. COSENTYX does not contain preservatives; therefore, administer the Sensoready pen or prefilled syringe within 1 hour after removal from the refrigerator. Discard any unused product remaining in the Sensoready pen or prefilled syringe.

2.7 Reconstitution and Preparation of COSENTYX Lyophilized Powder

COSENTYX lyophilized powder should be prepared and reconstituted with Sterile Water for Injection by a trained healthcare provider using aseptic technique and without interruption. The preparation time from piercing the stopper until end of reconstitution on average takes 20 minutes and should not exceed 90 minutes.

- a) Remove the vial of COSENTYX lyophilized powder from the refrigerator and allow to stand for 15 to 30 minutes to reach room temperature. Ensure the Sterile Water for Injection is at room temperature.
- b) Slowly inject 1 mL of Sterile Water for Injection into the vial containing COSENTYX lyophilized powder and direct the stream of Sterile Water for Injection onto the lyophilized powder.
- c) Tilt the vial at an angle of approximately 45 degrees and gently rotate between the fingertips for approximately 1 minute. Do not shake or invert the vial.
- d) Allow the vial to stand for about 10 minutes at room temperature to allow for dissolution. Note that foaming may occur.
- e) Tilt the vial at an angle of approximately 45 degrees and gently rotate between the fingertips for approximately 1 minute. Do not shake or invert the vial.
- f) Allow the vial to stand undisturbed at room temperature for approximately 5 minutes. The reconstituted COSENTYX solution should be essentially free of visible particles, clear to opalescent, and colorless to slightly yellow. Do not use if the lyophilized powder has not fully dissolved or if the liquid contains visible particles, is cloudy or discolored.
- g) Prepare the required number of vials (1 vial for the 150 mg dose or 2 vials for the 300 mg dose).
- h) The COSENTYX reconstituted solution contains 150 mg of secukinumab in 1 mL of solution. After reconstitution, use the solution immediately or store in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours. Do not freeze.
- i) If stored at 2°C to 8°C (36°F to 46°F), allow the reconstituted COSENTYX solution to reach room temperature (15 to 30 minutes) before administration. COSENTYX does not contain preservatives; therefore, administer within 1 hour after removal from 2°C to 8°C (36°F to 46°F) storage.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 150 mg/mL solution in a single-use Sensoready pen
- Injection: 150 mg/mL solution in a single-use prefilled syringe
- For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution (for healthcare professional use only)

4 CONTRAINDICATIONS

COSENTYX is contraindicated in patients with a previous serious hypersensitivity reaction to secukinumab or to any of the excipients [see *Warnings and Precautions* (5.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

COSENTYX may increase the risk of infections. In clinical trials, a higher rate of infections was observed in COSENTYX treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (1.2% versus 0.3%) were observed with COSENTYX compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis [see *Adverse Reactions* (6.1)]. The incidence of some types of infections appeared to be dose-dependent in clinical studies [see *Adverse Reactions* (6.1)].

Exercise caution when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and COSENTYX should be discontinued until the infection resolves.

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 COSENTYX should be monitored closely for signs and symptoms of active TB during and after treatment.

5.3 Inflammatory Bowel Disease

Caution should be used when prescribing COSENTYX to patients with inflammatory bowel disease. Exacerbations, in some cases serious, occurred in COSENTYX treated patients during clinical trials in plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX. In an exploratory study in 59 patients with active Crohn's disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease [*see Adverse Reactions (6.1)*].

5.4 Hypersensitivity Reactions

Anaphylaxis and cases of urticaria occurred in COSENTYX treated patients in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of COSENTYX should be discontinued immediately and appropriate therapy initiated [*see Adverse Reactions (6.1)*].

5.5 Risk of Hypersensitivity in Latex-sensitive Individuals

The removable cap of the COSENTYX Sensoready pen and the COSENTYX prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. The safe use of COSENTYX Sensoready pen or prefilled syringe in latex-sensitive individuals has not been studied.

5.6 Vaccinations

Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with COSENTYX should not receive live vaccines.

Non-live vaccinations received during a course of COSENTYX may not elicit an immune response sufficient to prevent disease.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Infections [*see Warnings and Precautions (5.1)*]
- Inflammatory Bowel Disease [*see Warnings and Precautions (5.3)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plaque Psoriasis

A total of 3430 plaque psoriasis subjects were treated with COSENTYX in controlled and uncontrolled clinical trials. Of these, 1641 subjects were exposed for at least 1 year.

Four placebo-controlled phase 3 trials in plaque psoriasis subjects were pooled to evaluate the safety of COSENTYX in comparison to placebo up to 12 weeks after treatment initiation, in Trials 1, 2, 3, and 4. In total, 2077 subjects were

evaluated (691 to COSENTYX 300 mg group, 692 to COSENTYX 150 mg group, and 694 to placebo group) [see *Clinical Studies (14)*].

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the COSENTYX groups than the placebo group during the 12-week placebo-controlled period of the placebo-controlled trials.

Table 1 Adverse Reactions Reported by Greater Than 1% of Subjects with Plaque Psoriasis Through Week 12 in Trials 1, 2, 3, and 4

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)

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: sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, impetigo, otitis media, otitis externa, inflammatory bowel disease, increased liver transaminases, and neutropenia.

Infections

In the placebo-controlled period of the clinical trials in plaque psoriasis (a total of 1382 subjects treated with COSENTYX and 694 subjects treated with placebo up to 12 weeks), infections were reported in 28.7% of subjects treated with COSENTYX compared with 18.9% of subjects treated with placebo. Serious infections occurred in 0.14% of patients treated with COSENTYX and in 0.3% of patients treated with placebo [see *Warnings and Precautions (5.1)*].

Over the entire treatment period (a total of 3430 plaque psoriasis subjects treated with COSENTYX for up to 52 weeks for the majority of subjects), infections were reported in 47.5% of subjects treated with COSENTYX (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of subjects treated with COSENTYX (0.015 per patient-year of follow-up).

Phase 3 data showed an increasing trend for some types of infection with increasing serum concentration of secukinumab. Candida infections, herpes viral infections, staphylococcal skin infections, and infections requiring treatment increased as serum concentration of secukinumab increased.

Neutropenia was observed in clinical trials. Most cases of secukinumab-associated neutropenia were transient and reversible. No serious infections were associated with cases of neutropenia.

Inflammatory Bowel Disease

Cases of inflammatory bowel disease, in some cases serious, were observed in clinical trials with COSENTYX. In the plaque psoriasis program, with 3430 patients exposed to COSENTYX over the entire treatment period for up to 52 weeks (2,725 patient-years), there were 3 cases (0.11 per 100 patient-years) of exacerbation of Crohn's disease, 2 cases (0.08 per

100 patient-years) of exacerbation of ulcerative colitis, and 2 cases (0.08 per 100 patient-years) of new onset ulcerative colitis. There were no cases in placebo patients (N=793; 176 patient-years) during the 12 week placebo-controlled period.

One case of exacerbation of Crohn's disease was reported from long-term non-controlled portions of ongoing clinical trials in plaque psoriasis [see *Warnings and Precautions* (5.3)].

Hypersensitivity Reactions

Anaphylaxis and cases of urticaria occurred in COSENTYX treated patients in clinical trials [see *Warnings and Precautions* (5.4)].

Psoriatic Arthritis

COSENTYX was studied in two placebo controlled psoriatic arthritis trials with 1003 patients (703 patients on COSENTYX and 300 patients on placebo). Of the 703 patients who received COSENTYX, 299 patients received a subcutaneous loading dose of COSENTYX (PsA1) and 404 patients received an intravenous loading dose of secukinumab (PsA2) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period of the trials in patients with psoriatic arthritis, the overall proportion of patients with adverse events was similar in the secukinumab and placebo-treatment groups (59% and 58%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the COSENTYX groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia. The safety profile observed in patients with psoriatic arthritis treated with COSENTYX is consistent with the safety profile in psoriasis.

Similar to the clinical trials in patients with psoriasis, there was an increased proportion of patients with infections in the COSENTYX groups (29%) compared to placebo group (26%) [see *Warnings and Precautions* (5.1)].

There were cases of Crohn's disease and ulcerative colitis that include patients who experienced either exacerbations or the development of new disease. There were three cases of inflammatory bowel disease, of which two patients received secukinumab and one received placebo [see *Warnings and Precautions* (5.3)].

Ankylosing Spondylitis

COSENTYX was studied in two placebo controlled ankylosing spondylitis trials with 590 patients (394 patients on COSENTYX and 196 patients on placebo). Of the 394 patients who received COSENTYX, 145 patients received a subcutaneous load of COSENTYX (study AS1) and 249 received an intravenous loading dose of secukinumab (study AS2) followed by COSENTYX administered by subcutaneous injection every four weeks. During the 16-week placebo-controlled period of the trials in patients with ankylosing spondylitis, the overall proportion of patients with adverse events was higher in the secukinumab groups than the placebo-treatment groups (66% and 59%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the COSENTYX groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, nausea, and upper respiratory tract infection. The safety profile observed in patients with ankylosing spondylitis treated with COSENTYX is consistent with the safety profile in psoriasis.

Similar to clinical trials in patients with psoriasis, there was an increased proportion of patients with infections in the COSENTYX groups (31%) compared to the placebo group (18%) [see *Warnings and Precautions* (5.1)].

In the ankylosing spondylitis program, with 571 patients exposed to COSENTYX there were 8 cases of inflammatory bowel disease during the entire treatment period (5 Crohn's (0.7 per 100 patient-years) and 3 ulcerative colitis (0.4 per 100 patient-years)). During the placebo-controlled 16-week period, there were 2 Crohn's disease exacerbations and 1 new onset ulcerative colitis case that was a serious adverse event in patients treated with COSENTYX compared to none of the patients treated with placebo. During the remainder of the study when all patients received COSENTYX, 1 patient developed Crohn's disease, 2 patients had Crohn's exacerbations, 1 patient developed ulcerative colitis, and 1 patient had an ulcerative colitis exacerbation [see *Warnings and Precautions* (5.3)].

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The immunogenicity of COSENTYX was evaluated using an electrochemiluminescence-based bridging immunoassay. Less than 1% of subjects treated with COSENTYX developed antibodies to secukinumab in up to 52 weeks of treatment. However, this assay has limitations in detecting anti-secukinumab antibodies in the presence of secukinumab; therefore the incidence of antibody development might not have been reliably determined. Of the subjects who developed antidrug antibodies, approximately one-half had antibodies that were classified as neutralizing. Neutralizing antibodies were not associated with loss of efficacy.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to COSENTYX with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

Drug interaction trials have not been conducted with COSENTYX.

7.1 Live Vaccines

Patients treated with COSENTYX may not receive live vaccinations [*see Warnings and Precautions (5.6)*].

7.2 Non-Live Vaccines

Patients treated with COSENTYX may receive non-live vaccinations. Healthy individuals who received a single 150 mg dose of COSENTYX 2 weeks prior to vaccination with a non-U.S. approved group C meningococcal polysaccharide conjugate vaccine and a non-U.S. approved inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive COSENTYX prior to vaccination. The clinical effectiveness of meningococcal and influenza vaccines has not been assessed in patients undergoing treatment with COSENTYX [*see Warnings and Precautions (5.6)*].

7.3 CYP450 Substrates

A role for IL-17A in the regulation of CYP450 enzymes has not been reported. The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF α , IFN) during chronic inflammation. Thus, COSENTYX, an antagonist of IL-17A, could normalize the formation of CYP450 enzymes. 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well controlled trials of COSENTYX in pregnant women. Developmental toxicity studies conducted with monkeys found no evidence of harm to the fetus due to secukinumab. COSENTYX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryofetal development study was performed in cynomolgus monkeys with secukinumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys that were administered secukinumab weekly by the subcutaneous route during the period of organogenesis at doses up to 30 times the maximum recommended human dose (MRHD; on a mg/kg basis at a maternal dose of 150 mg/kg).

A pre- and postnatal development toxicity study was performed in mice with a murine analog of secukinumab. No treatment related effects on functional, morphological or immunological development were observed in fetuses from pregnant mice that were administered the murine analog of secukinumab on gestation days 6, 11, and 17 and on postpartum days 4, 10, and 16 at doses up to 150 mg/kg/dose.

8.3 Nursing Mothers

It is not known whether secukinumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when COSENTYX is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of COSENTYX in pediatric patients have not been evaluated.

8.5 Geriatric Use

Of the 3430 plaque psoriasis subjects exposed to COSENTYX in clinical trials, a total of 230 were 65 years or older, and 32 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 years and older was not sufficient to determine whether they responded differently from younger subjects.

10 OVERDOSAGE

Doses up to 30 mg/kg intravenously have been administered in clinical trials without dose-limiting toxicity. In the event of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Secukinumab is a recombinant human monoclonal IgG1/ κ antibody that binds specifically to IL-17A. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Secukinumab has a molecular mass of approximately 151 kDa; both heavy chains of secukinumab contain oligosaccharide chains.

COSENTYX Injection

COSENTYX injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. COSENTYX is supplied in a single-use Sensoready pen with a 27-gauge fixed ½-inch needle, or a single-use prefilled syringe with a 27-gauge fixed ½-inch needle. The removable cap of the COSENTYX Sensoready pen or prefilled syringe contains natural rubber latex.

Each COSENTYX Sensoready pen or prefilled syringe contains 150 mg of secukinumab formulated in: L-histidine/histidine hydrochloride monohydrate (3.103 mg), L-methionine (0.746 mg), polysorbate 80 (0.2 mg), trehalose dihydrate (75.67 mg), and Sterile Water for Injection, USP, at pH of 5.8.

COSENTYX for Injection

COSENTYX for injection is supplied as a sterile, preservative free, white to slightly yellow, lyophilized powder in single-use vials. Each COSENTYX vial contains 150 mg of secukinumab formulated in L-histidine/histidine hydrochloride monohydrate (4.656 mg), polysorbate 80 (0.6 mg), and sucrose (92.43 mg). Following reconstitution with 1 mL Sterile Water for Injection, USP, the resulting pH is approximately 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.

12.2 Pharmacodynamics

Elevated levels of IL-17A are found in psoriatic plaques. Treatment with COSENTYX may reduce epidermal neutrophils and IL-17A levels in psoriatic plaques. Serum levels of total IL-17A (free and secukinumab-bound IL-17A) measured at Week 4 and Week 12 were increased following secukinumab treatment. These pharmacodynamic activities are based on small exploratory studies. The relationship between these pharmacodynamic activities and the mechanism(s) by which secukinumab exerts its clinical effects is unknown.

Increased numbers of IL-17A producing lymphocytes and innate immune cells and increased levels of IL-17A have been found in the blood of patients with psoriatic arthritis and ankylosing spondylitis.

12.3 Pharmacokinetics

The PK properties of secukinumab observed in psoriatic arthritis and ankylosing spondylitis patients were similar to the PK properties displayed in plaque psoriasis patients.

Absorption

Following a single subcutaneous dose of either 150 mg (one-half the recommended dose) or 300 mg in plaque psoriasis patients, secukinumab reached peak mean (\pm SD) serum concentrations (C_{max}) of 13.7 ± 4.8 mcg/mL and 27.3 ± 9.5 mcg/mL, respectively, by approximately 6 days post dose.

Following multiple subcutaneous doses of secukinumab, the mean (\pm SD) serum trough concentrations of secukinumab ranged from 22.8 ± 10.2 mcg/mL (150 mg) to 45.4 ± 21.2 mcg/mL (300 mg) at Week 12. At the 300 mg dose at Week 4 and Week 12, the mean trough concentrations resulted from the Sensoready pen were 23% to 30% higher than those from the lyophilized powder and 23% to 26% higher than those from the prefilled syringe based on cross-study comparisons.

Steady-state concentrations of secukinumab were achieved by Week 24 following the every 4 week dosing regimens. The mean (\pm SD) steady-state trough concentrations ranged from 16.7 ± 8.2 mcg/mL (150 mg) to 34.4 ± 16.6 mcg/mL (300 mg).

In healthy subjects and subjects with plaque psoriasis, secukinumab bioavailability ranged from 55% to 77% following subcutaneous dose of 150 mg (one-half the recommended dose) or 300 mg.

Distribution

The mean volume of distribution during the terminal phase (V_z) following a single intravenous administration ranged from 7.10 to 8.60 L in plaque psoriasis patients. Intravenous use is not recommended [see *Dosage and Administration (2)*].

Secukinumab concentrations in interstitial fluid in lesional and non-lesional skin of plaque psoriasis patients ranged from 27% to 40% of those in serum at 1 and 2 weeks after a single subcutaneous dose of secukinumab 300 mg.

Elimination

The metabolic pathway of secukinumab has not been characterized. As a human IgG1 κ monoclonal antibody secukinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The mean systemic clearance (CL) ranged from 0.14 L/day to 0.22 L/day and the mean half-life ranged from 22 to 31 days in plaque psoriasis subjects following intravenous and subcutaneous administration across all psoriasis trials. Intravenous use is not recommended [see *Dosage and Administration (2)*].

Dose Linearity

Secukinumab exhibited dose-proportional pharmacokinetics in subjects with psoriasis over a dose range from 25 mg (approximately 0.083 times the recommended dose) to 300 mg following subcutaneous administrations.

Weight

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

Specific Populations

Hepatic or Renal Impairment:

No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of secukinumab was conducted.

Age: Geriatric Population:

Population pharmacokinetic analysis indicated that the clearance of secukinumab was not significantly influenced by age in adult subjects with plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. Subjects who are 65 years or older had apparent clearance of secukinumab similar to subjects less than 65 years old.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of COSENTYX. Some published literature suggests that IL-17A directly promotes cancer cell invasion in vitro, whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male and female mice that were administered a murine analog of secukinumab at subcutaneous doses up to 150 mg/kg once weekly prior to and during the mating period.

14 CLINICAL STUDIES

14.1 Plaque Psoriasis

Four multicenter, randomized, double-blind, placebo-controlled trials (Trials 1, 2, 3, and 4) enrolled 2403 subjects (691 randomized to COSENTYX 300 mg, 692 to COSENTYX 150 mg, 694 to placebo, and 323 to a biologic active control) 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score greater than or equal to 12, and who were candidates for phototherapy or systemic therapy.

- Trial 1 enrolled 738 subjects (245 randomized to COSENTYX 300 mg, 245 to COSENTYX 150 mg, and 248 to placebo). Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to COSENTYX received 300 mg or 150 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the

same dose every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 were then crossed over to receive COSENTYX (either 300 mg or 150 mg) at Weeks 12, 13, 14, 15, and 16 followed by the same dose every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.

- Trial 2 enrolled 1306 subjects (327 randomized to COSENTYX 300 mg, 327 to COSENTYX 150 mg, 326 to placebo, and 323 to a biologic active control). COSENTYX and placebo data are described. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to COSENTYX received 300 mg or 150 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 then crossed over to receive COSENTYX (either 300 mg or 150 mg) at Weeks 12, 13, 14, 15, and 16 followed by the same dose every 4 weeks. All subjects were followed for up to 52 weeks following first administration of study treatment.
- Trial 3 enrolled 177 subjects (59 randomized to COSENTYX 300 mg, 59 to COSENTYX 150 mg, and 59 to placebo) and assessed safety, tolerability, and usability of COSENTYX self-administration via prefilled syringe for 12 weeks. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks for up to 12 weeks total.
- Trial 4 enrolled 182 subjects (60 randomized to COSENTYX 300 mg, 61 to COSENTYX 150 mg, and 61 to placebo) and assessed safety, tolerability, and usability of COSENTYX self-administration via Sensoready pen for 12 weeks. Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks for up to 12 weeks total.

Endpoints

In all trials, the endpoints were the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline to Week 12 and treatment success (clear or almost clear) on the Investigator’s Global Assessment modified 2011 (IGA). Other evaluated outcomes included the proportion of subjects who achieved a reduction in PASI score of at least 90% (PASI 90) from baseline at Week 12, maintenance of efficacy to Week 52, and improvements in itching, pain, and scaling at Week 12 based on the Psoriasis Symptom Diary[®].

The PASI is a composite score that takes into consideration both the percentage of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling). The IGA is a 5-category scale including “0 = clear”, “1 = almost clear”, “2 = mild”, “3 = moderate” or “4 = severe” indicating the physician’s overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of “clear” or “almost clear” consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque, and none to minimal focal scaling.

Baseline Characteristics

Across all treatment groups the baseline PASI score ranged from 11 to 72 with a median of 20 and the baseline IGA score ranged from “moderate” (62%) to “severe” (38%). Of the 2077 plaque psoriasis subjects who were included in the placebo-controlled trials, 79% were biologic-naïve (have never received a prior treatment with biologics) and 45% were non-biologic failures (failed to respond to a prior treatment with non-biologics therapies). Of the patients who received a prior treatment with biologics, over one-third were biologic failures. Approximately 15% to 25% of trial subjects had a history of psoriatic arthritis.

Clinical Response

The results of Trials 1 and 2 are presented in Table 2.

Table 2 Clinical Outcomes at Week 12 in Adults with Plaque Psoriasis in Trials 1 and 2

	Trial 1			Trial 2		
	COSENTYX 300 mg (N=245) n (%)	COSENTYX 150 mg (N=245) n (%)	Placebo (N=248) n (%)	COSENTYX 300 mg (N=327) n (%)	COSENTYX 150 mg (N=327) n (%)	Placebo (N=326) n (%)
PASI 75 response	200 (82)	174 (71)	11 (4)	249 (76)	219 (67)	16 (5)
IGA of clear or almost clear	160 (65)	125 (51)	6 (2)	202 (62)	167 (51)	9 (3)

The results of Trials 3 and 4 are presented in Table 3.

Table 3 Clinical Outcomes at Week 12 in Adults with Plaque Psoriasis in Trials 3 and 4

	Trial 3			Trial 4		
	COSENTYX 300 mg (N=59) n (%)	COSENTYX 150 mg (N=59) n (%)	Placebo (N=59) n (%)	COSENTYX 300 mg (N=60) n (%)	COSENTYX 150 mg (N=61) n (%)	Placebo (N=61) n (%)
	PASI 75 response	44 (75)	41 (69)	0 (0)	52 (87)	43 (70)
IGA of clear or almost clear	40 (68)	31 (53)	0 (0)	44 (73)	32 (52)	0 (0)

Examination of age, gender, and race subgroups did not identify differences in response to COSENTYX among these subgroups. Based on post-hoc sub-group analyses in patients with moderate to severe psoriasis, patients with lower body weight and lower disease severity may achieve an acceptable response with COSENTYX 150 mg.

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.

With continued treatment over 52 weeks, subjects in Trial 1 who were PASI 75 responders at Week 12 maintained their responses in 81% (161/200) of the subjects treated with COSENTYX 300 mg and in 72% (126/174) of subjects treated with COSENTYX 150 mg. Trial 1 subjects who were clear or almost clear on the IGA at Week 12 also maintained their responses in 74% (119/160) of subjects treated with COSENTYX 300 mg and in 59% (74/125) of subjects treated with COSENTYX 150 mg. Similarly in Trial 2, PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with COSENTYX 300 mg and in 82% (180/219) of subjects treated with COSENTYX 150 mg. Trial 2 subjects who were clear or almost clear on the IGA also maintained their responses in 80% (161/202) of subjects treated with COSENTYX 300 mg and in 68% (113/167) of subjects treated with COSENTYX 150 mg.

Among the subjects who chose to participate (39%) in assessments of patient reported outcomes, improvements in signs and symptoms related to itching, pain, and scaling, at Week 12 compared to placebo (Trials 1 and 2) were observed using the Psoriasis Symptom Diary[®].

14.2 Psoriatic Arthritis

The safety and efficacy of COSENTYX were assessed in 1003 patients, in 2 randomized, double-blind, placebo-controlled studies (PsA1 and PsA2) in adult patients, age 18 years and older with active psoriatic arthritis (greater than 3 swollen and greater than 3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of PsA of at least 5 years across both studies. At baseline, over 62% and 47% of the patients had enthesitis and dactylitis, respectively. Overall, 32% of patients discontinued previous treatment with anti-TNF α agents due to either lack of efficacy or intolerance. In addition, approximately 55% of patients from both studies had concomitant methotrexate (MTX) use. Patients with different subtypes of PsA were enrolled including polyarticular arthritis with no evidence of rheumatoid nodules (80%), asymmetric peripheral arthritis (62%), distal interphalangeal involvement (59%), spondylitis with peripheral arthritis (20%) and arthritis mutilans (7%).

PsA1 Study evaluated 397 patients, who were treated with COSENTYX 75 mg, 150 mg or 300 mg subcutaneous treatment at Weeks 0, 1, 2, 3 and 4, followed by the same dose every 4 weeks. Patients receiving placebo were re-randomized to receive COSENTYX (either 150 mg or 300 mg every 4 weeks) at Week 16 or Week 24 based on responder status. The primary endpoint was the percentage of patients achieving an ACR20 response at Week 24.

PsA2 Study evaluated 606 patients, who were treated with secukinumab 10 mg/kg, intravenous treatment (or placebo) at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg subcutaneous COSENTYX treatment (or placebo) every 4 weeks. Patients receiving placebo were re-randomized to receive COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status.

Clinical Response

In PsA1, patients treated with 150 mg or 300 mg COSENTYX demonstrated a greater clinical response including ACR20, ACR50, and ACR 70 compared to placebo at Week 24 (Table 4). Responses were similar in patients regardless of concomitant methotrexate treatment. Responses were seen regardless of prior anti-TNF α exposure.

In patients with coexistent plaque psoriasis receiving COSENTYX (n=99), the skin lesions of psoriasis improved with treatment, relative to placebo, as measured by the Psoriasis Area Severity Index (PASI).

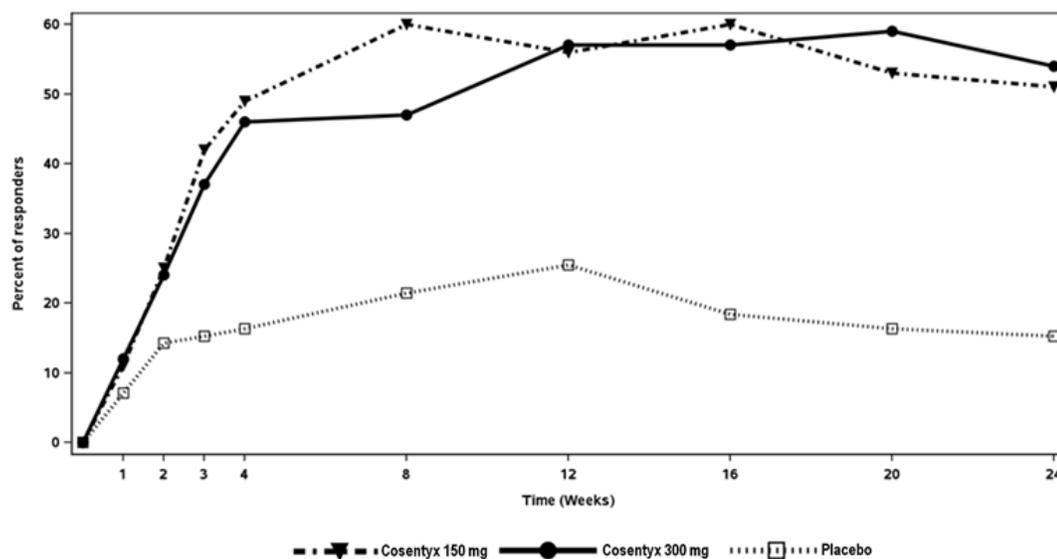
Table 4 Responses^a in PsA1 Study at Week 16 and Week 24

	COSENTYX 150 mg (N=100)	COSENTYX 300 mg (N=100)	Placebo (N=98)	Difference from placebo (95% CI)	
				COSENTYX 150 mg	COSENTYX 300 mg
ACR20 response					
Week 16 (%)	60	57	18	42 (30, 54)	38 (26, 51)
Week 24 (%)	51	54	15	36 (24, 48)	39 (27, 51)
ACR50 response					
Week 16 (%)	37	35	6	31 (21, 42)	28 (18, 39)
Week 24 (%)	35	35	7	28 (18, 38)	28 (17, 38)
ACR70 response					
Week 16 (%)	17	15	2	15 (7, 23)	13 (5, 20)
Week 24 (%)	21	20	1	20 (12, 28)	19 (11, 27)

^a Patients who met escape criteria (less than 20% improvement in tender or swollen joint counts) at Week 16 were considered non-responders

The percentage of patients achieving ACR20 response by visit is shown in Figure 1. Patients on placebo who received COSENTYX without a loading regimen achieved similar ACR20 responses over time (data not shown).

Figure 1 Percent of Patients Achieving ACR 20 Response^a in PsA1 Study Through Week 24



^a Patients who met escape criteria (less than 20% improvement in tender or swollen joint counts) at Week 16 were considered non-responders

The improvements in the components of the ACR response criteria are shown in Table 5.

Table 5 Mean Change from Baseline in ACR Components at Week 16^a (PsA1 Study)

	COSENTYX 150 mg (N=100)	COSENTYX 300 mg (N=100)	Placebo (N=98)
No. of Swollen Joints			
Baseline	12.0	11.2	12.1
Mean change at Week 16	-4.86	-5.83	-3.22
Number of Tender Joints			
Baseline	24.1	20.2	23.5
Mean change at Week 16	-10.70	-10.01	-1.77
Patient's assessment of Pain			
Baseline	58.9	57.7	55.4
Mean change at Week 16	-22.91	-23.97	-7.98
Patient Global Assessment			
Baseline	62.0	60.7	57.6
Mean change at Week 16	-25.47	-25.40	-8.25
Physician Global Assessment			
Baseline	56.7	55.0	55.0
Mean change at Week 16	-29.24	-34.71	-14.95
Disability Index (HAQ)			
Baseline	1.2200	1.2828	1.1684
Mean change at Week 16	-0.45	-0.55	-0.23
CRP (mg/L)			
Baseline	14.15	10.88	7.87
Mean Change at Week 16 ^b	-8.41	-7.21	0.79

^a Week 16 rather than Week 24 data are displayed to provide comparison between arms prior to placebo escape to COSENTYX.

^b Mean Change based upon observed data

Improvements in enthesitis and dactylitis scores were observed in each COSENTYX group compared to placebo at Week 24.

Physical Function and Health Related Quality of Life

Improvement in physical function as assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) demonstrated that the proportion of patients who achieved at least -0.3 improvement in HAQ-DI score from baseline was greater in the COSENTYX 150 mg and 300 mg groups compared to placebo at Week 16 and 24. At Week 16 in PsA1 study, estimated mean change from baseline was -0.23 in the placebo group compared with -0.45 in the COSENTYX 150 mg group and -0.55 in the COSENTYX 300 mg group.

14.3 Ankylosing Spondylitis

The safety and efficacy of COSENTYX were assessed in 590 patients in two randomized, double-blind, placebo-controlled studies (AS1 and AS2) in adult patients 18 years of age and older with active ankylosing spondylitis. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) greater or equal to 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. At baseline, approximately 14 % and 26% used concomitant methotrexate or sulfasalazine, respectively. Overall, 33% of patients discontinued previous treatment with anti-TNF α agents due to either lack of efficacy or intolerance.

AS1 Study evaluated 219 patients, who were treated with COSENTYX 75 mg or 150 mg subcutaneous treatment at Weeks 0, 1, 2, 3 and 4, followed by the same dose every 4 weeks. At Week 16, patients receiving placebo were re-randomized to either COSENTYX 75 mg or 150 mg every 4 weeks. The primary endpoint was the percentage of patients achieving an ASAS20 response at Week 16.

AS2 Study evaluated 371 patients, who were treated with secukinumab 10 mg/kg intravenous treatment at Weeks 0, 2, and 4 (for both treatment arms) or placebo, followed by either 75 mg or 150 mg subcutaneous COSENTYX treatment every 4 weeks or placebo. Patients receiving placebo were re-randomized to receive COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status.

Clinical Response

In AS1, patients treated with 150 mg COSENTYX demonstrated greater improvements in ASAS 20 and ASAS 40 responses compared to placebo at Week 16 (Table 6). Responses were similar in patients regardless of concomitant therapies.

Table 6 ASAS20 and ASAS40 Responses in All AS Patients at Week 16 in Study AS1

	COSENTYX 150 mg (n = 72)	Placebo (n = 74)	Difference from placebo (95% CI)
ASAS20 response, %	61	28	33 (18, 48)
ASAS40 response, %	36	11	25 (12, 38)

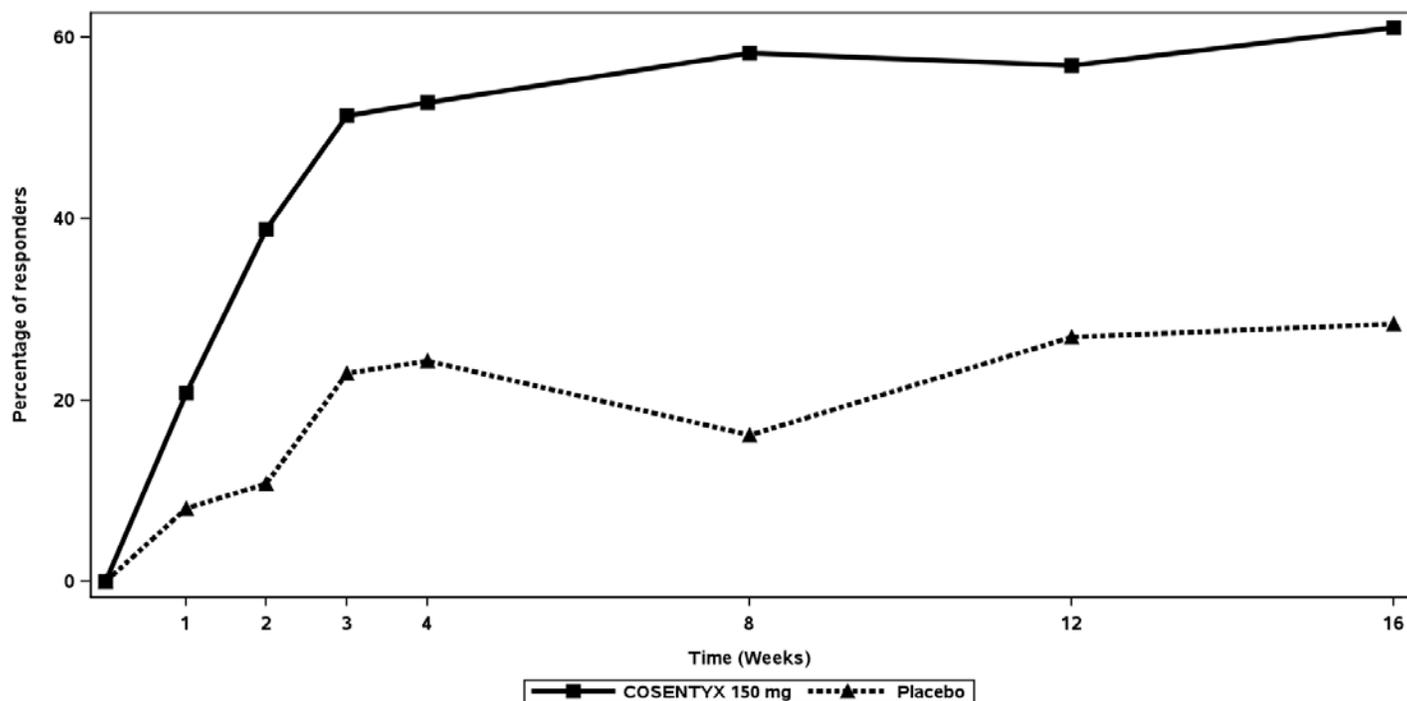
The improvements in the main components of the ASAS20 response criteria and other measures of disease activity are shown in Table 7.

Table 7 ASAS20 Components and Other Measures of Disease Activity at Week 16 (AS1 Study)

	COSENTYX 150 mg (N = 72)		Placebo (N = 74)	
	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline
ASAS20 Response criteria				
-Patient Global Assessment of Disease Activity (0-100 mm) ¹	67.5	-27.7	70.5	-12.9
-Total spinal pain (0-100 mm)	66.2	-28.5	69.2	-10.9
-BASFI (0-10) ²	6.2	-2.2	6.1	-0.7
-Inflammation (0-10) ³	6.5	-2.5	6.5	-0.8
BASDAI Score⁴	6.6	-2.2	6.8	-0.9
BASMI⁵	3.6	-0.51	3.9	-0.22
hsCRP⁶ (mg/L) Mean Change at Week 16	27.0	-17.2	15.9	0.8
1. Percent of subjects with at least a 20% and 10 unit improvement measured on a Visual Analog Scale (VAS) with 0= none, 100= severe 2. Bath Ankylosing Spondylitis Functional Index 3. Inflammation is the mean of two patient-reported stiffness self-assessment in BASDAI 4. Bath Ankylosing Spondylitis Disease Activity Index 5. Bath Ankylosing Spondylitis Metrology Index 6. High sensitivity C-reactive protein / mean change based upon observed data				

The percent of patients achieving ASAS 20 responses by visit is shown in Figure 2. Patients on placebo who received COSENTYX without a loading regimen achieved similar ASAS20 responses over time (data not shown).

Figure 2 ASAS20 Responses in all AS1 Study Patients Over Time Up to Week 16



COSENTYX treated patients showed improvement compared to placebo-treated patients in health-related quality of life as assessed by ASQoL at Week 16.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

COSENTYX Sensoready pen:

- NDC 0078-0639-41: Carton of two 150 mg/mL (300 mg dose) Sensoready pens (injection)
- NDC 0078-0639-68: Carton of one 150 mg/mL single-use Sensoready pen (injection)

COSENTYX prefilled syringe:

- NDC 0078-0639-98: Carton of two 150 mg/mL (300 mg dose) single-use prefilled syringes (injection)
- NDC 0078-0639-97: Carton of one 150 mg/mL single-use prefilled syringe (injection)

The removable cap of the COSENTYX Sensoready pen and prefilled syringe contains natural rubber latex. Each Sensoready pen and prefilled syringe is equipped with a needle safety guard.

COSENTYX vial (for healthcare professional use only):

- NDC 0078-0657-61: Carton of one 150 mg lyophilized powder in a single-use vial (for injection)

16.2 Storage and Handling

COSENTYX Sensoready pens, prefilled syringes and vials must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep the product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming do not shake. COSENTYX does not contain a preservative; discard any unused portion.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling [*Medication Guide and Instructions for Use*].

Patient Counseling

Instruct patients to read the Medication Guide before starting COSENTYX therapy and to reread the Medication Guide each time the prescription is renewed.

Advise patients of the potential benefits and risks of COSENTYX.

Infections

Inform patients that COSENTYX may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the doctor and contacting their doctor if they develop any symptoms of infection [*see Warnings and Precautions (5.1)*].

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [*see Warnings and Precautions (5.4)*].

Instruction on Injection Technique

Perform the first self-injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer COSENTYX, instruct him/her in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of COSENTYX [*see Medication Guide and Instructions for Use*].

Instruct patients or caregivers in the technique of proper syringe and needle disposal, and advise them not to reuse these items. Instruct patients to inject the full amount of COSENTYX (1 or 2 subcutaneous injections of 150 mg) according to the directions provided in the Medication Guide and Instructions for Use. Dispose of needles, syringes and pens in a puncture-resistant container.

Manufactured by:

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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MEDICATION GUIDE

COSENTYX® (koe-sen'-tix)
(secukinumab) Injection

What is the most important information I should know about COSENTYX?

COSENTYX is a medicine that affects your immune system. COSENTYX may increase your risk of having serious side effects such as:

Infections. COSENTYX may lower the ability of your immune system to fight infections and may increase your risk of infections.

- Your healthcare provider should check you for tuberculosis (TB) before starting treatment with COSENTYX.
- If your healthcare provider feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with COSENTYX and during treatment with COSENTYX.
- Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with COSENTYX. **Do not take COSENTYX if you have an active TB infection.**

Before starting COSENTYX, tell your healthcare provider if you:

- are being treated for an infection
- have an infection that does not go away or that keeps coming back
- have TB or have been in close contact with someone with TB
- think you have an infection or have symptoms of an infection such as:
 - fever, sweats, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in your phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinate more often than normal

After starting COSENTYX, call your healthcare provider right away if you have any of the signs of infection listed above. Do not use COSENTYX if you have any signs of infection unless you are instructed to by your healthcare provider.

See “**What are the possible side effects of COSENTYX?**” for more information about side effects.

What is COSENTYX?

COSENTYX is a prescription medicine used to treat adults:

- with moderate to severe plaque psoriasis that involves large areas or many areas of the body, and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet or UV light alone or with systemic therapy)
- with active psoriatic arthritis
- with active ankylosing spondylitis

COSENTYX may improve your psoriasis, psoriatic arthritis and ankylosing spondylitis but it may also lower the ability of your immune system to fight infections.

It is not known if COSENTYX is safe and effective in children.

Do not take COSENTYX:

Do not use COSENTYX if you have had a severe allergic reaction to secukinumab or any of the other ingredients in COSENTYX. See the end of this Medication Guide for a complete list of ingredients in COSENTYX.

Before taking COSENTYX, tell your healthcare provider about all of your medical conditions, including if you: have any of the conditions or symptoms listed in the section “**What is the most important information I should know about COSENTYX?**”

- have inflammatory bowel disease (Crohn’s disease or ulcerative colitis)
- are allergic to latex. The needle cap on the COSENTYX Sensoready® pen and prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take COSENTYX **should not** receive live vaccines.
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if COSENTYX can harm your unborn baby. You and your healthcare provider should decide if you will use COSENTYX.
- are breastfeeding or plan to breastfeed. It is not known if COSENTYX passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I use COSENTYX?

See the detailed “Instructions for Use” that comes with your COSENTYX for information on how to prepare and inject a dose of COSENTYX, and how to properly throw away (dispose of) used COSENTYX Sensoready pens and prefilled syringes.

- Use COSENTYX exactly as prescribed by your healthcare provider.
- If your healthcare provider decides that you or a caregiver may give your injections of COSENTYX at home, you should receive training on the right way to prepare and inject COSENTYX. Do not try to inject COSENTYX yourself, until you or your caregiver has been shown how to inject COSENTYX by your healthcare provider.
- COSENTYX comes in a Sensoready pen or prefilled syringe that you or your caregiver may use at home to give injections. Your healthcare provider will decide which type of COSENTYX is best for you to use at home.
- Your healthcare provider will prescribe the dose of COSENTYX that is right for you.
 - If your prescribed dose of COSENTYX is **150 mg**, you must give **1 injection** of COSENTYX for each dose.
 - If your prescribed dose of COSENTYX is **300 mg**, you must give **2 injections** for each dose.
- COSENTYX is given as an injection under your skin (subcutaneous injection), in your upper legs (thighs) or stomach-area (abdomen) by you or a caregiver. A caregiver may also give you an injection of COSENTYX in your upper outer arm.
- **Do not** give an injection in an area of the skin that is tender, bruised, red or hard, or in an area of skin that is affected by psoriasis.
- Each injection should be given at a different site. **Do not** use the 2-inch area around your navel (belly button).
- If you inject more COSENTYX than prescribed, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of COSENTYX?

See “**What is the most important information I should know about COSENTYX?**”

- Inflammatory bowel disease. New cases of inflammatory bowel disease or “flare-ups” can happen with COSENTYX, and can sometimes be serious. If you have inflammatory bowel disease (ulcerative colitis or Crohn’s disease), tell your healthcare provider if you have worsening disease symptoms during treatment with COSENTYX or develop new symptoms of stomach pain or diarrhea.
- Serious allergic reactions. Get emergency medical help right away if you get any of the following symptoms of a serious allergic reaction:
 - feel faint
 - swelling of your face, eyelids, lips, mouth, tongue, or throat
 - trouble breathing or throat tightness
 - chest tightness
 - skin rash

If you have a severe allergic reaction, do not give another injection of COSENTYX.

The most common side effects of COSENTYX include:

- cold symptoms
- diarrhea
- upper respiratory infections

These are not all of the possible side effects of COSENTYX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COSENTYX?

- Store COSENTYX in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep COSENTYX in the original carton until ready for use to protect from light.
- Do not freeze COSENTYX.
- Do not shake COSENTYX.

Keep COSENTYX and all medicines out of the reach of children.

General information about the safe and effective use of COSENTYX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COSENTYX for a condition for which it was not prescribed. Do not give COSENTYX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about COSENTYX that is written for health professionals.

What are the ingredients in COSENTYX?

Active ingredient: secukinumab

Inactive ingredients: Sensoready pen and prefilled syringe: L-histidine/histidine hydrochloride monohydrate, L-methionine, polysorbate 80, trehalose dihydrate, and sterile water for injection.

Vial: L-histidine/histidine hydrochloride monohydrate, polysorbate 80, and sucrose.

For more information, call 1-888-669-6682 or go to www.COSENTYX.com

Manufactured by: **Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936**

T20XX-XX/T20XX-XX

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: Month/Year

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Summary Review
NDA/BLA # Supplement #	BLA 125504 s01, s05 (Psoriatic Arthritis, administratively split) and s02 (Ankylosing Spondylitis)
Applicant Name	Novartis
Date of Submission	s01-March 18, 2015; s02-March 23, 2015
PDUFA Goal Date	S01, s05-January 18, 2016; s02-January 23, 2016
Proprietary Name / Established (USAN) Name	Cosentyx / secukinumab
Dosage Forms / Strength	150 mg/mL single-use Sensoready® pen, 150 mg/mL solution in a single-use prefilled syringe (PFS), and 150 mg lyophilized powder in a single-use vial
Proposed Indication(s)	1. Active Psoriatic Arthritis 2. Active Ankylosing Spondylitis
Action:	<i>Approval for s01, s02; Complete Response for s05</i>

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
CDTL Review	Janet Maynard, MD, MHS
Medical Officer Review	Raj Nair, MD
Statistical Review	Primary: Yongman Kim, PhD; Secondary: Gregory Levin, PhD
Pharmacology Toxicology Review	Primary: Lawrence Steven Leshin, DVM, PhD; Secondary: Marcie Wood, PhD
CMC Review/OBP Review	Primary: Yongmin Liu, PhD; Secondary: Rashmi Rawat, PhD
Clinical Pharmacology Review	Primary: Lei He, PhD; Secondary: Ping Ji, PhD
OSE/DMEPA	Primary: Teresa McMillan, PharmD; Secondary: Kendra Worthy, PharmD
OMP/DMPP/Patient Labeling	Primary: Aman Sarai, BSN, RN; Secondary: Shawna Hutchins, MPH, BSN, RN; LaShawn Griffiths, MSHS- PH, BSN, RN
OPDP	Adewale Adeleye, PharmD, MBA

OND=Office of New Drugs
 CDTL=Cross-Discipline Team Leader
 CMC/OBP=Chemistry, Manufacturing, Controls/Office of Biotechnology Products
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OMP/DMPP=Office of Medical Policy/Division of Medical Policy Programs
 OPDP=Office of Prescription Drug Promotion

1. Introduction

This summary review will address two supplemental biologics license applications (sBLA) for BLA 125504 for Cosentyx™ (secukinumab). Secukinumab is a fully human monoclonal antibody IgG1κ antibody that binds to interleukin-17A (IL-17A). It was first approved in the United States (US) on January 21, 2015 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The recommended dose for plaque psoriasis is 300 mg by subcutaneous (SC) injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg by subcutaneous injection every 4 weeks. For some patients, a dose of 150 mg may be acceptable. It is available in a single-use pen, a prefilled syringe (PFS), and a lyophilized powder.

The Applicant, Novartis Pharmaceuticals Corporation, submitted a supplemental application on March 18, 2015 for a new indication of active psoriatic arthritis (PsA), and another supplemental application on March 23, 2015 for a new indication of active ankylosing spondylitis (AS). The supplemental applications for these two indications each contained two phase 3 studies and were independent of each other. However, because of the close timing of the applications, the same review team was assigned to both submissions. Also, because the pattern and design of the phase 3 studies in PsA and AS were similar, both applications raised the same issue of interpretability of results to be expected with chronic maintenance dosing. This is because of the high loading dose exposures, which exceeded the exposures expected with the maintenance dosing regimen alone, and extended through the controlled periods of the studies.

2. Background

Psoriatic Arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Approximately 80% of patients with PsA have skin involvement with psoriasis prior to or at the time of diagnosis with PsA. PsA can affect the peripheral and axial joints. The clinical manifestations of PsA can include:

- Distal arthritis, characterized by involvement of the distal interphalangeal (DIP) joints
- Asymmetric oligoarthritis, in which less than five joints are affected in an asymmetric distribution
- Symmetric polyarthritis, that affects the small joints of the hands and feet and can be indistinguishable from RA
- Arthritis mutilans, characterized by a destructive and deforming arthritis
- Spondyloarthritis, including both sacroiliitis and spondylitis.

Clinical development programs in PsA share common features with RA programs, including the use of similar endpoints such as the American College of Rheumatology (ACR) response criteria levels of improvement (i.e. ACR20, 50, 70), the Health Assessment Questionnaire-

Disability Index (HAQ-DI), and structural (i.e. radiographic) endpoints. Since the advent of biologic therapies (since ~1998), there have been five TNF inhibitors approved for PsA (etanercept, infliximab, adalimumab, golimumab, and certolizumab), as well as the IL12/23 inhibitor ustekinumab, and the small molecule PDE4 inhibitor apremilast. Secukinumab would be the first IL17 inhibitor approved for this indication.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic and progressive disease of the axial skeleton manifested by back pain and progressive stiffness of the spine. The disease can also involve the hips, shoulders, peripheral joints, entheses, and digits. AS is a well-characterized form of spondyloarthritis (SpA): a family of disorders characterized by inflammation around entheses (the sites of ligament insertion into bone), an association with human leukocyte antigen (HLA)-B27, and radiographic sacroiliitis. The mean AS prevalence per 10,000 is estimated to be 31.9 in North America.¹

The efficacy endpoints assessed in AS programs generally focus on validated measures of improvement in the signs and symptoms of AS. As structural changes in AS occur very slowly—over decades, rather than years—clinical development programs in AS have focused on improvement in signs and symptoms of AS, rather than changes in radiographic disease progression. Thus, most of the endpoints evaluated to support drug approval in AS involve patient reported outcomes related to pain and functional status, rather than radiographic markers of disease progression. These endpoints included Assessment in Ankylosing Spondylitis (ASAS) responses^{2,3,4}, Bath AS Functional Index (BASFI)⁵, and Bath AS Disease Activity Index (BASDAI).

Since 2003, five TNF inhibitors have been approved for the treatment of AS: etanercept, infliximab, adalimumab, golimumab, and certolizumab. TNF inhibitor treatment has demonstrated efficacy for multiple aspects of clinical disease activity in AS, but it is not yet known whether treatment has a beneficial effect on structural damage progression.

Regulatory History

In multiple pre-submission interactions with Novartis dating back to 2010, the primary issues discussed for both PsA and AS development plans included:

- The justification for the dose selection, which was derived primarily from data on secukinumab in RA. In initial written responses provided by FDA in January 2010, FDA considered the Applicant's rationale for using dose-ranging studies in RA to select doses for the AS and PsA trials reasonable. However, at the end-of-phase-2 (EOP2) meeting in March 2011, FDA noted that similar posology observed for TNF inhibition in RA, PsA and AS may not apply with IL17 inhibition, and that dose-

¹ Dean LE. *Rheumatology (Oxford)*. 2014;53(4):650-7.

² Anderson JJ, et al. *Arthritis Rheum* 2001;44(8):1876-1886.

³ van der Heijde D, et al. *Arthritis Rheum* 2005;52(2):386-94.

⁴ Sieper J, et al. *Ann Rheum Dis* 2009;68 suppl 2:iii1-44.

⁵ Calin A, et al. *J Rheumatol* 1994;21(12):2281-2285.

ranging in each indication would be desirable. Additionally, FDA noted that results for the 300 mg every 4 weeks dose regimen chosen appeared to be similar to the 75 mg every 4 week dose regimen, therefore the rationale for its selection as the dose moving forward was unclear.

- The use of a loading dose. The FDA raised two primary concerns with the proposed use of a loading dose:
 - There was no clear rationale for why a loading dose would be needed.
 - The potential impact of the loading dose on the interpretability of the efficacy and safety data, particularly with the intravenous (IV) loading regimen, which resulted in much higher exposures over an extended period that included the primary endpoint time point.
 - Because of these concerns, FDA recommended that secukinumab also be studied without a loading dose.
- At the pre-BLA meeting in April 2014, in addition to discussions about the loading regimen, FDA also noted that there would be limited data (i.e. from a single study) to evaluate the 300 mg dose regimen and the radiographic endpoint.

3. CMC/Device

There were no CMC or device data in these submissions. No changes to the approved drug product were proposed.

4. Nonclinical Pharmacology/Toxicology

There were no pharmacology/toxicology data in these submissions. No changes to the currently approved labeling pertaining to the nonclinical data were proposed.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology data submitted in this sBLA included pharmacokinetic (PK) data and immunogenicity data from the PsA and AS trials. The PK of secukinumab appears to be similar among the different populations (healthy volunteers, psoriasis, PsA, and AS). The incidence of anti-drug antibody (ADA) formation was low and there did not appear to be an obvious impact on PK, efficacy, or safety, based on these limited data.

In the phase 3 studies in PsA (F2306 and F2312) patients received either IV (F2306) or SC (F2312) loading doses. For the patients who received loading dose of IV 10 mg/kg at weeks 0, 2, and 4 and then 150 mg SC every 4 weeks, the trough concentrations at Week 24 (24 ± 14 $\mu\text{g/mL}$) appeared higher than those at Week 52 (19 ± 8 $\mu\text{g/mL}$), suggesting there was still additional exposure attributable to the IV loading regimen at Week 24 in Study F2306. With

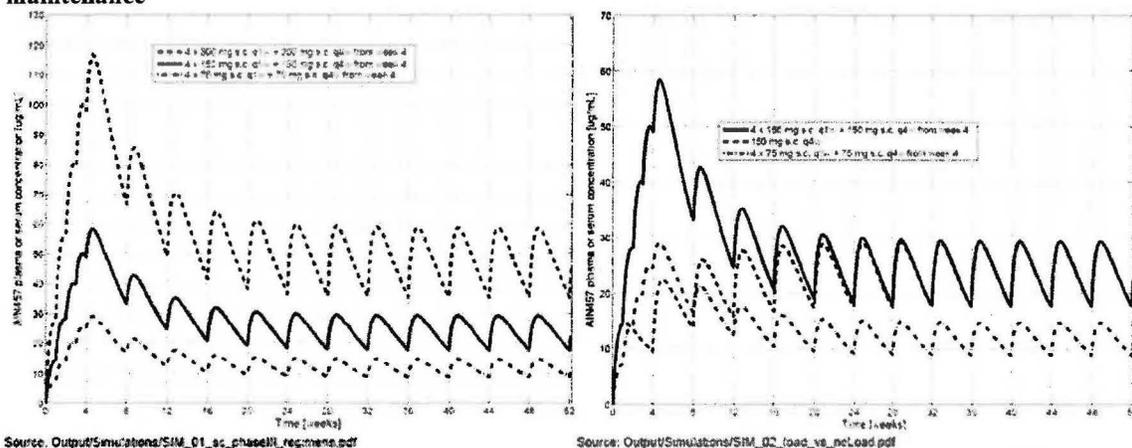
the loading doses of SC 150 mg once a week for five weeks and then 150 mg every four weeks, the trough concentrations at week 16 ($22 \pm 10 \mu\text{g/mL}$) were higher than those at Week 24 ($19 \pm 10 \mu\text{g/mL}$), suggesting there was still additional exposure attributable to the SC loading regimen at Week 16 in Study F2312. Similar findings were noted in the phase 3 studies in AS (F2305 and F2310).

Although the true extent of the additional exposure relative to no loading is not known, the Applicant performed population PK analyses to simulate the exposure of the IV and SC loading regimens. In figure 1 below, the left figure provides the simulated concentration profile of the SC load with SC maintenance regimens, for reference. The right figure provides a comparison of the 150 mg SC load/150 mg maintenance regimen (solid line) and the 75 mg SC load/75 mg maintenance regimen (lower dashed line) with the 150 mg maintenance regimen without a loading dose (middle dashed line). This suggests additional exposure from the load would be expected through Week 28.

Figure 1 Simulated Concentration Profiles

Left: SC load with SC Maintenance Regimens for 300 mg, 150 mg and 75 mg

Right: 150 mg SC load/SC maintenance and 75 mg SC load/SC maintenance vs. no load 150 mg maintenance



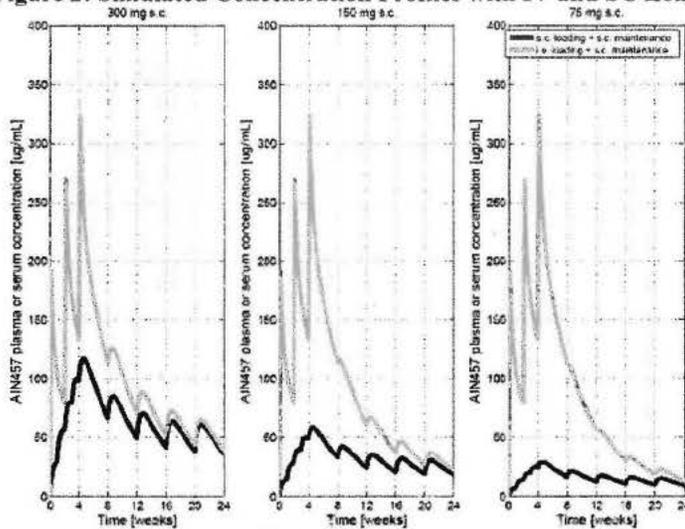
Source: Output/Simulations/SIM_01_sc_phaseIII_regimens.pdf

Source: Output/Simulations/SIM_02_load_vs_noLoad.pdf

Source: Sponsor simulation, from FDA Clinical Pharmacology Review

As illustrated in Figure 2 below, the impact of the IV load is a 3 to 13-fold higher exposure than is obtained with the SC loading regimen, with higher exposures observed through at least Week 24 compared to the 150 mg and 75 mg SC load/SC maintenance regimens, and through Week 20 compared to the 300 mg SC load/SC maintenance regimen. The potential impact of this additional exposure on the interpretation of the efficacy results will be discussed further in sections 7 below.

Figure 2: Simulated Concentration Profiles with IV and SC Loads + maintenance regimens



Source: Output/Simulations/SIM_D3_all_phaseIII_regimens.pdf

Source: Sponsor Simulation, FDA Clinical Pharmacology Review

6. Clinical Microbiology

There were no new clinical microbiology data in these submissions and there are no outstanding issues that preclude approval.

7. Clinical/Statistical-Efficacy

The key features of the Phase 3 studies in PsA and AS are summarized in Tables 1 and 2 below. The phase 3 studies in PsA and AS followed similar patterns: one study included an IV loading regimen followed by a maintenance regimen of 75 mg, 150 mg, or placebo given subcutaneously every 4 weeks, and one study included a subcutaneous loading regimen of the same doses given at baseline and weekly for the first 4 weeks, followed by those doses given at the maintenance dosing interval of every 4 weeks. The 300 mg dose was only studied in PsA Study F2312.

Table 1: Summary of Phase 3 Studies in PsA

Study (Phase) [dates]	Patients	Duration (weeks)	Loading dose	Maintenance dose	Number per arm	Primary Endpoint (notable secondary endpoint)	Total N
CAIN457F2306 (Phase 3) [9/11-10/13]	Active PsA (~30% TNF-IR)	52 weeks, 1 ^o endpoint at 24 weeks	10 mg/kg IV (wks 0, 2, 4) or PBO	75 mg SC Q4W	202	ACR20 (wk 24) (X-ray (wk 24))	606
				150 mg SC Q4W	202		
				Placebo	202		
CAIN457F2312 (Phase 3) [4/13-5/14]	Active PsA (~40% TNF-IR)	52 weeks (interim 24 weeks provided), 1 ^o endpoint at 24 weeks	75, 150, or 300 mg SC (wks 0, 1, 2, 3, 4) or PBO	75 mg SC Q4W	99	ACR20 (wk 24)	397
				150 mg SC Q4W	100		
				300mg SC Q4W	100		
				Placebo	98		

Abbreviations: PsA=psoriatic arthritis; TNF-IR=tumor necrosis factor-inadequate response; IV=intravenous; SC=subcutaneous;

ACR=American College of Rheumatology

Source: Summary of Clinical Efficacy, modified from Table 1-5, pages 26; Table 3 of the PsA CDTL review by Dr. Janet Maynard

Table 2: Summary of Phase 3 Studies in AS

Study (Phase) [dates]	Patients	Duration (weeks)	Loading dose	Maintenance dose	Number per arm	Primary Endpoint	Total N
CAIN457F2305 (Phase 3) [10/11-12/13]	Active AS (27% TNF-IR)	52 weeks, 1° endpoint at 16 weeks, escape at week 16, all patients on secukinumab after week 24	10 mg/kg IV (wks 0, 2, and 4) or PBO	75 mg SC Q4W 150 mg SC Q4W Placebo	124 125 122	ASAS20 (wk 16)	371
CAIN457F2310 (Phase 3) [10/12-8/14]	Active AS (39% TNF-IR)	52 weeks, 1° endpoint at 16 weeks, no escape at week 16, all patients on secukinumab after week 16	75 or 150 mg SC (wks 0, 1, 2, 3, and 4) or PBO	75 mg SC Q4W 150 mg SC Q4W Placebo	74 74 74	ASAS20 (wk 16)	222

Source: modified from Tables 1-3 (page 24), Summary of Clinical Efficacy; Table 5 of the AS CDTL review by Dr. Maynard

For PsA, the Applicant is seeking approval of the 150 mg and 300 mg dose regimens. For AS, the Applicant is seeking approval of the 150 mg dose regimen. Of note, although all studies were 52 weeks in duration, the primary endpoint in the PsA studies was at 24 weeks, whereas in the AS studies the primary endpoint was at 16 weeks. The timing of the primary and secondary endpoint evaluations was an important factor influencing the interpretability of the results because of the loading dose exposures, as will be discussed further below. In the PsA studies, patients on placebo who were nonresponders at Week 16 escaped to secukinumab treatment, and all patients received secukinumab after Week 24. In the AS studies, all patients received secukinumab after Week 24 (Study F2305) or Week 16 (Study F2310).

Results for Secukinumab in Psoriatic Arthritis

Primary endpoint results for Study F2306 and Study F2312 are summarized in Table 3 below. Secukinumab treatment at 75 mg, 150 mg, and 300 mg was associated with a higher proportion of ACR20 responders at Week 24. The American College of Rheumatology (ACR) 20 is a 20% or greater improvement in tender joint count and swollen joint count, with at least 20% improvement in at least 3 of 5 following domains: patient global assessment, physician global assessment, patient assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI), and acute phase reactants (C-reactive protein or erythrocyte sedimentation rate).

Table 3: Primary Endpoint Results: Proportion of ACR20 Responders at Week 24

	Treatment Group	n/N (%)	Comparison	Odds Ratio (95% CI)	P-value
Study F2306 IV load	Secukinumab 75 mg (n=202)	102/202 (51)	vs. placebo	5.5 (3.5, 8.9)	<0.0001
	Secukinumab 150 mg (n=202)	101/202 (50)	vs. placebo	5.4 (3.4, 8.6)	<0.0001
	Placebo (n=202)	35/202 (17)	--	--	--
Study F2312 SC load	Secukinumab 75 mg (n=99)	29/99 (29)	vs. placebo	2.3 (1.1, 4.7)	0.02
	Secukinumab 150 mg (n=100)	51/100 (51)	vs. placebo	6.5 (3.3, 13.1)	<0.0001
	Secukinumab 300 mg (n=100)	54/100 (54)	vs. placebo	6.8 (3.4, 13.6)	<0.0001
	Placebo (n=98)	15/98 (15)	--	--	--

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Tables 4 (page 20) and 25 (page 42-3); Table 5 of the PSA CDTL Review by Dr. Maynard

Secukinumab 150 mg (Studies F2306 and F2312) and 300 mg (Study F2312 only) was associated with a consistent benefit for secondary endpoints such as PASI75 (Psoriasis Area

Severity Index, 70% improvement), PASI90, change from baseline in DAS28-CRP, change from baseline in HAQ-DI, change from baseline in the SF-36 PCS and the presence of dactylitis or enthesitis at Week 24. Although secukinumab 75 mg showed a benefit for these secondary endpoints in Study F2306, it was not associated with similar improvement in Study F2312. This difference in results may have been due to the effects of the IV loading regimen in Study F2306 masking the true effect of the 75 mg dose.

The difference in secondary endpoint results between the two studies with the 75 mg dose illustrates the difficulty with the interpretation of the data from Study F2306, which is the only study containing radiographic data on structural damage, which was assessed as change from baseline in the modified Total Sharp Score (mTSS) at Week 24. As shown in Table 4 below, both the 75 and 150 mg doses of secukinumab were associated with a similar magnitude of difference in change from baseline to Week 24 in mTSS, compared to placebo.

Table 4: Results for Change from Baseline in mTSS at Week 24 in Study F2306

	Treatment Group	n	Mean Change	Comparison	Mean Difference (SE)	P-value
Study F2306 IV load	Secukinumab 75 mg (n=202)	181	0.02	vs. placebo	-0.54 (0.22)	0.0132
	Secukinumab 150 mg (n=202)	185	0.13	vs. placebo	-0.47 (0.20)	0.0212
	Placebo (n=202)	179	0.57			

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Table 14, page 29; Table 7 of the PsA CDTL review by Dr. Maynard

While these results support a conclusion that secukinumab has a beneficial effect on structural outcomes, it is not at all clear what dose of secukinumab may be needed chronically to provide this effect. As was noted in Section 5 above, the IV load exposure would be expected to far exceed the exposure of the maintenance dosing regimen, and additional exposure would be persistent through Week 24. Therefore one must conclude that the treatment effect on the radiographic outcome is due to the IV load exposure, and it is not clear whether the SC load/SC maintenance regimen, or a SC maintenance regimen alone, would give sufficient exposure to provide a benefit on radiographic outcomes. Therefore, the radiographic data from Study F2306 are insufficient to be instructive to prescribers (b) (4)

While these exposure concerns would also apply to the primary and other secondary endpoints, exploratory analyses on ACR response rates over the 52 weeks of the studies support the ability of the chronic SC maintenance regimens to provide a benefit for clinical responses once the effect of the loading regimens has dissipated. Data on the subgroup of placebo patients who were switched to secukinumab without a loading dose also support the efficacy of the chronic SC maintenance regimens. Unfortunately, similar analyses could not be done for the radiographic outcome, which involves very small changes over a long time period, making it especially difficult to interpret results without a control group.

Results for Secukinumab in Ankylosing Spondylitis

Primary endpoint results for Study F2305 and Study F2310 are summarized in Table 5 below. Secukinumab treatment at 150 mg was associated with a higher proportion of ASAS20 responders at Week 16. Secukinumab 75 mg was associated with a higher proportion of ASAS20 responders in Study F2305, which had a large IV load, but only a numerical improvement in the proportion of responders in Study F2310, which had the SC loading regimen. Similar to the trend observed in the PsA studies, this difference in results for the 75 mg dose likely reflects the impact of the IV load, although both loading regimens likely had an impact on results, as will be discussed further below.

The Assessment in Ankylosing Spondylitis (ASAS) 20 response is an improvement of 20% and an absolute improvement of at least 1 unit (on a scale of 0 to 10) in at least 3 of 4: patient global assessment, total back pain, function assessed by the Bath AS Functional Index (BASFI), and inflammation (from the last two stiffness assessments in the Bath AS Disease Activity Index [BASDAI]). There must also be no worsening of >1 unit in the remaining domain.

Table 5: Primary Endpoint Results: ASAS20 Response at Week 16

	Treatment Group	n/N (%)	Comparison	Odds Ratio (95% CI)	P-value
Study F2305 IV load	Secukinumab 75 mg (n=124)	74/124 (60)	vs. placebo	3.8 (2.2, 6.4)	<0.0001
	Secukinumab 150 mg (n=125)	76/125 (61)	vs. placebo	3.9 (2.3, 6.6)	<0.0001
	Placebo (n=122)	35/122 (29)			
Study F2310 SC load	Secukinumab 75 mg (n=73)	30/73 (41)	vs. placebo	1.8 (0.9, 3.6)	0.10
	Secukinumab 150 mg (n=72)	44/72 (61)	vs. placebo	4.4 (2.1, 9.0)	<0.0001
	Placebo (n=74)	21/74 (28)			

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Tables 4 (page 17) and 16 (page 34); Table 6 of the AS CDTL review by Dr. Maynard

In contrast to the results for the secondary endpoints in the PsA studies, which were obtained at Week 24, both secukinumab 75 mg and 150 mg were associated with a benefit for secondary endpoints at Week 16, such as ASAS40 responders, change from baseline in hsCRP, ASAS 5/6 responders, change from baseline in BASDAI, change from baseline in SF36-PCS (Short Form 36-Physical Component Summary), change from baseline in ASQoL (Ankylosing Spondylitis Quality of Life), and proportion of patients with ASAS partial remission. However, at Week 16, both the IV loading regimen and the SC loading regimen were likely contributing to higher exposures, as discussed in Section 5 above. Similar to those described for the PsA trials, exploratory analyses were performed of the AS studies. A similar proportion of patients in the studies through 52 weeks had clinical responses, supporting the effectiveness of the chronic maintenance regimen. Additionally, analyses evaluating the patients randomized to placebo who crossed over to secukinumab at 16 or 24 weeks and had no loading doses suggested that these patients achieved similar ASAS20 responses without the loading regimen.

Efficacy Conclusions

In summary, there is substantial evidence of efficacy of secukinumab for the treatment of PsA and the treatment of AS. There are sufficient data available to support a conclusion that the chronic maintenance dosing regimen of secukinumab will be effective for clinical responses once the loading dose exposure has dissipated. There is inadequate evidence to conclude that the SC loading dose/SC maintenance regimen would be effective for inhibiting the progression of structural damage related to PsA, as the only study with the radiographic endpoint utilized a large IV loading dose which produced much higher exposures than would be obtained with the SC loading dose/SC maintenance regimen, and higher exposure from the IV load persisted throughout the observation period (24 weeks).

8. Safety

Safety Overview

Secukinumab has been approved since January 21, 2015 for moderate to severe plaque psoriasis, and psoriasis patients represent the majority of the accrued exposure with this product. In the original BLA safety database, the primary safety concerns identified included an increased risk of infections, and a possible signal of increased exacerbations of Crohn's disease (CD). Both of these issues were highlighted as Warnings. Other warnings include hypersensitivity, latex-related hypersensitivity, and a warning against concomitant use of live vaccines. Worsening of inflammatory bowel disease (IBD) is a unique concern and will be discussed in further detail below.

Adequacy of the Safety Database

In the original BLA in plaque psoriasis, a total of 3430 patients were treated with secukinumab in controlled and uncontrolled studies. Of these, 2751 patients were treated for at least 6 months, and 1641 patients were treated for at least 1 year. In the PsA development program, a total of 1045 patients were studied, with 974 receiving secukinumab for any period of time, 865 patients treated for at least 24 weeks, and 453 patients treated for at least 52 weeks of secukinumab. Interim safety data from the first 24 weeks of Study 2312 were provided along with 52 weeks of safety data from Study F2306. In the AS development program, a total of 650 patients were studied, with 571 patients receiving secukinumab for any period of time, 535 patients treated for at least 24 weeks, and 444 patients treated for at least 52 weeks. The safety database in PsA and AS was adequate to evaluate the safety of secukinumab in these two conditions and the relative safety compared to the currently approved indication of plaque psoriasis.

Deaths

There was one death in the PsA trials: a patient in the IV-75 mg group who had a history of cardiovascular disease and stroke, who presented on Day 245 with severe hemiplegia and died due to an intracranial hemorrhage. There were three deaths in the AS trials: one in the placebo group due to suicide on Day 80, one in the IV-75 mg group due to respiratory failure on Day 706, and one in the 75 mg SC group due to an acute myocardial infarction on Day 29. These 4

deaths were consistent with each patient's risk factors and comorbidities, and did not suggest a particular concern related to secukinumab treatment.

Serious Adverse Events

The first 16 weeks of the phase 3 PsA trials was evaluated in order to provide the cleanest comparison of placebo to secukinumab. After Week 16, placebo patients who met escape criteria (for lack of response) were switched to secukinumab. Overall, the incidence of serious adverse events (SAEs) was low, and was not increased in the secukinumab treatment arms (~3%) compared to placebo (4%). This same pattern was observed during the 16-week placebo-controlled period of the phase 3 AS trials (again ~3% with secukinumab, 4% with placebo). There did not appear to be a dose-dependent pattern in SAEs, but it is not clear whether this would have been detectable in light of the loading dose exposures, as discussed above. In general, the pattern of SAEs was consistent with the underlying patient population and with immunosuppressives. However, there were several IBD-related SAE in the AS trials, as will be discussed further below.

Common Adverse Events

Approximately 50 to 70% of patients in each treatment group experienced an adverse event during the first 16 weeks of the phase 3 studies. The most common adverse events occurring in at least 2% of patients and at a higher incidence than placebo include:

- In the PsA studies: nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia
- In the AS studies: nasopharyngitis, nausea, and upper respiratory tract infection

Immunogenicity

There was a low rate of immunogenicity in the PsA and AS phase 3 studies: 7/1003 (0.7%) secukinumab-treated patients in the PsA studies, and 3/581 (0.5%) secukinumab-treated patients in the AS studies. There were no notable trends of clinical impact of anti-drug antibodies on efficacy or safety.

Adverse Events of Interest

Inflammatory Bowel Disease

In the original psoriasis studies, there were 3,430 patients on secukinumab and nine adverse events related to IBD (4 Ulcerative Colitis [UC], 4 CD, 1 anal fistula, 1 cholangitis sclerosing). Of the 323 patients on etanercept, there was one case of UC. There were no cases in the placebo group. In the secukinumab group, of the four UC cases, three patients were newly diagnosed and one patient had a flare. Of the four CD cases, one patient was newly diagnosed and the other three were disease exacerbations, including one that occurred during the maintenance period.

Patients in the PsA trials could have a history of Crohn's disease or other prior gastrointestinal disease. Patients were excluded if they had active inflammatory bowel disease. In PsA, there were four cases of IBD (any secukinumab: n=3, placebo: n=1) during the entire treatment period of the studies (24 weeks for Study F2312 and 52 weeks for Study F2306). In the placebo group, there was one new diagnosis of CD and in the secukinumab group there were 2 cases of diarrhea hemorrhagic (one of the cases was a diagnosis of ulcerative colitis 2 years after the onset of diarrhea hemorrhagic) and 1 newly diagnosed CD. In the secukinumab treatment arm, one of the cases related to IBD was serious as it required the patient to be hospitalized.

Patients in the AS trials could have a history of Crohn's disease or other prior gastrointestinal disease. Patients were excluded if they had active inflammatory bowel disease. In AS, there were eight cases of IBD during the entire 52-week treatment period of the studies. During the controlled 16 week period, there were two CD exacerbations and one new UC case that was an SAE compared to none in placebo. During the remainder of the study when all patients received secukinumab, one patient developed CD, there were 2 CD exacerbations, one patient had a UC exacerbation, and one patient developed UC. Thus, during the 52-week treatment period, there were 3 UC cases, of which two were new UC cases and one was a UC exacerbation. There were no cases in the placebo arm. The exposure adjusted incidence rate per 100 patient-years was 1.2 for the any secukinumab dose group compared to 0 for the placebo group.

It should be noted that psoriasis, psoriatic arthritis, and ankylosing spondylitis have all been reported in the literature to be associated with an increased incidence of inflammatory bowel disease (for psoriasis and PsA, the association has been reported with CD rather than UC)⁶. Therefore when cases are observed in clinical trials, it may be difficult to distinguish whether the investigational treatment is simply not effective for IBD and allows the background incidence to become apparent, or whether the investigational treatment may increase the risk. In this regard, it is informative that the Applicant evaluated the efficacy of secukinumab in CD in a phase 2, randomized, double blind study in 59 patients with active CD.⁷ The primary outcome measure was the Crohn's Disease Activity Index (CDAI) change from baseline to 6 weeks after infusion 1. The primary and secondary endpoint analyses showed consistent trends toward worse outcomes on secukinumab as compared to placebo. In addition, the severity of adverse events was higher on secukinumab than placebo, including worsening of Crohn's disease. Cases of CD (both new and worsening) have been reported in trials of other IL17 inhibitors⁸ as well, suggesting that IL17 inhibition mechanistically may be ineffective and even detrimental with respect to IBD. Based on the accruing data, the existing Warning on exacerbation of Crohn's disease should be expanded to include ulcerative colitis and to include new onset IBD.

⁶ Li W et al., "Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women." *Ann Rheum Dis* 2013; 72:1200-1205

⁷ Hueber W et al., "Secukinumab a human anti-IL17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial." *Gut* 2012; 61(12):1693-1700.

⁸ Yiu Z and Griffiths C, "Interleukin 17-A inhibition in the treatment of psoriasis." *Exp Rev Clin Immunol*, 2016, 12(1)

Infections

During the first 16 weeks of the phase 3 PsA studies a slightly higher incidence of infections were reported in the secukinumab treatment groups (29%) compared to the placebo groups (26%). During the 16-week controlled period of the AS studies, the difference between secukinumab and placebo was larger, with 31% of secukinumab patients experiencing an infection compared to 18% of placebo-treated patients. The most common infections in both phase 3 programs were nasopharyngitis and upper respiratory tract infections. Multiple candida-related infections were reported in the PsA and AS phase 3 studies. In the PsA studies, 15 candida infections were reported in the secukinumab groups compared to 0 in the placebo group. In the AS studies there were 6 candida infections in the secukinumab groups compared to 0 in the placebo group. One herpes zoster event was reported in the PsA studies and one in the AS studies. Overall the incidence and pattern of infections was consistent with the psoriasis program.

Malignancies

A total of 6 malignancies were reported in the phase 3 PsA studies (24 weeks for Study F2312 and 52 weeks for Study F2306). This included 3 basal cell carcinomas, one squamous cell carcinoma, and one prostate cancer case in the secukinumab treatment groups and one case of intraductal proliferative breast lesion in the placebo group. A total of 5 malignancies were reported in the 52-week period of the phase 3 AS studies. These included one B-cell lymphoma, one bladder transitional cell carcinoma, one breast cancer, and one malignant melanoma in the secukinumab groups, and one case of lymphoma in a placebo-treated patient. Keeping in mind the limited placebo-periods, these small imbalances do not suggest a major concern and the types of malignancies are consistent with the patient population. In the psoriasis clinical development program, the exposure-adjusted incidence of malignancies was not increased compared to placebo.

Hypersensitivity

No cases of anaphylaxis were reported in the phase 3 PsA or the phase 3 AS studies. Rash occurred in 2% of patients in both phase 3 programs. Urticaria was reported in 1% of patients in the PsA studies, and eczema and dermatitis were both reported in 1% of patients in the AS studies. None of these cases were SAE.

Suicidal Ideation and Behavior

Suicidal ideation and behavior is a safety consideration in PsA and psoriasis patients, who have been reported to be at increased risk of depression compared to healthy peers. Thus, the Agency requested the Applicant conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). This analysis was also performed on the AS studies. These evaluations did not reveal specific safety signals.

Cardiovascular Safety

An independent Cardiovascular and Cerebrovascular Safety Adjudication Committee (CCV-AC) was established to review and adjudicate potential major adverse cardiovascular event (MACE) cases in a blinded manner on a program-wide basis. Potential cases of MACE were identified according to the following pre-specified criteria in the CCV-AC Charter:

- Preferred terms belong to the 2 NMQs of MACE (myocardial infarction) and MACE (strokes)
- Preferred terms with a fatal outcome belonging to the SOC of “cardiac disorders” or “vascular disorders,” plus the preferred term of “death.”

In the PsA studies, seven adjudicated cases were confirmed cases, including 3 myocardial infarctions and 4 strokes. All of the patients had prior or active cardiovascular disease or relevant risk factors. In the phase 3 AS studies, a total of four MACE cases were reported over the entire treatment period. Of these four cases, three met the criteria for adjudication. These cases included 2 myocardial infarctions and 1 stroke. All of these patients also had prior or active cardiovascular disease and/or cardiovascular risk factors.

The overall exposure-adjusted incidence rate of adjudication-confirmed MACE over the treatment period in the phase 3 PsA studies was 0.73 per 100 patient years (95% CI: 0.3 to 1.5). The Applicant noted that the exposure-adjusted MACE rate is similar to that anticipated for patients with spondyloarthritis, including PsA and AS. A recent study⁹ in PsA patients demonstrated an incident rate of 0.57 per 100 patient years, which is similar to the observed rate in the phase 3 PsA studies. While there were no cases observed in the placebo group, the short exposure duration yields a broad confidence interval of 0 to 3.49. Similarly, the exposure-adjusted incidence of adjudication and confirmed MACE in the phase 3 AS studies was 0.43 per 100 patient-years (95% CI: 0.09 to 1.27), and the confidence interval for the placebo group was 0 to 5.8.

Similar findings were noted during the clinical development program in psoriasis and the Division of Cardio-Renal Products was consulted during review of that application. They concluded that the results were not suggestive of a cardiovascular safety issue. I believe the same conclusion applies to the results for the PsA and AS studies.

Safety Conclusions

Overall, the safety profile of secukinumab in PsA and AS appears to be consistent with the known safety profile of secukinumab as demonstrated in psoriasis. No new safety signals have been identified. However, additional cases of inflammatory bowel disease in PsA and AS corroborate and expand on the signal observed in the psoriasis studies. Based on these cases, expansion and elaboration of the current warning regarding Crohn’s disease is warranted.

9. Advisory Committee Meeting

⁹ Ogdie A, et al. *Ann Rheum Dis* 2014;74:326-32.

No Advisory Committee meeting was warranted or convened for these supplemental applications.

10. Pediatrics

The Applicant submitted a full waiver request from the requirements of the Pediatric Research Equity Act (PREA) for the PsA and AS indications, based on the rationale that studies would be impossible or impractical due to the rarity of these specific diagnoses in children. These waiver requests were discussed with the Pediatric Review Committee (PeRC) on October 17, 2015, and PeRC concurred with the waivers.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Cosentyx, already approved.
- Physician labeling:
 - Addition of PsA and AS indications, population PK, efficacy and safety
 - The PsA and AS dosing regimens will allow for being given with or without the subcutaneous load
 - The Warning on exacerbation Crohn's disease will be expanded to include ulcerative colitis cases and new onset cases
 -  (b) (4)
- Carton and immediate container labels: Already approved, no changes.
- Patient labeling/Medication guide: Cosentyx has an approved medication guide which will be amended to account for the changes to the prescribing information.

13. Decision/Action/Risk Benefit Assessment

• Regulatory Action

The actions on sBLA 125504 supplement 1 for the treatment of psoriatic arthritis and supplement 2 for the treatment of ankylosing spondylitis will be approval. Supplement 1 was administratively split, and the claim for inhibition of radiographic progression in psoriatic arthritis patients (supplement 5) will receive a complete response.

• Risk Benefit Assessment

Supplement 1: The risk-benefit profile is favorable of secukinumab for the treatment of active psoriatic arthritis in adults. Substantial evidence was provided that secukinumab treatment was associated with improvement in clinical responses, including ACR responses, HAQ-DI improvement, and improvement in skin manifestations. The safety profile of secukinumab was consistent with the known safety profile of secukinumab as established in the approved plaque psoriasis population.

Supplement 2: The risk-benefit profile is favorable of secukinumab for the treatment of active ankylosing spondylitis in adults. Substantial evidence was provided that secukinumab treatment was associated with improvement in clinical responses, as captured by ASAS20 response criteria, ASAS40 response criteria, BASDAI, and hsCRP. The safety profile of secukinumab was consistent with the known safety profile of secukinumab as established in the approved plaque psoriasis population.

- **Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

A REMS is not warranted on the basis of the data in these submissions.

- **Other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted on the basis of the data in these submissions.

- **Comments to Applicant for Supplement 5 Complete Response**

Deficiency comment:

- The submitted data do not provide substantial evidence to support the claim of inhibition of the progression of structural damage in psoriatic arthritis for the 150 mg every 4 weeks and 300 mg every 4 weeks dosing regimens of secukinumab, because the high exposures associated with the intravenous load used in Study F2306 obscured the treatment effect of these maintenance dosing regimens for the radiographic endpoint.

Information needed to address the deficiency:

- Provide data from a randomized, controlled clinical trial of secukinumab 150 mg and secukinumab 300 mg, administered subcutaneously every 4 weeks, to demonstrate the efficacy and balancing safety of these two dosing regimens for improving radiographic outcomes in patients with active psoriatic arthritis.

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/s/

SARAH K YIM
01/15/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

OFFICER/EMPLOYEE LIST

OFFICIAL EMPLOYEE LIST
sBLA 125504 S-01/S-02

The following FDA officers or employees participated in the decision to approve this application:

Abugov, Robert
Adewale, Adeley
Anic, Gabriella
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Chowdhury, Badrul A
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Levin, Gregory
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 23, 2015
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 125504/Supplement 1; it is anticipated that this will be split into two supplements (one for active psoriatic arthritis and one for inhibition of radiographic response in psoriatic arthritis)
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	March 18, 2015
PDUFA Goal Date	January 18, 2016
Proprietary Name / Established (USAN) names	Cosentyx (secukinumab)
Dosage forms / Strength	150 mg/mL single-use Sensoready® pen, 150 mg/mL solution in a single-use prefilled syringe (PFS), and 150 mg lyophilized powder in a single-use vial
Proposed Indication(s)	1. Active psoriatic arthritis
Recommended:	1. <i>Approval for active psoriatic arthritis</i> 2. <i>Complete response for inhibition of radiographic progression in psoriatic arthritis</i>

1. Introduction

This is a supplemental biologics license application (sBLA) 125504, supplement 1, for Cosentyx™ (secukinumab) in psoriatic arthritis (PsA). Secukinumab is a fully human monoclonal antibody IgG1κ antibody that binds to interleukin-17A (IL-17A). It was first approved in the United States (US) on January 21, 2015 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The recommended dose for plaque psoriasis is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg by subcutaneous injection every 4 weeks. For some patients, a dose of 150 mg may be acceptable. It is available in a single-use pen, a prefilled syringe (PFS), and a lyophilized powder. A Risk Evaluation and Mitigation Strategy (REMS) was not required at the time of approval.

The Applicant's proposed indication is: "COSENTYX is indicated for the treatment of adult patients with active psoriatic arthritis. (b) (4)

(b) (4)
In the supplement, the Applicant proposed

(b) (4)
The current plan is to split the supplement to accommodate the potential for differing actions for PsA and radiographic progression in PsA.

The PDUFA goal date for this application is January 18, 2016, with a standard review clock. Of note, the Applicant submitted a separate supplement for ankylosing spondylitis on March 23, 2015 (sBLA 125504/2). The Division plans to take action on both of these supplements at the same time. See the CDTL review dated December 23, 2015 for a review of the ankylosing spondylitis supplement.

2. Background

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. It is similar to rheumatoid arthritis (RA), as both are forms of inflammatory arthritis. However, there are multiple differences between PsA and RA. First, the prevalence of PsA (~0.3-1% of the population) is lower than the prevalence of RA (~1% of the population). In addition, PsA affects women and men equally, while RA affects women two to three times more frequently than men. The mean age of onset of PsA is slightly younger (~40 years) than the mean age of onset of RA (50-75 years old).

Approximately 80% of patients with PsA have skin involvement with psoriasis prior to or at the time of diagnosis with PsA. PsA can affect the peripheral and axial joints. The clinical manifestations of PsA can include:

- Distal arthritis, characterized by involvement of the distal interphalangeal (DIP) joints
- Asymmetric oligoarthritis, in which less than five joints are affected in an asymmetric distribution
- Symmetric polyarthritis, that affects the small joints of the hands and feet and can be indistinguishable from RA
- Arthritis mutilans, characterized by a destructive and deforming arthritis
- Spondyloarthritis, including both sacroiliitis and spondylitis.

Some patients have only one clinical manifestation, while others have overlapping manifestations. Similar to RA, patients with PsA can develop destructive disease characterized by radiographic progression of structural damage.

The goals of treatment are to improve signs and symptoms and prevent radiographic progression. Outcome measures utilized for RA, such as the American College of Rheumatology (ACR) response criteria, Health Assessment Questionnaire Disability Index (HAQ-DI or HAQ), and change from baseline in Sharp score as modified by van der Heijdi (vdH-S), have been validated for use in PsA as well, have been used successfully in previous clinical trials of PsA, and were used in the secukinumab PsA trials.

Although TNF inhibition has been previously demonstrated to be beneficial for the treatment of signs and symptoms and inhibition of radiographic progression in PsA, IL-17 inhibitors such as secukinumab have not previously been approved for the treatment of signs and symptoms or inhibition of radiographic progression for PsA. In addition, no IL-17 inhibitors have been approved for the treatment of signs and symptoms or inhibition of radiographic progression in RA. In contrast, all previous TNF inhibitors were approved for inhibition of radiographic progression in PsA after approval for inhibition of radiographic progression in RA (Table 1). Ustekinumab, which inhibits IL-12/23, and is approved for PsA, but not

rheumatoid arthritis, (b) (4)

Table 1: Drugs Approved for the Treatment of Psoriatic Arthritis (PsA) After 1998

	Etanercept (Enbrel)	Infliximab (Remicade)	Adalimumab (Humira)	Golimumab (Simponi)	Certolizumab (Cimzia)	Ustekinumab (Stelara)	Apremilast (Otezla)	Secukinumab (Cosentyx)
Mechanism of Action	TNF-inhibitor	TNF-inhibitor	TNF-inhibitor	TNF-inhibitor	TNF-inhibitor	IL-12/23 inhibitor	PDE4 inhibitor	IL-17 inhibitor
Year of approval for RA	1998	1999	2002	2009	2009	N/A	N/A	N/A
Date of approval for PsA	1/15/02	5/18/05	10/3/05	4/24/09	9/27/13	9/20/13	4/21/14	Under review
Previous or concurrent RA approval?	Yes	Yes	Yes	Yes	Yes	No	No	No
Previous or concurrent psoriasis approval?	Yes	Yes	Yes	No	No	Yes	No (subsequently approved for psoriasis)	Yes
Number of RA radiographic studies (b) (4)	2	2	2	0 (2 trials performed; (b) (4))	2	N/A	N/A	N/A
Number of PsA radiographic studies (b) (4)	1	1	2	0 (1 trial performed; (b) (4))	1	0 (2 trials performed; (b) (4))	N/A	Data under review, 1 trial performed

Abbreviations: TNF=tumor necrosis factor; PDE4=phosphodiesterase 4 inhibitor; N/A=not applicable, CR=complete response
 Source: Reviewer generated

Regulatory History

On September 20, 2005, the IND 12678 for secukinumab in RA was opened. Subsequently, this IND was expanded to include PsA and ankylosing spondylitis (AS). On January 29, 2010, the Sponsor was given written feedback given regarding the proposed dose and dosing regimen for PsA and AS. The Sponsor was informed that it would be reasonable to select doses for the AS and PsA trials based on phase 2 RA dose-finding studies and a scientific rationale on the role of IL-17 in these three diseases that suggests that IL-17 blockade with secukinumab should have similar posology in these diseases.

On March 7, 2011 (meeting minutes dated April 8, 2011), an end-of-phase 2 meeting was held. It was noted that an IL-17 inhibitor represents a new pharmacologic class, and it is unclear if the exposure-efficacy relationship in one indication can be extrapolated to a different indication. Recognizing the written feedback that was provided on January 29, 2010, it was noted that the Sponsor's approach was at their risk. It was noted that the best foundation for the posology across diseases can only be obtained via sufficient dose-ranging in each indication. In addition, concerns were raised about the use of a loading dose, especially an IV loading regimen of 10 mg/kg IV since it would produce a much greater exposure than the

maintenance dose. Further, it was noted that it was unclear why 300 mg SC every 4 weeks maintenance dose regimen was chosen instead of 75 mg SC every 4 weeks for the phase 3 trials. Based on the efficacy data, the results appeared similar for the 75 mg and 300 mg regimens. Concerns were raised regarding the assessment of a radiographic endpoint at week 52 given the lack of a control group. Given that the study had a 24 week controlled period, it was recommended that radiographs be assessed at 24 weeks or an active control be added to the study. Concerns were raised regarding the proposed statistical analyses, especially related to the handling of missing data. The Sponsor proposed two phase 3 studies in RA, one phase 3 study in PsA, and one phase 3 study in AS to [REDACTED] (b) (4)

[REDACTED] (b) (4) Therefore, in addition to two RA trials, the Sponsor was told to conduct two trials in patients with PsA and two trials in patients with AS to provide independent substantiation of the efficacy of secukinumab [REDACTED] (b) (4).

On April 18, 2012, the Sponsor was provided Type C written responses. In the responses it was reiterated that [REDACTED] (b) (4)

[REDACTED] Concerns were raised regarding incorporating SC and IV loading doses into the studies. The Sponsor was asked to provide clinical data to justify the proposed loading dose. It was noted that the IV loading strategy would result in much higher exposure to secukinumab than the SC loading strategy up to the primary endpoint at Week 24. Thus, it would be unclear if efficacy data from the IV regimen could be extrapolated to the subcutaneous regimen and additional studies might be required.

On April 30, 2014 (meeting minutes dated August 4, 2014), a pre-BLA meeting for PsA (meeting minutes dated August 4, 2014) was held. Several concerns regarding the loading regimen were raised. First, it was noted that the loading dose with much greater exposure than the maintenance dose would make it difficult to assess and interpret the efficacy of secukinumab as it would be unclear if the observed clinical responses will be maintained. It did not appear that there would be adequate data to support a recommended maintenance dose regimen, making it difficult to adequately label secukinumab. The Sponsor was asked to provide justification for the loading regimen, including supportive data (with and without the loading dose) to provide evidence that the loading dose is necessary. Further, the Sponsor was asked to provide adequate data to support the chosen dose and dosing regimen. Since very different loading regimens were utilized in the two phase 3 trials in PsA, depending on the proposed dose, dosing regimen, and desired labeling claims, it might be necessary to perform an additional study. Specific concerns were raised regarding the proposed 300 mg SC dose, which was only evaluated in one study, and the potential for radiographic inhibition claims, which was only evaluated in one study and was only evaluated in the context of the IV loading regimen. In addition, there was discussion of the presentation and analysis of the safety data.

On September 10, 2014, the Sponsor was provided with Type C written responses regarding the design of a study that would evaluate patients with active PsA with and without a loading regimen. The Division recommended assessment of clinical response at earlier time points and a comparison of the clinical response with and without a loading regimen.

Secukinumab (BLA 125504) for moderate to severe plaque psoriasis was approved on January 21, 2015.

The Applicant submitted this sBLA for PsA (supplement 1) on March 18, 2015.

3. CMC/Device

Primary Reviewer: Yongmin Liu, PhD; Team Leader: Rashmi Rawat, PhD

- **General product quality considerations**

No CMC or device data were included in this submission. No changes to the currently approved presentations, manufacturing, or controls were proposed in this submission.

- **Facilities review/inspection**

No outstanding issues.

- **Product Quality Microbiology**

Not applicable.

- **Other notable issues (resolved or outstanding)**

There are no other notable issues.

4. Nonclinical Pharmacology/Toxicology

Pharm-Tox Reviewer: Lawrence Steven Leshin, DVM, PhD; Supervisor: Marcie Wood, PhD

- **General nonclinical pharmacology/toxicology considerations**

No nonclinical studies were submitted to or required for this application. Relevant pharmacology/toxicology information for secukinumab is described in Sections 8 and 13 of the current package insert.

- **Other notable issues (resolved or outstanding)**

There are no other notable issues. From a nonclinical pharmacology/toxicology perspective, the application is recommended for approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology reviewer: Lei He, PhD; Clinical pharmacology team leader: Ping Ji, PhD

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc**

The general clinical pharmacology data were reviewed in the original BLA for plaque psoriasis. The clinical pharmacology data submitted in this supplemental BLA includes pharmacokinetic (PK), immunogenicity, and exposure-response data from the PsA trials F2306 and F2312, which used the currently marketed pre-filled syringe (PFS) presentation. In addition, PK data are included from a phase 2a proof-of-concept study in PsA.

The PK of secukinumab has been evaluated in healthy volunteers and patient populations. Secukinumab PK is similar among different populations (Table 2).

Table 2: PK of Secukinumab (Determined by NCA) in Different Populations

Study	Population	Dose	C _{max} (mcg/mL)	T _{max} (day)	T _{1/2} (day)	CL (L/d)	V _z (L)	F
A2106	HVs	300 mg SC (PFS)	43.2	5.0	25.9	--	--	--
		300 mg SC (LYO)	42.0	5.0	26.6	--	--	--
A2104	HVs	10 mg/kg IV	255	0.09	29.8	0.12	5.05	--
A2103	PsO	1 mg/kg IV	24.1	0.09	27.1	0.22	7.10	0.60
		150 mg SC	11.8	8.50	22.2	--	--	--
A2206	PsA	2×10 mg/kg IV	424	0.09	29.8	0.161	6.81	--
A2209	AS	2×10 mg/kg IV	364	21.08	28.1	0.157	6.06	--
		2×1 mg/kg IV	33.1	21.08	27.3	0.172	6.48	--
		2×0.1 mg/kg IV	5.51	21.12	34.3	0.118	5.83	--

NCA=non-compartmental analysis ; HV=healthy volunteers; PsO=psoriasis; PsA=psoriatic arthritis; AS=ankylosing spondylitis
Source: Dr. He's Clinical Pharmacology Review dated 12/11/15, Table 6, page 16

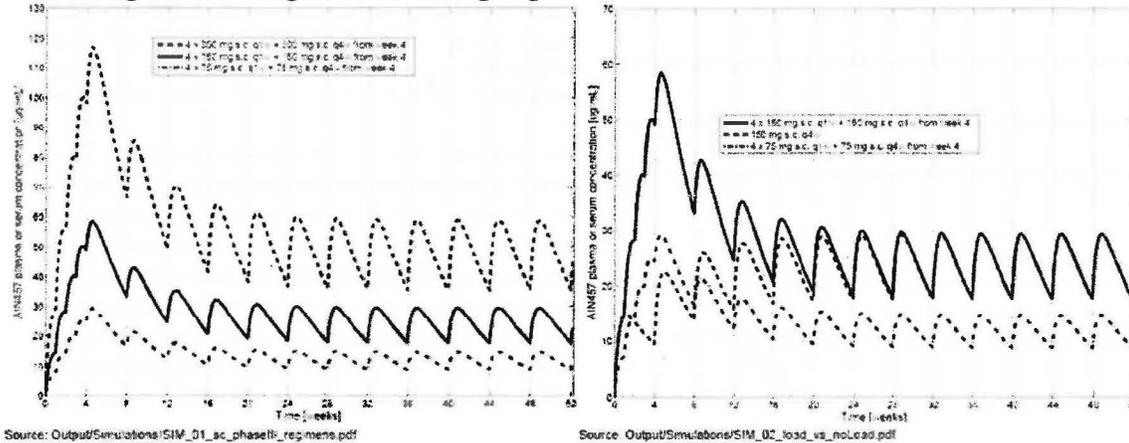
In population PK analysis, the estimates of CL of secukinumab in PsA were consistent across studies and dose levels suggesting the dose-proportionality of secukinumab PK in the dose ranges from SC 75 mg to SC 300 mg. Based on population PK analysis, body weight was identified as the significant intrinsic factor contributing to the inter-subject variability in secukinumab exposure in patients with PsA. Co-administration of methotrexate was found not to influence secukinumab PK significantly.

Loading

In the phase 3 studies (F2306 and F2312) patients received either IV (F2306) or SC (F2312) loading doses. For the patients who received loading dose of IV 10 mg/kg at weeks 0, 2, and 4 and then 150 mg SC every 4 weeks, the trough concentrations at Week 24 (24±14 µg/mL) appeared higher than those at Week 52 (19±8 µg/mL). Similarly, with the loading doses of SC 150 mg once a week for five weeks and then 150 mg every four weeks, the trough concentrations at week 16 (22±10 µg/mL) were higher than those at Week 24 (19±10 µg/mL). Therefore, time to reach steady state concentrations was about 24 weeks or later.

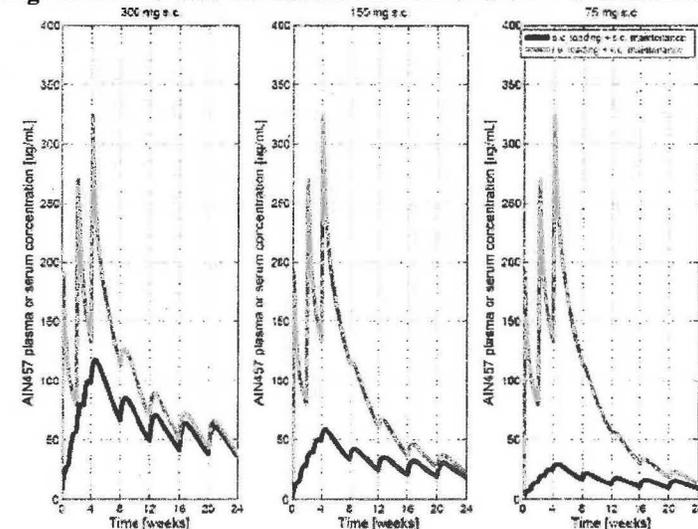
The Applicant performed population PK analyses to simulate the concentration profiles of the IV and SC loading regimen. These analyses demonstrate the high exposure with the SC load compared to no load regimen (Figure 1), the fact that the effect of the load may still be present at the time of efficacy endpoint assessments at Weeks 16-24 (Figure 1, Figure 2), and the markedly higher exposure with the IV than the SC load (Figure 2). The potential impact of the loading regimen on the efficacy and safety is discussed in Sections 7 and 8, respectively.

Figure 1: Simulated Concentration Profiles of SC loading and SC maintenance 300 mg, 150 m, and 75 mg Phase 3 Regimens and Regular Q4W Dosing Regimen



Source: Dr. He's Clinical Pharmacology Review dated 12/11/15, Figure 4-9, page 38

Figure 2: Simulated Concentration Profiles with IV and SC Loading Dosing Regimens



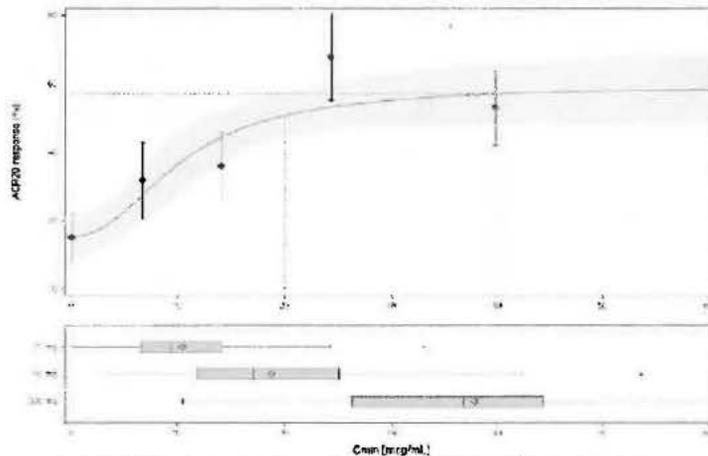
I.v. loading refers to 3 x 10 mg/kg i.v. q2w; s.c. loading is 4 x s.c. dose (300 mg, 150 mg or 75 mg, respectively for each panel) q1w; s.c. maintenance is s.c. dose (300 mg, 150 mg or 75 mg, respectively for each panel) q4w from week 4 in case of s.c. loading and from week 8 in case of i.v. loading.

Source: Dr. He's Clinical Pharmacology Review dated 12/11/15, Figure 4-10, page 38

Dose/Exposure-Response for Efficacy and Safety

Exploratory exposure-response analyses were performed based on the response rate at Week 24 and trough concentration (C_{min}) at Week 24 in Study F2312. The exposure-response curve flattens at C_{min} levels that are higher than 20 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC 150 mg-SC 150mg dosing regimen (SC load followed by SC maintenance). Doubling of the C_{min} from 20 to 40 mcg/mL induces an improvement of ~ 5% in the ACR20 response rates (Figure 3).

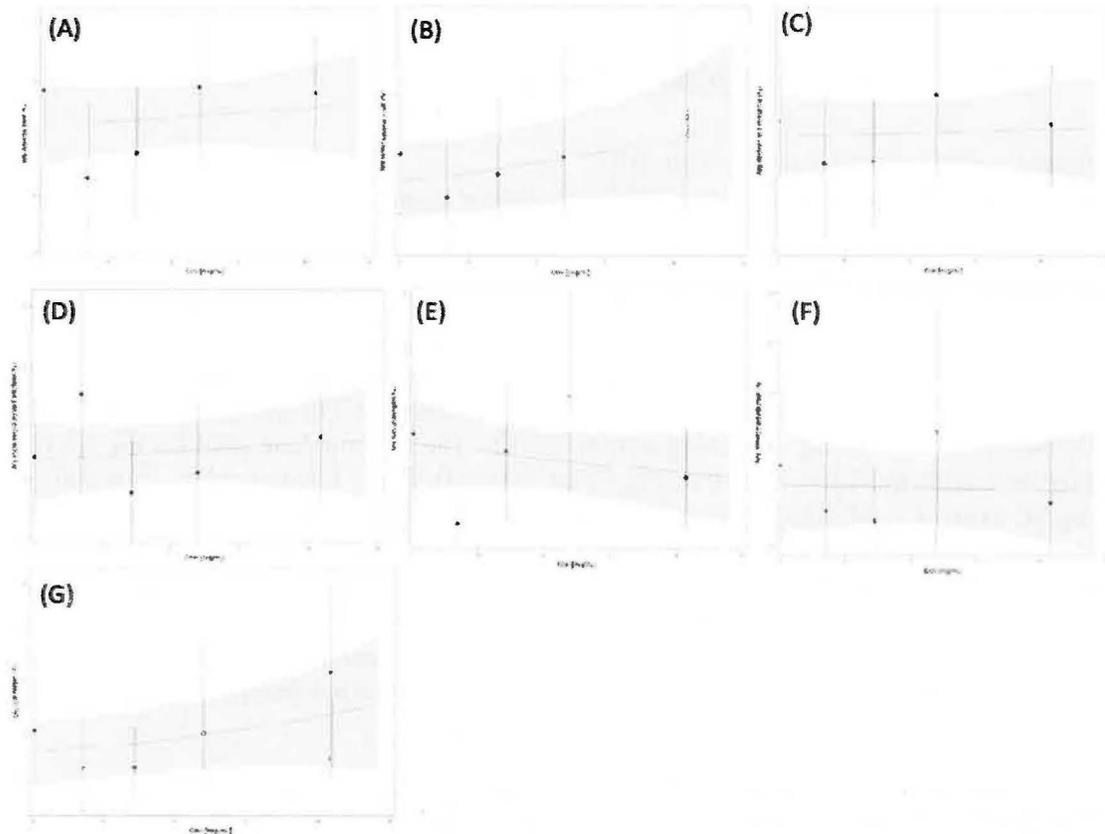
Figure 3: ACR20 Response Rate versus C_{min} Concentration at Week 24 (F2312)



Source: Dr. He's Clinical Pharmacology Review dated 12/11/15, Figure 3, page 9

Similar analyses were performed to evaluate for an exposure-response relationship for the following categories of adverse events: any adverse events, any serious adverse events, infections and infestations, upper respiratory tract infection, nasopharyngitis, urinary tract infection, and oral herpes. There was no evidence of an effect of C_{min} in those categories of adverse events, except for serious adverse events and oral herpes where an increasing trend with exposure was seen.

Figure 4: Occurrence of any AE (A), any SAE (B), any infection (C), upper respiratory tract infection (D), nasopharyngitis (E), urinary tract infection (F), oral herpes (G) versus Cmin concentration at Week 16 (F2312)



Y-axis represents various categories of AEs and x-axis represents Cmin concentration
Source: Dr. He's Clinical Pharmacology Review dated 12/11/15, Figure 5, page 11

Immunogenicity

The immunogenicity data showed that 4 out of 606 patients in Study F2306 and 3 out of 397 patients in Study F2312 were positive for anti-secukinumab antibodies post dose. Thus, the incidence of ADA formation was low. The anti-secukinumab antibody rate appeared comparable in patients with loading doses (n=4) and in patients who switched from placebo to secukinumab without a load (n=3). There was no evidence of an impact of anti-secukinumab antibodies on secukinumab PK, efficacy, or safety. However, the number of subjects with positive anti-drug antibody was small and no definitive conclusions can be drawn.

- **Other notable issues (resolved or outstanding)**

From a Clinical Pharmacology perspective, the application is acceptable for approval for the treatment active PsA in adult patients provided that the Applicant and the Agency come to a mutually satisfactory agreement with the language in the labeling.

6. Clinical Microbiology

No new clinical microbiology data were included in the supplement.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Raj Nair, MD

Statistical reviewer: Yongman Kim, PhD; Statistical team Leader: Gregory Levin, PhD

Overview of the clinical program

The primary evidence of efficacy is derived from study CAIN457F2306 (F2306) and study CAIN457F2312 (F2312) (Table 3). The study design features were similar in terms of eligibility criteria, study schedule, and efficacy outcome variables and analysis. The primary difference between the trials was the use of subcutaneous (SC) or intravenous (IV) loading and the addition of a 300 mg SC dosing arm in F2312. The loading dose used for the active treatment arms in F2306 was 10 mg/kg IV at Weeks 0, 2 and 4, followed by 75 mg SC or 150 mg SC every 4 weeks (hereafter referred as IV-75 mg and IV-150 mg regimens). The IV loading dose used in this study is not being proposed for marketing. The loading doses used in F2312 were 5 weekly SC injections of 75 mg, 150 mg, or 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 75 mg SC, 150 mg SC or 300 mg SC, respectively, every 4 weeks (hereafter referred to as 75 mg SC, 150 mg SC, and 300 mg SC regimens). It is the 150 and 300 mg doses (with SC loading doses) evaluated in Study F2312 that are being proposed for marketing.

Table 3: Summary of Phase 3 Studies in Psoriatic Arthritis (PsA) Submitted in BLA

Study (Phase) [dates]	Patients	Duration (weeks)	Loading dose	Maintenance dose	Number per arm	Primary Endpoint (notable secondary endpoint)	Total N
CAIN457F2306 (Phase 3) [9/11-10/13]	Active PsA (~30% TNF-IR)	52 weeks, 1 ^o endpoint at 24 weeks	10 mg/kg IV (wks 0, 2, 4) or PBO	75 mg SC Q4W 150 mg SC Q4W Placebo	202 202 202	ACR20 (wk 24) (X-ray (wk 24))	606
CAIN457F2312 (Phase 3) [4/13-5/14]	Active PsA (~40% TNF-IR)	52 weeks (interim 24 weeks provided), 1 ^o endpoint at 24 weeks	75, 150, or 300 mg SC (wks 0, 1, 2, 3, 4) or PBO	75 mg SC Q4W 150 mg SC Q4W 300mg SC Q4W Placebo	99 100 100 98	ACR20 (wk 24)	397

Abbreviations: PsA=psoriatic arthritis; TNF-IR=tumor necrosis factor-inadequate response; IV=intravenous; SC=subcutaneous; ACR=American College of Rheumatology

Source: Summary of Clinical Efficacy, modified from Table 1-5, pages 26

F2306

Study F2306 was a randomized, double-blind, placebo-controlled, multicenter study of secukinumab in prefilled syringes. Patients were randomized to one of three treatment groups: secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg SC starting at Week 8 and injected every 4 weeks, secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then 150 mg SC starting at Week 8 and injected every 4 weeks, or placebo. At randomization, patients were stratified by TNF α -inhibitor inadequate responder (TNF α -IR) status, which was

defined as active disease despite stable treatment with anti-TNF α for at least three months at a stable dose or for at least one dose in the case of lack of tolerance. Of note, a history of inadequate response to anti-TNF inhibitor treatment does not identify a specific group of patients and is subject to interpretation given that it is based on patient history. Approximately 30% of patients were planned to be TNF α -IR. At Week 16, patients on placebo who were non-responders were re-randomized (1:1) to receive either secukinumab 75 mg or 150 mg SC every 4 weeks in a blinded fashion. Non-responder was defined as <20% improvement from baseline in both tender and swollen joint counts. At Week 24, patients on placebo who were classified as responders at week 16 were re-randomized (1:1) to receive either secukinumab 75 mg or 150 mg. Thus, all patients received secukinumab after Week 24. There were no escape options for patients randomized to secukinumab.

The primary efficacy endpoint in the studies was the American College of Rheumatology 20% (ACR20) response criteria. Secondary endpoints included Psoriasis Area and Severity Index 75 (PASI75), PASI90, Disease Activity Score 28-CRP (DAS28-CRP), Short Form 36 (SF36)-physical component summary (PCS), Health Assessment Questionnaire –Disability Index (HAQ-DI), van der Heijde-modified total Sharp score (vdH-mTSS), ACR50, presence of dactylitis (pooled secukinumab regimen), and presence of enthesitis (pooled secukinumab regimen). The primary and secondary endpoints were assessed at Week 24.

Study F2312

Study F2312 was a randomized, double-blind, double-dummy, placebo-controlled, multicenter study of SC secukinumab in prefilled syringes of secukinumab 75 mg SC (n=99), 150 mg SC (n=100), or 300 mg (n=100) versus placebo (n=98) in patients with active PsA. All patients received doses at baseline, Weeks 1, 2, 3, and 4 followed by SC dosing every 4 weeks. At randomization, patients were stratified as TNF α -IR, which was defined in the same manner as study F2306. Approximately 40% of randomized patients were planned to be TNF α -IR. At Week 16, patients on placebo who were non-responders were re-randomized (1:1) to receive either secukinumab 150 mg SC or 300 mg SC every 4 weeks in a blinded fashion for up to 5 years. Non-responder was defined as <20% improvement from baseline in both tender and swollen joint counts. Patients on placebo who were responders at Week 16 were re-randomized (1:1) at Week 24 to receive secukinumab 150 mg SC or 300 mg SC every 4 weeks. Thus, all patients received secukinumab after Week 24. There were no formal escape options for patients randomized to secukinumab.

The primary and secondary endpoints were the same in F2306 as F2312, except F2312 did not include an assessment of radiographic endpoints.

Brief Description of Efficacy Endpoints

- *ACR Response Rates*

In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in RA, which have since been used in drug development for clinical trials in RA.¹ A modified version of the ACR response rate has been utilized to

evaluate efficacy in PsA. Since the pattern of peripheral joint involvement in PsA is different than that of RA, increased joint counts to cover distal interphalangeal of the hands and both proximal and distal interphalangeal joints of the feet are utilized. Thus, The ACR response rate for PsA includes an assessment of 78 joints for tenderness and 76 joints for swelling, as compared to 68 and 66 joints, respectively for RA.

The ACR20 response is calculated as a $\geq 20\%$ improvement in:

- tender joint count (based on 78 joints) and
- swollen joint count (based on 76 joints) and
- 3 of the 5 remaining domains:
 - Patient global assessment (measured on a Visual Analog Scale (VAS), 0-100)
 - Physician global assessment (measured on a VAS, 0-100)
 - Patient's assessment of pain (measured on a VAS, 0-100)
 - Patient's assessment of physical function (Health Assessment Questionnaire-Disability Index (HAQ-DI) score)
 - Acute phase reactant (high sensitivity C-reactive protein [hsCRP] or erythrocyte sedimentation rate [ESR])

ACR50 and ACR70 are similarly calculated, replacing the 20% with 50% and 70% improvement from baseline, respectively.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

The Health Assessment Questionnaire – Disability Index (HAQ-DI) was used to assess the long-term influence of chronic disease on functional ability and activity restriction. The HAQ-DI includes 20 items in 8 categories of functioning in daily life that assess the ability to perform a task over the past week as without any difficulty (0), with some difficulty (1), with much difficulty (2), and unable to do (3). The HAQ-DI score can range from 0 to 3, with 0 indicating no disease, and 3 indicating worst possible disease.² A change in score of ≥ 0.3 is considered as being a clinically important difference for the indication of PsA.

- *Disease Activity Score (DAS-28)*

The DAS28 is a composite index of disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and erythrocyte sedimentation rate (ESR) results.³ An alternative equation is available for use with c-reactive protein (CRP) results. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10.

- *Psoriasis Area and Severity Index (PASI)*

¹ Felson DT, et al. *Arthritis Rheum* 1995;38(6):727-35.

² Fries JF, et al. *Arthritis Rheum* 1980; 23(2)137-45.

³ J Fransen, et al. *Clin Exp Rheumatol* 2005;23(Suppl 39):S93-S99.

The PASI assessment was conducted for patients in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline. The PASI assessed the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling, and thickness.

The head, trunk, upper limbs, and lower limbs were assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions was assigned a score of 0-4. The area covered by lesions on each body region was estimated as a percentage of the total area of that particular body region. PASI scores could range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretical maximum of 72.0.

Based on precedent the following definitions were used:

- PASI75 responders: $\geq 75\%$ improvement (reduction) in PASI score from baseline,
- PASI90 responders: $\geq 90\%$ improvement (reduction) in PASI score from baseline.
- *Leeds Dactylitis Index (LDI)*

The LDI basic measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitis digit. The ratio of circumference is multiplied by a tenderness score, using a modification of LDI which is a binary score (1 for tender, 0 for nontender). If both sides are considered involved, or the circumference of the contralateral digit could not be obtained, the number was compared with data provided in the standard reference tables. The dactylitis count is the number of fingers and toes with dactylitis, with a range of 0-20.

- *Leeds Enthesitis Index (LEI)*

LEI is a validated enthesitis index that uses 6 sites for evaluation of enthesitis (right and left): lateral epicondyle humerus, proximal Achilles, and medial condyle femur.

- *van der Heijde - Modified Total Sharp Score for PsA (vdH-mTSS)*

The vdH-mTSS for PsA⁴ is a method based on the vdH-mTSS method for assessing erosions and joint space narrowing in the hands and feet in RA.⁵ It is a detailed scoring method evaluating erosions, joint space narrowing, (sub)luxation, ankyloses, gross osteolysis, and pencil in cup phenomena. In addition to the joints evaluated for RA, the DIPs of the hands are assessed. Erosions were assessed for each hand (20 locations per hand) and each foot (6 locations per foot). The maximum erosion score was 200 for all 40 hand locations, and 120 for all 12 feet locations. Thus, the total possible erosion score was 320. Joint space narrowing was assessed in each hand (20 locations per hand) and foot (6 locations per foot). The maximum score was 160 for all 40 hand joints, and 48 for all 12 feet joints. Thus, the total

⁴ van der Heijde D, et al. Ann Rheum Dis 2005;64(suppl II):ii61-ii64.

⁵ van der Heijde D, et al. J Rheumatol 2000;27:261-3.

possible joint space narrowing score was 208. Pencil-in-cup and gross osteolysis was evaluated and considered a maximal score for the feature. For vdH-mTSS for PsA, the range of scores is 0 - 528.

Dose Selection

The proposed dose is 300 mg SC at Weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks for patients with coexistent moderate to severe plaque psoriasis (b) (4)

For all other patients, the recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 150 mg every 4 weeks. The currently approved dose for moderate to severe plaque psoriasis is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. The current prescribing information notes that for some patients with moderate to severe plaque psoriasis, a dose of 150 mg may be acceptable.

The Applicant selected the studied doses based on dose-efficacy relationship data from secukinumab studies in PsA and RA, dose-efficacy predictions from studies in moderate to severe plaque psoriasis, and PK models used to predict dose-exposure relationships. The Applicant performed phase 2 studies in PsA and RA (Table 4). Specifically, one phase 2 study with IV dosing in PsA (study CAIN457A2206 [A2206]) and one phase 2 dose-ranging study with SC dosing in RA (study CAIN457F2201 [F2201]) examined different aspects of dosing.

Table 4: Summary of Phase 2 Studies in PsA and RA Submitted in BLA

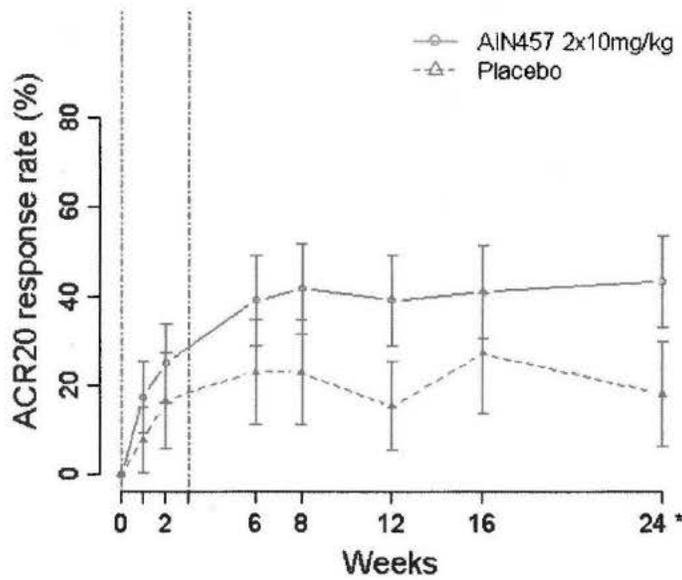
Study (Phase) [dates]	Patient population	Duration (weeks)	Loading dose	Maintenance dose	Primary Endpoint (notable secondary endpoint)	N
CAIN457A2206 (Phase 2) [3/09-12/10]	Active PsA	24	None	2 infusions of 10 mg/kg (day 1 and 22)	ACR20 (wk 6)	42
CAIN457F2201 (Phase 2) [7/09-3/11]	Active RA	16 (I°) 60 (E)	None	25, 75, 150, or 300 mg SC Q4W	ACR20 (wk 16)	237

Source: Summary of Clinical Efficacy, modified from Tables 1-4, page 25

Study A2206 was a phase 2, randomized, double-blind, placebo-controlled, multicenter, 2-arm study comparing two IV doses of secukinumab 10 mg/kg to placebo after 6 weeks in patients with PsA (n=42). Patients received secukinumab (n=28) or placebo (n=14) as single IV doses on Day 1 and Day 22 and were followed for 24 weeks. The primary efficacy assessment was based on ACR20 response rates at Week 6 which were 9/23 (39.1%) for secukinumab and 3/13 (23.1%) for placebo (p=0.27) (Figure 5). While the difference in ACR20 response rates was not statistically different for the secukinumab group compared to placebo, there were numerically greater ACR20, ACR50, and ACR70 responses for secukinumab compared with placebo at all time-points up to Week 24.

Study F2201 was a phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter dose ranging study in patients with active RA despite stable treatment with methotrexate (n=237). Patients were randomized (1:1:1:1:1) to one of the following five treatment groups: secukinumab 25 mg SC Q4W (n=54), 75 mg SC Q4W (n=49), 150 mg SC Q4W (n=43), 300 mg SC Q4W (n=41), or placebo SC Q4W (n=50). The primary efficacy assessment was ACR20 response at Week 16. There was a trend toward greater ACR20 responses with increasing doses of secukinumab for the 25 mg, 75 mg, 150 mg, and 300 mg doses (34%, 47%, 47%, 54%, respectively) versus placebo (36%) (Figure 6).

Figure 5: Mean (SE) ACR20 Responder Rate Over Time per Treatment (PD analysis set) (Study A2206)



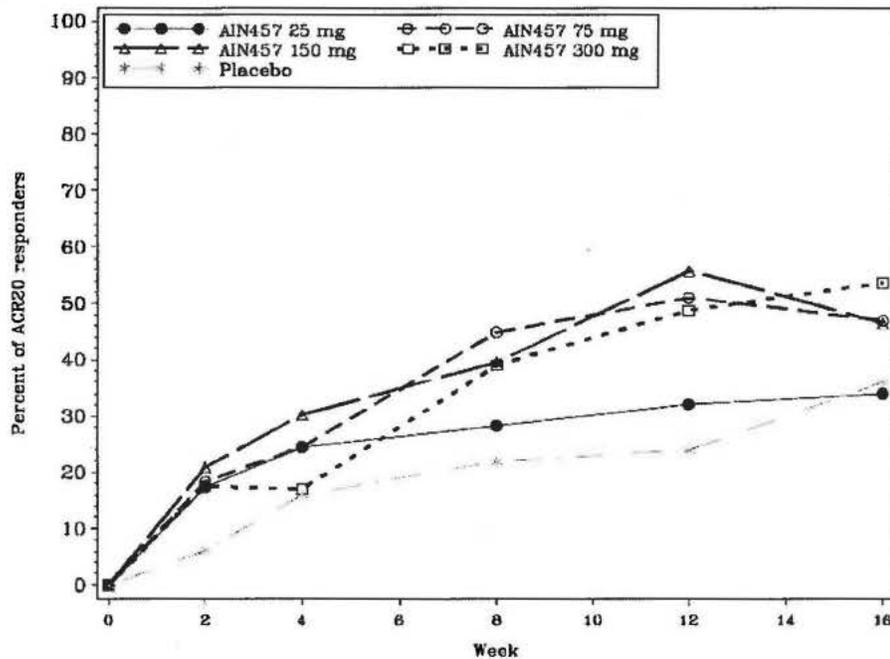
* Week 24 or EOS if early discontinuation.

Dashed blue lines indicate administration of study medication at Day1 and Day22.

Source: PT-Figure 14.2-1.2

Source: Clinical Study Report, Study CAIN457A2206, Figure 11-2, page 100

Figure 6: ACR20 Response over Time Through Week 16, LOCF (full analysis set) (Study F2201)



Source: PT-Figure 14.2-1.1

Source: Clinical study Report, Study CAIN457F2001, Figure 11-1, page 127

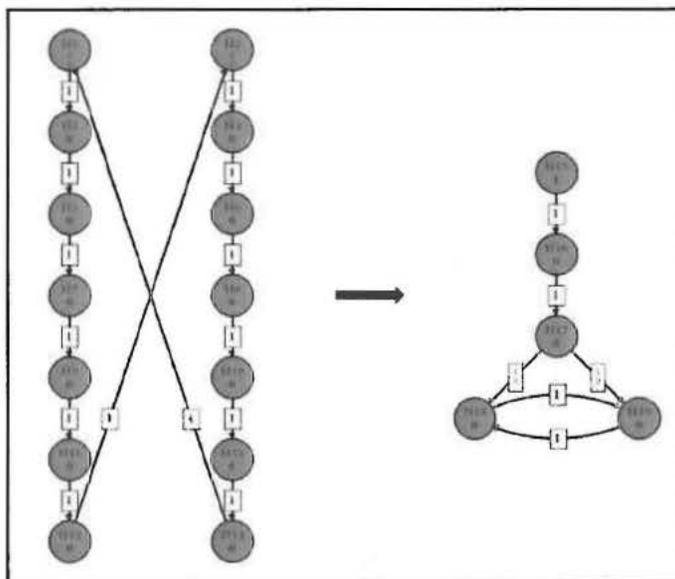
The Applicant felt the results of early proof of concept studies in PsA and RA indicated that a loading regimen, with more frequent initial medication administration, is needed to achieve an early response at a clinically relevant level. The Applicant elected to use two different loading regimens (one with SC doses and the other with IV doses) in their phase 3 program. While there are limitations to comparisons across study and across indication, the overall trajectory of response is similar in RA (Figure 6) and PsA (Figure 5), regardless of whether initial loading doses were utilized. The Applicant did not provide a direct comparison of clinical responses with and without a loading dose. As noted in the regulatory history section above, at multiple meetings, the Agency review team questioned the need for and the justification for the proposed loading regimen (Section 2).

Statistical considerations

The primary analysis population was the Full Analysis Set (FAS) defined as all randomized patients. To evaluate the effect of missing data, the Applicant was asked to perform additional sensitivity analyses including tipping point analyses for the primary endpoint. See the statistical review for additional details.

The primary and secondary efficacy endpoints were tested for each secukinumab dose versus placebo in a testing strategy designed to protect the family-wise type 1 error rate at $\alpha=5\%$ (two-sided). In Study F2305, the Applicant proposed a hierarchical testing procedure with a graphical approach to adjust for the multiple doses and endpoints (Figure 7). A similar strategy was utilized in study F2310 (Figure 8).

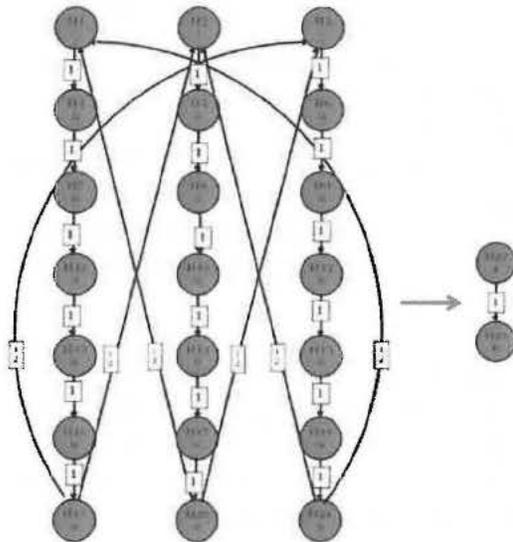
Figure 7: Multiple Testing Strategy in Study F2306



- Primary objective:**
H1: secukinumab 75 mg sc is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24
H2: secukinumab 150 mg sc is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24
- Secondary objectives:**
H3: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis
H4: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis
H5: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis
H6: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis
H7: secukinumab 75 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24
H8: secukinumab 150 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24
H9: secukinumab 75 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for SF36 PCS at Week 24
H10: secukinumab 150 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
H11: secukinumab 75 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
H12: secukinumab 150 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
H13: secukinumab 75 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
H14: secukinumab 150 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
H15: secukinumab pooled regimen (75 mg and 150 mg sc) is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24
H16: secukinumab pooled regimen (75 mg and 150 mg sc) is not different to placebo regimen with respect to presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline
H17: secukinumab pooled regimen (75 mg and 150 mg sc) is not different to placebo regimen with respect to presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline
H18: secukinumab 75 mg sc is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24
H19: secukinumab 150 mg sc is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24

Source: Clinical Study Report, Study CAIN457F2306, modified from Figure 9-2, page 116

Figure 8: Multiple Testing Strategy in Study F2312



Primary objective:

- H1: secukinumab 75 mg sc is not different to placebo regimen with respect to ACR20 response at Week 24
- H2: secukinumab 150 mg sc is not different to placebo regimen with respect to ACR20 response at Week 24
- H3: secukinumab 300 mg sc is not different to placebo regimen with respect to ACR20 response at Week 24

Secondary objectives:

- H4: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24
- H5: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24
- H6: secukinumab 300 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24
- H7: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI90 response at Week 24
- H8: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI90 response at Week 24
- H9: secukinumab 300 mg sc is not different to placebo regimen with respect to PASI90 response at Week 24
- H10: secukinumab 75 mg sc is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at Week 24
- H11: secukinumab 150 mg sc is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at Week 24
- H12: secukinumab 300 mg sc is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at Week 24
- H13: secukinumab 75 mg sc is not different to placebo regimen with respect to the change from baseline in SF36-PCS at Week 24
- H14: secukinumab 150 mg sc is not different to placebo regimen with respect to the change from baseline in SF36-PCS at Week 24
- H15: secukinumab 300 mg sc is not different to placebo regimen with respect to the change from baseline in SF36-PCS at Week 24
- H16: secukinumab 75 mg sc is not different to placebo regimen with respect to the change from baseline in HAQ-DI at Week 24
- H17: secukinumab 150 mg sc is not different to placebo regimen with respect to the change from baseline in HAQ-DI at Week 24
- H18: secukinumab 300 mg sc is not different to placebo regimen with respect to the change from baseline in HAQ-DI at Week 24
- H19: secukinumab 75 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
- H20: secukinumab 150 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
- H21: secukinumab 300 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
- H22: secukinumab pooled regimen (75 mg and 150 mg and 300 mg sc) is not different to placebo regimen with respect to proportion of patients with dactylitis at Week 24 in the subset of patients with dactylitis at baseline
- H23: secukinumab pooled regimen (75 mg and 150 mg and 300 mg sc) is not different to placebo regimen with respect to proportion of patients with enthesitis at Week 24 in the subset of patients with enthesitis at baseline

Source: Clinical Study Report, Study CAIN457F2312, modified from Figure 9-2, page 94

Patient population

The patient population enrolled in studies F2306 and F2312 consisted of adults with active PsA, fulfilling the CASPAR classification criteria. The baseline demographic and disease characteristics of the studies were similar and generally reflective of patients with active PsA.

The majority of patients were white (80% to 96%), less than 65 years of age (89% to 94%), and had a mean age of 47 to 50 years. On average, one half of the patients were female. Approximately two-thirds of patients were naïve to TNF α inhibitors (63% to 71%) and about half used methotrexate (44% to 60%) at baseline. The mean time since diagnosis of PsA was ~7 years. Patients had active PsA with an average of approximately 24 tender joints and 13 swollen joints. The presence of PsA subtypes were generally balanced across treatment groups. Approximately 50-60% of patients had distal interphalangeal joint arthritis, 60-68% had asymmetric peripheral arthritis, 72-90% had polyarticular arthritis, <25% had spondylitis, and <10% had arthritis mutilans. Approximately half of the patients had psoriasis \geq 3% body surface area (BSA), approximately 60% had enthesitis, and approximately 47% had dactylitis at baseline.

A total of 1,003 randomized patients were included in both placebo-controlled efficacy studies F2306 (N=606) and F2312 (N=397). The majority of patients completed Week 24 in Study F2312 (90% to 97%) and Week 52 in Study CAIN457F2306 (80% to 89%). The Applicant provided an interim analysis for Study F2312 and the vast majority of patients were ongoing (81.6% to 93.0%) and had not reached Week 52 at the time of the interim lock.

- **Efficacy review**

Primary endpoint

The primary endpoint for both phase 3 studies was the proportion of patients experiencing an ACR20 response at Week 24. As shown in Table 5 below, all secukinumab treatment regimens were associated with a statistically greater proportion of ACR20 responders compared to placebo in studies F2306 and F2312. In study F2306, the proportion of ACR responders was similar for the 75 mg and 150 mg dose regimens. However, this observation may have been influenced by the large IV loading dose that was administered in this study. In study F2312, the proportion of ACR20 responders was similar for the 150 mg and 300 mg dose regimens and both were numerically higher than the 75 mg dose regimen. Patients in this study received a SC loading regimen with a lower exposure than the IV loading regimen. The proportion of patients with ACR20 responses was 3% higher in the secukinumab 300 mg group compared to the 150 mg group. In subgroup analyses, there was a greater proportion of ACR20 responders with the 300 mg treatment regimen compared to the 150 mg regimen for patients with weight >100 kg and for patients with a history of inadequate response to TNF-inhibitors.

In the pre-specified primary analysis, patients who met escape criteria at Week 16 were considered non-responders in the primary analysis. Given that disproportionately more patients met escape criteria on placebo, Dr. Kim performed sensitivity analyses to assess the robustness of the primary analysis. In addition, the Applicant submitted tipping point analysis results for the primary endpoint. Results of the sensitivity and tipping point analyses were consistent with the primary analysis results.

Evaluation of secukinumab on the individual variables of the ACR response revealed improvement in all of these variables consistent with the primary efficacy analysis for both

doses in study F2306. In study F2312, there was a general trend of favorable improvement with the secukinumab 150 mg and 300 mg dose groups, but much less so with the 75 mg dose group when compared to placebo.

Table 5: Applicant's Analyses of ACR20 Response at Week 24 in Studies F2306 and F2312

	Treatment Group	n/N (%)	Comparison	Odds Ratio (95% CI)	P-value
Study F2306	Secukinumab 75 mg (n=202)	102/202 (51)	vs. placebo	5.5 (3.5, 8.9)	<0.0001
	Secukinumab 150 mg (n=202)	101/202 (50)	vs. placebo	5.4 (3.4, 8.6)	<0.0001
	Placebo (n=202)	35/202 (17)	--	--	--
Study F2312	Secukinumab 75 mg (n=99)	29/99 (29)	vs. placebo	2.3 (1.1, 4.7)	0.02
	Secukinumab 150 mg (n=100)	51/100 (51)	vs. placebo	6.5 (3.3, 13.1)	<0.0001
	Secukinumab 300 mg (n=100)	54/100 (54)	vs. placebo	6.8 (3.4, 13.6)	<0.0001
	Placebo (n=98)	15/98 (15)	--	--	--

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Tables 4 (page 20) and 25 (page 42-3)

Secondary endpoints

Secondary endpoints included proportion of patients with >3% psoriasis skin involvement experiencing a PASI75, PASI90, DAS28-CRP, SF36-PCS, HAQ-DI, dactylitis, and enthesitis. Study F2306 also included mTSS and these results will be discussed separately. As summarized in Table 6, results for the secondary endpoints were consistent with the primary efficacy results in supporting a conclusion of treatment benefit associated with secukinumab treatment. As noted for the primary endpoint, in study F2306, the results of the secondary endpoints were similar for the 75 mg and 150 mg dose regimens. However, this observation may have been influenced by the large IV loading dose that was administered in this study. In study F2312, the results for the secondary endpoints were statistically significant for the 150 mg and 300 mg dose regimens, but not the 75 mg dose regimen. The 75 mg dose regimen is not proposed for labeling. In general, there were numerically higher proportions of responders or larger mean changes for the secukinumab 300 mg group compared to the secukinumab 150 mg group. While many of these differences were small, it may be reasonable to include consideration of the 300 mg dose for patients who continue to have active psoriatic arthritis despite treatment with the 150 mg dose.

The Applicant has proposed inclusion of the proportion of patients with HAQ-DI Improvement >0.3 (b) (4). These results were not statistically significant for the 75 mg dose group, but were for the 150 mg and 300 mg dose groups (b) (4)

Since there is considerably less missing data at Week 16 than Week 24, it is recommended that results for the continuous endpoints, such as the ACR components and HAQ-DI be included at this time point. Estimated effects at Week 16 are more reliable because of considerably less missing data at Week 16 than Week 24. However, the effect of the loading dose may be more pronounced at Week 16 than Week 24.

Table 6: Secondary Endpoints (except mTSS) in Studies F2306 and F2312

	F2306			F2312			
	SCK 75 mg	SCK 150 mg	Placebo	SCK 75 mg	SCK 150 mg	SCK 300 mg	Placebo
PASI75 at Week 24							
% of patients	61	65	8	28	48	63	16
OR (95% CI), p-value	22.1 (9.9, 49.2), <0.0001	19.7 (8.9, 44), <0.0001	--	2.1 (0.7, 5.8), 0.17	5.7 (2.1, 15.3), 0.0006	9.5 (3.3, 27), <0.0001	--
PASI90 at Week 24							
% of patients	49	45	4	12	33	49	9
OR (95% CI), p-value	27.4 (9.3, 80.5), <0.0001	24.6 (8.3, 72.3), <0.0001	--	1.4 (0.4, 5.4), 0.64	6.4 (1.9, 21.5), 0.0029	10.7 (3.1, 36.8), 0.0002	--
Change from Baseline in DAS28-CRP at Week 24							
LS Mean change from baseline	-1.67	-1.62	-0.77	-1.12	-1.58	-1.61	-0.96
Mean difference (SE), p-value	-0.9 (0.15), <0.0001	-0.85 (0.15), <0.0001	--	-0.16 (0.19), 0.38	-0.62 (0.18), 0.0008	-0.65 (0.18), 0.0004	--
Change from Baseline in SF36-PCS at Week 24							
LS Mean change from baseline	5.41	5.91	1.82	4.38	6.39	7.25	1.95
Mean difference (SE), p-value	3.59 (0.87), <0.0001	4.09 (0.87), <0.0001	--	2.42 (1.22), 0.048	4.44 (1.22), 0.0003	5.30 (1.22), <0.0001	--
Change from Baseline in HAQ-DI at Week 24							
LS Mean change from baseline	-0.41	-0.40	-0.17	-0.32	-0.48	-0.56	-0.31
Mean difference (SE), p-value	-0.25 (0.06), <0.0001	-0.23 (0.06), <0.0001	--	-0.01 (0.08), 0.92	-0.17 (0.08), 0.0278	-0.25 (0.08), 0.0013	--
Presence of dactylitis at Week 24							
% of patients	43	52	85	70	50	44	85
OR (95% CI), p-value*	0.12 (0.07, 0.24), <0.0001	0.17 (0.09, 0.33), <0.0001	--	0.51 (0.13, 1.91), 0.31	0.16 (0.04, 0.58), 0.0056	0.14 (0.04, 0.50), 0.0021	--
Presence of enthesitis at Week 24							
% of patients	51	54	87	68	58	52	79
OR (95% CI), p-value	0.13 (0.07, 0.26), <0.0001	0.15 (0.08, 0.30), <0.0001	--	0.58 (0.26, 1.26), 0.17	0.36 (0.17, 0.79), 0.01	0.29 (0.13, 0.65), 0.003	--

Abbreviations: SCK=secukinumab; PASI=Psoriatic Area and Severity Index; DAS28-CRP=disease activity score 28-C-reactive protein; SF36-PCS=short form 36-physical component summary; HAQ-DI=health assessment questionnaire-disability index; OR=odds ratio; CI=confidence interval; SE=standard error

*P-value from pooled doses was <0.0001 for study F2306 and 0.01 for study F2312

^P-value from pooled doses was <0.0001 for study F2306 and 0.006 for study F2312

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Tables 7 (page 24), 8 (25), 10 (26), 12 (28), 18 (31), 20 (31), 28 (47-8), 29 (48), 33 (51), 35 (52), 37 (53)

Inhibition of radiographic progression

Assessment of radiographic progression was based on radiographs assessments at baseline and Week 24. For placebo patients who met the escape criteria at Week 16, radiographs were assessed at the Week 16 visit and Week 24 data were imputed based on the Baseline and Week 16 data using linear extrapolation. They did not have radiographs assessed at Week 24. For secukinumab subjects, the actual Week 24 values were used in the analysis.

The mean change in mTSS at Week 24 in patients treated with secukinumab regimens was statistically significantly less compared to patients treated with placebo (Table 7).

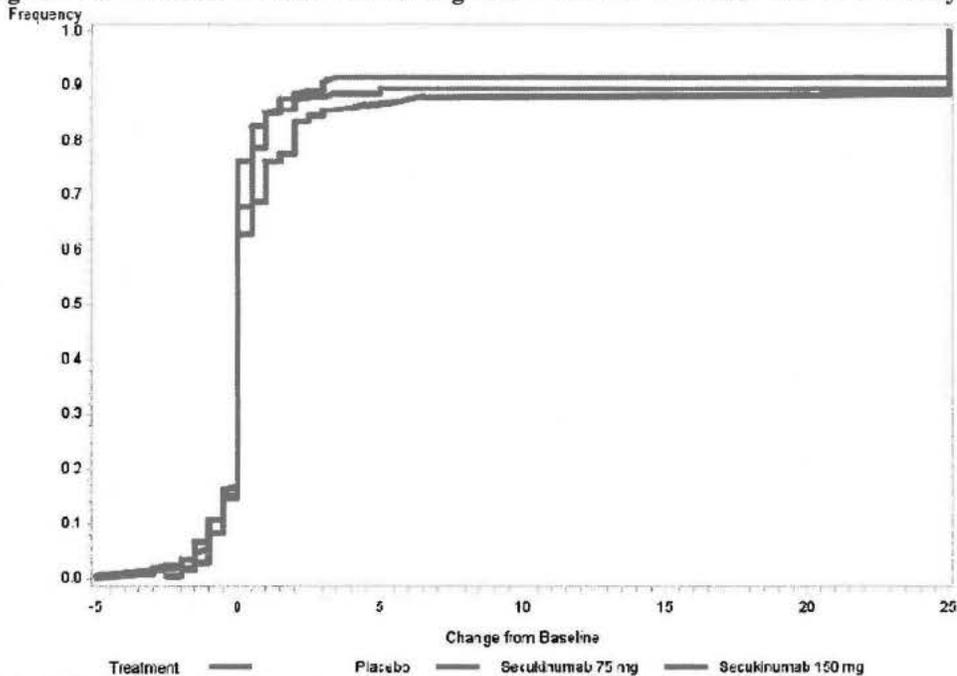
Dr. Kim performed numerous sensitivity analyses to evaluate the robustness of the results. His analyses utilizing ANCOVA and last available observed changes for placebo patients who crossed over to secukinumab at Week 16 were consistent with the Applicant's pre-specified analysis with linearly extrapolated data for placebo escapers or other missing data. However, an analysis excluding outliers defined as absolute changes greater than 7 units (which was considered extreme) did not show statistically significant difference between the secukinumab 150 mg group and the placebo group. The cumulative distribution curves with worst score imputation for missing data only showed some separation of the curves between secukinumab regimens and placebo (Figure 9). A notable limitation of the data is that the study utilized a dosing regimen that is not proposed for marketing. As noted in Section 5, this dosing regimen is associated with substantially higher loading dose that causes much greater exposure than the proposed dosing regimen. It is unclear if efficacy results with this higher exposure will also be seen with the proposed lower dose regimen. In addition, the evidence is based on a single study and there is no supportive data from another indication, such as RA. Lastly, patients who escaped at Week 16 did not have x-rays at Week 24. Thus, the analyses rely on strong and untestable assumptions via linear extrapolation. Thus, although the data are suggestive of a possible benefit, it is not possible to make definitive conclusions about the treatment effect of secukinumab on structural damage progression in PsA.

Table 7: Analysis of Change from Baseline in mTSS at Week 24 in Study F2306

	Treatment Group	n	Mean Change	Comparison	Mean Difference (SE)	P-value
Study F2306	Secukinumab 75 mg (n=202)	181	0.02	vs. placebo	-0.54 (0.22)	0.0132
	Secukinumab 150 mg (n=202)	185	0.13	vs. placebo	-0.47 (0.20)	0.0212
	Placebo (n=202)	179	0.57			

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Table 14, page 29

Figure 9: Cumulative Distribution of Change from Baseline in mTSS at Week 24 in Study F2306



Note: Missing data were imputed with the worst score.
Source: Dr. Yongman Kim's Statistical Review dated 12/11/15, page 30

Efficacy by previous response to anti-TNF/300 mg dose regimen

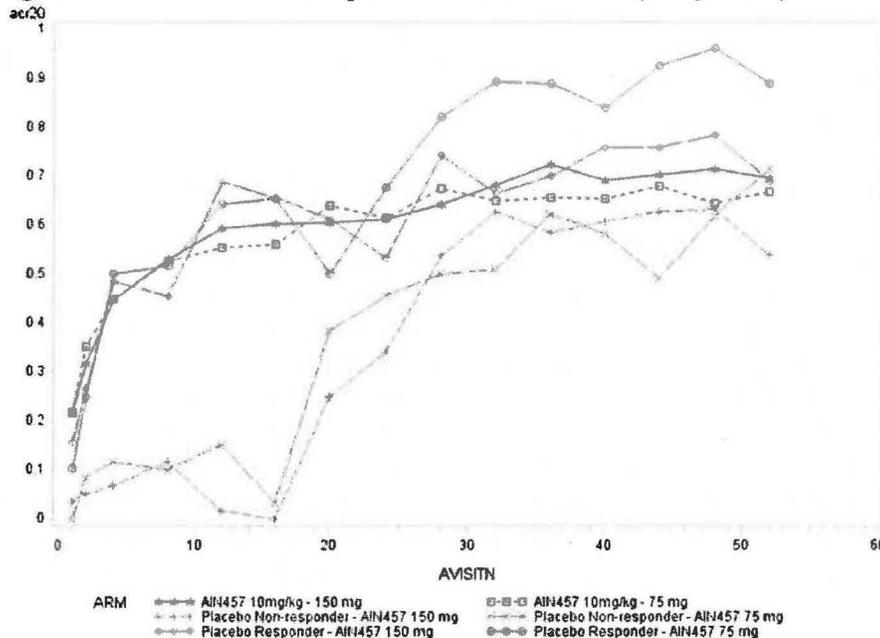
(b) (4)

. In study F2312, in the subgroup of patients with psoriasis, the PASI90 response rate for secukinumab 300 mg dose (49%) was numerically higher than the rate for the secukinumab 150 mg dose (33%). These results, combined with the results from the psoriasis program that supported approval of the 300 mg dose for the psoriasis indication support the Applicant's use of the secukinumab 300 mg dose in the subset of PsA patients with moderate to severe psoriasis. In the subgroup of TNF α inhibitor-IR the ACR20 response rate for the secukinumab 300 mg dose (46%) was numerically higher than the rate for the secukinumab 150 mg dose (30%). This was one of many prospectively planned subgroup analyses and it is difficult to determine whether the heterogeneity is true or due to chance. Further, a history of inadequate response to anti-TNF inhibitor treatment does not identify a specific group of patients and is subject to interpretation given that it is based on patient history. It is unclear if failure to respond to one TNF-inhibitor defines a specific patient population. (b) (4)

Loading dose considerations

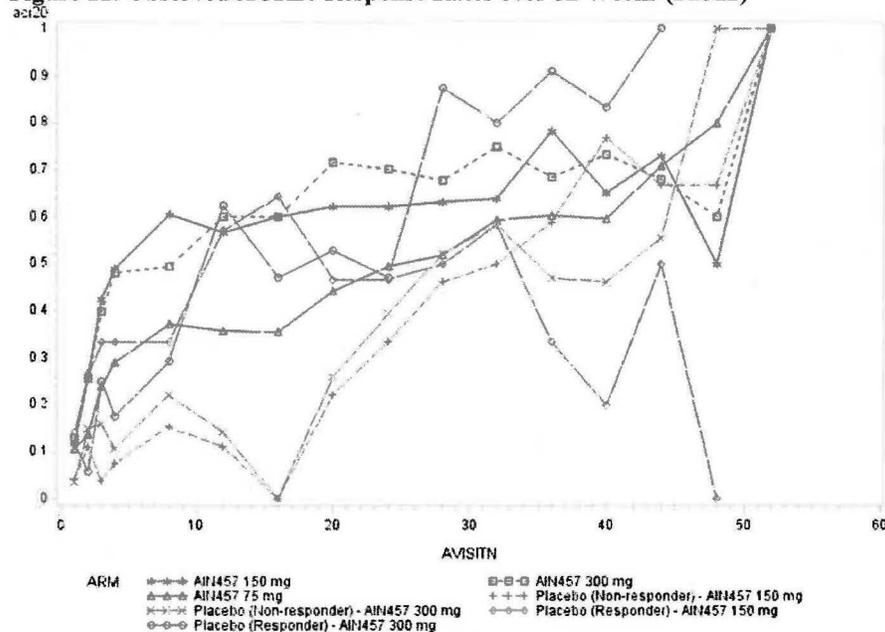
The use of loading doses in both studies was a major consideration during the review. There was a clinical concern that the loading doses may have impacted the efficacy results at 24 weeks due to residual effects of the loading doses. Thus, there was a question of whether efficacy would be maintained over time or if the efficacy would ultimately decline over time. Given these concerns, FDA performed exploratory analyses evaluating the patients randomized to placebo who crossed over to secukinumab at 16 or 24 weeks and had no loading doses. While there are limitations to these analyses given their post-hoc nature, impact of dropout, and small number of patients, they suggested that even without a loading dose, patients achieved similar ACR20 responses in both studies (see statistical review). In addition, the responses over 52 weeks were evaluated to assure that efficacy did not decline over time (Figure 10, Figure 11). There are limitations to these analyses due to survivor bias since patients who are doing well tend to remain in the study. However, these results do suggest that efficacy did not decrease markedly during the maintenance dosing phase. Thus, these data and analyses provide support for the Applicant's proposed dosing regimen.

Figure 10: Observed ACR20 response rates over 52 weeks (Study F2306)



Source: Dr. Yongman Kim's Statistical Review dated 12/11/15, page 63

Figure 11: Observed ACR20 Response Rates over 52 Weeks (F2312)



Source: Dr. Yongman Kim's Statistical Review dated 12/11/15, page 65

- Includes discussion of notable efficacy issues both resolved and outstanding

The clinical and statistical teams are in agreement that studies F2306 and F2312 provide substantial evidence of efficacy of secukinumab for PsA. In addition, the review team is in agreement that the efficacy results from the PsA trials do not justify the loading dose for all patients, but it can be an option for some patients. Further, the team is in agreement that some patients may have better responses with 300 mg compared to 150 mg. Thus, there is consideration of whether the higher 300 mg dose regimen should be an option for some patients with PsA, while the recommended dose is 150 mg. The review team agrees that for PsA patients with moderate to severe plaque psoriasis, and for consistency with the approved labeling for the psoriasis indication, the dosage and administration will be the same as for patients with plaque psoriasis (300 mg by SC injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. For some patients a dose of 150 mg may be acceptable).

8. Safety

Secukinumab has been approved since January 21, 2015 for moderate to severe plaque psoriasis, and psoriasis patients represent the majority of the accrued exposure with this product. In the original BLA safety database, infections occurred in the secukinumab safety database. In placebo controlled trials, a higher rate of infections was observed in secukinumab-treated patients compared to placebo-treated patients. Serious infections were included in the Warnings section of the label.

Exacerbations of Crohn's disease (CD), in some cases serious, were observed in secukinumab-treated patients during clinical trials. Of note, the Applicant evaluated the efficacy of

secukinumab in CD (b) (4) in a phase 2, randomized, double blind study in 59 patients with active CD (AIN457A2202). The primary outcome measure was the Crohn's Disease Activity Index (CDAI) change from baseline to 6 weeks after infusion 1. The primary and secondary endpoint analyses showed consistent trends toward worse outcomes on secukinumab as compared to placebo. In addition, the severity of adverse events was remarkably higher on secukinumab than placebo, including worsening of Crohn's disease.

(b) (4) In the psoriasis studies, there were 3,430 patients on secukinumab and nine adverse events related to inflammatory bowel disease (IBD) (4 ulcerative colitis, 3 CD, 1 anal fistula, and 1 cholangitis sclerosing). Of the 323 patients on etanercept, there was one case of IBD related to ulcerative colitis (UC). In the secukinumab group, of the four UC cases, three patients were newly diagnosed and one patient had a flare. Of the three CD cases, one patient was newly diagnosed and the other two were exacerbations. An additional exacerbation of Crohn's disease occurred during the maintenance period. The current secukinumab label includes a Warning for exacerbations of CD. It does not include information related to the development of IBD or exacerbations of UC.

- **Discuss the adequacy of the database, major findings/signals, special studies, etc.**

In the PsA trials, 1,045 patients with PsA were studied in two phase 3 studies (CAIN457F2312, N=397) and CAIN457F2306, N=606) and one phase 2 study (CAIN457A2206, N=42) along with its extension CAIN457A2206E1 (N=28). Studies CAIN457F2306 and CAIN457F2312 are ongoing, but safety data from at least 24 weeks (F2312) or 52 weeks (F2306) were included in the application. In the two phase 3 studies in PsA, 974 patients received any exposure to secukinumab, 865 patients received at least 24 weeks of secukinumab, and 453 patients received at least 52 weeks of secukinumab. Thus, the majority of the safety experience with secukinumab has been in the psoriasis clinical development program, where over 3,340 psoriasis patients were exposed to at least one dose of secukinumab, 2,751 patients had at least 6 months of exposure, and 1,641 patients were treated for at least one year. However, the safety data provided from the PsA trials are adequate to evaluate the safety profile of secukinumab in PsA and provide an assessment of the relative safety in PsA versus psoriasis.

In general, the safety profile of secukinumab in PsA appears to be consistent with the safety profile of secukinumab in psoriasis. However, given the observation of new cases and exacerbations of both UC and CD throughout the secukinumab development programs, the label will be updated to reflect a more generalized risk of IBD, rather than just being restricted to CD.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

There was one death in the PsA trials: one in the IV-75 mg group due to an intracranial hemorrhage. The patient was a 57 year old woman with multiple risk factors for a

cerebrovascular accident, including hypertension, chronic renal insufficiency, congestive heart failure, diabetes mellitus, and prior stroke and vascular disease. The patient received the last dose of study medication on Day 225 and presented on Day 245 with severe hemiplegia. The patient was found to have a severe intracranial venous sinus thrombosis. A causal relationship with secukinumab could not be established.

Serious Adverse Events

Overall, in the first 16 weeks of the phase 3 PsA trials, the proportion of patients with serious adverse events (SAEs) was not elevated in the secukinumab treatment arms (~3%) compared to placebo (4%). There was a numerical increase in the proportion of patients with serious infections in the secukinumab 300 mg SC dose group compared to the 75 mg and 150 mg doses and placebo, but this was based on a very small number of affected patients (n=3, 3% for secukinumab 300 mg vs. 0 for 75 mg SC, n=1, 1% for 150 mg SC and n=1, 0.3% for placebo). Erysipelas (n=2) was the only serious infection reported in more than a single patient in the Any secukinumab group.

There did not appear to be a dose-dependent relationship for SAEs when comparing between the 75 mg SC, 150 mg SC, and 300 mg SC dose groups (4%, 1%, and 5%, respectively) and no marked difference was observed for the IV dose groups (IV-75 mg: 3% and IV-150 mg: 5%). In the secukinumab groups, the SAEs included cerebrovascular accident (n=2), erysipelas (n=2), abdominal pain (n=1), angina pectoris (n=1), and atrial fibrillation (n=1).

Discontinuations Due to Adverse Events

During the first 16 weeks, the proportion of patients with AEs causing discontinuation of study treatment was low and was not elevated in the secukinumab groups (2%) compared to the placebo group (3%).

Common Adverse Events

Approximately 48-65% of patients in each treatment group (placebo, secukinumab 75 mg, secukinumab 150 mg, secukinumab 300 mg, secukinumab 10 mg/kg-75 mg, and secukinumab 10 mg/kg-150 mg) experienced an adverse event during the first 16 weeks of the phase 3 PsA trials. After 16 weeks, patients receiving placebo who were non-responders were switched to secukinumab, so the first 16 weeks reflect truly controlled results. Comparing the proportion of adverse events between the three groups that received the subcutaneous loading regimen, there appeared to be a greater proportion of patients with specific adverse events in the 300 mg compared to the 150 or 75 mg dose groups, but many of these were lower than placebo. During the 16-week placebo-controlled period of the trials, the overall proportion of patients with adverse events was similar in the secukinumab and placebo-treatment groups (59% and 58%, respectively). The adverse events that occurred at a proportion of at least 2% and at a higher proportion in the secukinumab groups than the placebo groups during the 16-week placebo-controlled period were nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia.

- **Immunogenicity**

Approximately 0.1% of patients treated with secukinumab in the phase 3 PsA studies developed anti-drug antibodies (ADA) to secukinumab. No clear trends regarding the impact of ADA positivity on efficacy or safety were evident on the basis of this submission. See Section 5 for additional discussion of immunogenicity.

- **Special safety concerns**

Inflammatory Bowel Disease

In the original psoriasis studies, there were 3,430 patients on secukinumab and nine adverse events related to IBD (4 UC, 4 CD, 1 anal fistula, 1 cholangitis sclerosing). In the secukinumab group, of the four UC cases, three patients were newly diagnosed and one patient had a flare. Of the four CD cases, one patient was newly diagnosed and the other three were disease exacerbations. There was one new onset case of ulcerative colitis in the etanercept treatment group and none in the placebo. The current secukinumab label includes a Warning for exacerbations of CD. It does not include information related to the development of IBD or exacerbations of UC.

Patients in the PsA trial could have a history of Crohn's disease or other prior gastrointestinal disease. Patients were excluded if they had active inflammatory bowel disease. In PsA, there were four cases of IBD during the entire treatment period (any secukinumab: n=3, placebo: n=1). In the placebo group, there was one new diagnosis of CD and in the secukinumab group there were 2 cases of diarrhea hemorrhagic (one of the cases was a diagnosis of ulcerative colitis 2 years after the onset of diarrhea hemorrhagic) and 1 newly diagnosed CD. In the secukinumab treatment arm, one of the cases related to IBD was serious as it required the patient to be hospitalized.

Hypersensitivity

No cases of anaphylaxis were reported in the phase 3 PsA studies. During the entire treatment period, cases of hypersensitivity events, including rash (2%) and urticarial (1%) were reported, but were non-serious.

Infections

During the first 16 weeks, the overall incidence of infections and infestations (SOC) was higher in the any secukinumab group compared with the placebo group (29% vs. 26%, respectively). There was no clinically meaningful difference between the 150 mg and 300 mg SC groups (30% and 29%, respectively). The most common infections in the any secukinumab group were nasopharyngitis and upper respiratory tract infections. One serious infection of tonsillitis occurred during the 16 week controlled period in a patient receiving IV-150 mg.

Over the entire treatment period, a total of 15 candida infections, the most common being oral candidiasis, were reported across secukinumab-treated groups (vs. 0 in the placebo group). There were two cases of esophageal candidiasis. Dose-dependency was observed in the exposure adjusted incidence rate of Canida infections. Over the entire treatment period, there were three opportunistic infections (two cases of esophageal candidiasis and one case of herpes zoster cutaneous disseminated). The current secukinumab label includes information regarding the risk of candida and herpes viral infections.

The profile of infections was similar between the first 16 weeks and the entire treatment period. In addition, the profile of infections was similar in the PsA program compared to the psoriasis program.

Malignancies

A total of 6 malignancies occurred in the phase 3 PsA trials during the entire treatment period (five in the secukinumab groups and one in the placebo group). In the secukinumab treatment group, there were three basal cell carcinomas, one squamous cell carcinoma, and one prostate cancer. In the placebo group, there was one case of intraductal proliferative breast lesion. The types of malignancies that were observed would be expected in the underlying patient populations.

Immune/Administration Reactions

The Applicant performed a search for administration or immune reactions, including allergic reactions, anaphylaxis and immunogenicity utilizing the following queries: Immune/administration reactions by broad NMQ, comprised of 3 SMQs of anaphylactic reactions, angioedema and severe cutaneous adverse reactions, and 5 High Level Group Terms of administration site reactions, allergic conditions, autoimmune disorders, immune disorders NEC, and immunology and allergy investigations. During the first 16 weeks, the incidence of immune/administration reactions was higher in the placebo group (14%) than in the secukinumab-treated groups (13%).

Suicidal Ideation and Behavior

Suicidal ideation and behavior is a submission specific safety consideration in PsA and psoriasis. Thus, the Agency requested the Applicant conduct a retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for patients with PsA and plaque patients. This evaluation did not reveal specific safety signals.

Cardiovascular Safety

An independent Cardiovascular and Cerebrovascular Safety Adjudication Committee (CCV-AC) was established to review and adjudicate potential major adverse cardiovascular event

(MACE) cases in a blinded manner on a program-wide basis. Potential cases of MACE were identified according to the following pre-specified criteria in the CCV-AC Charter:

- Preferred terms belong to the 2 NMQs of MACE (myocardial infarction) and MACE (strokes)
- Preferred terms with a fatal outcome belonging to the SOC of “cardiac disorders” or “vascular disorders,” plus the preferred term of “death.”

Seven adjudicated cases were confirmed cases, including 3 myocardial infarctions and 4 strokes. All of the cases had prior or active cardiovascular disease or relevant risk factors. Similar findings were noted during the clinical development program in psoriasis and the Division of Cardiorenal Products was consulted during review of that application. It was not felt that the results were suggestive of a cardiovascular safety issue. Similarly, the types of events noted in the studies in PsA would be anticipated in the patient population. The overall exposure-adjusted incidence rate of adjudication-confirmed MACE over the treatment period in the phase 3 PsA studies was 0.73 per 100 patient years (95% CI: 0.3 to 1.5). The Applicant noted that the exposure-adjusted MACE rate is similar to that anticipated for patients with spondyloarthritis, including PsA and AS. A recent study⁶ in PsA patients demonstrated an incident rate of 0.57 per 100 patient years, which is similar to the observed rate in the phase 3 PsA studies. While there were no cases observed in the placebo group, the short exposure duration yields a broad confidence interval of 0 to 3.49.

Potential Impact of Loading Regimen

No differences in safety as noted by loading regimen for any of the major safety analyses.

- **Safety conclusions**

Dr. Nair has concluded that the safety profile of secukinumab in the PsA studies is consistent with the known safety profile of secukinumab from the psoriasis experience, and no new safety signals have been identified. I concur with Dr. Nair’s conclusions.

- **Discussion of notable safety issues (resolved or outstanding)**

See above.

9. Advisory Committee Meeting

Secukinumab is an approved product, and no issues were identified in these submissions that warranted advisory committee discussion. Therefore, no advisory committee meeting was convened.

⁶ Ogdie A, et al. *Ann Rheum Dis* 2014;74:326-32.

10. Pediatrics

- **Peds exclusivity board review** – PPSR/WR – Not applicable
- **PeRC Review Outcome**—PMCs, deferrals, waivers, pediatric plan, peds assessment

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Applicant requested, and was granted, a full waiver from PREA requirements for the reason that studies are impossible or highly impractical. This is because the subset of children who would develop PsA is difficult to specifically diagnose among patients with juvenile idiopathic arthritis. This was discussed at the Pediatric Review Committee (PeRC) meeting on October 17, 2015, and PeRC was in agreement with granting the waiver.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues or concern**—Not applicable.
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **Office of Scientific Investigation (OSI) audits**—Not performed for this supplemental application. Inspections were done with the original BLA and no issues were identified to warrant clinical study site inspections for this submission.
- **Other outstanding regulatory issues**—None

12. Labeling

- **Proprietary name**—Consentyx (Already approved)
- **Physician labeling**

The Division of Dermatology and Dental Products (DDDP) approved secukinumab for the treatment of moderate to severe plaque psoriasis on January 21, 2015. Thus, DDDP is the primary division for the secukinumab labeling and was involved in labeling discussions with the Applicant. Labeling discussions are ongoing at the time of this review. Major issues and points of discussion are highlighted below:

- 1) Indications and usage—“COSENTYX is indicated for the treatment of adult patients with active psoriatic arthritis. (b) (4)
(b) (4)
 - The statement regarding the (b) (4) will be moved to the dosage and administration section.

2) Dosage and Administration— (b) (4) patients with coexistent moderate to severe plaque psoriasis (b) (4)

- While it is reasonable for patients with PsA with coexistent moderate to severe plaque psoriasis to follow the dosing and administration instructions for plaque psoriasis. (b) (4)

(b) (4) Further, it is unclear if a loading dose is needed and the wording will be updated to reflect that doses for PsA can be administered with or without a loading regimen. It may be reasonable to offer the 300 mg dose as an option for the management of psoriatic arthritis.

- 3) Warnings and Precautions: The sections related to infections and inflammatory bowel disease will be updated to provide additional data regarding the experiences in AS and PsA. In addition, the language in the current “exacerbation of Crohn’s disease” section will be strengthened to note that both new onset and worsening cases of inflammatory bowel disease have occurred and that this safety signal has been seen in all of the secukinumab development programs. The text regarding hypersensitivity reactions will be changed back to the currently approved language.
- 4) Adverse Reactions section: The Applicant originally proposed a statement noting that the safety in PsA was similar to that seen in the psoriasis development program. The Adverse Reactions section will be updated to include additional information regarding the safety experience in PsA.
- 5) Clinical Studies section:

- There are ongoing discussions with DDDP regarding the most appropriate way to display information regarding changes in psoriasis skin manifestations during the clinical trial. The Applicant proposed (b) (4)

(b) (4) However, there were questions about the clinical meaningfulness of these data given that patients with milder psoriasis were included in these analyses. Thus, the proposal to the Applicant is to include a more general statement regarding the efficacy for skin manifestations, as measured by the PASI (b) (4)

- (b) (4)
- (b) (4)

- Language and data pertaining to other endpoints in the clinical studies section will also need revision.
- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above. The proposed package insert was reviewed by the Office of Prescription Drug Promotion (OPDP) and changes were recommended.

Labeling negotiations are ongoing with the Applicant at the time of this review.

- **Carton and immediate container labels (if problems are noted)**

The labeling was reviewed by DMEPA and no recommended changes were recommended.

- **Patient labeling/Medication guide (if considered or required)**

The Division of Medical Policy Programs (DMPP) reviewed the Medication Guide. Given the other labeling changes, revisions to the Medication Guide will be needed. Negotiations are ongoing at the time of this review.

6) Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this supplemental BLA for psoriatic arthritis provided agreement can be reached with the Applicant on revisions to the proposed labeling changes.

I recommend a complete response for inhibition of radiographic progression in patients who have psoriatic arthritis.

- **Risk Benefit Assessment**

The risk-benefit profile is favorable of secukinumab for the treatment of active psoriatic arthritis in adults. Substantial evidence was provided that secukinumab treatment was associated with improvement in clinical responses, as captured by ACR response criteria, HAQ-DI, PASI ^{(b) (4)}. The safety profile of secukinumab was consistent with the known safety profile of secukinumab as established in the approved plaque psoriasis population.

- **Recommendations for Postmarketing Risk Evaluation and Management Strategies**

A Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements or commitments are warranted on the basis of this supplemental BLA.

- **Recommended comments to applicant**

Recommended comments to the Applicant regarding inhibition of structural progression in psoriatic arthritis:

- The submitted data do not provide substantial evidence to support the claims of inhibition of structural damage progression for the proposed dosing regimen due to the use of a dosing regimen with a higher exposure.
 - Provide data from a blinded, controlled clinical trial to demonstrate efficacy for inhibition of structural damage progression.

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

/s/

JANET W MAYNARD
12/23/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type Biologic License Application
Application Number(s) 125504/1
Priority or Standard standard

Submit Date(s) March 18, 2015
Received Date(s) March 18, 2015
PDUFA Goal Date January 18, 2016
Division / Office Division of Pulmonary, Allergy,
and Rheumatology

Reviewer Name(s) Raj Nair, MD
Review Completion Date December 9, 2015

Established Name secukinumab
(Proposed) Trade Name Cosentyx
Therapeutic Class IL-17A inhibitor
Applicant Novartis

Formulation(s) 150 mg/mL solution in single-
use pen; 150 mg/mL solution
in pre-filled syringe; 150 mg
lyophilized powder in single-
use vial for reconstitution
Dosing Regimen 150 mg SC injection at weeks
0,1,2,3, and 4 followed by
every 4 weeks

300 mg SC injection at weeks 0, 1,2,3, and 4 followed by every 4 weeks in patients with

 (b) (4)

moderate to severe psoriasis

Indication(s)	Psoriatic arthritis
Intended Population(s)	psoriatic arthritis

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for supplemental biologic license application (sBLA) 125504/1, secukinumab for the treatment of psoriatic arthritis (PsA), is **approval**. This recommendation is based on adequate evidence of efficacy and safety for the proposed indication. Of note, secukinumab was approved for moderate to severe plaque psoriasis on January 21, 2015.

To support this application, the Applicant submitted data from two phase 3 clinical studies in PsA. Study F2306 consisted of a 2 year double-blind period. The Applicant submitted data to Week 52. During the double-blind period, 202 patients received 10 mg/kg IV loading doses of secukinumab followed by a 75 mg subcutaneous maintenance dose, 202 patients received an 10 mg/kg IV loading doses of secukinumab followed by a 150 mg subcutaneous maintenance dose, and 202 patients received placebo. After week 24, all patients received secukinumab. Patients were included who met CIASsification criteria for Psoriatic ARthritis (CASPAR) and with symptoms for at least 6 months with moderate to severe PsA, including ≥ 3 tender joints and ≥ 3 swollen joints at Baseline. Study F2312 consisted of a 52-week double-blind period. The Applicant submitted an interim analysis at week 24. During the double-blind period, 99 patients received 5 weekly subcutaneous loading doses followed by a 75 mg subcutaneous maintenance dose, 100 patients received 5 weekly subcutaneous loading doses followed by a 150 mg subcutaneous maintenance dose, 100 patients received 5 weekly subcutaneous loading doses followed by a 300 mg subcutaneous maintenance dose, and 98 patients received placebo. After week 24, all patients received secukinumab. Patients were included who met CASPAR and had symptoms for at least 6 months with moderate to severe PsA, including ≥ 3 tender joints and ≥ 3 swollen joints at Baseline.

From an efficacy and safety perspective, studies F2306 and F2312 provided sufficient data to support the use of secukinumab for PsA.

1.2 Risk Benefit Assessment

Introduction

This document provides a clinical review of secukinumab (Cosentyx®) for the proposed indication of PsA.

Secukinumab is a fully human monoclonal anti-human antibody of the IgG1/kappa isotype that targets interleukin-17A (IL-17A). IL-17A is mainly produced by Th17 cells and is elevated in several autoimmune diseases, including PsA.

Background on the Proposed Indication: Psoriatic Arthritis

The Applicant's proposed indication is psoriatic arthritis (PsA). PsA is a chronic, inflammatory arthritis that affects approximately 15% of patients with psoriasis. The Applicant has used CASPAR to identify patients with PsA¹. These criteria were used in clinical trials to support product registration in PsA. To meet CASPAR criteria, patients must have inflammatory articular disease and at least 3 points in the following 5 categories:

- Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
 - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist. (2 points)
 - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. (1 point)
 - A family history of psoriasis is defined as a history of psoriasis in a first- or second degree relative according to patient report. (1 point)
- Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (1 point)
- A negative test result for the presence of rheumatoid factor by any method except latex (1 point)
- Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (1 point)
- Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (1 point)

Depending on severity of disease, patients can be treated with NSAIDs, DMARDs, and anti-TNF drugs.

Overview of Clinical Program

The Applicant submitted the results from two phase 3 trials, each with 24-week controlled periods as the primary basis for efficacy and safety of secukinumab for the treatment of signs and symptoms of PsA:

- Trial F2306: Randomized, 24-week placebo-controlled, double-blind period with active PsA (52-week interim analysis)

¹ Taylor W, Gladman D, Helliwell et al. Classification criteria for psoriatic arthritis. *Arthritis Rheum* 2006; 54:2665-73.

- Trial F2312: Randomized, 24-week placebo-controlled, double-blind period with active PsA (24-week interim analysis)

During the double blind period for study F2306, 606 patients were randomized to secukinumab 75 mg SC every 4 weeks with an initial IV loading dose, 150 mg SC every 4 weeks with an initial IV loading dose, or placebo. The dose was based on previous phase 2 studies in PsA and rheumatoid arthritis (RA). Patients were included in the trial who met CASPAR and with symptoms for at least 6 months with moderate to severe PsA who must have at baseline ≥ 3 tender joints and ≥ 3 swollen joints. The primary and secondary analyses were pre-specified in this overall population.

During the double blind period for study F2312, 397 patients were randomized to secukinumab 75 mg SC every 4 weeks with a SC load, 150 mg SC every 4 weeks with a SC load, 300 mg SC every 4 weeks with a SC load, or placebo. The dose was based on previous phase 2 studies in PsA and rheumatoid arthritis (RA). Patients were included in the trial that met CASPAR and had symptoms for at least 6 months with moderate to severe PsA who must have at baseline ≥ 3 tender joints and ≥ 3 swollen joints. The primary and secondary analyses were pre-specified in this overall population.

The different dosing regimens and the use of loading doses were major considerations during the review. The studies F2306 and F2312 used different loading regimens and F2312 used a 300 mg every 4 weeks maintenance dose that was not studied in F2306. The ability of the study medication to maintain efficacy without the loading dose was examined. In addition, the use of secukinumab 300 mg every 4 weeks for subgroups specified by the Applicant was also examined.

Summary of Efficacy

The studies F2306 and F2312 were submitted as the primary source of efficacy data for secukinumab in the treatment of PsA. Both trials consisted of a 24-week, placebo-controlled double-blind period at which time the primary efficacy endpoint was measured. At week 16 or 24, patients randomized to placebo were re-randomized to secukinumab without a loading dose. The primary endpoint was ACR20 response at week 24. Secondary analyses were performed at Week 24. The trials were well controlled and had endpoints that were considered acceptable for efficacy evaluations in PsA.

In the pre-specified primary analysis of study F2306, secukinumab met the primary and secondary endpoints. In study F2306, patients received 10 mg/kg IV loading doses at weeks 0, 2, and 4. Given the magnitude of exposure from the IV loading dose, it was unclear if the treatment effect seen at the time of the primary endpoint was attributable to the SC dosing or was due to continued effects from the IV loading dose. Thus, there were concerns regarding whether maintenance of effect was established. Specifically, there was concern that chronic treatment might not maintain similar levels of efficacy

since patients would have lower exposures than during the initial loading dose phase. In order to evaluate the effect of the loading dose, the placebo patients randomized to secukinumab were analyzed and appeared to have similar responses in ACR20 without a load as those who were initially randomized to secukinumab and received a loading dose.

In the pre-specified primary analysis of study F2312, secukinumab met the primary endpoint. The 75 mg dose did not meet secondary endpoints, the 150 mg dose met most secondary endpoints, and the 300 mg dose met all secondary endpoints. In study F2312, patients received 5 weekly loading doses of SC secukinumab. Given the magnitude of exposure from the higher SC loading doses, it was unclear if the treatment effect seen at the time of the primary endpoint was attributable to the maintenance dosing or continued effects from the SC loading doses. There were concerns regarding whether efficacy would be maintained. Thus, additional analyses were performed evaluating the placebo patients randomized to secukinumab without a loading dose and were shown to have similar responses in ACR20 without a load as those who were initially randomized to secukinumab and received a loading dose. Further, these patients were able to maintain clinical responses.

While there are limitations to the analyses for placebo patients who switched to secukinumab without loading dose they provide evidence that secukinumab is effective without the administration of a loading dose and would be anticipated to provide efficacy as maintenance therapy for PsA.

Summary of Safety

The safety information for secukinumab in PsA is obtained from two phase 3 studies during which 974 patients received one dose of secukinumab. The Applicant submitted 16 weeks of double-blind, placebo-controlled data and up to 52 weeks of safety data. The median duration of treatment was 112 days with a range of 8 to 226 days.

One death was reported in study F2306 on Day 248. A 75 year old white female died on Day 248 of the study due to intracranial hemorrhage.

Serious adverse events (SAEs) were low and comparable across groups and placebo. The 300 mg dose appeared to have a slightly higher rate of serious infections compared to the 150 mg or placebo.

The most common AEs occurring in the secukinumab treatment groups were nasopharyngitis (7%), upper respiratory tract infection (6.3%), headache (5%), nausea (2.8%), diarrhea (2.4%), and hypercholesterolemia (2.4%). Besides diarrhea, the secukinumab treatment groups had a higher percentage of these common adverse events when compared to placebo

Due to specific safety concern with secukinumab, analyses were conducted related to AEs of special interest including infections, malignancies, MACE events, hypersensitivity reactions, inflammatory bowel disease, and hematologic cytopenias.

There were additional cases of new onset inflammatory bowel disease and flares of inflammatory bowel disease similar to what was seen in psoriasis trials. Due to a consistent pattern of cases of new inflammatory bowel disease and flares, the prescribing information will be updated to expand the current warning of worsening of Crohn's disease to new onset and worsening of inflammatory bowel disease.

In general, the overall safety profile was consistent with what was seen in the psoriasis clinical program and no new safety signals were detected.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not recommended because no new safety issues were identified in this submission.

1.4 Recommendations for Postmarket Requirements and Commitments

Studies to achieve compliance with PREA

The juvenile equivalents of PsA are extremely rare. The Sponsor has submitted a full waiver request for pediatric patients under the age of 18 years with PsA. The Sponsor's justification is based on the argument that studies would be impossible or impractical due to the uncommon occurrence of PsA in children. The most widely accepted classification system used in children with inflammatory arthritis at the current time is the International League of Associations of Rheumatology (ILAR) classification system for juvenile idiopathic arthritis (JIA). This classification system defines seven discrete categories of arthritis starting before the age of 16 years. One of the seven categories represents a pediatric form of PsA.

The prevalence of juvenile PsA is estimated to be about 1 to 10 per 33,000 children. Based on the low disease prevalence, the Applicant requests a waiver for pediatric PsA patients under the age of 18. Previously, the Agency has waived studies in pediatric PsA due to similar rationale.

2 Introduction and Regulatory Background

2.1 Product Information

Proposed Trade Name (established name): Cosentyx (secukinumab)

Proposed Age group: adult patients

Proposed Dose Regimen: for patients with coexistent moderate-to-severe plaque psoriasis (b) (4), 300 mg SC at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. For all other patients 150 mg SC at weeks 0, 1, 2, 3, and 4 followed by 150 mg every 4 weeks.

Pharmacological class: monoclonal antibody to IL-17A

Description: Secukinumab is a fully human monoclonal IgG1 κ antibody that binds to interleukin-17A (IL-17A) and blocks its interaction with the IL-17 receptor.

How supplied: Currently there are three approved dosage forms listed in the secukinumab prescribing information. It is available for injection as either a 150 mg/mL single use Sensoready® pen, a 150 mg/mL single use pre-filled syringe, and a 150 mg lyophilized powder in a single-use vial for reconstitution. No changes to the approved dosage forms are proposed in this supplement.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 shows the products that have been approved for use in the United States for PsA since 2002. Pathways that have been targeted for treatment of PsA have included TNF, IL-12 and IL-23, and phosphodiesterase 4 (PDE4) inhibitors. Secukinumab has a novel mechanism of action in that it inhibits IL-17.

Table 1. Approved products for the treatment of PsA in the US since 2002

Product	BLA/NDA (Sponsor)	Date of approval for PsA	Characteristic	ROA
Etanercept (Enbrel)	103795 (Immunex)	2002	Fusion protein (TNF-inhibitor)	SC
Infliximab (Remicade)	103772 (Centocor)	2005	Monoclonal antibody (TNF-inhibitor)	IV
Adalimumab (Humira)	125057 (Abbott)	2005	Monoclonal antibody (TNF-inhibitor)	SC

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Golimumab (Simponi)	125289 (Centocor)	2009	Monoclonal antibody (TNF-inhibitor)	SC
Ustekinumab (Stelara)	125261 (Centocor)	2013	Monoclonal antibody (IL-12 and IL-23)	SC
Certolizumab (Cimzia)	125160 (UCB)	2013	Humanized, pegylated Fab' fragment (TNF inhibitor)	SC
Apremilast (Otezla)	206088 (Celgene)	2014	PDE4 inhibitor	PO

Source: reviewer generated

2.3 Availability of Proposed Active Ingredient in the United States

Secukinumab is commercially available in the United States. Secukinumab received FDA approval on January 21, 2015 for the treatment of moderate to severe plaque psoriasis.

2.4 Important Safety Issues with Consideration to Related Drugs

Table 2 displays adverse reactions that have been associated with the use of secukinumab and appear to the Warnings and Precautions section of the secukinumab label.

Table 2. Overview of safety concerns with IL-17A inhibitors

Location in label	Safety concerns
Warnings/Precautions	1. Infections 2. Tuberculosis 3. Crohn's disease 4. Hypersensitivity reactions

Source: adapted from secukinumab prescribing information

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An overview of the important regulatory interactions pertaining to the current submission is shown in Table 3. The IND (12678) was opened for secukinumab in RA on September 20, 2005. This IND was subsequently expanded to include PsA and AS. On January 29, 2010, the Applicant was given written feedback regarding the proposed dose and dosing regimen for PsA and AS. The Applicant was told that it was reasonable to select doses for AS and PsA trials based on phase 2 RA dose-finding studies. On April 8, 2011, the Applicant had an EOP2 meeting with the FDA. Recognizing the written feedback given on January 29, 2010, FDA raised concerns that the dosing rationale for secukinumab (b) (4)

(b) (4) was unclear. Specifically, it was uncertain whether exposure-efficacy relationships could be extrapolated across indications as secukinumab had a new mechanism of action. Therefore, whether secukinumab would act similarly across indications was uncertain. It was recommended to the Applicant that all indications should include two phase 3 studies to provide independent substantiation of efficacy in each autoimmune indication. An additional concern was raised regarding the loading doses being used in the ankylosing spondylitis (AS) and PsA programs. The loading doses provided much greater exposure than the proposed maintenance doses. The Applicant was asked to study lower loading doses. In addition, the Applicant was asked to study the intended-to-be-marketed presentations during phase 3 trials to determine the safety and efficacy of these presentations prior to potential market introduction.

On April 18, 2012, the Applicant was provided Type C responses from the FDA. The FDA raised concerns that the proof of concept studies in each indication (RA, PsA, and AS) appeared to have varying effect sizes. The FDA repeated that each indication would require two studies to independently substantiate the efficacy of secukinumab. The FDA requested that the Applicant provide rationale for the loading dose proposed. The Applicant proposed a study using SC loading and another study using IV loading. The FDA raised concerns that the two loading regimens were not similar and that a single study with SC loading regimen would not be adequate. It appeared additional studies would be required.

On April 30, 2014, the Applicant had a pre-sBLA meeting with the FDA. Major concerns during the pre-sBLA meeting were that the maintenance dose effectiveness could not be determined based on high loading doses used in the clinical development program. Since only one study studied the 300 mg dose of secukinumab, there were concerns of whether sufficient information would be available to determine the efficacy of secukinumab 300 mg. Concerns were also raised regarding the radiographic data in PsA because radiographic endpoints were only evaluated in one study that utilized IV loading doses.

On September 10, 2014, the Applicant received written responses for a Type C meeting. The Applicant was asked to provide data to support a loading regimen and it was recommended that the Applicant compare the use of secukinumab with or without load in PsA patients. The FDA explained that radiographic data from patients receiving load and no load would need to be collected to support a radiograph claim. The FDA stated that the Applicant would need to provide adequate data to support the chosen dosing regimen.

Table 3. Overview of regulatory interactions for the PsA program

Type of meeting (date)	FDA recommendations and key discussion topics
End of phase 2 meeting (April 8, 2011)	<ol style="list-style-type: none"> 1. It is unclear whether exposure-efficacy relationship can be extrapolated to a different indication 2. Concerns that loading dose produces a much greater exposure than maintenance dose; recommended studying lower loading doses 3. Two trials in PsA are necessary to provide independent substantiation of efficacy of secukinumab in PsA 4. All intended-to-be-marketed presentations should be studied for safety and effectiveness in phase 3 trials
Type C guidance (April 18, 2012)	<ol style="list-style-type: none"> 1. Posology could be different in various rheumatic diseases; therefore, it is unclear whether exposure-efficacy relationships can be extrapolated across indications 2. Provide justification that a loading dose is required in the clinical development program
Pre-sBLA meeting (April 30, 2014)	<ol style="list-style-type: none"> 1. Concerns that loading dose will provide much greater exposure than maintenance dose 2. Unclear whether there is sufficient information for the 300 mg dose 3. Data appear inadequate to support inhibition of radiographic progression
Type C guidance (September 10, 2014)	<ol style="list-style-type: none"> 1. Provide data to support a loading regimen 2. Provide adequate data to support chosen dose 3. Conduct a study with a loading dose versus no loading dose regimen 4. Radiographic studies should include dosing regimens with or without load

Abbreviations: LIVI=concentrate for solution, LYO=lyophilisate
 Source: reviewer generated

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic sBLA submission was well-organized and complete and there were no major amendments.

3.2 Compliance with Good Clinical Practices

According to the Applicant, studies F2306 and F2312 were conducted in compliance with good clinical practice (GCP) guidelines, as described in the 1996 International Committee on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the

Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects), and other applicable local/regional regulations and guidelines regarding the conduct of clinical studies. A signed informed consent form was obtained from each patient prior to enrollment and IRB approval was obtained by the investigators.

As secukinumab is an approved product and there were no concerns regarding compliance with good clinical practice, the Office of Scientific Investigation was not requested to perform routine audits of clinical sites.

3.3 Financial Disclosures

The Sponsor submitted FDA Form 3454 certifying that the Applicant did not enter into any financial arrangement with the clinical investigators in the secukinumab studies whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, the Sponsor certified that each clinical investigator was required to disclose to the Sponsor whether the investigator had proprietary interest in secukinumab or a significant equity interest in the Sponsor as defined in 21 CFR 52.2(b). Finally, the Sponsor certified that no listed investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

One investigator received \$10000-20000 to speak and consult in study F2306 and >\$25000 to speak for study F2312 out of 1398 investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new chemistry manufacturing and controls data were submitted with this supplement for review

4.2 Clinical Microbiology

No new clinical microbiology data were submitted with this supplement for review.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology data were submitted with this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

No new data on the mechanism of action were submitted with the current supplement for review. Secukinumab is a recombinant high-affinity, fully monoclonal anti-human antibody that targets interleukin-17A. IL-17A is a pro-inflammatory cytokine involved in the pathophysiology of several autoimmune diseases.

4.4.2 Pharmacodynamics

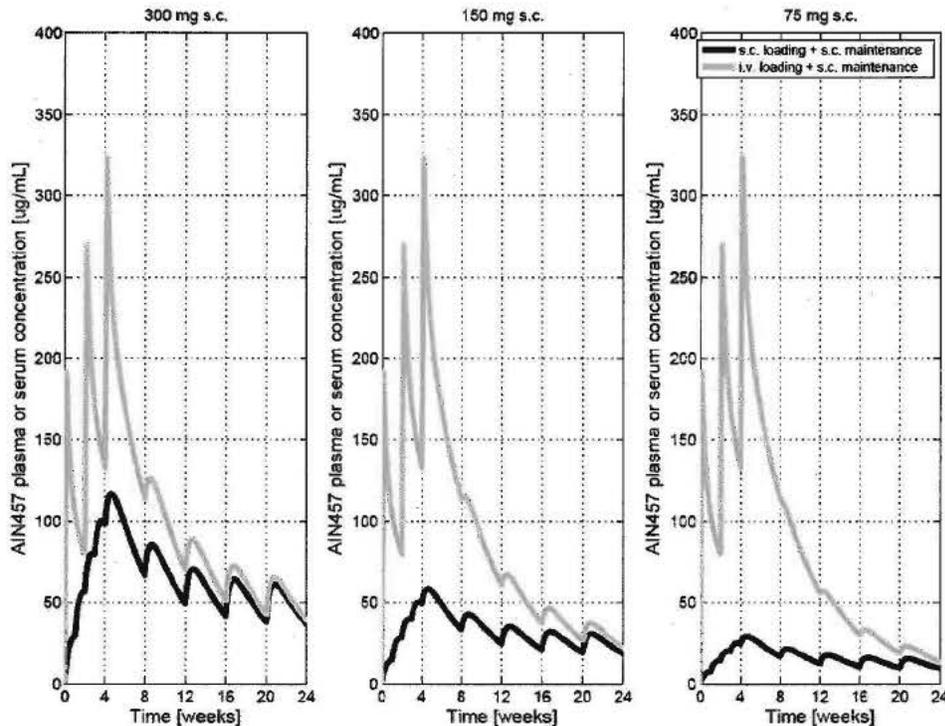
No new pharmacodynamics data were submitted with the current supplement for review.

4.4.3 Pharmacokinetics

Figure xx shows simulated concentration profiles for the IV and SC loading doses. The IV loading dose that was simulated was the 10 mg/kg dose at weeks 0, 2, and 4 and then the plasma serum concentration is simulated based on the SC maintenance dose that the patient would continue to receive. The graph shows simulated concentrations for the SC loading doses of 300, 150, and 75 mg from left to right. The SC loading doses were weekly injections for 5 weeks.

The graphs show that the SC 300 mg loading regimen followed by 300 mg secukinumab every 4 weeks was the closest to approximating the IV loading dose regimen. However, initial concentrations of secukinumab from week 0 through 8 were much higher with the IV loading dose. The difference in secukinumab exposure was greater between the IV loading doses and the 150 mg and 75 SC loading doses.

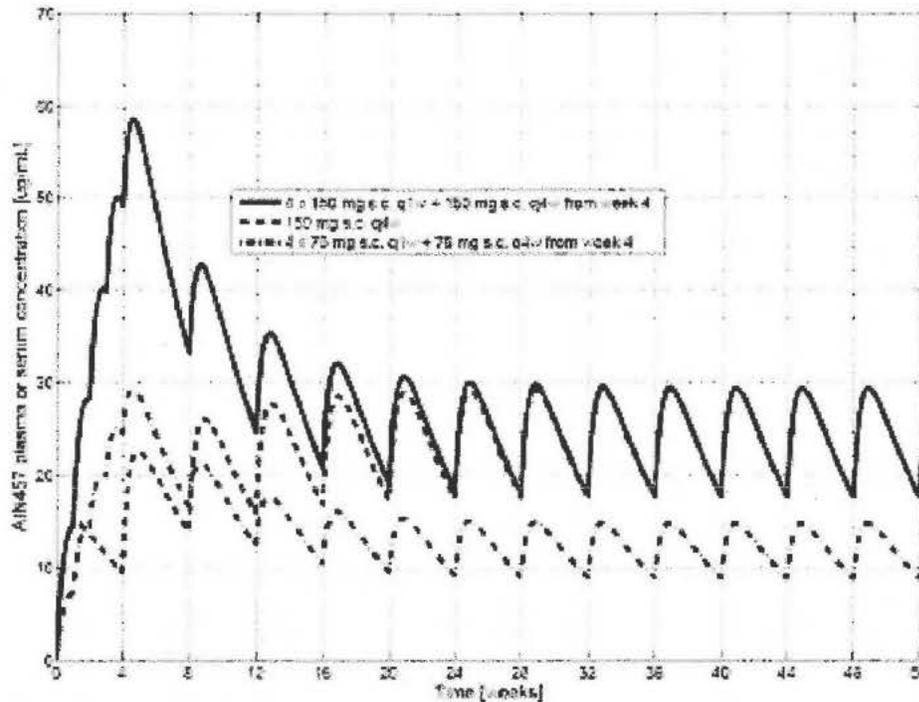
Figure 1. AIN457 IV and SC loading dose regimens: simulated concentrations profiles in PsA



Source: Applicant addendum to summary of clinical pharmacology, p. 50

Figure xx shows the simulated concentration over time for secukinumab with SC doses of 75 mg and 150 mg. The top, solid line shows the concentration of secukinumab with 5 weekly loading doses of 150 mg secukinumab SC followed by 150 mg every 4 weeks. The middle dashed line shows the 150 mg dose every 4 weeks without a loading dose. The bottom dashed line shows the concentration of the 75 mg SC every 4 weeks dose with a loading dose of 75 mg weekly for 5 weeks. The loading dose appears to achieve higher concentrations with the 150 mg dose but over time the concentration comes to the same level as the 150 mg without loading dose. The 75 mg group does not obtain the same simulated concentration as the 150 mg groups.

Figure 2. AIN457 simulated concentrations: with and without SC loading dose



Source: Applicant addendum to summary of clinical pharmacology, p. 49

Reviewer's comment: The IV loading dose and 150 mg and 300 mg SC loading doses appear to provide much higher secukinumab exposures initially than during the maintenance dosing phase. Further, the exposure with the IV loading doses is markedly higher than the exposure with the SC loading doses. The concentration for those who do not take a loading dose takes some time to reach similar concentrations as those with a loading dose. In addition, the pharmacokinetic effect of the loading dose appears to be present near the time of efficacy endpoint assessments at week 16. Due to the large initial loading doses, conclusions on whether efficacy could be maintained without repeat loading doses was a concern as well as whether the initial loading doses would lead to issues with safety. These issues are discussed further in Sections 6.1.4 and 6.1.5.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Sponsor submitted data from two phase 3 trials in their sBLA to support the approval of secukinumab in the treatment of PsA:

- F2306-a randomized, double-blind, parallel-group, placebo-controlled trial. The Applicant submitted data to Week 52.
- F2312-a randomized, double-blind, parallel-group, placebo-controlled trial. The Applicant submitted data to Week 52.

The phase 3 studies remained controlled with placebo for 24 weeks. After 24 weeks, all patients received secukinumab. These studies were informed by previous phase 2 studies in PsA (A2206) and rheumatoid arthritis (F2201). An overview of the relevant phase 2 and phase 3 studies is in Table 4.

Table 4. Studies submitted to support sBLA 125504/1

Study #, phase	Study design	Population	N	Dose, route, regimen
A2206 Phase 2	Randomized, double-blind, placebo controlled study	PsA	42	10 mg/kg IV at Day 0, 22
F2201 Phase 2	16 wk, randomized, double-blind, placebo controlled, dose finding study	Rheumatoid arthritis	237	25, 75, 150, or 300 mg SC at week 0, 4, 8, 12
F2306 Phase 3	24 wk randomized, double-blind, placebo-controlled multicenter study	PsA	606	10 mg/kg IV at wks 0, 2,4, followed by 75 or 150 mg SC q4wk from wk 8 to 104
F2312 Phase 3	24 week, randomized, double-blind, placebo-controlled, multi-center study	PsA	397	75, 150, 300 mg SC at wks 0,1,2,3 followed by every 4 wks from wk 4 to 256

Source: adapted from 125504/1 Clinical Overview, p. 11-12

Table 5 lists the phase 3 studies performed by the Applicant in psoriasis. The individual psoriasis studies will not be reviewed in detail. The psoriasis studies provide additional patients exposed to secukinumab and will be reviewed in the safety section of this review.

Table 5. Summary of phase 3 studies in psoriasis

Study #	Study design	Population	N	Dose, route, regimen
A2302	Randomized,	Psoriasis	737	150, 300 mg SC every wk for

	double-blind, placebo controlled, multicenter study			4 weeks then every 4 weeks until week 48
A2303	Randomized, double-blind, placebo controlled, multicenter study	Psoriasis	1303	150, 300 mg SC every wk for 4 weeks then every 4 weeks until week 48
A2308	Randomized, double-blind, placebo controlled, multicenter study	Psoriasis	177	150, 300 mg SC every wk for 4 weeks then every 4 weeks until week 48
A2309	Randomized, double-blind, placebo controlled, multicenter study	Psoriasis	182	150, 300 mg SC every wk for 4 weeks then every 4 weeks until week 48
A2304	Randomized, double-blind, multicenter study	Psoriasis	965	150, 300 mg SC every wk for 4 weeks then every 4 weeks until week 12

Source: adapted from 125504/1 Clinical Overview, p. 14

5.2 Review Strategy

Efficacy: Trials 2306 and 2312 served as the Phase 3 trials for the evaluation of the efficacy of secukinumab in the treatment of signs and symptoms of PsA. The trials were well controlled and had endpoints that are considered acceptable for efficacy evaluation of PsA. Each trial used different loading doses with study F2306 using an IV loading dose regimen and study F2312 using a SC loading dose regimen. Study F2306 studied 75 mg or 150 mg every 4 weeks maintenance doses of secukinumab. Study F2312 studied 75 mg, 150 mg, or 300 mg every 4 weeks maintenance doses of secukinumab. Efficacy and safety were evaluated in both trials. All patients had active disease.

Safety: The major safety evaluation of secukinumab for the treatment of signs and symptoms of PsA was F2306 and F2312. The primary analyses focused on data through week 16- the double-blind, placebo-controlled period. The Applicant also provided 52 week safety data which included patients who switched from placebo to secukinumab as escape therapy.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Study CAIN457A2206 (A2206), phase 2 study in PsA

The following description for the protocol comes from the A2206 clinical study report dated May 16, 2012.

Title: Randomized, double-blind placebo-controlled multi-center proof-of-concept study to assess the efficacy of AIN457 in patients with psoriatic arthritis

Study dates: The first patient's first visit was March 18, 2009 and the last patient's last visit was December 22, 2010.

Sites: 11 centers in Germany (5), Netherlands (2), and United Kingdom (4) recruited patients for study A2206.

Objectives of study A2206: The primary objective of the study was to evaluate the efficacy of AIN457 at 6 weeks based on the proportion of patients achieving ACR20 response.

Overall design of A2206: Study A2206 was a 24 week, randomized, double blind, placebo controlled, proof of concept study to evaluate the AIN457 for treatment of patients with active PsA.

Patient selection for study A2206: 42 patients with active PsA based on CASPAR were planned for recruitment to the study.

Inclusion Criteria:

1. Males or females, aged 18-65 at the time of consent.
2. All female patients who had negative pregnancy test results at screening (urine) and baseline.
3. Male patients who were willing to use simultaneously two acceptable methods of contraception (e.g. spermicidal gel plus condom) for entire duration of the study, up to the study completion visit and at least for 6 months post last dose of AIN457.
4. Eligibility for study participation was based on a diagnosis of PsA in accordance with CASPAR plus the following mandatory criteria:
 - a. involvement of at least three swollen and tender peripheral joints
 - b. Patient Global Assessment (PGA) \geq 40 (VAS 0-100mm)
 - c. inflammatory pain \geq 40 (VAS 0-100mm)
 - d. disease was inadequately controlled on at least one disease modifying anti-rheumatic drug (DMARD) given for at least three months at the maximum tolerated dose
 - e. RF \leq 100 IU and negative cyclic citrullinated peptide (CCP) enzyme-linked immunosorbent assay (ELISA) test.
5. No evidence of liver disease or liver injury

Exclusion Criteria:

1. At the time of assessment had any of the following:
 - a) arthritis fulfilling classification criteria for RA;
 - b) seronegative spondyloarthropathy fulfilling classification criteria of ankylosing spondylitis (modified New York criteria);

- c) a positive CCP ELISA result past or present
2. At the time of assessment had drug-induced psoriasis
3. Men who were planning to initiate a pregnancy
4. Participation in any clinical trial using an investigational drug within 4 weeks prior to initial dosing or five half-lives of the investigational agent, whichever was longer
5.
 - (a) For previous use of immunosuppressive agents such as cyclosporine, or leflunomide a wash-out period of at least 1 month or 5 half-lives, whichever was longer, was required. If on previous treatment with anti-TNF- α therapy (or other biological therapy)
 - (b) Patients who were on NSAIDs were required to be kept on a stable dose 4 weeks before baseline and throughout the study.
6. In case of coexisting skin psoriasis, within 1 month of randomization, received any systemic medications/treatments that could affect psoriasis or PASI evaluation
7. Within 2 weeks of randomization, used topical medications/treatments that could affect psoriasis or PASI evaluation
8. Positive HIV, Hepatitis B surface antigen (HBsAg) or Hepatitis C test result. Any active systemic infection within the past 2 weeks of screening
9. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, chronic inflammatory diseases
10. Patients with active or history of clinically significant cardiac abnormalities,
11. History of renal trauma, glomerulonephritis, or patient with one kidney.
12. History of severe hypersensitivity to any biological agents (antibody or soluble receptor), a history of serious allergic reaction.
13. History of malignancy (other than basal cell carcinoma or adequately treated carcinoma in-situ of the cervix).
14. Conditions associated with an immune-compromised .
15. Purified Protein Derivative (PPD) tuberculin skin test reaction of ≥ 10 mm at screening or within 6 months prior to the screening visit
16. Liver disease or liver injury as indicated by abnormal liver function tests
17. Total white blood cells (WBC) count which fell outside the range of 4500–11,000/ μ l, or platelets $<100,000/\mu$ l at screening.
18. History of severe hypersensitivity to any biological agents (antibody or soluble receptor), including serious allergic reaction (hypotension, wheezing, urticaria), lupus-like syndrome, or demyelinating disease.

Treatments in study A2206: The investigational drug was 50 mg lyophilizate vials and matching placebo. The drug was reconstituted for infusion. Each patient received 10 mg/kg AIN457 or matching placebo intravenously on Day 1 and Day 22.

Selection of doses in study A2206: The dose was selected based on previous proof-of concept studies in RA and Crohn's disease. Both studies used two 10 mg/kg doses. The Applicant noted an acceptable efficacy and safety profile in these studies. The

Applicant also conducted preclinical in-vivo experiments that a dose range of 3 to 10 mg/kg reduced inflammation and tissue destruction associated with IL-17A.

Concomitant medications in study A2206: Concomitant methotrexate up to 25 mg per week was allowed as long as patients remained on a stable dose. Stable doses of NSAIDs, paracetamol, tramadol, and prednisone up to the equivalent of 10 mg per day were allowed in the study.

Results of the study were used for selection of doses rationale for F2306 and F2312.

5.3.2. Study CAIN457F2201 (F2201), phase 2 study in rheumatoid arthritis

Title: A 16-week multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-finding study to evaluate the efficacy, safety and tolerability of subcutaneous secukinumab (AIN457) followed by an extension phase up to a total of 60 weeks in patients with active rheumatoid arthritis despite stable treatment with methotrexate.

Study dates: The first visit for the first patient was July 14, 2009 and the last visit for the last patient was March 4, 2011.

Sites: 54 centers in Belgium (1), Czech Republic (4), Germany (6), Hungary (3), Japan (5), Korea (4), Poland (3), Russia (9), Slovakia (3), United States (12), and Taiwan (4).

Objectives of Study F2201: The primary objective was to assess at Week 16 the efficacy (ACR20 criteria) and safety of various doses of secukinumab (AIN457) compared to placebo as add-on therapy in patients with active RA despite stable treatment with methotrexate (MTX).

Overall Design of F2201: This was a double-blind, randomized, parallel-group, placebo controlled, dose finding study in RA patients. The treatment period was 48 weeks and patients were randomized to one of five treatment groups: secukinumab 300 mg SC every 4 weeks, 150 mg SC every 4 weeks, 75 mg SC every 4weeks, 25 mg SC every 4 weeks, or placebo SC every 4 weeks.

Patient selection for F2201: It was planned to screen 290 patients with rheumatoid arthritis on a stable dose of methotrexate to allow for randomization of 200 patients. Patients who fulfilled ACR 1987 revised classification for RA for at least 3 months were enrolled in the study. They needed to have active RA and be on a stable of methotrexate for at least 4 weeks.

Inclusion Criteria

Patients were included in the study if they fulfilled the following criteria:

1. Patients who gave written informed consent before any assessment was performed.

2. Male or non-pregnant, non-lactating female patients at least 18 years of age.
3. Diagnosed with RA classified by ACR 1987 revised criteria. Patients with active RA treated with MTX for at least 3 months and currently being treated with a stable dose of MTX for at least 4 weeks.
4. At Baseline: Disease activity criteria defined by ≥ 6 of 28 tender joints and ≥ 6 of 28 swollen joints. WITH either
 - Screening value of hsCRP ≥ 10 mg/L.
 - OR ESR ≥ 28 mm/1st hr.
5. Patients who failed any DMARDs including biologic DMARDs agents and any DMARDs used in combination with MTX, were allowed entry into study after appropriate wash-out period (except for MTX) prior to baseline.
6. Patients who were taking systemic corticosteroids had to be on a stable dose of ≤ 10 mg/d prednisone or equivalent for at least 4 weeks before randomization.
7. Patients who were regularly taking NSAIDs or COX-2 inhibitors or paracetamol/acetaminophen as part of their RA therapy were required to be on a stable dose for at least 4 weeks before randomization.
8. Patients who were taking NSAIDs or COX-2 inhibitors or paracetamol/acetaminophen PRN within 4 weeks before randomization had to stop their medication at least 24 hours before a study visit.
9. Patients had to be taking folic acid supplementation before randomization.
10. All patients receiving current vaccinations, especially influenza and pneumococcal as clinically indicated could be included.

Exclusion Criteria

1. RA patients functional status class IV classified according to the ACR 1991 revised criteria.
2. Patients who were taking high potency opioid analgesics
3. Any therapy by intra-articular injections required for treatment of acute RA flare within 4 weeks before randomization.
4. Pregnant or nursing (lactating) women
5. Women of child-bearing potential,
6. Male patients who did not consent to practice contraception during the study.
7. Inflammatory diseases other than RA
8. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, infectious or gastrointestinal conditions
9. Significant medical problems
10. History of clinically significant liver disease or liver injury
11. History of renal trauma, glomerulonephritis, or patients with one kidney, or a creatinine level exceeding 1.5 mg/dl.
12. Screening total WBC count $< 3,000/\mu\text{L}$, or platelets $< 100,000/\mu\text{L}$ or neutrophils $< 1,500/\mu\text{L}$ or hemoglobin < 8.5 g/dL.
13. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.

14. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection
15. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization.
16. History of lymphoproliferative disease or any known malignancy or history of malignancy within the past 5 years (except for non-melanoma skin cancer that had been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix, colon polyps with non-invasive malignancy that was removed).
17. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator rendered the patient unsuitable for the trial.
18. Inability or unwillingness to undergo repeated venipuncture
19. Any medical or psychiatric condition which, in the Investigator's opinion, would have precluded the participant from adhering to the protocol or completing the study as per protocol.
20. Previous exposure to secukinumab or other biologic targeting IL-17 or IL-17 receptor.
21. Use of any investigational drug other than RA therapy and/or devices at the time of randomization or within 30 days or 5 half-lives of randomization, whichever was longer.
22. Plans for administration of live vaccines during the study period or 6 weeks prior to first study drug administration.

Results of the study were used for selection of doses rationale for F2306 and F2312.

5.3.3 Study CAIN457F2306 (F2306), phase 3 study in PsA

Title: A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis

Study dates: The first visit for the first patient was September 8, 2011. This is a 52 week interim analysis where the last Week 52 visit was conducted on October 9, 2013.

Sites: 112 centers in 19 countries (Argentina 8 centers, Australia 2 centers, Belgium 3 centers, Brazil 3 centers, Bulgaria 4 centers, Canada 5 centers, Czech Republic 3 centers, Germany 14 centers, Israel 4 centers, Italy 4 centers, Philippines 9 centers, Poland 2 centers, Romania 4 centers, Russian Federation 6 centers, Singapore 3 centers, Slovakia 2 centers, Thailand 4 centers, United Kingdom 5 centers, United States 27 centers).

Objectives of study F2306: The primary objective of study F2306 was to demonstrate that the efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response.

Overall design of study F2306: This was a double-blind, randomized, parallel-group, placebo controlled design. A 4 week screening period running up to 4 weeks to assess eligibility preceded a treatment period of two years. At baseline, patients were randomized to one of three treatment groups:

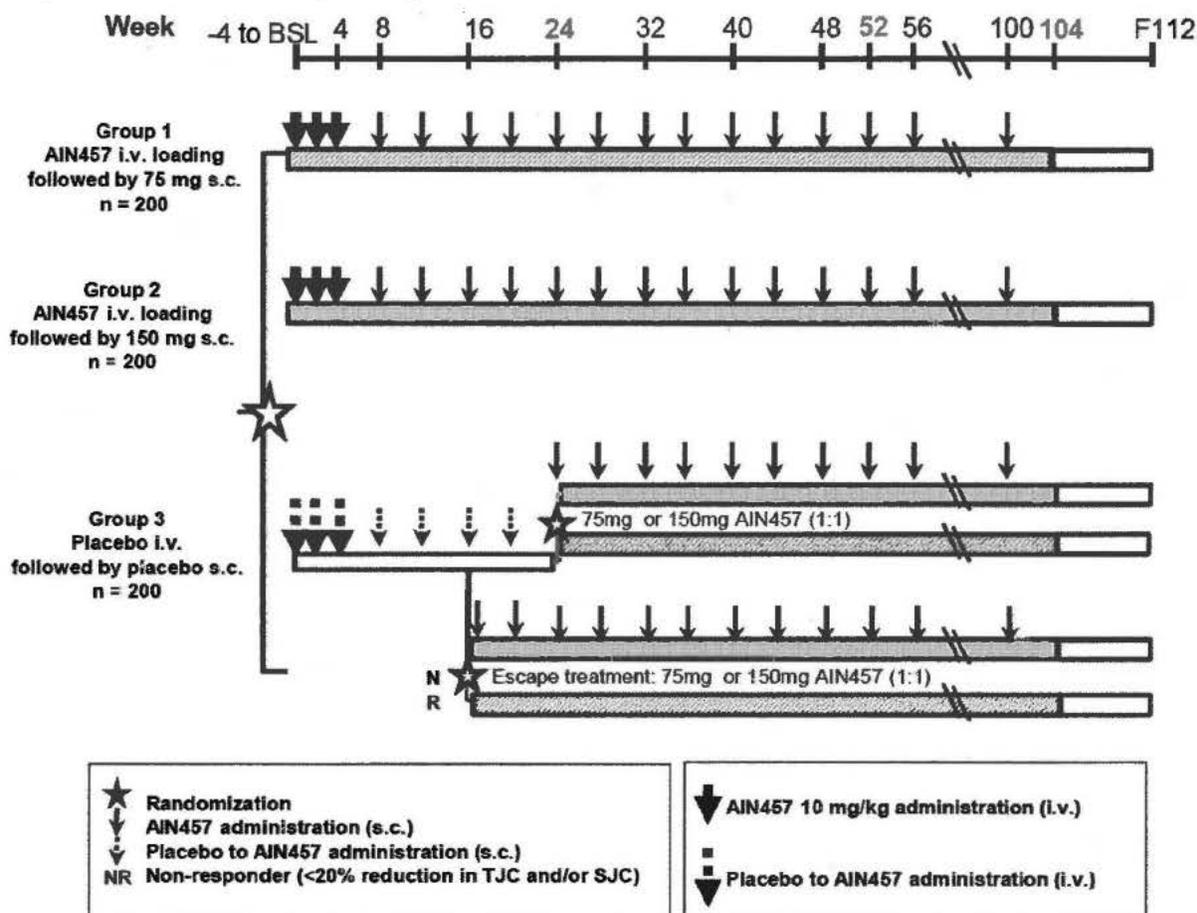
- Secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg SC every 4 weeks,
- Secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg SC every 4 weeks,
- Placebo IV at baseline, Weeks 2 and 4, then placebo SC starting at Week 8 and Week 12

At Week 16, all patients were classified as responders or non-responders. Responders were defined as patients who had $\geq 20\%$ improvement from baseline in both tender and swollen joint counts. Patients who did not achieve responder status were classified as non-responders. Patients who were randomized to placebo at baseline were re-randomized to receive double blind treatment, as follows:

- Placebo responders remained on placebo until Week 24. At Week 24, these patients received either secukinumab 75 or 150 mg every 4 weeks.
- Placebo non-responders were re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg SC every 4 weeks.

Rescue medication was not allowed until week 24 in this study. A follow-up visit was done 12 weeks after last study treatment administration for patients who early terminated the study or for patients who completed the study but did not enter the extension study. The study design is shown in Figure 3.

Figure 3. F2306: Study design



Source: F2306 clinical study report, p. 62

Patient selection for study F2306:

Study F2306 enrolled patients who met the following main inclusion and exclusion criteria:

Inclusion criteria:

1. Patient should be able to understand and communicate with the investigator and give a written, signed and dated informed consent
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. Diagnosis of PsA classified by CASPAR with symptoms for at least 6 months with moderate to severe PsA who must have at Baseline ≥ 3 tender joints out of 78 and ≥ 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each)
4. Rheumatoid factor (RF) and anti-CCP antibodies negative
5. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis or a documented history of plaque psoriasis

6. Stable NSAID dose with inadequate control of symptoms or intolerant to NSAIDs
7. Stable corticosteroids of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization to remain on a stable dose up to Week 24
8. Stable MTX (≤ 25 mg/week) to remain on a stable dose throughout the study
9. Patients on MTX were to be on folic acid supplementation at randomization
10. Patients who were on a DMARD other than MTX had to discontinue the DMARD 28 days prior to randomization
11. Patients who were on a TNF alpha inhibitor must have had experienced an inadequate response to previous or current treatment with a TNF alpha inhibitor given at an approved dose for at least 3 months or have stopped treatment due to safety/tolerability problems after at least one administration of a TNF alpha inhibitor

Exclusion criteria:

1. Patients taking high potency opioid analgesics
2. Patients who had ever received biologic immunomodulating agents except for those targeting TNF alpha, investigational or approved
3. Patients who had previously been treated with more than 3 different TNF alpha inhibitors
4. Use of any investigational drug and/or devices within 4 weeks of randomization or 5 half-lives of the investigational drug
5. Ongoing use of prohibited psoriasis treatments / medications
6. Any intramuscular, intra-articular or IV corticosteroid treatment within 4 weeks before randomization
7. Any therapy by intra-articular injections within 4 weeks before randomization
8. Previous treatment with any cell-depleting therapies
9. Pregnant or nursing (lactating) women
10. Women of child-bearing potential unwilling to use effective contraception during the study and for 16 weeks after stopping treatment.
11. Active ongoing inflammatory diseases other than PsA
12. Significant medical diseases / problems
13. History of clinically significant liver disease or liver injury
14. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a creatinine level exceeding 1.5 mg/dl (132.6 $\mu\text{mol/L}$) at screening
15. Screening total white blood cell (WBC) count $< 3,000/\mu\text{l}$, or platelets $< 100,000/\mu\text{l}$ or neutrophils $< 1,500/\mu\text{l}$ or hemoglobin < 8.5 g/dl (85 g/L)
16. Active systemic infections during the last two weeks prior to randomization
17. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection
18. Chest X-ray with evidence of ongoing infectious or malignant process, obtained within 3 months of screening
19. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years
21. Current severe progressive or uncontrolled disease

22. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
23. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
24. Plans for administration of live vaccines during the study period or 6 weeks prior randomization

Treatments in study F2306:

Secukinumab 150 mg Powder for Solution for SC injection or IV infusion was provided in glass vials containing 150 mg secukinumab as lyophilized cake. The 150 mg Powder for Solution was used to prepare both the 75 mg and the 150 mg dose.

Secukinumab placebo (for SC injection): Secukinumab placebo to 150 mg Powder for Solution for SC injection was provided in glass vials as lyophilized cake. Each vial contained a mixture of inactive excipients, matching the composition of the secukinumab 150 mg Powder for Solution.

Reference therapy (Secukinumab placebo for IV infusion): 100 mL 0.9% NaCl solution was to be used as placebo for IV secukinumab, and was to be provided locally.

At baseline, eligible patients were to be randomized to one of the following 3 treatment arms in a ratio of 1:1:1:

- Group 1: Secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg SC starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg SC starting at Week 8 and injected every 4 weeks
- Group 3: Placebo IV at baseline, Weeks 2 and 4, then placebo SC starting at Week 8 and Week 12.

Selection of doses in study F2306: The Applicant used two studies to justify their dose selection. In study A2206, 42 PsA patients were treated with two doses of 10 mg/kg secukinumab IV separated by 21 days or placebo. ACR20 at week 6 was the key endpoint and conclusions were that secukinumab showed evidence of therapeutic benefit in moderate to severe PsA patients. 9/23 (39%) on secukinumab achieved ACR20 response compared to 3/13 (23%) placebo patients. The second study, F2201, examined SC doses of secukinumab in RA patients. Doses were 25, 75, 100, or 300 mg of secukinumab at weeks 0, 4, 8, and 12 or placebo. ACR20 at week 16 was the key endpoint. ACR20 at week 16 was the key endpoint. ACR20 responses were 18/53 (34%) for the 25 mg secukinumab dose, 23/49 (46.9%) for the 75 mg dose, 20/43 (46.5%) for the 150 mg dose, 22/41 (53.7%) for the 300 mg dose, and 18/50 (36%) for placebo. The conclusion was that doses 75-300 showed numerical improvement in ACR20..

The Applicant used these two studies and dose exposure predictions from pharmacokinetic models to determine their doses. The doses that were selected for study F2306 were:

- Secukinumab 10 mg/kg IV at weeks 0, 2, and 4 and then 75 mg SC starting at week 8 and injected every 4 weeks
- Secukinumab 10 mg/kg IV at weeks 0, 2, and 4 and then 150 mg SC starting at week 8 and injected every 4 weeks
- Placebo IV at weeks 0, 2, and 4 and then placebo mg SC starting at week 8 and week 12

At week 16, placebo responders continued to receive SC placebo every 4 weeks until they were randomized at week 24 to either 75 mg or 150 mg SC secukinumab every 4 weeks.

At week 16, patients who were placebo non-responders were randomized to either 75 mg or 150 mg SC secukinumab every 4 weeks. No loading doses were administered to placebo non-responders or responders.

Concomitant medications in study F2306:

The investigator was to instruct the patient to notify the study site about any new medications (including over-the-counter drugs, calcium and vitamins) taken after the patient enrolled into the study.

Patients on MTX were to be treated with stable treatment of MTX (≤ 25 mg/week) for at least 4 weeks before randomization and maintained stable throughout the treatment period. Patients on MTX had to take folic acid supplementation during the trial to minimize the likelihood of MTX associated toxicity.

Treatment with systemic corticosteroids was allowed if the dose was stable for at least 2 weeks before randomization and maintained stable throughout the study period. A maximum dosage of 10 mg equivalent of daily prednisone was allowed. Corticosteroid dose reductions were permitted after Week 24.

Intra-articular corticosteroids were not permitted within 4 weeks prior to baseline and up to week 24. After week 24, no more than 1 joint per 24-week period was to be injected. Injection of intra-articular steroids was not permitted within 8 weeks prior to Weeks 24, 52, and 104.

Patients on regular use of NSAIDs or paracetamol/acetaminophen had to be on stable dose for at least 2 weeks before randomization to allow inclusion and during the treatment period. Patients could continue to do so after randomization, however, they had to refrain from any intake during at least 24 hours before a visit with disease activity assessment. Any changes to the NSAIDs, opioids, or paracetamol/acetaminophen treatment during the trial were recorded.

Prohibited therapies in study F2306

Table 6 shows the therapies that were prohibited in study F2306 and the corresponding washout periods. For topical skin treatments, mild to moderate corticosteroids and treatments to face, scalp, and genital areas during screening were allowed.

Table 6. F2306: Prohibited therapies

Prohibited therapies	Washout period prior to randomization
Etanercept	4 weeks
Infliximab	8 weeks
Adalimumab, golimumab, certolizumab	10 weeks
Unstable dose of MTX	4 weeks
Other DMARD (except MTX)	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine washout	4 weeks
Unstable dose of NSAIDs	2 weeks
Systemic corticosteroid >10 mg prednisone equivalent	2 weeks
Intra-articular steroid injections up to week 24	4 weeks
Oral or topical retinoids	4 weeks
Photochemotherapy	4 weeks
Phototherapy	2 weeks
Topical skin treatments	2 weeks
Any investigational treatment	4 weeks or 5 half lives
Analgesics (other than low strength)	4 weeks
Live vaccinations up to week 24	6 weeks

Source: adapted from F2306 clinical study report, p. 77

Patient stopping rules in study F2306

Study treatment must be discontinued and the subject withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that subject. The following circumstances require study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events
 - Any severe or serious adverse event that is not compatible with administration of study treatment
 - Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or noninvasive malignant colon polyps which are being or have been removed
 - Life threatening infection
- Administration of a live vaccine up to Week 24

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- Any of the following laboratory
 - AST or ALT value >5 x ULN
 - Hemoglobin value <85 g/L (8.5 g/dL) and decreased by at least 20 g/L (2 g/dL) from screening
 - Creatinine value >2 x ULN
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any other protocol deviation that results in a significant risk to the subject's safety

Trial monitoring and evaluations for study F2306

Table 7 shows the trial monitoring and evaluations that were performed during the first 52 weeks of study F2306.

Table 7. F2306:Assessment schedule

	SCR	Treatment Period I															
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	1-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Informed consent / optional PG-informed consent	X																
Inclusion/Exclusion criteria	X	X															
Relevant medical history/ current medical condition	X																
Cardiovascular medical history		X															
Previous psoriasis, psoriatic medical history and previous psoriasis/psoriatic arthritis therapies	X	X															
Smoking history		X															
Demography	X																
Physical Exam ¹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																
Weight	X	X								X							X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test ² or QuantiFERON TB-Gold test	X																
Rheumatoid factor (RF)	X																
Anti-CCP antibodies	X									X							X
Chest X-ray ³	X																
ECG (central)		X						X									X
Randomization		X						X ⁴		X ⁴							

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	SCR	Treatment Period 1															
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	≤-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Administration of I.V. study treatment		X		X	X												
Administration of s.c. study treatment						X	X	X	X	X	X	X	X	X	X	X	X
Prior medication	X	X															
Hematology, blood chemistry, local urinalysis	X	X	X	X	X	X	X	X	X	X	X	X		X			X
Serum pregnancy test	X																
Urine pregnancy test		X			X		X	X		X		X		X			X
Con medication/non drug therapy		Update as necessary throughout the study															
Adverse Events/SAE ⁶ (including injection site reaction & infections)		Update as necessary throughout the study															
MRI (swollen hand/wrist; TNF-naïve patients only) ¹²		X					X			X							
X-Ray (hands/wrists + feet)		X						X ⁸		X ¹⁰							X
Anti-nuclear antibodies (ANA)		X								X							X
Anti-dsDNA		X								X							X
Immunogenicity		X								X							X
PK assessments (at predose)		X			X			X		X							X
Tender & Swollen joint counts (TJC36 / SSC36)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of PsA pain (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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	SCR	Treatment Period 1															
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Patient's global assessment of disease activity (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's global assessment of disease activity (VAS scale)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Assessment Questionnaire (HAQ-DI)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
High sensitivity C-Reactive protein (hsCRP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte Sedimentation Rate (ESR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Leeds Dacryitis Index	X	X		X	X	X	X	X		X		X					X
Leeds Enthesitis Index	X	X		X	X	X	X	X		X		X					X
PASI (only if $\geq 3\%$ of BSA at BSL)		X	X	X	X	X	X	X		X		X					X
IGA (only if $\geq 3\%$ of BSA at BSL)		X	X	X	X	X	X	X		X		X					X
Target Lesion Score (TLS: only if target lesion with ≥ 2 cm diameter)		X	X	X	X	X	X	X		X		X					X
sdNAPSI (only in patients with nail involvement)		X	X	X	X	X	X	X		X		X					X
WPAL-GH		X						X		X							X
SF-36 Acute Form v2		X			X	X	X	X		X							X
FACIT-Fatigue v4		X			X	X	X	X		X							X
PsAQoL		X			X	X	X	X		X							X
EQ-5D v3L		X			X	X	X	X		X							X
DLQI (only if $\geq 3\%$ of BSA at BSL)		X			X	X	X	X		X							X
Lipids ⁶		X				X		X		X							X

	SCR	Treatment Period 1															
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52
Cardiovascular panel		X						X		X							X
Serum biomarkers related to targeted pathway		X								X							X
Pharmacogenetics ⁷		X															
Treatment Period 1 Completion Form ¹¹																	X
Treatment Period 2 Completion Form																	
Follow-up period Completion Form																	

Source: F2306 clinical study report, p. 81-84

Efficacy endpoints

The primary efficacy variable was the clinical response to treatment according to ACR20 individual improvement in disease activity at Week 24. A patient was defined as an ACR20 responder if, and only if, the following three conditions hold

1. they had a $\geq 20\%$ improvement in the number of tender joints (based on 78 joints)
2. they had a $\geq 20\%$ improvement in the number of swollen joints (based on 76 joints)
3. they had a $\geq 20\%$ improvement in three of the following five domains
 - a. Patient Global Assessment (measured on a VAS scale, 0-100)
 - b. Physician Global Assessment (measured on a VAS scale, 0-100)
 - c. Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
 - d. Disability (HAQ-DI© score)
 - e. Acute phase reactant (hsCRP or ESR)

Ranked key secondary efficacy variables that were analyzed at week 24 were:

1. PASI75
2. PASI90
3. DAS28-CRP
4. SF36-PCS
5. HAQ-DI
6. ACR50
7. Van der Heijde-modified total Sharp score (vdH-mTSS)
8. Dactylitis
9. Enthesitis

The PASI assessment was conducted for patients in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline (Visit 2). The PASI assessed the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness.

The DAS28-CRP is a measure of disease activity based on Swollen and Tender Joint Counts, CRP, and the Patient Global Assessment. A DAS28 score > 5.1 implies active disease, and ≤ 3.2 low disease activity. The following 28 joints were assessed for tenderness and swelling: metacarpophalangeal I-V (10), thumb interphalangeal (2), hand proximal interphalangeal II-V (8), wrist (2), elbow (2), shoulders (2), and knees (2).

The following formulas were used to calculate the DAS28 with CRP (mg/L):

$$\text{DAS28-CRP} = 0.56 \cdot \sqrt{\text{TJC28}} + 0.28 \cdot \sqrt{\text{SJC28}} + 0.36 \cdot \ln(\text{CRP}+1) + 0.014 \cdot \text{PGA} + 0.96$$

The Van der Heijde-modified total Sharp score (vdH-mTSS) for PsA is a detailed scoring method evaluating erosions, joint space narrowing, subluxation, ankylosis, gross osteolysis, and pencil in cup phenomena. The DIPs of the hands are evaluated as

the additional joint evaluated in rheumatoid arthritis. Gross osteolysis and pencil in cup is scored separately. The maximum possible score for erosions is 200 for the hands and 120 for the feet; the maximum possible score for joint space narrowing is 160 for the hands and 48 for the feet. Thus, the maximum possible scores are 320 for erosions, 208 for joint space narrowing, and 528 for the total score.

An ACR50 responder was defined as $\geq 50\%$ improvement in the swollen and tender joint count and $\geq 50\%$ improvement in at least 3 of the 5 domains described for the ACR20.

Statistics in study F2306

Populations: The populations specified in the clinical study report were:

- Randomized set: The randomized set was defined as all patients who were randomized. Mis-randomized patients are treated as screen failures.
- Full analysis set (FAS): The FAS was comprised of all patients from the randomized set to whom study treatment had been assigned. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned to at randomization.
- Safety set: The safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were evaluated according to treatment received.

Database locks: A database lock was conducted at Week 52 and will be conducted after all patients have completed the study.

Methods for the primary efficacy endpoint:

The statistical hypothesis for ACR20 being tested was that there was no difference in the proportion of patients fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens vs. placebo regimen.

The primary endpoint of ACR20 at Week 24 was analyzed via logistic regression with treatment and TNF-alpha inhibitor status as factors and weight as a covariate. Odds ratios were computed for comparisons of secukinumab regimens vs. placebo regimen utilizing the logistic regression model fitted.

For patients meeting the criteria for early escape at Week 16, their ACR20 was set to nonresponse at Week 24. This applied for all three treatment regimens in order to minimize bias.

Handling of Missing Data for the Primary Efficacy Endpoint:

Missing data for ACR20 response data up to 1-year (Week 52) was handled as follows:

1. Patients who dropped out of the trial for any reason were considered non-responders from the time they dropped out through Week 52.

2. Patients who did not have the required data to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) at baseline and at the specific time point were classified as non-responders.

Methods for secondary endpoints:

The following primary and secondary hypotheses were included in the sequential testing strategy, and type-I-errors were set such that a family-wise type-I-error of 5% is kept:

Primary objective:

H1: Secukinumab 75 mg SC is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

H2: Secukinumab 150 mg SC is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

Secondary objectives:

H3: Secukinumab 75 mg SC. is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of patients who have $\geq 3\%$ skin involvement with psoriasis

H4: Secukinumab 150 mg SC is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of patients who have $\geq 3\%$ skin involvement with psoriasis

H5: Secukinumab 75 mg SC is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of patients who have $\geq 3\%$ skin involvement with psoriasis

H6: Secukinumab 150 mg SC is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of patients who have $\geq 3\%$ skin involvement with psoriasis

H7: Secukinumab 75 mg SC is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24

H8: Secukinumab 150 mg SC is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24

H9: Secukinumab 75 mg SC is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24

H10: Secukinumab 150 mg SC is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24

H11: Secukinumab 75 mg SC is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI© at Week 24

H12: Secukinumab 150 mg SC is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI© at Week 24

H13: Secukinumab 75 mg SC is not different to placebo regimen with respect to ACR50 response at Week 24

H14: Secukinumab 150 mg SC is not different to placebo regimen with respect to ACR50 response at Week 24

H15: Secukinumab pooled regimen (75 mg and 150 mg SC) is not different to placebo regimen with respect to structural damage (vdH-mTSS) at Week 24

H16: Secukinumab pooled regimen (75 mg and 150 mg SC) is not different to placebo regimen with respect to presence of dactylitis at Week 24 in the subset of patients who have dactylitis at baseline

H17: Secukinumab pooled regimen (75 mg and 150 mg SC) is not different to placebo regimen with respect to presence of enthesitis at Week 24 in the subset of patients who have enthesitis at baseline

H18: Secukinumab 75 mg SC is not different to placebo regimen with respect to structural damage (vdH-mTSS) at Week 24

H19: Secukinumab 150 mg SC is not different to placebo regimen with respect to structural damage (vdH-mTSS) at Week 24

The family-wise error was set to $\alpha=5\%$ and it was controlled with the hierarchical testing strategy. Each of the hypotheses (H1 and H2) was tested simultaneously at $\alpha/2$. If at least one of H1 and/or H2 were/was rejected, then H3 and/or H4, respectively, was tested until H13 and H14. Once all hypotheses within the first family for a secukinumab regimen were rejected, then the respective $\alpha/2$ could be passed on to the other regimen's hypotheses within the family, if they were not already rejected at $\alpha/2$. Only when all H1 ~ H14 were rejected, the objective on joint structure endpoint at Week 24 for testing pooled secukinumab doses vs. placebo (H15) were tested at α . If H15 was rejected, then H16 was tested at α . Similarly if H16 was rejected, then H17 was tested at α . If these pooled hypotheses were all rejected, then hypotheses concerning individual regimens of secukinumab vs. placebo (H18 and H19) could be tested for a particular regimen at $\alpha/2$. Once the hypothesis of structure damage for a secukinumab regimen was rejected, then the respective $\alpha/2$ could be passed on to the other regimen's hypothesis, if it was not already rejected at $\alpha/2$. Of note, in the description above, rejection of a hypothesis referred to rejection of the two-sided hypothesis; however the level of a rejected hypothesis was only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect was in favor of secukinumab.

PASI 75 response and PASI 90 at Week 24 were evaluated for those patients in whom the assessment occurred due to sufficient skin involvement (at least 3% BSA affected with psoriasis). These binary variables were evaluated in the same fashion as ACR response, i.e. a logistic regression model with treatment and randomization strata as factors and weight as a covariate.

Definitions of Safety Endpoints in Study F2306

AE definition: An AE was defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing the Informed Consent Form even if the event was not considered to be related to study treatment.

An SAE was defined as an event which:

- was fatal or life-threatening
- results in persistent or significant disability/incapacity

- constituted a congenital anomaly/birth defect
- required in-patient hospitalization or prolongation of existing hospitalization
- was medically significant, i.e. defined as an event that jeopardized the patient or could have required medical or surgical intervention to prevent one of the outcomes listed above

Treatment-emergent AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 and summarized by presenting the number and percentage of patients having any AE, having an AE in each primary system organ class (SOC), and having each individual AE. AEs were also summarized by standardized MedDRA query using a narrow search. Laboratory parameters were analyzed with respect to Common Terminology Criteria for Adverse Events (CTCAE) grades.

5.3.4 Study CAIN457F2312 (F2312), phase 3 study in PsA

The following description of the protocol from the study comes from the Applicant's clinical study report dated October 22, 2014.

Title: A Phase III randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 24 weeks and to assess the long term efficacy, safety and tolerability up to 5 years in patients with active PsA.

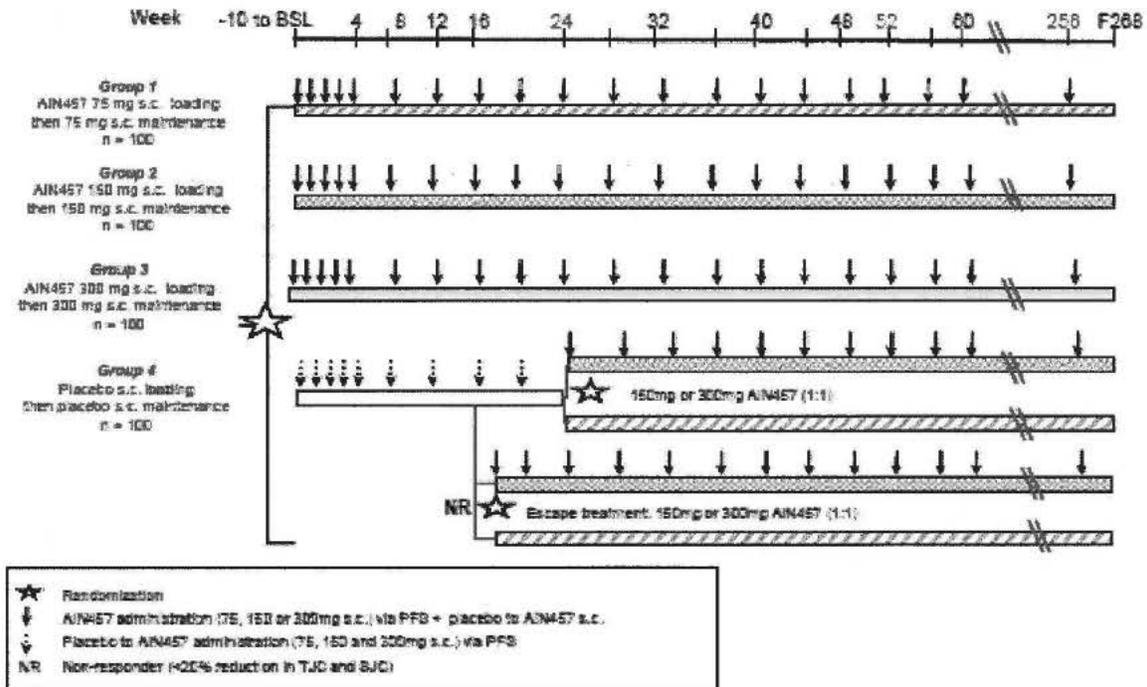
Study dates: The first patient's first visit was April 14, 2013 and the last patient's 24 week visit was May 12, 2014.

Study sites: Patients were enrolled from 76 centers in 10 countries (Australia, Belgium, Canada, Czech Republic, Germany, Poland, Russia Federation, Thailand, United Kingdom, and United States of America)

Objectives of study F2312: The primary objective of study F2312 was to demonstrate that the efficacy of secukinumab 75 mg or 150 mg or 300 mg at Week 24 is superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response.

Overall design: Study F2312 was a randomized, double-blind, placebo-controlled Phase 3 multicenter study of subcutaneous secukinumab to demonstrate the efficacy at 24 weeks and to assess the long-term efficacy, safety, and tolerability in patients with active PsA

Figure 4. F2312: Study design



Source: F2312 clinical study report, p. 54

Patient selection for study F2312: Study F2312 randomized patients who met the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Male or non-pregnant, non-lactating female patients at least 18 years of age
2. Diagnosis of PsA classified by CASPAR and with symptoms for at least 6 months with moderate to severe PsA
3. RF and Anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening.
4. Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis
5. Patients with PsA should have taken NSAIDs for at least 4 weeks prior to randomization
6. Patients taking corticosteroids had to be on a stable dose of ≤ 10 mg/day prednisone
7. Patients taking MTX (≤ 25 mg/week) were allowed to continue their medication if the dose was stable for at least 4 weeks before randomization
8. Patients who were on a DMARD other than MTX had to discontinue the
9. Patients who were on a TNF α inhibitor must have had experienced an inadequate response to previous or current treatment with a TNF α inhibitor given at an approved dose for at least 3 months or had stopped treatment due to safety/tolerability problems

Exclusion criteria:

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process
2. Patients taking high potency opioid analgesics
3. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor
4. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug
5. Ongoing use of prohibited psoriasis treatments / medications
6. History of hypersensitivity to the study drug or its excipient or to drugs of similar chemical classes.
7. Any intramuscular, intra-articular or intravenous corticosteroid treatment within 4 weeks before randomization
8. Patients who were previously treated with more than 3 different TNF α inhibitors
9. Patients who ever received biologic immunomodulating agents
10. Previous treatment with any cell-depleting therapies
11. Pregnant or nursing (lactating) women
12. Women of child-bearing potential
13. Significant medical problems or diseases
14. History of clinically significant liver disease or liver injury
15. History of renal trauma, glomerulonephritis, or patients with one kidney only,
16. Screening total White Blood Cells (WBC) count <3,000/ μ L, or platelets <100,000/ μ L or neutrophils <1,500/ μ L or hemoglobin <8.5 g/dL (85g/L)
17. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection
18. History of lymphoproliferative disease or any known malignancy or history of malignancy within the past 5 years
19. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator rendered the subject unsuitable for the trial
20. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

Trial Population: The study population comprised of male and female patients, 18 years or older who were diagnosed with moderate to severe PsA according to CASPAR criteria and had at baseline ≥ 3 tender joints out of 78 and ≥ 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each)

Treatments in study F2312:

Secukinumab was provided as follows:

- secukinumab 75 mg and 150 mg provided in 0.5 mL and 1.0 mL respectively in PFS for SC injection
- placebo provided in 0.5 mL and 1.0 mL PFS for SC injection

Patients were randomized to one of the following groups:

- Group 1- 75 mg secukinumab: secukinumab 75 mg (0.5 mL) plus placebo (2 x 1.0 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Group 2 - 150 mg secukinumab: secukinumab 150 mg (1.0 mL) plus placebo (0.5 mL and 1.0 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Group 3 - 300 mg secukinumab: secukinumab 300 mg (2 x 1.0 mL) plus placebo (0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Group 4 - placebo: Placebo (2 x 1.0 mL and 1x 0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.

Selection of doses in study F2312: The Applicant used two studies to justify their dose selection. In study A2206, 42 PsA patients were treated with two doses of 10 mg/kg secukinumab IV separated by 21 days or placebo. ACR20 at week 6 was the key endpoint and conclusions were that secukinumab showed evidence of therapeutic benefit in moderate to severe PsA patients. 9/23 (39%) on secukinumab achieved ACR20 response compared to 3/13 (23%) placebo patients. The second study, F2201, examined SC doses of secukinumab in RA patients. Doses were 25, 75, 100, or 300 mg doses of secukinumab at weeks 0, 4, 8, and 12 or placebo. ACR20 at week 16 was the key endpoint. ACR20 responses were 18/53 (34%) for the 25 mg secukinumab dose, 23/49 (46.9%) for the 75 mg dose, 20/43 (46.5%) for the 150 mg dose, 22/41 (53.7%) for the 300 mg dose, and 18/50 (36%) for placebo. The conclusion was that doses 75-300 showed numerical improvement in ACR20.

The Applicant used these two studies and dose exposure predictions from pharmacokinetic models to determine their doses. The doses that were selected for study F2312 were:

- secukinumab 75 mg at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- secukinumab 150 mg at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- secukinumab 300 mg at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.
- Placebo at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.

Placebo patients were classified as responder or non-responders at week 16. Responders were defined as patients who had $\geq 20\%$ improvement from baseline in both tender and swollen joint counts. Patients who did not achieve responder status were classified as non-responders. At week 16, patients who were placebo non-responders were re-randomized in a 1:1 ratio to receive secukinumab 150 mg SC or 300 mg SC every 4 weeks. Patients who were placebo responders continued to receive

placebo every 4 weeks until Week 24. Starting at Week 24, these patients were re-randomized to secukinumab 150 mg SC or 300 mg SC every 4 weeks regardless of responder status.

Concomitant medications in study F2312:

The investigator was to instruct the patient to notify the study site about any new medications (including over-the-counter drugs, calcium and vitamins) taken after the patient enrolled into the study.

Patients on MTX were to be treated with stable treatment of MTX (≤ 25 mg/week) for at least 4 weeks before randomization and maintained stable throughout the treatment period. Patients on MTX had to take folic acid supplementation during the trial to minimize the likelihood of MTX associated toxicity.

Treatment with systemic corticosteroids was allowed if the dose was stable for at least 2 weeks before randomization and maintained stable throughout the study period. A maximum dosage of 10 mg equivalent of daily prednisone was allowed. Corticosteroid dose reductions were permitted after Week 24.

Intra-articular corticosteroids were not permitted within 4 weeks prior to baseline and up to week 24. After week 24, no more than 1 joint per 24-week period was to be injected. Injection of intra-articular steroids was not permitted within 8 weeks prior to Weeks 24, 52, and 104.

Patients on regular use of NSAIDs or paracetamol/acetaminophen had to be on stable dose for at least 2 weeks before randomization to allow inclusion and during the treatment period. Patients could continue to do so after randomization, however, they had to refrain from any intake during at least 24 hours before a visit with disease activity assessment. Any changes to the NSAIDs, opioids, or paracetamol/acetaminophen treatment during the trial were recorded.

Prohibited therapies in study F2312

Prohibited therapies were the same as in study F2306 and shown in Table 6.

Patient Stopping Rules in Study F2312

Study treatment must be discontinued and the subject withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that subject. The following circumstances require study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events
 - Any severe or serious adverse event that is not compatible with administration of study treatment
 - Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma

of the cervix or noninvasive malignant colon polyps which are being or have been removed

- Life threatening infection
- Administration of a live vaccine up to Week 24
- Any laboratory abnormalities that in the judgment of the investigator were clinically significant and were deemed to place the patient at a safety risk for continuation in the study
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any other protocol deviation that results in a significant risk to the subject's safety

Trial monitoring and evaluations for Study F2312

Trial monitoring and evaluations for study F2312 are presented in Table 8.

Table 8. Overview of monitoring in study F2312

Week	Screening ¹		Treatment Period 1										Treatment Period 2							
	- 10 to - 4	≤ - 4 to BSL	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*	
Visit No.	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Informed consent & optional PG informed consent	X																			
Inclusion/Exclusion criteria	X	X	X																	
Relevant medical history/ current medical condition	X																			
Washout evaluation/instruction	X																			
Smoking history			X																	
Cardiovascular medical history			X																	
Demography	X																			
Psoriasis/psoriatic arthritis medical history and previous therapies	X																			
PsA CASPAR Criteria		X																		
Physical Exam ²		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X																		
Weight		X	X									X							X	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PPD skin test ³ or QuantiFERON TB-Gold test		X																		
Chest X-ray / MRI ⁴		X																		
ECG			X							X									X	
Randomization via IRT			X							X ⁵		X ⁵								
Administration of sc study treatment via PFS at study site			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant medication/ non-drug therapy	X		Update as necessary																	

Clinical Review
Raj Nair
125504/1
Secukinumab (Cosentyx)

Week	Screening ¹		Treatment Period 1												Treatment Period 2							
	- 10 to - 4	≤ - 4 to BSL	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*			
Visit No.	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Adverse Events/SAEs ⁶ (incl. injection site reaction & occurrence of infections)	X	Update as necessary																				
Hematology, blood chemistry, urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum pregnancy test	X																					
Urine pregnancy test ⁶		X					X		X	X		X		X		X			X			
ANA		X										X							X			
Anti-dsDNA		X										X							X			
Immunogenicity		X										X							X			
Anti-CCP	X																					
Rheumatoid factor (RF)	X																					
PK assessments (at pre-dose)			X				X			X		X							X			
High sensitivity C-Reactive protein (hsCRP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Erythrocyte Sedimentation Rate (ESR) ⁹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Tender and swollen joint counts (TJC78, SJC78)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Patient's assessment of PsA pain (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Patient's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Patient's global assessment of psoriasis and arthritis disease activity (VAS)			X		X		X	X	X	X		X		X		X			X			
Physician's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Health Assessment Questionnaire (HAQ-DI)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Leeds Dactylitis Index (LDI)			X		X		X	X	X	X		X		X		X			X			

Week	Screening ¹		Treatment Period 1												Treatment Period 2							
	- 10 to - 4	≤ - 4 to BSL	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*			
Visit No.	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Leeds Enthesitis Index (LEI)			X		X		X	X	X	X		X		X		X			X			
PASI (only if ≥ 3% of BSA at BSL)			X	X	X		X	X	X	X		X		X		X			X			
IGAm2011 (only if ≥ 3% of BSA at BSL)			X	X	X		X	X	X	X		X		X		X			X			
mNAPSI (only in patients with nail involvement of hands) incl. VAS physician's assessment of nail disease			X				X	X	X	X		X		X		X			X			
SF-36 v2			X				X	X	X	X		X							X			
FACIT-Fatigue v4			X				X	X	X	X		X							X			
EQ-5D v3L			X				X	X	X	X		X							X			
DLQI (only if ≥ 3% of BSA at BSL)			X				X	X	X	X		X							X			
PsAQoL			X				X	X	X	X		X							X			
WPAI-GH			X							X		X							X			
Lipids ⁷			X					X		X		X							X			
Cardiovascular panel			X							X		X							X			
Serum biomarker related to targeted pathway			X									X							X			
Pharmacogenetics ⁸			X																			
Treatment period 1 completion form												X										
Treatment period 2 completion form																			X			

Clinical Review
Raj Nair
125504/1
Secukinumab (Cosentyx)

Week	Screening ¹		Treatment Period 1										Treatment Period 2							
	- 10 to - 4	≤ - 4 to BSL	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*	
Visit No.	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Adverse Events/SAEs ⁶ (incl. injection site reaction & occurrence of infections)	X	Update as necessary																		
Hematology, blood chemistry, urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test		X																		
Urine pregnancy test ⁹			X				X		X	X		X		X		X			X	
ANA			X									X							X	
Anti-dsDNA			X									X							X	
Immunogenicity			X									X							X	
Anti-CCP	X																			
Rheumatoid factor (RF)	X																			
PK assessments (at pre-dose)			X				X			X		X							X	
High sensitivity C-Reactive protein (hsCRP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Erythrocyte Sedimentation Rate (ESR) ⁹		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tender and swollen joint counts (TJC78, SJC76)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's assessment of PsA pain (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of psoriasis and arthritis disease activity (VAS)			X		X		X	X	X	X		X		X		X			X	
Physician's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health Assessment Questionnaire (HAQ-DI)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Leeds Dactylitis Index (LDI)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Week	Screening ¹		Treatment Period 1										Treatment Period 2							
	- 10 to - 4	≤ - 4 to BSL	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*	
Visit No.	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	

¹ If subject's washout period was ≤ 4 weeks, Visit 1 and 2 could be performed on the same day.
² These assessments were source documentation only and were not entered into the eCRF
³ The PPD skin test could be performed at any time during the screening period but it had to be read within 72 hrs and before randomization
⁴ If patients did not have a chest X-ray available within 3 months of screening, an X-ray was to be performed after it was certain the subject met inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation. In some sites selected by Novartis, the X-ray assessment could be replaced by chest MRI assessment.
⁵ Patients on placebo were re-assigned/re-randomized at Week 16 and at Week 24
⁶ AEs /SAEs occurring after the subject had provided informed consent had to be reported
⁷ Sample had to be obtained fasting
⁸ Pharmacogenetic samples were only to be collected after separate PG informed consent was signed.
⁹ Kits were provided by central lab and test was performed locally
^{*} These assessments were also to be conducted for patients who discontinued:
Patients who prematurely discontinued during Treatment Period 1 had to return for assessments associated with Week 24 visit (4 weeks after the last study treatment) and the follow-up visit (Week F268) 12 weeks after the last study treatment. Patients who prematurely discontinued during Treatment Period 2 had to return and complete assessments associated with Week 52 visit (4 weeks after the last study treatment) and the follow-up visit (WeekF268) 12 weeks after the last study treatment.

Source: F2312 study report, p. 70-73

Efficacy endpoints

Primary Efficacy Endpoint: The primary efficacy variable was the clinical response to treatment according to ACR20 individual improvement in disease activity at Week 24. A patient was defined as an ACR20 responder if, and only if, the following three conditions hold

1. they had a ≥ 20% improvement in the number of tender joints (based on 78 joints)

2. they had a $\geq 20\%$ improvement in the number of swollen joints (based on 76 joints)
3. they had a $\geq 20\%$ improvement in three of the following five domains
 - a. Patient Global Assessment (measured on a VAS scale, 0-100)
 - b. Physician Global Assessment (measured on a VAS scale, 0-100)
 - c. Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
 - d. Disability (HAQ-DI© score)
 - e. Acute phase reactant (hsCRP or ESR)

The secondary efficacy variables analyzed at week 24 included:

- PASI75 in the subgroup of patients who had $\geq 3\%$ skin involvement
- PASI90 in the subgroup of patients who had $\geq 3\%$ skin involvement
- change from baseline in DAS28-CRP
- change in SF-36 PCS from baseline
- change in HAQ-DI from baseline
- ACR50 criteria
- presence of dactylitis
- presence of enthesitis

Statistics in study F2306:

Populations: The populations specified in the clinical study report were:

- Randomized set: The randomized set was defined as all patients who were randomized. Mis-randomized patients are treated as screen failures.
- Full analysis set (FAS): The FAS was comprised of all patients from the randomized set to whom study treatment had been assigned. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned to at randomization.
- Safety set: The safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were evaluated according to treatment received.

Database locks: Database locks were performed at week 24, week 52, and after all patients have completed the study

Methods for the primary efficacy endpoint:

The statistical hypothesis for ACR20 being tested was that there was no difference in the proportion of patients fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens vs. placebo regimen.

The primary endpoint of ACR20 at Week 24 was analyzed via logistic regression with treatment and TNF-alpha inhibitor status as factors and weight as a covariate. Odds

ratios were computed for comparisons of secukinumab regimens vs. placebo regimen utilizing the logistic regression model fitted.

For patients meeting the criteria for early escape at Week 16, their ACR20 was set to nonresponse at Week 24. This applied for all four treatment regimens in order to minimize bias.

Handling of Missing Data for the Primary Efficacy Endpoint:

Missing data for ACR20 response data up to 1-year (Week 52) was handled as follows:

1. Patients who dropped out of the trial for any reason were considered non-responders from the time they dropped out through Week 52.
2. Patients who did not have the required data to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) at baseline and at the specific time point were classified as non-responders.

Methods for secondary efficacy endpoints:

The following hypotheses were included in the testing strategy, and type-I-errors were set such that a family-wise type-I-error of 5% was kept:

Primary objectives:

H1: Secukinumab 75 mg SC is not different to placebo regimen with respect to ACR20 response at week 24

H2: Secukinumab 150 mg SC is not different to placebo regimen with respect to ACR20 response at week 24

H3: Secukinumab 300 mg SC is not different to placebo regimen with respect to ACR20 response at week 24

Secondary objectives:

H4: Secukinumab 75 mg SC is not different to placebo regimen with respect to PASI75 response at Week 24

H5: Secukinumab 150 mg SC is not different to placebo regimen with respect to PASI75 response at Week 24

H6: Secukinumab 300 mg SC is not different to placebo regimen with respect to PASI75 response at week 24

H7: Secukinumab 75 mg SC is not different to placebo regimen with respect to PASI90 response at week 24

H8: Secukinumab 150 mg SC is not different to placebo regimen with respect to PASI90 response at week 24

H9: Secukinumab 300 mg SC is not different to placebo regimen with respect to PASI90 response at week 24

H10: Secukinumab 75 mg SC is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at week 24

H11: Secukinumab 150 mg SC is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at week 24

- H12: Secukinumab 300 mg SC is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at week 24
- H13: Secukinumab 75 mg SC is not different to placebo regimen with respect to the change from baseline in SF36-PCS at week 24
- H14: Secukinumab 150 mg SC is not different to placebo regimen with respect to the change from baseline in SF36-PCS at week 24
- H15: Secukinumab 300 mg SC is not different to placebo regimen with respect to the change from baseline in SF36-PCS at week 24
- H16: Secukinumab 75 mg SC is not different to placebo regimen with respect to the change from baseline in HAQ-DI at week 24
- H17: Secukinumab 150 mg SC is not different to placebo regimen with respect to the change from baseline in HAQ-DI at week 24
- H18: Secukinumab 300 mg SC is not different to placebo regimen with respect to the change from baseline in HAQ-DI at week 24
- H19: Secukinumab 75 mg SC is not different to placebo regimen with respect to ACR50 response at Week 24
- H20: Secukinumab 150 mg SC is not different to placebo regimen with respect to ACR50 response at Week 24
- H21: Secukinumab 300 mg SC is not different to placebo regimen with respect to ACR50 response at Week 24
- H22: Secukinumab pooled regimen (75 mg and 150 mg and 300 mg) is not different to placebo regimen with respect to proportion of patients with dactylitis at Week 24 in the subset of patients with dactylitis at baseline
- H23: Secukinumab pooled regimen (75 mg and 150 mg and 300 mg) is not different to placebo regimen with respect to proportion of patients with enthesitis at Week 24 in the subset of patients with enthesitis at baseline

The family-wise error was set to $\alpha=5\%$ and was controlled with the proposed hierarchical testing strategy.

Each of the hypotheses (H1, H2, and H3) for the primary objective for each secukinumab regimen versus placebo were tested simultaneously at $\alpha/3$. If at least one of H1 and/or H2 and/or H3 were/was rejected, then H4 and/or H5 and/or H6, respectively, was tested. Similar process applied until H19 to H21. Once all hypotheses within the first family for a secukinumab regimen were rejected, then the respective $\alpha/3$ could be passed on to the other regimen's hypotheses within the family, if they were not already rejected at $\alpha/3$. Only when all H1 ~ H21 were rejected, the objective on the proportion of patients with dactylitis at Week 24 for testing pooled secukinumab doses versus placebo (H22) was tested at α . If H22 was rejected, then H23 was tested at α .

Definitions of Safety Endpoints in Study F2312:

AE definition: An AE was defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing the Informed Consent Form even if the event was not considered to be related to study treatment.

An SAE was defined as an event which:

- was fatal or life-threatening
- results in persistent or significant disability/incapacity
- constituted a congenital anomaly/birth defect
- required in-patient hospitalization or prolongation of existing hospitalization
- was medically significant, i.e. defined as an event that jeopardized the patient or could have required medical or surgical intervention to prevent one of the outcomes listed above

Treatment-emergent AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 and summarized by presenting the number and percentage of patients having any AE, having an AE in each primary system organ class (SOC), and having each individual AE. AEs were also summarized by standardized MedDRA query using a narrow search. Laboratory parameters were analyzed with respect to Common Terminology Criteria for Adverse Events (CTCAE) grades.

6 Review of Efficacy

Efficacy Summary

Trials F2306 and F2312 were submitted as the primary source of efficacy data for secukinumab in the treatment of PsA. Both trials consisted of a 24-week double-blind, placebo-controlled period followed by continued treatment with secukinumab. The Applicant submitted data to Week 52. The primary efficacy analysis was at Week 24. The primary endpoint was the proportion of patients who achieved ACR20 response at Week 24. Secondary efficacy analyses were performed at Week 24. This trial was well-controlled and had endpoints that are considered acceptable for efficacy evaluations in PsA.

In the pre-specified primary analyses, secukinumab met the primary and secondary endpoints in study F2306. In study F2312, secukinumab met the primary endpoints for the 75, 150, and 300 mg doses. The 300 mg dose met all secondary endpoints. The 150 mg dose met all secondary endpoints except for ACR50 and mean change in HAQ-DI from baseline. The 75 mg was not statistically superior to placebo for any of the secondary endpoints at Week 24.

Additional subgroup analyses were conducted to examine the efficacy of secukinumab without a loading dose in patients who were switched from placebo to secukinumab. We recognize that these subgroup analyses are exploratory and should be interpreted cautiously. In general, the best test of validity is not significance, but independent substantiation of results. In studies F2306 and F2312, the placebo patients who were switched to secukinumab were evaluated for ACR20 response. Both studies showed

that placebo patients, all of whom received no loading dose, were able to achieve ACR20 responses and maintain ACR20 responses for 32 weeks.

6.1 Indication

The Applicant proposed the following indication in the application: "treatment of adult (b) (4) with active psoriatic arthritis (PsA) (b) (4)"

6.1.1 Methods

F2306 and F2312 served as the two studies to evaluate the efficacy of secukinumab for the treatment of active PsA (b) (4). The trials were well controlled and utilized endpoints used in other programs to support approval for PsA. Both studies used a loading dose with study F2306 using an IV loading dose and study F2312 using SC loading doses. Study F2306 used two maintenance doses of 75 mg or 150 mg secukinumab SC every 4 weeks. Study F2312 used three maintenance doses of 75, 150, or 300 mg secukinumab SC every 4 weeks. Both studies were placebo controlled to week 24. Both studies re-randomized placebo non-responders to secukinumab at week 16. Both studies re-randomized placebo responders at week 24 to secukinumab. Given the differences in the studies, including the loading doses evaluated and the maintenance doses studied, the results of these studies will be presented separately.

6.1.2 Demographics

6.1.2.1 F2306 Demographics

Table 9 displays the baseline demographics in trial F2306. In the overall PsA study population, the three treatment groups had similar baseline demographics. The patients enrolled were predominantly white with an average age of almost 50 years. The patients enrolled were typical of a PsA population. 15-20% of the enrolled patients were Asian ethnicity.

Table 9. F2306: Baseline demographic characteristics

Characteristics	AIN457 10 mg/kg-75 mg N=202	AIN457 10 mg/kg-150 mg N=202	Placebo N=202
Age (years) Mean±SD Median (range)	48.8±12.23 50 (20-76)	49.6±11.76 51 (22-73)	48.5±11.9 49 (21-77)
Gender, n (%) Female	118 (58.4)	106 (52.5)	106 (52.5)
Weight (kg) Mean±SD Median (range)	84.45±19.61 82 (44-155.1)	84.23±21.05 83 (50-163.3)	80±20.47 79.85 (32-152.4)
Height (cm) Mean±SD Median (range)	167.51±10.13 167 (145-201)	167.94±10.29 168 (143-200)	166.54±10.14 167 (144-190.5)
Race, n (%) White Black Asian	165 (81.7) 2 (1) 33 (16.3)	162 (80.2) 3 (1.5) 36 (17.8)	154 (76.2) 0 (0) 46 (22.8)

Source; adapted from F2306 clinical study report, p. 134

Table 10 shows the baseline disease characteristics in study F2306. No clinically significant differences in joint counts and inflammatory markers were seen among the treatment arms. The enrolled patients were consistent with an active PsA population. The baseline disease measures were relatively balanced among treatment groups for most baseline disease characteristics.

Table 10. F2306: Baseline disease measures

Baseline Characteristics	AIN457 10 mg/kg-75 mg N=202	AIN457 10 mg/kg-150 mg N=202	Placebo N=202
Mean DAS28 CRP score (SD)	4.891 (1.15)	4.782 (1.09)	4.93 (1.10)
Presence of enthesitis (%)	63.9	62.4	57.9
Presence of dactylitis (%)	51.5	51.5	57.4
Mean TJC78 (SD)	23.4 (17.19)	23.8 (16.4)	25.1 (18.41)
Mean SJC76 (SD)	12.7 (11.11)	12.5 (9.38)	14.9 (13.06)
Patients with Ps _s ≥3% of BSA, n (%)	108 (53.5)	108 (53.5)	109 (54)

Source: adapted from F2306 clinical study report, pp. 137-140

Table 11 shows baseline PASI scores in the subset of patients who had baseline psoriasis ≥3% of body surface area (BSA). The mean baseline PASI scores were lower

in patients who received the 75 mg maintenance dose of secukinumab versus patients who received the 150 mg maintenance dose or placebo.

Table 11. F2306: Baseline PASI scores in patients with baseline psoriasis \geq 3% of BSA

Baseline Characteristics	AIN457 10 mg/kg-75 mg N=108	AIN457 10 mg/kg-150 mg N=108	Placebo N=109
Baseline PASI score, mean (SD)	10.7 (8.8)	15.6 (13.9)	15.1 (11.6)

Source: adapted from F2306 clinical study report, p. 140

Table 12 shows the medications taken prior to enrollment in study F2306 for each treatment group. The medications were relatively balance among groups. The percentage of patients taking prednisone in the 150 mg maintenance dose of secukinumab group was slightly higher that the placebo and 75 mg maintenance dose group.

Table 12. F2306: Prior medications

Prior medication n, (%)	AIN457 10 mg/kg-75 mg N=202	AIN457 10 mg/kg-150 mg N=202	Any AIN457 N=404	Placebo N=202
Any medication	129 (63.9)	148 (73.3)	277 (68.6)	137 (67.8)
Sulfasalazine	24 (11.9)	24 (11.9)	48 (11.9)	29 (14.4)
Diclofenac	10 (5)	10 (5)	20 (5)	2 (1)
Prednisone	4 (2)	15 (7.4)	19 (4.7)	5 (2.5)
Methotrexate	48 (23.8)	50 (24.8)	98 (24.3)	52 (25.7)
Etanercept	35 (17.3)	28 (13.9)	63 (15.6)	38 (18.8)
Adalimumab	28 (13.9)	25 (12.4)	53 (13.1)	26 (12.9)
Leflunomide	23 (11.4)	28 (13.9)	51 (12.6)	26 (12.9)
Infliximab	18 (8.9)	28 (13.9)	46 (11.4)	26 (12.9)
Ibuprofen	10 (5)	7 (3.5)	17 (4.2)	10 (5)
Meloxicam	4 (2)	11 (5.4)	15 (3.7)	5 (2.5)

Source: adapted from F2306 clinical study report, p. 337-354

Table 13 shows concomitant medications taken during study F2306. The placebo group took a lower percentage of systemic glucocorticoids. All other medications were relatively well balanced.

Table 13. F2306: Concomitant medications

Concomitant medication n, (%)	Any AIN457 10 mg/kg-75 mg N=292	Any AIN457 10 mg/kg-150 mg N=295	Any AIN457 N=587	Placebo N=202
Any medication	289 (99)	293 (99.3)	582 (99.1)	198 (98)
Omeprazole	67 (22.9)	64 (21.7)	131 (22.3)	36 (17.8)
NSAIDs	198 (67.8)	211 (71.5)	409 (69.7)	138 (68.3)
Systemic glucocorticoids	75 (25.7)	80 (27.1)	155 (26.4)	34 (16.8)
Topical glucocorticoids	20 (6.8)	13 (4.4)	33 (5.6)	8 (4)
Amoxicillin	28 (9.6)	31 (10.5)	59 (10.1)	6 (3)
Methotrexate	174 (59.6)	178 (60.3)	352 (60)	117 (57.9)
Folic acid	179 (61.3)	177 (60)	356 (60.6)	122 (60.4)
Paracetamol	67 (22.9)	83 (28.1)	150 (25.6)	28 (13.9)
TNF inhibitor	2 (0.7)	3 (1)	5 (0.9)	0 (0)

Source: adapted from F2306 clinical study report, p. 1646-1714

Reviewer comments: The decreased usage of systemic glucocorticoids in the placebo group potentially could lead to a difference in ACR20 response. However, the similar baseline disease characteristics among the placebo and secukinumab groups are reassuring. The difference in prednisone usage based on the submitted protocol was random and not due to a difference in enrollment between treatment and placebo groups. The Applicant provided a stratified analysis of ACR20 response based on concomitant systemic glucocorticoid usage for studies F2306 and F2312 which showed no difference in ACR20 response based on use of systemic glucocorticoid usage (data not shown).

6.1.2.2 F2312 Demographics

The baseline demographics for study F2312 are shown in Table 14. The study did not have the percentage of Asian patients seen in study F2306 which was likely due to difference in study sites used for enrollment. The genders enrolled were balanced and the population was predominantly White which is consistent with a PsA population.

Table 14. F2312: Baseline demographic characteristics

Characteristics	AIN457 75 mg N=99	AIN457 150 mg N=100	AIN457 300 mg N=100	Placebo N=98
Age (years)				
Mean±SD	48.6±11.4	46.5±11.7	46.9±12.6	49.9±12.5
Median (range)	51 (21-71)	46.5 (20-67)	46.5 (23-77)	51 (20-77)
Gender, n (%)				
Female	52 (52.5)	45 (45)	49 (49)	59 (60.2)
Weight (kg)				
Mean±SD	85.6±20.6	91.2±19.8	85.4±18.4	86.2±19.8
Median (range)	87.4 (48-132)	91.4 (47-147)	83 (52-161)	85.6 (54-147)
Height (cm)				
Mean±SD	168.5±9.8	170.7±9.8	170.5±9.6	168.9±9.6
Median (range)	167 (146-193)	170.8 (153-203)	169.3 (142-198)	168.5 (148-189)
Race, n (%)				
White	90 (91)	90 (90)	96 (96)	94 (96)
Black	0 (0)	0 (0)	1 (1)	0 (0)
Asian	5 (5)	6 (6)	2 (2)	1 (1)

Source: adapted from F2312 clinical study report, p. 112

The baseline characteristics were consistent with a PsA population with active disease and were similar to the baseline characteristics of patients who were enrolled in study F2306.

Table 15. F2312: Baseline disease measures

Baseline Characteristics	AIN457 75 mg N=99	AIN457 150 mg N=100	AIN457 300 mg N=100	Placebo N=98
Mean DAS28 CRP score (SD)	4.7 (1)	4.9 (1.1)	4.7 (1)	4.7 (1)
Presence of enthesitis (%)	69	64	56	66
Presence of dactylitis (%)	33	32	46	28
Mean TJC78 (SD)	22 (16.3)	24 (19.4)	20 (13.3)	23 (19)
Mean SJC76 (SD)	11 (9.2)	12 (10)	11 (7.8)	12 (10.7)
Patients with Ps≥3% of BSA, n (%)	50 (50.5)	58 (58)	41 (41)	43 (43.9)

Source: adapted from F2312 clinical study report, p. 118-119

Table 16 shows the medications used prior to start of the study. Most patients were on previous medication for the treatment of PsA. Over 75% of patients were taking NSAIDs and more than half of patients were taking methotrexate in each group. The

prior medications used in each group were balanced including comparisons between the secukinumab groups and placebo.

Table 16. F2312: Prior medications

	AIN457 75 mg N=99 n (%)	AIN457 150 mg N=100 n (%)	AIN457 300 mg N=100 n (%)	Any AIN457 N=299 n (%)	Placebo N=98 n (%)
Any	97 (98)	95 (95)	95 (95)	287 (96)	95 (96.9)
NSAIDs	76 (76.8)	77 (77)	83 (83)	236 (78.9)	80 (81.6)
MTX	62 (62.6)	59 (59)	56 (56)	177 (59.2)	63 (64.3)
TNF inhibitor					
Paracetamol	13 (13.1)	13 (13)	13 (13)	39 (13)	14 (14.3)
sulfasalazine	13 (13.1)	12 (12)	13 (13)	38 (12.7)	13 (13.3)
leflunomide	13 (13.1)	10 (10)	9 (9)	32 (10.7)	15 (15.3)
Systemic glucocorticoids	31 (31.3)	32 (32)	28 (28)	91 (30.4)	32 (32.7)

Source: adapted from F2312 clinical study report, p. 340-344

Table 17 shows concomitant medications that were used during study F2312 through week 16. Almost all patients used concomitant medications during the study and over 65% of patients in all groups used NSAIDs. Approximately 40 to 45% of patients took methotrexate during the study. The use of concomitant medications was balanced across study arms including between the placebo and secukinumab arms.

Table 17. F2312: Concomitant medications to week 16

	AIN457 75 mg N=99 n (%)	AIN457 150 mg N=100 n (%)	AIN457 300 mg N=100 n (%)	Any AIN457 N=299 n (%)	Placebo N=98 n (%)
Any	86 (86.9)	87 (87)	95 (95)	268 (89.6)	92 (93.9)
NSAIDs	62 (62.6)	68 (68)	77 (77)	207 (69.2)	74 (75.5)
MTX	43 (43.4)	42 (42)	41 (41)	126 (42.1)	45 (45.9)
Paracetamol	14 (14.1)	16 (16)	17 (17)	47 (15.7)	18 (18.4)
Tramadol	2 (2)	6 (6)	6 (6)	14 (4.7)	3 (3.1)
Systemic glucocorticoids	22 (22.2)	26 (26)	21 (21)	69 (23.1)	25 (25.5)
Topical glucocorticoids	6 (6.1)	6 (6)	6 (6)	18 (6)	6 (6.1)

Source: adapted from F2312 clinical study report, p. 1382-1385

6.1.3 Subject Disposition

6.1.3.1 F2306 Disposition

Table 18 shows the disposition of patients at the week 52 analysis. Of the 202 patients who started in the placebo group, 123 non-responders were re-randomized to either 75 mg SC of AIN457 or 150 mg SC of AIN457 at week 16, 60 responders were re-randomized to either 75 mg SC of AIN457 or 150 mg SC of AIN457 at week 24, and 4 patients discontinued before receiving AIN457. 86% of patients who started in the AIN457 10 mg/kg IV-75mg SC group completed week 52 and 89% of the patients who started in the AIN457 10 mg/kg IV-150 mg SC group completed week 52.

Table 18. F2306: Patient disposition to week 52

	AIN457 10 mg/kg- 75 mg N=202 n (%)	AIN457 10 mg/kg- 150 mg N=202 n (%)	Placebo N=202 n (%)	Placebo non- responder AIN 457- 75 mg N=62 n (%)	Placebo non- responder AIN-457 150 mg N=61 n (%)	Placebo responder AIN 457- 75 mg N=31 n (%)	Placebo responder AIN-457 150 mg N=33 n (%)
Randomized	202	202	202	62	61	31	33
Completed week 52	174 (86.1)	180 (89.1)	161 (79.7)	55 (88.7)	51 (83.6)	27 (87.1)	28 (84.8)
Discontinued week 52	28 (13.9)	22 (10.9)	41 (20.3)	7 (11.3)	10 (16.4)	4 (12.9)	5 (15.2)
Adverse event	6 (3)	5 (2.5)	9 (4.5)	2 (3.2)	2 (3.3)	1 (3.2)	1 (3)
Lack of efficacy	6 (3)	7 (3.5)	13 (6.4)	1 (1.6)	5 (8.2)	1 (3.2)	0
Lost to follow up	1 (0.5)	1 (0.5)	4 (2)	0	0	1 (3.2)	2 (6.1)
Physician decision	6 (3)	4 (2)	2 (1)	1 (1.6)	0	0	0
Pregnancy	0	0	1 (0.5)	1 (1.6)	0	0	0
Protocol deviation	2 (1)	0	0	0	0	0	0
Subject/guardian decision	6 (3)	5 (2.5)	12 (5.9)	2 (3.2)	3 (4.9)	1 (3.2)	2 (6.1)
Death	1 (0.5)	0	0	0	0	0	0

Source: adapted from F2306 clinical study report, p. 131

6.1.3.2 F2312 Disposition

Table 19 shows the disposition of patients to week 24. 88 placebo patients were re-randomized to secukinumab. Of these 88 placebo patients, 55 were non-responders who started receiving secukinumab (150 mg every 4 weeks: 27 patients and 300 mg every 4 weeks: 28 patients) at week 16. 33 patients who were placebo responders were re-randomized at week 24 to secukinumab (150 mg every 4 weeks: 16 patients and 300 mg every 4 weeks: 17 patients). A higher percentage of placebo patients discontinued at week 24 as compared to the other secukinumab arms.

Table 19. F2312: Patient disposition to week 24

	AIN457 75 mg N=99 n (%)	AIN457 150 mg N=100 n (%)	AIN457 300 mg N=100 n (%)	Placebo N=98 n (%)
Randomized	99	100	100	98
Completed week 24	93 (93.9)	95 (95)	97 (97)	88 (89.8)
Discontinued week 24	6 (6.1)	5 (5)	3 (3)	10 (10.2)
Adverse event	3 (3)	0 (0)	2 (2)	4 (4.1)
Lack of efficacy	2 (2)	3 (3)	0 (0)	3 (3.1)
Physician decision	0 (0)	1 (1)	0 (0)	0 (0)
Subject/guardian decision	1 (1)	1 (1)	1 (1)	3 (3.1)

Source: adapted from F2312 clinical study report, p. 107

Reviewer's comment: The placebo patients were withdrawn from placebo at different time points in studies F2306 and F2312 depending on whether patients were responders or non-responders to placebo. Non-responders were withdrawn from placebo and placed on SC secukinumab at week 16. Placebo responders at week 16 were placed on SC secukinumab at week 24 regardless of responder status at week 24. All placebo patients who were placed on secukinumab were blinded to the dose of SC secukinumab that they received. In study F2306, placebo patients were re-randomized to either 75 mg or 150 mg SC secukinumab every 4 weeks. In study F2312, patients were re-randomized to either 150 or 300 mg SC secukinumab every 4 weeks. The re-randomized placebo patients were not given loading doses of secukinumab.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 F2306 Analysis of primary endpoint

Table 20 shows the proportion of patients who achieved ACR20 response at week 24. Both secukinumab doses were statistically superior to placebo. Roughly 50% of patients achieved ACR20 response in the active drug groups compared to 17% in the placebo group.

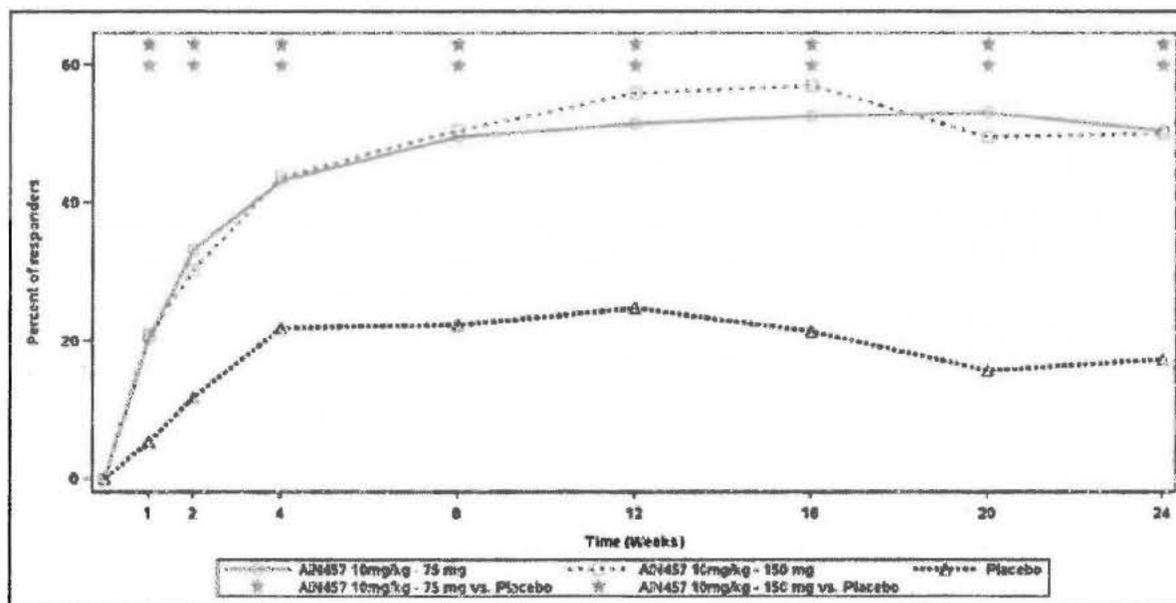
Table 20. F2306: ACR20 response at week 24

Treatment group	n/M (%)	Odds ratio	95% CI	p-value
AIN457 10 mg/kg-75 mg (N=202)	102/202 (50.5)	5.53	(3.46, 8.85)	<.0001
AIN457 10 mg/kg-150 mg (N=202)	101/202 (50)	5.39	(3.37, 8.62)	<.0001
Placebo (N=202)	35/202 (17.3)	--	--	--

Source: adapted from F2306 clinical study report, p. 148

Figure 5 shows the percent of patients who had ACR20 response over time to week 24 for the secukinumab groups and placebo group. Non-responder imputation was used to account for missing data. A majority of patients who achieved ACR20 response achieved it by Week 4. Both secukinumab arms were superior to placebo but the two maintenance doses of secukinumab did not show any difference between doses in efficacy for ACR20 response.

Figure 5. F2306: ACR20 response to week 24



Source: F2306 Clinical study report, p. 149

Reviewer's comment: In study F2306, the secukinumab arms were superior to placebo. The two doses of secukinumab did not separate to week 24. Both secukinumab arms received large IV doses of 10 mg/kg IV secukinumab at weeks 0, 2, and 4. The IV loading doses may have contributed to the efficacy at week 24 and may explain why the

75 mg and 150 mg dose had similar ACR20 responses at week 24. A significant consideration during the review was whether efficacy would be maintained since the exposure from the maintenance doses would be much lower than the initial loading doses. Additional analyses were performed on the placebo patients who did not receive loading doses, as discussed in section 6.1.9 to evaluate this concern.

6.1.4.2 F2312 Analysis of primary endpoint

Table 21 shows the proportion of patients who attain ACR20 response at Week 24 by treatment arm. All active treatment arms were superior to placebo in achieving ACR20 response. The 150 mg and 300 mg SC arms of the study achieved approximately a 50% response in ACR20 and the 75 mg SC arm achieved approximately a 30% ACR20 response versus a 15% response in the placebo arm.

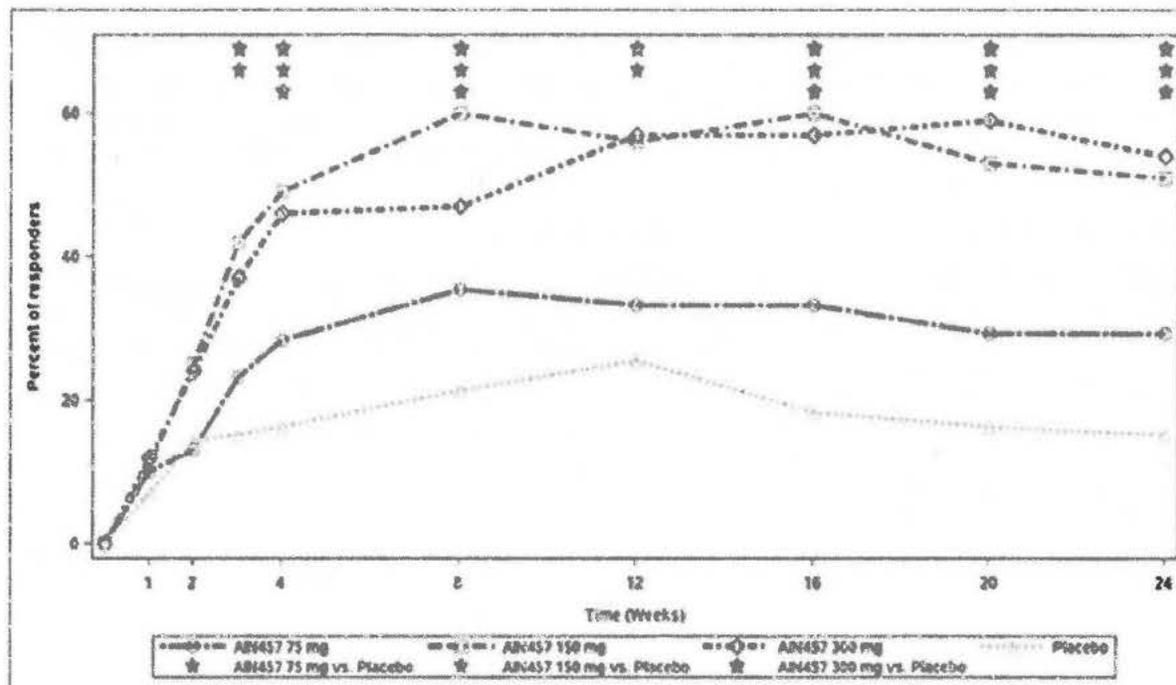
Table 21. F2312: ACR20 response at week 24

Treatment group	n/M (%)	Odds ratio	95% CI	p-value
AIN457 75 mg (N=99)	29/99 (29.3)	2.32	(1.14, 4.73)	0.02
AIN457 150 mg (N=100)	51/100 (51)	6.52	(3.25, 13.08)	<0.0001
AIN457 300 mg (N=100)	54/100 (54)	6.81	(3.42, 13.56)	<0.0001
Placebo (N=98)	15/98 (15.3)	--	--	--

Source adapted from F2312 clinical study report, p. 129-130

Figure 6 shows ACR20 response over time to week 24. The 150 mg and 300 mg dose groups appeared to be similar in obtaining ACR20 response and the two curves did not appear to separate over time. The 75 mg dose group appeared to attain response less quickly and did not have as high a proportion of patients achieve ACR20 response as compared to the 150 mg and 300 mg SC arms.

Figure 6. F2312: ACR20 response to week 24



■ p < 0.05

Source: F2312 clinical study report, p. 131

Reviewer's comment: All secukinumab arms were superior to placebo at week 24. The ACR20 responses for the 150 mg and 300 mg SC arms were numerically superior to the 75 mg SC arm. The 150 mg and 300 mg arms had higher loading doses and greater initial exposures than the 75 mg arm. The 150 mg arm received 5 weekly doses of 150 mg secukinumab SC and the 300 mg arm received 5 weekly doses of 300 mg secukinumab SC to begin the study before receiving SC doses every 4 weeks. The 75 mg arm received 5 weekly doses of 75 mg SC secukinumab. A significant consideration during the review was whether efficacy would be maintained since the exposure from the maintenance doses would be lower than the initial loading doses. Additional analyses were performed on the placebo patients who did not receive loading doses, as discussed in section 6.1.9 to evaluate this concern.

Given that the 150 mg and 300 mg doses appeared to have similar efficacy on the primary endpoint, the 150 mg dose was considered a sufficient dose for the treatment of PsA.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1. F2306 Analysis of Secondary Endpoints

Table 22 shows the efficacy results for secondary endpoints at week 24 as performed in the statistical hierarchy. Individual scores were tested in the hierarchy until reaching the van der Heijde modified total Sharp score. The pooled van der Heijde modified total Sharp score was tested followed by the pooled presence of dactylitis, and pooled presence of enthesitis. Lastly, the individual doses for van der Heijde modified total Sharp score were tested. The individual doses for presence of dactylitis or enthesitis were not tested in the hierarchy.

Table 22. F2306: Secondary endpoints at week 24

Secondary endpoint	Secukinumab 10 mg/kg-75 mg (N=202)	Secukinumab 10 mg/kg- 150 mg (N=202)	Pooled secukinumab	placebo
PASI75	64.8% P<.0001	61.1% P<.0001	--	8.3%
PASI90	49.1% P<.0001	45.4% P<.0001	--	3.7%
DAS28-CRP	-1.67 P<.0001	-1.62 P<.0001	--	-.77
SF-36 PCS	5.41 P<.0001	5.91 P<.0001	--	1.82
HAQ-DI	-0.41 P<.0001	-0.4 P<.0001	--	-0.17
ACR50	30.7% P<.0001	34.7% P<.0001	--	7.4%
Van der Heijde modified total Sharp score	.02 P=.0132	.13 P=.0212	.08 P=.0113	.57
Presence of dactylitis	43.3% P<.0001	51.9% P<.0001	47.6% P<.0001	84.5%
Presence of enthesitis	51.2% P<.0001	54% P<.0001	52.5% P<.0001	87.2%

Source: adapted from F2306 clinical study report, p. 150

In study F2306 both treatment arms were superior to placebo for all measured secondary endpoints.

Reviewer's comments: While the 75 mg and 150 mg treatment arms were both superior to placebo at Week 24 for all secondary endpoints, of concern was that the treatment arms received 10 mg/kg IV doses of secukinumab at week, 0, 2, and 4 which may have affected the secondary endpoints at Week 24. A significant consideration during the review was whether efficacy would be maintained since the exposure from the maintenance doses would be lower than the initial loading doses. Additional analyses were performed on the placebo patients who did not receive loading doses, as discussed in section 6.1.9 to evaluate this concern.

Patients with baseline psoriasis BSA>3% had significant improvement of PASI 75 and 90 scores in study F2306.

6.1.5.2 F2312 Analysis of Secondary Endpoints

Table 23 shows the analysis of secondary endpoints at week 24 as performed in the statistical hierarchy. The 75 mg arm did not achieve a statistically superior response to placebo on any of the secondary endpoints. The 300 mg arm was statistically superior to placebo for all secondary endpoints evaluated in the statistical hierarchy and the 150 mg dose was statistically superior to placebo for most secondary endpoints with the exception of HAQ-DI and ACR50.

Table 23. F2312: Secondary efficacy endpoints at week 24

Secondary endpoint	Secukinumab 75 mg (N=99)	Secukinumab 150 mg (N=100)	Secukinumab 300 mg (N=100)	Pooled secukinumab	placebo
PASI75	28% 0.165	48% 0.0017	63% <.0001	--	16%
PASI90	12% 0.6421	33% 0.0057	49% 0.0005	--	9%
DAS28-CRP	-1.12 0.6421	-1.58 0.0057	-1.61 0.0013	--	-0.96
SF-36 PCS	4.38 0.6421	6.39 0.0057	7.25 0.0013	--	1.95
HAQ-DI	-0.32 0.9195	-0.48 0.0555	-0.56 0.004	--	-0.31
ACR50	18% 0.9195	35% 0.0555	35% 0.004	--	7%
Presence of dactylitis	--	--	--	53.2% 0.9195	85.2%
Presence of enthesitis	--	--	--	59.6% 0.9195	78.5%

Source: adapted from F2312 clinical study report, p. 133

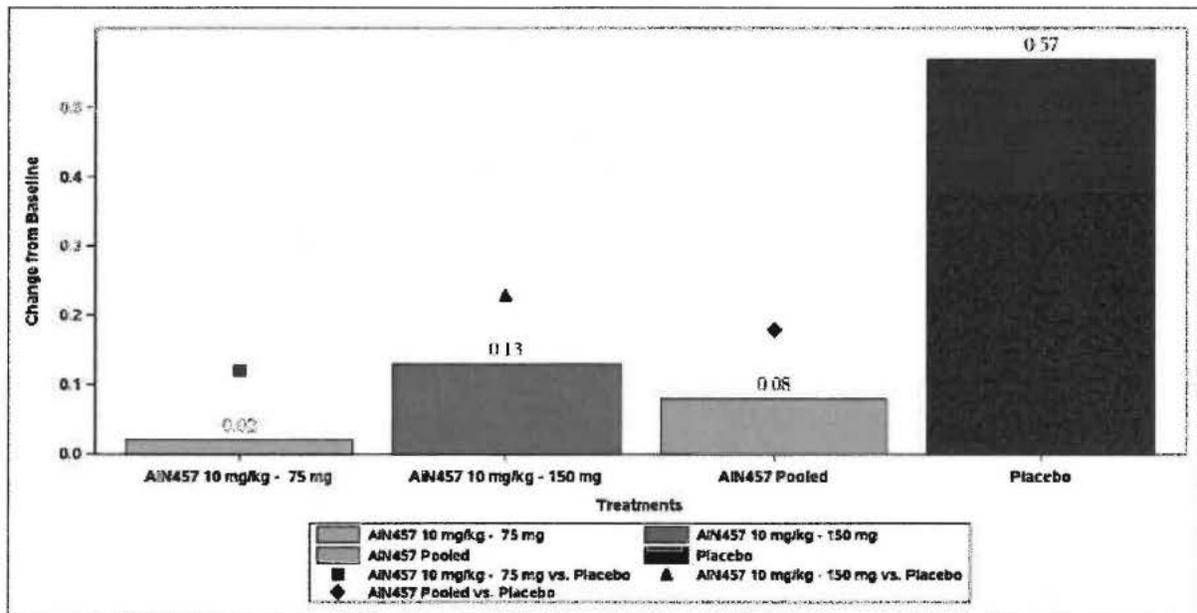
Reviewer's comment: The 300 mg dose arm met all secondary endpoints and the 150 mg dose arm met most secondary endpoints. As with analysis of the primary endpoint, the loading doses used were concerning as to whether they had an effect on the 24 week secondary efficacy endpoints. A significant consideration during the review was whether efficacy would be maintained since the exposure from the maintenance doses would be lower than the initial loading doses. Additional analyses were performed on the placebo patients who did not receive loading doses, as discussed in section 6.1.9 to evaluate this concern.

Patients with baseline psoriasis BSA>3% had significant improvement of PASI 75 and 90 scores in the 150 mg and 300 mg secukinumab dose arms. The percent of patients achieving PASI 75 and 90 scores in the 300 mg group was numerically higher than the 150 mg secukinumab group.

6.1.6 Other Endpoints

Figure 7 shows changes in the PsA modified van der Heijde-Sharp (PsA-modified vdH-S) score from baseline to Week 24. With a loading dose, the pooled AIN457 doses trended towards a decreased PsA-modified vdH-S score; however, the AIN457 study arms used large IV loading doses which may have had an effect on the 24 week endpoint.

Figure 7. Change in PsA-modified vdH-S score from baseline to week 24



- Statistically significant at 0.05 level.

Source: F2306 clinical study report, p. 1583

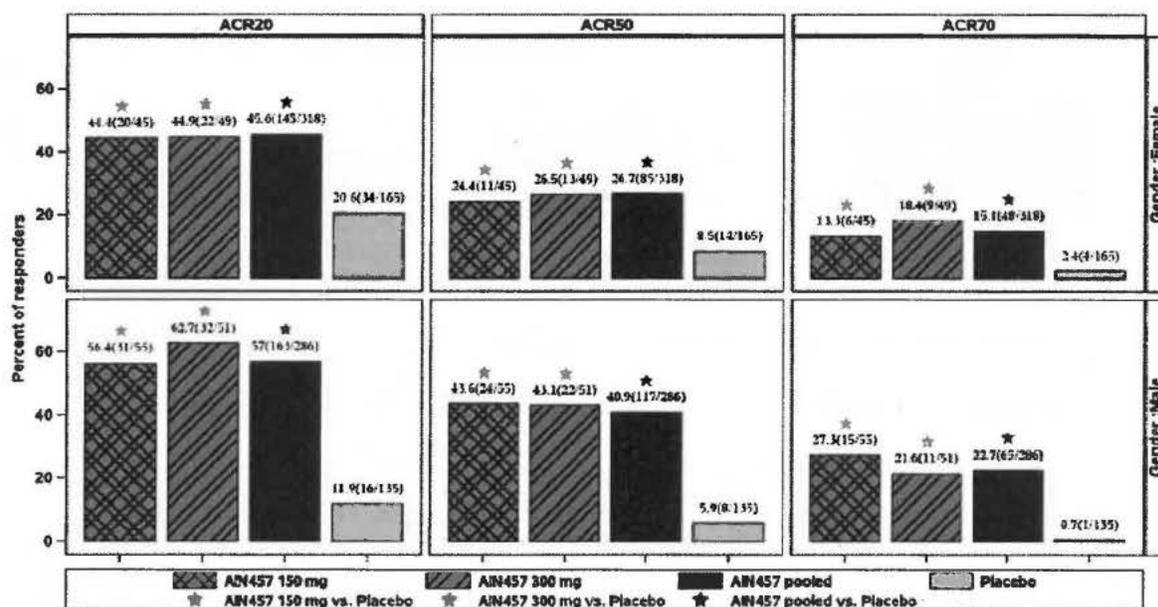
Reviewer's comments: The data provided were not sufficient to establish that the proposed dose for PsA could inhibit structural progression of radiographic disease. The studies utilized an IV loading dose regimen, with markedly higher exposures than the proposed SC loading regimen. This IV loading dose regimen is not proposed for approval. There is no way to determine whether the recommended dosing by the Applicant would have effects on radiographic inhibition as data using the recommended dosing regimen was not provided. Therefore, an additional study assessing radiographic progression using the recommended dose for PsA would need to be conducted in order to determine whether secukinumab is able to change radiographic progression in PsA. In addition to these concerns, the effect of secukinumab on radiographic progression in PsA was only evaluated in one study and there are no supportive data from a similar disease, such as RA.

6.1.7 Subpopulations

Gender

Figure 8 shows the percent of patients who had ACR20, 50, and 70 responses using non-responder imputation by gender. Both genders had significant improvement in ACR20, 50, and 70 responses when compared to placebo for 150 mg and 300 mg dose groups. Treatment differences in favor of pooled secukinumab were higher for males compared to females for ACR20, ACR50, and ACR70 at week 24.

Figure 8. Pooled phase 3 PsA studies: ACR20, ACR50, and ACR70 response at week 24 by gender



*P-value < 0.05

Source: Applicant's PsA summary of clinical efficacy, p. 108

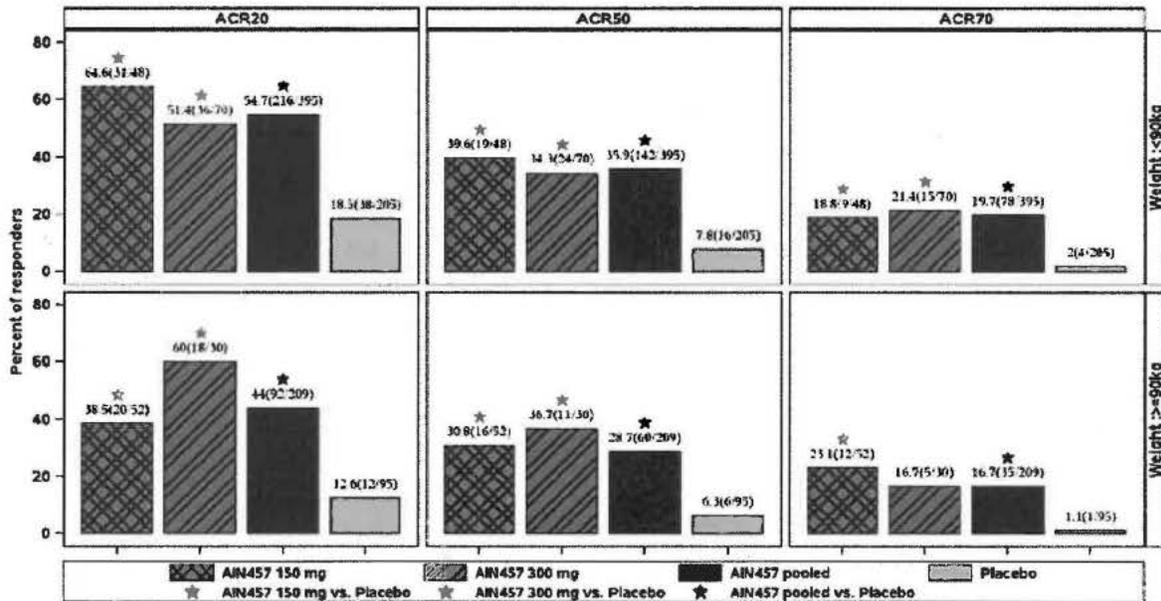
Race

The study population was predominantly White with Asians serving as the only other group with any significant enrollment. There were no efficacy differences noted between Whites and Asians in the pooled studies.

Body Weight

Figure 9 shows the percent of patients who had ACR20, 50, and 70 responses using non-responder imputation by weight. Treatment differences for patients <90 kg and patients ≥90 kg appeared similar in the pooled secukinumab groups for ACR20, 50, and 70 response

Figure 9. Pooled phase 3 PsA studies: ACR20, ACR50, and ACR70 response at week 24 by weight



*P-value < 0.05

Source: Applicant's PsA summary of clinical efficacy, p. 110

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(b) (4)
 (b) (4)
 TNF α inadequate responders were defined as patients who did not have an adequate response to TNF inhibitors for at least 3 months or received at least one dose of TNF inhibitor and were either intolerant to medication or needed to discontinue for safety reasons. Patients who had received more than 3 TNF inhibitors were excluded from the study. The Sponsor submitted efficacy data with the 300 mg SC dose in study F2312. Study F2306 did not use a 300 mg dose arm.

Table 24 shows the ACR20 response based on previous TNF inhibitor usage. The 300 mg arm had an ACR20 response that was numerically greater than the 150 mg and 75 mg dose groups while in the TNF naïve arm, the 150 mg arm had a numerically greater ACR20 response when compared to the 300 mg arm. The 300 mg arm of TNF α inadequate responders had an ACR20 response that was statistically superior to placebo.

Table 24. F2312: ACR20 response by TNF inhibitor usage at week 24

%	AIN457 75 mg	AIN457 150 mg	AIN457 300 mg	Placebo
TNF α inadequate responders	14.7	29.7	45.5	14.3
TNF α naïve	36.9	63.5	58.2	15.9

Source: reviewer generated

Reviewer's comments: The 300 mg dose was evaluated in only one study (b) (4)

The population of TNF α inadequate responders has not been previously established as a distinct group and the definition that the Applicant has provided only requires the failure of one TNF α inhibitor which may not be appropriate. Further, this definition is based on patient history and does not appear to rigorously select a distinct group of individuals. (b) (4)

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

6.1.9.1 F2306 Discussion of Persistence of Efficacy and/or Tolerance Effects

Table 25 shows the percent of patients who had ACR20 response at week 52 by treatment group. In addition to showing the response of the treatment arms who received secukinumab with a loading dose at baseline, the table shows the response for the placebo arms after they receive secukinumab without a loading dose. The placebo patients who received secukinumab 75 mg SC every 4 weeks had ACR20 responses of 65 to 77% and those who received secukinumab 150 mg SC every 4 weeks had ACR20 responses of 44 to 61%.

Table 25. F2306: ACR20 response at Week 52

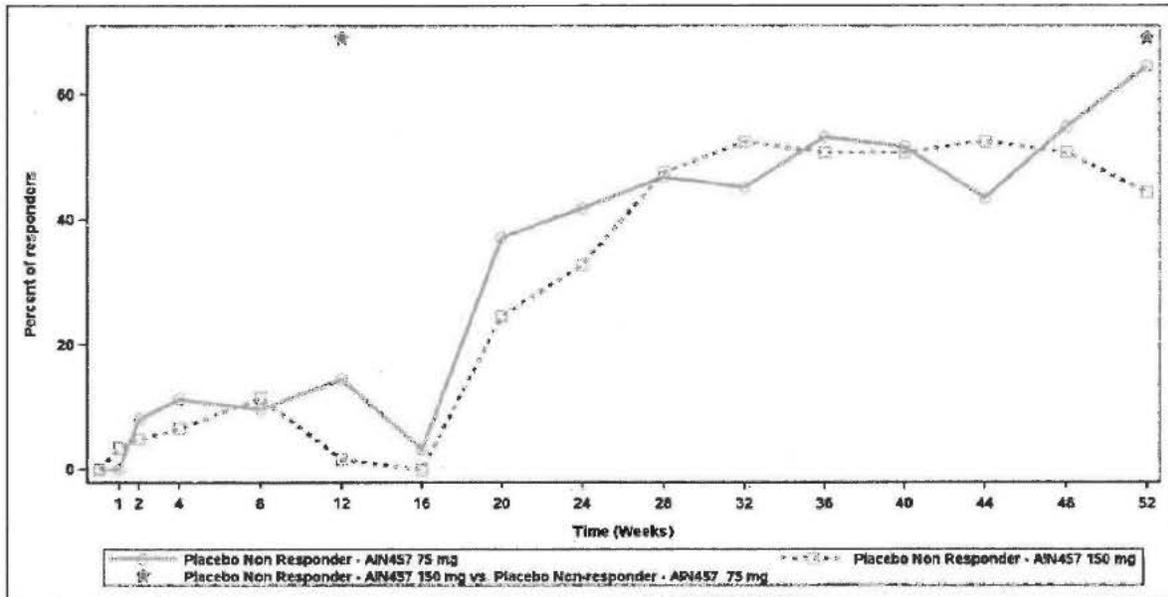
Treatment group	n/N (%)
AIN457 10 mg/kg-75 mg	115/202 (56.9)
AIN457 10 mg/kg-150 mg	121/202 (59.9)
Placebo non-responder AIN457 75 mg	40/62 (64.5)
Placebo non-responder AIN457 150 mg	27/61 (44.3)
Placebo responder AIN457 75 mg	24/31 (77.4)
Placebo responder AIN457 150 mg	20/33 (60.6)

Source: adapted from clinical study report, p. 449

Figure 10 shows the percent of non-responders in the placebo group patients with ACR20 responses. The patients who were non-responders in the placebo group received either 75 mg or 150 mg of SC secukinumab every 4 weeks at week 16 without a loading dose. 4 weeks after receiving active treatment, secukinumab 75 mg or 150

mg appeared to quickly increase the percent of ACR20 responders and maintain the effect for an additional 36 weeks.

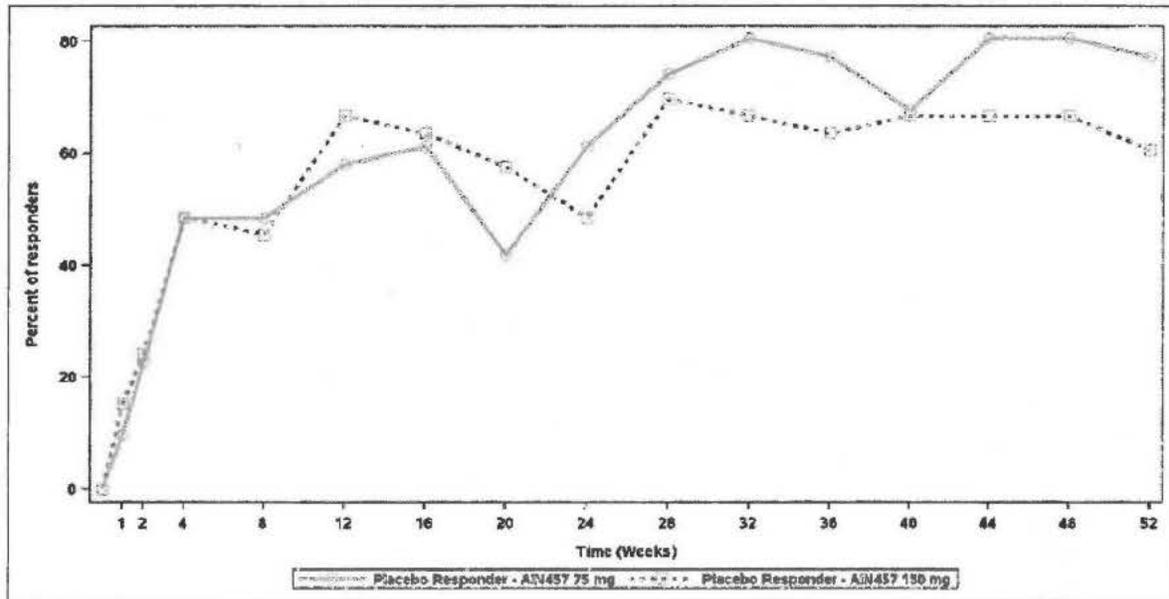
Figure 10. F2306: ACR20 response for placebo non-responder group



Source: F2306 clinical study report, p. 1581

Figure 11 shows ACR20 response in patients who were placebo responders and were placed on 75 or 150 mg of SC secukinumab at week 20 without a loading dose. The placebo responders appeared to have maintenance of ACR20 response to week 52.

Figure 11. F2306: ACR20 response for placebo responder group



Source: F2306 clinical study report, p. 1582

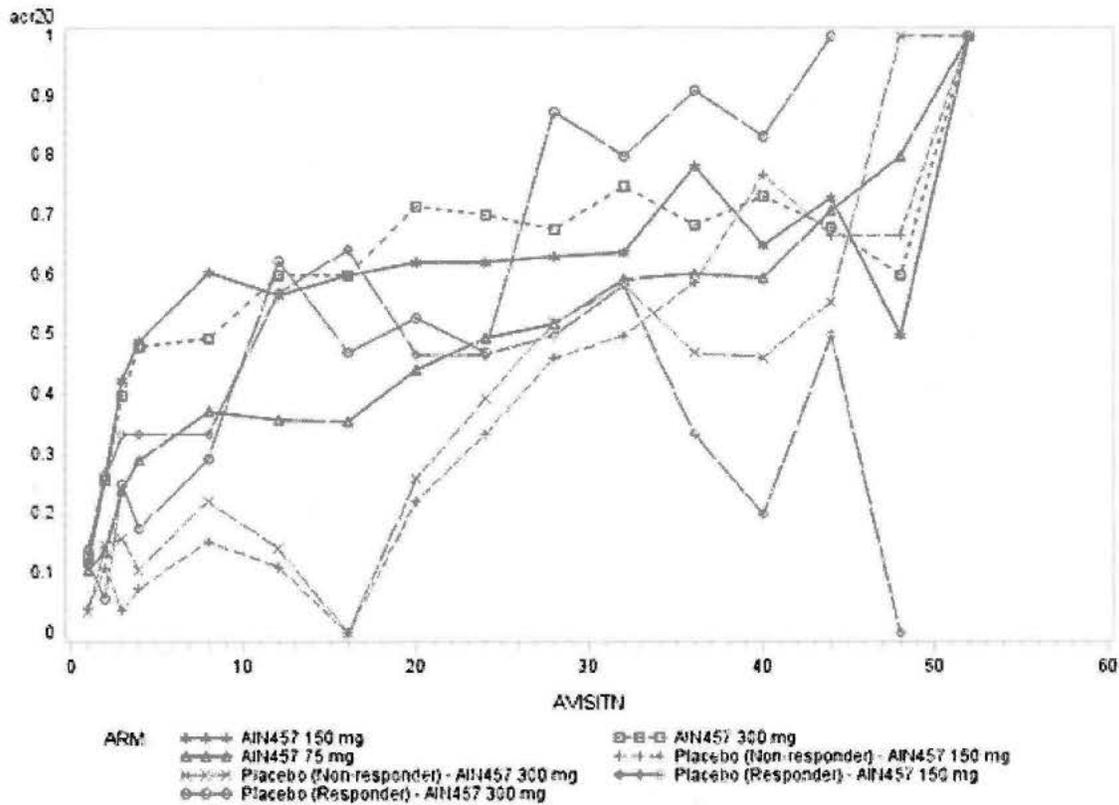
Reviewer's comments: Collectively, the data provided by patients who went on to receiving secukinumab after starting in the placebo group showed that patients without load were able to achieve ACR20 responses. Particularly in the non-responder groups, the percent of patients achieving ACR20 responses rose sharply 4 weeks after starting secukinumab therapy. These data provide support for the hypothesis that the efficacy of secukinumab will be maintained, even in the absence of the exposures associated with the loading dose. They also raise the possibility that a loading dose is not needed for the indication of PsA. In the placebo group, it appeared that patients could maintain efficacy after switching to secukinumab for up to 36 weeks. Therefore, it is reasonable that secukinumab can maintain efficacy without a loading dose.

6.1.9.2 F2312 Discussion of Persistence of Efficacy and/or Tolerance of Effects

Figure 12 shows ACR20 responses over 52 weeks using non-responder imputation for missing data. The data provided was from the 24 week interim analysis so missing data was an issue beyond week 36 as data from for a portion of patients who had not completed the later visits in study F2312 was not available at the time of the 24 week interim analysis. Most groups improved over time including the non-responders who received placebo initially and then received secukinumab without a loading dose. Of interest, the non-responder groups were able to achieve mean ACR20 responses over 50% despite not receiving an initial load when switched to secukinumab therapy from placebo. Patients appeared to have response within 4 weeks without the loading dose.

Figure 12. F2312: ACR20 response over 52 weeks

PsA Study F2312 Observed ACR20 over 52 Weeks by Randomized Group



Source: generated by FDA statistics reviewer

Reviewer's comment: Limited conclusions can be drawn from the F2312 data which has no true control group after assessment of primary endpoint and has limited numbers especially with the later study visits in F2312. It appeared that patients who received secukinumab in the placebo groups could achieve ACR20 responses without the use of a loading dose. It is unclear whether a loading dose is necessary to achieve ACR20 response in PsA patients. Based on the data from the placebo patients who start on secukinumab, it does appear that secukinumab can maintain efficacy without a loading dose. Therefore, it appears that secukinumab can be administered every 4 weeks chronically without repeating the loading dose.

The ability to make conclusions based on placebo data from studies F2306 and F2312 is limited as the placebo patients are only a subset of the overall study population with limited numbers. Further, there is no control group to compare the effects seen in the placebo patients who were switched to active secukinumab dosing. However, as efficacy was seen in both F2306 and F2312 for the placebo patients switched to SC

secukinumab without a loading dose, it is reassuring that SC secukinumab without a loading dose can be effective in treating PsA.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues/analyses in this review.

7 Review of Safety

Safety Summary

The safety information for secukinumab in PsA is obtained from two phase 3 studies during which 974 patients received at least one dose of secukinumab. The Applicant submitted 16 weeks of double-blind, placebo-controlled data and up to 52 weeks of safety data. The median duration of treatment was 112 days with a range of 8 to 226 days.

One death was reported in study F2306 on Day 248. A 75 year old white female died on Day 248 of the study due to intracranial hemorrhage.

Serious adverse events (SAEs) were low and comparable across groups and placebo. The 300 mg dose appeared to have a slightly higher rate of serious infections compared to the 150 mg or placebo.

The proportion of patients with adverse events (AEs) leading to discontinuation was balanced across placebo and treatment groups. The most common AEs occurring in the secukinumab treatment groups were nasopharyngitis (7%), upper respiratory tract infection (6.3%), headache (5%), nausea (2.8%), diarrhea (2.4%), and hypercholesterolemia (2.4%). Besides diarrhea, the secukinumab treatment groups had a higher percentage of these common adverse events when compared to placebo.

Due to specific safety concern with secukinumab, analyses were conducted related to AEs of special interest including infections, malignancies, MACE events, hypersensitivity reactions, inflammatory bowel disease, and hematologic cytopenias.

Overall, no new safety signals were identified in trials F2306 and F2312 and secukinumab had similar safety profile in PsA compared to the safety profile reflected in the product label. While no new safety signals were identified, additional cases of new inflammatory bowel disease and worsening of disease were seen in the PsA and AS trials collectively. Therefore, the prescribing information will be updated to caution prescribers on the use of secukinumab in patients at risk for inflammatory bowel disease.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.2 (Review Strategy) for an overview of the two phase 3 studies used to evaluate the safety of secukinumab in PsA.

7.1.2 Categorization of Adverse Events

The Sponsor's categorization of adverse events with preferred terms is consistent with the investigator's verbatim terms including the most common adverse events leading to discontinuation.

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

In this sBLA review, pooling is performed for studies F2306 and F2312. In addition to the pooling of the two phase 3 PsA trials, the Applicant has provided pooled data for the psoriasis and PsA trials and pooled data for all indications. Table 26 shows how patients were pooled to assess safety for the PsA indication and the number of patients included in each pool.

Table 26. Studies included for pooling to assess clinical safety in PsA

Pool	N	Studies
A (PsA trials)	974 (any AIN457) 300 (placebo)	F2306, F2312
B (PsA trials and psoriasis trials)	3928 (any AIN457) 994 (placebo)	F2306, F2312, A2302, A2303, A2304, A2308, A2309
B1 (PsA trials and PsA patients in psoriasis trials)	1472 (any AIN457) 416 (placebo)	F2306, F2312, A2303, A2303, A2304
C (all secukinumab trials)	6200 (any AIN457) 1665 (placebo)	A2101, A2102, A2103, A2202, A2202E1, A2204, A2206, A2206E1, A2208, A2209, A2209E1, A2211, A2211E1, A2212, A2220, A2223, A2225, A2302, A2302E1, A2303, A2304, A2304E1, A2307, A2308, CA2309, B2201, B2203, C2301, C2301E1, C2302, C2302E1, C2303, C2303E1, CPJMR001 2201, CPJMR009 2202, F2201, F2206, F2208, F2305, F2306, F2310, F2312

Source: reviewer generated

7.2 Adequacy of Safety Assessments

In the safety assessment from the secukinumab PsA trials, 974 patients received at least one dose of secukinumab. Safety data for secukinumab treated patients who escaped from placebo were not included in the placebo group after escape, but rather were presented according to the dose of secukinumab to which they escaped. Thus, patients may have been counted more than once. The Applicant defined the “any secukinumab” group as patients who were randomized to any dose of secukinumab plus any patients who escaped from placebo to secukinumab. This is a reasonable manner in which to analyzed safety data.

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

See Section 6.1.2 (Demographics) for the baseline characters in studies F2306 and F2312. The demographic tables include all randomized patients. There were adequate numbers for analysis for the gender and weight subgroups.

7.2.2 Explorations for Dose Response

The Applicant conducted analyses to determine any safety difference based on whether patients received the 10 mg/kg IV at weeks 0, 2, and 4 loading dose versus weekly SC dosing (75 mg, 150 mg, or 300 mg) for 5 weeks. In addition, the Applicant searched for differences in AEs based on the dose of secukinumab patients received every 4 weeks (75, 150, or 300 mg) following the loading dose.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was included in this submission.

7.2.4 Routine Clinical Testing

Table 27 shows routine clinical testing that was performed during the first 52 weeks of study F2306 to assess safety. The types and frequencies of safety tests were adequate to assess the safety of secukinumab in PsA. These safety tests were adequate to evaluate the known secukinumab associated AEs.

Table 27. F2306: Clinical testing to elicit AEs, vital signs, and laboratory and parameters

Evaluation	Frequency to week 52
AE review	Update as necessary throughout study
Physical Examination/vital signs	All visits
Tuberculosis testing	Screening
Laboratory analyses (hematology, chemistry, urinalysis)	Screening, Week 0, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 40, 52
Cardiovascular panel	Weeks 0, 16, 24, 52
Chest X-ray	Screening
ECG	Week 0, 12, 52
Serum pregnancy test	Screening
Urine pregnancy test	Weeks 0, 4, 12, 16, 24, 32, 40, and 52

Source: adapted from F2306 clinical study report, p. 81-84

Table 28 shows routine clinical testing that was performed during the first 52 weeks of study F2312 to assess safety. The types and frequencies of safety tests were adequate to assess the safety of secukinumab in PsA. These safety tests were adequate to evaluate the known secukinumab associated AEs.

Table 28. F2312: Clinical testing to elicit AEs, vital signs, and laboratory and parameters

Evaluation	Frequency to week 52
AE review	Update as necessary throughout study
Physical Examination/vital signs	All visits
Tuberculosis testing	Screening
Laboratory analyses (hematology, chemistry, urinalysis)	Screening, Week 0, 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 40, 52
Cardiovascular panel	Weeks 0, 16, 24, 52
Chest X-ray	Screening
ECG	Week 0, 12, 52
Serum pregnancy test	Screening
Urine pregnancy test	Weeks 0, 4, 12, 16, 24, 32, 40, and 52

Source: adapted from F2312 clinical study report, p. 70-73

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific drug-drug interaction, clearance, or interaction studies were performed for secukinumab in studies F2306 and F2312.

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

Studies F2306 and F2312 incorporated monitoring for toxicities associated with secukinumab such as infections, injection site reactions, hypersensitivity, inflammatory bowel disease, malignancies, and MACE events. Details of these analyses are found in Section 7.3.5 (Submission Specific Primary Safety Concerns).

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in study F2312.

There was one death secondary to intracranial hemorrhage in study F2306. The event occurred in a 57 year old white female on Day 243 of the study. The patient was hospitalized for nausea, vomiting, and worsening of urinary tract infection. On admission, the patient was somnolent to stuporous and had left hemiplegia. She was diagnosed with esophagitis, urosepsis, hemiplegia and intracranial venous sinus thrombosis. The patient went into septic shock with consumption coagulopathy and multiorgan failure. The patient died on Day 248.

Reviewer's comments: There was not a clear causal relationship between the death related to intracranial hemorrhage and secukinumab treatment. The patient had numerous baseline cardiovascular risk factors, including hypertension, chronic renal insufficiency, intermittent atrial fibrillation, congestive heart failure, diabetes mellitus, prior stroke/thromboembolism, and vascular disease.

7.3.2 Nonfatal Serious Adverse Events

Table 29 shows the SAEs that occurred during the entire treatment period for the phase 3 PsA studies. The table shows the number of patients who had a SAE over the time exposed and reports incidence rates per 100 patient years. There were not many SAEs during the course of the study. Events appeared to be similar across dose groups and similar to placebo.

Table 29. Pooled phase 3 PsA studies: Exposure adjusted incidence of most frequent SAEs by preferred term over entire treatment period

Preferred term n/EX (IR)	Any AIN457 75 mg N=391	Any AIN457 150 mg N=438	Any AIN457 300 mg N=145	Any AIN457 N=974	Placebo N=300
Any SAE	34/407 (8.4)	41/420 (9.8)	7/87 (8.1)	82/913 (9)	14/103 (13.6)
Erysipelas	1/420 (0.2)	2/444 (0.5)	1/90 (1.1)	4/953 (0.4)	1/105 (0.9)
Non-cardiac chest pain	0/420 (0)	2/445 (0.4)	1/90 (1.1)	3/954 (0.3)	1/105 (0.9)
Osteoarthritis	1/420 (0.2)	2/443 (0.5)	0/90 (0)	3/953 (0.3)	1/106 (0.9)
Sepsis	3/420 (0.7)	0/445 (0)	0/90 (0)	3/955 (0.3)	1/106 (0.9)
Atrial fibrillation	2/419 (0.5)	0/445 (0)	0/90 (0)	2/954(0.2)	0/106 (0)
Cerebrovascular accident	2/419 (0.5)	0/445 (0)	0/90 (0)	2/954 (0.2)	0/106 (0)
Coronary artery disease	0/420 (0)	2/444 (0.5)	0/90 (0)	2/954 (0.2)	1/105 (0.9)
Deep vein thrombosis	0/420 (0)	2/444 (0.5)	0/90 (0)	2/954 (0.2)	0/106 (0)
Diverticulitis	0/420 (0)	2/444 (0.5)	0/90 (0)	2/954 (0.2)	0/106 (0)
Myocardial infarction	2/420 (0.5)	0/445 (0)	0/90 (0)	2/955 (0.2)	0/106 (0)
Pneumonia	2/420 (0.5)	0/445 (0)	0/90 (0)	2/955 (0.2)	0/106 (0)
Psoriatic arthropathy	0/420 (0)	2/444 (0.5)	0/90 (0)	2/954 (0.2)	0/106 (0)
Septic shock	2/420 (0.5)	0/445 (0)	0/90 (0)	2/955 (0.2)	1/106 (0.9)
Vertigo	2/418 (0.5)	0/445 (0)	0/90 (0)	2/953 (0.2)	0/106 (0)
Calculus urinary	0/420 (0)	0/445 (0)	1/90 (1.1)	1/955 (0.1)	0/106 (0)
Cervical radiculopathy	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)
Crohn's disease	1/420 (0.2)	0/445 (0)	0/90 (0)	1/955 (0.1)	1/106 (0.9)
Dehydration	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)
Intervertebral disc protrusion	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)
Limb traumatic amputation	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)
Migraine	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)
Nephrolithiasis	0/420 (0)	1/445 (0.2)	0/90 (0)	1/955 (0.1)	1/105 (0.9)
Osteomyelitis	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)
Sinusitis	0/420 (0)	0/445 (0)	1/90 (1.1)	1/955 (0.1)	1/105 (0.9)
Subcutaneous abscess	0/420 (0)	0/445 (0)	1/89 (1.1)	1/954 (0.1)	0/106 (0)

Source: adapted from Applicant PsA summary of clinical safety, p. 90-91

The types of serious adverse events were consistent with those seen during the psoriasis clinical program and no new safety signals were detected.

7.3.3 Dropouts and/or Discontinuations

Table 30 shows the AEs that led to discontinuation in the pooled phase 3 PsA studies over the entire treatment period. No more than one AE per preferred term led to a discontinuation. Of the discontinuations of clinical interest, one patient who switched from placebo to 75 mg of secukinumab developed CTCAE grade 2 leukopenia. In the 75 mg group, one patient discontinued due to Crohn's disease and another discontinued due to colitis (see inflammatory bowel disease in section 7.3.5). Two infections (urosepsis and pneumonia) led to discontinuation. One patient taking 75 mg of secukinumab developed angioedema and one in the 150 mg group developed hypersensitivity. One patient receiving 150 mg of secukinumab developed drug induced liver injury.

Table 30. Pooled phase 3 secukinumab studies: AEs leading to dropouts and discontinuations over the entire treatment period

Preferred term n (%)	Any AIN457 75 mg N=391 n (%)	Any AIN457 150 mg N=438 n (%)	Any AIN457 300 mg N=145 n (%)	Any AIN457 N=974 n (%)	Placebo N=300 n (%)
Any preferred term	16 (4.1)	11 (2.5)	2 (1.4)	29 (3)	10 (3.3)
Psoriatic arthropathy	1 (0.3)	1 (0.2)	0	2 (0.2)	0
Abdominal pain	0	1 (0.2)	0	1 (0.1)	0
Angioedema	1 (0.3)	0	0	1 (0.1)	0
Appendiceal abscess	1 (0.3)	0	0	1 (0.1)	0
Calculus urinary	0	0	1 (0.7)	1 (0.1)	0
Cerebrovascular accident	1 (0.3)	0	0	1 (0.1)	0
Cholelithiasis	1 (0.3)	0	0	1 (0.1)	0
Colitis	1 (0.3)	0	0	1 (0.1)	0
Crohn's disease	1 (0.3)	0	0	1 (0.1)	1 (0.3)
Drug-induced liver injury	0	1 (0.2)	0	1 (0.1)	0
Fatigue	0	1 (0.2)	0	1 (0.1)	0
Headache	0	1 (0.2)	0	1 (0.1)	0
Hyperlipidemia	1 (0.3)	0	0	1 (0.1)	0

Hypersensitivity	0	1 (0.2)	0	1 (0.1)	1 (0.3)
Hypotension	0	1 (0.2)	0	1 (0.1)	0
Leukopenia	1 (0.3)	0	0	1 (0.1)	0
Local swelling	0	1 (0.2)	0	1 (0.1)	0
Malaise	0	1 (0.2)	0	1 (0.1)	0
Multiple injuries	1 (0.3)	0	0	1 (0.1)	0
Musculoskeletal chest pain	1 (0.3)	0	0	1 (0.1)	0
Pneumonia	1 (0.3)	0	0	1 (0.1)	0
Prostate cancer	0	1 (0.2)	0	1 (0.1)	0
Generalized rash	0	0	1 (0.7)	1 (0.1)	0
Rosacea	0	1 (0.2)	0	1 (0.1)	0
Squamous cell carcinoma	1 (0.3)	0	0	1 (0.1)	0
Systemic lupus erythematosus	1 (0.3)	0	0	1 (0.1)	0
Urosepsis	1 (0.3)	0	0	1 (0.1)	0
Viral infection	0	1 (0.2)	0	1 (0.1)	0
Visual acuity reduced transiently	0	1 (0.2)	0	1 (0.1)	0

Source: Applicant PsA summary of clinical safety, p. 101-102

During the first 16 weeks, the overall rate of AEs causing discontinuation was low and comparable among treatment groups. All AEs leading to discontinuation were single occurrence in any treatment group. In the secukinumab treatment group, the adverse events leading to discontinuation included abdominal pain, angioedema, urinary calculus, cerebrovascular accident, cholelithiasis, hyperlipidemia, hypersensitivity, non-cardiac chest pain, generalized rash, squamous cell carcinoma, systemic lupus erythematosus, and viral infection. Of note, the current secukinumab prescribing information contains a warning regarding the risk of exacerbation of Crohn's disease, infections, and hypersensitivity reactions. No new safety signals were detected in the current database.

7.3.4 Significant Adverse Events

See section 7.3.5 for AEs of interest. AEs leading to discontinuation are discussed in section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

Submission specific primary safety concerns include immune/administration reactions, hypersensitivity events, inflammatory bowel disease, infections, neutropenia, MACE events, malignancies and suicide.

Immune/administration reactions

Table 31 shows the exposure adjusted incidence rate of immune/administration reactions based on the Applicant's MedDRA query. The incidence rate is per 100 patient years. Reactions were more common in the 300 mg group versus the 75 mg and 150 mg dose groups. The most common preferred terms that were associated with immune/administration reactions were cough, pruritis, rash, conjunctivitis, and mouth ulceration.

Table 31. Immune/administration reactions over the entire treatment period

	AIN457 75 mg N=391 n/EX (IR)	AIN457 150 mg N=438 n/EX (IR)	AIN457 300 mg N=145 n/EX (IR)	AIN457 Any dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Immune/administration reactions	98/355 (27.6)	117/355 (33)	30/76 (39.3)	245/786 (31.2)	43/95 (45.1)

Source: adapted from Applicant PsA summary of clinical safety, p. 108

Notably, the incidence of immune/administration reactions was higher in the placebo group than the any secukinumab group. No new safety signals related to immune/administration reactions were noted.

Hypersensitivity

Table 32 shows the number of hypersensitivity events that occurred during the two phase 3 PsA trials. Events of hypersensitivity were based on narrow standard MedDRA query. Incidence rates reported are per 100 patient years. Exposure adjusted incidence rates for the 300 mg group were higher than the 75 mg and 150 mg doses.

Table 32. Hypersensitivity events over the entire treatment period

	AIN457 75 mg N=391 n/EX (IR)	AIN457 150 mg N=438 n/EX (IR)	AIN457 300 mg N=145 n/EX (IR)	AIN457 Any dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Hypersensitivity	31/401 (7.7)	40/416 (9.6)	12/86 (14)	83/903 (9.2)	22/101 (21.7)

Source: adapted from Applicant PsA summary of clinical safety, p. 112

The current secukinumab prescribing information includes a warning related to hypersensitivity. While there were cases of hypersensitivity reactions in the PsA

studies, they were more common in the placebo treatment group than the secukinumab treatment group.

Inflammatory Bowel Disease

Table 33 shows the exposure adjusted incidence rate of inflammatory bowel disease based on the Applicant's MedDRA query. The incidence rate is per 100 patient years. Two patients receiving secukinumab were diagnosed with Crohn's disease and one patient was diagnosed as having ulcerative colitis. In the placebo group one patient was diagnosed with Crohn's disease.

One patient who was in the secukinumab 75 mg group with IV load presented with two episodes of hemorrhagic diarrhea on Day 65 and Day 110 of the study and was later diagnosed with ulcerative colitis.

A patient who was in the secukinumab 300 mg group developed hemorrhagic diarrhea on Day 52. The patient was later diagnosed with diverticulitis.

One additional patient in the secukinumab 75 mg group with IV load presented with severe diarrhea on Day 138. The patient was eventually diagnosed with Crohn's disease.

Table 33. Inflammatory bowel disease over the entire treatment period

	AIN457 75 mg N=391 n/EX (IR)	AIN457 150 mg N=438 n/EX (IR)	AIN457 300 mg N=145 n/EX (IR)	AIN457 Any dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
AEs					
Inflammatory bowel disease	2/419 (0.5)	0/445 (0)	1/89 (1)	3/953 (0.3)	1/105 (1)
Hemorrhagic diarrhea	1/419 (0.2)	0/445 (0)	1/89 (1)	2/953 (0.2)	0/106 (0)
Crohn's disease	1/420 (0.2)	0/445 (0)	0/90 (0)	1/955 (0.1)	1/105 (1)
SAEs					
Inflammatory bowel disease	1/420 (0.2)	0/445 (0)	0/90 (0)	1/955 (0.1)	1/105 (1)
Crohn's disease	1/420 (0.2)	0/445 (0)	0/90 (0)	1/955 (0.1)	1/105 (1)

Source: adapted from Applicant PsA summary of clinical safety, p. 117

Reviewer's comment: Two new cases of inflammatory bowel disease (one ulcerative colitis, one Crohn's disease) were seen in the secukinumab group. The signal was similar to what was seen in the psoriasis studies. As the new cases of inflammatory bowel disease appear to be consistent across indications, the prescribing section for Warnings and Precautions will be updated to include warnings for new cases and potential flares of inflammatory bowel disease.

Infections

Table 34 shows the exposure adjusted incidence rates of infections per 100 person years over the entire treatment period. The exposure time is censored for the first event. Most reported infections were upper respiratory tract infections. The 300 mg

dose appeared to have a slightly higher rate of infections and serious infections when compared to the other dose groups.

Table 34. Infections and opportunistic infections over the entire treatment period

	AIN457 75 mg N=391 n/EX (IR)	AIN457 150 mg N=438 n/EX (IR)	AIN457 300 mg N=145 n/EX (IR)	AIN457 Any dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
AEs					
Infections and infestations	200/274 (73)	234/262 (89)	60/63 (95)	494/600 (82)	83/87 (95)
Upper respiratory tract	136/322 (42)	149/336 (44)	42/76 (56)	327/734 (45)	48/96 (50)
Candida infections	5/417 (1)	7/440 (2)	3/89 (3)	15/946 (2)	0/105 (0)
SAEs					
Infections and infestations	9/418 (2)	12/437 (3)	4/88 (5)	25/943 (3)	3/105 (3)
Upper respiratory tract	0/420 (0)	1/443 (0.2)	1/90 (1)	2 /953 (0)	1/105 (1)
Candida	0/420 (0)	1/445 (0.2)	0/90 (0)	1/955 (0)	0/106 (0)

Source: adapted from Applicant PsA summary of clinical safety, p. 124

During the 16 week placebo controlled period, there was a small increase in the overall incidence of infections in PsA patients treated with secukinumab (29%) compared to placebo (26%), but no imbalance between the 300 and 150 mg SC doses (30% and 29%, respectively). The majority of infections consisted of upper respiratory tract infections (high level terms), such as nasopharyngitis (preferred term) and upper respiratory tractions (preferred term). The findings were similar in the studies in psoriasis.

During the 16 week placebo controlled period, there was a slightly higher proportion of patients with serious adverse events related to infections in the secukinumab treatment groups (1.3%) than the placebo group (0.3%).

Also consistent with the psoriasis program, there was a small increase in the risk of localized candidiasis infections. A dose effect was only apparent in Pool A. During the entire treatment period, a total of 15 cases of candida infection were reported for secukinumab patients, with 5 cases in the first 16 weeks and 10 more cases thereafter. There were no cases of Candida infection in the placebo group. The majority of cases were oral candidiasis. Esophageal candidiasis was reported in 2 patients with PsA. The current prescribing information indicates the risk of candidiasis with secukinumab exposure. This information is contained within the Warnings and Precautions and the Adverse Reactions sections.

Herpes viral infections occurred in a higher proportion of patients treated with secukinumab than placebo. There was one case of herpes zoster cutaneous disseminated in the secukinumab treatment group. The current prescribing information contains data regarding the risk of herpes.

There were no serious opportunistic infections and no cases of reactivation of either tuberculosis or Hepatitis B.

Neutropenia

Table 35 shows the events of neutropenia that were reported based on narrow MedDRA query over the entire treatment period for the pooled PsA studies. Neutropenia was observed in 16 patients who received secukinumab and 7 patients who received placebo over the entire treatment period. The incidence rate of neutropenia was higher in the placebo group (6.7) than the secukinumab group (1.7). There were no SAEs due to neutropenia.

Table 35. Pooled phase 3 studies: Neutropenia events over the entire treatment period

	AIN457 75 mg N=391 n/EX (IR)	AIN457 150 mg N=438 n/EX (IR)	AIN457 300 mg N=145 n/EX (IR)	AIN457 Any dose N=974 n/EX (IR)	Placebo N=300 n/EX (IR)
Neutropenia	9/412 (2.2)	5/440 (1.1)	2/89 (2.3)	16/941 (1.7)	7/104 (6.7)

Source: adapted from Applicant PsA summary of clinical safety, p. 135

In the psoriasis submission, the incidence of neutropenia was higher for the secukinumab group than placebo. In the current submission for PsA, neutropenia reported as adverse events were transient, lasting only one visit and normalizing at the next subsequent visit. No new safety signals related to neutropenia were detected.

Major Cardiovascular Events (MACE)

Table 36 shows the number of major cardiovascular events (MACE) that occurred during the entire treatment period for the pooled phase 3 studies. 7 adjudicated events of MACE occurred in the secukinumab group and 0 in the placebo group. One of the MACE occurred in the first 16 weeks of the study. There was no dose relationship seen between MACE and secukinumab. Of note, after 24 weeks, all patients received secukinumab. Thus, there was much greater exposure to secukinumab than placebo.

In analyses in Pool C, based on adjudication-confirmed MACE cases, secukinumab was comparable to placebo in the exposure-adjusted incidence rates of 0.40 (CI 0.26 to 0.59) for Any secukinumab dose group and 0.39 (C 0.05 to 1.4) for placebo. In the psoriasis submission, the exposure-adjusted incidence of potential MACE was comparable between secukinumab and placebo on AEs (IR=0.42 for Any secukinumab dose vs. 0.59 for placebo).

Table 36. Pooled phase 3 studies: MACE events over the entire treatment period

N (%)	AIN457 75 mg N=391	AIN457 150 mg N=438	AIN457 300 mg N=145	AIN457 Any dose N=974	Placebo N=300
Myocardial infarction					

Clinical Review
Raj Nair
125504/1
Secukinumab (Cosentyx)

Yes	2 (0.5)	1 (0.2)	0	3 (0.3)	0
Indeterminate	0	0	0	0	0
Stroke					
Yes	4 (1)	0	0	4 (0.4)	0
Indeterminate	0	0	0	0	0
Cardiovascular death					
Yes	0	0	0	0	0
Indeterminate	1 (0.3)	0	0	1 (0.1)	0
Total MACE (Yes)	6 (1.5)	1 (0.2)	0	7 (0.7)	0

Source: adapted from Applicant PsA summary of clinical safety, p. 139

Reviewer's comments: The PsA population is at higher risk for cardiovascular events. While there was an imbalance in cardiovascular events with 7 events occurring in the secukinumab group and none in the placebo, this may reflect the greater exposure to secukinumab than placebo. The placebo controlled period is short and patients in the placebo arm may not have been followed long enough to have MACE occurrences. All of the observed cases in the study had concomitant risk factors for development of cardiovascular events. Similar observations were noted during the review of the original BLA for psoriasis and DDDP consulted DCRP. It was not felt that the imbalance reflected a convincing signal for CV safety concern. In addition, the similar exposure-adjusted incidence rates are reassuring.

Malignancy

Malignancies were rare in the pooled phase 3 studies. Of the malignancy SAEs, two were uncomplicated skin tumors reported in the 75 mg secukinumab group, one with SC loading dose and one with IV loading dose. One case of prostate cancer with bone metastasis occurred on Day 261 in a patient who received 150 mg of secukinumab with an IV loading dose.

Reviewer's comments: The type of malignancies observed in the PsA studies would be anticipated in the evaluated patient population.

Suicidal Ideation and Behavior

Suicidal ideation and behavior is an adverse event of interest given the possibility for an increased risk in patients with psoriasis and PsA. The Applicant reviewed 9 phase 3 trials in PsA, psoriasis, and AS for a suicide signal using C-CASA. 4499 patients who received secukinumab and 1190 patients who received placebo were evaluated with C-CASA. 442 (9.5%) patients were identified as having a SAE or relevant non-serious AE (333 in psoriasis/PsA, 67 in AS, and 48 in placebo). 2 out of 3928 psoriasis/PsA patients adjudicated to suicidality compared to 0 in the psoriasis/PsA placebo group. One case was suicidal ideation and the other was a suicidal attempt. In the AS studies, 0 of 571 patients adjudicated suicidality and 2 out of 196 patients adjudicated to suicidality, The events were one completed suicide and one suicidal ideation. In this sample of patients taken from the psoriasis, PsA, and AS, there did not appear to be a safety signal indicating an increased risk for suicide with exposure to secukinumab.

7.4 Supportive Safety Results

7.4.1 Common Adverse Event

Table 37 shows the common adverse events that occurred in the pooled phase 3 studies over the entire treatment period. The incidence rate is reported per 100 patients and is calculated by dividing number of adverse events over exposure time. The table shows adverse events by preferred term that had an incidence rate of at least 3 in the AIN457 any dose group. Small dose related increases were seen for infections, headache, diarrhea, pruritis, rash, increased ALT, gastroesophageal reflux disease, alopecia, palpitations and epistaxis.

Table 37. Common adverse events in pooled phase 3 PsA trials over the entire treatment period

	AIN457 75 mg N=391 n/Ex (IR)	AIN457 150 mg N=438 n/Ex (IR)	AIN457 300 mg N=145 n/Ex (IR)	AIN457 Any dose N=974 n/Ex (IR)	Placebo N=300 n/Ex (IR)
Upper respiratory tract infection	59/384 (15.4)	69/399 (17.3)	18/94 (21.4)	146/867 (16.8)	18/102 (17.6)
Nasopharyngitis	64/370 (17.3)	61/396 (15.4)	15/85 (17.6)	140/852 (16.4)	19/101 (18.7)
Headache	30/394 (7.6)	29/421 (6.9)	8/85 (9.4)	67/900 (7.4)	12/103 (11.7)
Back pain	28/401 (7)	18/431 (4.2)	3/89 (3.4)	49/921 (5.3)	5/104 (4.8)
Diarrhea	18/407 (4.4)	21/427 (4.9)	6/88 (6.8)	45/921 (4.9)	9/103 (8.7)
Bronchitis	11/412 (2.7)	22/430 (5.1)	5/88 (5.7)	38/930 (4.1)	8/104 (7.7)
Hypertension	21/405 (5.2)	13/436 (3)	4/88 (4.6)	38/929 (4.1)	8/104 (7.7)
Arthralgia	17/408 (4.2)	16/435 (3.7)	4/88 (4.5)	37/932 (4)	7/105 (6.7)
Psoriatic arthropathy	18/410 (4.4)	17/436 (3.9)	2/90 (2.2)	37/936 (4)	3/105 (2.9)
Nausea	18/407 (4.4)	12/436 (2.8)	5/87 (5.7)	35/930 (3.8)	6/104 (5.8)
Sinusitis	11/413 (2.7)	15/437 (3.4)	9/87 (10.3)	35/937 (3.7)	6/105 (5.7)
Urinary tract infection	10/414 (2.4)	21/427 (4.9)	3/89 (3.4)	34/930 (3.7)	6/104 (5.8)
Cough	10/412 (2.4)	20/429 (4.7)	3/88 (3.4)	33/930 (3.5)	8/104 (7.7)
Psoriasis	18/410 (4.4)	11/440 (2.5)	2/89 (2.3)	31/938 (3.3)	5/104 (4.8)
Gastroenteritis	9/414 (2.2)	17/433 (3.9)	3/89 (3.4)	29/935 (3.1)	3/105 (2.9)
Pharyngitis	10/413 (2.4)	13/434 (3)	5/89 (5.6)	28/936 (3)	0/106 (0)

Ex=exposure in patient years. IR=incidence rate per 100 patient years

Source: adapted from PsA summary of clinical safety, p. 64

During the first 16 weeks of Pool A trials, the most common preferred terms ($\geq 2\%$) that occurred at a greater proportion in the secukinumab than placebo treatment groups

were nasopharyngitis, upper respiratory tract infection, headache, nausea, and hypercholesterolemia. In general, these common AEs were similar in the psoriasis studies.

Reviewer's comments: The adverse events that occurred in the pooled PsA trials were similar to the common adverse events that were seen in the psoriasis trials. No new safety signals were identified.

7.4.2 Laboratory Findings

In the pooled phase 3 studies for the entire treatment period, Grade 1 and Grade 2 neutropenia was reported with comparable frequency across the secukinumab dose groups. Grade 3 neutropenia was observed in 4 patients, with one additional case reported after Week 16 in the any 75 mg group. The absolute incidence of Grade 3 neutropenia in the entire treatment period remained low and comparable across the secukinumab dose groups (0.7%, 0.5% and 0.3% for any 300 mg, any 150 mg and any 75 mg, respectively). Most cases were transient and reversible.

Grade 1 or 2 abnormalities in hemoglobin, lymphocytes and platelets showed no differences across the secukinumab dose groups. For leukocytes, Grade 2 values were infrequent and showed no dose relationship (2.8%, 2.3% and 2.6% for Any 300 mg, Any 150 mg and Any 75 mg, respectively). Six patients had Grade 3 abnormalities in lymphocytes (4, 0.9% on any 150 mg; 2, 0.5% on any 75 mg). There were no Grade 3 values for hemoglobin or platelets. No Grade 4 abnormalities were reported in any parameter.

Most abnormalities in clinical chemistry parameters over the entire treatment period of the Phase 3 PsA studies of Pool A were of Grade 1 or 2 values. There was no indication of a dose effect in any clinical chemistry parameter. Grade 3 abnormalities were reported for ALT, AST, creatinine, GGT, increased fasting glucose, decreased fasting glucose and triglycerides. Rates were low and comparable between the secukinumab dose groups. Grade 4 abnormalities were reported in a small number of patients for decreased fasting glucose (2 patients in the any 150 mg group), increased fasting glucose (1 patient in the Any 75 mg group) and triglycerides (1 patient in the any 75 mg group and 3 patients in the any 150 mg group).

7.4.3 Vital Signs

Table 38 shows the newly occurring vital sign abnormalities that occurred during the entire treatment period in the phase 3 PsA studies. Approximately 30-40% of patients developed high systolic or diastolic blood pressure. 17-20% of patients developed a low sitting pulse rate. Similar vital signs occurred in the 16 week period of the pooled phase 3 PsA studies and were comparable to placebo (data not shown). No dose dependent changes were seen in the vital sign abnormalities.

Table 38. Vital sign abnormalities for pooled phase 3 PsA trials

n/m (%)	AIN457 75 mg N=391	AIN457 150 mg N=438	AIN457 300 mg N=145	AIN457 Any dose N=974
Sitting systolic BP (mmHg)				
High only	111/317 (35)	124/362 (34.3)	36/121 (29.8)	271/800 (33.9)
Low only	7/389 (1.8)	9/438 (2.1)	0/142 (0)	16/969 (1.7)
High and low	0/316 (0)	0/362 (0)	0/120 (0)	0/798 (0)
Sitting diastolic BP (mmHg)				
High only	132/351 (37.6)	160/396 (40.4)	40/120 (33.3)	332/867 (38.3)
Low only	31/388 (8)	36/432 (8.3)	13/141 (9.2)	80/961 (8.3)
High and low	3/349 (0.9)	6/390 (1.5)	1/118 (0.8)	10/857 (1.2)
Sitting pulse rate (bpm)				
High only	12/389 (3.1)	9/436 (2.1)	3/141 (2.1)	24/966 (2.5)
Low only	66/362 (18.2)	87/412 (21.1)	23/135 (17)	176/909 (19.4)
High and low	0/361 (0)	3/410 (0.7)	1/133 (0.8)	4/904 (0.4)

Source: adapted from PsA summary of clinical safety, p. 173

7.4.4 Electrocardiograms (ECGs)

Two patients had QTc prolongation in groups who received secukinumab. One patient with a history of atrial fibrillation, ventricular extrasystoles, mitral valve replacement, chronic heart failure, hyperlipidemia and hypertension received IV loading dose followed by 150 mg secukinumab every 4 weeks. The patients had a QTcF that was 469 msec which worsened to 505 msec at Week 16. The CTcF was 490 msec at week 52. None of the events required discontinuation of study medication.

An additional patient who was a placebo non-responder who was re-randomized to 75 mg secukinumab had a QTc interval at baseline of 482/478 msec. The QTc interval worsened to 529/528 at week 52. The prolonged QTc interval was reported as a non-serious adverse event of mild severity.

One patient who received placebo had an abnormal QTcF at baseline which worsened to 501 msec at week 16.

Similar to the psoriasis program, there was no evidence for important drug induced prolongation of the QT interval or PR interval in the submitted data.

7.4.5 Special Safety Studies/Clinical Trials

This supplement did not involve special safety studies or clinical trials.

7.4.6 Immunogenicity

For the PsA studies, immunogenicity samples were taken at baseline prior to initiation of study treatment, and weeks 24, 52, 104, and 112. Samples from 996 patients were taken. Of the 17 patients who tested positive for anti-drug antibodies (ADA), 16 patients had positive ADA prior to initiation of study treatment. One patient who received 75 mg of secukinumab developed ADA at week 24. 10 patients reverted to a seronegative status during the course of the study. 8 of 996 patients tested positive for both ADA and neutralizing antibodies. The ADA did not appear to have any effects on pharmacokinetics, safety, or efficacy of secukinumab.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Most adverse events that occurred in the secukinumab groups did not appear to be dose dependent in the PsA studies. The 300 mg group did have numerically higher incidence of immune/administration reactions, hypersensitivity events, infection and infestations when compared to the 150 mg secukinumab group. These findings were consistent with the findings in the psoriasis trials.

7.5.2 Time Dependency for Adverse Events

No time to event analyses were performed in this submission. The Applicant did provide incidence rates based on exposure to medication which was used to review the adverse events in sections 7.3 and 7.4.

7.5.3 Drug-Demographic Interactions

The Applicant performed subgroup analyses for gender, age, race, and body weight. Table 39 shows the adverse events that occurred by gender over the entire treatment period in the pooled phase 3 PsA studies. The Applicant noted that AEs occurred more frequently in females as compared to males but the adverse events in placebo showed a similar pattern with more reports of AEs in females as compared to males.

Table 39. Pooled phase 3 studies: AEs by gender over entire treatment period

n/EX (IR)	Subgroup	Any AIN457 75 mg	Any AIN457 150 mg	Any AIN457 300 mg	Any AIN457	Placebo
N	Male	174	215	67	456	135
	Female	217	223	78	518	165
Any AE	Male	126/76 (165.1)	167/78 (214.6)	39/24 (160.8)	332/178 (186.1)	72/28 (256.3)
	Female	170/82 (206.3)	175/69 (252.8)	55/18 (305.1)	400/170 (235.8)	109/29 (382)
Infections and infestations	Male	89/124 (71.9)	104/138 (75.5)	25/33 (76.7)	218/294 (74.1)	33/39 (84.1)
	Female	109/152 (71.9)	129/125 (103.2)	35/31 (114.9)	273/307 (88.9)	49/48 (102.6)
MSK disorders	Male	49/154 (31.7)	37/191 (19.4)	8/40 (20)	94/385 (24.4)	14/44 (32)
	Female	56/196 (28.6)	56/189 (29.6)	12/43 (27.9)	124/429 (28.9)	31/52 (59.6)
GI disorders	Male	38/160 (23.9)	44/185 (23.7)	14/37 (38)	96/381 (25.2)	11/44 (25)
	Female	50/195 (25.6)	55/188 (29.2)	14/41 (34.5)	119/424 (28.1)	28/52 (53.7)
Skin disorders	Male	34/163 (20.9)	37/190 (19.5)	4/42 (9.6)	75/394 (19)	8/44 (18)
	Female	32/210 (15.3)	37/203 (18.2)	16/41 (39.4)	85/454 (18.7)	22/55 (40.4)
Nervous system disorders	Male	20/172 (11.6)	27/198 (13.7)	7/39 (18.1)	54/408 (13.2)	11/43 (25.4)
	Female	40/199 (20.1)	42/195 (21.5)	11/42 (26.4)	93/436 (21.4)	18/55 (32.6)

Source: adapted from PsA summary of clinical safety, p. 183-184

No other drug-demographic interactions were seen with age, race, or body weight.

7.5.4 Drug-Disease Interactions

No drug-disease interaction data were submitted.

7.5.5 Drug-Drug Interactions

The Applicant has conducted study A2224, a vaccine study in healthy volunteers. Subjects treated with secukinumab or placebo received meningococcal and inactivated influenza vaccinations. The subjects were able to mount an immune response of at least 4-fold increase in antibody titers to meningococcal and influenza antigens.

The Applicant has stated that live vaccines should not be given concurrently with secukinumab.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

There was insufficient clinical data from the use of secukinumab in pregnant women with PsA to assess the safety of secukinumab use during pregnancy and lactation. Immunoglobulins are excreted in human milk so caution should be exercised in prescribing secukinumab to women who are breast feeding

7.6.3 Pediatrics and Assessment of Effects on Growth

The juvenile equivalents of PsA are extremely rare. The Applicant submitted a full waiver request because the necessary studies would be impossible or highly impracticable as only few children exist to be studied. The Agency has previously waived studies for juvenile equivalents of PsA based on similar rationale. Thus, a waiver is reasonable for evaluation of juvenile equivalents of PsA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose on secukinumab were reported in the PsA studies. There is no known potential for abuse of secukinumab and no abuse studies have been conducted.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120 day safety update. Data from this submission did not reveal any new issues not already commented on.

8 Postmarket Experience

No post-marketing data were submitted in this submission.

9 Appendices

9.1 Literature Review/References

Taylor W, Gladman D, Helliwell et al. Classification criteria for psoriatic arthritis. *Arthritis Rheum* 2006; 54:2665-73.

9.2 Labeling Recommendations

The following are major changes recommended for the Applicant's proposed labeling for secukinumab. These recommendations may change after internal labeling discussion and after labeling discussions with the Applicant.

Dosage and Administration

1. The Applicant proposed that secukinumab be used as 150 mg SC every week for 5 doses and then every 4 weeks for the indication of PsA. The Applicant further recommended that patients who have moderate to severe PsA (b) (4) (b) (4) be placed on 300 mg SC every week for 5 weeks followed by 300 mg every 4 weeks. (b) (4) (b) (4)

Due to the ability of placebo patients to show efficacy without a load after switching to secukinumab, it is uncertain whether a load is necessary in dosing secukinumab for PsA. Therefore, providers will have the option to start secukinumab for the indication of PsA with or without a loading dose.

PsA patients with concomitant moderate to severe psoriasis will be referred to the psoriasis dosing section for dosing recommendations.

Warnings and Precautions

2. New cases of ulcerative colitis and Crohn's disease were seen in the PsA and AS studies along with worsening of disease. Further, severe and serious Crohn's flares were seen in a study of secukinumab for use in Crohn's disease. The study was discontinued due to lack of efficacy. Therefore, the Warnings and Precautions will be expanded to warn that new cases of inflammatory bowel disease and worsening of inflammatory bowel disease can occur with the use of secukinumab.

Clinical Trials Experience

Clinical Review
Raj Nair
125504/1
Secukinumab (Cosentyx)

3. In the PsA section, additional information on the adverse events that occurred during the PsA trials will be provided.

Clinical Studies

4. A statement stating that patients on placebo who received secukinumab without a loading regimen achieved similar ACR20 responses as patients who received a loading regimen was added.

5. The information on [REDACTED] (b) (4) [REDACTED] was removed due to the concerns listed above under Dosage and Administration.

[REDACTED] (b) (4)

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this application as decisions regarding approval of this supplement were made internally and did not require additional input from qualified experts in the field.

Clinical Review
 Raj Nair
 125504/1
 Secukinumab (Cosentyx)

Clinical Investigator Financial Disclosure
 Review Template

Application Number: 125504-1

Submission Date(s): March 18, 2015

Applicant: Novartis

Product: secukinumab

Reviewer: Raj Nair

Date of Review: December 11, 2015

Covered Clinical Studies (Name and/or Number): AIN457F2306 and AIN457F2312

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>1400</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Reviewer comments:

The Sponsor has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed form 3454 and financial disclosure summary.

The sponsor certifies that the covered studies, F2306 and F2312, are not funded by variable compensations and none of the investigators in the study hold any form of property interest in the product. Novartis has examined its financial data regarding significant payments of other sorts made to all investigators who participated in the study and equity information as provided by those investigators, as defined in 21 CFR 54.2.

Certification:

Per US FDA Form 3454, certification is provided for 1400 investigators listed in the study report indicating:

- Certified investigators. A total of 1400 investigators are certified as having no Financial Arrangements as defined in 21 CFR 54.4.
- No due diligence activities were required for this covered study.

Note that all investigators are assessed for equity, significant payments of other sorts, variable compensation, and propriety interest. Significant payments of other sorts and other financial arrangements are checked via internal Novartis procedures.

Disclosure:

Per US FDA Form 3455, one of the 1400 investigators listed in the study report had significant payments of other sorts as defined in 21 CFR 54.4. One clinical investigator received payments in excess of \$25,000, other than payments for conducting the clinical trials.

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

/s/

RAJ NAIR
12/11/2015

JANET W MAYNARD
12/11/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

CHEMISTRY REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products**

Memorandum of Review:

STN:	125504/-S1 and -S2
Subject:	Supplement-1 and-2 are submitted to provide efficacy, pharmacology/toxicology, and clinical pharmacology information for indications of psoriatic arthritis and ankylosing spondylitis respectively, and to make relevant changes to the labeling.
Date:	12/16/15
Review/Revision Date:	12/16/15
Primary Reviewer:	Yongmin Liu, Ph.D.; DBRRII/OBP/OPQ/CDER
Secondary Reviewer:	Rashmi Rawat, Ph.D. Team Leader, DBRRII/OBP/OPQ/CDER
Assigned RPM:	Laura Musse
Consults:	None
Applicant:	Novartis
Product:	Cosentyx™ (Secukinumab)
Indication:	Psoriatic arthritis (S1) and ankylosing spondylitis (S2)
Filing Action Date:	Supplement-1: 03/18/2015 and Supplement-2: 03/23/2015

I. Summary Basis of Recommendation:

- a. **Recommendation:** From product quality perspective, I recommend approval of these supplemental Biological License Applications.
- b. **Justification:** No changes are made to control manufacturing and chemistry section (Module 3) of the BLA. No CMC-related labeling changes are proposed in the updated labels for both supplements

II. Review:

Introduction:

Secukinumab is a human monoclonal antibody directed against interleukin-17A (IL-17A, also known as IL-17). IL-17A levels are elevated in many inflammatory and autoimmune conditions. By binding to IL-17A, Secukinumab inhibits the interaction of IL-17A with its receptor and the subsequent release of pro-inflammatory cytokines, chemokines, and mediators of tissue damage. Secukinumab was approved on January 21, 2015, for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products**

In current submissions, two efficacy supplements were submitted to support the use of Secukinumab for the treatment of psoriatic arthritis and ankylosing spondylitis. The sponsor has stated that no changes are made to the module 3 of the BLA that contains the chemistry, manufacturing and control (CMC) information.

For both supplements the sponsor has included the environmental assessment that claims a categorical exclusion as per 21CFR part 25.31.

Reviewer's comments:

Supplement 1 and 2 contain efficacy and safety information regarding using Secukinumab for the treatment of psoriatic arthritis and ankylosing spondylitis respectively.

The supplements do not contain any new chemistry, manufacturing and control (product quality) information. No CMC-related labeling changes are proposed in the updated labels for these supplements. The sponsor's claim of categorical exclusion for environmental exclusion is acceptable.

Conclusion:

Recommendation: I recommend approval of Supplement-1 and supplement-2 from the product quality perspective.

III. Future Inspection Items: None.

IV. Signatures:

Printed Name:	Electronic Signature:
Primary Reviewer	Yongmin Liu -A <small>Digitally signed by Yongmin Liu -A DN: cn=US, o=U.S. Government, ou=HHS, ou=NHL, ou=People, cn=Yongmin Liu -A, 0.9.2342.1.2.100.100.1.1-001.065928 Date: 2015.12.17 15:35:13 -05'00'</small>
Secondary Reviewer	Rashmi Rawat -A <small>Digitally signed by Rashmi Rawat -A DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=Rashmi Rawat -A, 2.5.2.342.1.2.200.100.1.1-0014137532 Date: 2015.12.17 15:46:26 -05'00'</small>

Revision History:

Prepared by YL 12/16/15
Concurrence by RR 12/16/15

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

PHARMACOLOGY REVIEW(S)

Secondary Pharmacology and Toxicology Review for BLA 125-504

TO: BLA 125-504 (Novartis)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: December 18, 2015

Efficacy supplements were submitted to this BLA for the use of Cosentyx (secukinumab) for the treatment of psoriatic arthritis and ankylosing spondylitis (March 18, 2015, and March 23, 2015). Secukinumab is a fully human monoclonal antibody that binds and neutralizes IL-17A. Secukinumab was originally approved on January 21, 2015, for the treatment of moderate to severe plaque psoriasis in adults. A nonclinical pharmacology and toxicology review was previously completed on August 7, 2014, by Dr. Jill Merrill.

The current submissions include clinical data to support approval of this product for the new indications. No new nonclinical toxicology studies were included. One pharmacology study was submitted and evaluated the ability of secukinumab to suppress IL-17A/TNF α and IL-17AF/TNF α costimulated MMP-3 release in cultured fibroblast-like synoviocytes from rheumatoid arthritis patients. The results of this study were not proposed for inclusion in product labeling, and Dr. Leshin agreed that this is unnecessary. See the review by Dr. Leshin dated December 11, 2015. I concur with Dr. Leshin's recommendation.

There are no outstanding Pharmacology and Toxicology issues for this product, and efficacy supplements for the use of secukinumab for the treatment of psoriatic arthritis and ankylosing spondylitis are approvable from the nonclinical perspective.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: **125504**
Supporting document/s: SD-60 (S-1), SD-61 (S-2)
CDER stamp date: March 18, 2015, March 23, 2015
Product: **Cosentyx (secukinumab)**
Indication: **Psoriatic Arthritis (S-1)**
Ankylosing Spondylitis (S-2)
Applicant: **Novartis**
Review Division: DPARP
Reviewer: L. Steven Leshin, D.V.M., Ph.D.
Supervisor/Team Leader: Marcie Wood, Ph.D.
Division Director: Badrul Chowdhury, M.D., Ph.D.
Project Manager: Laura Musse

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 205504 are owned by Novartis or are data for which Novartis has obtained a written right of reference. Any information or data necessary for approval of BLA 205504 that Novartis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 205504.

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Figure 1: Potentiation of MMP-3 release from human FLS by IL-17A or IL-17AF in combination with TNF 10

1 Executive Summary

1.1 Introduction

Two efficacy supplements were submitted for the use of secukinumab (AIN457) for the treatment of psoriatic arthritis and ankylosing spondylitis. Secukinumab, as the brand name Cosentyx, was approved on January 21, 2015, for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is a human monoclonal antibody directed against interleukin-17A (IL-17A, also known as IL-17). IL-17A levels are elevated in many inflammatory and autoimmune conditions. By binding to IL-17A, secukinumab inhibits the interaction of IL-17A with its receptor and the subsequent release of proinflammatory cytokines, chemokines, and mediators of tissue damage. In the nonclinical submission for psoriatic arthritis (SD-60) the sponsor submitted one nonclinical pharmacology study, which is reviewed herein. There no additional pharmacology or toxicology studies submitted. Refer to the original pharmacology-toxicology review of August 7, 2014, by Dr. Jill Merrill for all previous pharmacology and toxicology information concerning secukinumab.

1.2 Brief Discussion of Nonclinical Findings

There was one pharmacology study submitted. This study demonstrated that secukinumab suppressed IL-17A/TNF α and IL-17AF/TNF α costimulated MMP-3 release in cultured fibroblast-like synoviocytes obtained from patients with rheumatoid arthritis. Basal levels of MMP-3 were minimal in these studies so the effect of secukinumab on unstimulated MMP-3 release could not be determined. The study supports the hypothesis that neutralization of the bioactivity of IL-17A and/or IL-17AF may contribute to the inhibition of the structural damage in inflammatory and autoimmune diseases by inhibiting the release of metalloproteinases such as MMP-3, an extracellular matrix endoproteinases.

1.3 Recommendations

1.3.1 Approvability

Yes, from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The sponsor made no labeling changes concerning the nonclinical information and there are no changes necessary.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)	1229022-83-6 875356-43-7 (H chain) 875356-44-8 (L chain)
Generic Name	Secukinumab
Code Name	AIN457
Chemical Name	Secukinumab
Molecular Formula/Molecular Weight	C ₆₈₅₄ H ₁₀₁₃₄ N ₁₇₅₄ O ₂₀₄₂ S ₄₄ / 147.9 kDa
Structure or Biochemical Description	AIN457 is an IgG antibody and consists of (b) (4) heavy chains and (b) (4) light chains joined together by disulfide bonds.
Pharmacologic Class	Fully human monoclonal antibody that binds and neutralizes IL-17A

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 12678 (DPARP) for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis indications

IND 100418 (DDDP) for psoriasis

(b) (4)

2.3 Drug Formulation

Composition of one vial of lyophilized AIN457 150 mg powder solution:

Ingredient	Theoretical amount (mg)
AIN457	150.00
Sucrose, NF	92.43
L-Histidine, USP	4.66
Polysorbate 80, NF	0.60

(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Refer to the review by the medical officer.

2.7 Regulatory Background

The original BLA for the treatment of psoriasis was approved on January 21, 2015. The submissions of efficacy supplements for the treatment of psoriatic arthritis and ankylosing spondylitis soon followed on March 18, 2015, and March 23, 2015, respectively. The Division decided to incorporate the review of the two supplements into one review. Except for one pharmacology study, there were no additional nonclinical studies submitted in these two efficacy supplements. Refer to the initial Pharmacology-Toxicology review of Dr. Jill Merrill of August 7, 2014, for all nonclinical studies concerning pharmacology, ADME and toxicokinetics, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology, and special toxicology studies.

3 Studies Submitted**3.1 Studies Reviewed**

Report / Location	Title
RD-2014-00571	Inhibition of MMP-3 release from human synoviocytes stimulated with TNF in combination with IL-17A and IL-17AF by secukinumab (AIN457)

3.2 Studies Not Reviewed

There were 17 reference publications submitted, but not formally reviewed.

3.3 Previous Reviews Referenced

BLA 205504 Pharmacology and Toxicology Review of August 7, 2014

Pharmacology Toxicology Supervisor Review of August 7, 2014

Pharmacology Toxicology Associate Director Tertiary Review of May 16, 2014

4 Pharmacology**4.1 Primary Pharmacology**

There was one pharmacology study submitted in supplement SD-60.

Study Title: **Inhibition of MMP-3 release from human synoviocytes stimulated with TNF in combination with IL-17A and IL-17AF by secukinumab (AIN457)**

Report: **RD-2014-00571**

Location: Module 4.2.1.1

Study Conducted from February 4, 2013, to June 16, 2014

Non-GLP

Key Study Findings

- Secukinumab (AIN457) inhibited IL-17-induced release of tissue degrading protease (metalloproteinase 3, MMP-3) from primary human rheumatoid arthritis fibroblast-like synoviocytes in an in vitro study.
- In this in vitro system, IL-17A (30 pM) or IL-17AF (1nM) alone or TNF α (60 pM) elicited low levels of MMP-3 secretion. The addition of both IL-17A and TNF α potentiated MMP-3 release compared to either cytokine by itself.
- Secukinumab inhibited MMP-3 release induced by IL-17A-TNF α costimulation ($IC_{50} = 0.067 \pm 0.004$ nM), and also inhibited MMP-3 release by heterodimeric IL-17AF-TNF α -induced costimulation ($IC_{50} = 4.471 \pm 0.595$ nM).

Methods

Human fibroblast-like synoviocytes were obtained from a commercial supplier of rheumatoid arthritis patient synoviocytes. These were cultured in a synoviocyte growth media. This study was an extension of a previous study [Report RD-2013-00026: Inhibition of IL-6 release from human synoviocytes stimulated with TNF in combination with IL-17A, IL-17 A/F or IL-17 F by secukinumab (AIN457)] submitted in the original BLA application. The original BLA review also indicated that within the human IL-17 family (IL-17A through IL-17F), IL-17A and IL-17F share the highest amino acid sequence homology (50%).

Cells were transferred to microwell plates and costimulated with either 1 ng/ml (0.03 nM) IL-17A or 30 ng/ml (ca. 1 nM) IL-17AF in combination with 1 ng/ml (60 pM) TNF α , provided in a volume of 20 μ l/well. Controls with no stimulation and with single TNF α or IL-17 stimulation were included in all experiments. Culture supernatants were collected after overnight incubation, and MMP-3 levels were determined by an ALPHA (amplified luminescent proximity homogenous assay) detection technology in an ELISA assay, or by a different and more common ELISA kit. Both MMP-3 and pro-MMP-3 were detected in ALPHA-ELISA assay. It was unclear if larger precursors of MMP-3 were also detected in the second ELISA method.

Results

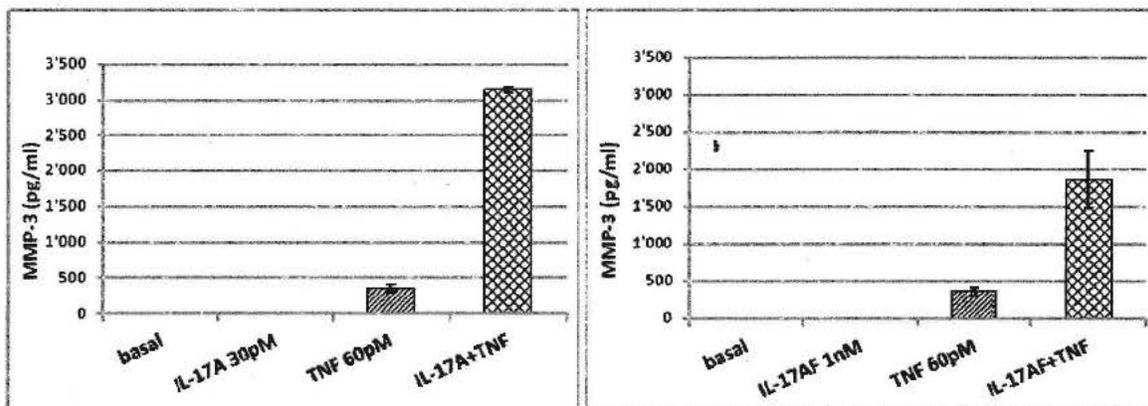
Stimulation of fibroblast-like synoviocytes with 30 pM IL-17A alone had no effect on MMP-3 release. TNF α alone resulted in a small increase in MMP-3. However, the combination of IL-17A with TNF α greatly potentiated (10.7-fold increase) MMP-3 release. The heterodimer, IL-17AF, was less potent than IL-17A and was used at a 33-fold higher concentration (1 nM IL-17AF) to achieve comparable MMP-3 levels. Costimulation of IL-17AF with TNF α produced a 10.9-fold increase in MMP-3 levels in the culture supernatant compared to TNF α alone.

The addition of secukinumab to cultures costimulated with 30 pM IL-17A and 60 pM TNF α reduced the secretion of MMP-3 in a dose-related manner ($IC_{50} = 0.067 \pm 0.004$ nM). At the high dose, minimal MMP-3 secretion was approximately similar to that of TNF α stimulation alone. There was no inhibition by the control antibodies, IgG1 or human anti-cyclosporine A. Similar, but less potent inhibitory responses occurred with

IL-17AF and TNF α costimulation in the presence of secukinumab (IC₅₀ = 4.471 \pm 0.595 nM).

Figure 1: Potentiation of MMP-3 release from human FLS by IL-17A or IL-17AF in combination with TNF

Primary human FLS were stimulated overnight with 30 pM IL-17A and 60 pM TNF alone or in combination (left graph:



Exp01_14), or with 1 nM IL-17AF and 60 pM TNF alone or in combination (right graph: Exp14_14). MMP-3 release was measured by AlphaLISA®

11. Integrated Summary and Safety Evaluation

The pharmacology study demonstrated that secukinumab suppressed IL-17A/TNF α and IL-17AF/TNF α costimulated MMP-3 release in cultured fibroblast-like synoviocytes obtained from patients with rheumatoid arthritis. Basal levels of MMP-3 were minimal in these studies so the effect of secukinumab on unstimulated MMP-3 release could not be determined. However, this may not be that critical since IL-17 and TNF α , as well as serum MMP-3, are elevated in many types of arthritic disease.

Although the mechanism of the therapeutic effect on secukinumab has not been completely established, evidence presented here supports the hypothesis that neutralization of the bioactivity of IL-17A and/or IL-17AF may contribute to the inhibition of the structural damage in inflammatory and autoimmune diseases by inhibiting the release of metalloproteinases such as MMP-3, an extracellular matrix endoproteinases.

This study was not incorporated into the revised label by the sponsor (Section 12.1 or 12.2), and the reviewer agrees that it is unnecessary to include in the label.

Efficacy supplements for the use of secukinumab (AIN457) for the treatment of psoriatic arthritis and ankylosing spondylitis are approvable from the nonclinical perspective.

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/s/

LAWRENCE S LESHIN
12/11/2015

MARCIE L WOOD
12/11/2015

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/s/

MARCIE L WOOD
12/18/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: BLA 125,504/0060

Drug Name: Cosentyx™ (secukinumab) 150 mg s.c.

Indication(s): Treatment of Psoriatic Arthritis (PsA)

Applicant: Novartis Pharmaceuticals Corporation

Date(s): Submitted: March 18, 2015
PDUFA: January 18, 2016

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Yongman Kim, Ph.D.

Concurring Reviewers: Gregory Levin, Ph.D.
Thomas Permutt, Ph.D.

Medical Division: Division of Pulmonary, Allergy, and Rheumatology Products

Clinical Team: Raj Nair, M.D.
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Project Manager: Michelle Jordan Garner

Keywords: BLA, clinical studies, early escape, missing data

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1 EXECUTIVE SUMMARY

Novartis Pharmaceuticals Corporation has proposed Cosentyx™ (secukinumab) for the treatment of psoriatic arthritis (PsA). The applicant submitted the results from two phase 3 clinical trials, CAIN457F2306 and CAIN457F2312 (F2306 and F2312 for short hereafter), to support the efficacy of secukinumab for the treatment of PsA. The applicant claims that the results from these trials provide substantial evidence of efficacy by the predefined primary efficacy endpoint ACR20 at Week 24.

Based on my review of the data from the two phase 3 studies, F2306 and F2312, there is sufficient evidence to support the efficacy of secukinumab 150 mg and 300 mg in treating patients with PsA. The analysis of the primary efficacy endpoint, ACR20 at Week 24, was statistically significant in the two studies reviewed. This evidence was further supported by the analyses of secondary endpoints, including DAS28-CRP, HAQ-DI, SF-36 PCS, PASI75, PASI90, and mTSS at Week 24. Therefore, from a statistical perspective, the overall package provided substantial evidence of secukinumab's efficacy benefit.

2 INTRODUCTION

2.1 Overview

This application was submitted on March 18, 2015 in support of secukinumab 150 mg for the treatment of patients with psoriatic arthritis. The original secukinumab Biological License Application (BLA #125,504) was submitted to the Division of Dermatology and Dental Products. The original BLA was approved January 21, 2015 for the indication of moderate to severe plaque psoriasis. Cosentyx™ is supplied as 150 mg secukinumab in 1 mL of sterile solution for injection in a single use prefilled SensoReady® pen, as a single-use prefilled syringe, and as 150 mg secukinumab as a powder for solution for injection in a single-use glass vial.

Secukinumab is a fully human monoclonal IgG1κ antibody that selectively binds to and neutralizes the pro-inflammatory cytokine interleukin-17A (IL-17A) by blocking its interaction with the IL-17 receptor; thus inhibiting the release of pro-inflammatory cytokines, chemokines, and mediators of tissue damage resulting from IL-17A-mediated autoimmune and inflammatory diseases. Increased numbers of IL-17A producing lymphocytes and innate immune cells and increased levels of IL-17A have been found in the blood of patients with psoriatic arthritis and affected skin of patients with plaque psoriasis. Furthermore higher frequency of IL-17-producing cells was detected in the synovial fluid of patients with psoriatic arthritis.

The submission included the results from two phase 3, randomized, double-blind, placebo-controlled studies, F2306 and F2312, that were similar in design. The objective of the phase 3 studies was to evaluate the efficacy and safety of secukinumab compared with placebo in

patients with PsA. In each study, patients were to receive randomized, double-blind study treatment for 24 weeks. The primary efficacy outcome variable was the response rate of ACR20 at Week 24.

History of Drug Development and Regulatory Interactions

The secukinumab clinical development program for PsA was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products under IND 12,678. Communication with the applicant regarding their development plan is documented under this IND. Pertinent parts of the statistical portion of those communications are summarized herein.

In March 2011, the applicant had an End-of-Phase 2 meeting with the Division, where input was received regarding the proposed phase 3 program. The Division provided the following statistical comments on the proposed analysis plans for studies in PsA and rheumatoid arthritis:

Statistical methodology and sample size

Based on the protocol synopses provided in your briefing package, we have the following concerns, comments, and questions about your statistical methodology and sample size in Studies 302, 309, 305, 306, 301, and 303:

- 1. Your proposed sample sizes for each study appear reasonable to assess your endpoints in Studies 302, 309, 306, and 305.*
- 2. Your proposed strategy for missing data imputation using last observation carried forward (LOCF) is not acceptable. Any patient who discontinues for any reason or any patient who enters escape treatment should be considered a non-responder for efficacy analyses of binary endpoints (e.g., ACR response, HAQ response, MCR, ASAS20 response, ASAS40 response).*
- 3. Reasons for discontinuation should be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision', 'withdraw consent', etc. You should provide a plan in your protocols to contact patients if they are 'lost to follow-up', so that a more informative category can be assigned.*
- 4. Clarify the meaning of nonparametric ANCOVA planned for analysis of the radiographic structural endpoint (e.g., change from baseline in mTSS at Week 52).*
- 5. You should conduct sensitivity analyses (e.g., analyzing observed data, mixed model repeated measures, etc.) assessing the impact of the linear extrapolation on the analysis of the radiographic structural endpoint (e.g., change from baseline in mTSS at Week 52) in Studies 302, 306, 301, and 303.*
- 6. If you intend to make labeling claims based on the results from the analyses of secondary endpoints, your statistical analysis plan must include sufficient details regarding missing data, and the method you will use to control the probability of Type 1 error (i.e. incorporate these endpoints in your gate-keeping strategy).*

Hierarchical Analyses

Your hierarchical testing strategy appears reasonable in Studies 302, 306, 301, and 303.

In April 2012, the Division provided the following statistical comments on the proposed protocols and analysis plan:

- *We consider the primary variables a separate family from secondary variables. Design your test to control overall two-sided Type-I error within the primary variable family to 0.05.*
- *Ensure that you record informative reasons for discontinuation of treatment or withdrawal from the study, avoiding less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdrew consent', in favor of categories relevant to safety or effectiveness, such as 'treatment ineffective' or 'adverse reaction.'*
- *You propose last observation carried forward to impute missing data for missing HAQ-DI. In general, this approach is not acceptable because it assumes patient outcome does not change after dropout. In your statistical analysis plan, discuss what your primary analysis for HAQ-DI response is estimating. Clarify whether it is intended to reflect what patients would have experienced if they were compelled to take the drug regardless of their desire to withdraw from treatment, or whether it is intended to reflect what they actually experienced, or whether it is intended only to reflect what those remaining on treatment experienced. Correspondingly, clarify whether your choice of imputations impute HAQ-DI as if patients continued assigned treatment, reverted to placebo, or reverted to standard of care. From your conclusions concerning the estimand and imputation, clarify the effects of your proposed analysis on the FAS population proposed to evaluate effectiveness (i.e. whether it maintains the original randomization, or will only a certain subset of the population be analyzed, e.g. patients who remained in the study to Week 24). Clarify whether the estimand is appropriate for this study, given the probable mechanisms of treatment discontinuation. Propose sensitivity analyses and articulate how they compensate for any weaknesses in your approach.*
- *If you intend to provide rescue therapies which differ by randomized treatment, ensure that blinding is maintained during and after any assessments of patient eligibility for such therapies.*

In April 2015, after the filing meeting, the Division sent the following statistical Information Request (IR) to the Applicant to help explore the potential effect of missing data on the reliability of efficacy results:

1. *We request analyses on observed data for all endpoints proposed for inclusion on the product label.*
2. *For continuous endpoints, to avoid the untenable assumption that unobserved data is missing-at-random, provide analyses of covariance at each endpoint.*
3. *For primary endpoints, in addition to analyses on observed data only, examine the potential effects of missing data and rescue on your results using tipping point sensitivity analyses. The tipping point analyses should vary assumptions about average values of the primary endpoint among the subsets of patients on the secukinumab and placebo arms who withdrew from treatment prior to the planned endpoint.*

2.1.1 Specific Studies Reviewed

The focus of this review is on the efficacy data from two phase 3 efficacy studies, F2306 and F2312. The design of the two studies is described in Table 1.

Table 1. Clinical Trials Reviewed

Trial No.	Phase	Design	Treatment Arms	Number of Patients	Dates
-----------	-------	--------	----------------	--------------------	-------

F2306	3	52-week, randomized, double-blind, parallel-group, placebo-controlled	secukinumab 75 mg	202	09/2011- 10/2013 (52 weeks cut for interim analysis)
			secukinumab 150 mg	202	
			Placebo	202	
F2312	3	24-week, randomized, double-blind, parallel-group, placebo- controlled	secukinumab 75 mg	99	04/2013- 05/2014 (24 weeks cut for interim analysis)
			secukinumab 150 mg	100	
			secukinumab 300 mg	100	
			Placebo	98	

Source: Reviewer

2.2 Data Sources

BLA 125-504 can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study reports, protocols, statistical analysis plans, and all referenced literature can be found in the EDR. The program codes used in statistical analyses and the electronic data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

[\\cdsesub1\evsprod\BLA125504\0060\m5\datasets\ain457f2306\analysis\adam\datasets](#)
[\\cdsesub1\evsprod\BLA125504\0060\m5\datasets\ain457f2312\analysis\adam\datasets](#)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data were acceptable in terms of quality and integrity. I was able to derive the primary and secondary efficacy endpoints for the studies reviewed. No noticeable deviations between the raw datasets and analysis datasets relevant to primary and secondary endpoints were identified. The statistical analyses of my derived endpoints were consistent with the applicant's analyses.

Based on the information provided in this submission, each study seemed to be conducted properly and was consistent with the history of regulatory interactions and protocol revisions/amendments.

3.2 Evaluation of Efficacy

The applicant conducted two phase 3, randomized, double- blind, placebo-controlled

international studies, F2306 and F2312. In nearly all study design features (eligibility criteria, study schedule, primary efficacy outcome variable and analysis, secondary and exploratory efficacy outcome measures and analyses), the studies were similar. The two studies differed mainly in the choice of subcutaneous (sc) or intravenous (iv) loading and the addition of a 300 mg sc dosing arm in F2312. The loading dose used for the active treatment arms in F2306 was 3×10 mg/kg iv at Weeks 0, 2 and 4, followed by 75 mg sc or 150 mg sc every 4 weeks (hereafter referred as iv-75 mg and iv-150 mg regimens). The iv loading dose used in this study is not being proposed for marketing. The loading doses used in F2312 were 4 weekly sc injections of 75 mg, 150 mg or 300 mg at Weeks 0, 1, 2 and 3, followed by 75 mg sc, 150 mg sc or 300 mg sc, respectively, every 4 weeks (hereafter referred to as 75 mg sc, 150 mg sc and 300 mg sc regimens). It is the 150 and 300 mg doses (with sc loading doses) evaluated in Study F2312 that are being proposed for marketing.

3.2.1 Study F2306

The objective of the study was to evaluate the efficacy and safety of secukinumab 75 mg and 150 mg compared with placebo in patients with PsA. Patients were to receive randomized study treatment in a double-blind manner for 52 weeks.

Study Design and Endpoints

The study used a double-blind, randomized, parallel-group, placebo-controlled design. A screening period running up to 4 weeks before randomization was used to assess eligibility followed by a treatment period of two years (Figure 1). At baseline (BSL), subjects whose eligibility was confirmed were randomized to one of three treatment groups:

- Group 1: Secukinumab iv (10mg/kg) at BSL, Weeks 2 and 4, then secukinumab 75 mg sc starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab iv (10mg/kg) at BSL, Weeks 2 and 4, then secukinumab 150 mg sc starting at Week 8 and injected every 4 weeks
- Group 3: Placebo iv at BSL, Weeks 2 and 4, then placebo sc starting at Week 8 and injected every 4 weeks.

Randomization was stratified according to whether patients were TNF α inhibitor incomplete responders (IR) or TNF α inhibitor naïve. Thirty percent of subjects were planned to be TNF α inhibitor inadequate responders to ensure a representative subject population for the assessment of efficacy and safety. Thus, it was planned to randomize approximately 180 TNF α inhibitor IR subjects and 420 TNF α inhibitor naïve subjects.

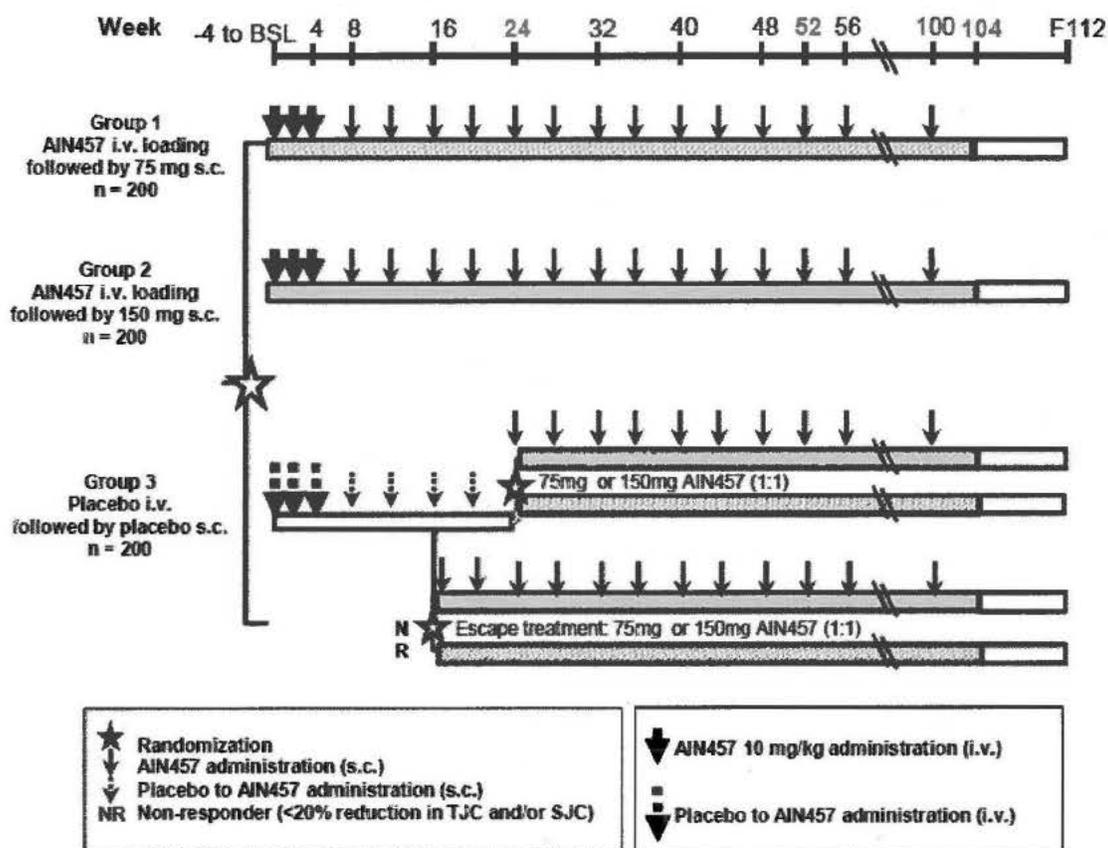
At Week 16 (Visit 8), all subjects were classified as responders ($\geq 20\%$ improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to placebo at baseline were re-randomized by the Interactive Response Technology (IRT) to receive double blind treatment up to 2 years, as follows:

- Subjects on secukinumab placebo (Group 3) who were responders remained on placebo until Week 24. At Week 24, these subjects received either secukinumab 75 or 150 mg sc every 4 weeks (as dictated by the re-randomization).

- Subjects on secukinumab placebo (Group 3) who were non-responders were re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg sc every 4 weeks.

Rescue medication, defined as any new therapeutic intervention or a significant change to ongoing therapy, was not allowed until Week 24. However, subjects deemed not to be benefiting from the study treatment by the investigator or for any reason on their own accord were free to discontinue participation in the study at any time.

Figure 1. Study Schema for Study F2306



Source: Excerpted from the Clinical Study Report for Study F2306 (page 12575).

The population enrolled in the study consisted of adults with active PsA. In addition, patients with cardiovascular morbidities and patients who had previously failed other biologic therapies were included. This population consisted of a group of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) negative patients at least 18 years of age, fulfilling the CASPAR (classification criteria for psoriatic arthritis) criteria with active PsA. Active PsA is defined as the presence of at least 3 out of 78 tender joints and at least 3 out of 76 swollen joints at baseline despite current or previous NSAIDs, DMARDs, and/or TNF α inhibitor therapy. CASPAR criteria consisted of establishing inflammatory articular disease with at least 3 points

from the following features: current psoriasis, a history of psoriasis (unless current psoriasis was present), a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis), dactylitis, juxta-articular new bone formation, RF negativity and nail dystrophy. Current psoriasis, history of psoriasis and family history of psoriasis were each assigned a score of 2 while all other features were assigned a score of 1.

The primary efficacy endpoint was the American College of Rheumatology 20 (ACR20) response at Week 24. A patient was defined as an ACR20 responder if, and only if, the following three conditions were met:

1. they had a $\geq 20\%$ improvement in the number of tender joints (based on 78 joints)
2. they had a $\geq 20\%$ improvement in the number of swollen joints (based on 76 joints)
3. they had a $\geq 20\%$ improvement in three of the following five domains
 - Patient Global Assessment (measured on a VAS scale, 0-100)
 - Physician Global Assessment (measured on a VAS scale, 0-100)
 - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
 - Disability (HAQ-DI[®] score)
 - Acute phase reactant (hsCRP or ESR)

The applicant used hsCRP to calculate ACR response; ESR was only used when hsCRP was missing.

The secondary efficacy variables were the Psoriasis Area Severity Index 75 (PASI75), PASI90, Disease Activity Score 28-C-Reactive Protein (DAS28-CRP), Short Form-36 Physical Component Summary (SF-36 PCS), Health Assessment Questionnaire-Disability Index (HAQ-DI), ACR50, dactylitis, enthesitis, and van der Heijde-modified total Sharp score (vdH-mTSS), all assessed at Week 24.

Statistical Methodologies

The primary analysis population was the Full Analysis Set (FAS) defined as all randomized patients.

The efficacy variables were analyzed with a logistic regression model for binary endpoints or a mixed-effects repeated measures model (MMRM) for continuous endpoints. The logistic regression model included terms for treatment regimen and TNF-alpha inhibitor status as factors, and weight as a covariate. The MMRM included terms for treatment regimen, analysis visit, and TNF-alpha inhibitor status as factors, weight and baseline value as continuous covariates, and treatment by analysis visit and baseline by analysis visit as interaction terms. An unstructured covariance structure was assumed for this model. Changes in vdH-mTSS were analyzed with a non-parametric ANCOVA model¹. The ANCOVA model included terms for treatment regimen and TNF-alpha inhibitor status as factors, and weight and baseline value as continuous covariates.

¹ Koch GG, Tangen CM, Jung JW, et al. (1998) Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. *Statistics in Medicine*; 17:1863-92.

The data for subjects who met rescue criteria at Week 16 were handled as follows:

1. For binary endpoints, subjects were considered as non-responders. This was done for all treatment regimens.
2. For continuous endpoints, the applicant carried out analyses intending to estimate what would have happened if the subjects had stayed on the original treatment. The data collected after subjects switched to secukinumab were treated as missing for placebo subjects and were analyzed using a mixed-effects repeated measures model under the missing-at-random (MAR) assumption. For secukinumab subjects, the actual values were used in the analysis.
3. For the radiographic endpoint, change in vdH-mTSS, placebo patients who met the criteria had radiographs assessed at the Week 16 visit and Week 24 data was imputed based on Baseline and Week 16 data using linear extrapolation (LE). They did not have radiographs assessed at Week 24. For secukinumab subjects, the actual Week 24 values were used in the analysis.

Missing data for ACR20 response and other binary efficacy variables (e.g. ACR50, ACR70, HAQ-DI response, etc.) for data up to 1-year (week 52) were handled as follows:

1. Subjects who dropped out of the trial for any reason were considered non-responders from the time they dropped out through week 52.
2. Subjects who did not have the required data to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) at baseline and at the specific time point were classified as non-responders.

Therefore, these binary endpoints should in fact be considered composite response endpoints defined by: (1) achieving at least 20% improvement in both the swollen and tender joint counts at Week 16; (2) remaining in the study through the time point of interest (e.g., Week 24); *and* (3) achieving a response in the outcome of interest at the time point of interest (e.g., ACR20 at Week 24).

Continuous variables (e.g. ACR components, DAS, etc.) were analyzed using a mixed effects repeated measures model assuming the missing at random mechanism. For analyses of these parameters, if all post-baseline values were missing then these missing values were not imputed and this subject was removed from the analysis of the corresponding variable, i.e. it might be that the number of subjects providing data to an analysis was smaller than the number of subjects in the FAS.

The impact of missing data on the primary analysis results was assessed by repeating the logistic regression model using different ways to handle missing data. These included:

- Multiple imputation
- Observed data analysis.

The multiple imputation method incorporated the uncertainty in the imputed values into the analysis, but did not sufficiently assess sensitivity of results to violations in the assumption about

the missing data mechanism since the method assumed a missing at random mechanism. The applicant's observed data analysis used actually assessed data after escape (instead of considering these patients to be non-responders) and attempts to evaluate an intention-to-treat or de facto estimand, i.e., the difference in outcomes in all randomized patients regardless of adherence or use of ancillary therapies. For the primary endpoint ACR20, the observed data analysis helps ensure that the effect in the primary analysis was not driven entirely by differences in the probability of meeting escape and dropping out early, i.e., that there was also an effect on signs and symptoms (ACR20 response) at Week 24. However, the observed data analysis was still conducted in the subset of patients who completed Week 24 assessments, thus relying on a missing at random assumption about dropouts. Therefore, I also conducted an intent-to-treat analysis with post-escape observed data and non-responder imputation for dropouts. I carried out similar sensitivity analyses incorporating observed post-escape data for secondary endpoints.

In addition, after the filing meeting, based on concerns about the handling of non-responders at Week 16, we sent an information request for additional sensitivity analyses including tipping point analyses for the primary endpoint, and the applicant submitted sensitivity analyses as per the IR.

The primary and secondary efficacy endpoints were tested for each secukinumab dose versus placebo in a testing strategy designed to protect the family-wise type 1 error rate at $\alpha=5\%$ (two-sided). The applicant proposed a hierarchical testing procedure with a graphical approach to adjust for the multiple doses and endpoints (Figure 2). Comparisons to placebo in the testing hierarchy for vdH-mTSS, dactylitis and enthesitis were based on pooled data across the secukinumab doses and if superiority was demonstrated based on pooled data then individual doses were evaluated.

The following primary and secondary hypotheses were included in the sequential testing strategy:

Primary objective:

H1: secukinumab 75 mg sc is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

H2: secukinumab 150 mg sc is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 24

Secondary objectives:

H3: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis

H4: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis

H5: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI90 response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis

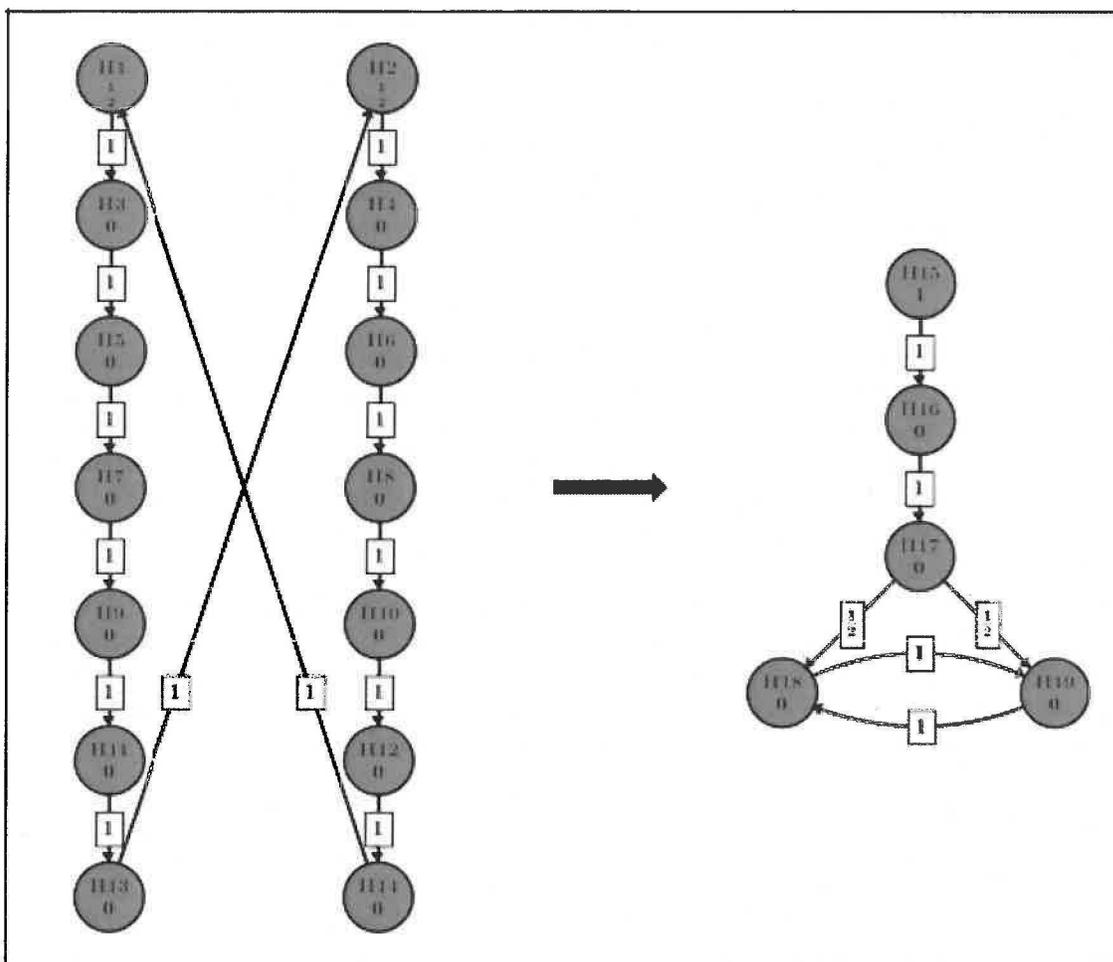
H6: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI90

response at Week 24 in the subgroup of subjects who have $\geq 3\%$ skin involvement with psoriasis

H7: secukinumab 75 mg sc is not different to placebo regimen with respect to the improvement

(change) from baseline for DAS28-CRP at Week 24
H8: secukinumab 150 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for DAS28-CRP at Week 24
H9: secukinumab 75 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
H10: secukinumab 150 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for SF36-PCS at Week 24
H11: secukinumab 75 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
H12: secukinumab 150 mg sc is not different to placebo regimen with respect to the improvement (change) from baseline for HAQ-DI at Week 24
H13: secukinumab 75 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
H14: secukinumab 150 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24
H15: secukinumab pooled regimen (75 mg and 150 mg sc) is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at week 24
H16: secukinumab pooled regimen (75 mg and 150 mg sc) is not different to placebo regimen with respect to presence of dactylitis at Week 24 in the subset of subjects who have dactylitis at baseline
H17: secukinumab pooled regimen (75 mg and 150 mg sc) is not different to placebo regimen with respect to presence of enthesitis at Week 24 in the subset of subjects who have enthesitis at baseline
H18: secukinumab 75 mg sc is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24
H19: secukinumab 150 mg sc is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24

Figure 2. Multiple testing strategy



Source: Excerpted from the Clinical Study Report for Study F2306 (page 12626).

Following are excerpts from the study report explaining the graphical approach to sequentially rejective testing procedure:

The family-wise error will be set to $\alpha=5\%$ and it will be controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses will be separated into two families, hypotheses H1 ~ H14 will be the first family and hypotheses H15 ~ H19 will be the second family. The second family hypotheses will be tested only when all hypotheses in the first family have been rejected. Each of the hypotheses (H1 and H2) for the primary objective (based on signs and symptoms at week 24) for each secukinumab regimen versus placebo will be tested simultaneously at $\alpha/2$. If at least one of H1 and/or H2 are/is rejected, then H3 and/or H4, respectively, is tested. If at least one of H3 and/or H4 is rejected, the hypothesis H5 and/or H6, is tested, respectively. Similar process applies until H13 and H14. Once all hypotheses within the first family for a secukinumab regimen are rejected, then the respective $\alpha/2$ can be passed on to the other regimen's hypotheses within the family, if they are not already rejected at $\alpha/2$. Only when all H1 ~ H14 are rejected, the objective on joint structure endpoint at Week 24 for testing pooled secukinumab doses versus placebo (H15) will be tested at α . If H15 is rejected, then H16 is tested at α . Similarly if H16

is rejected, then H17 is tested at α . If these pooled hypotheses are all rejected, then hypotheses concerning individual regimens of secukinumab versus placebo (H18 and H19) can be tested for a particular regimen at $\alpha/2$. Once the hypothesis of structure damage for a secukinumab regimen is rejected, then the respective $\alpha/2$ can be passed on to the other regimen's hypothesis, if it is not already rejected at $\alpha/2$. Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

Sample Size Calculation

Two secukinumab doses were tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), so the overall two-sided type I error rate of 5% was split to 2.5% two-sided for each comparison for the sample size calculations. A placebo response rate of about 25% after 24 weeks was assumed based on the results for the TNF α inhibitor naïve population in a historical study, and 15% was assumed based on the results for the TNF α inhibitor IR population in a historical study. Based on the weighted average, the overall placebo rate was expected to be 22%. The response on secukinumab was assumed to be 55% in the TNF α inhibitor naïve population and 35% in the TNF α inhibitor IR-population. Based on the weighted average, the overall rate on a dose of secukinumab was expected to be 49%. For the primary endpoint, ACR20 in the overall population, 200 subjects per group would yield approximately 99% power to detect a treatment difference in the response rates between the secukinumab regimens and placebo with the above assumptions using a Fisher's exact test.

Changes in the statistical analysis plan

There were three amendments to the original protocol (May 5, 2011): Amendment 1 (August 4, 2013), Amendment 2 (December 18, 2012), and Amendment 3 (December 6, 2013). The applicant claimed that these amendments were made prior to unblinding and analyses of the efficacy data. The changes included the following:

- To expand the statistical hierarchy (primary plus ranked secondary variables) to include more endpoints which are relevant to determining the overall therapeutic value of a therapy for PsA. These endpoints include but are not limited to PASI75, PASI90, DAS28-CRP, HAQ-DI, SF-36, dactylitis and enthesitis. Psoriatic arthritis (PsA) is a multifaceted chronic disabling disease that can present as different clinical phenotypes: peripheral arthritis, axial disease, skin and nail disease, dactylitis, and enthesitis, and hence defining outcome measures has been a challenge. Traditionally endpoints for PsA studies focused only on peripheral arthritis endpoints relevant for rheumatoid arthritis. However recently there has been additional interest by Health Authorities and the scientific community in endpoints specific/more relevant for such patients (PRO e.g. SF36) and overall extra, skin related endpoints (PASI 75/90), dactylitis and enthesitis, hence these have been added in the proposed amendment hierarchy. Recent labels for Ustekinumab (Stelara), working on the same pathway as secukinumab, approved in Nov 2013 mentions skin related endpoints (PASI 90), dactylitis and enthesitis. Prior to finalizing original protocol for CAIN457F2306 there were no new approved therapies with this in the label. Thus the endpoints at that time were based on then existing knowledge. Thus it is critical that we align our analyses and endpoints with new precedence and hence the emerging demands of the field. The additional hierarchical considerations do not add any new assessments for patients; all this data is being collected already, we are only now reorganizing the

hierarchy of secondary endpoints in line with new knowledge.

- In addition, the analysis is changed to include all subjects in Full Analysis Set (FAS) which includes TNF α inhibitor naïve as well as TNF α inhibitor inadequate responders (TNF-IR) rather than focusing only on the subset of subjects who are TNF α inhibitor naïve, as the FAS would be more representative of the general population of PsA patients. There were no new therapies approved when original protocol for CAIN457F2306 was written and thus TNF α inhibitor naïve patients were target population in line with the then existing labels/indications. The shift from TNF α inhibitor naïve to FAS, to increase the generalizability of the study findings is also in keeping with the recently approved Ustekinumab label that has also been studied in mixed population of both TNF α inhibitor naïve as well as TNF-IR patients.

Patient Disposition, Demographic and Baseline Characteristics

A total of 606 patients were randomized. The majority (85%) of patients completed 52 weeks of active treatment and 91% of patients completed 24 weeks (Table 2). Slightly more patients in the placebo group discontinued treatment prior to Week 24 and Week 52 compared to the secukinumab treatment groups. The most common reasons for discontinuation prior to Week 52 were adverse event and lack of efficacy with comparable rates in the secukinumab treatment groups but slightly greater rates in the placebo group.

Of the 202 patients in the placebo group, 187 patients were re-randomized (1:1) to secukinumab 75 mg or 150 mg. Of the placebo patients who were re-randomized, 4 patients discontinued before receiving secukinumab, 123 non-responding patients received secukinumab starting at Week 16 (75 mg: 62 patients and 150 mg: 61 patients), and 60 patients continued on placebo until Week 24 and then received either secukinumab 75 mg (28 patients) or 150 mg (32 patients).

Table 2. Patients' Accountability, N (%) (All Randomized Patients)

Disposition/Reason	SCK 75 mg n (%)	SCK 150 mg n (%)	Placebo n (%)	Placebo Non-responder SCK 75 mg n (%)	Placebo Non-responder SCK 150 mg n (%)	Placebo Responder SCK 75 mg n (%)	Placebo Responder SCK 150 mg n (%)
Randomized	202 (100)	202 (100)	202 (100)				
Completed Wk16	189 (94)	191 (95)	183 (93)	62 (100)	61 (100)	28 (100)	32 (100)
Non-responder at Wk16	46 (24)	51 (26)	123 (66)				
Re-randomized at Wk16				62 (100)	61 (100)		
Completed Wk24	187 (93)	188 (93)	174 (86)	57 (92)	59 (97)	28 (100)	30 (94)
Completed Wk52	174 (86)	180 (89)	161 (80)				
Discontinued Wk52	28 (14)	22 (11)	41 (20)				
Adverse event	6 (3)	5 (2)	9 (5)				
Lack of efficacy	6 (3)	7 (4)	13 (6)				
Other	16 (8)	10 (5)	19 (9)				

Note: SCK stands for secukinumab.

Source: Reviewer & the Clinical Study Report for Study F2306 (page 131).

The demographic and baseline disease characteristics were generally balanced and comparable between the treatment groups (Table 3). Overall, the average patient in the study was 49 years old, 80 kg in weight, and had 8 years of duration of PsA. The majority of patients were Caucasian and approximately 54% of patients were female. About 70% of patients were naïve to TNF alpha inhibitors and about 60% of patients used methotrexate at baseline.

Table 3. Patients' Demographic and Baseline Characteristics by Treatment

	SCK 75 mg N=202	SCK 150 mg N=202	Placebo N=202
Age (years)			
N	202	202	202
Mean	49	50	49
SD	12	12	11
Median	50	51	49
Min-Max	20-76	22-73	21-77
Gender, n (%)			
Female	118 (58)	106 (53)	106 (53)
Male	84 (42)	96 (47)	96 (47)
Race, n (%)			
White	165 (82)	162 (80)	154 (76)
Black	2 (1)	4 (2)	0 (0)
Asian	33 (16)	36 (18)	46 (23)
Other	2 (1)	1 (1)	2 (1)
Weight (kg)			
N	202	202	202
Mean	84	84	80
SD	20	21	21
Median	82	83	80
Min-Max	44-155	50-163	32-152
BMI (kg/m**2)			
N	201	200	202
Mean	30	30	29
SD	6	7	6
Median	29	28	27
Min-Max	17-51	17-59	15-60
DAS28CRP			
N	202	201	201
Mean	4.9	4.7	4.9
SD	1.2	1.1	1.1
Median	4.8	4.7	4.8
Min-Max	1.5-8.1	1.8-7.9	2.3-7.5
Enthesitis, n (%)			
Yes	129 (64)	126 (62)	117 (58)
No	73 (36)	76 (38)	85 (42)
Dactylitis, n (%)			
Yes	104 (52)	104 (52)	116 (57)
No	98 (48)	98 (48)	86 (43)
MTX use, n (%)			
Yes	122 (60)	121 (60)	125 (62)
No	80 (40)	81 (40)	77 (38)
Tender joint total score for PsA 78 joints			
N	202	202	202
Mean	23	24	25
SD	17	16	18
Median	19	21	19
Min-Max	3-75	3-78	1-78
Swollen joint total score for PsA 76 joints			
N	202	202	202

Mean	13	13	15
SD	11	9	13
Median	9	10	10
Min-Max	3-68	3-56	2-66
Patients global assessment of disease (PsA) activity			
N	202	201	201
Mean	56	55	56
SD	23	24	22
Median	55	53	57
Min-Max	0-100	4-100	1-100
Physicians global assessment of disease (PsA) activity			
N	198	199	200
Mean	54	58	57
SD	18	19	19
Median	56	59	57
Min-Max	0-100	1-100	1-100
Psoriatic arthritis pain today			
N	202	200	201
Mean	55	56	57
SD	22	24	21
Median	57	58	59
Min-Max	0-100	4-100	3-100
Naive to TNF alpha inhibitors, n (%)			
Yes	142 (70)	143 (71)	143 (71)
No	60 (30)	59 (29)	59 (29)
Time since first diagnosis of psoriatic arthritis (years)			
N	200	201	201
Mean	8	8	7
SD	9	9	8
Median	5	5	4
Min-Max	0-49	0-46	0-48
HAQ-DI			
N	201	200	201
Mean	1.3	1.2	1.2
SD	0.7	0.7	0.6
Median	1.3	1.3	1.1
Min-Max	0.0-2.9	0.0-3.0	0.0-2.8
Number of prior anti-TNF PsA therapies, n (%)			
0	142 (70)	143 (71)	142 (70)
1	35 (17)	39 (19)	36 (18)
≥2	25 (13)	20 (10)	24 (12)
Patients with psoriasis ≥3% of BSA, n (%)			
Yes	108 (54)	108 (54)	109 (54)
No	94 (46)	94 (46)	93 (46)

Source: Excerpted from the Clinical Study Report for Study F2306 (pages 134- 141).

Results and Conclusions

Primary Efficacy Endpoint – ACR20 at Week 24

The analysis of the primary endpoint showed statistically significantly greater ACR20 responses at Week 24 for both secukinumab regimens compared to placebo. As pre-specified in the protocol, all dropouts prior to Week 24 were treated as non-responders.

There was some dropout prior to Week 24 (7% of active and 14% of placebo) on both arms, in addition to a substantial proportion of patients meeting escape criteria at Week 16 (25% of active and 66% of placebo), as dictated by the design, with disproportionately more meeting the escape criteria (and thus being considered non-responders in the primary analysis) on placebo. As a result, the treatment effect in the primary analysis was primarily driven by an effect on tender and swollen joint counts at Week 16 rather than on ACR20 response at Week 24. Therefore, I consider the observed data sensitivity analysis that includes outcomes collected after escape to be important, as this analysis attempts to evaluate the effect on ACR20 at Week 24 regardless of whether subjects met the escape criteria at Week 16, discontinued study treatment, or dropped out of the study.

The applicant's primary and sensitivity analyses appeared to support efficacy of both secukinumab regimens – statistically significant difference in ACR20 responses at Week 24 between each secukinumab regimen and placebo. The estimated effects using the observed post-escape data were smaller than in the other analyses, as might be expected due to the considerable number of placebo patients who crossed over to secukinumab at Week 16.

Table 4. Applicant's analyses of ACR20 response at Week 24

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Primary analysis with NRI	SCK 75mg (N=202)	102/202 (51)	vs. Placebo	5.5	(3.5, 8.9)	<0.0001
	SCK 150mg (N=202)	101/202 (50)	vs. Placebo	5.4	(3.4, 8.6)	<0.0001
	Placebo (N=202)	35/202 (17)				
Sensitivity analysis with multiple imputation	SCK 75mg (N=202)	(53)	vs. Placebo	5.2	(3.2, 8.3)	<0.0001
	SCK 150mg (N=202)	(53)	vs. Placebo	5.2	(3.3, 8.3)	<0.0001
	Placebo (N=202)	(20)				
Sensitivity analysis with observed data	SCK 75mg (N=202)	115/187 (62)	vs. Placebo	2.0	(1.3, 3.1)	0.0013
	SCK 150mg (N=202)	115/188 (61)	vs. Placebo	2.0	(1.3, 3.0)	0.0019
	Placebo (N=202)	81/174 (47)				

Source: Excerpted from the Clinical Study Report for Study F2306 (pages 17857- 17858).

I also conducted an analysis based on all observed data, including outcomes post-escape to secukinumab. My analysis considered patients who dropped out of the study to be non-responders and was generally consistent with the applicant's observed data analysis, and supported the conclusion of efficacy of the secukinumab 75 mg and 150 mg dosing regimens over placebo.

Table 5. Reviewer's analysis of ACR20 response at Week 24

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Sensitivity analysis with observed data for subjects who met	SCK 75mg (N=202)	115/202 (57)	vs. Placebo	2.2	(1.4, 3.3)	0.0002
	SCK 150mg (N=202)	115/202 (57)	vs. Placebo	2.2	(1.4, 3.2)	0.0002

In addition, in the response to FDA’s IR after the filing meeting, the applicant submitted the following tipping point analysis results for the primary endpoint:

Table 4-5 shows the distribution of ACR20 status by randomized treatment. The 15 missing from AIN457 10mg/kg - 75mg arm, 14 missing from AIN457 10mg/kg - 150mg, and 28 missing as well as 46 patients with ACR20 response who were randomized to placebo but already switched to AIN457 at Week 24, are the uncertain values (if they had remained on their randomized treatment). Please note under this worst-case (on missing value and rescued patients) scenario although placebo arm has an ACR20 response rate of 54%, only 35 with observed ACR20 response were still on placebo at Week 24 out of 202 patients randomized to placebo.

Table 4-5 Distribution of ACR20 status at Week 24 in CAIN457F2306

	Actual Data	Worst Case on missing value and early escaped patients for AIN457		
		Analyzed as	Response rate	P-value*
AIN457 10mg/kg - 75mg	72 observed non-response	72 non-response	56.9% (115/202)	0.548
	115 observed response	115 response		
	15 missing	15 non-response		
AIN457 10mg/kg - 150mg	73 observed non-response	73 non-response	56.9% (115/202)	0.548
	115 observed response	115 response		
	14 missing	14 non-response		
Placebo at randomization	23 observed non-response on placebo	23 non-response	54.0% (109/202)	--
	70 observed non-response on AIN457	70 non-response		
	35 observed response on placebo	35 response		
	46 observed response on AIN457	46 response		
	28 missing	28 response		

*P value is from Chi-square test.

For a comparison of an AIN457 regimen versus placebo, the following notations are made.
 J: Number of responders in uncertain cases from patients randomized to a secukinumab dose
 K: Number of responders in uncertain cases from patients randomized to placebo
 Between-treatment comparisons were performed using a chi-square test comparing each randomized AIN457 dose versus placebo, for each possible combinations of J and K. Table 4-6 shows the counts for the comparisons, where J takes value from 0 to 15 for AIN457 iv -75mg and from 0 to 14 for AIN457 iv - 150mg, and K from 0 to 74.

Table 4-6 Counts in tipping point analysis for F2306

	AIN457 10mg/kg - 75mg	AIN457 10mg/kg - 150mg	Placebo
Response	115 + J	115 + J	35 + K
Non-response	72 + (15-J)	73 + (14-J)	93 + (46 + 28 - K)

Figure 4-3 and Figure 4-4 show the p values that are ≥ 0.05 from these chi-square tests. For a given number, r, of responders out of the uncertain cases in the AIN457 treatment groups (15 for iv-75 mg and 14 for iv-150 mg), placebo-treated patients needed 61 more, i.e. r+61, responders out of the 74 uncertain cases to achieve a p-value ≥ 0.05 . The placebo response in the missing/rescue patients required for the comparison of IV-75 or IV-150 to lose statistical significance would have to exceed 61/74 (81%). That response rate would exceed by 20% the response rate of patients who remained on placebo (who were responding at week 16) which was

only 35/58 (60%). This high response rate in placebo patients not responding at week 16 (or who dropped out) is extremely implausible. Therefore, the results presented for ACR20 at week 24 for iv-150 and iv-75 are robust irrespective to the analysis approach for the rescue and missing data.

Figure 4-3 Tipping point analysis of ACR20 at Week 24 for iv-75

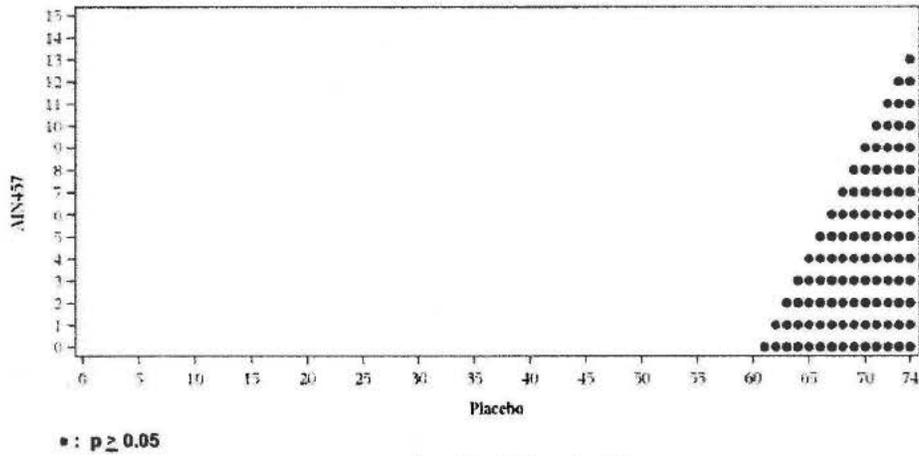
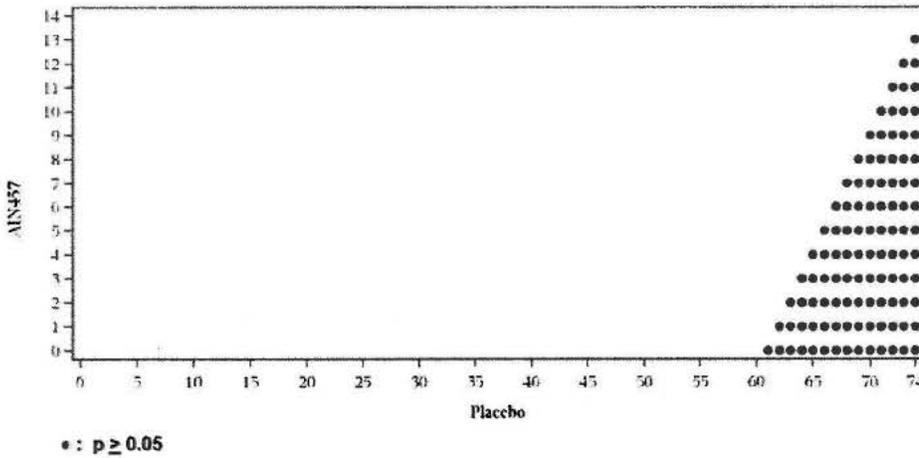


Figure 4-4 Tipping point analysis for ACR20 for iv-150



In my opinion, the applicant's interpretation of the tipping point analysis results appears reasonable and resolves our concern with the handling of placebo patients who crossed over to the secukinumab treatment at Week 16 due to non-response.

Components of ACR20 response at Week 24

I was able to confirm the results of the applicant's analyses of the components of the primary endpoint, ACR20 response at Week 24. Analyses of all the components of ACR were statistically significant in favor of both secukinumab doses and there was no single component driving the efficacy in terms of ACR20 response. A key limitation of these analyses at Week 24 is the small subset of placebo patients remaining at Week 24 (e.g., 59 out of 202 randomized patients for tender joint count), as the majority of placebo patients met escape criteria and crossed over to secukinumab at Week 16. The considerable escape destroys the integrity of randomization, although it is likely that the subset of patients remaining on placebo at Week 24 represents a healthy subset of the randomized population, thus leading to conservative inference in comparisons against the secukinumab arms. Because of the considerable proportion of patient either having crossed over from placebo to secukinumab or having missing data at Week 24, I carried out additional analyses of the ACR20 components and key continuous secondary endpoints at Week 16 (prior to escape). Results are relatively similar to those at Week 24 and are presented in the Appendix.

Table 6. Applicant's analysis of ACR20 components at Week 24

	Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
Adjusted TJC	SCK 75mg (N=202)	188	-13.2	vs. Placebo	-9.4 (1.6)	(-12.5, -6.3)	<0.0001
	SCK 150mg (N=202)	189	-14.1	vs. Placebo	-10.3 (1.6)	(-13.4, -7.2)	<0.0001
	Placebo (N=202)	59	-3.8				
Adjusted SJC	SCK 75mg (N=202)	188	-8.8	vs. Placebo	-3.6 (0.8)	(-5.3, -2.0)	<0.0001
	SCK 150mg (N=202)	189	-8.7	vs. Placebo	-3.5 (0.8)	(-5.2, -1.9)	<0.0001
	Placebo (N=202)	59	-5.1				
Patient's global assessment of disease activity	SCK 75mg (N=202)	188	-20.0	vs. Placebo	-12.6 (2.9)	(-18.3, -6.8)	<0.0001
	SCK 150mg (N=202)	189	-20.6	vs. Placebo	-13.1 (2.9)	(-18.9, -7.4)	<0.0001
	Placebo (N=202)	58	-7.4				
Physician's global assessment of disease activity	SCK 75mg (N=202)	188	-34.5	vs. Placebo	-21.6 (2.2)	(-25.8, -17.3)	<0.0001
	SCK 150mg (N=202)	188	-37.3	vs. Placebo	-24.4 (2.2)	(-28.6, -20.1)	<0.0001
	Placebo (N=202)	58	-12.9				
HAQ-DI	SCK 75mg (N=202)	187	-0.42	vs. Placebo	-0.25 (0.06)	(-0.36, -0.13)	<0.0001
	SCK 150mg (N=202)	189	-0.40	vs. Placebo	-0.23 (0.06)	(-0.35, -0.12)	<0.0001
	Placebo (N=202)	58	-0.17				
Patient's assessment of PsA pain	SCK 75mg (N=202)	188	-20.3	vs. Placebo	-13.7 (2.9)	(-19.4, -8.0)	<0.0001
	SCK 150mg (N=202)	189	-20.8	vs. Placebo	-14.1 (2.9)	(-19.8, -8.4)	<0.0001
	Placebo (N=202)	58	-6.7				
ESR (mm/hr)	SCK 75mg (N=202)	190	-10.6	vs. Placebo	-6.1 (2.0)	(-10.1, -2.1)	0.0029

	SCK 150mg (N=202)	190	-12.9	vs. Placebo	-8.5 (2.0)	(-12.5, -4.5)	<0.0001
	Placebo (N=202)	59	-4.5				
hsCRP* (mg/L)	SCK 75mg (N=202)	188	0.51	vs. Placebo	0.64	(0.51, 0.79)	<0.0001
	SCK 150mg (N=202)	190	0.52	vs. Placebo	0.64	(0.51, 0.79)	<0.0001
	Placebo (N=202)	59	0.81				

Source: Reviewer & the Clinical Study Report for Study F2306 (pages 1022, 1048, 1074, 1100, 1126, 1152, 1178).

*log(hsCRP) was used in the MMRM analysis and the LSmean difference were back-transformed (exponentiation) to the ratio between treatment groups.

In summary, the study showed statistically significant evidence in favor of the secukinumab 75 mg and 150 mg dosing regimens on the ACR20 response at Week 24 (primary efficacy endpoint). Several sensitivity analyses were conducted to assess the robustness of the primary analysis. The conclusions from these analyses were consistent in general.

Secondary Efficacy Endpoints

I was able to confirm the results of the applicant's analyses of the secondary endpoints. I also conducted sensitivity analyses to assess the impact of missing data due to early escape and dropout from the study. All p-values for the secondary endpoints presented here are nominal.

Key Secondary Endpoints – PASI75 & PASI90 at Week 24

The applicant's results of PASI75 and PASI90 analyses are summarized in Table 7. The same statistical method (logistic regression) used in the ACR20 analysis was employed for these endpoints. The analysis set for these endpoints was the subset of patients (a little more than half of all randomized patients) in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline.

Treatment with the secukinumab regimens resulted in statistically significantly higher PASI response rates than treatment with placebo.

Table 7. Applicant's analyses of PASI response at Week 24 (Psoriasis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
PASI75	SCK 75mg (N=108)	66/108 (61)	vs. Placebo	22.1	(9.9, 49.2)	<0.0001
	SCK 150mg (N=108)	70/108 (65)	vs. Placebo	19.7	(8.9, 44.0)	<0.0001
	Placebo (N=109)	9/109 (8)				
PASI90	SCK 75mg (N=108)	53/108 (49)	vs. Placebo	27.4	(9.3, 80.5)	<0.0001
	SCK 150mg (N=108)	49/108 (45)	vs. Placebo	24.6	(8.3, 72.3)	<0.0001
	Placebo (N=109)	4/109 (4)				

Source: Excerpted from the Clinical Study Report for Study F2306 (pages 499 & 515).

Key Secondary Endpoints - change from baseline in DAS28-CRP at Week 24

The mean reduction in DAS28-CRP at Week 24 in patients treated with the secukinumab regimens was statistically significantly greater compared to patients treated with placebo (Table 8). My sensitivity analysis with the same model but also incorporating observed post-escape data was consistent with results from the applicant's pre-specified analysis. However, the estimated effects were much different with the 2 approaches (Table 9). Also my cumulative distribution curves that included post-escape data and used worst score imputation for missing data showed separation of the curves between the secukinumab regimens and placebo (Figure 3).

Table 8. Applicant's analysis of change from baseline in DAS28-CRP at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	186	-1.67	vs. Placebo	-0.90 (0.15)	(-1.19, -0.61)	<0.0001
SCK 150mg (N=202)	188	-1.62	vs. Placebo	-0.85 (0.15)	(-1.14, -0.56)	<0.0001
Placebo (N=202)	58	-0.77				

Source: Excerpted from the Clinical Study Report for Study F2306 (page 531).

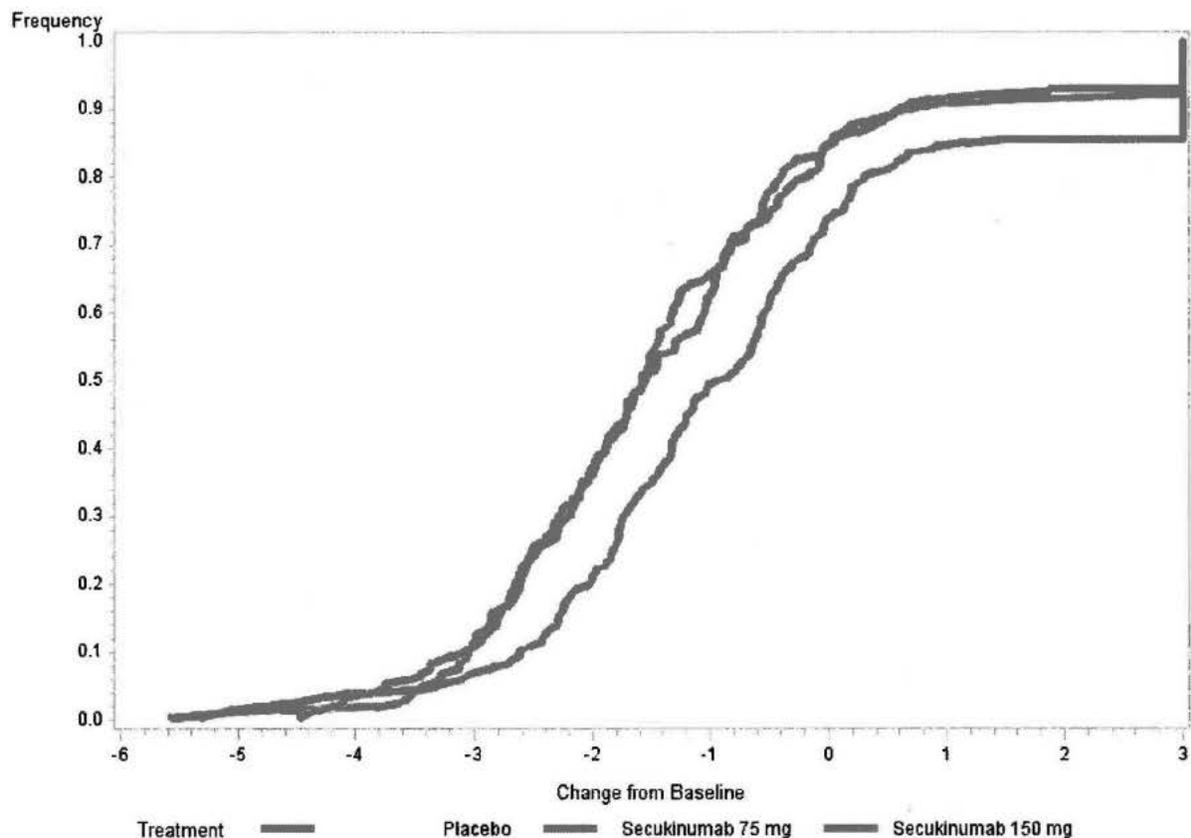
Table 9. Reviewer's observed post-escape data analysis of change from baseline in DAS28-CRP at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	186	-1.67	vs. Placebo	-0.53 (0.12)	(-0.76, -0.29)	<0.0001
SCK 150mg (N=202)	188	-1.62	vs. Placebo	-0.48 (0.12)	(-0.71, -0.24)	<0.0001
Placebo (N=202)	173	-1.14				

Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.

Source: Reviewer.

Figure 3. Cumulative distribution of change from baseline in DAS28-CRP at Week 24



Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints - change from baseline in SF36-PCS at Week 24

The mean change in SF36-PCS at Week 24 in patients treated with the secukinumab regimens was statistically significantly greater compared to patients treated with placebo (Table 10). My sensitivity analysis with the same model but also incorporating observed post-escape data was consistent with results from the applicant's pre-specified analysis. However, the estimated effects were much different with the 2 approaches (Table 11). Also my cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab regimens and placebo (Figure 4).

Table 10. Applicant's analysis of change from baseline in SF36-PCS at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	191	5.41	vs. Placebo	3.59 (0.87)	(1.87, 5.30)	<0.0001
SCK 150mg (N=202)	190	5.91	vs. Placebo	4.09 (0.87)	(2.38, 5.80)	<0.0001
Placebo (N=202)	63	1.82				

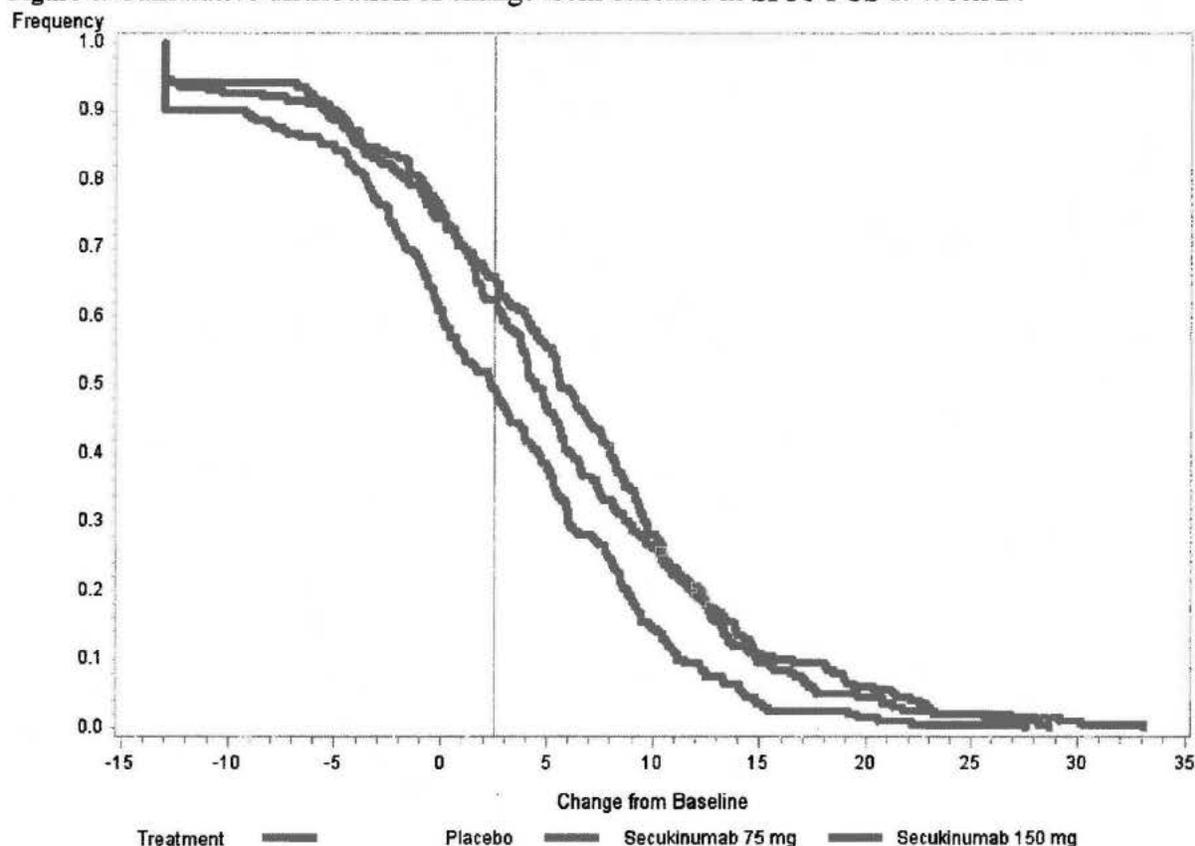
Source: Excerpted from the Clinical Study Report for Study F2306 (page 571).

Table 11. Reviewer’s observed post-escape data analysis of change from baseline in SF36-PCS at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	191	5.41	vs. Placebo	2.42 (0.71)	(1.03, 3.80)	0.0007
SCK 150mg (N=202)	190	5.91	vs. Placebo	2.92 (0.71)	(1.53, 4.31)	<0.0001
Placebo (N=202)	182	2.99				

Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.
Source: Reviewer.

Figure 4. Cumulative distribution of change from baseline in SF36-PCS at Week 24



Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints - change from baseline in HAQ-DI at Week 24

The mean change in HAQ-DI at Week 24 in patients treated with the secukinumab regimens was statistically significantly greater compared to patients treated with placebo (Table 12). My observed data sensitivity analysis was consistent with results from the applicant’s pre-specified analysis. However, the estimated effects were much different with the 2 approaches (Table 13). Also my cumulative distribution curves with worst score imputation for missing data

showed separation of the curves between the secukinumab regimens and placebo (Figure 5).

Table 12. Applicant's analysis of change from baseline in HAQ-DI at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	187	-0.41	vs. Placebo	-0.25 (0.06)	(-0.36, -0.13)	<0.0001
SCK 150mg (N=202)	189	-0.40	vs. Placebo	-0.23 (0.06)	(-0.35, -0.12)	<0.0001
Placebo (N=202)	58	-0.17				

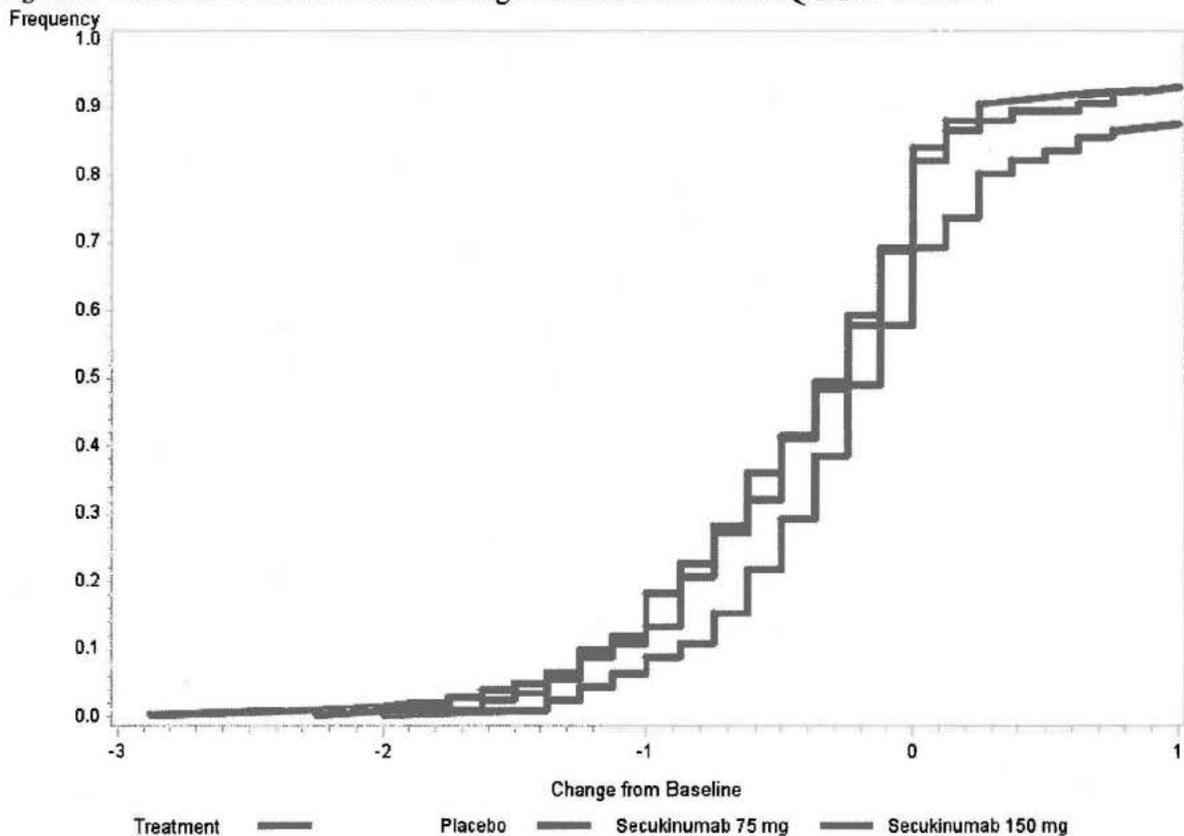
Source: Excerpted from the Clinical Study Report for Study F2306 (page 713).

Table 13. Reviewer's observed post-escape data analysis of change from baseline in HAQ-DI at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	187	-0.41	vs. Placebo	-0.15 (0.05)	(-0.25, -0.06)	0.0020
SCK 150mg (N=202)	189	-0.40	vs. Placebo	-0.14 (0.05)	(-0.24, -0.04)	0.0045
Placebo (N=202)	177	-0.26				

Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.
Source: Reviewer.

Figure 5. Cumulative distribution of change from baseline in HAQ-DI at Week 24



Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints - change from baseline in mTSS at Week 24

The mean change in mTSS at Week 24 in patients treated with secukinumab regimens was statistically significantly less compared to patients treated with placebo (Table 14). My sensitivity analysis with the same model, using the last available observed (LAO) changes for placebo patients who crossed over to secukinumab at Week 16, was consistent with results from the applicant's pre-specified analysis with linearly extrapolated (LE) data for placebo escapers or for other missing data (Table 15). My other sensitivity analysis with a parametric ANCOVA analysis was also consistent with results from the applicant's pre-specified analysis (Table 16). However, my analysis with the same model excluding outliers defined as absolute changes greater than 7 units which were considered extreme by the FDA clinical team showed a statistically significant difference between the secukinumab 75 mg group and placebo group, but did not show a statistically significant difference between the secukinumab 150 mg group and placebo group (Table 17). The cumulative distribution curves with worst score imputation for missing data only showed some separation of the curves between secukinumab regimens and placebo, but approximately 50 percent of patients showed no change (Figure 6). Analyses targeting the intention-to-treat estimand including Week 24 data in all randomized patients (including placebo patients who escaped) were not possible for this endpoint because only Week 16 x-rays were taken in patients who were non-responders with respect to tender and swollen joint counts at Week 16.

Table 14. Applicant's analysis of change from baseline in mTSS at Week 24

Treatment Group	n	Mean Change	Comparison	Mean Difference (SE)	p-value
SCK 75mg (N=202)	181	0.02	vs. Placebo	-0.54 (0.22)	0.0132
SCK 150mg (N=202)	185	0.13	vs. Placebo	-0.47 (0.20)	0.0212
Placebo (N=202)	179	0.57			

Source: Excerpted from the Clinical Study Report for Study F2306 (page 822).

Table 15. Reviewer's ANCOVA analysis of change from baseline in mTSS at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	181	0.02	vs. Placebo	-0.56 (0.19)	(-0.94, -0.18)	0.0038
SCK 150mg (N=202)	185	0.12	vs. Placebo	-0.46 (0.19)	(-0.83, -0.08)	0.0175
Placebo (N=202)	179	0.58				

Note: ANCOVA model includes terms for treatment, TNF α status as factors and weight and baseline score as covariates.
Source: Reviewer.

Table 16. Reviewer's sensitivity ANCOVA analysis of LAO change from baseline in mTSS at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	182	-0.03	vs. Placebo	-0.51 (0.16)	(-0.82, -0.20)	0.0011

SCK 150mg (N=202)	186	0.10	vs. Placebo	-0.39 (0.15)	(-0.69, -0.08)	0.0127
Placebo (N=202)	179	0.48				

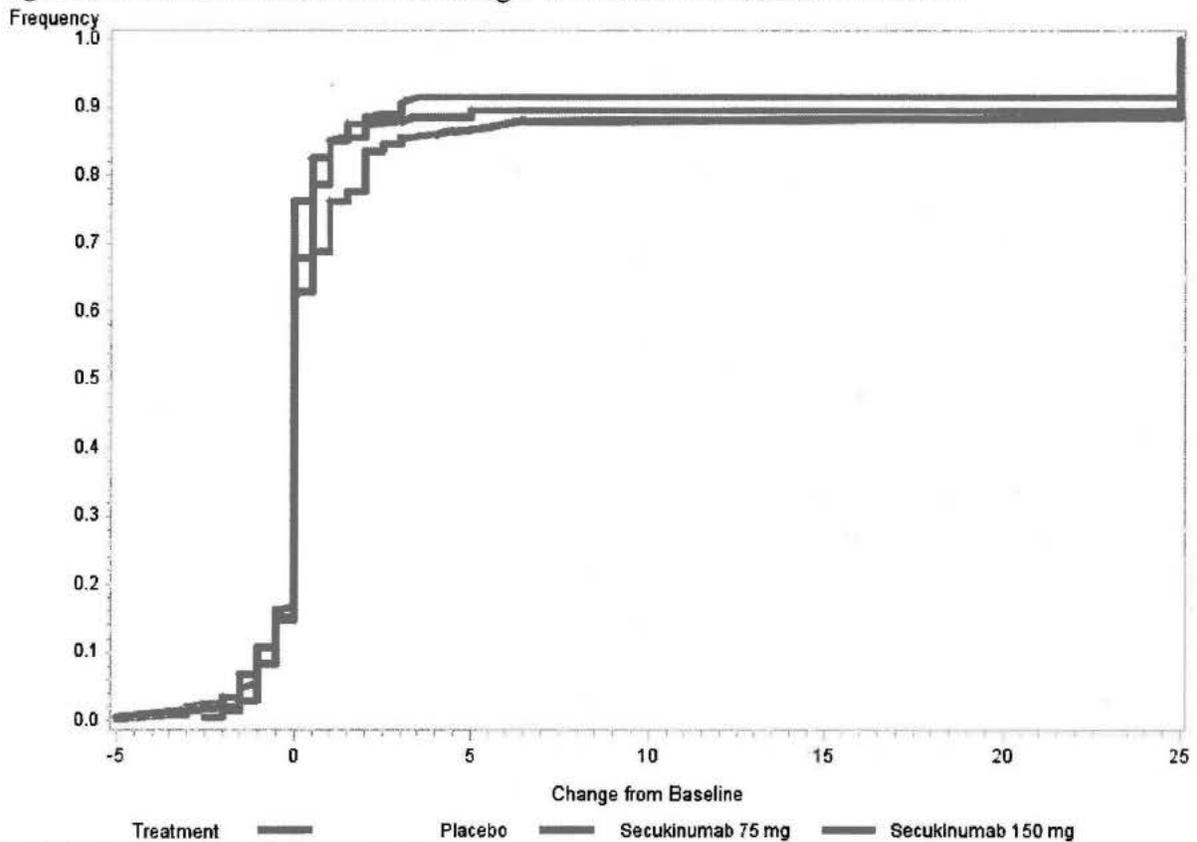
Note: Last available observations (LAO) for placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.
Source: Reviewer.

Table 17. Reviewer’s ANCOVA analysis of change from baseline in mTSS at Week 24 excluding outlying subjects ($|\Delta|$ greater than 7 units)

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=202)	179	-0.08	vs. Placebo	-0.46 (0.13)	(-0.72, -0.20)	0.0004
SCK 150mg (N=202)	185	0.16	vs. Placebo	-0.22 (0.13)	(-0.48, 0.03)	0.0850
Placebo (N=202)	176	0.38				

Note: ANCOVA model includes terms for treatment, TNF α status as factors and weight and baseline score as covariates. There were 2 patients in secukinumab 75mg group and 3 patients in placebo group with absolute changes greater than 7 units.
Source: Reviewer.

Figure 6. Cumulative distribution of change from baseline in mTSS at Week 24



Note: Missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints – Presence of Dactylitis at Week 24

Based on the applicant's analysis and my sensitivity analyses, the study data appeared to support efficacy of the secukinumab regimens – there were statistically significant differences in the presence of dactylitis at Week 24 between each secukinumab regimen and placebo, in the subset of patients with dactylitis at baseline.

Table 18. Applicant's analyses of dactylitis presence at Week 24 (Dactylitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Analysis with NRI	SCK 75mg (N=104)	45/104 (43)	vs. Placebo	0.12	(0.07, 0.24)	<0.0001
	SCK 150mg (N=104)	54/104 (52)	vs. Placebo	0.17	(0.09, 0.33)	<0.0001
	SCK pooled (N=208)	99/208 (48)	vs. Placebo	0.15	(0.08, 0.27)	<0.0001
	Placebo (N=116)	98/116 (85)				

Source: Excerpted from the Clinical Study Report for Study F2306 (pages 913).

Table 19. Reviewer's analysis of dactylitis presence at Week 24 (Dactylitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Sensitivity analysis with retrieved dropout	SCK 75mg (N=104)	34/104 (33)	vs. Placebo	0.34	(0.19, 0.61)	0.0003
	SCK 150mg (N=104)	44/104 (42)	vs. Placebo	0.48	(0.27, 0.85)	0.0119
	SCK pooled (N=208)	78/208 (49)	vs. Placebo	0.40	(0.25, 0.66)	0.0003
	Placebo (N=116)	67/116 (58)				

Source: Reviewer

Key Secondary Endpoints – Presence of Enthesitis at Week 24

Based on the applicant's analysis and my sensitivity analyses, the study data appeared to support efficacy of the secukinumab regimens – there were statistically significant differences in the presence of enthesitis at Week 24 between each secukinumab regimen and placebo, in the subset of patients with enthesitis at baseline.

Table 20. Applicant's analyses of enthesitis presence at Week 24 (Enthesitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Analysis with NRI	SCK 75mg (N=129)	66/129 (51)	vs. Placebo	0.13	(0.07, 0.26)	<0.0001
	SCK 150mg (N=126)	68/126 (54)	vs. Placebo	0.15	(0.08, 0.30)	<0.0001
	SCK pooled (N=255)	134/255 (53)	vs. Placebo	0.14	(0.08, 0.26)	<0.0001
	Placebo (N=117)	102/117 (87)				

Source: Excerpted from the Clinical Study Report for Study F2306 (pages 929).

Table 21. Reviewer's analysis of enthesitis presence at Week 24 (Enthesitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Sensitivity analysis with retrieved dropout	SCK 75mg (N=129)	59/129 (46)	vs. Placebo	0.48	(0.28, 0.85)	0.0110
	SCK 150mg (N=126)	54/126 (43)	vs. Placebo	0.45	(0.26, 0.80)	0.0059

SCK pooled (N=255) Placebo (N=117)	113/255 (44) 70/117 (60)	vs. Placebo	0.47	(0.29, 0.77)	0.0025
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Source: Reviewer

Long-term efficacy analysis – observed ACR20 response over 52 weeks

I conducted a descriptive analysis to numerically compare the secukinumab 75 mg and 150 mg dosing regimens with regard to ACR20 over 52 weeks without statistical hypothesis testing. The analysis was based on observed data instead of non-responder imputed data for subjects who met the Week 16 escape criteria. Observed ACR20 responses on the two dosing regimens were similar, with response rates of 60-70%, after Week 24.

Table 22. Reviewer’s analysis of observed ACR20 response over 52 weeks

Week	SCK 75 mg	SCK 150 mg
	n/N (%)	n/N (%)
1	41/190 (22)	42/192 (22)
2	67/191 (35)	61/193 (32)
4	87/194 (45)	88/197 (45)
8	100/190 (53)	102/192 (53)
12	104/188 (55)	113/190 (59)
16	106/189 (56)	115/191 (60)
20	121/189 (64)	112/185 (61)
24	115/187 (62)	115/188 (61)
28	121/179 (68)	121/188 (64)
32	119/183 (65)	125/183 (68)
36	115/175 (66)	131/181 (72)
40	114/174 (66)	125/181 (69)
44	112/165 (68)	125/178 (70)
48	109/169 (65)	128/179 (72)
52	115/172 (67)	121/174 (70)

Source: Reviewer

In summary, study data demonstrated that both doses of secukinumab, 75 mg and 150 mg, were superior compared to placebo with respect to the primary endpoint of ACR20 at Week 24 and all the secondary endpoints at Week 24 in the multiplicity adjustment hierarchy – PASI75, PASI90, DAS28-CRP, SF-36 PCS, HAQ-DI, ACR50, mTSS, dactylitis, and enthesitis. Analyses of all the

endpoints remained statistically significant in sensitivity analyses using different approaches to handle missing data due to early escape or dropout.

3.2.2 Study F2312

The objective of the study was to evaluate the efficacy and safety of secukinumab 75 mg, 150 mg, and 300 mg compared with placebo in patients with PsA. Patients were to receive randomized study treatment in a double blind manner for 52 weeks.

Study Design and Endpoints

The study used a double-blind, randomized, parallel-group, placebo-controlled design. A screening period running up to 10 weeks before randomization was used to assess eligibility followed by a treatment period of two years (Figure 7). At baseline (BSL), subjects whose eligibility was confirmed were randomized to one of four treatment groups:

- Group 1: Secukinumab 75 mg (0.5 mL) plus placebo (2 x 1.0 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4
- Group 2: Secukinumab 150 mg (1.0 mL) plus placebo (0.5 mL and 1.0 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4
- Group 3: Secukinumab 300 mg (2 x 1.0 mL) plus placebo (0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4
- Group 4: Placebo (2 x 1.0 mL and 1 x 0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4

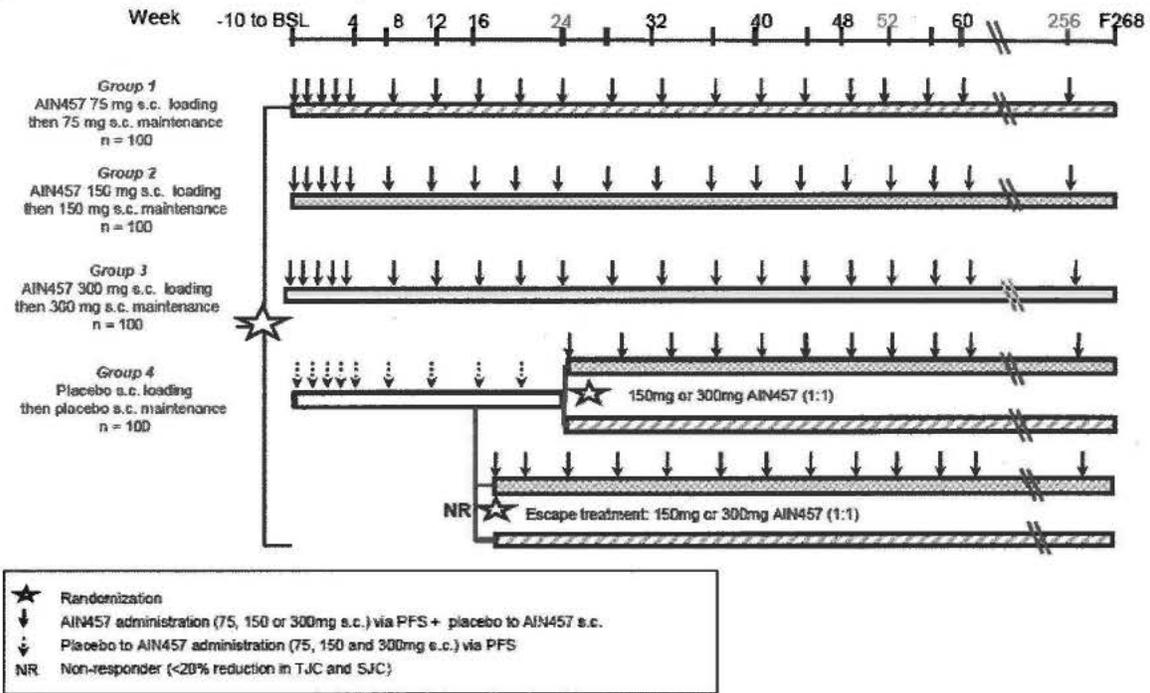
At randomization, patients were stratified as TNF α inhibitor naïve or TNF α inhibitor inadequate responders. Approximately 40% of the randomized patients were planned to be TNF α -IR in order to evaluate the efficacy and safety in this patient population. Therefore, it was planned to randomize approximately 240 TNF α inhibitor naïve patients and 160 TNF α -IR patients.

At Week 16, all subjects were classified as responders ($\geq 20\%$ improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to Groups 1, 2, and 3 continued to receive study treatment as described above regardless of responder status. Subjects who were randomized to placebo at baseline were re-randomized by the Interactive Response Technology to receive double blind treatment up to 52 weeks, as follows:

- Subjects on secukinumab placebo (Group 4) who were responders remained on placebo until Week 24. At Week 24, these subjects received either secukinumab 150 or 300 mg sc every 4 weeks (as dictated by the re-randomization).
- Subjects on secukinumab placebo (Group 4) who were non-responders were re-randomized (1:1) at Week 16 to receive either secukinumab 150 mg or 300 mg sc every 4 weeks.

Rescue medication was not allowed until Week 24. However, subjects deemed not to be benefiting from the study treatment by the investigator or for any reason on their own accord were free to discontinue participation in the study at any time.

Figure 7. Study Schema for Study F2312



Source: Excerpted from the Clinical Study Report for Study F2312 (page 54).

The population enrolled in the study consisted of adults with active PsA. In addition, patients with cardiovascular morbidities and patients who had previously failed other biologic therapies were included. This population consisted of a group of RF and anti-CCP negative patients at least 18 years of age, fulfilling the CASPAR criteria with active PsA. Active PsA is defined as the presence of at least 3 out of 78 tender joints and at least 3 out of 76 swollen joints at baseline despite current or previous NSAIDs, DMARDs and/or TNF α inhibitor therapy. CASPAR criteria consisted of establishing inflammatory articular disease with at least 3 points from the following features: current psoriasis, a history of psoriasis (unless current psoriasis was present), a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis), dactylitis, juxta-articular new bone formation, RF negativity and nail dystrophy. Current psoriasis, history of psoriasis and family history of psoriasis were each assigned a score of 2 while all other features were assigned a score of 1.

The primary efficacy endpoint was the ACR20 response at Week 24. The secondary efficacy variables were PASI75, PASI90, DAS28-CRP, SF-36 PCS, HAQ-DI, ACR50, dactylitis and enthesitis at Week 24.

Statistical Methodologies

The statistical methods including analysis set, models, handling data for subjects who met

rescue criteria at Week 16 and missing data due to dropout were same as in the Study F2306.

After the filing meeting, we sent an information request for additional sensitivity analyses including tipping point analyses for the primary endpoint, and the applicant submitted sensitivity analyses as per the IR.

The primary and secondary efficacy endpoints were tested for each secukinumab dose versus placebo in a testing strategy designed to protect the family-wise type 1 error rate at $\alpha=5\%$ (two-sided). The applicant proposed a hierarchical testing procedure with a graphical approach to adjust for the multiple doses and endpoints (Figure 8). Comparisons to placebo in the testing hierarchy for dactylitis and enthesitis were based on pooled data across the secukinumab doses. The following primary and secondary hypotheses were included in the sequential testing strategy:

Primary objective:

H1: secukinumab 75 mg sc is not different to placebo regimen with respect to ACR20 response at week 24

H2: secukinumab 150 mg sc is not different to placebo regimen with respect to ACR20 response at week 24

H3: secukinumab 300 mg sc is not different to placebo regimen with respect to ACR20 response at week 24

Secondary objectives:

H4: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24

H5: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI75 response at Week 24

H6: secukinumab 300 mg sc is not different to placebo regimen with respect to PASI75 response at week 24

H7: secukinumab 75 mg sc is not different to placebo regimen with respect to PASI90 response at week 24

H8: secukinumab 150 mg sc is not different to placebo regimen with respect to PASI90 response at week 24

H9: secukinumab 300 mg sc is not different to placebo regimen with respect to PASI90 response at week 24

H10: secukinumab 75 mg sc is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at week 24

H11: secukinumab 150 mg sc is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at week 24

H12: secukinumab 300 mg sc is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at week 24

H13: secukinumab 75 mg sc is not different to placebo regimen with respect to the change from baseline in SF36-PCS at week 24

H14: secukinumab 150 mg sc is not different to placebo regimen with respect to the change

from baseline in SF36-PCS at week 24

H15: secukinumab 300 mg sc is not different to placebo regimen with respect to the change from baseline in SF36-PCS at week 24

H16: secukinumab 75 mg sc is not different to placebo regimen with respect to the change from baseline in HAQ-DI at week 24

H17: secukinumab 150 mg sc is not different to placebo regimen with respect to the change from baseline in HAQ-DI at week 24

H18: secukinumab 300 mg sc is not different to placebo regimen with respect to the change from baseline in HAQ-DI at week 24

H19: secukinumab 75 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24

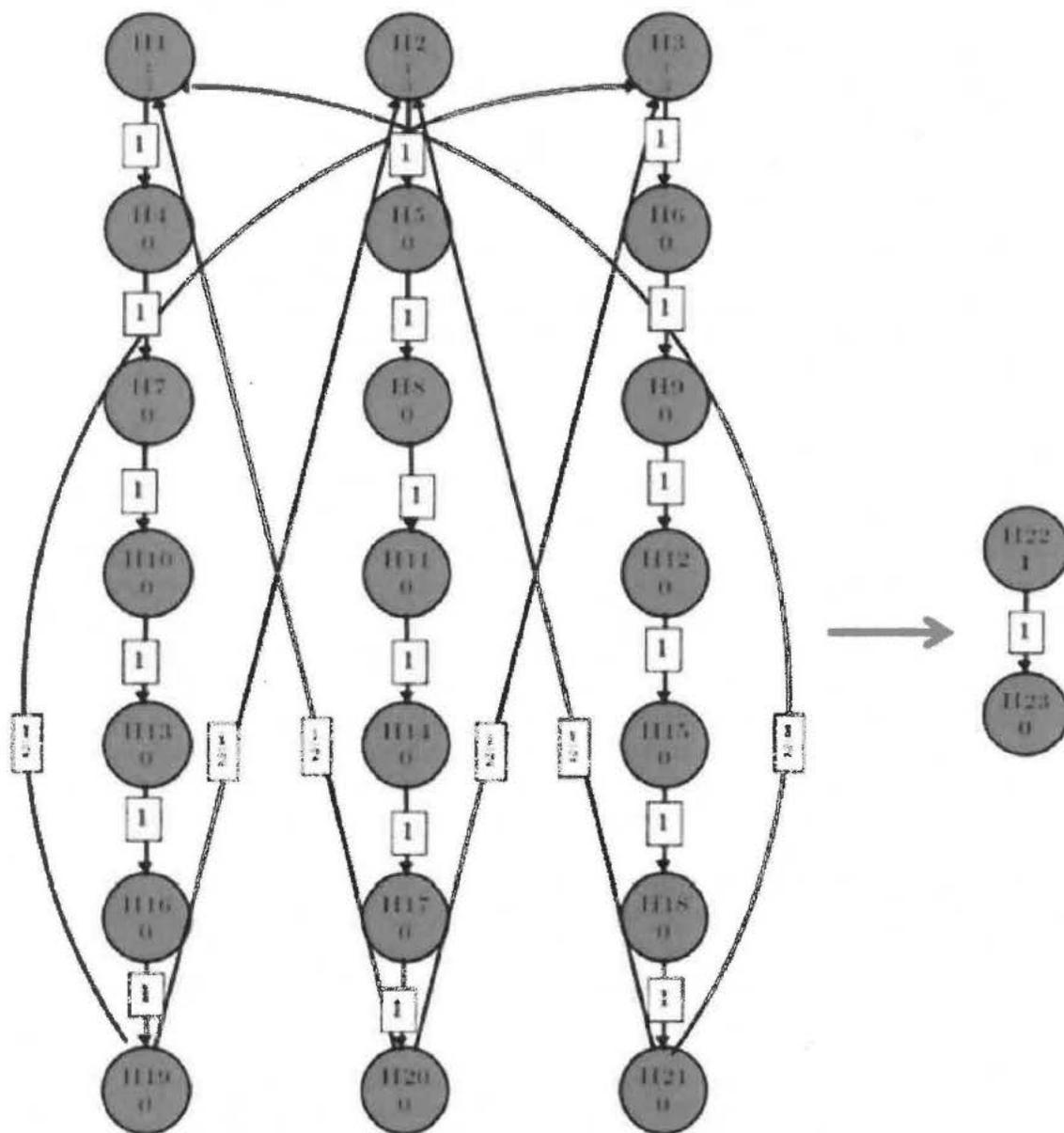
H20: secukinumab 150 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24

H21: secukinumab 300 mg sc is not different to placebo regimen with respect to ACR50 response at Week 24

H22: secukinumab pooled regimen (75 mg and 150 mg and 300 mg sc) is not different to placebo regimen with respect to proportion of patients with dactylitis at Week 24 in the subset of patients with dactylitis at baseline

H23: secukinumab pooled regimen (75 mg and 150 mg and 300 mg sc) is not different to placebo regimen with respect to proportion of patients with enthesitis at Week 24 in the subset of patients with enthesitis at baseline

Figure 8. Multiple testing strategy



Source: Excerpted from the Clinical Study Report for Study F2312 (page 94).

Following are excerpts from the study report explaining the graphical approach to sequentially rejective testing procedure:

The family-wise error was set to $\alpha=5\%$ and was controlled with the proposed hierarchical testing strategy. With this hierarchical testing approach, the hypotheses were separated into two families, hypotheses H1 ~ H21 were the first family and hypotheses H22 and H23 were the second family. The second family hypotheses were tested only when all hypotheses in the first family had been rejected. Each of the hypotheses (H1, H2, and H3) for the primary objective (based on ACR20 response at

Week 24) for each secukinumab regimen versus placebo were tested simultaneously at $\alpha/3$. If at least one of H1 and/or H2 and/or H3 were/was rejected, then H4 and/or H5 and/or H6, respectively, was tested. If at least one of H4 and/or H5 and/or H6 was rejected, the hypothesis H7 and/or H8 and/or H9, was tested, respectively. Similar process applied until H19 to H21. Once all hypotheses within the first family for a secukinumab regimen were rejected, then the respective $\alpha/3$ could be passed on to the other regimen's hypotheses within the family, if they were not already rejected at $\alpha/3$. Only when all H1 ~ H21 were rejected, the objective on the proportion of patients with dactylitis at Week 24 for testing pooled secukinumab doses versus placebo (H22) was tested at α . If H22 was rejected, then H23 was tested at α . Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis was only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect was in favor of secukinumab.

Sample Size Calculation

Three secukinumab doses were tested versus placebo with respect to the primary endpoint (ACR20 response at Week 24), so the overall two-sided type-I-error rate of 5% was split to 1.7% two-sided for each comparison for the sample size calculations. A placebo response rate of about 25% after 24 weeks was assumed based on the results for the TNF α inhibitor naive population, and 15% was assumed based on the results for the TNF α inhibitor IR population in historical studies. Based on the weighted average, the overall placebo rate was expected to be 21%. The response on secukinumab was assumed to be 55% in the TNF α inhibitor naïve population and 35% in the TNF α inhibitor IR-population. Based on the weighted average, the overall rate on a dose of secukinumab was expected to be 47%. For the primary endpoint, ACR20 in the overall population, 100 subjects per group would yield approximately 92% power to detect a treatment difference of 26% with the above assumptions using a Fisher's exact test.

Changes in the statistical analysis plan

There were two amendments to the original protocol (October 15, 2012): Amendment 1 (February 25, 2014), and Amendment 2 (July 4, 2014). The applicant claimed that these amendments were made prior to unblinding and analyses of the efficacy data. The changes included the following:

- To expand the statistical hierarchy (primary plus ranked secondary variables) to include endpoints which are relevant to determining the overall therapeutic value of a therapy for PsA. These endpoints include but are not limited to PASI75, PASI90, DAS28-CRP, HAQDI, SF-36, dactylitis and enthesitis. Psoriatic arthritis (PsA) is a multifaceted chronic disabling disease that can present as different clinical phenotypes: peripheral arthritis, axial disease, skin and nail disease, dactylitis, and enthesitis, and hence defining outcome measures has been a challenge. Traditionally endpoints for PsA studies focused only on peripheral arthritis endpoints relevant for rheumatoid arthritis. However recently there has been additional interest by Health Authorities and the scientific community in endpoints specific/more relevant for such patients (PRO e.g. SF36) and overall extra, skin related endpoints (PASI 75/90), dactylitis and enthesitis, hence these have been added in the proposed amendment hierarchy. Recent labels for Ustekinumab (Stelara), working on the same pathway as secukinumab, approved in Nov 2013 mentions skin related endpoints (PASI 90), dactylitis and enthesitis. Prior to finalizing original protocol for

CAIN457F2312 there were no new approved therapies with this in the label. Thus the endpoints at that time were based on then existing knowledge. Thus it is critical that we align our analyses and endpoints with new precedence and hence the emerging demands of the field. The additional hierarchical considerations do not add any new assessments for patients; all this data is being collected already, we are only now reorganizing the hierarchy of secondary endpoints in line with new knowledge.

- In addition, the analysis is changed to include all subjects in Full Analysis Set (FAS) which includes TNF α inhibitor naïve as well as TNF α inhibitor inadequate responders (TNF-IR) rather than focusing only on the subset of subjects who are TNF α inhibitor naïve, as the FAS would be more representative of the general population of PsA patients. There were no new therapies approved when original protocol for CAIN457F2312 was written and thus TNF α inhibitor naïve patients were target population in line with the then existing labels/indications. The shift from TNF α inhibitor naïve to FAS, to increase the generalizability of the study findings is also in keeping with the recently approved Ustekinumab label that has also been studied in mixed population of both TNF α inhibitor naïve as well as TNF-IR patients.

Patient Disposition, Demographic and Baseline Characteristics

A total of 397 patients were randomized, and 373 (94%) patients completed the 24 weeks of active treatment (Table 23). More patients in the placebo group (10%) discontinued treatment compared with all of the secukinumab treatment groups (3%-6%). The most common reason for discontinuation was adverse event, which occurred at a higher rate in the placebo group compared with the secukinumab groups. Lack of efficacy was the second most common reason for discontinuing treatment.

Of the 98 patients in the placebo group, 88 patients were re-randomized (1:1). Of the placebo patients who were re-randomized, 55 non-responding patients received secukinumab starting at Week 16 (150 mg: 27 patients and 300 mg: 28 patients) every 4 weeks, and 33 patients continued on placebo until Week 24 and then received either secukinumab 150 mg (16 patients) or 300 mg (17 patients) sc every 4 weeks. Overall, 88 patients in the placebo group completed Week 24.

Table 23. Patients' Accountability, N (%) (All Randomized Patients)

Disposition/Reason	SCK 75 mg n (%)	SCK 150 mg n (%)	SCK 300 mg n (%)	Placebo n (%)	Placebo Non-responder SCK 150 mg n (%)	Placebo Non-responder SCK 300 mg n (%)	Placebo Responder SCK 150 mg n (%)	Placebo Responder SCK 300 mg n (%)
Randomized	99 (100)	100 (100)	100 (100)	98 (100)				
Completed Wk16	93 (94)	100 (100)	95 (95)	88 (90)	27 (100)	28 (100)	16 (100)	17 (100)
Non-responder at Wk16	48 (48)	33 (33)	25 (25)	55 (55)				
Re-randomized at Wk16					27 (100)	28 (100)		
Completed Wk24	93 (94)	95 (95)	97 (97)	88 (89)	57 (92)	59 (97)	16 (100)	17 (100)

Discontinued Wk24	6 (6)	5 (5)	3 (3)	10 (10)
Adverse event	3 (3)	0 (0)	2(2)	4 (4)
Lack of efficacy	2 (2)	3 (3)	0 (0)	3 (3)
Other	1 (1)	2 (2)	1 (1)	3 (3)

Note: SCK stands for secukinumab.

Source: Reviewer & the Clinical Study Report for Study F2312 (page 106).

The demographic and baseline disease characteristics were generally well balanced and comparable between the treatment groups (Table 24). Overall, the average patient in the study was 48 years old, 80 kg in weight, and had 7 years of duration of PsA. The majority of patients were Caucasian and approximately 52% of patients were female. About 65% of patients were naïve to TNF alpha inhibitors and about 47% of patients used methotrexate at baseline.

Table 24. Patients' Demographic and Baseline Characteristics by Treatment

	SCK 75 mg N=99	SCK 150 mg N=100	SCK 300 mg N=100	Placebo N=98
Age (years)				
N	99	100	100	98
Mean	49	47	47	50
SD	11	12	13	13
Median	51	47	47	51
Min-Max	21-71	20-67	23-77	20-77
Gender, n (%)				
Female	52 (53)	45 (45)	49 (49)	59 (60)
Male	48 (47)	55 (55)	51 (51)	39 (40)
Race, n (%)				
White	90 (90)	90 (90)	96 (96)	94 (95)
Black	0 (0)	0 (0)	1 (1)	0 (0)
Asian	5 (5)	6 (6)	2 (2)	1 (1)
Other	5 (5)	4 (4)	1 (1)	3 (4)
Weight (kg)				
N	99	100	100	98
Mean	86	91	85	86
SD	21	20	18	20
Median	87	91	83	86
Min-Max	48-132	48-147	52-161	54-147
BMI (kg/m**2)				
N	99	100	100	98
Mean	30	31	29	30
SD	7	6	6	6
Median	30	30	28	29
Min-Max	19-59	20-48	19-48	20-50
DAS28CRP				
N	98	100	99	98
Mean	4.7	4.9	4.8	4.79
SD	1.0	1.1	1.0	1.0
Median	4.6	4.9	4.7	4.5
Min-Max	1.8-6.9	2.1-7.5	2.0-6.8	2.5-7.1
Enthesitis, n (%)				
Yes	68 (69)	64 (64)	56 (56)	65 (66)
No	30 (31)	36 (36)	44 (44)	33 (34)

Dactylitis, n (%)				
Yes	33 (34)	32 (32)	46 (46)	27 (28)
No	65 (66)	68 (68)	54 (54)	71 (72)
MTX use, n (%)				
Yes	47 (48)	44 (44)	44 (44)	50 (51)
No	52 (52)	56 (56)	56 (56)	48 (49)
Tender joint total score for PsA 78 joints				
N	99	100	100	98
Mean	22	24	20	23
SD	16	19	13	19
Median	18	18	17	17
Min-Max	4-78	3-78	3-78	3-77
Swollen joint total score for PsA 76 joints				
N	99	100	100	98
Mean	11	12	11	12
SD	9	10	8	11
Median	8	8	9	9
Min-Max	3-68	3-50	0-57	0-67
Patients global assessment of disease (PsA) activity				
N	98	100	99	98
Mean	59	62	61	58
SD	19	20	19	20
Median	61	66	64	59
Min-Max	3-94	7-98	6-96	4-98
Physicians global assessment of disease (PsA) activity				
N	98	100	99	98
Mean	59	57	55	55
SD	18	17	15	16
Median	60	59	55	58
Min-Max	6-94	20-92	18-93	11-85
Psoriatic arthritis pain today				
N	98	100	99	98
Mean	57	59	57	55
SD	21	20	19	22
Median	60	61	58	57
Min-Max	0-99	5-97	3-97	4-99
Naive to TNF alpha inhibitors, n (%)				
Yes	65 (66)	63 (63)	67 (67)	63 (64)
No	34 (34)	37 (37)	33 (33)	35 (36)
Psoriasis of hands and feet, n (%)				
Yes	43 (43)	62 (62)	39 (39)	40 (41)
No	56 (57)	38 (38)	61 (61)	58 (59)
Psoriasis of the nail, n (%)				
Yes				
No	76 (77)	75 (75)	63 (63)	65 (66)
	23 (23)	25 (25)	37 (37)	33 (34)
Time since first diagnosis of psoriatic arthritis (years)				
N	99	100	100	98
Mean	6	7	7	7
SD	7	8	7	8
Median	4	4	5	5
Min-Max	0-39	0-62	0-33	0-40
HAQ-DI				
N	98	100	99	98
Mean	1.2	1.2	1.3	1.2

SD	0.6	0.6	0.6	0.7
Median	1.3	1.3	1.3	1.3
Min-Max	0.0-2.8	0.0-2.4	0.0-2.5	0.0-2.8
Number of prior anti-TNF PsA therapies, n (%)				
0	65 (66)	63 (63)	67 (67)	63 (64)
1	21 (21)	26 (26)	16 (16)	16 (16)
≥2	13 (13)	11 (11)	17 (17)	19 (20)
Patients with psoriasis ≥3% of BSA, n (%)				
Yes	50 (51)	58 (58)	41 (41)	43 (44)
No	49 (49)	42 (42)	59 (59)	55 (56)

Source: Excerpted from the Clinical Study Report for Study F2312 (pages 231- 249).

Results and Conclusions

Primary Efficacy Endpoint – ACR20 at Week-24

The analysis of the primary endpoint showed statistically significantly greater ACR20 responses at Week 24 for all secukinumab regimens compared to placebo. As pre-specified in the protocol, all dropouts prior to Week 24 were treated as non-responders.

There was some dropout prior to Week 24 (3%-6% of active and 10% of placebo) on all arms, in addition to a substantial proportion of patients meeting escape criteria at Week 16 (25%-48% of active and 55% of placebo), as dictated by the design, with disproportionately more meeting the escape criteria (and thus being considered non-responders in the primary analysis) on placebo. As a result, the treatment effect in the primary analysis was primarily driven by an effect on tender and swollen joint counts at Week 16 rather than on ACR20 response at Week 24. Therefore, I consider the observed data sensitivity analysis that includes outcomes collected after escape to be important, as this analysis attempts to evaluate the effect on ACR20 at Week 24 regardless of whether subjects met the escape criteria at Week 16, discontinued study treatment, or dropped out of the study.

The applicant's primary and sensitivity analyses appeared to support efficacy of the secukinumab 150 mg and 300 mg dosing regimens – statistically significant difference in ACR20 responses at Week 24 between each secukinumab regimen and placebo. However, the statistical significance for the secukinumab 75 mg dosing regimen from the primary analysis was not supported by the sensitivity analyses, especially the analysis incorporating the observed post-escape data. The estimated effects using the observed post-escape data were smaller than in the other analyses, as might be expected due to the considerable number of placebo patients who crossed over to secukinumab at Week 16.

Table 25. Applicant's analyses of ACR20 response at Week 24

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Primary analysis with NRI	SCK 75mg (N=99)	29/99 (29)	vs. Placebo	2.3	(1.1, 4.7)	0.0200
	SCK 150mg (N=100)	51/100 (51)	vs. Placebo	6.5	(3.3, 13.1)	<0.0001

	SCK 300mg (N=100)	54/100 (54)	vs. Placebo	6.8	(3.4, 13.6)	<0.0001
	Placebo (N=98)	15/98 (15)				
Sensitivity analysis with multiple imputation	SCK 75mg (N=99)	(31)	vs. Placebo	2.2	(1.1, 4.5)	0.0300
	SCK 150mg (N=100)	(53)	vs. Placebo	6.1	(3.1, 12.3)	<0.0001
	SCK 300mg (N=100)	(57)	vs. Placebo	6.6	(3.3, 13.2)	<0.0001
	Placebo (N=98)	(17)				
Sensitivity analysis with observed data	SCK 75mg (N=99)	44/89 (49)	vs. Placebo	1.5	(0.8, 2.7)	0.2155
	SCK 150mg (N=100)	59/95 (62)	vs. Placebo	2.7	(1.5, 5.1)	0.0016
	SCK 300mg (N=100)	66/94 (70)	vs. Placebo	3.7	(2.0, 7.0)	<0.001
	Placebo (N=98)	35/87 (40)				

Source: Excerpted from the Clinical Study Report for Study F2312 (pages 10179, 10270, 10271).

I conducted an additional analysis based on all observed data, including outcomes post-escape to secukinumab, and considering dropouts to be non-responders. My analysis was generally consistent with the applicant's observed data analysis and supported the conclusion of efficacy of the secukinumab 150 mg and 300 mg dosing regimens over placebo.

Table 26. Reviewer's analysis of ACR20 response at Week 24

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Sensitivity analysis with observed data for subjects who met escape criteria	SCK 75mg (N=99)	44/99 (44)	vs. Placebo	1.4	(0.8, 2.6)	0.2181
	SCK 150mg (N=100)	59/100 (59)	vs. Placebo	2.9	(1.6, 5.2)	0.0005
	SCK 300mg (N=100)	66/100 (66)	vs. Placebo	3.6	(2.0, 6.6)	<0.0001
	Placebo (N=98)	35/98 (36)				

Source: Reviewer

In addition, in response to FDA's IR after the filing meeting, the applicant submitted the following tipping point analysis results for the primary endpoint:

Table 4-3 shows the distribution of ACR20 response status by randomized treatment. The 10 patients missing from the 75 mg sc arm, 5 missing from the 150 mg SC arm, 6 missing from the 300 mg SC arm, and 11 patients missing from the placebo group as well as the 20 patients with ACR20 response who were randomized to placebo but already switched to AIN457 at Week 16, are the uncertain values (if they had remained on randomized treatment). The 35 rescued patients, randomized to placebo, who received secukinumab at week 16 and did not respond at week 24 were treated as non-responders for this analysis. This assumes that 8 weeks of secukinumab treatment is no worse than 8 weeks of additional placebo treatment for patients who were not responding to placebo after 16 weeks. Please note under this worst case scenario (on missing value and rescue patients), although placebo-treated patients have an ACR20 response rate of 47%, only 15 patients with observed ACR20 response were still on placebo at Week 24 out of 98 patients randomized to placebo.

Table 4-3 Distribution of ACR20 response status at Week 24 in CAIN457F2312

	Actual Data	Worst Case on missing value and early escaped patients for AIN457		
		Analyzed as	Response rate	P*
AIN457 – 75mg	45 observed non-response	45 non-response	44.4% (44/99)	0.725
	44 observed response	44 response		
	10 missing	10 non-response		
AIN457 – 150mg	36 observed non-response	36 non-response	59.0% (59/100)	0.089
	59 observed response	59 response		
	5 missing	5 non-response		
AIN457 – 300mg	28 observed non-response	28 non-response	66.0% (66/100)	0.007
	66 observed response	66 response		
	6 missing	6 non-response		
Placebo at randomization	17 observed non-response on placebo	17 non-response	46.9% (46/98)	--
	35 observed non-response on AIN457	35 non-response		
	15 observed response on placebo	15 response		
	20 observed response on AIN457	20 response		
	11 missing	11 response		

*P value is from Chi-square test.

There is no need to perform tipping point analysis for 300 mg sc, because even with the worst case on missing values and rescued patients the calculated response rate is clinically meaningful and statistically significant, $p = 0.007$.

For a comparison of the other secukinumab regimens versus placebo, the following notations are made.

J: Number of responders in uncertain cases from patients randomized to a secukinumab dose

K: Number of responders in uncertain cases from patients randomized to placebo

A Chi-square test was performed comparing each of 75 mg sc and 150 mg sc versus placebo, for each possible combination of J and K. Table 4-4 shows the counts for the comparisons, where J takes value from 0 to 10 for 75mg and from 0 to 5 for 150mg, and K from 0 to 31.

Note that the pre-specified analysis in the protocol used logistic regression with treatment and TNF-alpha inhibitor status as factors and weight as a covariate. A Chi-square test was used for this tipping point analysis because the model-based methodology requires assumptions about the response status for individual patients as opposed to the chi-square test which only requires the number of responders and non-responders.

Table 4-4 Counts in tipping point analysis for CAIN457F2312

	AIN457 75mg	AIN457 150mg	Placebo
Response	44 + J	59 + J	15 + K
Non-response	45 + (10-J)	36 + (5-J)	52 + (11 + 20 - K)

Figure 4-1 shows the p-values that are ≥ 0.05 from these chi-square tests for the pairwise comparisons. For a given number, r, of responders out of the 10 uncertain cases in the 75 mg sc arms, the placebo treatment group needs 15 or 16 more, i.e. $r+15$ or $r+16$, responders out of the 31 uncertain cases to get $p \geq 0.05$.

For 150 mg sc (Figure 4-2), there were only three combinations of J and K with a p-value ≥ 0.05 , which required 30 or 31 out of the 31 placebo uncertain cases to be responders while none of the 5 uncertain cases in the 150 mg sc group were responders, or all the 31 uncertain placebo cases were responders and 1 out of 5 uncertain cases in the 150 mg sc group was a responder. Thus the response rate in placebo patients with missing/rescue data would have to exceed 96% (30/31 or 31/31) with the same response on secukinumab being 0% or 20%. Novartis feels that it is conceivable that the secukinumab rate could be between 0 to 20%, but it is extremely unlikely that the placebo response rate would be so high in patients who were rescued after 16 weeks of placebo treatment for medical and ethical considerations or dropped out of the study for reasons which included lack of efficacy.

A tipping point did not exist in the comparisons of 300 mg sc group versus placebo as shown previously in Table 4-3.

Therefore, this analysis further supports the efficacy of the secukinumab 150mg and 300 mg sc doses.

Figure 4-1 Tipping point analysis of ACR20 at Week 24 for 75mg

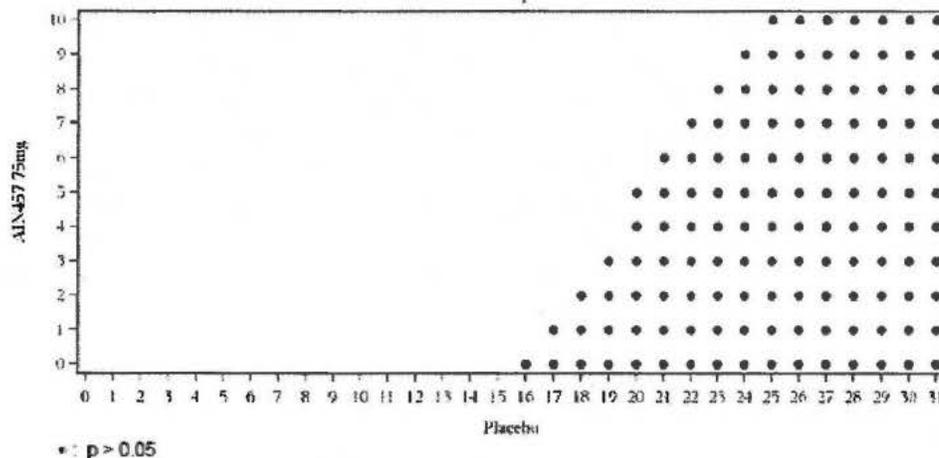
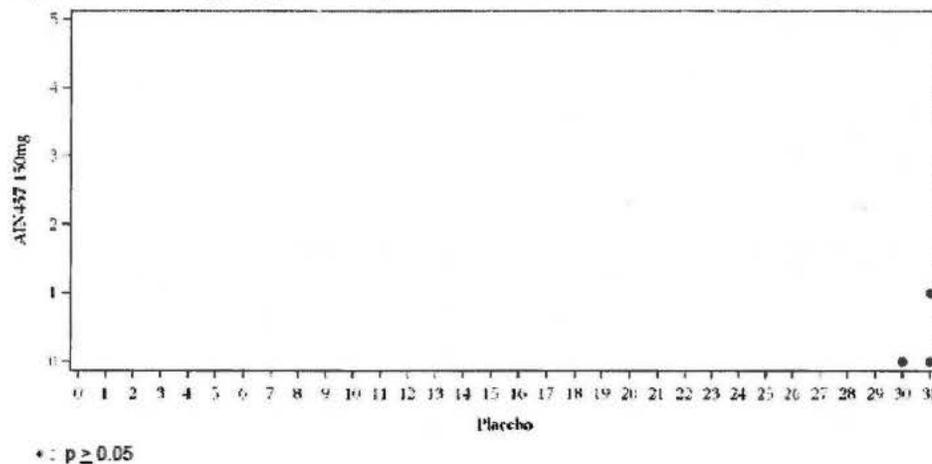


Figure 4-2 Tipping point analysis of ACR20 at Week 24 for 150mg



In my opinion, the applicant's interpretation of the tipping point analysis results appears reasonable and resolves our concern with the handling of placebo patients who crossed over to the secukinumab treatment at Week 16 due to non-response.

Components of ACR20 response at Week 24

I was able to confirm the results of the applicant's analyses of the components of the primary endpoint, ACR20 response at Week 24. Analyses of most components of ACR demonstrated a general trend of favorable outcomes with the secukinumab 150 mg and 300 mg dose groups, but much less so with the 75 mg dose group, when compared to placebo. A key limitation of these analyses at Week 24 is the small subset of placebo patients remaining at Week 24 (e.g., 33 out of 98 randomized patients for tender joint count), as the majority of placebo patients met escape criteria and crossed over to secukinumab at Week 16. The considerable escape destroys the integrity of randomization, although it is likely that the subset of patients remaining on placebo at Week 24 represents a healthy subset of the randomized population, thus leading to conservative inference in comparisons against the secukinumab arms. Because of the considerable proportion of patient either having crossed over from placebo to secukinumab or having missing data at Week 24, I carried out additional analyses of the ACR20 components and key continuous secondary endpoints at Week 16 (prior to escape). Results are relatively similar to those at Week 24 and are presented in the Appendix.

Table 27. Applicant's analysis of ACR20 components at Week 24

	Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
Adjusted TJC	SCK 75mg (N=99)	90	-8.7	vs. Placebo	-4.4 (2.1)	(-8.6, -0.2)	0.0407
	SCK 150mg (N=100)	95	-11.4	vs. Placebo	-7.1 (2.1)	(-11.3, -3.0)	0.0009
	SCK 300mg (N=100)	96	-10.8	vs. Placebo	-6.6 (2.1)	(-10.7, -2.4)	0.0022
	Placebo (N=98)	33	-4.3				
Adjusted SJC	SCK 75mg (N=99)	90	-5.3	vs. Placebo	-0.1 (1.1)	(-2.2, 2.0)	0.9030
	SCK 150mg (N=100)	95	-6.3	vs. Placebo	-1.2 (1.1)	(-3.3, 0.9)	0.2705
	SCK 300mg (N=100)	96	-7.3	vs. Placebo	-2.1 (1.1)	(-4.2, -0.1)	0.0452
	Placebo (N=98)	33	-5.1				
Patient's global assessment of disease activity	SCK 75mg (N=99)	89	-18.5	vs. Placebo	-8.3 (3.8)	(-15.8, -0.9)	0.0283
	SCK 150mg (N=100)	94	-25.8	vs. Placebo	-15.6 (3.8)	(-23.0, -8.2)	<0.0001
	SCK 300mg (N=100)	94	-26.7	vs. Placebo	-16.6 (3.8)	(-24.0, -9.2)	<0.0001
	Placebo (N=98)	33	-10.1				
Physician's global assessment of disease activity	SCK 75mg (N=99)	89	-25.7	vs. Placebo	-0.5 (3.1)	(-6.6, 5.7)	0.8851
	SCK 150mg (N=100)	94	-33.0	vs. Placebo	-7.8 (3.1)	(-13.9, -1.6)	0.0130
	SCK 300mg (N=100)	94	-38.5	vs. Placebo	-13.3 (3.1)	(-19.4, -7.2)	<0.0001
	Placebo (N=98)	33	-25.2				
HAQ-DI	SCK 75mg (N=99)	89	-0.32	vs. Placebo	-0.01 (0.08)	(-0.16, 0.15)	0.9195
	SCK 150mg (N=100)	95	-0.48	vs. Placebo	-0.17 (0.08)	(-0.32, -0.02)	0.0278
	SCK 300mg (N=100)	95	-0.56	vs. Placebo	-0.25 (0.08)	(-0.40, -0.10)	0.0013
	Placebo (N=98)	33	-0.31				
Patient's assessment of PsA pain	SCK 75mg (N=99)	89	-17.1	vs. Placebo	-5.4 (3.9)	(-13.1, 2.3)	0.1663
	SCK 150mg	94	-23.4	vs. Placebo	-11.7 (3.9)	(-19.3, -4.1)	0.0028

	(N=100) SCK 300mg	95	-22.4	vs. Placebo	-10.6 (3.9)	(-18.3, -3.0)	0.0064
	(N=100) Placebo (N=98)	33	-11.7				
ESR (mm/hr)	SCK 75mg (N=99)	90	-9.9	vs. Placebo	-3.1 (2.1)	(-7.3, 1.1)	0.1451
	SCK 150mg (N=100)	95	-8.2	vs. Placebo	-1.4 (2.1)	(-5.6, 2.8)	0.5040
	SCK 300mg (N=100)	96	-8.6	vs. Placebo	-1.9 (2.1)	(-6.0, -2.3)	0.3850
	Placebo (N=98)	34	-6.8				
hsCRP* (mg/L)	SCK 75mg (N=99)	88	0.58	vs. Placebo	0.77	(0.58, 1.02)	0.0725
	SCK 150mg (N=100)	92	0.55	vs. Placebo	0.73	(0.55, 0.97)	0.0309
	SCK 300mg (N=100)	95	0.55	vs. Placebo	0.74	(0.56, 0.98)	0.0353
	Placebo (N=98)	33	0.75				

Source: Reviewer & the Clinical Study Report for Study F2312 (pages 871, 889, 925, 943, 907, 979, 961).

*log(hsCRP) was used in the MMRM analysis and the LSmean difference were back-transformed (exponentiation) to the ratio between treatment groups.

In summary, the study showed statistically significant evidence in favor of the secukinumab 150 mg and 300 mg dosing regimens on the ACR20 response at Week 24 (primary efficacy endpoint). Several sensitivity analyses were conducted to assess the robustness of the primary analysis. The conclusions from these analyses were consistent in general.

Secondary Efficacy Endpoints

I was able to confirm the results of the applicant's analyses of the secondary endpoints. I also conducted sensitivity analyses to assess the impact of missing data due to early escape and dropout from the study. All p-values for the secondary endpoints presented here are nominal.

Key Secondary Endpoints – PASI75 & PASI90 at Week 24

The applicant's results of PASI75 and PASI90 analyses are summarized in Table 28. The same statistical method (logistic regression) used in the ACR20 analysis was employed for these endpoints. The analysis set for these endpoints was the subset of patients (approximately half of all randomized patients) in whom at least 3% of the body surface area was affected by psoriatic skin involvement at baseline.

Treatment with the secukinumab 150 mg or 300 mg dosing regimens resulted in statistically significantly higher PASI response rates than treatment with placebo. In addition, response rates tended to be greater on secukinumab 300 mg than secukinumab 150 mg for these psoriasis endpoints.

Table 28. Applicant's analyses of PASI response at Week 24 (Psoriasis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
PASI75	SCK 75mg (N=50)	14/50 (28)	vs. Placebo	2.1	(0.7, 5.8)	0.1650
	SCK 150mg	28/58 (48)	vs. Placebo	5.7	(2.1, 15.3)	0.0006

	(N=58) SCK 300mg (N=41) Placebo (N=43)	26/41 (63) 7/43 (16)	vs. Placebo	9.5	(3.3, 27.0)	<0.0001
PASI90	SCK 75mg (N=50)	6/50 (12)	vs. Placebo	1.4	(0.4, 5.4)	0.6421
	SCK 150mg (N=58)	19/58 (33)	vs. Placebo	6.4	(1.9, 21.5)	0.0029
	SCK 300mg (N=41) Placebo (N=43)	20/41 (49) 4/43 (9)	vs. Placebo	10.7	(3.1, 36.8)	0.0002

Source: Excerpted from the Clinical Study Report for Study F2312 (pages 464 & 481).

Key Secondary Endpoints - change from baseline in DAS28-CRP at Week 24

The mean reduction in DAS28-CRP at Week 24 in patients treated with the secukinumab 150 mg and 300 mg dosing regimens was statistically significantly greater compared to patients treated with placebo, but the mean reduction in patients treated with the secukinumab 75 mg dosing regimen was not (Table 29). My sensitivity analysis with the same model but also incorporating observed post-escape data was consistent with results from the applicant's pre-specified analysis. However, the estimated effects were much different with the 2 approaches (Table 30). Also my cumulative distribution curves that included post-escape data and used worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg or 300 mg dosing regimens and placebo. But the curves for secukinumab 75 mg dosing regimen and placebo were overlapping (Figure 9).

Table 29. Applicant's analysis of change from baseline in DAS28-CRP at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=99)	87	-1.12	vs. Placebo	-0.16 (0.19)	(-0.53, 0.20)	0.3763
SCK 150mg (N=100)	91	-1.58	vs. Placebo	-0.62 (0.18)	(-0.98, -0.26)	0.0008
SCK 300mg (N=100)	93	-1.61	vs. Placebo	-0.65 (0.18)	(-1.02, -0.29)	0.0004
Placebo (N=98)	32	-0.96				

Source: Excerpted from the Clinical Study Report for Study F2312 (page 499).

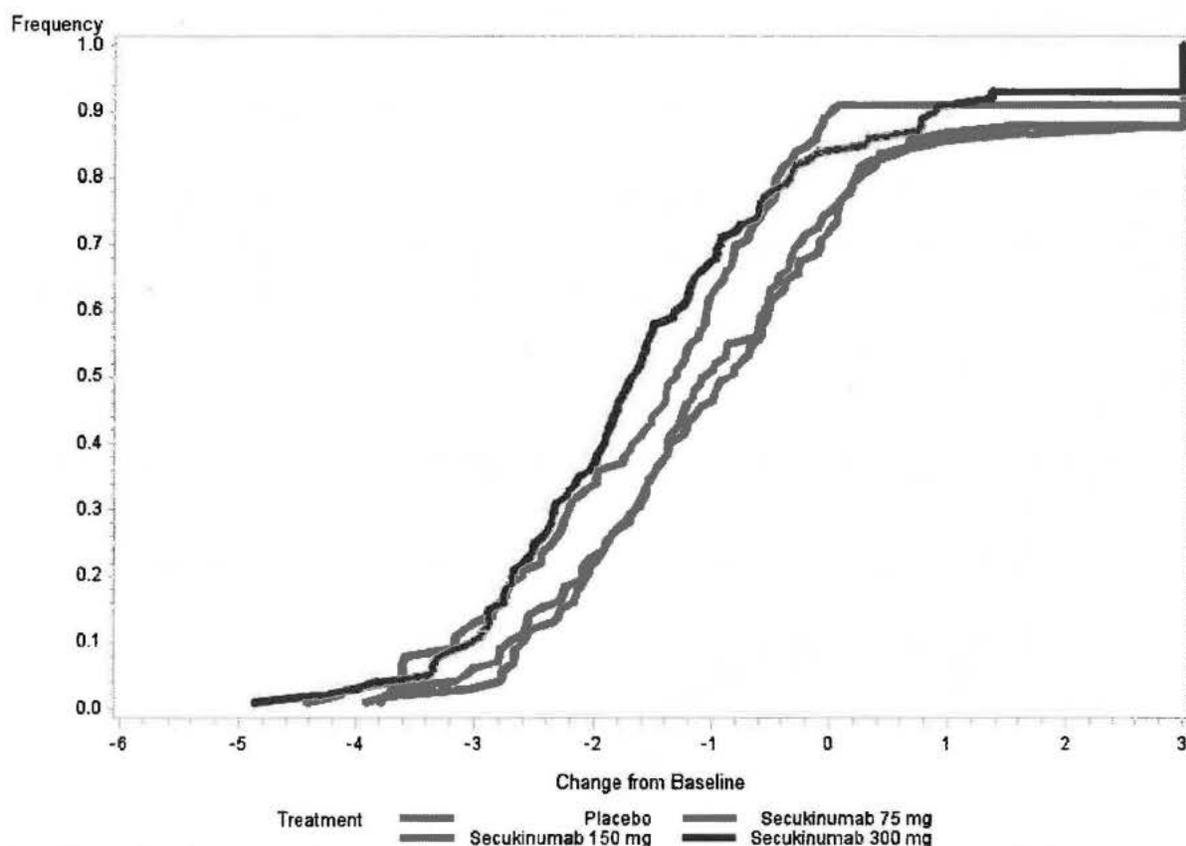
Table 30. Reviewer's observed post-escape data analysis of change from baseline in DAS28-CRP at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=99)	87	-1.12	vs. Placebo	0.05 (0.16)	(-0.26, 0.37)	0.3697
SCK 150mg (N=100)	91	-1.57	vs. Placebo	-0.40 (0.16)	(-0.71, -0.09)	0.0128
SCK 300mg (N=100)	93	-1.61	vs. Placebo	-0.44 (0.16)	(-0.75, -0.12)	0.0063
Placebo (N=98)	86	-1.18				

Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.

Source: Reviewer.

Figure 9. Cumulative distribution of change from baseline in DAS28-CRP at Week 24



Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints - change from baseline in SF36-PCS at Week 24

The mean change in SF36-PCS at Week 24 in patients treated with the secukinumab 150 mg and 300 mg dosing regimens was statistically significantly greater compared to patients treated with placebo, but the mean change in patients treated with the secukinumab 75 mg dosing regimen was not (Table 31). My sensitivity analysis with the same model but also incorporating observed post-escape data was consistent with results from the applicant's pre-specified analysis. However, the estimated effects were much different with the 2 approaches (Table 32). Also my cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg or 300 mg dosing regimens and placebo. But the curves for the secukinumab 75 mg dosing regimen and placebo were overlapping (Figure 10).

Table 31. Applicant's analysis of change from baseline in SF36-PCS at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=99)	91	4.38	vs. Placebo	2.42 (1.22)	(0.02, 4.83)	0.0482
SCK 150mg	96	6.39	vs. Placebo	4.44 (1.22)	(2.15, 6.83)	0.0003

(N=100)						
SCK 300mg	96	7.25	vs. Placebo	5.30 (1.22)	(2.91, 7.69)	<0.0001
(N=100)						
Placebo (N=98)	33	1.95				

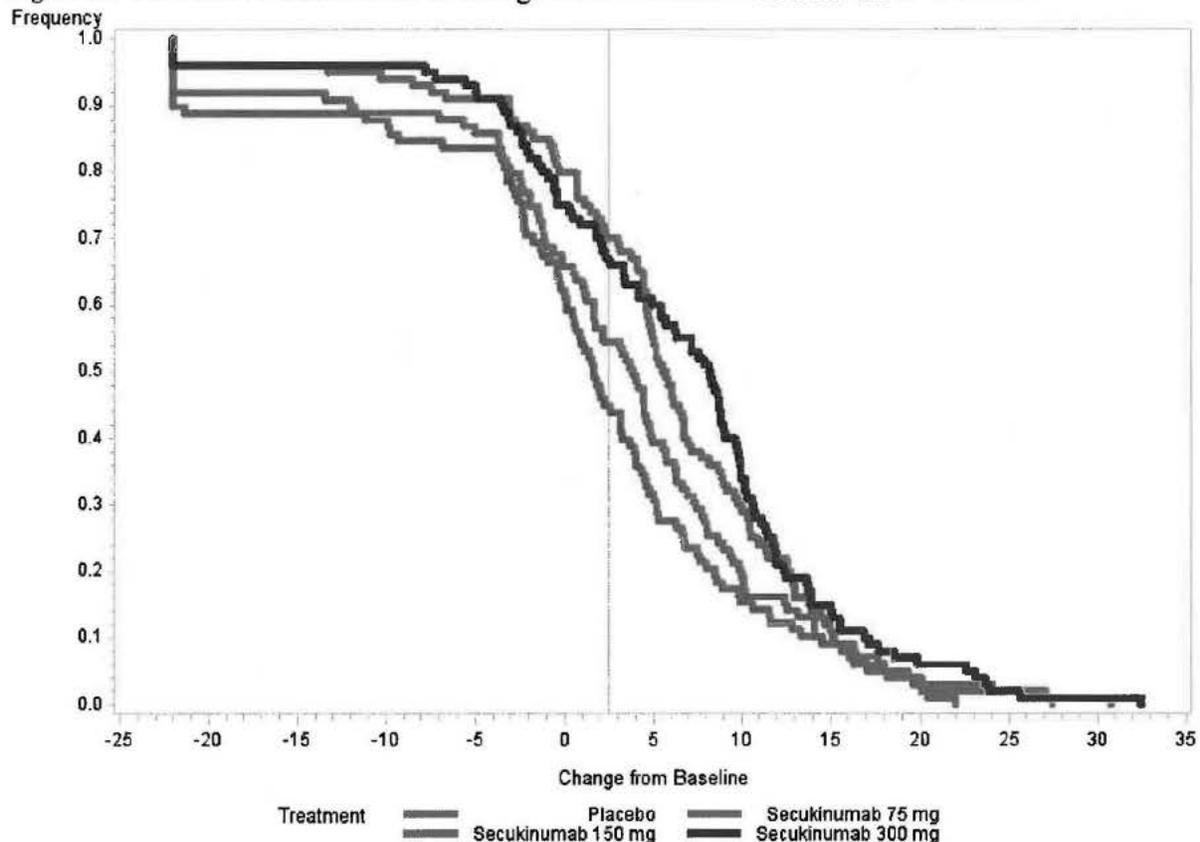
Source: Excerpted from the Clinical Study Report for Study F2312 (page 531).

Table 32. Reviewer’s observed post-escape data analysis of change from baseline in SF36-PCS at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=99)	91	4.37	vs. Placebo	0.79 (1.06)	(-1.30, 2.89)	0.4564
SCK 150mg (N=100)	96	6.38	vs. Placebo	2.81 (1.05)	(0.73, 4.88)	0.0081
SCK 300mg (N=100)	96	7.23	vs. Placebo	3.66 (1.06)	(1.58, 5.73)	0.0006
Placebo (N=98)	88	3.57				

Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.
Source: Reviewer.

Figure 10. Cumulative distribution of change from baseline in SF36-PCS at Week 24



Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints - change from baseline in HAQ-DI at Week 24

The mean change in HAQ-DI at Week 24 in patients treated with the secukinumab 300 mg dosing regimen was statistically significantly greater compared to patients treated with placebo, but the mean change in patients treated with the secukinumab 75 mg dosing regimen was not. Although the change in patients treated with the secukinumab 150 mg dosing regimen was nominally statistically significant, after adjusting for multiple testing, it was not statistically significant (Table 33). My observed data sensitivity analysis was consistent with results from the applicant's pre-specified analysis. However, the estimated effects were much different with the 2 approaches (Table 34). Also my cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg or 300 mg dosing regimens and placebo. But the curves for the secukinumab 75 mg dosing regimen and placebo were overlapping (Figure 11).

Table 33. Applicant's analysis of change from baseline in HAQ-DI at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=99)	89	-0.32	vs. Placebo	-0.01 (0.08)	(-0.16, 0.15)	0.9195
SCK 150mg (N=100)	95	-0.48	vs. Placebo	-0.17 (0.08)	(-0.32, -0.02)	0.0278
SCK 300mg (N=100)	95	-0.56	vs. Placebo	-0.25 (0.08)	(-0.40, -0.10)	0.0013
Placebo (N=98)	33	-0.31				

Source: Excerpted from the Clinical Study Report for Study F2312 (page 654).

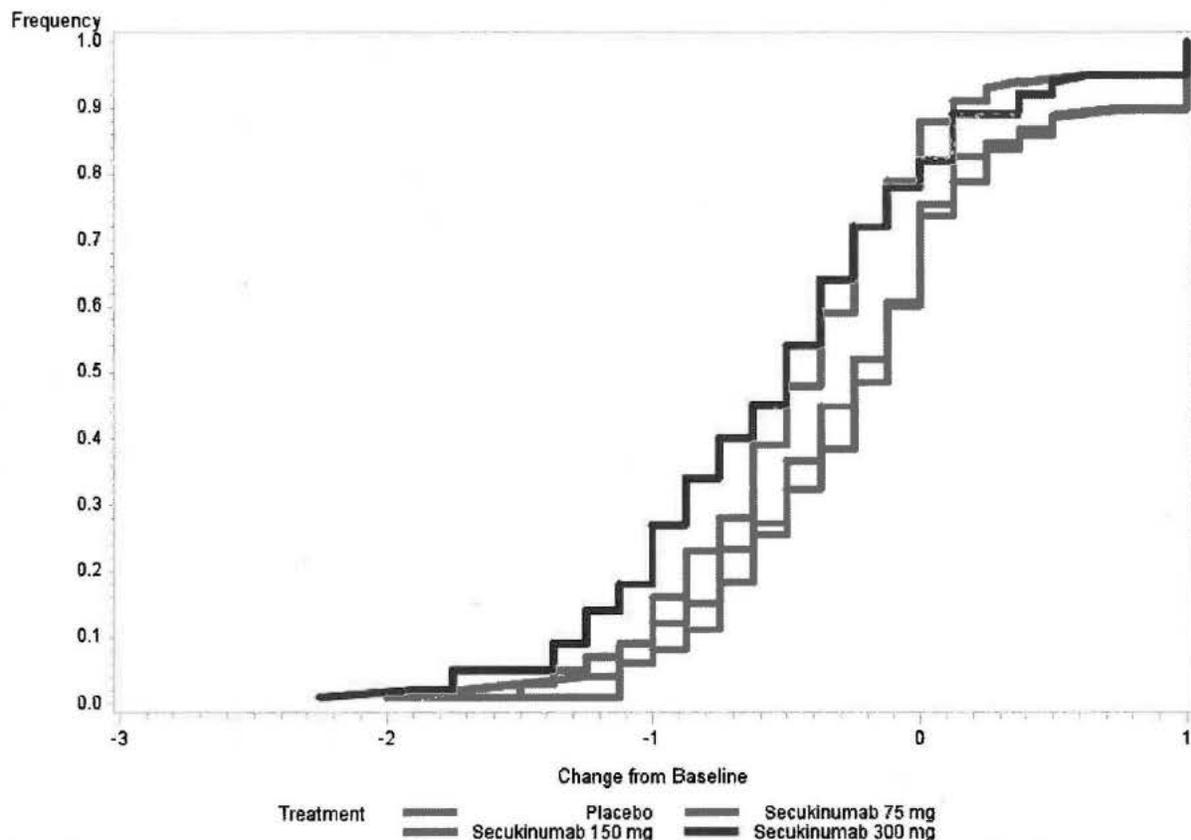
Table 34. Reviewer's observed post-escape data analysis of change from baseline in HAQ-DI at Week 24

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=99)	89	-0.32	vs. Placebo	0.02 (0.07)	(-0.12, 0.15)	0.7860
SCK 150mg (N=100)	95	-0.48	vs. Placebo	-0.14 (0.07)	(-0.28, -0.01)	0.0393
SCK 300mg (N=100)	95	-0.56	vs. Placebo	-0.22 (0.07)	(-0.36, -0.08)	0.0015
Placebo (N=98)	88	-0.34				

Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were not imputed.

Source: Reviewer.

Figure 11. Cumulative distribution of change from baseline in HAQ-DI at Week 24



Note: Observed data from placebo patients crossed to secukinumab regimen were used. Other missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints – Presence of Dactylitis at Week 24

The applicant’s analysis showed only nominally statistically significant lower rates in dactylitis presence at Week 24 for the secukinumab 150 mg and 300 mg groups or all pooled secukinumab groups when compared to placebo, in the subset of patients with dactylitis at baseline. My sensitivity analysis based on observed data did not show a statistically significant difference between any secukinumab group or all pooled secukinumab groups and placebo, although there were favorable trends.

Table 35. Applicant’s analyses of dactylitis presence at Week 24 (Dactylitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Analysis with NRI	SCK 75mg (N=33)	23/33 (70)	vs. Placebo	0.51	(0.13, 1.91)	0.3149
	SCK 150mg (N=32)	16/32 (50)	vs. Placebo	0.16	(0.04, 0.58)	0.0056
	SCK 300mg (N=46)	20/46 (44)	vs. Placebo	0.14	(0.04, 0.50)	0.0021
	SCK pooled (N=111)	59/111 (53)	vs. Placebo	0.23	(0.07, 0.72)	0.0114

Placebo (N=27) 23/27 (85)

Source: Excerpted from the Clinical Study Report for Study F2312 (pages 759).

Table 36. Reviewer’s analysis of dactylitis presence at Week 24 (Dactylitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Sensitivity analysis with retrieved dropout	SCK 75mg (N=33)	17/33 (52)	vs. Placebo	0.85	(0.29, 2.50)	0.7611
	SCK 150mg (N=32)	12/32 (38)	vs. Placebo	0.41	(0.14, 1.22)	0.1081
	SCK 300mg (N=46)	17/46 (37)	vs. Placebo	0.44	(0.16, 1.22)	0.1142
	SCK pooled (N=111)	46/111 (41)	vs. Placebo	0.52	(0.21, 1.27)	0.1499
	Placebo (N=27)	16/27 (59)				

Source: Reviewer

Key Secondary Endpoints – Presence of Enthesitis at Week 24

The applicant’s analysis showed only nominally statistically significant lower rates in enthesitis presence at Week 24 for the secukinumab 150 mg and 300 mg groups or all pooled secukinumab groups when compared to placebo, in the subset of patients with enthesitis at baseline. My sensitivity analysis based on observed data did not show a statistically significant difference between any secukinumab group or all pooled secukinumab groups and placebo, although trends were favorable.

Table 37. Applicant’s analyses of enthesitis presence at Week 24 (Enthesitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Analysis with NRI	SCK 75mg (N=68)	46/68 (68)	vs. Placebo	0.58	(0.26, 1.26)	0.1678
	SCK 150mg (N=64)	37/64 (58)	vs. Placebo	0.36	(0.17, 0.79)	0.0108
	SCK 300mg (N=56)	29/56 (52)	vs. Placebo	0.29	(0.13, 0.65)	0.0025
	SCK pooled (N=188)	112/188 (60)	vs. Placebo	0.39	(0.20, 0.77)	0.0060
	Placebo (N=65)	51/65 (79)				

Source: Excerpted from the Clinical Study Report for Study F2312 (pages 775).

Table 38. Reviewer’s analysis of enthesitis presence at Week 24 (Enthesitis Subset)

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Sensitivity analysis with retrieved dropout	SCK 75mg (N=68)	39/68 (57)	vs. Placebo	0.98	(0.47, 2.04)	0.9630
	SCK 150mg (N=64)	30/64 (47)	vs. Placebo	0.58	(0.28, 1.22)	0.1516
	SCK 300mg (N=56)	25/56 (45)	vs. Placebo	0.62	(0.29, 1.33)	0.2197
	SCK pooled (N=188)	94/188 (50)	vs. Placebo	0.72	(0.39, 1.32)	0.2825
	Placebo (N=65)	40/65 (62)				

Source: Reviewer

Long-term efficacy analysis – observed ACR20 response over 52 weeks

I conducted a descriptive analysis to numerically compare the secukinumab 75 mg, 150 mg, and 300 mg dosing regimens with regard to ACR20 over 52 weeks without statistical hypothesis testing. The analysis was based on observed data instead of non-responder imputed data for subjects who met the Week 16 escape criteria. Because many patients had not reached 52 weeks when the BLA was submitted, there was a limitation in the data for assessing ACR20 response trend over 52 weeks. ACR20 response probabilities over time tended to be similar on the 150 and 300 mg dose arms and greater than response probabilities on the 75 mg arm.

Table 39. Reviewer's analysis of observed ACR20 response over 52 weeks

Week	SCK 75 mg n/N (%)	SCK 150 mg n/N (%)	SCK 300 mg n/N (%)
1	10/95 (11)	11/94 (12)	12/92 (13)
2	13/95 (14)	25/96 (26)	24/93 (26)
3	23/96 (24)	42/99 (42)	37/93 (40)
4	28/96 (29)	49/100 (49)	46/96 (48)
8	35/94 (37)	60/99 (61)	47/95 (50)
12	33/92 (36)	56/99 (57)	57/95 (60)
16	33/93 (35)	60/100 (60)	57/95 (60)
20	41/93 (44)	59/95 (62)	68/95 (72)
24	44/89 (49)	59/95 (62)	66/94 (70)
28	44/85 (52)	55/87 (63)	61/90 (68)
32	45/76 (59)	51/80 (64)	60/80 (75)
36	32/53 (60)	43/55 (78)	41/60 (68)
40	22/37 (59)	26/40 (65)	30/41 (73)
44	17/24 (71)	19/26 (73)	17/25 (68)
48	8/10 (80)	6/12 (50)	6/10 (60)
52	1/1 (100)	2/2 (100)	1/1 (100)

Source: Reviewer

In summary, study data demonstrated that all doses of secukinumab 75 mg, 150 mg and 300 mg are superior to placebo with respect to the primary endpoint of ACR20 at Week 24. However, many of the secondary endpoints at Week 24 in the multiplicity adjustment hierarchy were not statistically significant. With the secukinumab 75 mg dose, none of the analyses of secondary endpoints were significant. With the secukinumab 150 mg dose, analyses of PASI75, PASI90, DAS28-CRP, and SF-36 PCS were statistically significant, but analyses of HAQ-DI, ACR50, dactylitis, and enthesitis were not. With the secukinumab 300 mg dose, analyses of PASI75,

PASI90, DAS28-CRP, SF-36 PCS, HAQ-DI, and ACR50 were significant, but analyses of dactylitis and enthesitis were not. However, all the endpoints that were shown to be statistically significant in the main analyses remained statistically significant in sensitivity analyses that included observed post-escape data, although estimated effects were smaller.

3.3 Evaluation of Safety

The assessment of the safety of the study drug was mainly conducted by the reviewing medical team. The reader is referred to Dr. Raj Nair's review for information regarding the safety profile of the drug.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The following are tabular and graphical presentations of results from subgroup analyses by demographics, region, and baseline disease characteristics in terms of ACR20 response at Week 24, based on integrated data from Studies F2306 and F2312, for the secukinumab 150 mg dose. The subgroup analyses were largely consistent with the results from the overall population in terms of ACR20 response, although there was some evidence of quantitative interactions between treatment and subgroups such as sex, region, and baseline TNF use – female, USA, and TNF-IR subgroups showed smaller, though still statistically significant, effects of secukinumab treatment relative to other complementary subgroups (Table 39 & Figure 12).

Table 40. Reviewer's Subgroup Analyses on ACR20 response at Week 24 – Studies F2306 and F2312 pooled

	SCK 150mg		Placebo		
	N	n(%)	N	n(%)	Odds ratio (95% CI)
Overall (p<0.001)^a					
	302	152(50)	300	50(17)	6.5 (3.3, 12.9)
Sex (p=0.02)^b					
Male	151	83(55)	135	16(12)	10.1 (5.4, 19.3)
Female	151	69(46)	165	34(21)	3.6 (2.2, 6.2)
Age (p=0.27)^b					
<50 yrs	161	82(51)	168	24(14)	7.2 (4.1, 12.6)
≥50 yrs	141	70(50)	132	26(20)	4.8 (2.7, 8.5)
Region (p=0.04)^b					
ROW ^c	225	126(56)	239	39(16)	7.4 (4.7, 11.6)
USA	77	26(34)	61	11(18)	2.5 (1.1, 5.7)
Race (p=0.91)^b					

White	252	118(47)	248	35(14)	5.9 (3.8, 9.3)
N-White	50	34(68)	52	15(29)	6.0 (2.4, 15.0)
Psoriasis (P=0.17)^b					
Y	166	96(58)	152	27(18)	7.5 (4.3, 12.8)
N	136	56(41)	148	23(16)	4.3 (2.4, 7.7)
TNF-naive (P=0.05)^b					
Y	206	118(57)	206	35(17)	7.7 (4.8, 12.5)
N	96	34(35)	94	15(16)	3.0 (1.5, 6.0)
Time Since PsA Diagnosis (P=0.53)^b					
<5 yrs	193	93(48)	207	31(15)	6.2 (3.7, 10.1)
≥5 yrs	109	59(54)	93	19(20)	4.9 (2.5, 9.4)

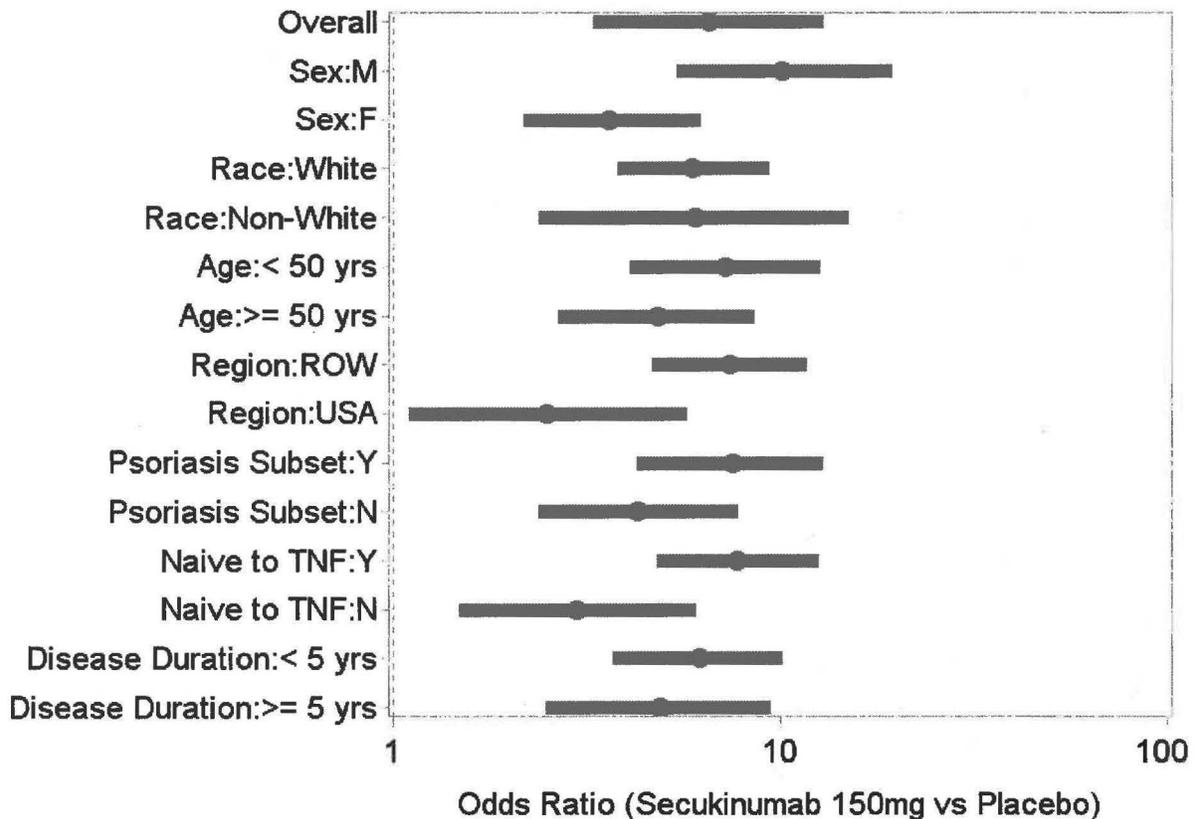
Source: Reviewer

[a] Logistic regression model with same covariates as primary analysis, also adjusting for study, comparing secukinumab 150 mg to placebo.

[b] Logistic regression model with same terms in [a] and with interaction between treatment arm and subgroup. P-value is for the interaction.

[c] ROW includes Argentina, Australia, Belgium, Bulgaria, Brazil, Canada, Czech Republic, Germany, Israel, Italy, Philippine, Poland, Romania, Russia, Singapore, Slovakia, Thailand, United Kingdom.

Figure 12. Reviewer's Subgroup Analyses on ACR20 response at Week 24 – Studies F2306 and F2312 pooled



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During my review of the application, several potential statistical issues were identified:

- Potential Effect of Escape and Missing Data on Reliability of Efficacy Results
- Efficacy of Proposed Maintenance Doses Given the Presence of Loading Doses
- Adequacy of Radiographic Data to Support a Claim
- Evidence to Support Proposed Dosing Recommendations

The first issue was the potential effect of escape and missing data. For the analysis of the primary endpoint, the applicant pre-specified an approach that considered patients who met early escape criteria or who dropped out to be non-responders. I found that this approach might be problematic for early escapers since the placebo group had disproportionately more non-responders at Week 16 compared to the active group, prior to the primary analysis time point of Week 24. Therefore, the treatment effect in the primary analysis might be driven entirely by an effect on escape criteria at Week 16 rather than an effect on ACR20 at Week 24. The applicant conducted a sensitivity analysis with missing-at-random multiple imputation, an analysis with observed post-escape data, and a tipping point analyses. I also conducted an additional sensitivity analysis with observed post-escape data that considered dropouts to be non-responders. Results from the sensitivity analyses suggested that secukinumab is efficacious notwithstanding the early escape and missing data.

Second, there was a clinical concern regarding the efficacy of the proposed secukinumab maintenance doses because patients in the active group received a loading dose, and it was possible that efficacy at 24 weeks may have been due to residual effects of the loading doses rather than the regular maintenance doses (i.e., efficacy would ultimately decline over time). The issue of the sufficiency of the maintenance doses, given the loading doses used, was partly resolved by exploratory analyses conducted in collaboration with the FDA clinical team. In particular, it was reassuring that placebo patients who crossed over to the secukinumab treatment after 16 weeks or 24 weeks and who had no loading dose showed similar ACR20 responses as the secukinumab treatment groups (see figures in the Appendix).

The third issue was the adequacy of the radiographic data to support an efficacy claim ^(b)₍₄₎. ^(b)₍₄₎ The analysis of radiographic data from study F2306 for inhibition of structural damage showed statistical significance in favor of secukinumab. However, the results were obtained from a study that utilized a different dosing regimen, with a markedly higher exposure due to the iv loading dose, than the dosing regimen proposed for approval. In addition, data were from a single study and Week 24 data were not collected in a substantial proportion of randomized patients, such that analyses evaluating the intention-to-treat estimand rely on strong and untestable assumptions (based on linear extrapolation) about the missing data. I also conducted

an outlier analysis excluding patients who had more than 7 units change from baseline in mTSS that FDA clinical team consider as outliers in which the statistical significance was not shown, implying that the outliers contributed to the statistical significance in the applicant's analysis.

Finally, I believe that there is sufficient evidence of efficacy to support the proposing 150 mg and 300 mg doses of secukinumab. The 300 mg dose was evaluated in only a single study, but the lower 150 mg dose demonstrated benefit with respect to the primary endpoint ACR20 and several important secondary endpoints in two independent placebo-controlled clinical trials. The applicant is proposing recommended dosing with the higher 300 mg dose in (b) (4) patients with psoriasis (b) (4). In Study F2312, in the subgroup of psoriasis patients, the PASI90 response rate for the secukinumab 300 mg dose (49%) was numerically higher than the rate for the secukinumab 150 mg dose (33%). These results, combined with the results from the psoriasis development program that supported approval of the 300 mg dose for the psoriasis indication, appear to support the applicant's claim for the use of the secukinumab 300 mg dose in the subset of PsA patients with psoriasis. (b) (4)

(b) (4)
This was one of many prospectively planned subgroup analyses and it is difficult to determine whether the heterogeneity is true or due to chance.

5.2 Collective Evidence

In the two phase 3 studies F2306 and F2312 reviewed, the analysis of the predefined primary efficacy endpoint, ACR20 at Week 24, was statistically significant. In Study F2306, the ACR20 response rates were 51%, 50%, and 17% for the secukinumab 75 mg, 150 mg, and placebo, respectively. In Study F2312, which included the proposed SC loading dose (rather than the IV loading dose used in Study F2306), the response rates were 29%, 51%, 54%, and 15% for the secukinumab 75 mg, 150 mg, 300 mg, and placebo, respectively.

More specifically, the efficacy data from Study F2306 provided statistical evidence of efficacy for the secukinumab 75 mg and 150 mg doses for treatment of PsA based on ACR20, the primary endpoint, and all the key secondary endpoints, including PASI75, PASI90, DAS28-CRP, SF-36 PCS, HAQ-DI, ACR50, mTSS, dactylitis, and enthesitis. The efficacy data from Study F2312 provided statistical evidence of efficacy for the secukinumab 150 mg and 300 mg doses based on the primary endpoint of ACR20 response and most of the key secondary endpoints. In this study, there was not statistical evidence of effects of the secukinumab 75 mg dose on any of the secondary endpoints. With the secukinumab 150 mg dose, analyses of PASI75, PASI90, DAS28-CRP, and SF-36 PCS were statistically significant, but analyses of HAQ-DI, ACR50, dactylitis, and enthesitis were not. With the secukinumab 300 mg dose, analyses of PASI75, PASI90, DAS28-CRP, SF-36 PCS, HAQ-DI, and ACR50 were statistically significant, but analyses of dactylitis, and enthesitis were not.

In summary:

- There was evidence of efficacy for the primary and most secondary endpoints for the 150 mg dose in both studies.
- There was evidence of efficacy for the primary and most secondary endpoints for the 300 mg dose in one study. Given the strong evidence of efficacy for the lower 150 mg dose from 2 independent studies, evidence from a single study is sufficient to support the efficacy of the 300 mg dose.
- There was less consistent evidence of and/or smaller effects for 75 mg, especially in the study without an iv loading dose.

Therefore, the overall package provides substantial evidence of efficacy for the proposed 150 and 300 mg doses for treating PsA.

5.3 Labeling Recommendations

The following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description and primary analysis results and their interpretation. However, I recommend that Week 16 rather than Week 24 results are included for continuous endpoints such as the ACR components and HAQ-DI. Estimated effects at Week 16 are more reliable because of considerably less missing data at Week 16 than Week 24. (b) (4) (1) evidence is based on a single study; (2) evidence is for a dosing regimen that is not proposed for marketing and one that included a substantially higher loading dose; and (3) patients who escaped at Week 16 did not get x-rays at Week 24, such that the analyses rely on strong and untestable assumptions via linear extrapolation. In addition, I recommend the removal of results from secondary and exploratory analyses that were not adjusted for multiplicity, except for endpoints agreed as clinically important.

14.2 Psoriatic Arthritis

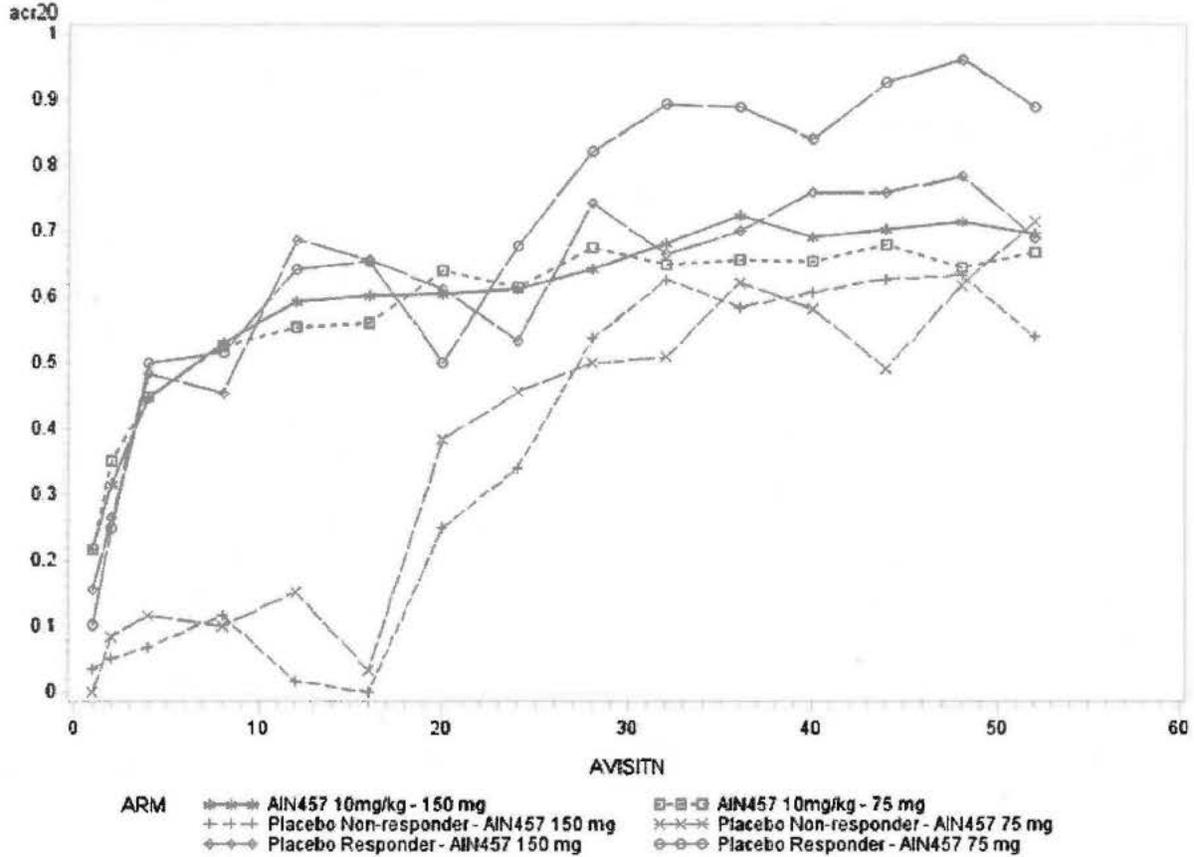
□ The safety and efficacy of COSENTYX were assessed in 1003 patients, in 2 randomized, double-blind, placebo-controlled studies (PsA1 and PsA2) in adult patients, age 18 years and older with active psoriatic arthritis (greater than 3 swollen and greater than 3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. Patients in these studies had a diagnosis of PsA of at least 5 years across both studies. At baseline, over 62% and 47% of the patients had enthesitis and dactylitis, respectively. Overall, 32% of patients discontinued previous treatment with anti-TNF α agents due to either lack of efficacy or intolerance (anti-TNF α -IR). PsA1 Study evaluated 606 patients, of which approximately 61% had concomitant methotrexate (MTX) use. Patients with different subtypes of PsA were enrolled including polyarticular arthritis with no evidence of rheumatoid nodules (b) (4), asymmetric peripheral arthritis (b) (4), distal interphalangeal involvement (b) (4), spondylitis with peripheral arthritis (b) (4) and arthritis mutilans (b) (4).



APPENDIX

Exploration for loading dose effects:

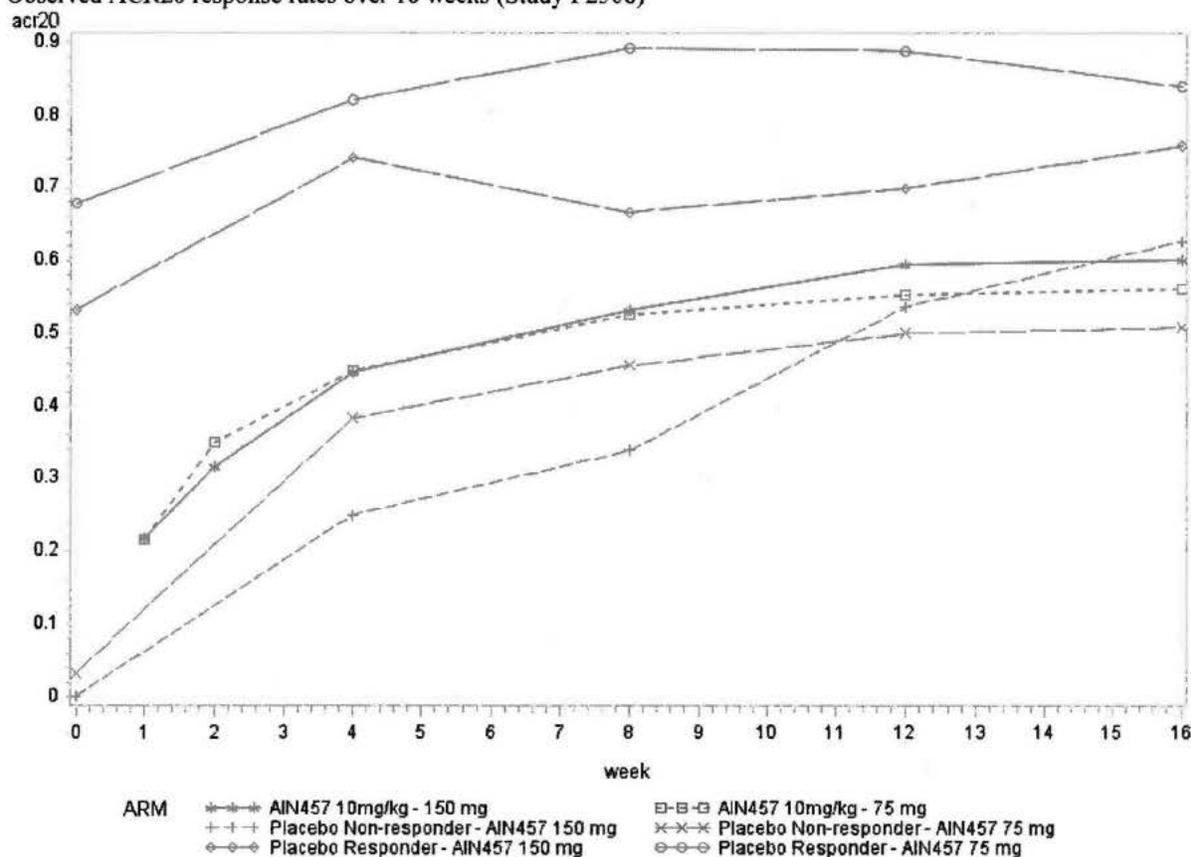
Observed ACR20 response rates over 52 weeks (Study F2306)



AVISITN	AIN457 10mg/kg - 150 mg n/N (%)	AIN457 10mg/kg - 75 mg n/N (%)	Placebo Non-responder - AIN457 150 mg n/N (%)	Placebo Non-responder - AIN457 75 mg n/N (%)	Placebo Responder - AIN457 150 mg n/N (%)	Placebo Responder - AIN457 75 mg n/N (%)
1	42/192 (22)	41/190 (22)	2/55 (4)	0/59 (0)	5/32 (16)	3/29 (10)
2	61/193 (32)	67/191 (35)	3/59 (5)	5/60 (8)	8/30 (27)	7/28 (25)
4	88/197 (45)	87/194 (45)	4/59 (7)	7/60 (12)	16/33 (48)	15/30 (50)
8	102/192 (53)	100/190 (53)	7/60 (12)	6/60 (10)	15/33 (45)	15/29 (52)
12	113/190 (59)	104/188 (55)	1/61 (2)	9/59 (15)	22/32 (69)	18/28 (64)
16	115/191 (60)	106/189 (56)	0/60 (0)	2/61 (3)	21/32 (66)	19/29 (66)
20	112/185 (61)	121/189 (64)	15/60 (25)	23/60 (38)	19/31 (61)	13/26 (50)
24	115/188 (61)	115/187 (62)	20/59 (34)	28/57 (46)	16/30 (53)	19/28 (68)
28	121/188 (64)	121/179 (68)	29/54 (54)	29/58 (50)	23/31 (74)	23/28 (82)

32	125/183 (68)	119/183 (65)	32/51 (63)	28/55 (51)	22/33 (67)	25/28 (89)
36	131/181 (72)	115/175 (66)	31/53 (58)	33/53 (62)	21/30 (70)	24/27 (89)
40	125/181 (69)	114/174 (66)	31/51 (61)	32/55 (58)	22/29 (76)	21/25 (84)
44	125/178 (70)	112/165 (68)	32/51 (63)	27/55 (49)	22/29 (76)	25/27 (93)
48	128/179 (72)	109/169 (65)	31/49 (63)	34/55 (62)	22/28 (79)	25/26 (96)
52	121/174 (70)	115/172 (67)	27/50 (54)	40/56 (71)	20/29 (69)	24/27 (89)

Observed ACR20 response rates over 16 weeks (Study F2306)

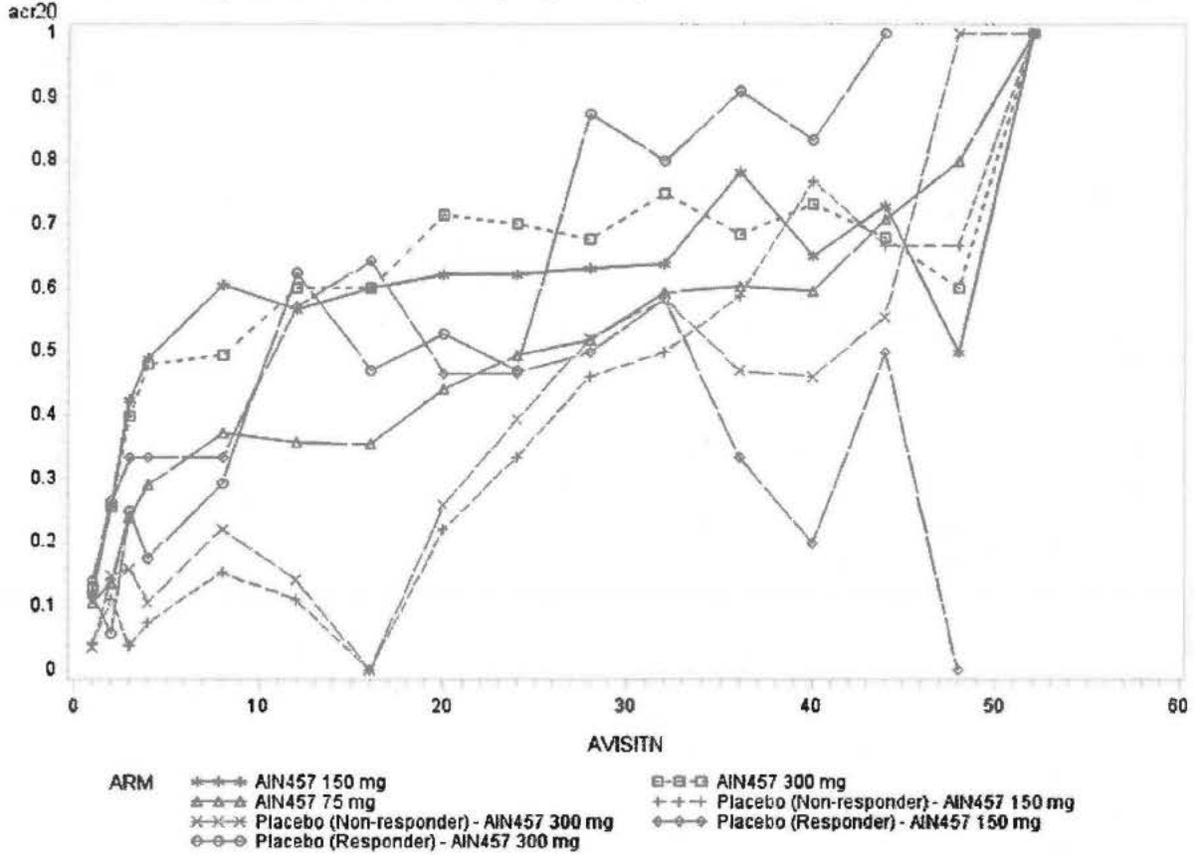


Note: Data for the placebo group were shifted 16 weeks to the left.

WEEK	AIN457 10mg/kg - 150 mg n/N (%)	AIN457 10mg/kg - 75 mg n/N (%)	Placebo Non-responder - AIN457 150 mg n/N (%)	Placebo Non-responder - AIN457 75 mg n/N (%)	Placebo Responder - AIN457 150 mg n/N (%)	Placebo Responder - AIN457 75 mg n/N (%)
0	-	-	0/60 (0)	2/61 (3)	16/30 (53)	19/28 (68)
1	42/192 (22)	41/190 (22)	-	-	-	-
2	61/193 (32)	67/191 (35)	-	-	-	-
4	88/197 (45)	87/194 (45)	15/60 (25)	23/60 (38)	23/31 (74)	23/28 (82)
8	102/192 (53)	100/190 (53)	20/59 (34)	26/57 (46)	22/33 (67)	25/28 (89)

12	113/190 (59)	104/188 (55)	29/54 (54)	29/58 (50)	21/30 (70)	24/27 (89)
16	115/191 (60)	106/189 (56)	32/51 (63)	28/55 (51)	22/29 (76)	21/25 (84)

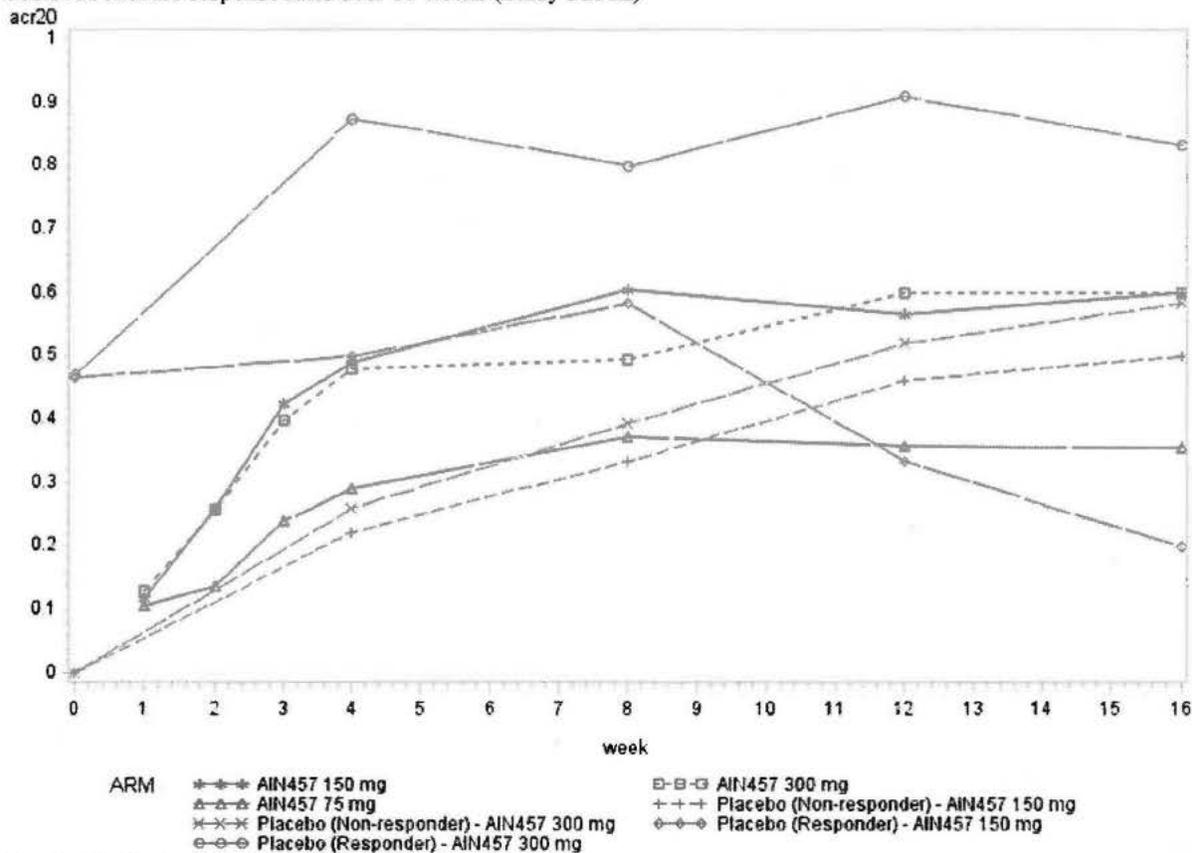
Observed ACR20 response rates over 52 weeks (Study F2312)



AVISITN	AIN457 150 mg	AIN457 300 mg	AIN457 75 mg	Placebo (Non-responder)	Placebo (Non-responder)	Placebo (Responder)	Placebo (Responder)
	n/N (%)	n/N (%)	n/N (%)	- AIN457 150 mg n/N (%)	- AIN457 300 mg n/N (%)	- AIN457 150 mg n/N (%)	- AIN457 300 mg n/N (%)
1	11/94 (12)	12/92 (13)	10/95 (11)	1/24 (4)	1/28 (4)	2/14 (14)	2/17 (12)
2	25/96 (26)	24/93 (26)	13/95 (14)	3/27 (11)	4/27 (15)	4/15 (27)	1/17 (6)
3	42/99 (42)	37/93 (40)	23/96 (24)	1/26 (4)	4/25 (16)	5/15 (33)	4/16 (25)
4	49/100 (49)	46/96 (48)	28/96 (29)	2/27 (7)	3/28 (11)	5/15 (33)	3/17 (18)
8	60/99 (61)	47/95 (50)	35/94 (37)	4/26 (15)	6/27 (22)	5/15 (33)	5/17 (29)
12	56/99 (57)	57/95 (60)	33/92 (36)	3/27 (11)	4/28 (14)	8/14 (57)	10/16 (63)
16	60/100 (60)	57/95 (60)	33/93 (35)	0/27 (0)	0/26 (0)	9/14 (64)	8/17 (47)
20	59/95 (62)	68/95 (72)	41/93 (44)	6/27 (22)	7/27 (26)	7/15 (47)	9/17 (53)
24	59/95 (62)	66/94 (70)	44/89 (49)	9/27 (33)	11/28 (39)	7/15 (47)	8/17 (47)

28	55/87 (63)	61/90 (68)	44/85 (52)	12/26 (46)	13/25 (52)	7/14 (50)	14/16 (88)
32	51/80 (64)	60/80 (75)	45/76 (59)	12/24 (50)	14/24 (58)	7/12 (58)	12/15 (80)
36	43/65 (78)	41/60 (68)	32/53 (60)	10/17 (59)	8/17 (47)	3/9 (33)	10/11 (91)
40	26/40 (65)	30/41 (73)	22/37 (59)	10/13 (77)	6/13 (46)	1/5 (20)	5/6 (83)
44	19/26 (73)	17/25 (68)	17/24 (71)	6/9 (67)	5/9 (56)	2/4(50)	2/2 (100)
48	6/12 (50)	6/10 (60)	8/10 (80)	2/3 (67)	3/3 (100)	0/1 (0)	0
52	2/2 (100)	1/1 (100)	1/1 (100)	2/2 (100)	1/1 (100)	0	0

Observed ACR20 response rates over 16 weeks (Study F2312)



Note: Data for the placebo group were shifted 16 weeks to the left.

WEEK	AIN457 150 mg n/N (%)	AIN457 300 mg n/N (%)	AIN457 75 mg n/N (%)	Placebo (Non-responder) - AIN457 150 mg n/N (%)	Placebo (Non-responder) - AIN457 300 mg n/N (%)	Placebo (Responder) - AIN457 150 mg n/N (%)	Placebo (Responder) - AIN457 300 mg n/N (%)
0	-	-	-	0/27 (0)	0/26 (0)	7/15 (47)	8/17 (47)
1	11/94 (12)	12/92 (13)	10/95 (11)	-	-	-	-
2	25/96 (26)	24/93 (26)	13/95 (14)	-	-	-	-
3	42/99 (42)	37/93 (40)	23/96 (24)	-	-	-	-

4	49/100 (49)	46/96 (48)	28/96 (29)	6/27 (22)	7/27 (26)	7/14 (50)	14/16 (88)
8	60/99 (61)	47/95 (50)	35/94 (37)	9/27 (33)	11/28 (39)	7/12 (58)	12/15 (80)
12	56/99 (57)	57/95 (60)	33/92 (36)	12/26 (46)	13/25 (52)	3/9 (33)	10/11 (91)
16	60/100 (60)	57/95 (60)	33/93 (35)	12/24 (50)	14/24 (58)	1/5 (20)	5/6 (83)

Table 41. Applicant's analysis of ACR20 components at Week 16 (Study F2306)

	Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
Adjusted TJC	SCK 75mg (N=202)	190	-11.8	vs. Placebo	-9.2 (1.4)	(-12.0, -6.5)	<0.0001
	SCK 150mg (N=202)	192	-12.3	vs. Placebo	-9.8 (1.4)	(-12.5, -7.1)	<0.0001
	Placebo (N=202)	185	-2.5				
Adjusted SJC	SCK 75mg (N=202)	190	-7.6	vs. Placebo	-4.1 (0.8)	(-5.8, -2.5)	<0.0001
	SCK 150mg (N=202)	192	-8.1	vs. Placebo	-4.6 (0.8)	(-6.2, -2.9)	<0.0001
	Placebo (N=202)	185	-3.5				
Patient's global assessment of disease activity	SCK 75mg (N=202)	190	-19.5	vs. Placebo	-16.0 (2.2)	(-20.3, -11.6)	<0.0001
	SCK 150mg (N=202)	191	-19.5	vs. Placebo	-15.9 (2.2)	(-20.2, -11.6)	<0.0001
	Placebo (N=202)	183	-3.6				
Physician's global assessment of disease activity	SCK 75mg (N=202)	187	-32.9	vs. Placebo	-25.4 (2.0)	(-29.3, -21.5)	<0.0001
	SCK 150mg (N=202)	188	-34.9	vs. Placebo	-27.4 (2.0)	(-31.3, -23.5)	<0.0001
	Placebo (N=202)	181	-7.5				
HAQ-DI	SCK 75mg (N=202)	189	-0.40	vs. Placebo	-0.25 (0.05)	(-0.34, -0.15)	<0.0001
	SCK 150mg (N=202)	190	-0.38	vs. Placebo	-0.23 (0.05)	(-0.32, -0.13)	<0.0001
	Placebo (N=202)	183	-0.15				
Patient's assessment of PsA pain	SCK 75mg (N=202)	190	-19.4	vs. Placebo	-14.5 (2.2)	(-18.8, -10.1)	<0.0001
	SCK 150mg (N=202)	190	-20.4	vs. Placebo	-15.4 (2.2)	(-19.8, -11.1)	<0.0001
	Placebo (N=202)	182	-5.0				
ESR (mm/hr)	SCK 75mg (N=202)	191	-12.0	vs. Placebo	-7.4 (1.5)	(-10.3, -4.5)	<0.0001
	SCK 150mg (N=202)	192	-14.9	vs. Placebo	-10.4 (1.5)	(-13.3, -7.5)	<0.0001
	Placebo (N=202)	186	-4.6				
hsCRP* (mg/L)	SCK 75mg (N=202)	189	0.55	vs. Placebo	0.58	(0.49, 0.69)	<0.0001
	SCK 150mg (N=202)	192	0.46	vs. Placebo	0.49	(0.41, 0.58)	<0.0001
	Placebo (N=202)	186	0.95				

Source: Reviewer & the Clinical Study Report for Study F2306 (pages 1022, 1048, 1074, 1100, 1126, 1152, 1178).

*log(hsCRP) was used in the MMRM analysis and the LSmean difference were back-transformed (exponentiation) to the ratio between treatment groups.

Table 42. Applicant's analysis of ACR20 components at Week 16 (Study F2312)

	Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
Adjusted TJC	SCK 75mg (N=99)	94	-4.8	vs. Placebo	-3.0 (1.9)	(-6.7, 0.7)	0.1104
	SCK 150mg (N=100)	100	-10.6	vs. Placebo	-8.9 (1.9)	(-12.6, -5.2)	<0.0001
	SCK 300mg (N=100)	97	-10.0	vs. Placebo	-8.2 (1.9)	(-11.9, -4.5)	<0.0001
	Placebo (N=98)	87	-1.8				
Adjusted SJC	SCK 75mg (N=99)	94	-3.1	vs. Placebo	0.1 (1.0)	(-1.8, 2.0)	0.9117
	SCK 150mg (N=100)	100	-4.8	vs. Placebo	-1.7 (1.0)	(-3.6, 0.2)	0.0828
	SCK 300mg (N=100)	97	-5.8	vs. Placebo	-2.7 (1.0)	(-4.5, -0.8)	0.0062
	Placebo (N=98)	87	-3.2				
Patient's global assessment of disease activity	SCK 75mg (N=99)	93	-13.8	vs. Placebo	-5.6 (3.0)	(-11.5, 0.3)	0.0626
	SCK 150mg (N=100)	100	-25.5	vs. Placebo	-17.3 (3.0)	(-23.2, -11.4)	<0.0001
	SCK 300mg (N=100)	96	-25.4	vs. Placebo	-17.3 (3.0)	(-23.1, -11.4)	<0.0001
	Placebo (N=98)	87	-8.2				
Physician's global assessment of disease activity	SCK 75mg (N=99)	93	-19.5	vs. Placebo	-4.6 (3.0)	(-10.5, 1.4)	0.1343
	SCK 150mg (N=100)	100	-29.3	vs. Placebo	-14.3 (3.0)	(-20.2, -8.4)	<0.0001
	SCK 300mg (N=100)	95	-34.8	vs. Placebo	-19.8 (3.0)	(-25.8, -13.9)	<0.0001
	Placebo (N=98)	87	-15.0				
HAQ-DI	SCK 75mg (N=99)	93	-0.26	vs. Placebo	-0.03 (0.06)	(-0.15, 0.10)	0.6669
	SCK 150mg (N=100)	100	-0.45	vs. Placebo	-0.22 (0.08)	(-0.35, -0.09)	0.0006
	SCK 300mg (N=100)	96	-0.55	vs. Placebo	-0.32 (0.08)	(-0.45, -0.19)	<0.0001
	Placebo (N=98)	87	-0.23				
Patient's assessment of PsA pain	SCK 75mg (N=99)	93	-13.0	vs. Placebo	-4.8 (3.1)	(-11.0, 1.3)	0.1251
	SCK 150mg (N=100)	100	-22.9	vs. Placebo	-14.8 (3.1)	(-20.9, -8.7)	<0.0001
	SCK 300mg (N=100)	96	-24.0	vs. Placebo	-15.8 (3.1)	(-22.0, -9.7)	<0.0001
	Placebo (N=98)	86	-8.2				
ESR (mm/hr)	SCK 75mg (N=99)	95	-9.5	vs. Placebo	-7.1 (1.8)	(-10.7, -3.6)	0.0001
	SCK 150mg (N=100)	100	-8.6	vs. Placebo	-6.2 (1.8)	(-9.8, -2.7)	0.0006
	SCK 300mg (N=100)	98	-10.3	vs. Placebo	-7.9 (1.8)	(-11.5, -4.4)	<0.0001
	Placebo (N=98)	89	-2.4				
hsCRP* (mg/L)	SCK 75mg (N=99)	94	0.59	vs. Placebo	0.63	(0.50, 0.80)	0.0002
	SCK 150mg (N=100)	100	0.61	vs. Placebo	0.66	(0.52, 0.84)	0.0006
	SCK 300mg (N=100)	98	0.47	vs. Placebo	0.51	(0.40, 0.64)	<0.0001

Placebo (N=98)	88	0.93
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Source: Reviewer & the Clinical Study Report for Study F2312 (pages 870, 888, 924, 942, 906, 978, 960).

*log(hsCRP) was used in the MMRM analysis and the LSmean difference were back-transformed (exponentiation) to the ratio between treatment groups.

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/s/

YONGMAN KIM
12/11/2015

GREGORY P LEVIN
12/11/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	125504 Supplement-01
Submission Date	03/18/2015
Brand Name	COSENTYX
Generic Name	Secukinumab
Clinical Pharmacology Reviewer	Lei He, Ph.D.
Clinical Pharmacology Team Leader	Ping Ji, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Novartis
Submission Type; Code	351(a); standard review
Formulation; Strength(s)	<ul style="list-style-type: none"> • Injection: 150 mg/mL solution in a single-use Sensoready pen • Injection: 150 mg/mL solution in a single-use prefilled syringe • For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution (for healthcare professional use only)
Indication	<p>Adult patients with active psoriatic Arthritis (PsA) (b) (4)</p> <p>(b) (4)</p>
Dosage Regimen	<ul style="list-style-type: none"> • For patients with coexistent moderate-to severe plaque psoriasis (b) (4) the recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. Each 300 mg dose is given as two subcutaneous injections of 150 mg. • For all other patients, the recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks.

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1. Executive Summary

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the proinflammatory cytokine interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. COSENTYX (Secukinumab, Novartis) was approved in the United States for the treatment of moderate to severe plaque psoriasis (PsO) on 01/21/2015 under BLA125504. The approved dosing regimen is 300 mg by subcutaneous (SC) injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks (Q4W). For some patients, 150 mg may be acceptable.

Novartis submitted BLA125504 Supplement-01 on 03/18/2015 seeking the approval of COSENTYX for the treatment of psoriatic arthritis (PsA) with the proposed dosing regimen of “150 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg starting at Week 4. For PsA patients [REDACTED] (b) (4) [REDACTED] with concomitant moderate to severe plaque psoriasis, the recommended dose of secukinumab is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 300 mg starting at Week 4.”

A total of three clinical trials in PsA patients have been submitted. Study A2206 is a Phase 2, randomized, double-blind, placebo-controlled, proof-of-concept study in PsA patients. Studies F2306 and F2312 are Phase 3, randomized, double-blind, placebo-controlled, multicenter studies in PsA patients to demonstrate the efficacy of secukinumab at Week 24.

1.1 Recommendations

From a Clinical Pharmacology perspective, the application is acceptable for approval for the treatment active PsA in adult patients provided that the Applicant and the Agency come to a mutually satisfactory agreement with the language in the labeling.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the proinflammatory IL-17A and inhibits its interaction with the IL-17 receptor. COSENTYX (Secukinumab, Novartis) was approved in the United States for the treatment of moderate to severe PsO on 01/21/2015 under BLA125504. The approved dosing regimen is 300 mg by SC injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg Q4W. For some patients, 150 mg may be acceptable.

Novartis submitted BLA125504 Supplement-01 on 03/18/2015 seeking the approval of COSENTYX for the treatment of PsA with the proposed dosing regimen of “150 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg starting at Week 4. For PsA patients (b) (4) with concomitant moderate to severe plaque psoriasis, the recommended dose of secukinumab is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 300 mg starting at Week 4.”

The PsA clinical development program includes 1 Phase 2 proof-of-concept study and 2 Phase 3 confirmatory studies in PsA. The review status is standard.

Pharmacokinetics

The PK properties of secukinumab in PsA patients were similar to those in plaque psoriasis patients.

Population PK analysis indicated that body weight is the only significant covariate (absolute change > 20%) affecting secukinumab PK in PsA, which was consistent with the findings in PsO. Methotrexate did not appear to influence secukinumab PK significantly.

Exposure-Response Relationship for Efficacy

The efficacy of secukinumab in PsA patients was evaluated in the two pivotal, placebo-controlled Phase 3 studies (Studies F2312 and F2306). Secukinumab SC150 mg-SC150 mg and SC300 mg-SC300 mg offered clinically meaningful benefit for patients in ACR20 at Week 24. Additional dose increase did not lead to additional increase in ACR20 response rate. Comparable response rates between IV loading regimen and SC 150 or 300 mg loading regimen indicated that additional exposure did not lead to clinically meaningful increase in efficacy.

In the exploratory exposure-response analyses based on the response rate and trough concentration at Week 24 in Study F2312, the exposure-response curve flattens at C_{min} levels that are higher than 20 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC150 mg-SC150 mg dosing regimen. A trend was also observed for increased responses with higher C_{min} concentrations for ACR50, ACR70, PASI (75/90), DAS28, and PASI75.

Exposure-Response Relationship for Safety

Exposure-response relationships from Phase 3 studies (Studies F2312 and F2306) showed no effect of exposure on the occurrence of any AE, infections and infestations, upper respiratory tract infections, nasopharyngitis, and urinary tract infection. Possible trend of higher occurrence of SAE and oral herpes with high exposure was observed. No effect of exposure on the occurrence of any AE or infections and infestation was observed in the subgroup analyses.

Dose Selection

During the clinical development of secukinumab, the SC or IV loading doses followed by

SC maintenance doses were evaluated in PsA patients. At the proposed dosing regimen, secukinumab met the pre-specified primary endpoint. Our exploratory post-hoc analysis further evaluated the effect of the loading dose on PK, immunogenicity, and efficacy. With the loading doses, the time to reach the steady state concentration was ~24 weeks (Study F2312) or longer (Study F2306). The anti-secukinumab antibody rate appeared comparable in patients with loading doses (n=4) and without loading doses (patients who switched from placebo to secukinumab, n=3). The placebo patients who were randomized to secukinumab treatment (without loading doses) appeared to have similar responses in ACR20 to those who were initially randomized to secukinumab treatment (with loading doses). These analyses indicate that although some residual effects of the loading doses still existed at Week 24 (primary efficacy assessment), secukinumab could remain effective after the loading dose effect is diminished or without the administration of a loading dose. However, there are limitations to the analyses for placebo patients who switched to secukinumab without loading dose.

Immunogenicity

In the PsA Phase 3 trials, less than 1% of subjects developed anti-secukinumab antibodies and there was no evidence of the impact of anti-secukinumab antibodies on secukinumab PK, efficacy, and safety. However, no definitive conclusion can be drawn on the lack of impact of ADA because of the small number of subjects with treatment-emergent ADA.

2. Question Based Review

2.1 Regulatory history

COSENTYX (Secukinumab, Novartis) was approved in the United States for the treatment of moderate to severe PsO on 01/21/2015 under BLA125504. The approved dosing regimen is 300 mg by SC injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg Q4W. For some patients, 150 mg may be acceptable.

Novartis submitted BLA125504 Supplement-01 on 03/18/2015 seeking the approval of COSENTYX for the treatment of PsA with the proposed dosing regimen of “150 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg starting at Week 4. For (b) (4) patients with concomitant moderate to severe plaque psoriasis, the recommended dose of secukinumab is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 300 mg starting at Week 4.”

2.2 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA.

The clinical pharmacology studies are summarized in Table 1.

Table 1. Overview of Clinical Development Program

Clinical Trial	Study ID	Population	Study Design	Treatment
Phase 2 proof-of-concept study	A2206	PsA (n=42)	Randomized, double-blind, placebo controlled	IV 10 mg/kg at D1 and D22 Placebo
Pivotal Phase 3 studies (primary endpoint analysis at Wk 24)	F2306	PsA (n=606)	Randomized, double-blind, placebo control	IV 10 mg/kg at Wks 0, 2 and 4, then SC 75 or 150 mg q4w from Wk 8 to Wk 104 Placebo at Wks 0, 2 and 4, then SC q4w at Wks 8 and 12 or Wks 8 to Wk 20
	F2312	PsA (n=387)	Randomized, double-blind, placebo control	SC 75, 150, 300 mg at Wks 0, 1, 2 and 3, then q4w from Wk 4 to Wk 256 SC PBO at Wks 0, 1, 2 and 3 then q4w at Wks 4 to 12 or Wks 4 to 20

2.3 General Attributes of the Drug

2.3.2 What are the proposed mechanism of action and therapeutic indications?

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to IL-17A cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines. The proposed indication is the treatment of PsA.

2.3.3 What are the proposed dosages and routes of administration?

The proposed dosing regimen for the treatment of PsA is:

- For patients with coexistent moderate-to-severe plaque psoriasis (b)(4) (b)(4) the recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. Each 300 mg dose is given as two subcutaneous injections of 150 mg.
- For all other patients, the recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks.

2.4 General Clinical Pharmacology

2.4.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The study design of clinical studies supporting the proposed indication is summarized in Table 1 under Section 2.2, including one Phase 2 proof-of-concept (POC) study and two pivotal Phase 3 trials in PsA.

2.4.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

In the Phase 2 POC study, Study A2206, the primary efficacy endpoint is ACR20

response at Week 6. In the Phase 3 confirmatory studies, Studies F2306 and F2312, the primary efficacy endpoint is ACR20 response at Week 24. Secondary efficacy variables in these studies reflected the multi-faceted aspects of active PsA disease, including skin disease, joint disease, physical function and health-related quality of life, as measured by PASI, DAS28-CRP, SF-36 PCS, HAQ-DI, ACR50, dactylitis and enthesitis. In Study F2306, the efficacy of secukinumab on joint structural damage as measured by vdH-mTSS was also assessed as a secondary efficacy endpoint.

2.4.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, total secukinumab concentrations, i.e., free secukinumab plus secukinumab bound to IL-17A, was determined in human serum using an ELISA method with an LLOQ of 80 ng/mL.

No new bioanalytical methods have been used in studies with PsA. Please refer to the Clinical Pharmacology Review for BLA125504 by Dr. Jie Wang for more details.

2.5 Dose/Exposure-Response

2.5.1 What are the characteristics of the dose/exposure-response relationship for efficacy?

There appears a dose/exposure-response relationship for ACR20 response rate of secukinumab in PsA patients.

The efficacy of secukinumab in PsA was evaluated in the two pivotal, placebo-controlled Phase 3 studies (Studies F2312 and F2306) (Figures 1 and 2). In Study F2312, the dose related superiority of secukinumab compared with placebo was demonstrated following all three doses (SC75mg-SC75mg, SC150mg-SC150mg, and SC300 mg-SC300 mg). At Week24, the ACR20 (primary endpoints), ACR50, and ACR70 response rates were similar between SC150mg-SC150mg and SC300 mg-SC300 mg, while the magnitude of effect of SC75mg-SC75mg was approximate half or less than half compared with SC150mg-SC150mg or SC300 mg-SC300 mg. For PASI75 and PASI90 response rate (secondary endpoints) at Week 24, both SC 150 mg and 300 mg regimens, but not SC75 mg, were superior to placebo, and SC300 mg appeared superior to SC150 mg. In Study F2306, both doses (IV10 mg/kg-SC75 mg and IV10 mg/kg-SC150 mg) were effective compared to placebo in reducing signs and symptoms associated with PsA at Week 24: the ACR20 response rate was 50.5% for secukinumab IV10 mg/kg-SC75 mg, 50.0% for secukinumab IV10 mg/kg-SC150 mg and 17.3% for placebo.

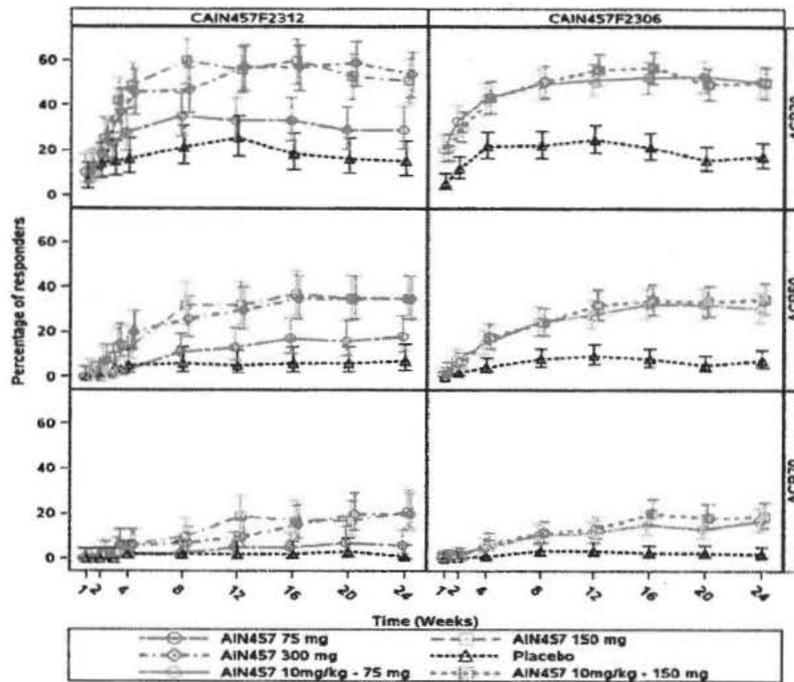


Figure 1. Time course of ACR20, ACR50 and ACR70 response rates (+ 95%CI) by study and treatment up to Week 24 (non-responder imputation) for studies F2312 and F2306 (based on individual study results) (Full analysis set)
 (Source: Figure 3-2, Summary of Clinical Efficacy for PsA)

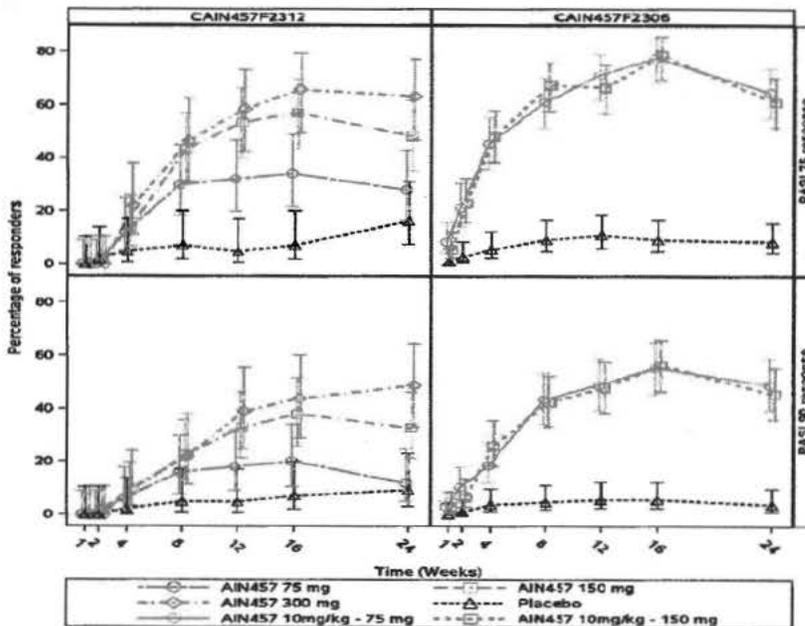


Figure 2. Time course of PASI75 and PASI90 response rates (+ 95%CI) by study and treatment up to Week 24 for studies F2312 and F2306 (based on individual study results) (Psoriasis subset)
 (Source: Figure 3-3, Summary of Clinical Efficacy for PsA)

Exploratory exposure-response analyses were also performed based on the response rate at Week 24 and trough concentration (C_{min}) at Week 24 in Study F2312. The exposure-response curve flattens at C_{min} levels that are higher than 20 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC150mg-SC150mg dosing regimen. Doubling of the C_{min} from 20 to 40mcg/mL induces an improvement of ~ 5% in the ACR20 response rates (Figure 3). A trend was also observed for increased responses with higher C_{min} concentrations for ACR50, ACR70, PASI (75/90), DAS28, and PASI75 (Figure 4).

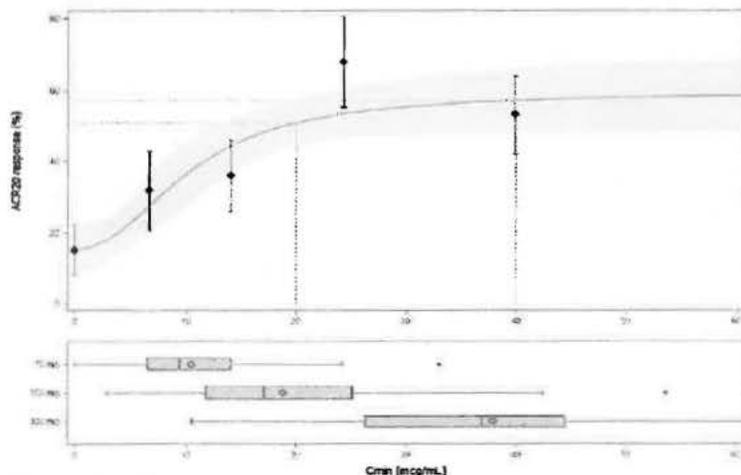


Figure 3. ACR20 response rate versus C_{min} concentration at Week 24 (F2312)
 (Source: Figure 4-1, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients)

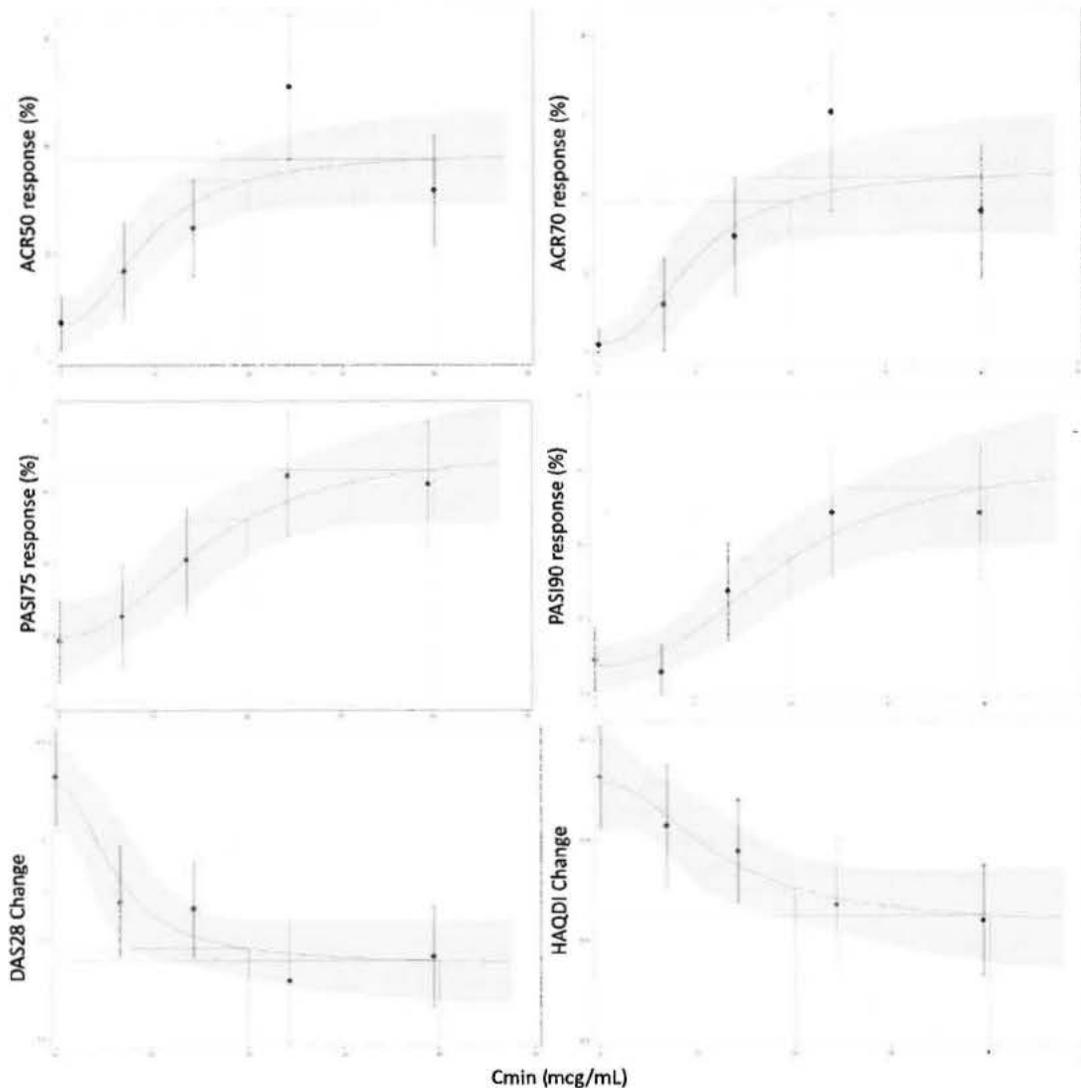


Figure 4. ACR50 response rate, ACR70 response rate, PASI75 response rate, PASI90 response rate, mean DAS28-CRP change from baseline, and mean HAQ-DI change from baseline versus Cmin concentration at Week 24 (F2312)

(Adapted from Figures 4-2 to 4-7, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients)

2.5.2 What are the characteristics of the exposure-response relationships for safety?

There appeared no clear trend for the exposure-response relationship for safety.

Figure 5 shows the exposure-response relationships for the following categories of AEs: any AE, any SAE, infections and infestations, upper respiratory tract infections, nasopharyngitis, urinary tract infection and oral herpes, respectively. There was no

evidence of an effect of Cmin in those categories of AEs, except for SAEs and oral herpes where an increasing trend with exposure was seen.

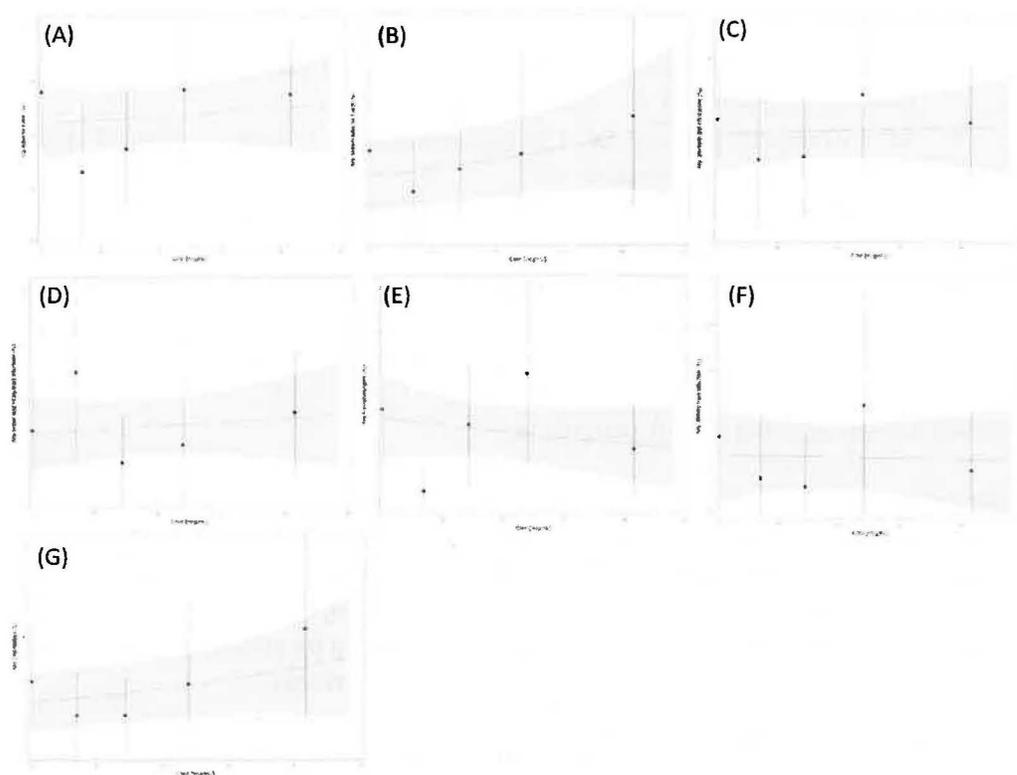


Figure 5. Occurrence of any AE (A), any SAE (B), any infections and infestations (C), upper respiratory tract infections (D), nasopharyngitis (E), urinary tract infection (F), oral Herpes (G) versus Cmin concentration at Week 16 (Study F2312): Y-axis represent various categories of AEs and X-axis represent Cmin concentration.

(Adapted from Figures 4-17, 4-18, 4-19, 4-20, 4-21, 4-22, and 4-23, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients)

2.5.3 Is the proposed dosing regimen for COSENTYX appropriate?

The two Phase 3 confirmatory studies in PsA were randomized, double-blind, placebo-controlled, multicenter studies in PsA to demonstrate the efficacy of secukinumab at Week 24 (Studies F2306 and F2312). The dosing regimens assessed in these two studies include:

Study F2306

- IV 10 mg/kg-SC 75mg: IV 10 mg/kg at Weeks 0, 2 and 4, then SC 75 mg q4w starting at Week 8
- IV 10 mg/kg-SC 150mg: IV 10 mg/kg at Weeks 0, 2 and 4, then SC 150 mg q4w starting at Week 8
- Placebo: non-responders were re-randomized (1:1) to receive SC 75 mg or

150 mg q4w starting at Week 16; responders were re-randomized (1:1) to receive SC 75 mg or 150 mg q4w starting at Week 24

Study F2312

- SC 75 mg-SC 75 mg: SC 75 mg at Weeks 0, 1, 2 and 3, then SC 75 mg q4w starting at Week 4
- SC 150 mg-SC 150 mg: SC 150 mg at Weeks 0, 1, 2 and 3, then SC 150 mg q4w starting at Week 4
- SC 300 mg-SC 300 mg: SC 300 mg at Weeks 0, 1, 2 and 3, then SC 300 mg q4w starting at Week 4
- Placebo: non-responders were re-randomized (1:1) to receive SC 150 mg or 300 mg q4w starting at Week 16; responders were re-randomized (1:1) to receive SC 150 mg or 300 mg q4w starting at Week 24

The proposed dosing regimen in PsA patients is:

- For patients with coexistent moderate-to-severe plaque psoriasis (b) (4) (b) (4) the recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.
- For all other patients, the recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks.

The proposed dosing regimen was investigated in the confirmative Phase 3 study F2312. The dosing regimen without loading dose was not evaluated in any of the confirmative studies. We evaluated the proposed dosing regimen based on its impact on PK, efficacy, and immunogenicity.

Efficacy

A SC loading dose followed by SC injections of either 75 mg, 150 mg or 300 mg showed statistical significance over placebo for the primary endpoint ACR20 at Week 24. Secukinumab SC 150 mg and 300 mg offered clinically meaningful benefit for patients in ACR20 at Week 24 (Figures 1 and 2). Additional dose increase did not lead to additional increase in ACR20 response rate. After switching to secukinumab, the response rate in placebo group was similar over time as the treatment groups in Study F2306 (Figure 6), indicating that secukinumab could remain effective after the loading dose effect is diminished or without the administration of a loading dose. Further assessments of secukinumab efficacy and safety from the pivotal trials will be reviewed in the medical and statistical reviews (Dr. Raj Nair and Dr. Yongman Kim).

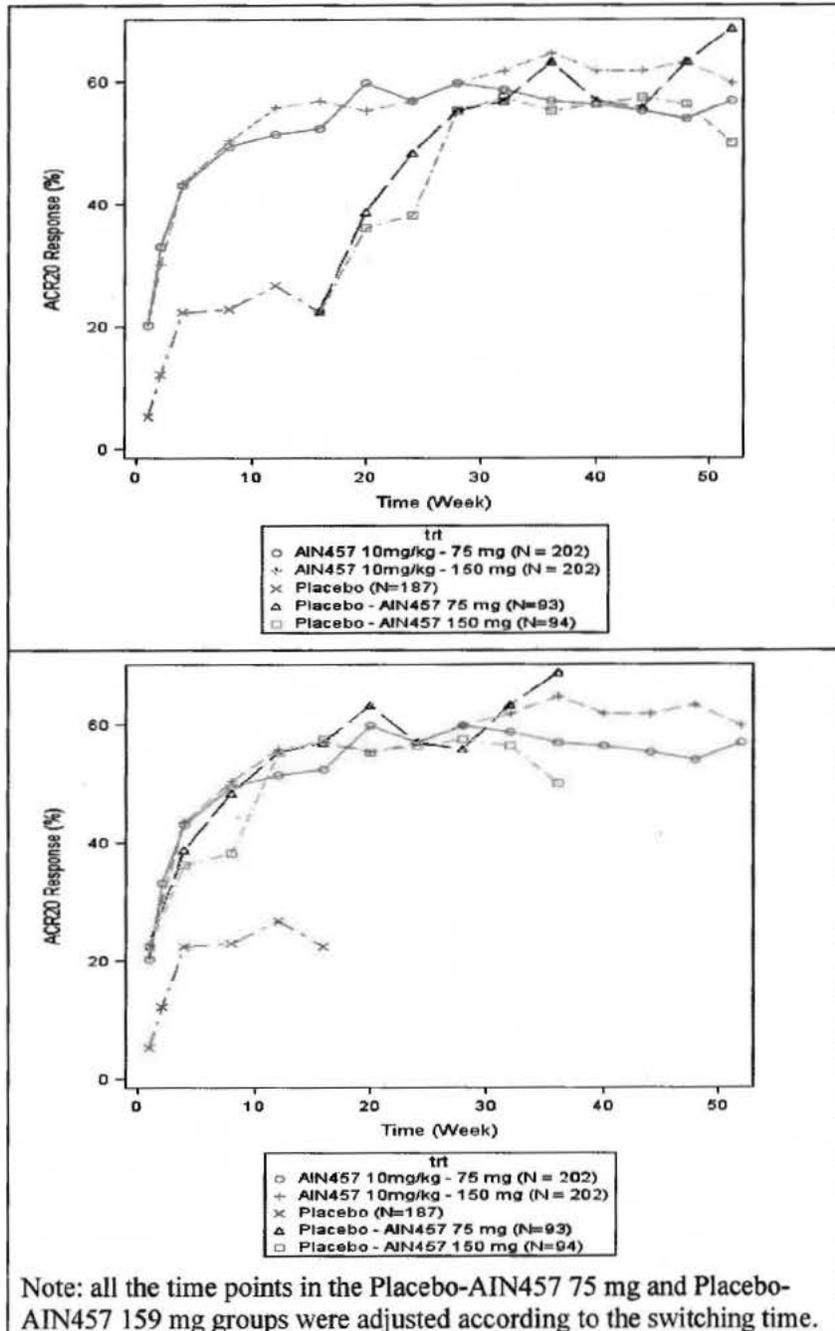


Figure 6. ACR20 response rate over time in Study F2306
(Data source: Table 14.2-1.5 Page 462 CSR F2306)

PK

With the loading doses of IV 10 mg/kg once a week for three weeks, the trough concentrations up to Week 24 appeared higher than those in Week 52 (Study F2306, Table 2). With the loading doses of SC 75 to 300 mg once a week for three weeks, the trough concentrations up to Week 16 appeared higher than those in Week 24 (Study

F2312, Table 3). Therefore, time to reach the steady state concentrations was about ~24 weeks or later.

Table 2. Secukinumab trough concentrations by treatment and visit in Study F2306

	Secukinumab 10 mg/kg-75 mg	Secukinumab 10 mg/kg-150 mg	Placebo non- responders – secukinumab 75 mg	Placebo non- responders – secukinumab 150 mg	Placebo responders – secukinumab 75 mg	Placebo responders – secukinumab 150 mg
	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)
Week 4	130 ± 36.6 (201)	134 ± 37.1 (201)	-	-	-	-
Week 16	31.7 ± 18.2 (175)	40.0 ± 20.6 (183)	0.506 ± 3.99 (62)	0.0275 ± 0.215 (61)	-	-
Week 24	16.2 ± 10.0 (176)	24.4 ± 13.7 (179)	7.73 ± 3.26 (55)	13.0 ± 4.76 (55)	0.910 ± 3.16 (27)	0.00 ± 0.00 (31)
Week 52	10.2 ± 4.86 (153)	18.6 ± 8.05 (163)	11.9 ± 6.16 (49)	17.3 ± 7.75 (48)	12.0 ± 5.19 (18)	16.0 ± 6.63 (25)

Week = time since starting secukinumab; Conc = secukinumab concentration.
Source: Listing 16.2.6-1.17 and Table 14.2-41.1.
(Source: Table 11-16, Study CAIN457F2306 report)

Table 3. Secukinumab trough concentrations by treatment and visit in Study F2312

Visit	AIN457 75 mg		AIN457 150 mg		AIN457 300 mg		Placebo non-responders 150 mg sc		Placebo non-responders 300 mg sc	
	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)
Week 4	79	24.9 ± 8.62	82	47.1 ± 13.3	80	98.4 ± 32.3	-	Placebo	-	Placebo
Week 16	69	12.0 ± 6.24	79	21.5 ± 10.2	79	43.1 ± 20.7	-	First dose	-	First dose
Week 24	74	10.6 ± 5.66	82	19.0 ± 9.87	83	38.8 ± 17.1	20	13.0 ± 6.65	11	28.1 ± 14.1

Conc = secukinumab concentration.
Sources: Listing 16.2.6-1.14 and Table 14.2-39.1.
(Source: Table 11-10, Study CAIN457F2312 report)

Immunogenicity

The immunogenicity data showed that 4 out of 606 patients in Study F2306 and 3 of 397 patients in Study F2312 were positive for anti-secukinumab antibodies post dose (Tables 4 and 5). In Study F2306, 3 placebo patients developed ADA after switching to secukinumab treatments and one patient with 10 mg/kg-150 mg developed ADA. In Study F2312, 1 placebo patient developed ADA after switching to secukinumab treatment of 150 mg and two patients with secukinumab 75 mg and 300 mg developed ADA. The anti-secukinumab antibody rate appeared comparable in patients with the loading doses (n=4) and in patients who switched from placebo to secukinumab without a load (n=3). However, the number of subjects with positive ADA was small and no definitive conclusion can be drawn.

Table 4. Overview of patients with anti-drug antibodies (ADA) in Study F2306

Patient ID	Group	Prior biologics	ADA ¹ (titer) / N-Ab	Impact on efficacy ²	AE possibly IG related (Day of onset) ³	PK ⁴
Patients with treatment emergent ADA (n=1)						
(b) (6)	Placebo Non-responder - AIN457 75 mg	None	Week 24 (no titer) / Yes	No	No	Normal
Patients with baseline and post-baseline persistent ADA (n=3)						
(b) (6)	AIN457 10mg/kg - 150 mg	None	BL (6.61) / Yes Week 24 (3.08) / Yes Week 52 (2.83) / Yes	No	No	Normal
	Placebo Non-responder - AIN457 150 mg	None	BL (no titer) / No Week 24 (no titer) / Yes Week 52 (17.8) / No Week 104 (no titer) / Yes	No	No	Normal
	Placebo Responder - AIN457 75 mg	Infliximab	BL (1.52) / Yes Week 24 (1.83) / Yes Week 52 (no titer) / Yes	No	Rhinitis allergic/ID-358 / non-SAE	NA, only 1 PK sample available
Patients with only baseline ADA (n=7)						
(b) (6)	AIN457 10mg/kg - 75 mg	Infliximab Etanercept	BL (no titer) / Yes	No	No	Normal
	AIN457 10mg/kg - 75 mg	Etanercept Adalimumab Abatacept	BL (2.35) / No	Possible	No	NA, only 1 BSL PK sample available
	AIN457 10mg/kg - 75 mg	None	BL (no titer) / No	No	No	Normal
	AIN457 10mg/kg - 75 mg	None	BL (3.97) / Yes	No	No	Normal
	AIN457 10mg/kg - 150 mg	None	BL (no titer) / No	No	No	Normal
	AIN457 10mg/kg - 150 mg	None	BL (1.55) / Yes	No	No	Normal
	Placebo Non-responder - AIN457 75 mg	None	BL (no titer) / Yes	Possible	No	Normal

(Source: Table 12-17, Study CAIN457F2306 report)

Table 5. Overview of patients with anti-drug antibodies (ADA) in Study F2312

Patient ID	Group	Prior biologics	ADA(titer) ¹ / N-Ab	Impact on efficacy ²	AE possibly IG related ³	PK ⁴
Patients with baseline and post-baseline persistent ADA (n=3)						
F2312-	(b) (6) AIN457 75 mg	None	Baseline (8.51) / No Week 24 (2.41) / No	None	None	Normal
F2312-	Placebo (Non-responder) - AIN457 150 mg	None	Baseline (8.43) / No Week 24 (2.65) / No	None	None	NA, Only 1 PK result available
F2312-	AIN457 300 mg	Etanercept	Baseline (6.50) / No Week 24 (6.94) / No	None	None	Normal
Patients with only baseline ADA (n=3)						
F2312-	(b) (6) Placebo (Non-responder) - AIN457 150 mg	None	Baseline (No titer) / No	None	None	Normal
F2312-	AIN457 75 mg	None	Baseline (No titer) / No	None	None	Normal
F2312-	Placebo (Non-responder) - AIN457 300 mg	Etanercept	Baseline (No titer) / No	None	None	Normal

ADA=anti-drug antibodies; IG=immunogenicity; N-Ab=neutralizing antibodies; NA=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Impact on efficacy = For patients who showed ADA at baseline, impact on efficacy is assessed by failure to achieve of >20% reduction in both tender and swollen joints for at least 2 consecutive visits while on secukinumab treatment.

³ IG-related AEs refers to preferred terms in the SMQ hypersensitivity

⁴ Normal PK was defined as: concentrations at Week 4, 16, 24 and 52 in individual patients that fit into the observed range for all patients without ADAs

Source: Listings 16.2.5-1.2, 16.2.6-1.1, 16.2.6-1.14, 16.2.7-1.1 and 16.2.8-1.2

(Source: Table 12-10, Study CAIN457F2312 report)

2.6 What are the PK characteristics of the drug?

2.6.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The PK of secukinumab was evaluated in healthy volunteers and patient populations. Secukinumab PK is similar among different populations (Table 6).

Table 6. PK of secukinumab (determined by NCA) in different populations

Study	Population	Dose	C _{max} (mcg/mL)	T _{max} (day)	T _{1/2} (day)	CL (L/d)	V _z (L)	F
A2106	HVs	300 mg SC (PFS)	43.2	5.0	25.9	--	--	--
		300 mg SC (LYO)	42.0	5.0	26.6	--	--	--
A2104	HVs	10 mg/kg IV	255	0.09	29.8	0.12	5.05	--
A2103	PsO	1 mg/kg IV	24.1	0.09	27.1	0.22	7.10	0.60
		150 mg SC	11.8	8.50	22.2	--	--	--
A2206	PsA	2×10 mg/kg IV	424	0.09	29.8	0.161	6.81	--
A2209	AS	2×10 mg/kg IV	364	21.08	28.1	0.157	6.06	--
		2×1 mg/kg IV	33.1	21.08	27.3	0.172	6.48	--
		2×0.1 mg/kg IV	5.51	21.12	34.3	0.118	5.83	--

(Adapted from Table 3-1, Addendum to Summary of Clinical Pharmacology)

2.6.3 What are the characteristics of drug absorption?

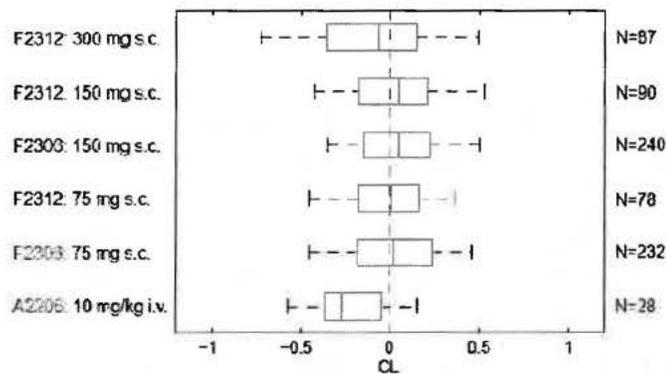
Based on population PK analysis, the bioavailability of secukinumab in PsA is 85% following the SC administration.

2.6.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

The exposure of secukinumab appears proportional to dose.

In study F2312, following SC 75, 150, or 300 mg at Weeks 0, 1, 2 and 3, then SC 75, 150, or 300 mg Q4W starting from Week 4, the pre-dose concentrations at Week 4 increased in a dose-proportional manner: 24.9, 47.1, and 98.4 mcg/mL at 75 mg, 150 mg, and 300 mg, respectively. At Week 24, when exposure was close to steady-state, mean concentrations were also dose-proportional: 10.6, 19.0 and 38.8 mcg/mL with inter-subject coefficients of variation of 53.5%, 51.8%, and 44.1% at 75 mg, 150 mg, and 300 mg, respectively.

In population PK analysis, the estimates of CL of secukinumab in PsA were consistent across studies and dose levels suggesting the dose-proportionality of secukinumab PK in the dose range from SC 75 mg to SC 300 mg (Figure 7):



Legend: 'Relative clearance' indicates relative to the clearance of CL = 0.19 L/Day in a 'typical' PsA patient of 84 kg (e.g. a relative clearance of 0.1 indicates a 10% relative increase in clearance). The left-most whisker represents 5th and the right-most whisker 95th percentile. The left border of the box represents 1st quartile (25%), the middle line is the second quartile (median), and the right border of the box is the 3rd quartile (75%).

Figure 7. Relative clearance by treatment group for secukinumab in psoriatic arthritis (after adjusting for bodyweight)

(Source: Figure 5-11, Population PK of secukinumab in PsA modeling report)

2.6.12 How do the PK parameters change with time following chronic dosing?

Based on the population PK analysis, residuals (PWRES, IWRES, and NPDE) versus time plots did not show time dependent trends, suggesting the time-independent PK of secukinumab following chronic dosing (Figure 8).

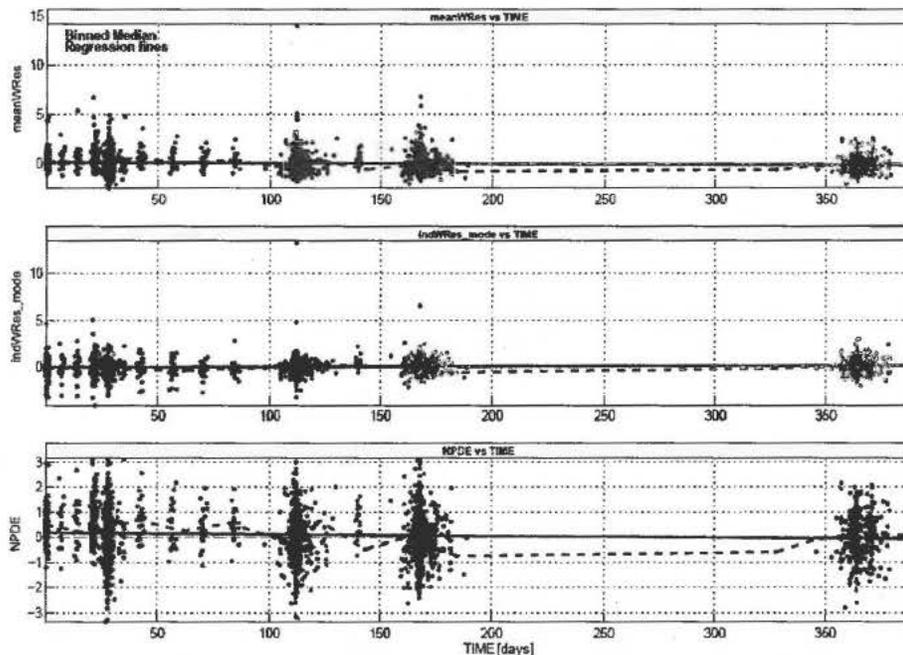


Figure 8. Model-based weighted residuals vs. time: No trend in residuals over time
(Source: Figure 5-12, Population PK of secukinumab in PsA modeling report)

2.7 Intrinsic Factors

2.7.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Based on the population PK analysis, body weight has been identified the significant intrinsic factor contributing the inter-subject variability in secukinumab exposure in PsA patients. The inter-subject variability on CL is 32%.

2.7.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Based on the dose-response relationships, for patients with coexistent moderate to severe plaque psoriasis, the recommended dose is 300 mg by SC injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks (See Section 2.5.1). For other patients, the recommended dose is 150 mg by SC injection at Weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks.

2.8 Extrinsic Factors

2.8.7 What are the drug-drug interactions?

No drug-drug interaction studies have been conducted with COSENTYX.

Population PK analysis in PsA and AS indicate the co-administration of methotrexate does not affect the disposition of secukinumab. Refer to the Pharmacometrics Review in Appendix 4.1 for more details.

2.8.8 Does the label specify co-administration of another drug?

For the treatment of PsA, COSENTYX is proposed to be used alone or in combination with methotrexate.

2.9 Pharmacodynamics

Total IL-17A (i.e. free IL-17A plus IL-17A complexed with secukinumab) can be regarded as a biomarker for secukinumab and is indicative of target engagement. Based on observations in healthy subjects and various patient populations, including PsA and AS, total IL-17A levels rise until a plateau is reached during one to two weeks after the first dose of secukinumab. Median maximum serum concentrations of total IL-17A are in a range between 100 and 150 pg/mL with a high inter-subject variability. In the elimination phase, the total IL-17A clearance is very similar to the secukinumab clearance (similar half-lives for bound IL-17A and secukinumab), suggesting the clearance of IL-17A exclusively in its bound form to secukinumab.

2.10 Immunogenicity

2.10.1. What is the incidence (rate) of the formation of the anti-drug/secukinumab antibodies (ADA)?

The incidence of ADA formation in clinical studies in PsA patients is summarized in the Table as blow. Overall, the incidence of treatment-emergent ADA formation is low (<1%).

Table 7. Summary of the incidence of ADA formation in patients with PsA

Study	Number of subject with ADA+	Subject ID		Cmin (µg/mL)	Responder (Y/N)
		Treatment-emergent ADA+ and nAb+	Non-treatment emergent ADA+ and nAb-		
F2206	0/42	NA	NA	NA	NA
F2306	4/606	(b) (6)	-	5.63	N
		-	(b) (6)	12.5	Y
		-	(b) (6)	11.7	N
		-	(b) (6)	NA	Y
F2312	3/397	-	(b) (6)	18.4	Y
		-	(b) (6)	23.3	N
		-	(b) (6)	35.0	N

Treatment-emergent ADA+: ADA is negative pre-dose and positive post-dose.

Non-treatment emergent ADA+: ADA is positive pre-dose and post-dose

nAb+: positive neutralizing antibodies

nAb-: negative neutralizing antibodies

2.10.2. What are the impacts of ADA on secukinumab PK, efficacy and safety?

There was no evidence of the impact of anti-secukinumab antibodies on secukinumab PK, efficacy, and safety. However, given the small number of subjects with treatment-emergent ADA, no definitive conclusion can be drawn on the lack of impact of ADA.

7 out of 1045 (0.67%) PsA patients were detected positive for anti-secukinumab antibodies. Only 1 of the 7 patients had neutralizing antibodies and the patient reverted to a seronegative state by Week 52. At Week 24, the secukinumab Cmin in most of these patients were comparable to the Cmin in all tested PsA patients (Mean 19.1 mcg/mL (SD 8.31 mcg/mL) [Range 8.49-33.6 mcg/mL]), except that the Cmin (5.63 mcg/mL) in Subject (b) (6) (nAb+) was slightly lower. By Week 24, 4 of the 7 patients were treatment non-responder while the other 3 patients were responder. No immunogenicity related AEs were reported.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. Labeling statements to be removed are shown in red strikethrough font and suggested labeling to be included is shown in underline blue font.



4. Appendix

4.1 Appendix –PM Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

BLA Number	125504 Supplement-01
Brand Name	COSENTYX
Drug Components	Secukinumab
Indication	Adult patients with active PsA, (b) (4) (b) (4)
Dosing Regimen	<ul style="list-style-type: none">For patients with coexistent moderate-to severe plaque psoriasis (b) (4) the recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. Each 300 mg dose is given as two subcutaneous injections of 150 mg.For all other patients, the recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks.
Pharmacometrics Primary Reviewer	Lei He, Ph.D.
Pharmacometrics Secondary Reviewer	Ping Ji, Ph.D.
Sponsor	Novartis

SUMMARY OF FINDINGS

The previously developed population PK model in psoriasis was used as a basis to support the development of the population PK model in PsA. A total of 2686 secukinumab serum concentrations of 755 patients from Studies A2206, F2306 and F2312 were used in the population PK analysis. The model has been repeated by the reviewer.

The purpose of this review is to address the following key questions.

1. Are there any covariates that influence the PK of secukinumab in PsA?

The influence of various covariates on secukinumab PK in PsA has been evaluated in the population model development (Table 4-1).

Only body weight met the criterion for potential clinical relevance (absolute change > 20%) and thus was retained in the final population PK model. The clearance and volumes vary with body weight in an allometric relationship and the allometric exponents

for clearance and central volume of distribution were estimated to be 0.8 and 0.44, respectively.

The co-medication of methotrexate was found not to influence secukinumab PK significantly.

Table 4-1 Candidate covariates

Covariate	Model parameter
Bodyweight	CL, V_c , Q_1 , V_{p1}
Age	CL
Gender	CL
Asian / non-Asian	CL
Time since first diagnosis of PsA	CL
Response status for anti-TNF α therapy (naïve or inadequate responders)	CL, V_c , V_{p1}
Number of previously used biologics	CL
Concomitant use of methotrexate	CL
CRP at baseline	CL
PASI score at baseline	CL
DAS28 score at baseline	CL

(Source: Table 4-2, Population PK of secukinumab in PsA modeling report)

2. What are the characteristics of the dose/exposure-response relationship for efficacy?

There appears a dose/exposure-response relationship for ACR20 response rate of secukinumab in PsA patients.

The efficacy of secukinumab in PsA was evaluated in the two pivotal, placebo-controlled Phase 3 studies (Studies F2312 and 2306) (Figures 4-1 and 4-2). In Study F2312, the dose related superiority of secukinumab compared with placebo was demonstrated following all three doses (SC75mg-SC75mg, SC150mg-SC150mg, and SC300 mg-SC300 mg). At Week24, the ACR20 (primary endpoints), ACR50, and ACR70 response rates were similar between SC150mg-SC150mg and SC300 mg-SC300 mg, while the magnitude of effect of SC75mg-SC75mg was approximate half or less than half compared with SC150mg-SC150mg or SC300 mg-SC300 mg. In Study F2306, both doses (IV10 mg/kg-SC75 mg and IV10 mg/kg-SC150 mg) were effective compared to placebo in reducing signs and symptoms associated with PsA at Week 24: the ACR20 response rate was 50.5% for secukinumab 10 mg/kg-75 mg, 50.0% for secukinumab 10 mg/kg-150 mg and 17.3% for placebo. For PASI75 and PASI90 response rate (secondary endpoints) at Week 24, both SC 150 mg and 300 mg regimens, but not SC75 mg, were superior to placebo, and SC300 mg appeared superior to SC150 mg.

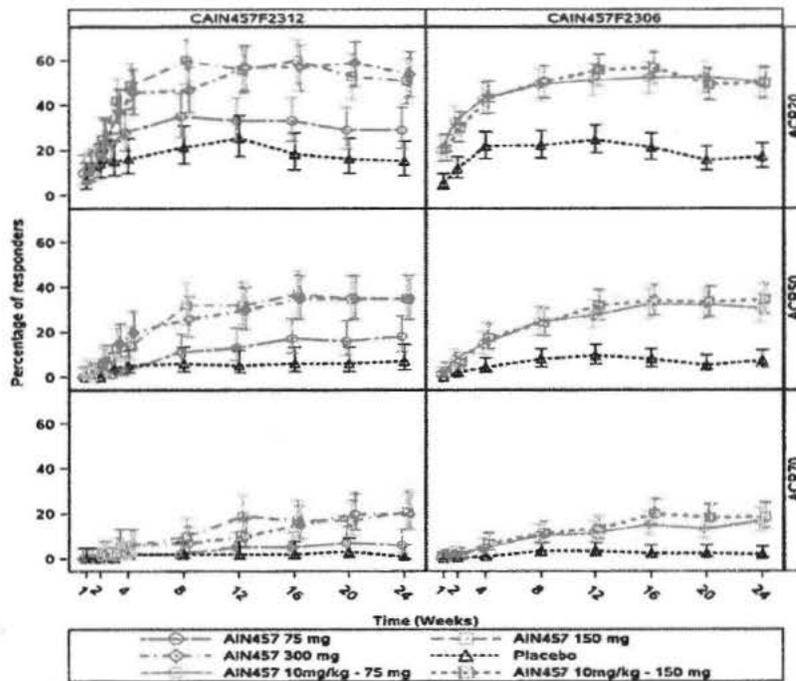


Figure 4-1. Time course of ACR20, ACR50 and ACR70 response rates (+ 95% CI) by study and treatment up to Week 24 (non-responder imputation) for studies F2312 and F2306 (based on individual study results) (Full analysis set)
 (Source: Figure 3-2, Summary of Clinical Efficacy for PsA)

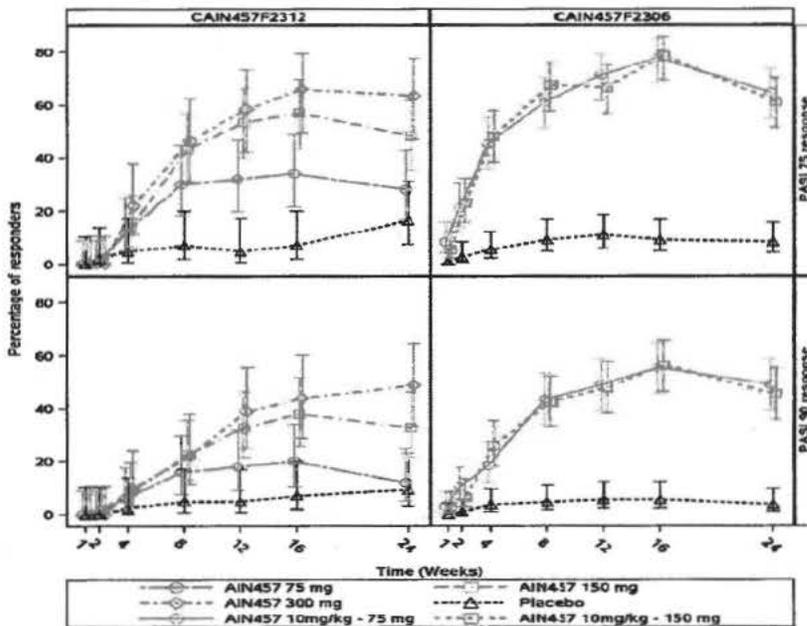


Figure 4-2. Time course of PASI75 and PASI90 response rates (+ 95% CI) by study and treatment up to Week 24 for studies F2312 and F2306 (based on individual study results) (Psoriasis subset)
 (Source: Figure 3-3, Summary of Clinical Efficacy for PsA)

Exploratory exposure-response analyses were also performed based on the response rate at Week 24 and trough concentration (Cmin) at Week 24. The exposure-response curve flattens at Cmin levels that are higher than 20 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC150 mg-SC150 mg dosing regimen. Doubling of the Cmin from 20 to 40mcg/mL induces an improvement of ~ 5% in the ACR20 response rates (Figure 4-3). A trend was also observed for increased responses with higher Cmin concentrations for ACR50, ACR70, PASI (75/90), DAS28, and PASI75 (Figure 4-4).

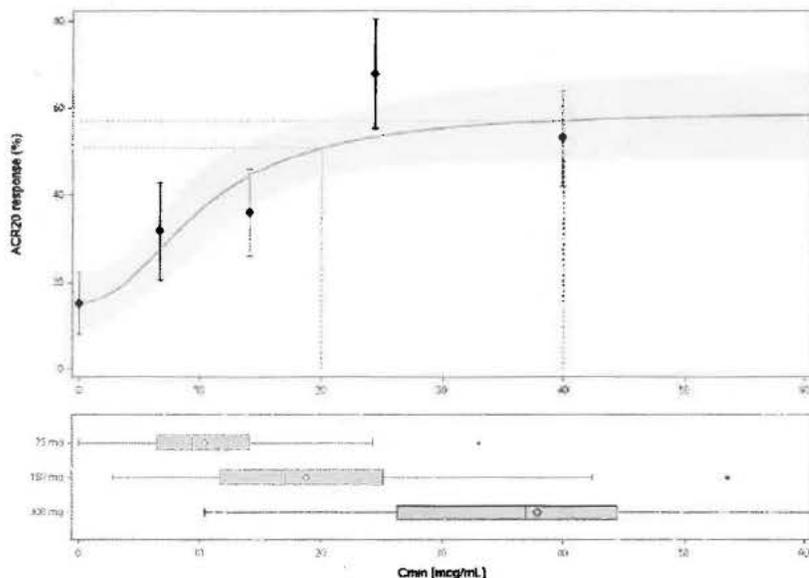


Figure 4-3. ACR20 response rate versus Cmin concentration at Week 24 (F2312)
 (Source: Figure 4-1, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients)

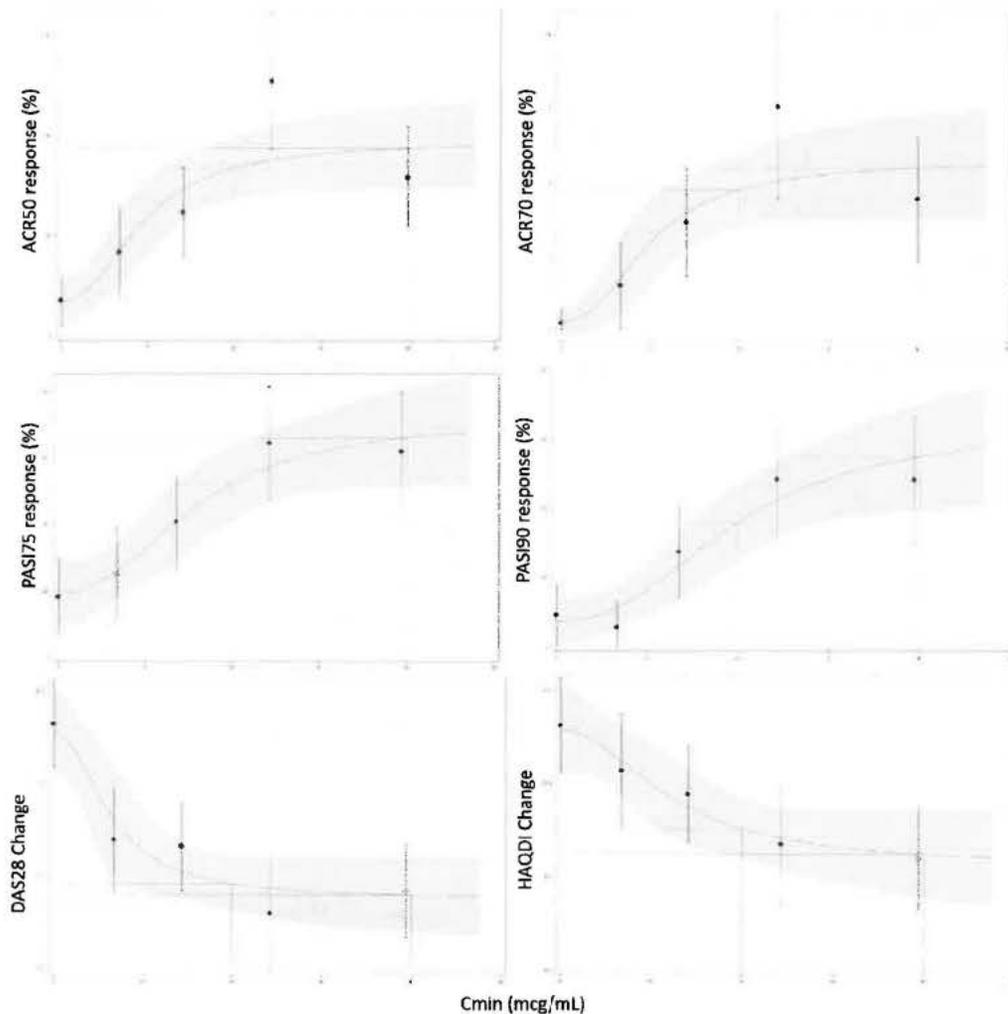


Figure 4-4. ACR50 response rate, ACR70 response rate, PASI75 response rate, PASI90 response rate, mean DAS28-CRP change from baseline, and mean HAQ-DI change from baseline versus Cmin concentration at Week 24 (F2312)

(Adapted from Figures 4-2 to 4-7, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients)

3. What are the characteristics of the exposure-response relationships for safety?

There appeared no clear trend for the exposure-response relationship for safety.

Figure 4-5 shows the exposure-response relationships for the following categories of AEs: any AE, any SAE, infections and infestations, upper respiratory tract infections, nasopharyngitis, urinary tract infection and oral herpes, respectively. There was no evidence of an effect of Cmin in those categories of AEs, except for SAEs and oral herpes where an increasing trend with exposure was seen.

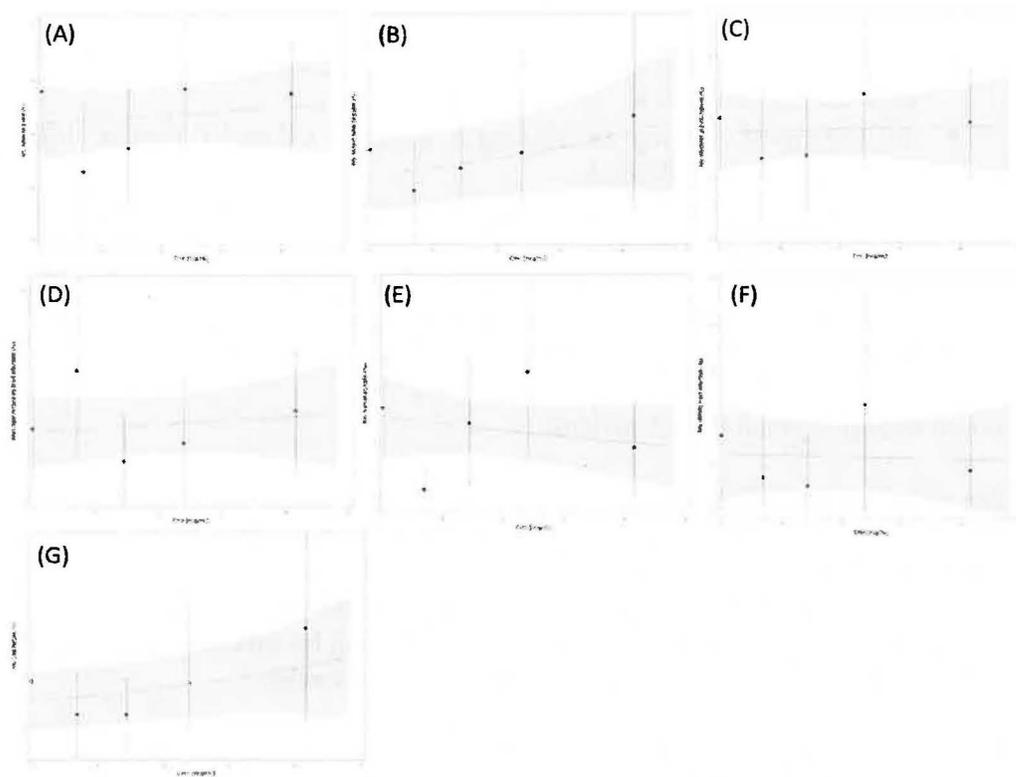


Figure 4-5. Occurrence of any AE (A), any SAE (B), any infections and infestations (C), upper respiratory tract infections (D), nasopharyngitis (E), urinary tract infection (F), oral Herpes (G) versus Cmin concentration at Week 16 (Study F2312): Y-axis represent various categories of AEs and X-axis represent Cmin concentration.

(Adapted from Figures 4-17, 4-18, 4-19, 4-20, 4-21, 4-22, and 4-23, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients)

4. Is the proposed dosing regimen for COSENTYX appropriate?

The two Phase 3 confirmatory studies in PsA were randomized, double-blind, placebo-controlled, multicenter studies in PsA to demonstrate the efficacy of secukinumab at Week 24 (Studies F2306 and F2312). The dosing regimens assessed in these two studies include:

Study F2306

- IV 10 mg/kg-SC 75mg: IV 10 mg/kg at Weeks 0, 2 and 4, then SC 75 mg q4w starting at Week 8
- IV 10 mg/kg-SC 150mg: IV 10 mg/kg at Weeks 0, 2 and 4, then SC 150 mg q4w starting at Week 8
- Placebo: non-responders were re-randomized (1:1) to receive SC 75 mg or 150 mg q4w starting at Week 16; responders were re-randomized (1:1) to receive SC 75 mg or 150 mg q4w starting at Week 24

Study F2312

- SC 75 mg-SC 75 mg: SC 75 mg at Weeks 0, 1, 2 and 3, then SC 75 mg q4w starting at Week 4
- SC 150 mg-SC 150 mg: SC 150 mg at Weeks 0, 1, 2 and 3, then SC 150 mg q4w starting at Week 4
- SC 300 mg-SC 300 mg: SC 300 mg at Weeks 0, 1, 2 and 3, then SC 300 mg q4w starting at Week 4
- Placebo: non-responders were re-randomized (1:1) to receive SC 150 mg or 300 mg q4w starting at Week 16; responders were re-randomized (1:1) to receive SC 150 mg or 300 mg q4w starting at Week 24

The proposed dosing regimen in PsA patients is:

- For patients with coexistent moderate to severe plaque psoriasis (b) (4) the recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.
- For all other patients, the recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks.

The proposed dosing regimen was investigated in the confirmative Phase 3 study F2312. The dosing regimen without loading dose was not evaluated in any of the confirmative studies. The proposed dosing regimen is evaluated based on its impact on PK, efficacy, safety and immunogenicity.

Efficacy

A SC loading dose followed by SC injections of either 75 mg, 150 mg or 300 mg showed statistical significance over placebo for the primary endpoint ACR20 at Week 24. Secukinumab SC 150 mg and 300 mg offered clinically meaningful benefit for patients in ACR20 at Week 24 (Figures 4-1 and 4-2). Additional dose increase did not lead to additional increase in ACR20 response rate. After switching to secukinumab, the response rate in placebo group was similar over time as the treatment groups in Study F2306 (Figure 4-6). However, there were limitations to the analysis for placebo patients who switched to secukinumab treatment. For Study F2312, the efficacy data after week 24 were not available. Further assessments of secukinumab efficacy and safety from the pivotal trials will be reviewed in the medical and statistical reviews (Dr. Raj Nair and Dr. Yongman Kim).

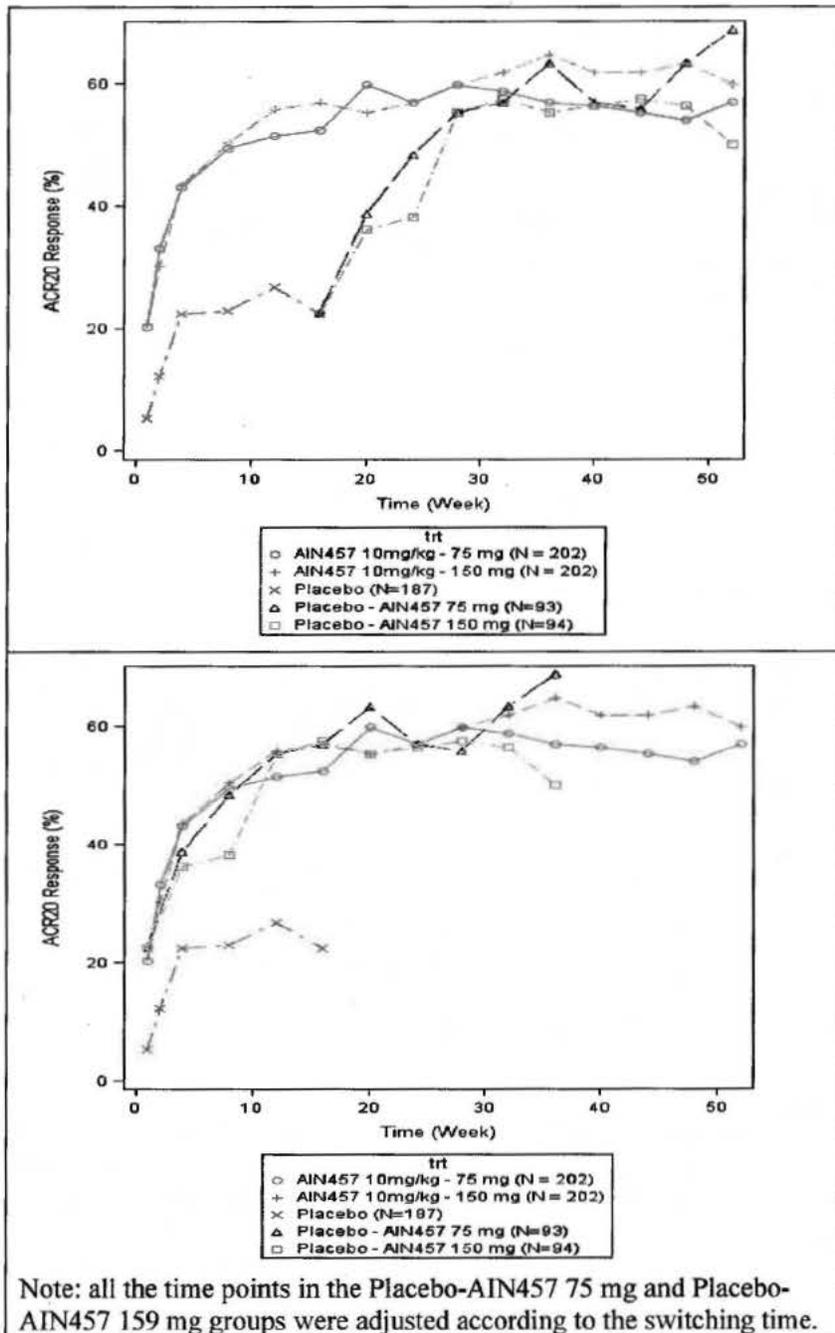


Figure 4-6. ACR20 response rate over time in Study F2306
(Data source: Table 14.2-1.5 Page 462 CSR F2306)

PK

With the loading doses of IV 10 mg/kg once a week for three weeks, the trough concentrations up to Week 24 appeared higher than those in Week 52 (Study F2306, Table 4-2). With the loading doses of SC 75 to 300 mg once a week for three weeks, the trough concentrations up to Week 16 appeared higher than those in Week 24 (Study

F2312, Table 4-3). Therefore, the time to steady state concentrations was ~24 weeks or later.

Table 4-2. Secukinumab trough concentrations by treatment and visit in Study F2306

	Secukinumab 10 mg/kg-75 mg	Secukinumab 10 mg/kg-150 mg	Placebo non- responders – secukinumab 75 mg	Placebo non- responders – secukinumab 150 mg	Placebo responders – secukinumab 75 mg	Placebo responders – secukinumab 150 mg
	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)
Week 4	130 ± 36.6 (201)	134 ± 37.1 (201)	-	-	-	-
Week 16	31.7 ± 18.2 (175)	40.0 ± 20.6 (183)	0.506 ± 3.99 (62)	0.0275 ± 0.215 (61)	-	-
Week 24	16.2 ± 10.0 (176)	24.4 ± 13.7 (179)	7.73 ± 3.26 (55)	13.0 ± 4.76 (55)	0.910 ± 3.16 (27)	0.00 ± 0.00 (31)
Week 52	10.2 ± 4.86 (153)	18.6 ± 8.05 (163)	11.9 ± 6.16 (49)	17.3 ± 7.75 (48)	12.0 ± 5.19 (18)	16.0 ± 6.63 (25)

Week = time since starting secukinumab; Conc = secukinumab concentration.

Source: Listing 16.2.6-1.17 and Table 14.2-41.1.

(Source: Table 11-16, Study CAIN457F2306 report)

Table 4-3. Secukinumab trough concentrations by treatment and visit in Study F2312

Visit	AIN457 75 mg		AIN457 150 mg		AIN457 300 mg		Placebo non- responders 150 mg sc		Placebo non- responders 300 mg sc	
	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)
Week 4	79	24.9 ± 8.62	82	47.1 ± 13.3	80	98.4 ± 32.3	-	Placebo	-	Placebo
Week 16	69	12.0 ± 6.24	79	21.5 ± 10.2	79	43.1 ± 20.7	-	First dose	-	First dose
Week 24	74	10.6 ± 5.68	82	19.0 ± 9.87	83	38.8 ± 17.1	20	13.0 ± 6.65	11	28.1 ± 14.1

Conc = secukinumab concentration.

Sources: Listing 16.2.6-1.14 and Table 14.2-39.1.

(Source: Table 11-10, Study CAIN457F2312 report)

Immunogenicity

The immunogenicity data showed that 4 out of 606 patients in Study F2306 and 3 of 397 patients in Study F2312 were positive for anti-secukinumab antibodies post dose (Tables 4 and 5). In Study F2306, 3 placebo patients developed ADA after switching to secukinumab treatments and one patient with 10 mg/kg-150 mg developed ADA. In Study F2312, 1 placebo patient developed ADA after switching to secukinumab treatment of 150 mg and two patients with secukinumab 75 mg and 300 mg developed ADA. The anti-secukinumab antibody rate appeared comparable with (n=4) and without (n=3) loading dose, however, the number of subjects with positive ADA was small and no definitive conclusion can be drawn.

Table 4-4. Overview of patients with anti-drug antibodies (ADA) in Study F2306

Patient ID	Group	Prior biologics	ADA ¹ (titer) / N-Ab	Impact on efficacy ²	AE possibly IG related (Day of onset) ³	PK ⁴
Patients with treatment emergent ADA (n=1)						
(b) (6)	Placebo Non-responder - AIN457 75 mg	None	Week 24 (no titer) / Yes	No	No	Normal
Patients with baseline and post-baseline persistent ADA (n=3)						
(b) (6)	AIN457 10mg/kg - 150 mg	None	BL (6.61) / Yes Week 24 (3.06) / Yes Week 52 (2.83) / Yes	No	No	Normal
	Placebo Non-responder - AIN457 150 mg	None	BL (no titer) / No Week 24 (no titer) / Yes Week 52 (17.6) / No Week 104 (no titer) / Yes	No	No	Normal
	Placebo Responder - AIN457 75 mg	Infliximab	BL (1.52) / Yes Week 24 (1.83) / Yes Week 52 (no titer) / Yes	No	Rhinitis allergic/D-356 / non-SAE	NA, only 1 PK sample available
Patients with only baseline ADA (n=7)						
(b) (6)	AIN457 10mg/kg - 75 mg	Infliximab Etanercept	BL (no titer) / Yes	No	No	Normal
	AIN457 10mg/kg - 75 mg	Etanercept Adalimumab Abatacept	BL (2.35) / No	Possible	No	NA, only 1 BSL PK sample available
	AIN457 10mg/kg - 75 mg	None	BL (no titer) / No	No	No	Normal
	AIN457 10mg/kg - 75 mg	None	BL (3.97) / Yes	No	No	Normal
	AIN457 10mg/kg - 150 mg	None	BL (no titer) / No	No	No	Normal
	AIN457 10mg/kg - 150 mg	None	BL (1.55) / Yes	No	No	Normal
	Placebo Non-responder - AIN457 75 mg	None	BL (no titer) / Yes	Possible	No	Normal

(Source: Table 12-17, Study CAIN457F2306 report)

Table 4-5. Overview of patients with anti-drug antibodies (ADA) in Study F2312

Patient ID	Group	Prior biologics	ADA(titer) ¹ / N-Ab	Impact on efficacy ²	AE possibly IG related ³	PK ⁴
Patients with baseline and post-baseline persistent ADA (n=3)						
F2312-	(b) (6) AIN457 75 mg	None	Baseline (8.51) / No Week 24 (2.41) / No	None	None	Normal
F2312-	Placebo (Non-responder) - AIN457 150 mg	None	Baseline (8.43) / No Week 24 (2.85) / No	None	None	NA, Only 1 PK result available
F2312-	AIN457 300 mg	Etanercept	Baseline (6.50) / No Week 24 (6.94) / No	None	None	Normal
Patients with only baseline ADA (n=3)						
F2312-	(b) (6) Placebo (Non-responder) - AIN457 150 mg	None	Baseline (No titer) / No	None	None	Normal
F2312-	AIN457 75 mg	None	Baseline (No titer) / No	None	None	Normal
F2312-	Placebo (Non-responder) - AIN457 300 mg	Etanercept	Baseline (No titer) / No	None	None	Normal

ADA=anti-drug antibodies; IG=immunogenicity; N-Ab=neutralizing antibodies; NA=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Impact on efficacy = For patients who showed ADA at baseline, impact on efficacy is assessed by failure to achieve of >20% reduction in both tender and swollen joints for at least 2 consecutive visits while on secukinumab treatment.

³ IG-related AEs refers to preferred terms in the SMQ hypersensitivity

⁴ Normal PK was defined as: concentrations at Week 4, 16, 24 and 52 in individual patients that fit into the observed range for all patients without ADAs

Source: Listings 16.2.5-1.2, 16.2.6-1.1, 16.2.6-1.14, 16.2.7-1.1 and 16.2.8-1.2

(Source: Table 12-10, Study CAIN457F2312 report)

INDIVIDUAL STUDY REVIEW

4.1.1 Population Pharmacokinetics of Secukinumab (AIN457) in Psoriatic Arthritis

Objectives

- To describe the PK of secukinumab in patients with PsA, using a population pharmacokinetics approach
- Use the model to estimate the effect of potentially important covariates, most notably bodyweight, gender, race, and disease characteristics on exposure.

Software

The PK model was constructed using the NLME modeling approach and was implemented in Monolix 4.3.2 Standalone (Lixoft, Paris, France) and NONMEM 7.2 (b) (4). All goodness-of-fit plots, other model diagnostics, and simulations were produced in Matlab using SBPOP package. The complete modeling task was executed in MODESIM high performance computing environment.

Data Source and Handling

This pooled analysis uses data from PoC and Phase 3 studies in PsA patients as summarized below. Study A2206 provides dense samples within hours and/or days after dose, and studies F2306 and F2312 provide only pre-dose trough samples (Table 4-6).

Serum concentration values determined before the first dosing and those below LLOQ were considered as missing. Records were also excluded either due to protocol violations or invalid samples.

The population PK model was built based on 2686 secukinumab serum concentrations from 755 patients (Table 4-7).

Table 4-6 Summary of clinical studies to be used in the population pharmacokinetic analyses

Study	Description	Regimens	Note
A2206	PoC PD study of efficacy of AIN457	<ul style="list-style-type: none"> • 2 x 10 mg/kg i.v. q3w • placebo 	PK samples taken pre-dose, 2, 3, 4 and 24 hours after infusion, and then at weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24/end of study
F2306*	Phase III efficacy safety and tolerability	<ul style="list-style-type: none"> • 3 x 10 mg/kg i.v. q2w + 150 mg s.c. q4w from week 8 • 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from week 8 • placebo + 150 mg s.c. q4w from week 24 • placebo + 75 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo 	PK samples at weeks 0, 4, 16, 24, 52
F2312**	Phase III efficacy, safety and tolerability	<ul style="list-style-type: none"> • 4 x 300 mg s.c. q1w + 300 mg s.c. q4w from week 4 • 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4 • 4 x 75 mg s.c. q1w + 75mg s.c. q4w from week 4 • placebo + 300 mg s.c. q4w from week 24 • placebo + 150 mg s.c. q4w from week 24 • placebo + 300 mg s.c. q4w from week 16 • placebo + 150 mg s.c. q4w from week 16 • placebo 	PK samples at weeks 0, 4, 16, 24

* F2306: Week 52 interim lock

** F2312: Week 24 interim lock

(Source: Table 3-1, Population PK of secukinumab in PsA modeling report)

Table 4-7 Summary table of PK analysis set by treatment group

Group	N	records	active doses	PK observations
A2206: 2 x 10 mg/kg i.v. q3w	28	497	55	442
F2306: 3 x 10mg/kg i.v. q2w + 150 mg s.c. q4w from week 8	191	3470	2766	704
F2306: 3 x 10 mg/kg i.v. q2w + 75 mg s.c. q4w from week 8	183	3286	2612	671
F2306: placebo + 150 mg s.c. q4w from week 16	49	828	488	98
F2306: placebo + 75 mg s.c. q4w from week 16	46	776	457	93
F2306: placebo + 75 mg s.c. q4w from week 24	3	51	24	6
F2312: 4 x 300 mg s.c. q1w + 300 mg s.c. q4w from week 4	87	1785	1551	234
F2312: 4 x 150 mg s.c. q1w + 150mg s.c. q4w from week 4	89	1110	878	232
F2312: 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4	78	977	773	204
F2312: placebo + 150 mg s.c. q4w from week 16	1	12	3	2
TOTAL	755	12792	9607	2686

Source: Output/04_CleanedDataExploration/14_summary_of_records_TRT.csv generated by Scripts/PK_01_data_exploration_and_preparation.m

(Source: Table 5-1, Population PK of secukinumab in PsA modeling report)

Population PK Model Development

Population PK analyses have been performed previously on pooled PK data from psoriasis patients, integrating a large Phase 3 study (A2302) with data from Phase 1 and 2 studies (A2102, A2103, A2211, A2212, A2220). The previously developed population

PK model in psoriasis was used as a basis to support the development of the population PK model in PsA.

The schematic for population PK model development is Base model development → Random effect model → Covariate model development → Final PK model evaluation → Simulation of PK profiles

Structural Model

Both two- and three- compartment model were explored and two-compartmental model with first-order absorption (for SC administration) and first-order elimination was selected. A first-order absorption rate constant (k_a) and bioavailability term (F_{abs1}) were used to characterize the rate and extent of the absorption process of the SC administration. Because of the lack of rich PK sampling with SC dosing in PsA studies, k_a was fixed at the previously estimated value in the psoriasis patient population. Subcutaneous bioavailability (F_{abs1}) (between 0 and 1) was described using a logit transformation. Baseline weight (WT_0) as a covariate was already included in the base model because of its known importance for monoclonal antibodies.

Random Effect Model

Between-subject variability in PK parameters is modeled using log-normal random effects of the form $\theta_i = \theta \times e^{\eta_i}$. For models including between-subject variability on bioavailability, random effect is modeled on a logit-scale:

$$\theta_i = \frac{\exp(\theta + \eta_i)}{1 + \exp(\theta + \eta_i)}$$

Residual variability is modeled using a combined (additive + proportional) error model.

Covariate Model Development

The impact of covariates was explored in a full covariate modeling approach. Rationale for the choice of particular covariate was clinical interest. The covariate modeling approach consisted of three steps:

- Step 1: include simultaneously all predefined covariates according to Table 4-8;
- Step 2: remove non-significant covariates at the significance level $p < 0.05$ in the Wald test;
- Step 3: test remaining covariates for clinical relevance. Covariates that change a PK parameter by more than 20% were considered potentially clinically relevant (evaluated graphically).
- Step 4: test the influence of chosen covariates on relevant PK metrics, assessed either using analytical expressions or by simulations.

Table 4-8 Considered candidate covariates

Covariate	Model parameter
Bodyweight	CL, V_c , Q_1 , V_{p1}
Age	CL
Gender	CL
Asian / non-Asian	CL
Time since first diagnosis of PsA	CL
Response status for anti-TNF α therapy (naïve or inadequate responders)	CL, V_c , V_{p1}
Number of previously used biologics	CL
Concomitant use of methotrexate	CL
CRP at baseline	CL
PASI score at baseline	CL
DAS28 score at baseline	CL

(Source: Table 4-2, Population PK of secukinumab in PsA modeling report)

Final Model

Model selection is based on a combination of judgment of model plausibility and robustness, objective function value (OFV), goodness-of-fit diagnostics, and simulation-based diagnostics.

The final model was described as below and the PK parameter estimates for the final model are shown in Table 4-9.

- 2 compartment model
- No lag-time
- Additive+proportional error model
- First-order absorption
- Linear bioavailability
- Estimation of all fixed effect parameters except k_a that was fixed to the value estimated in psoriasis PK model
- Estimation of all random effect parameters except on inter-compartmental clearance Q_1 , absorption rate k_a and bioavailability F_{abs1}
- WT0 as a covariate on clearance CL, central volume V_c and peripheral volume V_{p1}
- Covariance matrix for random effects on clearance CL and V_c .

Table 4-9 Parameters of final PK model

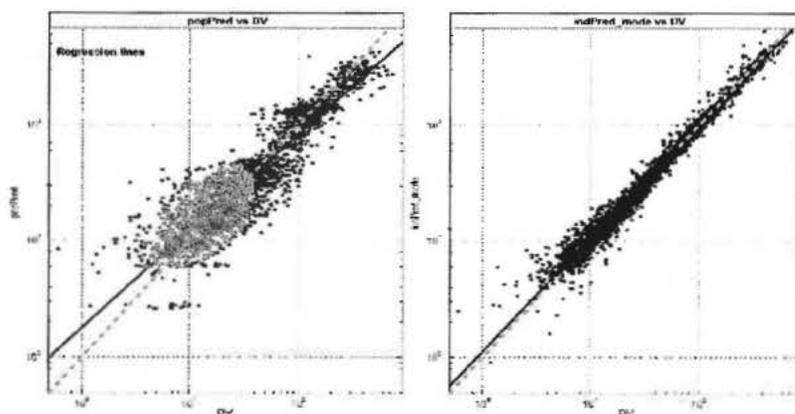
Name	Value	%RSE	Shrinkage (%)
<u>Structural parameters</u>			
CL [L/day]	0.19	2	
V _c [L]	3.66	4	
Q ₁ [L/day]	0.54	10	
V _{p1} [L]	2.45	5	
k _a [1/day]	0.18 (fixed)	-	
F _{abs1} (bioavailability)	85%	2	
<u>Covariate effect</u>			
WT0 on CL	0.71	8	
WT0 on V _c	0.44	37	
WT0 on V _{p1}	0.72	25	
<u>Inter-individual variability(std)</u>			
IIV on CL	0.32	3	7.9
IIV on V _c	0.36	8	33
IIV on Q ₁	-	-	-
IIV on V _{p1}	0.3	11	53
IIV on k _a	-	-	-
IIV on F _{abs1}	-	-	-
<u>Covariance</u>			
CL-V _c (corr)	0.66	8	
<u>Residual variability</u>			
Additive error (std)	2.37	5	
Proportional error (std)	0.11	4	
Objective Function Value (BIC)	21604		
Objective Function Value (-2xLL)	20511		

Source: Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MCNOLIX/RESULTS/pop_parameters.txt and Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/RESULTS/GOF_1_Cc_04_Random_Effects.pdf

(Source: Table 5-9, Population PK of secukinumab in PsA modeling report)

Final Model Evaluation

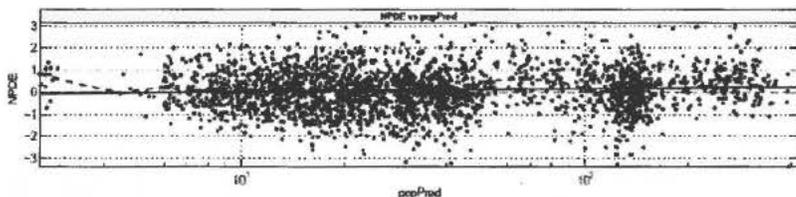
Goodness-of-fit: the diagnostic plots of the final model were shown in Figure 4-6. Overall, the 2-compartment model fit the PK data well, with a tendency to under-predict the higher concentration. Normalized prediction distribution errors (NPDE) versus population predictions show no evident trends (Figure 4-7).



Source: Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/RESULTS/GOF_OUTPUT_1_Cc/GOF_1_Cc_03_GOF_plots.pdf

Figure 4-7 Goodness-of-fit diagnostics for PK model

(Source: Figure 5-7, Population PK of secukinumab in PsA modeling report)



Source:
Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/RESULTS/GOF_OUTPUT_1_Cc/GOF_1_Cc_03_GOF_plots.pdf

Figure 4-7 NPDE over population prediction

(Source: Figure 5-8, Population PK of secukinumab in PsA modeling report)

Predictive Performance: Predictive performance of the models was assessed using visual predictive check (VPC). Figure 4-8 shows visual predictive checks for the 150 mg and 300 mg treatment groups in study F2312, respectively. The model-based prediction matches the time course and between-patient variability of the observed data.

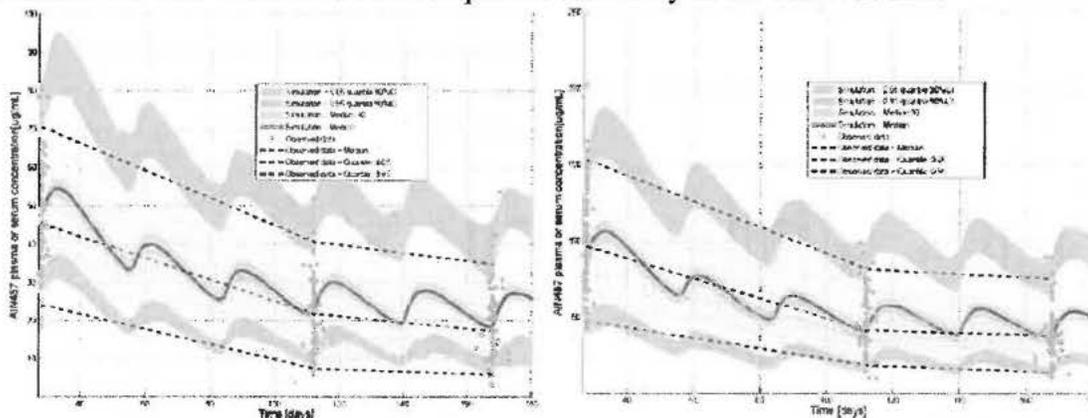


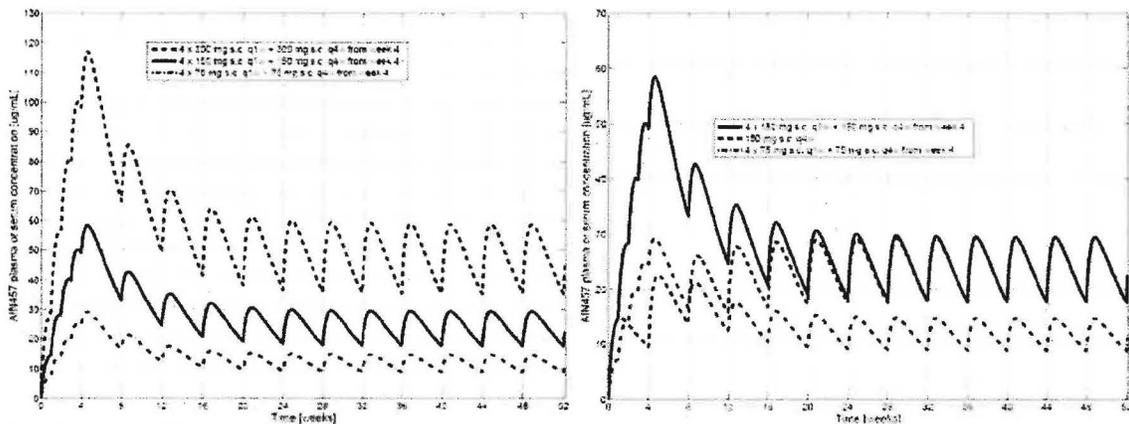
Figure 4-8 Visual predictive check for 4x150 mg SC q1w followed by 150 mg SC q4w from week 4 (Left) and 4x300 mg SC q1w followed by 300 mg SC q4w from week 4 (Right) in study F2312

(Source: Adapted from Figures 5-9 and 5-10, Population PK of secukinumab in PsA modeling report)

Simulation of PK Profiles

The final structural model is used to simulate PK profiles for a set of dosing regimens. Daily PK concentrations for 1000 subjects per dosing regimen were simulated. The simulated PK profiles were shown in Figures 4-9 and 4-10.

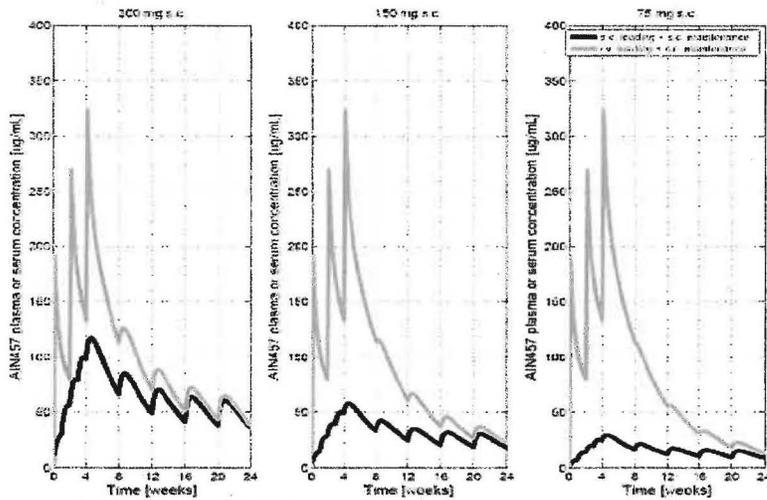
Due to the linear PK, the simulated secukinumab exposure levels are dose-proportional at steady state. Following regular 150 mg SC Q4W regimen (no loading), exposure levels which are comparable to 75 mg SC regimen (with loading) and 150 mg SC regimen (with loading) are reached after Week 12 and Week 20, respectively. Compared to SC loading regimen, IV loading regimen produces high peak concentrations but comparable exposure levels at Week 24.



Source: Output/Simulations/SIM_01_sc_phaseII_regimens.pdf

Source: Output/Simulations/SIM_02_load_vs_Load.pdf

Figure 4-9 Simulated concentration profiles of SC loading + SC maintenance 300 mg, 150 mg and 75 mg Phase 3 regimens and regular Q4W dosing regimen
 (Source: Adapted from Figures 5-13 and Figure 5-14, Population PK of secukinumab in PsA modeling report)



Source: Output/Simulations/SIM_03_all_phaseII_regimens.pdf

I.v. loading refers to 3 x 10 mg/kg i.v. q2w; s.c. loading is 4 x s.c. dose (300 mg, 150 mg or 75 mg, respectively for each panel) q1w; s.c. maintenance is s.c. dose (300 mg, 150 mg or 75 mg, respectively for each panel) q4w from week 4 in case of s.c. loading and from week 8 in case of i.v. loading.

Figure 4-10 Simulated concentration profiles with IV and SC loading dosing regimens
 (Source: Figure 5-15, Population PK of secukinumab in PsA modeling report)

4.1.2 Graphical Exploratory Analysis of Secukinumab (AIN457) Exposure-Response of Efficacy, Adverse Events and Radiographic Assessments in Psoriatic Arthritis Patients

Objective

Secukinumab exposure response relationships for efficacy and adverse events in study CAIN457F2312, and for radiographic assessments in study CAIN457F2306

Software

All analyses were performed with SAS version 9.4, using the SGPLOT and SGPANEL procedures for plotting purposes, and the NLMIXED procedure for model fitting.

Data Source

Study CAIN457F2312

A total of 386 patients contributed to the exposure-efficacy analyses and a total of 377 patients to the exposure-safety analyses.

- Efficacy endpoints: ACR (20/50/70), PASI (75/90), DAS28-CRP, and HAQ-DI at Week 24
- Safety: Crude incidence rates for the following treatment emergent adverse events up to Week 16
- Exposure: trough concentration (Cmin) at Week 16 (AEs) or 24 (efficacy)

Study CAIN457F2306

The Week 24 analysis included a total of 350 (respectively 179) patients in the AIN457 IV-SC (respectively, Placebo/AIN457) group. The Week 52 analysis included a total of 329 (respectively 147) patients in the AIN457 IV-SC (respectively, Placebo/AIN457) group.

- Radiographic endpoint: van der Heijde modified total Sharp score (vdH-mTSS) change with imputation at joint and segment levels or average of two readers at Week 24 and Week 52
- Exposure: Cmin at Week 24 and 52

Results

Study CAIN457F2312

The exposure-response relationship for ACR20/50/70 response rates and other efficacy endpoints at Week 24 are shown in Figures 4-3 and 4-4. The exposure-response curve flattens at Cmin levels that are higher than 20 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a 150 mg Q4W dosing as illustrated by the boxplots of observed Cmin concentrations at Week 24 in the different arms. Doubling of the Cmin from 20 to 40mcg/mL induces an improvement of ca. 5% in the ACR20/50/70 response rates. Similarly, a trend of increased responses with higher Cmin concentrations was observed for other efficacy endpoints.

Figure 4-5 shows the exposure-response relationships for the following categories of AEs: any AE, any SAE, infections and infestations, upper respiratory tract infections, nasopharyngitis, urinary tract infection and oral herpes, respectively. There was no evidence of an effect of Cmin in those categories of AEs, except for SAEs and oral herpes where an increasing trend with exposure was seen.

Study CAIN457F2306

The exposure-response relationship plots for vdH-mTSS change at Week 24 and from Week 24 to 52 are shown in Figures 4-11 and 4-12. Results indicate that a maintenance dose of 150 mg will generally achieve sufficient exposure to inhibit radiographic progression, as a majority of patients have Cmin concentrations higher than 15 mcg/mL.

4.2. Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

Phase 2a Proof-of-Concept Study in PsA

Study A2206

Title: Randomized, double-blind placebo-controlled multi-center proof-of-concept study to assess the efficacy of AIN457 in patients with psoriatic arthritis

Objectives

Primary: To evaluate the efficacy of AIN457 at 6 weeks based on the proportion of patients achieving ACR20 response.

Secondary:

- Efficacy: proportion of patients achieving at least 20%, 50%, and 70% improvement as measured by ACR response criteria; PsARC; DAS28; MASES, SPARCC and Leeds Dactylitis Index (LDI) basic; PASI.
- Safety and tolerability
- PK of AIN457 in PsA patients
- PD of AIN457 in synovial tissue obtained by biopsy of affected joints at baseline and week 6
- Health related quality of life (HRQoL) by using SF-36 and HAQ

Exploratory:

- Model concentrations of free IL-17 based on measurements of total IL-17 and to link free levels of IL-17 to DAS28 by a preliminary AIN457 dose to DAS28 response time model to allow for dose - regimen estimations
- To conduct exploratory studies to identify markers associated with short-term treatment response to AIN457
- To conduct exploratory analysis of selected upstream and downstream soluble protein markers
- To conduct immunohistological studies including assessment of T cell subsets in joint biopsies

Study Design and Treatment Schedule:

This was a randomized, double-blind, placebo controlled, multi-center proof-of-concept study of AIN457 in patients with active PsA. The study consisted of 3 parts: A screening period of 28 days; a treatment period of 3 weeks, and a follow-up period of 21 weeks. A total of 42 patients were recruited and randomized to either AIN457 2x10 mg/kg or placebo in a ratio of 2:1.

AIN457 was administered as an IV infusion (10 mg/kg) on Day 1 and Day 22, respectively. At the primary endpoint of 6 weeks, ACR response was determined,

whereby an ACR20 signified 20% improvement from baseline, ACR50 a 50% improvement from baseline, etc.

Concomitant methotrexate (MTX) up to 25 mg/week was allowed in the study provided patients remained on a stable dose as defined in the inclusion criteria. Patient who had received prior TNF blocking therapy were eligible, provided respective washout periods were adhered to. Stable doses of NSAIDs, paracetamol, tramadol (or equivalent) and prednisone up to 10 mg/day were allowed.

Test product

AIN457 50 mg lyophilizate vials (Formulation control # LYVI 7005405.005, Batch # Y017 0208, Y071 0409)

PD Assessment

PD assessments included quantification of serum total IL-17A and immunohistological assessments in synovial tissue biopsies.

PD (IL-17) blood samples were collected:

- On dosing days (Day 1 and Day 22) at pre-dose (0 h), 2, 3, 4, 24h.
- After the first infusion, samples were taken at Day 8 and Day 15.
- After the second infusion, samples were taken at Weeks 4, 6, 8, 10, 12, 16, 20, and 24.

PK Assessment

PK blood samples were collected:

- On dosing days (Day 1 and Day 22) at pre-dose (0 h), 2, 3, 4, 24h.
- After the first infusion, samples were taken at Day 8 and Day 15.
- After the second infusion, samples were taken at Weeks 4, 6, 8, 10, 12, 16, 20, and 24.

AIN457 serum concentration was analyzed by an ELISA assay with the LLOQ of 80 ng/mL.

Immunogenicity Assessment

Blood samples for immunogenicity assessment were collected at baseline, week 12, and week 24.

Anti-AIN457 antibodies were assessed in serum using (b) (4).

Results

All 42 subjects were analyzed for the safety analysis set. For PD analysis set five patients were excluded due to protocol deviations. For PK analysis one patient was excluded due to an SAE (breast cancer in-situ).

PD results

Effect of AIN457 on levels of IL-17

Due to stability issues with recombinant IL-17A and analytical interferences in serum samples, only qualitative but not quantitative data could be obtained for the time being. No results for total IL-17A measurements are reported in this report.

PD of AIN457 in synovial tissues

Due to the low number of patients who consented to a biopsy procedure (n = 4, two on AIN457 and two on placebo), no analyses could be performed.

PK results

The PK analysis was conducted using a noncompartmental method with WinNonlin, Phoenix version 6.1. The arithmetic mean concentration-time profiles on a linear and semi-logarithmic concentration scale over the complete sampling time period are shown in Figure 1 and the primary PK parameters of AIN457 are shown in Table 1.

Patients who received only one infusion, and/or had a too short PK sampling period for determination of their PK parameters, were excluded from the summary statistics for the PK parameters.

Results indicate that, following the first or second IV infusion, the inter-patient variability of C_{max} and AUC_{inf} is 26.6% and 18.4%, respectively. The mean serum clearance (CL) was 0.161 L/day and the mean apparent volume of distribution (V_z) was 6.81 L, which is very close to the total blood volume. The mean apparent termination half-life (T_{1/2}) was 29.8 days, ranging from 20.4 and 39.8 days.

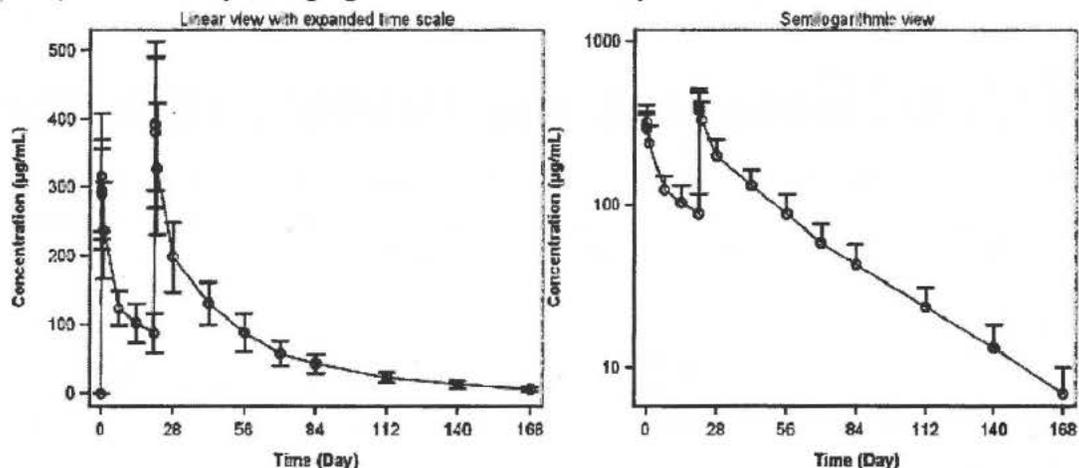


Figure 1. Arithmetic mean (SD) AIN457 concentration-time profiles
(Source: Figure 11-6, Study AIN457A2206 report)

Table 1. Summary statistics of PK parameters for AIN457 2 X 10 mg/kg group (PK analysis set)

Statistic	Tmax (day)	Cmax (µg/mL)	AUClast (day*µg/mL)	AUCinf (day*µg/mL)	Cl (L/day)	Vz (L)	T1/2 (day)
n	27	27	24	24	24	24	24
Mean (SD)	-	424 (113)	12300 (2240)	12600 (2320)	0.161 (0.0535)	6.81 (2.17)	29.8 (4.74)
CV% mean	-	26.6	18.2	18.4	33.3	31.9	15.9
Geo-mean	-	411	12100	12400	0.153	6.51	29.5
CV% geo-mean	-	25.7	19.1	19.5	31.1	30.6	16.7
Median	21.1	409	12800	13000	0.146	5.74	30.6
(min/max)	0.0833 - 23.1	262 - 731	8020 - 16700	8060 - 17000	0.0953 - 0.285	3.81 - 10.9	20.4 - 39.8

(Source: Table 11-7, Study AIN457A2206 report)

Immunogenicity

None of the patients tested for anti-AIN457 antibodies showed immunogenicity.

Conclusions

- Due to stability issues with recombinant IL-17A and analytical interferences in serum samples, no PD results were reported in this study.
- PK parameters of AIN457 were in the expected range for a monoclonal IgG1 antibody that interacts with a soluble target and consistent with previous experience in clinical trials.
- No evidence for immunogenicity was found neither in serial anti-AIN457 antibody measurements nor PK profiles.

Phase 3 Study in PsA

Study F2306

Title: A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis.

Objectives

Primary: to demonstrate that the efficacy of secukinumab 75 or 150 mg at Week 24 was superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response

Secondary:

- Other efficacy endpoints of secukinumab 75 or 150 mg at Week 24 (PASI75, PASI90, DAS28-CRP, SF36-PCS, HAQ-DI, ACR50, joint/bone structural damage, etc.)
- Safety and tolerability

Exploratory:

- The efficacy of secukinumab at Week 24 and other time points
- Immunogenicity

- PK/PD relationship of secukinumab
- Pharmacogenetic assessments

Study Design and Treatment Schedule: This pivotal Phase 3 study uses a double-blind, randomized, parallel-group, placebo controlled design. A screening period running up to 4 weeks before randomization was used to assess eligibility followed by a treatment period of two years. At baseline, patients whose eligibility was confirmed were to be randomized to one of three treatment groups:

- Group 1: Secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg SC starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab IV (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg SC starting at Week 8 and injected every 4 weeks
- Group 3: Placebo IV at baseline, Weeks 2 and 4, then placebo SC starting at Week 8 and Week 12

The patients were stratified according to being either TNF alpha inhibitor inadequate responders or TNF alpha inhibitor naïve patients. 30% of patients were planned to be TNF alpha inhibitor inadequate responders to ensure a representative patient population for the assessment of efficacy and safety. Thus, it was planned to randomize approximately 180 TNF alpha inhibitor inadequate responders and 420 TNF alpha inhibitor naïve patients.

At Week 16 (Visit 8), all patients were to be classified as responders ($\geq 20\%$ improvement from baseline in both tender and swollen joint counts) or non-responders. Patients who were randomized to placebo at baseline were to be re-randomized by the Interactive Response Technology (IRT) to receive double blind treatment up to 2 years, as follows:

- Patients on secukinumab placebo (Group 3) who were responders remained on placebo until week 24. At Week 24, these patients received either secukinumab 75 or 150 mg every 4 weeks (as dictated by the re-randomization)
- Patients on secukinumab placebo (Group 3) who were non-responders were rerandomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg SC every 4 weeks.

Patients who completed the study could be eligible to enter a planned extension trial.

The Study design is shown in the figure as below.

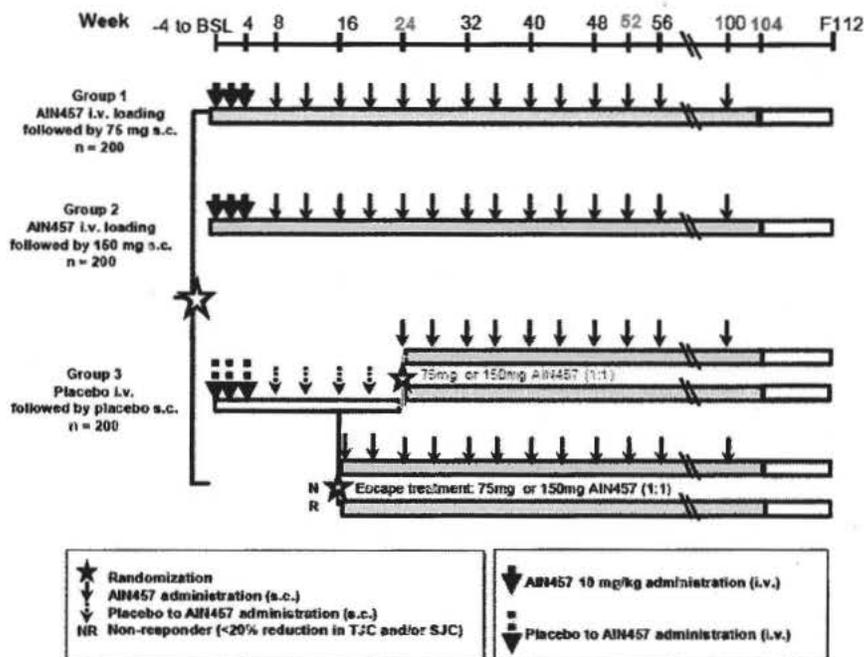


Figure 2. Study Design
(Source: Figure 9-1, Study CAIN457F2306 report)

Test Product

Study drug and strength	Formulation control number	Batch number
Secukinumab 150 mg	7006580.010	S0007, S0009, S0017
Placebo matching secukinumab 150 mg	7005406.005	Y103 0509, Y131 0609, Y002 0111, Y055 0511

(Source: Table 9-1, Study CAIN457F2306 report)

Secukinumab 150 mg Powder for Solution for SC injection or IV infusion was provided in glass vials each containing 150 mg secukinumab as lyophilized cake.

IV administration: Secukinumab active/placebo was administered IV as outlined in the pharmacist manual.

SC administration: Secukinumab active/placebo was administered using a 27Gx0.5'' needle (1 injection of 1 mL per visit) as outlined in the pharmacist manual.

PK Assessment

The PK samples were collected pre-dose at baseline and Weeks 4, 16, 24, 52, 104 (or 4 weeks after the last treatment in case of premature discontinuation), and 112 (follow-up).

An ELISA method was used for bioanalytical analysis of secukinumab in serum, with an LLOQ of 80 ng/mL.

Immunogenicity Assessment

Blood samples were collected at baseline and Weeks 24, 52, 104 (or 4 weeks after the last treatment in case of premature discontinuation), and 112 (follow-up).

Results

An overview of patients included in the analysis set is shown in Table 2.

Table 2. Analysis sets by treatment sequence (Randomized set)

Analysis Set	AIN457	AIN457	Placebo	Placebo	Placebo	Placebo	Placebo
	10 mg/kg - 75 mg	10 mg/kg - 150 mg		Non- responder - AIN457	Non- responder - AIN457	Responder - AIN457	Responder - AIN457
	N	N	N	75 mg N	150 mg N	75 mg N	150 mg N
Randomized set	202	202	202	62	61	31	33
Full analysis set	202	202	202	62	61	31	33
Safety set	202	202	202	62	61	31	33
Treated with AIN457 after re- randomization	--	--	183	62	61	28	32

Placebo column include patients randomized to placebo at the beginning and re-randomized to AIN457 later, as well as those prematurely discontinued without taking AIN457.

- Placebo patients who are not re-randomized are counted in the placebo total only.

(Source: Table 11-2, Study CAIN457F2306 report)

PK results

All mean trough serum concentrations are summarized in Table 3.

Following 10 mg/kg IV loading dose biweekly, the mean secukinumab concentrations were similar in 10 mg/kg-75 mg and 10 mg/kg-150 mg regimen groups at Week 4. After secukinumab 75 or 150 mg SC Q4W administration starting at Week 8, the secukinumab mean concentrations had decline due to the change of dosing regimen and administration route. The serial decline in mean trough concentrations at weeks 16, 24, and 52 reflect the large impact of the exposure resulting from the IV loading dose.

Table 3. Secukinumab concentrations by treatment and visit

	Secukinumab	Secukinumab	Placebo non- responders – secukinumab	Placebo non- responders – secukinumab	Placebo responders – secukinumab	Placebo responders – secukinumab
	10 mg/kg-75 mg	10 mg/kg-150 mg	75 mg	150 mg	75 mg	150 mg
	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)	Conc (µg/mL) (n)
Week 4	130 ± 36.6 (201)	134 ± 37.1 (201)	-	-	-	-
Week 16	31.7 ± 18.2 (175)	40.0 ± 20.6 (183)	0.506 ± 3.99 (62)	0.0275 ± 0.215 (61)	-	-
Week 24	16.2 ± 10.0 (176)	24.4 ± 13.7 (179)	7.73 ± 3.26 (55)	13.0 ± 4.76 (55)	0.910 ± 3.16 (27)	0.00 ± 0.00 (31)
Week 52	10.2 ± 4.86 (153)	18.6 ± 8.05 (163)	11.9 ± 6.16 (49)	17.3 ± 7.75 (48)	12.0 ± 5.19 (18)	16.0 ± 6.63 (25)

Week = time since starting secukinumab; Conc = secukinumab concentration.

Source: Listing 16.2.6-1.17 and Table 14.2-41.1.

(Source: Table 11-16, Study CAIN457F2306 report)

Immunogenicity results

Four patients were detected ADA positive post-treatment (Table 4). Treatment-emergent ADAs (i.e., negative at baseline, positive after start of study drug) were detected in only 1 patient (0.2%) (AIN457F2306- (b) (6)) from the Placebo non-responder –secukinumab 75 mg treatment group among 587 secukinumab-treated patients. However, an ADA titer could not be measured in this patient. The patient also had neutralizing antibodies. A subsequent sample collected at Week 52 was negative for ADAs.

Table 4. Overview of patients with anti-drug antibodies (ADA) in Study F2306

Patient ID	Group	Prior biologics	ADA ¹ (titer) /N-Ab	Impact on efficacy ²	AE possibly IG related (Day of onset) ³	PK ⁴
Patients with treatment emergent ADA (n=1)						
(b) (6)	Placebo Non-responder - AIN457 75 mg	None	Week 24 (no titer) / Yes	No	No	Normal
Patients with baseline and post-baseline persistent ADA (n=3)						
(b) (6)	AIN457 10mg/kg – 150 mg	None	BL (6.61) / Yes Week 24 (3.08) / Yes Week 52 (2.83) / Yes	No	No	Normal
	Placebo Non-responder - AIN457 150 mg	None	BL (no titer) / No Week 24 (no titer) / Yes Week 52 (17.8) / No Week 104 (no titer) / Yes	No	No	Normal
	Placebo Responder - AIN457 75 mg	Infliximab	BL (1.52) / Yes Week 24 (1.83) / Yes Week 52 (no titer) / Yes	No	Rhinitis allergic/D-356 / non-SAE	NA, only 1 PK sample available
Patients with only baseline ADA (n=7)						
(b) (6)	AIN457 10mg/kg - 75 mg	Infliximab Etanercept	BL (no titer) / Yes	No	No	Normal
	AIN457 10mg/kg - 75 mg	Etanercept Adalimumab Abatacept	BL (2.35) / No	Possible	No	NA, only 1 BSL PK sample available
	AIN457 10mg/kg - 75 mg	None	BL (no titer) / No	No	No	Normal
	AIN457 10mg/kg - 75 mg	None	BL (3.97) / Yes	No	No	Normal
	AIN457 10mg/kg – 150 mg	None	BL (no titer) / No	No	No	Normal
	AIN457 10mg/kg – 150 mg	None	BL (1.55) / Yes	No	No	Normal
	Placebo Non-responder - AIN457 75 mg	None	BL (no titer) / Yes	Possible	No	Normal

(Source: Table 12-17, Study CAIN457F2306 report)

Phase 3 Study in PsA

Study F2312

Title: A Phase 3 randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 24 weeks and to assess the long term efficacy, safety and tolerability up to 5 years in patients with Active Psoriatic Arthritis

Objectives

Primary: to demonstrate that the efficacy of secukinumab 75 or 150 or 300 mg at Week 24 was superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 response

Secondary:

- Other efficacy endpoints of secukinumab 75 or 150 or 300 mg at Week 24 (PASI75, PASI90, DAS28-CRP, SF36-PCS, HAQ-DI, ACR50, joint/bone structural damage, etc.)
- Safety and tolerability

Exploratory:

- Immunogenicity
- PK/PD relationship of secukinumab
- Pharmacogenetic assessments

Study Design and Treatment Schedule:

This multicenter study used a randomized, double-blind, double-dummy, placebo-controlled, parallel-group design, including a 10-week screening period followed by a treatment period of 52 weeks, and 4 years of additional long-term treatment. At baseline (BSL), patients whose eligibility was confirmed were randomized to 1 of 4 treatment groups:

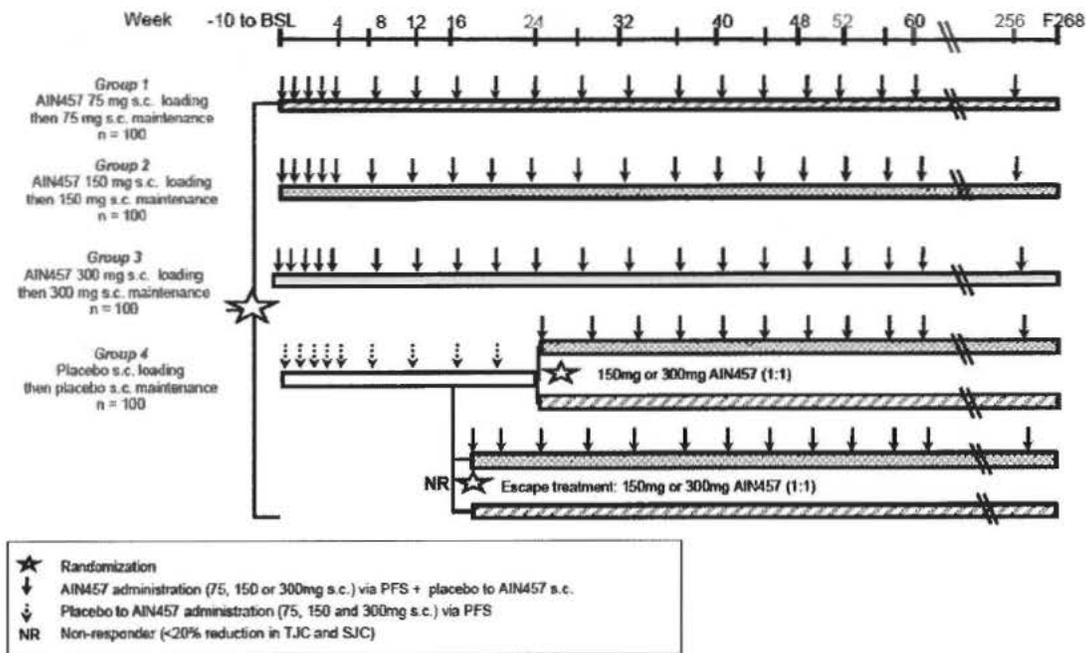
- Group 1 (75 mg)
 - Loading dose: SC 75 mg (0.5 mL) plus placebo (2 x 1.0 mL) at BSL, Weeks 1, 2, 3 and 4
 - Maintenance dose: SC 75 mg (0.5 mL) plus placebo (2 x 1.0 mL) Q4W starting at Week 4
- Group 2 (150 mg)
 - Loading dose: SC 150 mg (1.0 mL) plus placebo (0.5 mL and 1.0 mL) at BSL, Weeks 1, 2, 3 and 4
 - Maintenance dose: SC 150 mg (1.0 mL) plus placebo (0.5 mL and 1.0 mL) Q4W starting at Week 4
- Group 3 (300 mg)
 - Loading dose: SC 300 mg (2 x 1.0 mL) plus placebo (0.5 mL) at BSL, Weeks 1, 2, 3 and 4
 - Maintenance dose: SC 300 mg (2 x 1.0 mL) plus placebo (0.5) Q4W starting at Week 4

- Group 4 (placebo):
 - Placebo (2 × 1.0 mL and 1 × 0.5 mL) at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.

At Week 16, patients were classified as responders (ACR20 response defined as $\geq 20\%$ improvement from BSL in both tender and swollen joint counts) or non-responders. Patients who were randomized to Groups 1, 2, and 3 continued to receive study treatment as described above regardless of responder status. Patients who were randomized to placebo at BSL were re-randomized to receive double-blind treatment up to 52 weeks, as follows:

- Group 4 (placebo): Patients who were non-responders were re-randomized in a 1:1 ratio to receive secukinumab 150 mg SC or 300 mg SC Q4W.
- Group 4 (placebo): Patients who were responders continued to receive placebo Q4W until Week 24. Starting at Week 24, these patients received secukinumab 150 mg SC or 300 mg SC (1:1) Q4W regardless of responder status.

The Study design is shown in the figure as below.



BSL= baseline; n=number of patients; PFS=pre-filled syringe; sc=subcutaneous; SJC=Swollen Joint Count; TJC=Tender Joint Count

Figure 4. Study Design

(Source: Figure 9-1, Study CAIN457F2312 report)

Test Product

The investigational and control treatments are:

- Secukinumab 75 mg and 150 mg was provided in 0.5 mL and 1.0 mL respectively in PFS for SC injection.
- Placebo was provided in 0.5 mL and 1.0 mL PFS for SC injection.

Drug Product Description	Batch number	Basis/Variant
AIN457 Placebo /0.5 mL	Y067 0711A,	7008332.002
AIN457 Placebo /0.5 mL	Y067 0711	7008332.002
AIN457 Placebo /0.5 mL	Y104 1012	7008332.002
AIN457 Placebo /1 mL	Y031 0312	7008333.004
AIN457 Placebo /1 mL	Y001 0113	7008333.008
AIN457 Placebo /1 mL	Y118 1212	7008333.004
AIN457 150 mg/1 mL	S0004	7007916.008
AIN457 150 mg/1 mL	S0010	7007916.008
AIN457 150 mg/1 mL	S0008	7007916.008
AIN457 75 mg/0.5 mL	S0004	7009717.011

(Source: Table 9-1, Study CAIN457F2312 report)

PD Assessment

Samples were collected for serum biomarker assessment related to targeted pathway at baseline (Week 0), and Weeks 24 and 52.

PK Assessment

Blood samples were collected pre-dose at baseline (Week 0), and Weeks 4, 16, 24, and 52.

Serum secukinumab concentrations were determined by a validated ELISA method with a LLOQ of 80 ng/mL.

Immunogenicity Assessment

Blood samples were collected pre-dose at baseline (Week 0), and Weeks 24 and 52.

An electrochemiluminescence method was used for the detection of potential antiseckinumab antibody formation.

Results

PK results

Serum secukinumab concentrations are summarized by treatment and visit in Table 5. For secukinumab 75, 150, 300 mg treatment arms, at Week 4, the mean concentrations were in a dose-proportional manner. At Weeks 16 and 24, concentrations approached steady state during Q4W administration.

Table 5. Secukinumab concentrations by treatment and visit

Visit	AIN457 75 mg		AIN457 150 mg		AIN457 300 mg		Placebo non-responders 150 mg sc		Placebo non-responders 300 mg sc	
	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)	N	Conc (µg/mL)
Week 4	79	24.9 ± 8.62	82	47.1 ± 13.3	80	98.4 ± 32.3	-	Placebo	-	Placebo
Week 16	69	12.0 ± 6.24	79	21.5 ± 10.2	79	43.1 ± 20.7	-	First dose	-	First dose
Week 24	74	10.6 ± 5.68	82	19.0 ± 9.87	83	38.8 ± 17.1	20	13.0 ± 6.65	11	28.1 ± 14.1

Conc = secukinumab concentration.

Sources: Listing 16.2.6-1.14 and Table 14.2-39.1.

(Source: Table 11-10, Study CAIN457F2312 report)

Immunogenicity results

No treatment-emergent ADAs (ie, negative at baseline, positive after start of study drug) were detected in any patient. The overview of patients with anti-drug antibodies is summarized in the table as below.

Table 6. Overview of patients with anti-drug antibodies (ADA)

Patient ID	Group	Prior biologics	ADA(titer) ¹ / N-Ab	Impact on efficacy ²	AE possibly IG related ³	PK ⁴
Patients with baseline and post-baseline persistent ADA (n=3)						
F2312- (b) (6)	AIN457 75 mg	None	Baseline (8.51) / No	None	None	Normal
F2312- (b) (6)	Placebo (Non-responder) - AIN457 150 mg	None	Baseline (8.43) / No	None	None	NA, Only 1 PK result available
F2312- (b) (6)	AIN457 300 mg	Etanercept	Baseline (6.50) / No	None	None	Normal
Patients with only baseline ADA (n=3)						
F2312- (b) (6)	Placebo (Non-responder) - AIN457 150 mg	None	Baseline (No titer) / No	None	None	Normal
F2312- (b) (6)	AIN457 75 mg	None	Baseline (No titer) / No	None	None	Normal
F2312- (b) (6)	Placebo (Non-responder) - AIN457 300 mg	Etanercept	Baseline (No titer) / No	None	None	Normal

ADA=anti-drug antibodies; IG=immunogenicity; N-Ab=neutralizing antibodies; NA=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Impact on efficacy = For patients who showed ADA at baseline, impact on efficacy is assessed by failure to achieve of >20% reduction in both tender and swollen joints for at least 2 consecutive visits while on secukinumab treatment.

³ IG-related AEs refers to preferred terms in the SMQ hypersensitivity

⁴ Normal PK was defined as: concentrations at Week 4, 16, 24 and 52 in individual patients that fit into the observed range for all patients without ADAs

Source: Listings 16.2.5-1.2, 16.2.6-1.1, 16.2.6-1.14, 16.2.7-1.1 and 16.2.8-1.2

(Source: Table 12-10, Study CAIN457F2312 report)

4.3. Appendix – New Drug Application Filing and Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	125504 Supplement-01	SDN	168
Applicant	Novartis	Submission Date	03/18/2015
Generic Name	Secukinumab (AIN457, NVP-AIN457)	Brand Name	COSENTYX
Drug Class	Recombinant human IgG1κ monoclonal antibody against interleukin (IL)-17A		
Indication	Psoriatic Arthritis (PsA)		
Dosage Regimen	<p>The proposed dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg starting at Week 4.</p> <p>For PsA patients (b)(4) patients with concomitant moderate to severe plaque psoriasis, the recommended dose of secukinumab is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 300 mg starting at Week 4.</p>		
Dosage Form	<ul style="list-style-type: none"> ▪ 150 mg/mL in a single-use prefilled SensoReady® pen (autoinjector) for injection; ▪ 150 mg/mL in a single-use prefilled syringe for injection; ▪ 150 mg powder for solution in a single-use vial for injection 	Route of Administration	Subcutaneous
OCP Division	DCP2	OND Division	Pulmonary, Allergy, and Rheumatology Products
OCP Review Team Division	Primary Reviewer(s) Lei He, PhD	Secondary Reviewer/ Team Leader Ping Ji, PhD	
Pharmacometrics			
Genomics			
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	5/17/2015	74-Day Letter Date	5/29/2015
Review Due Date	12/11/2015	PDUFA Goal Date	1/18/2016
Application Fileability			
<p>Is the Clinical Pharmacology section of the application fileable?</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If no list reason(s)</p>			
<p>Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If yes list comment(s)</p>			
<p>Is there a need for clinical trial(s) inspection?</p> <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p>If yes explain</p>			

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
<input type="checkbox"/> Metabolism Characterization			
<input type="checkbox"/> Transporter Characterization			
<input type="checkbox"/> Distribution			
<input type="checkbox"/> Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
<input type="checkbox"/> Absolute Bioavailability			
<input type="checkbox"/> Relative Bioavailability			
<input type="checkbox"/> Bioequivalence			
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
Human Pharmacokinetics			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
Intrinsic Factors			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input checked="" type="checkbox"/> Patients	4	Study CAIN457A2206 (PsA); Study CAIN457F2201(RA); Study CAIN457F2306 (PsA); Study CAIN457F2312 (PsA). Bioanalytical report (10) (Please see Attachment 1)	
Pharmacokinetics/Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<input type="checkbox"/> QT			

Pharmacometrics			
<input checked="" type="checkbox"/> Population Pharmacokinetics	1	Population pharmacokinetics of secukinumab (AIN457) in psoriatic arthritis Modeling Report	
<input checked="" type="checkbox"/> Exposure-Efficacy	1	Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in psoriatic arthritis patients	
<input type="checkbox"/> Exposure-Safety			
Total Number of Studies		In Vitro	In Vivo
Total Number of Studies to be Reviewed			4
			16

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/s/

LEI HE
12/11/2015

PING JI
12/11/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s001

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 29, 2015

To: Badrul Chowdhury, MD, PhD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Acting Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Focused Review of Patient Labeling: Medication Guide
(MG)

Drug Name (established name): COSENTYX (secukinumab)

Dosage Form and Route: Injection for subcutaneous use

Application Type/Number: BLA 125504

Supplement Number: S-001 and S-002

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On, March 18, 2015 and March 23, 2015, Novartis Pharmaceuticals submitted for the Agency's review supplemental Biological Applications (sBLA 001 and 002) for the indication of psoriatic arthritis and ankylosing spondylitis respectively. COSENTYX (secukinumab) was originally approved on January 21, 2015 for the indication of moderate to severe plaque psoriasis.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a December 23, 2015, request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to review the Applicant's combined label submitted on December 4, 2015 for S-001 and S-002 for the Applicant's proposed Medication Guide (MG) for COSENTYX (secukinumab) injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft COSENTYX (secukinumab) MG received on December 4, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on December 23, 2015.
- Draft COSENTYX (secukinumab) Prescribing Information (PI) received on December 4, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on December 23, 2015.

3 REVIEW METHODS

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 page(s) of draft labeling has been Withheld in Full as b4 (CCI/TS) immediately after this page

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/s/

AMANPREET K SARAI
12/29/2015

SHAWNA L HUTCHINS
12/29/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: December 15, 2015

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 125504 S-01 and S-02

Product Name and Strength: Cosentyx (Secukinumab) For Injection, 150 mg/vial
Cosentyx (Secukinumab) Injection, 150 mg/mL Prefilled Syringe
Cosentyx (Secukinumab) Injection, 150 mg/mL SensoReady Pen

Product Type: Single ingredient product and Drug-device combination product

Rx or OTC: Rx

Applicant/Sponsor Name: Novartis

Submission Date: March 18, 2015 and November 25, 2015

OSE RCM #: 2015-1014

DMEPA Primary Reviewer: Teresa McMillan, PharmD

DMEPA Team Leader: Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review responds to a request from Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the Prescribing Information for Cosentyx (secukinumab), BLA 125261 for areas of vulnerability that could lead to medication errors.

On March 18, 2015, Novartis submitted two efficacy supplements S-01 and S-02 proposing two new indications, Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G-N/A

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing two new indications, Psoriatic Arthritis and Ankylosing Spondylitis. The proposed dose and frequency of secukinumab is 150 mg by subcutaneous injection every four weeks with or without a loading regimen of 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4. The currently approved dosage forms and strengths support the proposed Psoriatic Arthritis and Ankylosing Spondylitis dose and frequency.

Our FAERS search for this review identified wrong dose (n=144), wrong frequency (n=137), and wrong route of administration errors (n=7). However, an analysis of the Cosentyx Dosage and Administration Section in the prescribing information determined that the route of administration, frequency, and dose are clearly stated and are unlikely to be the cause of confusion resulting in these types of wrong medication errors. The carton labeling and container labels also adequately state the route of administration and strength. Additionally, none of the cases stated confusion resulting from the prescribing information, carton labeling, and container labels; therefore no changes are recommended at this time based on the

identified cases. In addition, device malfunction cases (n=56) were identified. These cases involved patients receiving incomplete injections (injections were assumed to be complete but once device removed drug is expelled from device) or the device misfired. The cases stated that either the device failed to activate then misfired, the user failed to hold until the second click, or the user did not identify the correct end of the pen to perform the injection. These medication errors were also reported during the human factors validation study¹ for this product. These errors were expected and are known errors for auto injectors in general. Therefore, DMEPA considers these residual risks no different than those that occur with other auto injectors currently marketed and of minimal risk to the patient's safety.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Prescribing Information is acceptable and we do not have any recommendations at this time.

¹ Mena-Grillasca C. Human Factors, Label, Labeling and Packaging Review for Cosentyx (secukinumab). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 27. RCM No.: 2013-2700

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cosentyx that Novartis submitted on March 18, 2015 and November 25, 2015.

Table 2. Relevant Product Information for Cosentyx	
Initial Approval Date	January 21, 2015
Active Ingredient	secukinumab
Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Proposed Indications	<ul style="list-style-type: none"> • <u>Psoriatic Arthritis</u> • <u>Ankylosing Spondylitis</u>
Route of Administration	Subcutaneous
Dosage Form	Powder for Injection (vial) Solution for Injection (pre-filled syringe and auto-injector)
Strength	150 mg per vial 150 mg/mL (pre-filled syringe and auto-injector)
Dose and Frequency	<u>Psoriasis</u> 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
Proposed Dose and Frequency	<ul style="list-style-type: none"> • <u>Psoriatic Arthritis</u> 150 mg by subcutaneous injection every 4 weeks with or without a loading regimen of 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4. • <u>Ankylosing Spondylitis</u> 150 mg by subcutaneous injection every 4 weeks with or without a loading regimen of 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4.
How Supplied	150 mg powder for injection in Single Use vials 150 mg/mL injection in a single dose pre-filled syringe

	150 mg/mL injection in a single dose autoinjector In cartons of 1 unit or 2 units
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 9, 2015, we searched the L:drive and AIMS using the terms, Cosentyx and secukinumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous relevant review², and we confirmed that our previous recommendations to the Human Factors protocol were considered.

²Mena-Grillasca C. Human Factors, Label, Labeling and Packaging Review for Cosentyx (secukinumab). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 27. RCM No.: 2013-2700.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 30, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.³

Date Range	January 21, 2015 (initial approval date) to November 30, 2015
Product	Secukinumab [active ingredient] Cosentyx [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified 409 cases, of which 344 described errors relevant for this review. Table 4 summarizes the reported types of errors and outcomes for the 344 relevant cases.

We excluded 65 cases because they described wrong technique [removing device too soon or admitting to not following the Instructions for Use (n=19)], incorrect storage (n=18), missed

³ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

dose (n=14), no medication error reported (n=6), adverse event unrelated to Cosentyx (n=3), accidental exposure (n=2), known adverse event to Cosentyx (n=1), wrong formulation [patient dispensed prefilled syringe instead of the pen (n=1)], and wrong drug [patient placed her Cosentyx next to her dogs Sentinel and took the wrong drug (n=1)].

Table 4. Characteristics of the U.S. Medication Error Reports in FAERS Associated	
Type of Error	# of Cases
Wrong dose (administered one pen/syringe of 150 mg instead of two pens/syringe for a prescribed dose of 300 mg dose)	144
Wrong frequency (administered Cosentyx outside of prescribed frequency of administration)	137
Device Malfunction (incomplete injections)	56
Wrong Route (drug administered intravenously or intramuscularly)	7
Outcome	
Serious [other outcome not reported or hospitalization (not reported as a result of medication error)]	24
Non-serious	288
No reported	32

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number for the cases relevant for this review.

FAERS Case

11179840
11180724
11180735
11180880
11180917
11180923
11180924
11180958
11181285
11181472
11181508
11181604
11181737
11191365
11230132
11233628
11233885
11233886
11236741
11236826
11236849
11237021
11237240
11237399
11237409
11237671
11237817
11238396
11238824
11242756
11242758
11243239

11243240
11245987
11246097
11258255
11258452
11263433
11263741
11264949
11264950
11266829
11268104
11269325
11269745
11269748
11271682
11271702
11272581
11274635
11274844
11274892
11274895
11275005
11275176
11275836
11278385
11282152
11282157
11282160
11282558
11285703
11285774
11285840
11287153
11290480
11290535
11291063

11294877
11294906
11294919
11307936
11307982
11308182
11308218
11308614
11309830
11310813
11311033
11311065
11311076
11312255
11312413
11316589
11318802
11319457
11322004
11322392
11322976
11322978
11322981
11322984
11325051
11328961
11329156
11330295
11334847
11334949
11339443
11343299
11343350
11345843
11348918
11349591

11349609
11349642
11349671
11355223
11359742
11360068
11363436
11363458
11363492
11363543
11368655
11368747
11370705
11371589
11374365
11375288
11379466
11379510
11379518
11379753
11379765
11379786
11381316
11383727
11385770
11385794
11390027
11390131
11394001
11394249
11394351
11394371
11394672
11396969
11398186
11398231

11398588
11398702
11401780
11403887
11409104
11409127
11409297
11409372
11409485
11415162
11415286
11418903
11418910
11418920
11419051
11419083
11419308
11419394
11419402
11419416
11419422
11419479
11419552
11419560
11419576
11419596
11419602
11419617
11419627
11419868
11420009
11420111
11421492
11422563
11427894
11429472

11433270
11433455
11436399
11438236
11438371
11440089
11440090
11442902
11444470
11444660
11449727
11451454
11451597
11457088
11459012
11465122
11465318
11465349
11465408
11465562
11466805
11466886
11467280
11467281
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11475682
11482158
11486080
11486261
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11486840
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11487598
11490219
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11493235
11497114
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11510710
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11512372
11514435
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11529057
11529226
11533841
11534409
11534424
11537004
11539441
11540231
11543883
11544476
11544613
11544764
11544773
11545311
11546195
11549458
11559537
11559571
11561071
11580431
11580621
11580788
11581164
11583476
11583675
11585644

11591150
11591153
11591981
11594577
11595470
11595617
11595724
11603404
11603699
11604434
11604436
11610303
11614817
11615075
11617970
11618003
11618021
11618272
11618689
11618990
11619478
11619578
11619811
11621820
11624806
11625002
11629604
11631591
11633846
11634064
11641824
11642836
11654474
11656712
11657003
11658730

11659368
11663640
11663816
11675561
11683907
11692392
11692758
11693136
11703588
11704325
11712902
11713722
11714632
11716206
11717912
11717914
11726617
11726959
11732003
11734081
11734497
11734633
11735314
11741194
11741332
11741690
11742720
11749152
11749634
11750929
11752900
11756654
11756919
11757311
11766784
11767713

11771300
11772072
11776214
11776279
11776345
11776647
11776738
11776826
11780622
11780941
11781050
11781054
11781056
11782875
11784046
11784549
11784856
11785044
11785046

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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/s/

TERESA S MCMILLAN
12/15/2015

KENDRA C WORTHY
12/15/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: December 15, 2015

To: Laura Musse, RN, MS, CRNP
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: BLA# 125504/S-01 and S-02 - COSENTYX™ (secukinumab)
injection, for subcutaneous use (Cosentyx)

Reference is made to DPARP's consult request dated May 19, 2015, requesting review of the proposed Package Insert (PI) for COSENTYX™ (secukinumab) injection, for subcutaneous use (Cosentyx). The PI has been updated as part of the above efficacy supplements for Cosentyx.

OPDP has reviewed the proposed PI entitled, "BLA125504 proposed combined PsA.AS.docx" that was sent via e-mail from DPARP to OPDP on December 7, 2015. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
12/15/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 03, 2015

To: Badrul Chowdhury, MD, PhD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
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From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted Medication Guides
(MGs)

Drug Name (established name): COSENTYX (secukinumab)

Dosage Form and Route: Injection for subcutaneous use

Application Type/Number: BLA 125504

Supplement Number: S-001 and S-002

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On, March 18, 2015 and March 23, 2015, Novartis Pharmaceuticals submitted for the Agency's review supplemental Biological Applications (sBLA 001 and 002) for the added indication of psoriatic arthritis and ankylosing spondylitis respectively. Cosentyx (secukinumab) was originally approved on January 21, 2015 for the indication of moderate to severe plaque psoriasis.

On November 25, 2015, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guides (MGs) for Cosentyx (secukinumab) injection for subcutaneous use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MGs for Cosentyx (secukinumab) injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft Cosentyx (secukinumab) MGs received on March 18, 2015 and March 23, 2015.
- Draft Cosentyx (secukinumab) Prescribing Information (PI) received on March 18, 2015 and March 23, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on November 25, 2015.
- Cosentyx (secukinumab) MG approved January 15, 2015.

3 CONCLUSIONS

We find the Applicant's proposed MGs are acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MGs.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/03/2015

MARCIA B WILLIAMS
12/03/2015