

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125504Orig1s002

Trade Name: COSENTYX

Generic Name: secukinumab

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: January 15, 2016

Indications: 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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**CENTER FOR DRUG EVALUATION AND
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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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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)

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 1.2 Psoriatic Arthritis
- 1.3 Ankylosing Spondylitis

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- 2.2 Psoriatic Arthritis
- 2.3 Ankylosing Spondylitis
- 2.4 Assessment Prior to Initiation of COSENTYX
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- 6.2 Immunogenicity

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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).

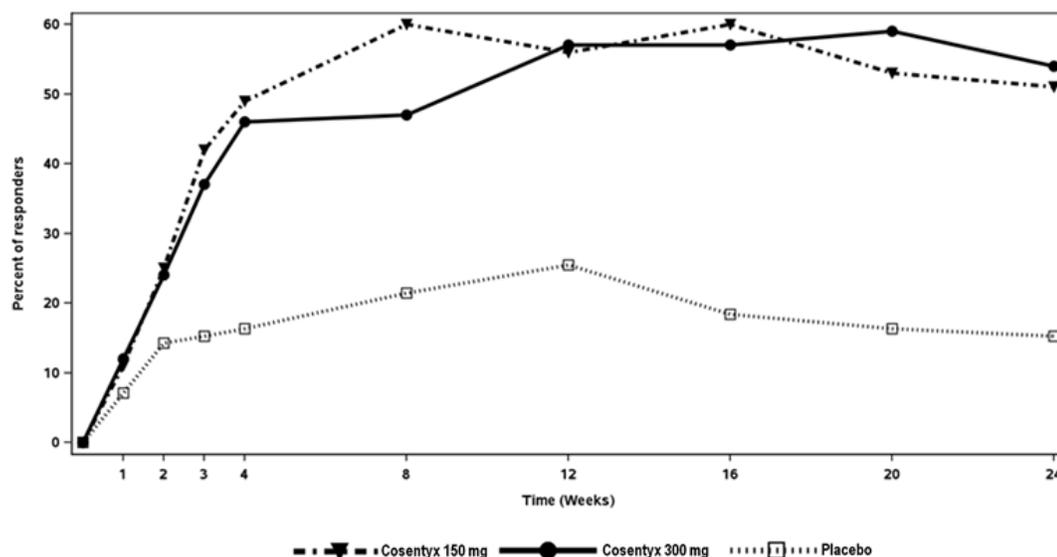
Table 4 Responses^a in PsA1 Study at Week 16 and Week 24

	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)

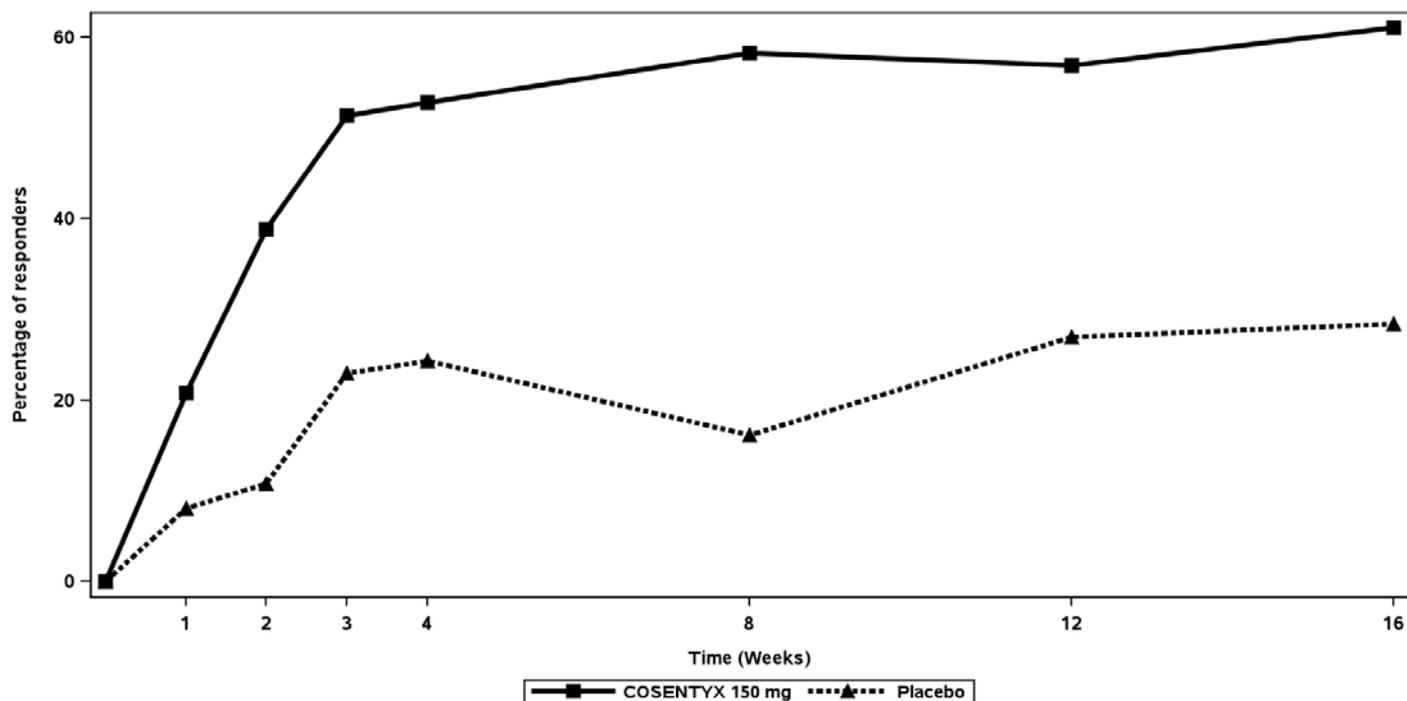
The improvements in the main components of the ASAS20 response criteria and other measures of disease activity are shown in Table 7.

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:
125504Orig1s002

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:ii1-44.

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

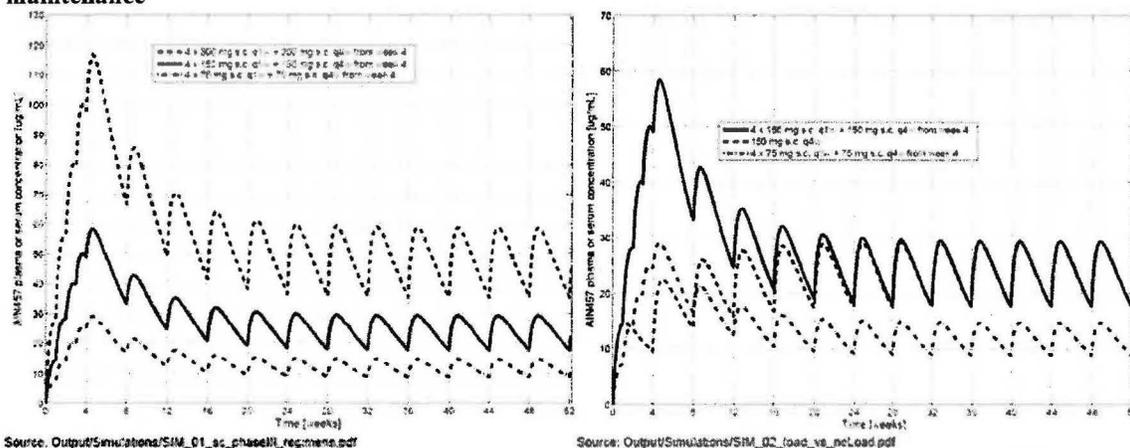
the loading doses of SC 150 mg once a week for five weeks and then 150 mg every four weeks, the trough concentrations at week 16 ($22 \pm 10 \mu\text{g/mL}$) were higher than those at Week 24 ($19 \pm 10 \mu\text{g/mL}$), suggesting there was still additional exposure attributable to the SC loading regimen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

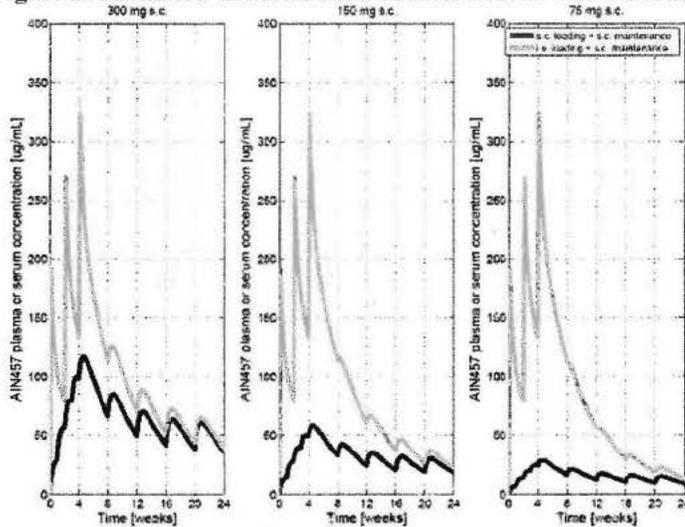
Right: 150 mg SC load/SC maintenance and 75 mg SC load/SC maintenance vs. no load 150 mg maintenance



Source: 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 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; 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 ^o 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 ^o 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:

125504Orig1s002

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
Adevale, Adeley
Anic, Gabriella
Barnes, Sandy
Chowdhury, Badrul A
He, Lei
Hutchins, Shawana
Levin, Gregory
Maynard, Janet
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Owens, Lissa
Rawat, Rashmi
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Yim, Sarah

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s002

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 2
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	March 23, 2015
PDUFA Goal Date	January 23, 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 ankylosing spondylitis
Recommended:	Approval

1. Introduction

This is a supplemental biologics license application (sBLA) 125504, supplement 2, for Cosentyx™ (secukinumab) in ankylosing spondylitis (AS). 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 ankylosing spondylitis."

The PDUFA goal date for this application is January 23, 2016, with a standard review clock. Of note, the Applicant submitted a separate supplement for psoriatic arthritis on March 18, 2015 (sBLA 125504/1). 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 psoriatic arthritis supplement.

2. Background

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 majority of research performed over the last two decades has used the modified New York Criteria⁶ to identify patients with AS (Table 1). In addition, these criteria were used in clinical trials performed to support product registration for AS in the United States. The AS criteria are anchored by radiographic changes of the sacroiliac (SI) joint.

Table 1: Modified New York Criteria for Ankylosing Spondylitis (AS)

Clinical Criteria <ul style="list-style-type: none">• Low Back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest• Restriction of motion of the lumbar spine in both the sagittal and frontal planes• Restriction of chest expansion relative to normal values correlated for age and sex
Radiologic criterion <ul style="list-style-type: none">• Sacroiliitis grade ≥ 2 bilaterally, or grade 3-4 unilaterally
Definitive ankylosing spondylitis is present if the radiologic criterion is associated with at least one clinical criterion

Source: van der Linden S. Arthritis Rheum 1984;27(4):361-8.

Since 2003, five Tumor necrosis Factor (TNF) inhibitors have been approved for the treatment of AS: Enbrel (etanercept[®]), Remicade (infliximab[®]), Humira (adalimumab[®]), Simponi (golimumab[®]), and Cimzia (certolizumab[®]). TNF inhibitors 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.

Relevant Regulatory History

On September 20, 2005, the IND 12678 for secukinumab in RA was opened. Subsequently, this IND was expanded to include psoriatic arthritis (PsA) and 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.

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

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 16 or 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 August 29, 2014, the sponsor was provided with Type C written responses regarding the design of a study that would evaluate patients with active AS 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 AS (supplement 2) on March 23, 2015. The Applicant

(b) (4)

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 AS studies F2305 and F2310, which used the currently marketed pre-filled syringe (PFS) presentation. In addition, PK data are included from a phase 2 proof-of-concept study in AS (A2209) and its extension (A2209E).

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 12/15/15, Table 6, page 14

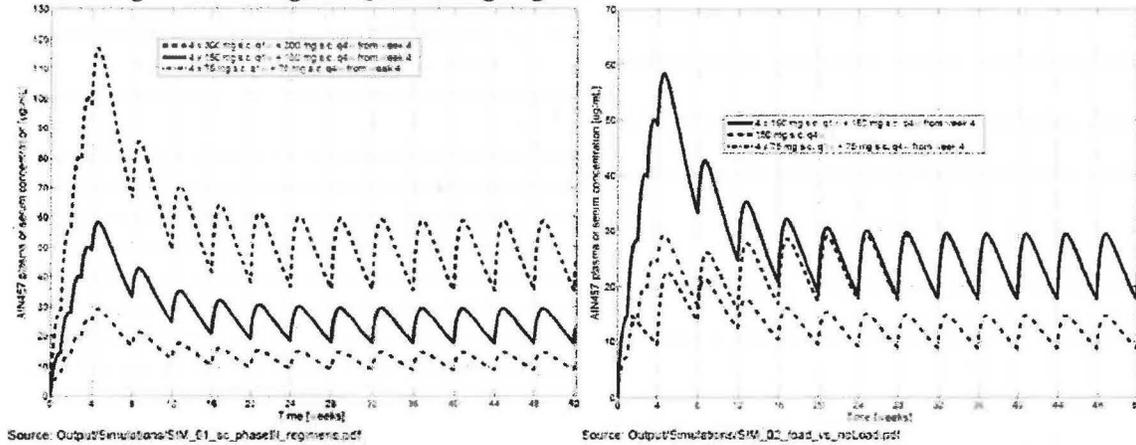
In population PK analysis, the estimates of CL of secukinumab in AS were consistent across studies and dose levels suggesting the dose-proportionality of secukinumab PK. Based on population PK analysis, body weight was identified as the significant intrinsic factor contributing to the inter-subject variability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

Loading

In the phase 3 studies (F2305 and F2310) patients received either IV (F2305) or SC (F2310) 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 (26±12 µg/mL) appeared higher than those at Week 52 (20±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 (23±11 µg/mL) were higher than those at Week 24 (20±10 µg/mL) and Week 52 (21±9 µg/mL). Therefore, time to reach steady state concentrations was about 16 weeks or later.

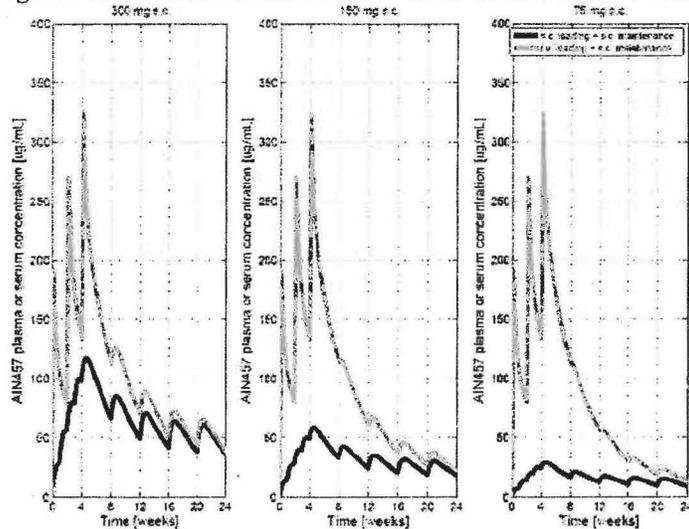
The Applicant performed population PK analyses to simulate the concentration profiles of the IV and SC loading regimen. These analyses demonstrate the high exposure with the SC load compared to no load regimen (Figure 1), the fact that the effect of the load may still be present at the time of efficacy 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 mg, and 75 mg Phase 3 Regimens and Regular Q4W Dosing Regimen



Source: Dr. He's Clinical Pharmacology Review dated 12/15/15, Figure 4-4, page 35

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



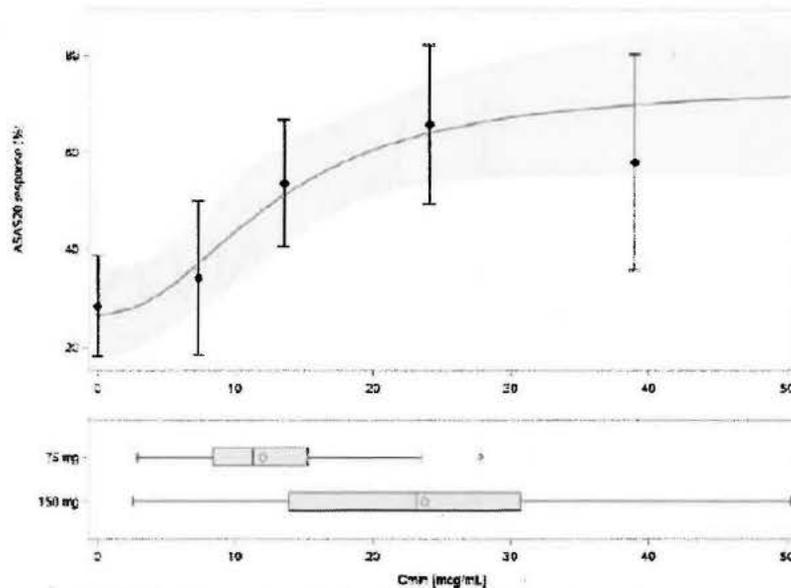
Source: Output/Simulations/SIM_03_all_phaseIII_regimens.pdf
I.v. loading refers to 3 x 10 mg/kg i.v. q2w; s.c. loading is 4 x s.c. dose (300 mg, 150 mg or 75 mg, respectively for each panel) q1w; s.c. maintenance is s.c. dose (300 mg, 150 mg or 75 mg, respectively for each panel) q4w from week 4 in case of s.c. loading and from week 8 in case of i.v. loading.

Source: Dr. He's Clinical Pharmacology Review dated 12/15/15, Figure 4-5, page 36

Dose/Exposure-Response for Efficacy and Safety

See Section 7 for a discussion of the effect of the loading regimen on the efficacy assessment. Exploratory exposure-response analyses were performed based on the response rate at Week 16 and trough concentration (C_{min}) at Week 16. The exposure-response curve flattens at C_{min} levels that are higher than 25 mcg/mL, which approximately corresponds to the mean steady state levels that are achieved following a SC 150 mg-SC 150 mg dosing regimen (SC load followed by SC maintenance) at Week 16. Increase in the C_{min} beyond 25 mcg/mL induces limited improvement in ASAS20 response rates (Figure 3).

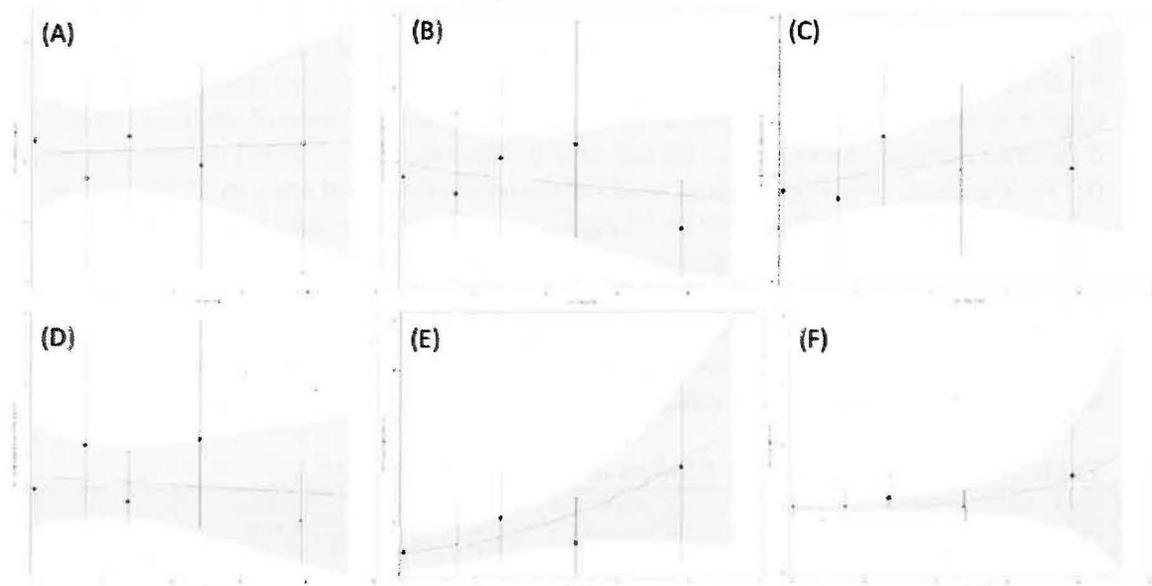
Figure 3: ASAS20 Response Rate versus C_{min} Concentration at Week 16



Source: Dr. He's Clinical Pharmacology Review dated 12/15/15, Figure 2, page 8

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, and oral herpes. There was no evidence of an effect of C_{min} was observed on adverse event rates for the following categories: any adverse event, any serious adverse event, and upper respiratory tract infection. A trend toward increased rates for infections and infestations, nasopharyngitis, and oral herpes with higher C_{min} was observed.

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



Y-axis represent various categories of AEs and x-axis represent Cmin concentration
Source: Dr. He's Clinical Pharmacology Review dated 12/15/15, Figure 4, page 10

Immunogenicity

The immunogenicity data showed that 3 out of 371 patients in Study F2305 and 0 out of 210 patients in Study F2310 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=1) and in patients who switched from placebo to secukinumab without a load (n=2). 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 AS 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 CAIN457F2305 (F2305) and study CAIN457F2310 (F2310) (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) (F2310) or intravenous (IV) (F2305) loading. The loading dose used for the active treatment arms in F2305 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 F2310 were 5 weekly SC injections of 75 mg or 150 mg at Weeks 0, 1, 2, 3, and 4 followed by 75 mg SC or 150 mg SC, respectively, every 4 weeks (hereafter referred to as 75 mg SC or 150 mg SC regimens). It is the 150 mg dose (with SC loading doses) evaluated in Study F2310 that is being proposed for marketing.

Table 3: Summary of Phase 3 Studies in AS Submitted in BLA

Study (Phase) [dates]	Patients	Duration (weeks)	Loading dose	Maintenance dose	Number per arm	Primary Endpoint (notable secondary endpoint)	Total N
CAIN457F2305 (Phase 3) [10/11-12/13]	Active AS (27% TNF-IR)	52 weeks, 1 ^o 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 ^o 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

F2305

Study F2305 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 failure to achieve an

ASAS20 response. 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 Assessment of Spondyloarthritis International Society 20 criteria (ASAS20). Secondary endpoints included ASAS40 response, change from baseline in high-sensitivity C-reactive protein (hsCRP), proportion of patients achieving an ASAS 5/6 response, change from baseline in total Bath Ankylosing Spondylitis Disease Activity (BASDAI), change from baseline in short form-36 physical component summary (SF-36 PCS), change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL), and the proportion of patients achieving an ASAS partial remission. The primary and secondary endpoints were assessed at Week 16.

Study F2310

Study F2310 was a randomized, double-blind, placebo-controlled, multicenter study of SC secukinumab in prefilled syringes of secukinumab 75 mg SC or 150 mg SC versus placebo in patients with active AS. 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 F2305. Approximately 40% of randomized patients were planned to be TNF α -IR. At Week 16, patients on placebo who were re-randomized (1:1) to receive either secukinumab 75 mg SC or 150 mg SC every 4 weeks in a blinded fashion. Unlike Study F2305, there were no escape criteria in Study F2310 for patients on secukinumab or placebo. All patients received secukinumab after Week 16.

The primary and secondary endpoints were the same in F2305 as F2310.

Brief Description of Efficacy Endpoints

The efficacy endpoints assessed in AS programs generally focus on validated measures of improvement in the signs and symptoms of AS. As radiographic disease progression in AS is slow, clinical AS programs 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).

An ASAS response is a composite, patient-reported outcome endpoint. The components of this endpoint include: patient's global assessment, total back pain, function assessed using the

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:ii1-44.

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

BASFI, and inflammation assessed using the BASDAI. See Table 5 for an overview of the ASAS and other endpoints utilized in the AS clinical program.

Table 4: Outcome Measures in AS Clinical Program

Instrument	Definition	Range
ASAS (Assessment in Ankylosing Spondylitis) 20 response	<p>A patient is classified as having an ASAS20 response if both of the following is achieved:</p> <ul style="list-style-type: none"> An improvement of 20% and an absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains: <ol style="list-style-type: none"> Patient's global assessment (VAS 0 to 100) Pain: assessed by total back pain (VAS 0 to 100) Function: assessed using the BASFI (0-10 cm) Inflammation: assessed using the last two stiffness assessments in the BASDAI (mean duration and severity of morning stiffness) (0-10 cm) <p>Absence of deterioration from baseline (where deterioration is defined as a net worsening of >1 unit [on a scale of 0 to 10]) in the potential remaining domain</p>	Yes or No
Bath AS Functional Index (BASFI)	A functional instrument (a higher score indicates worse function) based on the patient's assessment of his/her ability to perform 10 selected activities during the past week using a visual analogue scale ranging from easy to impossible. The BASFI is the mean of these 10 questions.	0 to 10
Bath AS Disease Activity Index (BASDAI)	A summary of 6 self-assessments (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness). The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1. The mean of the last two scales provide an assessment of stiffness that is used in the ASAS.	0 (none) to 10 (very severe)
Bath AS Metrology Index (BASMI)	Comprises the sum of 5 measures of hip and spine mobility [i.e. tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe)	0 to 10 (lower score indicates better function)

Abbreviations: VAS=visual analogue scale

In the Applicant's studies the 100 mm VAS scales for patient's global assessment of disease activity and spinal pain were equivalently scaled to a 10 cm scale to fit the generalized ASAS response criteria.

Source: Reviewer generated

ASAS40 response is defined similarly to ASAS20 response, but with 40% improvement in the mentioned domains and ≥ 2 units in each of the 4 core domains on a scale of 10.

An **ASAS 5/6 responder** achieved a 20% improvement from baseline in 5 of the following 6 domains: total back pain, patient global, function (BASFI score), the mean morning stiffness score in the BASDAI, c-reactive protein (CRP) and spine mobility (BASMI lateral spinal flexion assessment).

ASAS partial remission is defined as a value of ≤ 2 units in each of the 4 core domains of the ASAS response on a scale of 10.

The Ankylosing Spondylitis Quality of Life (ASQoL) is an 18-item questionnaire used in AS to assess health related quality of life. The MCID has been reported to be 1.8.⁶ The ASQoL contains 18 items with dichotomous yes/no response options, assessing whether the patient experiences limitations on life quality due to negative experiences with mobility/energy, self-care and mood/emotion. A single point is assigned for each "yes" response and no points for each "no" response, resulting in an overall score that ranges from 0 to 18. As such, a lower score indicates a better quality of life (less negative impact on quality of life). The recall period is "at the moment."

The medical outcome short form health survey (SF-36) is an instrument used to measure health-related quality of life. It consists of 8 subscales that are scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed.

Dose Selection

The proposed dose is 150 mg SC at Weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks for patients with active AS. 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 RA, dose-efficacy predictions from studies in moderate to severe plaque psoriasis, and phase 2 data in AS. The Applicant performed phase 2 studies in AS and RA (Table 5). Specifically, one phase 2 study with IV dosing in AS (study CAIN457A2209 [A2209]) and one phase 2 dose-ranging study with SC dosing in RA (study CAIN457F2201 [F2201]) examined different aspects of dosing.

Study A2209 was a 2-part, phase 2, randomized, double-blind, placebo-controlled, multicenter, study comparing IV doses of 10 mg/kg, 1 mg/kg, or 0.1 mg/kg of secukinumab to placebo in patients with AS. In part 1, a total of 30 patients were randomized 4:1 to receive either two infusions of secukinumab 10 mg/kg IV or placebo spaced three weeks apart. In part 2, a total of 30 patients were randomized to receive two infusions spaced three weeks apart of either secukinumab 0.1 mg/kg, secukinumab 1 mg/kg, or secukinumab 10 mg/kg in a 2:2:1 ratio. Patients were followed for 25 weeks. In part 1, the primary endpoint was ASAS20 response at 6 weeks. In part 2, the primary endpoint was change from baseline in BASDAI at Week 6. In part 1, the ASAS20 response at week 6 was 14/23 (61%) for the secukinumab 10 mg/kg group compared to 1/6 (17%) for the placebo group. In part 2, the adjusted mean change from baseline in BASDAI at week 6 was -1.2, -2.02, and -1.87 for the 0.1 mg/kg, 1 mg/kg, and 10 mg/kg dose groups.

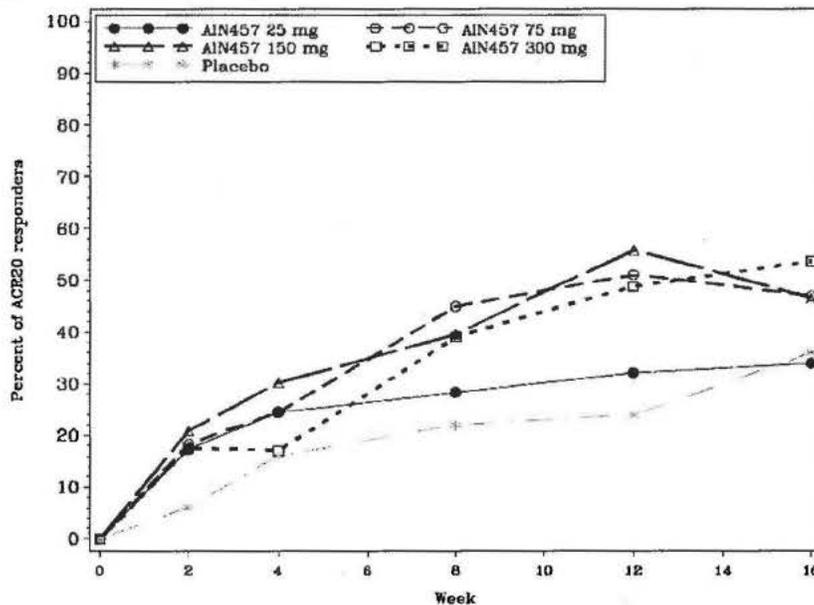
⁶ Davis JE, et al. *Arthritis Rheum* 2007;57(6):1050-7.

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%). At Week 8, the ACR responses were 45%, 40%, and 39% for the 75 mg, 150 mg, and 300 mg dose groups compared to the placebo response rate of 22%.

Table 5: Summary of Phase 2 Studies in AS and RA Submitted in BLA

Study (Phase) [dates]	Patient population	Duration (weeks)	Loading dose	Maintenance dose	Primary Endpoint	N
CAIN457A2209 (Phase 2) [3/09-4/11]	Active AS	25	None	Part 1: 2 infusions of 10 mg/kg IV or placebo separated by 3 weeks Part 2: 0.1, 1, or 10 mg/kg separated by 3 weeks	Part 1: ASAS20 week 6 Part 2: BASDAI week 6	Part 1: 30 Part 2: 30
CAIN457F2201 (Phase 2) [7/09-3/11]	Active RA	16 (1°) 60 (E)	None	25, 75, 150, or 300 mg SC Q4W	ACR20 (wk 16)	237

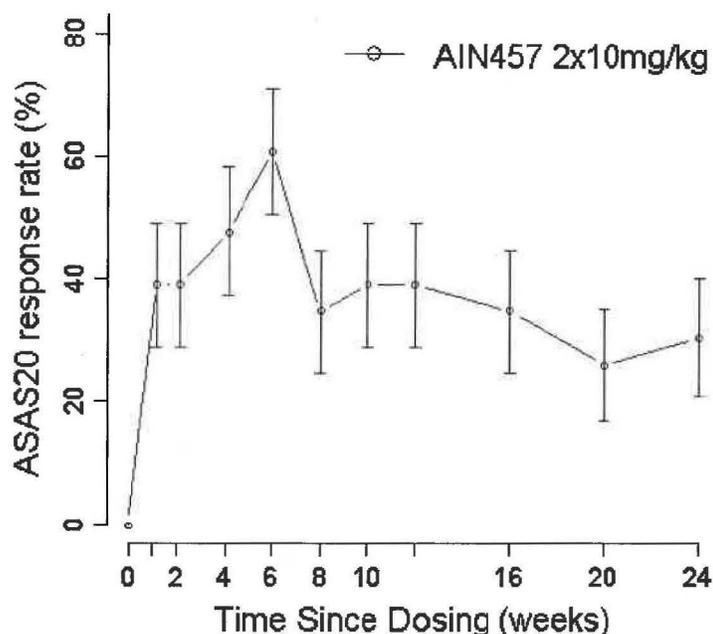
Figure 5: ACR20 Response over time through Week 16, LOCF (full analysis set) (F2201)



Source: PT-Figure 14.2-1.1

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

Figure 6: Mean (SE) ASAS20 Responder Rate over Time with Secukinumab (PD analysis set)



Source: Figure 11-3, page 104, Clinical Study Report, Study CAIN457A2209

The Applicant felt the results of early proof of concept studies in AS and RA and data from plaque psoriasis 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 AS program. While there are limitations to comparisons across study and across indication, the overall trajectory of response is similar in RA (Figure 5) and AS (Figure 6), 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). The Applicant did not provide a direct comparison (with and without loading) to assess the utility of the loading regimen in patients with AS.

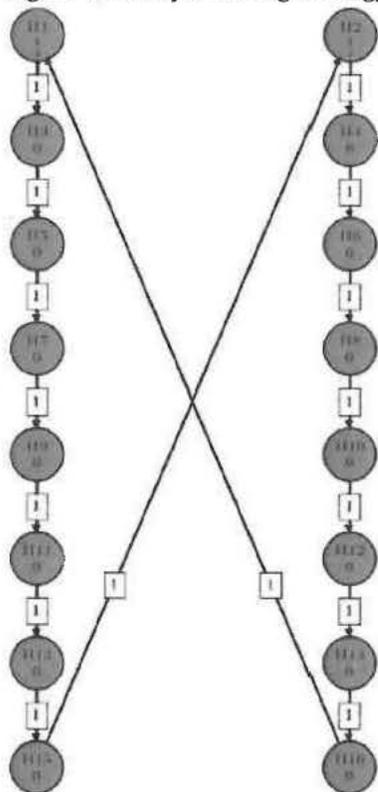
Statistical considerations

The primary analysis population was the Full Analysis Set (FAS) defined as all randomized patients. The primary analysis was conducted on the FAS via logistic regression with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate. 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). The same strategy was utilized in study F2310.

Figure 7: Multiple Testing Strategy in Studies F2305 and F2310



Primary objective:

- H1: secukinumab 75 mg SC is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16
- H2: secukinumab 150 mg SC is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

Secondary objectives:

- H3: secukinumab 75 mg SC is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16
- H4: secukinumab 150 mg SC is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16
- H5: secukinumab 75 mg SC is not different to placebo regimen with respect to hsCRP at Week 16
- H6: secukinumab 150 mg SC is not different to placebo regimen with respect to hsCRP at Week 16
- H7: secukinumab 75 mg SC is not different to placebo regimen with respect to ASAS5/6 response at Week 16
- H8: secukinumab 150 mg SC is not different to placebo regimen with respect to ASAS5/6 response at Week 16
- H9: secukinumab 75 mg SC is not different to placebo regimen with respect to total BASDAI at Week 16
- H10: secukinumab 150 mg SC is not different to placebo regimen with respect to total BASDAI at Week 16
- H11: secukinumab 75 mg SC is not different to placebo regimen with respect to SF-36 PCS at Week 16
- H12: secukinumab 150 mg SC is not different to placebo regimen with respect to SF-36 PCS at Week 16
- H13: secukinumab 75 mg SC is not different to placebo regimen with respect to ASQoL at Week 16
- H14: secukinumab 150 mg SC is not different to placebo regimen with respect to ASQoL at Week 16
- H15: secukinumab 75 mg SC is not different to placebo regimen with respect to ASAS partial remission at Week 16
- H16: secukinumab 150 mg SC is not different to placebo regimen with respect to ASAS partial remission at Week 16

Source: Statistical Review by Dr. Kim dated 12/11/15, Study CAIN457F2305, modified from Figure 2, page 13

Patient population

The patient population enrolled in studies F2305 and F2310 consisted of adults with moderate to severe active AS, fulfilling the modified New York criteria for AS. The baseline demographic and disease characteristics of the studies were similar and generally reflective of patients with active AS. The majority of patients were white (55% to 96%) and had a mean age of 40 to 44 years. The majority of patients were male (64% to 72%). Approximately two-thirds of patients were naïve to TNF α inhibitors (63% to 71%) and 11% to 18% used methotrexate at baseline. The mean time since diagnosis of AS was ~7 years. Patients had active AS, with a baseline median global assessment of disease activity score of 63 to 69 and baseline median BASDAI scores 6.20 to 6.87. The median hsCRP value across all treatment groups was 8.1 mg/L. Disease history and baseline characteristics were generally similar in the treatment arms and between studies.

A total of 590 randomized patients were included in both placebo-controlled efficacy studies F2305 (N=371) and F2310 (N=219). The majority of patients completed Week 52 in both studies (82% to 90%). The Applicant provided data to Week 52 from each study.

- **Efficacy review**

Primary endpoint

The primary endpoint for both phase 3 studies was the proportion of patients experiencing an ASAS20 response at Week 16. As shown in Table 6 below, in study F2305 both secukinumab treatment regimens were associated with a statistically greater proportion of ASAS20 responders compared to placebo. In study F2310, the 150 mg, but not the 75 mg secukinumab treatment regimen was associated with a statistically greater proportion of ASAS20 responders compared to placebo. In study F2305, the proportion of ASAS20 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 F2310, the proportion of ASAS20 responders was numerically higher for the 150 mg than the 75 mg dose regimen. Comparing the proportion of responders on the 150 mg treatment regimen between studies, a similar proportion of patients had an ASAS20 response in study F2305 (IV load) than study F2310 (SC load). Given that no additional treatment benefit was seen with the IV load compared to the SC load, the Applicant proposes utilizing a SC load rather than an IV load.

To assess the robustness of the primary analysis, both the FDA and the Applicant conducted sensitivity analyses, including tipping point analyses. These sensitivity analyses support the efficacy of secukinumab and were consistent with the primary analysis.

Evaluation of secukinumab on the individual components of the ASAS20 response at Week 16 revealed improvement in all of these variables consistent with the primary efficacy analysis for both doses in study F2305. In study F2310, all components of the ASAS were statistically significant for the secukinumab 150 mg regimen compared to placebo and there was no single component driving the efficacy in terms of ASAS20 response. There was a general trend of favorable improvement with the secukinumab 75 mg compared to placebo, but much less than the 150 mg dose regimen.

Table 6: Applicant's Analyses of ASAS Response at Week in Studies F2305 and F2310

	Treatment Group	n/N (%)	Comparison	Odds Ratio (95% CI)	P-value
Study F2305	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	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)

Secondary endpoints

Secondary endpoints included proportion of patients with ASAS40, hsCRP, ASAS5/6, BASDAI, SF36-PCS, ASQoL, and ASAS partial remission. All of the secondary endpoints were assessed at Week 16. As summarized in Table 7, 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 F2305, 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 F2310, the results for the secondary endpoints were statistically significant for the 150 mg dose regimen, but not the 75 mg dose regimen after adjusting for multiplicity. The 75 mg dose regimen is not proposed for labeling.

Dr. Kim performed multiple sensitivity analyses using different approaches to handle missing data due to dropout. Analyses of these endpoints demonstrated similar results in these sensitivity analyses.

In terms of spinal mobility, in Study F2310, both secukinumab groups achieved numerically greater changes from baseline in BASMI linear scores at all time points up to Week 16 compared with placebo. However, at Week 16, neither dose group had a statistically greater improvement in BASMI score compared to placebo, as reflected in the LS mean change from baseline with -0.51 for secukinumab 150 mg SC (unadjusted p=0.05) and -0.29 for secukinumab 75 mg SC (unadjusted p=0.65) versus -0.22 for placebo. The trend towards improvement in BASMI for the 150 mg dose group is supportive of the overall efficacy findings.

Table 7: Secondary Endpoints in Studies F2305 and F2310

	F2305			F2310		
	SCK 75 mg	SCK 150 mg	Placebo	SCK 75 mg	SCK 150 mg	Placebo
ASAS40 at Week 16						
% of patients	33	42	13	26	36	11
OR (95% CI), p-value	3.4 (1.8, 6.4), 0.0003	4.9 (2.6, 9.3), <0.0001	--	3.0 (1.2, 7.5), 0.02	5.1 (2.1, 12.4), 0.0004	--
Change from Baseline in hsCRP at Week 16						
Exp (LS Mean change from baseline)	0.45	0.40	0.97	0.61	0.55	1.13
Ratio (95% CI), p-value	0.46 (0.36, 0.59), <0.0001	0.41 (0.32, 0.52), <0.0001	--	0.54 (0.41, 0.71), <0.0001	0.49 (0.37, 0.64), <0.0001	--
ASAS5/6 at Week 16						
% of patients	45	49	13	34	43	8
OR (95% CI), p-value	5.6 (3.0, 10.6), <0.0001	6.5 (3.5, 12.4), <0.0001	--	6.1 (2.3, 16.3), 0.0003	9.2 (3.5, 24.1), <0.0001	--
Change from Baseline in BASDAI at Week 16						
LS Mean change from baseline	-2.34	-2.32	-0.59	-1.92	-2.19	-0.85
Mean difference (SE), p-value	-1.75 (0.25), <0.0001	-1.74 (0.24), <0.0001	--	-1.07 (0.35), 0.003	-1.34 (0.35), <0.0001	--
Change from Baseline in SF36-PCS at Week 16						
LS Mean change from baseline	5.64	5.57	0.96	4.77	6.06	1.92
Mean difference (SE), p-value	4.68 (0.83), <0.0001	4.61 (0.82), <0.0001	--	2.84 (1.11), 0.01	4.14 (1.11), 0.0002	--
Change from Baseline in ASQoL at Week 16						
LS Mean change from baseline	-3.61	-3.58	-1.04	-3.33	-4.00	-1.37
Mean difference (SE), p-value	-2.57 (0.59), <0.0001	-2.54 (0.59), <0.0001	--	-1.96 (0.75), 0.01	-2.63 (0.74), 0.0005	--
ASAS Partial Remission at Week 16						
% patients	16	15	3	15	14	4
OR (95% CI), p-value	5.8 (1.9, 17.5), 0.002	5.3 (1.7, 16.1), 0.003	--	4.3 (1.1, 16.2), 0.03	3.9 (1.0, 15), 0.05	--

All p-values shown are nominal

Abbreviations: SCK=secukinumab; ASAS=Assessment of Spondyloarthritis International Society criteria; hsCRP=high sensitivity c-reactive protein; BASDAI=Bath Ankylosing Spondylitis Disease Activity; SF36-PCS=short form 36-physical component summary; ASQoL=Ankylosing Spondylitis Quality of Life; OR=odds ratio; CI=confidence interval; SE=standard error

Source: Adapted from Dr. Yongman Kim's Statistical Review dated 12/11/15, Tables 6 (page 20), 7 (20-21), 8 (21-22), 9 (22), 10 (23), 11 (24), 12 (25), 18 (35), 19 (36), 20 (37), 21 (37), 22 (38), 23 (39), 24 (40)

Efficacy by previous response to anti-TNF α therapy

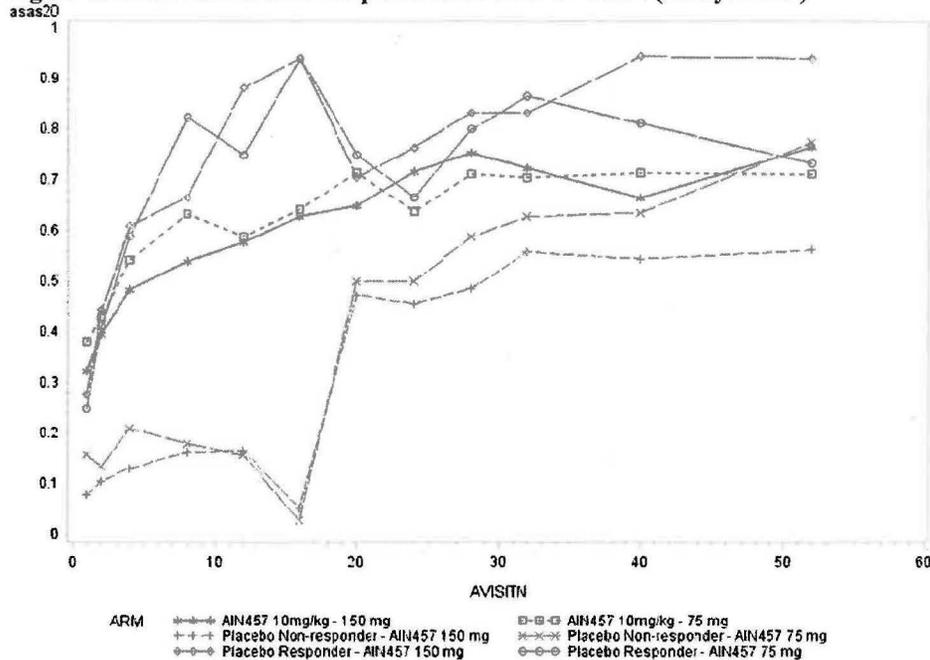
The Applicant proposed labeling to note that the clinical response was similar regardless of previous history of inadequate response to TNF α therapy. The ASAS20 response rate for the secukinumab 150 mg dose was numerically similar regardless of previous TNF α therapy. This was one of many prospectively planned subgroup analyses and it is difficult to determine whether the observed findings are 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.

Loading dose considerations

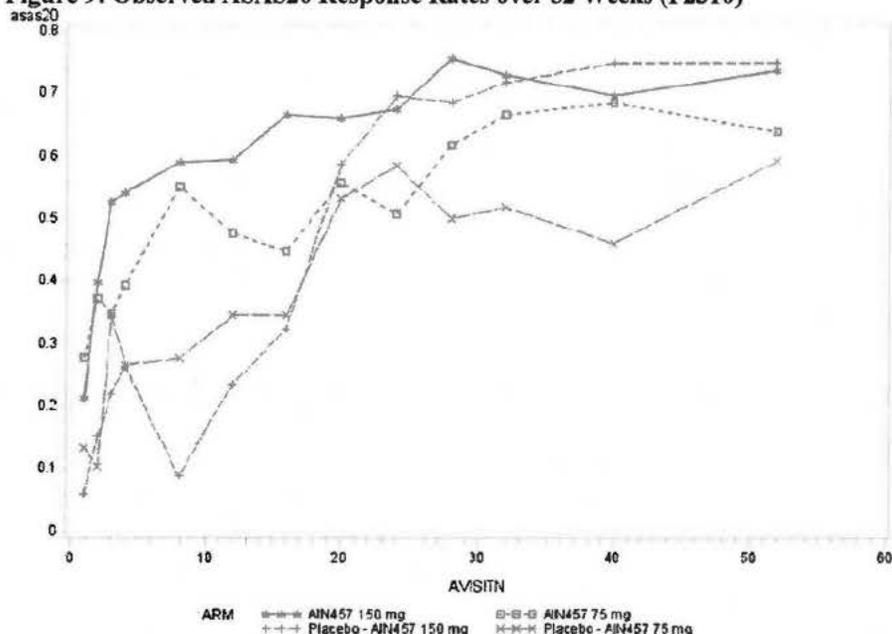
The use of loading doses in both studies was a major consideration during the review. There was a clinical concern that the loading doses may have impacted the efficacy results at 16 weeks due to residual effects of the loading doses in terms of drug exposure. Thus, there was a question of whether efficacy 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 ASAS20 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 8, Figure 9). 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 8: Observed ASAS20 Response Rates over 52 weeks (Study F2305)



Source: Dr. Yongman Kim's Statistical Review dated 12/11/15, page 48

Figure 9: Observed ASAS20 Response Rates over 52 Weeks (F2310)



Source: Dr. Yongman Kim's Statistical Review dated 12/11/15, page 50

- Includes discussion of notable efficacy issues both resolved and outstanding

The clinical and statistical teams are in agreement that studies F2305 and F2310 provide substantial evidence of efficacy of secukinumab for AS. The recommended dosing regimen will be 150 mg SC every 4 weeks. In addition, the review team is in agreement that the efficacy results from the AS trials do not justify the loading dose for all patients, but it can be offered as an option for patients.

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 AS trials, 650 patients with AS were studied in two phase 3 studies (CAIN457F2305, N=371) and CAIN457F2310, N=219) and one phase 2 study (CAIN457A2209, N=60) along with its extension CAIN457A2209E1 (N=39). In the two phase 3 studies in AS, 571 patients received any exposure to secukinumab, 535 patients received at least 24 weeks of secukinumab, and 444 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 AS trials are adequate to evaluate the safety profile of secukinumab in AS and provide an assessment of the relative safety in AS versus psoriasis.

In general, the safety profile of secukinumab in AS 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 risks related to 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 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. The patient who died of respiratory failure was noted to have cardiac failure and bilateral pulmonary fibrosis, but no pulmonary CT scan or bronchial biopsy was performed to confirm the diagnosis or provided additional insight into the case. The patient died after approximately 2 years on active treatment. The patient had cardiorespiratory risk factors at baseline, including 20 year smoking history, hypertension, and dyspnea. A causal relationship with secukinumab was not clearly established. The patient who died of an acute myocardial infarction had multiple baseline

cardiac risk factors. Deaths related to cardiovascular disease are consistent with those that might be expected in the underlying patient population.

Serious Adverse Events

Overall, in the 16-week placebo controlled period of the phase 3 AS trials, the proportion of patients with serious adverse events (SAEs) was not elevated in the secukinumab treatment arms (~3%) compared to placebo (4%). The proportion of patients with serious gastrointestinal disorders was higher in the any secukinumab group compared to the placebo group, but this was based on a small number of patients affected (n=4; 1% versus n=0). There did not appear to be a dose-dependent relationship for SAEs when comparing between the 75 mg SC and 150 mg SC groups (6% and 6%, respectively) and no dose-dependent relationship was observed for the IV dose groups (IV-75 mg: 2% and IV-150 mg: 2%). In the secukinumab groups, the SAEs (n=1 for each) included colitis ischemic, colitis microscopic, colitis ulcerative, costochondritis, Crohn's disease, hepatic enzyme increased, hyperparathyroidism, lumbar hernia, malignant melanoma, myocardial infarction, nuclear magnetic resonance imaging brain abnormal, respiratory failure, tonsillitis, and uveitis. A discussion of the SAEs related to IBD is included below.

Discontinuations Due to Adverse Events

In the 16-week placebo controlled period, the proportion of patients with AEs causing discontinuation of study treatment was low and was not elevated in the secukinumab groups (3%) compared to the placebo group (5%).

Common Adverse Events

Approximately 58-70% of patients in each treatment group (placebo, secukinumab 75 mg, secukinumab 150 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 AS trials. After 16 weeks, patients receiving placebo switched to secukinumab, so the first 16 weeks reflect truly controlled results. Comparing the proportion of adverse events between the two groups that received the subcutaneous loading regimen, there appeared to be a greater proportion of patients with specific adverse events in the 150 mg dose group compared to the 75 mg dose group, but many of these were lower than placebo. The most common adverse events (proportion >2%) occurring in the any secukinumab group (and at a greater proportion than placebo) included nasopharyngitis, dyslipidemia, nausea, leukopenia, mouth ulceration, upper respiratory tract infection, and gastroenteritis.

- **Immunogenicity**

Approximately 0.3% of patients treated with secukinumab in the phase 3 AS 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 AS 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 AS, there were eight cases of IBD during the entire treatment period. 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 entire 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. While the current safety findings are consistent with the findings in the psoriasis and psoriatic arthritis trials, we will suggest a modification to the current warning to indicate that the risk of worsening or new onset inflammatory bowel disease, including both Crohn's disease and ulcerative colitis.

Hypersensitivity

No cases of angioedema or anaphylactic reaction were reported in the phase 3 AS studies. During the entire treatment period, cases of hypersensitivity events, including rash (2%), eczema (1%), and dermatitis (1%) were reported, but were non-serious and mild or moderate in severity.

Infections

During the 16 week controlled period, the overall incidence of infections and infestations (SOC) was higher in the any secukinumab group compared with the placebo group (31% vs. 18% respectively). The most common infections in the any secukinumab group were nasopharyngitis (11%) and upper respiratory tract infections (3%). The proportion of patients with infections was similar in the 75 mg SC and 150 mg SC groups (30% and 33%, respectively). One serious infection of tonsillitis occurred during the 16 week controlled period in a patient receiving IV-150 mg.

A total of 6 candida infections, the most common being oral candidiasis, were reported across secukinumab-treated groups (vs. 0 in the placebo group). All reported candida infections were mild. Over the entire treatment period, one opportunistic infection (herpes zoster cutaneous disseminated) was reported. 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 AS program compared to the psoriasis program.

Malignancies

A total of 5 malignancies occurred in the phase 3 AS trials during the entire treatment period. Four malignancies occurred in patients treated with secukinumab (B-cell lymphoma, bladder transitional cell carcinoma, breast cancer, and malignant melanoma) and one malignancy occurred in a patient treated with placebo (lymphoma). 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 16 week controlled period, the incidence of immune/administration reactions was higher in the placebo group (19%) than in the secukinumab-treated groups (12%).

Suicidal Ideation and Behavior

Suicidal ideation and behavior is a submission specific safety consideration in psoriatic arthritis 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 psoriatic arthritis and plaque patients. This evaluation did not reveal specific safety signals. In the AS program, there was one completed suicide in a patient treated with placebo.

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.”

A total of four MACE cases were reported over the entire treatment period of the phase 3 AS studies. Of these four cases, three met the criteria for adjudication. These cases included 2 myocardial infarctions and 1 stroke. All of the cases had cardiovascular risk factors. Similar findings were noted during the clinical development program in psoriasis and the Division of Cardioresenal 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 AS would be anticipated in the patient population. The overall exposure-adjusted incidence rate of adjudication and confirmed MACE over the treatment period in the phase 3 AS studies was 0.43 per 100 patient years (95% CI: 0.09 to 1.27). The Applicant noted that the exposure-adjusted MACE rate is similar to that anticipated for patients with spondyloarthritis, including PsA and AS. A review by Papagoras et al 2013⁷, noted that the magnitude of increased cardiovascular risk is similar between PsA and AS (compared to the general population) across multiple large studies of between 1.2 and 1.4 for cardiovascular disease in patients with AS and comparable standardized mortality rate in PsA of 1.33 to 1.84. A recent study⁸ 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 5.8.

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 AS 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

⁷ Papagoras C, et al. Clin Exp Rheumatol 2013;31(4):612-20.

⁸ Ogdie A, et al. Ann Rheum Dis 2014;74:326-32.

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.

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 submitted a full waiver request for pediatric patients based on the rationale that studies would be impossible or impractical due to the rarity of specific axial spondyloarthritis diagnoses in children. The Agency has previously waived studies for juvenile equivalents of AS based on a similar rationale. This waiver request was discussed with the Pediatric Review Committee (PeRC) on October 17, 2015, and PeRC agreed with granting a full 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 considerations. Labeling discussions are ongoing at the time of this review. Major issues and points of discussion are highlighted below:

- 1) **Dosage and Administration**—“The recommended dose is 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 150 mg every 4 weeks.”

- It is unclear if a loading dose is needed and the wording will be updated to reflect that doses for AS can be administered with or without a loading regimen.
- 2) 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.
 - 3) Adverse Reactions section: The Applicant originally proposed a statement noting that the safety in AS 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 AS.
 - 4) Clinical Studies section:

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- 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.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

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

- **Risk Benefit Assessment**

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.

- **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**

There are no additional comments to the applicant.

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/s/

JANET W MAYNARD
12/23/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125504Orig1s002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type Biologic License Application
Application Number(s) 125504/2
Priority or Standard Standard

Submit Date(s) March 23, 2015
Received Date(s) March 23, 2015
PDUFA Goal Date January 23, 2016
Division / Office Division of Pulmonary, Allergy,
and Rheumatology

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

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 at weeks
0,1,2,3,and 4 followed by 150
mg every 4 weeks
Indication(s) Ankylosing spondylitis

Intended Population(s) Adults with ankylosing
spondylitis

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) 125504/2, secukinumab for the treatment of ankylosing spondylitis (AS), is **approval**. This recommendation is based on adequate evidence of efficacy and safety for the proposed indication.

To support this application, the Applicant submitted data from two clinical studies in ankylosing spondylitis: study F2305 and study F2310. The study F2305 consisted of a 24 week double-blind period followed by an uncontrolled period. The Sponsor submitted data to Week 52. During the double blind period, 124 patients received an IV loading dose of secukinumab followed by a 75 mg subcutaneous maintenance dose, 125 patients received an IV loading dose of secukinumab followed by a 150 mg subcutaneous maintenance dose, and 122 patients received placebo. During the uncontrolled period, placebo patients were switched to secukinumab. Thus, all patients received secukinumab after 24 weeks. Patients were included who met Modified New York Criteria for ankylosing spondylitis with x-ray evidence of AS, BASDAI \geq 4, and had spinal pain. The study F2310 consisted of a 16 week double-blind period followed by an uncontrolled period. The Sponsor submitted data to Week 52. During the placebo controlled period, 73 patients received a subcutaneous loading dose followed by a 75 mg subcutaneous maintenance dose, 72 patients received a subcutaneous loading dose followed by a 150 mg subcutaneous maintenance dose, and 74 patients received placebo. Patients were included who met Modified New York Criteria for ankylosing spondylitis with x-ray evidence of AS, BASDAI \geq 4, and had spinal pain.

From an efficacy and safety perspective, studies F2305 and F2310 provided sufficient data to support the use of secukinumab for AS.

1.2 Risk Benefit Assessment

Introduction

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

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 ankylosing spondylitis.

Background on the Proposed Indication: Ankylosing Spondylitis

The Applicant's proposed indication is ankylosing spondylitis (AS). AS is a well-characterized, chronic, and progressive form of axial spondyloarthritis. The majority of research performed over the last two decades has used the modified New York Criteria to identify patients with AS. Further, these criteria were used in the clinical trials performed to support product registration in AS. These criteria are presented in Table 1.

Table 1. Modified New York Criteria for Ankylosing Spondylitis

Clinical Criteria <ul style="list-style-type: none">• Low Back pain and stiffness for longer than 3 months, which improve with exercise, but are not relieved by rest• Restriction of motion of the lumbar spine in both the sagittal and frontal planes• Restriction of chest expansion relative to normal values correlated for age and sex
Radiologic criterion <ul style="list-style-type: none">• Sacroiliitis grade ≥ 2 bilaterally, or grade 3-4 unilaterally
Definitive ankylosing spondylitis is present if the radiologic criterion is associated with at least one clinical criterion

Source: van der Linden S. Arthritis Rheum 1984;27(4):361-8.

Overview of Clinical Program

The Applicant submitted the results from two trials, with either a 16- or 24-week controlled periods as the primary basis for efficacy and safety of secukinumab for the treatment of signs and symptoms of ankylosing spondylitis:

- Trial F2305: Randomized, placebo-controlled, 24-week double-blind period followed by an uncontrolled period in patients with active ankylosing spondylitis (52 week interim analysis)
- Trial F2310: Randomized, placebo-controlled, 16-week double-blind period followed by an uncontrolled period in patients with active ankylosing spondylitis (52 week interim analysis)

During the double-blind period for study F2305, 371 patients were randomized to secukinumab 75 mg SC every 4 weeks with a IV load, 150 mg SC every 4 weeks with a IV load, or placebo. The dose was based on previous phase 2 studies in AS and rheumatoid arthritis (RA). Patients were included in the trial who met Modified New York Criteria for ankylosing spondylitis. Patients in study F2305 had active disease, which was defined by having Bath AS Disease Activity Index (BASDAI) ≥ 4 and spinal pain ≥ 4 . The primary and secondary analyses were pre-specified in this overall population.

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During the double-blind period for study F2310, 219 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, or placebo. The dose was based on previous phase 2 studies in AS and rheumatoid arthritis (RA). Patients were included in the trial who met Modified New York Criteria for ankylosing spondylitis. Patients in study F2310 had active disease, which was defined by having Bath AS Disease Activity Index (BASDAI) ≥ 4 and spinal pain ≥ 4 . The primary and secondary analyses were pre-specified in this overall population.

The different dosing regimens were a major consideration during the review. Studies F2305 and F2310 used different loading regimens. The necessity of a loading dose and the impact of the loading dose on the assessment of efficacy and safety were considered.

Summary of Efficacy

Studies F2305 and F2310 were submitted as the primary source of efficacy data for secukinumab in the treatment of ankylosing spondylitis. In both studies, the primary endpoint was the proportion of patients achieving ASAS20 response at week 16 for both studies. The trials were well-controlled and had endpoints that are considered acceptable for efficacy evaluations in AS.

In the pre-specified primary analyses of study F2305, secukinumab met the primary and key secondary endpoints. In study F2305, 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 continued effects from the IV loading dose. A key consideration was whether the efficacy results would be maintained in the absence of the large loading dose. Thus, FDA performed analyses of placebo patients randomized to secukinumab who did not receive a loading dose. These analyses showed similar responses in ASAS20 without a load as those who were initially randomized to secukinumab and received a loading dose. These data suggest that efficacy with secukinumab will be maintained with chronic dosing.

In the pre-specified primary analysis of study F2310, the proposed 150 mg dose of secukinumab met the primary endpoints and most secondary endpoints. The 75 mg dose of secukinumab did not meet primary or secondary endpoints. In study F2310, patients randomized to the secukinumab arms received 5 weekly SC doses of secukinumab initially before switching to secukinumab SC every 4 weeks. Placebo patients switched to secukinumab after assessment of the primary endpoint and these patients achieved similar ASAS20 responses without a weekly SC loading dose as patients who were randomized to active secukinumab at the beginning of study F2310.

We recognize that these subgroup analyses are exploratory and should be interpreted cautiously. In general, the best test of validity in subgroup analyses is not significance,

but independent substantiation of results. In studies F2305 and F2310, placebo patients were able to show ASAS20 responses after receiving secukinumab at 150 mg every 4 weeks without a loading dose. These results suggest efficacy responses will be maintained with chronic secukinumab administration.

Summary of Safety

The safety information for secukinumab in ankylosing spondylitis was obtained from two phase 3 studies during which 571 patients received a dose of secukinumab. The median duration of treatment was 442 days with the minimum amount of days on secukinumab being 8 days and the maximum number was 757 days.

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. A causal relationship with secukinumab could not be established for any of these deaths.

Serious adverse events (SAEs) were low and comparable across dose groups. The most common SAEs by system organ class (SOC) were “gastrointestinal disorders”, “injury, poisoning, and procedural complications”, and “infections and infestations”. There were 3 SAEs related to inflammatory bowel disease in patients taking secukinumab in the phase 3 AS studies.

Overall, the rate of AEs leading to discontinuation was low. The percent of discontinuations was higher in the 150 mg group versus the 75 mg group. The AEs leading to discontinuation that occurred in 2 patients on secukinumab were Crohn’s disease, dyspnea, decreased hemoglobin, increased hepatic enzyme, pregnancy, and transaminases increased.

The most common adverse events by preferred term are nasopharyngitis (18.7%), diarrhea (9.3%), headache (9.3%), upper respiratory tract infection (9.1%), and oropharyngeal pain (6%). These common AEs were very similar to what has been seen in the PsA and psoriasis programs.

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 multiple cases of new onset inflammatory bowel disease and worsening of inflammatory bowel disease. Currently, the prescribing information includes information regarding the risk of exacerbation of Crohn’s disease, but it does not describe a risk of inflammatory bowel disease (IBD), including new onset disease. While the safety findings were consistent with the psoriasis and PsA programs, the prescribing information will be updated to reflect the risk of new onset and worsening of IBD. Otherwise, no new safety signals were identified in the phase 3 AS studies.

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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

There are no recommendations for postmarket requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

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

Proposed Age group: adult patients

Proposed Dose Regimen: 150 mg by subcutaneous (sc) injection 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. The Applicant has not proposed any additional presentations specific for the AS indication.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2 shows the biologic therapies available for treatment of AS in the US. Biologics for treating AS have targeted the TNF α pathway. Secukinumab has a novel mechanism of action in that it inhibits IL-17.

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Table 2. Biologic therapies available for treatment of AS in the US

Product	BLA (Sponsor)	Date of approval for AS†	Characteristic	ROA
Etanercept (Enbrel®)	103795 (Immunex)	7/24/03	Fusion protein (TNF-inhibitor)	SC
Infliximab (Remicade®)	103772 (Centocor)	12/17/04	Monoclonal antibody (TNF-inhibitor)	IV
Adalimumab (Humira®)	125057 (Abbott)	8/28/06	Monoclonal antibody (TNF-inhibitor)	SC
Golimumab (Simponi®)	125289 (Centocor)	4/24/09	Monoclonal antibody (TNF-inhibitor)	SC
Certolizumab pegol (Cimzia®)	125160 UCB Inc	10/17/2013	Humanized, pegylated Fab' fragment (TNF inhibitor)	SC

Abbreviations: BLA=Biologics License Applications; ROA=route of administration; SC=subcutaneous; IV=intravenous; RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis
† NSAIDs (e.g., celecoxib, diclofenac, indomethacin, naproxen, sulindac) and steroids (e.g., betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone) are also approved for the treatment of AS

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 psoriasis.

2.4 Important Safety Issues With Consideration to Related Drugs

Table 3 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 3. Overview of safety concerns with IL-17A inhibitors

Location in label	Safety concerns
Warnings/Precautions	<ol style="list-style-type: none">1. Infections2. Tuberculosis3. Crohn's disease4. 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 4. On April 8, 2011, the Applicant had an EOP2 meeting with the FDA. FDA raised concerns that the dosing rationale (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 the loading doses being used in the AS program. The loading doses provided much greater exposure than the proposed maintenance doses. The Applicant was asked to study lower loading doses. The Applicant was also 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 (b) (4) 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 whether a single study with subcutaneous loading regimen would be adequate. It appeared additional studies may be required.

On August 29, 2014, the Applicant had a Type C meeting with the FDA. The FDA continued to have concerns with the IV loading regimen in one phase 3 AS study which provided a 10-fold greater exposure compared to the sc loading regimen used in the second phase 3 study for AS. A further concern was that in study F2310 which employed the sc loading regimen, it appeared that efficacy may not be maintained.

Table 4. Overview of regulatory interactions for the ankylosing spondylitis 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 AS are necessary to provide independent substantiation of efficacy of secukinumab in AS 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
Type C guidance (August 29, 2014)	<ol style="list-style-type: none"> 1. Reiterated concerns with the use of a loading dose with much greater exposure than the proposed maintenance dose 2. Concerns that efficacy is not maintained following initial loading doses 3. Provide justification of chosen dose and regimen. An additional study may be necessary to provide data that observed clinical responses are maintained 4. Study CAIN457F2320 would potentially provide additional data to determine whether a loading dose is required for AS

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 F2305 and F2310 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

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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). No potentially conflicting financial interests were identified.

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.

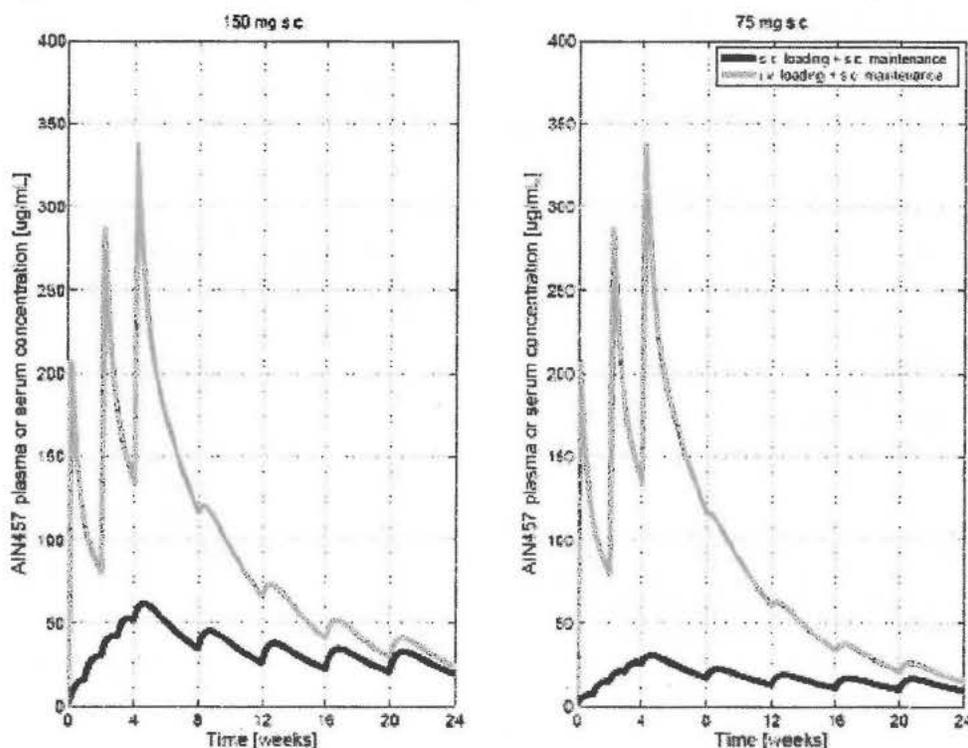
4.4.2 Pharmacodynamics

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

4.4.3 Pharmacokinetics

The Applicant did perform simulations of serum concentration profiles for IV and SC loading doses of secukinumab at 75 and 150 mg doses as shown in Figure 1. The PK model was based on data collected from the psoriasis studies using secukinumab. With the IV load, patients would be expected to receive much higher concentrations of secukinumab in the first 0-12 weeks when compared to SC loading.

Figure 1. Simulated concentration profiles with IV and SC loading dose regimens



Source: Applicant summary of clinical efficacy, p. 100

Reviewer's comment: *The exposure with the IV loading doses is markedly higher than the exposure with the SC loading doses. 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 ankylosing spondylitis (Table 5):

- F2305- a randomized, double-blind, parallel-group, placebo-controlled trial. The Applicant submitted data to Week 52.

- F2310- a randomized, double-blind, parallel-group, placebo-controlled trial. The Applicant submitted data to Week 52.

In addition, the Applicant submitted supportive information from a phase 2 study in ankylosing spondylitis (A2209) and a phase 2 study in rheumatoid arthritis (F2201) (Table 5).

Table 5. Studies submitted to support sBLA 125504/2

Study #, phase, study initiation date	Study Design	Population	N	Dose, route, regimen
A2209 Phase 2 March 16, 2009	Randomized, double blind, placebo controlled	Ankylosing spondylitis	60	Part 1: 2 doses of 10 mg/kg IV 3 weeks apart Part 2: two doses of 0.1, 1, or 10 mg IV 3 wks apart
F2201 Phase 2 July 14, 2009	Double blind, placebo controlled	Rheumatoid arthritis	237	25, 75, 150 or 300 mg SC at wks 0,4,8,12
F2305 Phase 3 October 19, 2011	Randomized, double blind, placebo controlled	Ankylosing spondylitis	371	10 mg/kg IV wks 0,2,4 followed by 75 or 150 mg SC every 4 wks
F2310 Phase 3 October 18, 2012	Randomized, double blind, placebo controlled	Ankylosing spondylitis	219	75, 150 mg SC at wks 0,1,2,3 followed by 75, 150 mg SC every 4 weeks

Source: adapted from 125504/2 Clinical Overview, p. 10-11

5.2 Review Strategy

Efficacy: Trials F2305 and F2310 served as the phase 3 trials for the evaluation of the efficacy of secukinumab in the treatment of signs and symptoms of ankylosing spondylitis. This trial was well controlled and had endpoints that are considered acceptable for efficacy evaluation in AS. Each trial used a different loading dose. F2305 used an IV loading dose and F2310 used a SC loading dose. 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 AS was trials F2305 and F2310. The primary safety analyses focused on data through Week 16- the double-blind, placebo-controlled period. The Applicant also provided the Week 52 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 CAIN457A2209 (A2209)

The following description of the protocol for the study comes from the applicant's clinical study report dated February 28, 2012.

Table 6. Study A2209 Protocol Amendment History

Amendment	Date	Major modifications
Amendment #1	Sep 9, 2008	<ul style="list-style-type: none"> Confirm that stable doses of MTX, SSZ, and low-dose corticosteroid were allowed in the study
Amendment #2	Sep 12, 2008	<ul style="list-style-type: none"> Correction of ASAS40, ASAS 5/6, and BASMI Use of gadolinium in MRI Alcohol/drug testing removed at screening Clarified used of NSAID in study
Amendment #3	Feb 4, 2009	<ul style="list-style-type: none"> Clarify study termination criteria Clarify reconstitution of study vials Clarify study endpoints in protocol and synopsis
Amendment #4	Aug 14, 2009	<ul style="list-style-type: none"> Allow early interim analysis in fewer patients
Amendment #5	Feb 9, 2010	<ul style="list-style-type: none"> Introduce additional dose arms at lower dose levels Allow additional interim analyses
Amendment #6	Apr 22, 2010	<ul style="list-style-type: none"> Added alternative drug preparation to all arms of study to ensure blinding

Abbreviations: MTX= methotrexate, SSZ= sulfasalazine
Source: adapted from A2209 Clinical Study report, p 89-90

Title: Study A2209 is entitled, "Randomized, placebo-controlled, double-blind, multi-center phase 2, proof-of-concept study to assess the efficacy of AIN457 in patients with moderate to severe ankylosing spondylitis."

Study Dates: The first patient was enrolled March 16, 2009 and the last patient completed the study on May 5, 2011.

Sites: The study was conducted in 16 centers in 4 countries including 10 centers in the United States. The four countries were United States, Germany, Netherlands, and United Kingdom.

Objectives of study A2209: The primary objectives of the study were to:

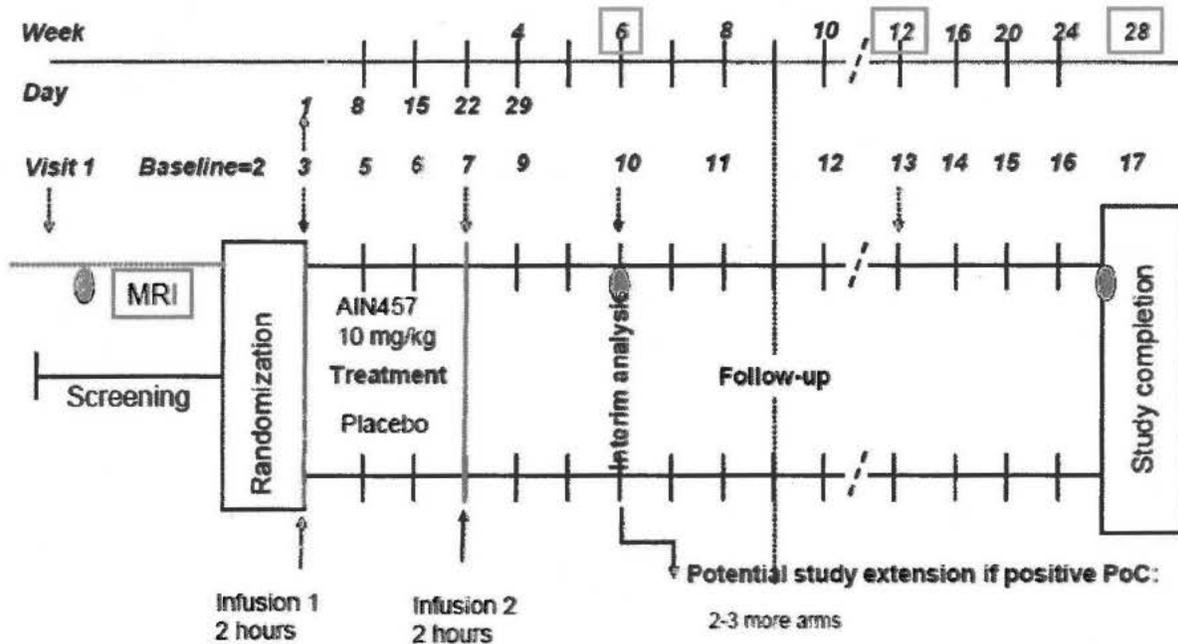
- Part 1: evaluate the efficacy of AIN457 at 6 weeks based on the proportion of patients achieving an ASAS20 response
- Part 2: evaluate the efficacy of lower doses of AIN457 at 6 weeks based on the change in BASDAI score

Overall design of study A2209: Study A2209 was a 2-part, phase 2, double-blind, placebo-controlled, proof-of-concept study in patients with a diagnosis of moderate to severe ankylosing spondylitis.

Patients in Part 1 of the study received 2 infusions separated by 3 weeks of AIN457 10 mg/kg IV or placebo. In Part 2 of the study, patients received 2 infusions separated by 3 weeks of AIN457 (0.1, 1, 10 mg/kg IV). Patients who were dosed with 10 mg/kg IV AIN457 in Part 1 of the study were allowed to continue in Part 2 of the study at the 10 mg/kg IV dose.

Error! Reference source not found. shows the schema for the patients enrolled into A2209. 30 patients each were enrolled for Part 1 and Part 2 of the study. Patients were randomized in a 4:1 (AIN457: placebo) ratio for Part 1 of the study. For Part 2 of the study, patients from Part 1 were randomized to one of 3 dose groups of AIN457 (0.1, 1, or 10 mg/kg IV). More patients were randomized in the two lower dose groups (0.1, 1 mg/kg IV) than the higher dose group (10 mg/kg IV) at a ratio of 2:2:1.

Figure 2. A2209: Study design



Source: A2209 Clinical study report, p. 54

Table 7 shows the study assessments performed for the study. The investigational product was administered at Day 1 and Day 22 for both Part 1 and Part of A2209.

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Table 7. A2209: Study Assessments

Study Phase	SCR	BSL	Treatment														EOS						
¹ Visit numbers	1	2	3				4	5	6	7				8	9	10	11	12	13	14	15	16	17
Week							4	5	6	7				8	9	10	11	12	13	14	15	16	17
Day	-28 to -2	-1	1				2	8	15	22				23	29	6	8	10	12	16	20	24	28
Time (h)			0	2 ⁷	3 ⁷	4 ⁷	24			0	2 ⁷	3 ⁷	4 ⁷	24	29								
Inclusion / exclusion criteria	X	X ²																					
Medical history	X	X ²																					
Current medical conditions	X	X ²																					
Demography	X																						
Physical examination	X ³	X ²	X ⁴				X	X	X ²	X ³				X	X	X	X	X	X ²	X	X	X	X ³
Hepatitis and HIV screen	X																						
Pregnancy test (serum)	X																						
Pregnancy test (urine)		X								X ⁵							X		X	X	X	X	X
PPD tuberculin skin test	X ⁴																						
Drug administration record			X							X													
Study completion information																							X
Comments	As required																						
Vital signs and body measurements:																							
Body height	X																						

Study Phase	SCR	BSL	Treatment														EOS						
¹ Visit numbers	1	2	3				4	5	6	7				8	9	10	11	12	13	14	15	16	17
Week							4	5	6	7				8	9	10	11	12	13	14	15	16	17
Day	-28 to -2	-1	1				2	8	15	22				23	29	6	8	10	12	16	20	24	28
Time (h)			0	2 ⁷	3 ⁷	4 ⁷	24			0	2 ⁷	3 ⁷	4 ⁷	24	29								
Body weight	X	X								X ⁶				X			X		X	X			X
Body temperature	X	X	X ⁶	X ⁸	X ²	X ⁶		X	X	X ⁶	X ⁸	X ⁶	X ⁶	X	X	X	X	X	X	X	X	X	X
Blood pressure, pulse rate	X	X	X ⁶	X ⁸	X ²	X ⁶		X	X	X ⁶	X ⁸	X ⁶	X ⁶	X	X	X	X	X	X	X	X	X	X
ECG	X					X								X									X
Hematology, Blood chemistry, Urinalysis	X	X					X	X	X					X	X	X	X	X	X	X	X	X	X
Adverse events			As required																				
Prior / concomitant medications / therapies	X	X ²	As required																				
ASAS core set domains (1-6)	X	X						X	X						X	X	X	X	X	X	X	X	X
44- joint-count	X	X					X	X						X	X	X	X	X	X	X	X	X	X
MASES & LEI	X	X					X	X						X	X	X	X	X	X	X	X	X	X
Physician's global assessment	X	X					X	X						X	X	X	X	X	X	X	X	X	X
MRI ⁹		X														X							X
SF-36 & ASQoL		X													X				X				X
Immunogenicity		X																	X				X
PK			X ⁶	X	X	X	X	X	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X
PD (IL-17)			X ⁶	X	X	X	X	X	X	X ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X
Soluble marker panel			X ⁶							X ⁶						X							X

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Study Phase	SCR	BSL	Treatment														EOS							
¹ Visit numbers	1	2	3				4	5	6	7					8	9	10	11	12	13	14	15	16	17
Week								1	2	3						4	6	8	10	12	16	20	24	28
Day	-28 to -2	-1	1				2	8	15	22					23	29								
Time (h)			0	2 ²	3 ²	4 ²	24			0	2 ²	3 ²	4 ²	24										
Pharmacogenomics (mRNA)			X ⁴				X	X		X ⁴							X							X
Pharmacogenetic		X																						
Flow cytometry	X		X ⁴														X							X

SCR = screening visit; BSL = baseline visit; EOS = end of study visit.

¹ Visit structure given for internal programming purpose only.

² Review of inclusion / exclusion criteria and current medical conditions is required at first baseline evaluation.

³ A complete physical exam must be done at these visits. At the remaining time points, the physical exam should focus on major body systems, including heart, lungs, abdomen, extremities, skin (including oral mucosa) and lymph nodes.

⁴ PPD skin test check will be performed 48 to 72 hours thereafter. Test can be performed within 6 months prior to screening.

⁵ Part 1 only: MRI scans (including T1 and STIR images) are collected at BSL (as close as possible and prior to first treatment with study drug; i.e. preferably within 2 weeks prior) and at week 6 (± 1 week) and week 28 (± 1 week).

⁶ Pre-dose.

⁷ Hours post start of infusion.

⁸ Measurements will be pre-infusion and then every 15 minutes during the infusion (for 2 hours) and every 30 minutes during 2 hours after the end of infusion.

Source: A2209 clinical study report, p. 1451-1453

Patient selection for study A2209: Study A2209 enrolled 60 patients. 30 were enrolled into Part 1 of the study and 30 were enrolled into Part 2 of the study. The expectation was that that at least 24 subjects would complete Part 2 of the study. Up to 10 patients on previous TNF inhibitor therapy could be enrolled in Part 1 of the study.

Inclusion Criteria:

1. Males or females, aged 18-65 at time of consent.
2. Patients with moderate to severe AS fulfilling the modified New York criteria for a diagnosis of AS and whose disease is not controlled on NSAIDs (on at least one NSAID over a period of at least 3 months at maximum dose).
3. All female subjects must have negative pregnancy test results at screening and baseline.

Women of childbearing potential (WoCBP) must be using simultaneously double-barrier or two acceptable methods of contraception from the time of screening and for the duration of the study, through study completion and 6 months post last dose of AIN457. Women on hormone contraception should be on this regimen for at least 2 months prior to study start.

Female subjects who report surgical sterilization must have had the procedure at least six months prior to initial dosing. If female subjects have male partners who have undergone vasectomy, the vasectomy must have occurred more than six months prior to first dosing.

4. Male subjects willing to use simultaneously two acceptable methods of contraception (e.g. spermicidal gel plus condom) for entire duration of the study and at least 6 months post last dose of AIN457.

5. Able to communicate well with the investigator, and to understand and comply with the requirements of the study. Understand and sign the written informed consent.

6. No evidence of liver disease or liver injury as indicated by abnormal liver function tests

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7. Patients with a history of immunization against influenza (within past 12 months) and/or history of pneumococcal vaccination will be included

8. History or presence of psoriasis or inflammatory bowel disease will be recorded.

Exclusion Criteria:

1. Women of child-bearing potential who are not willing to follow the restrictions in inclusion criteria 3, are not allowed in the study. Men who are not willing to follow the restrictions in inclusion criteria 4 are not allowed in the study.

Male or female patients who plan to conceive during the time course of the study and 6 months post last infusion of AIN457 are not eligible.

2. 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 is longer, and for any other limitation of participation based on local regulations.

3. For patients who were previously treated with TNF blockers, a washout period will be applied

4. For patients who were previously treated with immunosuppressive agents other than methotrexate (MTX), sulfasalazine (SSZ), and systemic corticosteroids, a 1-month washout period prior to baseline is required.

5. Positive human immunodeficient virus (HIV: ELISA and Western blot) test result, Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.

6. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric, chronic inflammatory diseases with the exception of psoriatic arthritis or other disease which in the clinical judgment of the investigator would make the patient unsuitable for the trial.

7. Liver disease or liver injury as indicated by abnormal liver function

8. Subjects with active or history of clinically significant cardiac abnormalities

9. History of renal trauma, glomerulonephritis, or patient with one kidney.

10. History of malignancy (other than basal cell carcinoma or adequately treated carcinoma in- situ of the cervix).

11. Unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.

12. Conditions associated with an immune-compromising condition such as recent major surgical procedure; or history of drug or alcohol abuse within the 6 months prior to dosing.

13. Purified Protein Derivative (PPD) tuberculin skin test reaction of ≥ 10 mm at screening or within 6 months prior to the screening visit, according to national guidelines

14. Total WBC count which falls outside the range of 4500–11,000/ μ l, or platelets $<100,000/\mu$ l at screening.

15. History of severe hypersensitivity to any biological agents (antibody or soluble receptor)

16. Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing or longer if required by local regulation.

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17. Patients with acute or subacute anterior uveitis requiring specialty care by an ophthalmologist.
18. Patients with a diagnosis of fibromyalgia.
19. Patients with total ankylosis of the spine (end stage disease).
20. Patients fulfilling criteria of psoriatic arthritis.
21. Part 1 only: Patients with metal implants (e.g. aneurysm clips), shrapnel or cardiac pacemakers.
22. Part 1 only: Patients who do not fit into the MRI scanner (e.g. patients with obesity).
23. Part 1 only: Patients suffering from uncontrollable claustrophobia who cannot tolerate the confines of the MRI scanner.

Treatments in study A2209:

In Part 1 of the 30 study patients received 2 infusions separated by 3 weeks of AIN457 10 mg/kg IV or placebo. The patients were more likely to receive AIN457 as they were randomized 4:1 in favor of AIN457 over placebo.

In Part 2 of the study, 30 patients were randomized 2:2:1 to receive 0.1, 1, or 10 mg/kg IV of AIN457 respectively.

Selection of doses in study A2209: The Applicant based the dosing of AIN457 on studies in rheumatoid arthritis (A2201) and Crohn's disease (A2202) which used two 10 mg/kg IV doses of AIN457. The Applicant states that the dose range in between 3-10 mg/kg is expected to provide a reduction in inflammation and tissue destruction associated with IL-17A.

Concomitant medications in study A2209: Paracetamol was permitted as a rescue medication for acute pain secondary to ankylosing spondylitis. Any concomitant medication that was used to treat adverse events or provided as rescue medication was recorded as concomitant medications/significant non-drug therapies.

Prohibited therapies in study A2209: While there were no listed medications as prohibited, the Applicant specified washout periods for investigational drugs, immunosuppressive drugs and biologic therapies. The listed exclusion criteria provide further details on the drugs requiring washout periods prior to enrollment in study A2209.

Patient stopping rules in study A2209: Patients were able to voluntarily withdraw from the study at any time. After the first dose of study medication, if there was persistent high activity of disease, the study treatment had to be stopped and investigators would provide would determine conventional therapy for active disease. If there was evidence of a clinically relevant acute infection prior to the second infusion, patients were discontinued from the study and not allowed to receive the second dose of medicine.

Study monitoring and evaluations for study A2209: See Table 7 for study assessments conducted during study A2209. Inclusion and exclusion criteria were reviewed at the first visit. A complete physical examination was done at the visits. The Sponsor collected ASAS core set domains, laboratory examinations, vital signs, PK, PD, pharmacogenomics, pharmacogenetic and flow cytometry studies throughout the trial.

Efficacy Endpoints

Primary Endpoint: The Applicant defined ASAS20 response rate at week 6 as the primary efficacy variable for Part 1 of the study. A patient was defined as an ASAS20 responder if both of the following conditions were met:

1. A $\geq 20\%$ improvement and an absolute improvement ≥ 1 unit in 3 of the following 4 domains:
 - a. Patient global assessment (0-10 point visual analog scale)
 - b. Pain (0-10 point visual analog scale)
 - c. Function (0-10 point BASFI scale)
 - d. Inflammation (mean of two morning stiffness questions from BASDAI, each with 0-10 point scale)
2. No deterioration in the potential remaining domain (deterioration is defined as $\geq 20\%$ worsening and an absolute worsening of ≥ 1 unit)

The Applicant defined change in BASDAI scores at week 6 as the primary efficacy variable in Part 2 of the study.

Study A2209 was used for dose selection in studies F2305 and F2310 and results are provided in the dose selection section for studies F2305 and F2310.

5.3.2 F2201

Study F2201 is summarized in section 5.3.2 of the clinical review for sBLA 125504/1.

5.3.3 F2305

The following description of the protocol for the study comes from the applicant's clinical study report dated October 15, 2014.

Title: A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis

Study dates: The first patient was enrolled on October 19, 2011 and the data cutoff date was December 10, 2013 for the 52 week analysis. The study is ongoing.

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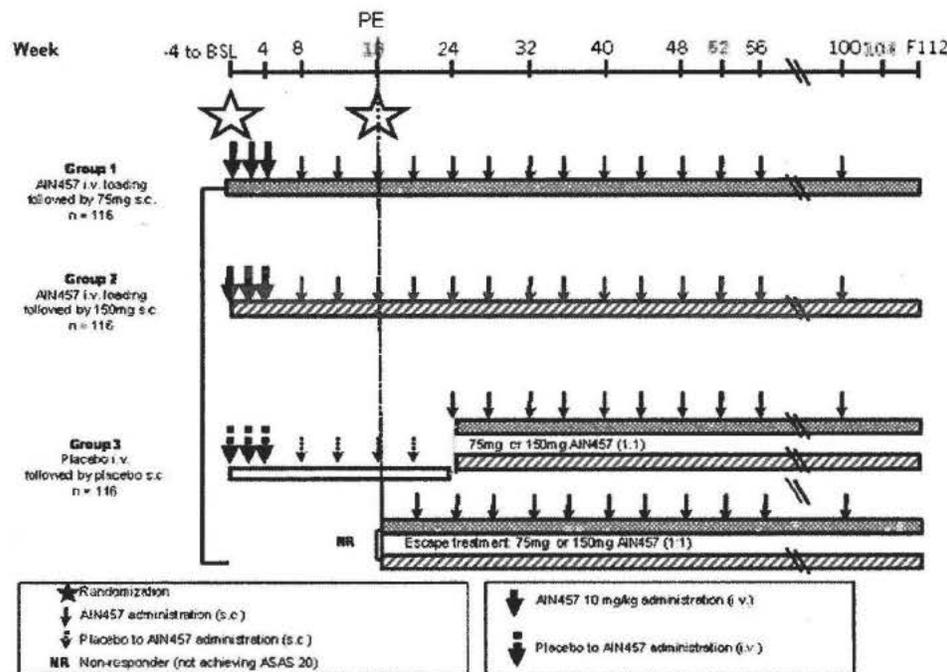
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Sites: The study was conducted at 65 centers in 14 countries. The countries were Belgium, Bulgaria, Canada, France, Germany, Italy, Mexico, Netherlands, Peru, Russian Federation, Taiwan, Turkey, United Kingdom, and United States.

Objectives of study F2305: The primary objective was to demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 20 (Assessment of Spondyloarthritis International Society criteria) response.

Overall Design of Study F2305: This was a double-blind, randomized, parallel-group, placebo-controlled phase 3 study in patients with active ankylosing spondylitis. The study design is shown in Table 8.

Table 8. F2305: Study design



Source: F2305 clinical study report, p. 52

Patient selection for study F2305: Study F2305 randomized patients who met the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Patients able to understand and communicate with the investigator, comply with the requirements of the study, and give a written, signed and dated informed
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. Diagnosis of moderate to severe AS with prior documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS with active AS and a BASDAI ≥ 4 (0-10) and spinal pain as measured by VAS ≥ 4 cm at baseline
4. Patient had to be on NSAIDs at the highest recommended dose for at least 3 months with an inadequate response or failure to respond, or less than 3 months if therapy had to be withdrawn due to intolerance, toxicity or contraindications
5. Patient who are regularly taking NSAIDs (COX-1 or COX-2 inhibitors) are required to be on a stable dose for at least 2 weeks before randomization
6. Patients who have been on an anti-TNF- α agent (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months or have been intolerant to at least one administration of an anti-TNF- α agent
7. Patients who have previously been on a TNF- α inhibitor were allowed entry into study after appropriate wash-out period prior to randomization

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8. Patients taking MTX (7.5 to 25 mg/week) or Sulfasalazine (≤ 3 g/day) must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks before randomization

9. Patients on MTX must be on stable folic acid supplementation before randomization

10. Patients who are on a DMARD other than MTX or Sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed

11. Patients taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization

Exclusion Criteria:

1. Chest X-ray with evidence of ongoing infectious or malignant process

2. Patients with total ankylosis of the spine

3. Patients taking high potency opioid analgesics

4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor

5. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug

6. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes

7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization

8. Any intramuscular corticosteroid injection within 2 weeks before randomization

9. Patients previously treated with any biological immunomodulating agents except for those targeting TNF α

10. Previous treatment with any cell-depleting therapies

11. Pregnant or nursing (lactating) women,

12. Women of child-bearing potential, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment.

13. Active ongoing inflammatory diseases other than AS

14. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy

15. Significant medical problems or diseases

16. History of clinically significant liver disease or liver injury

17. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 μ mol/L)

18. Screening total WBC count $< 3,000/\mu$ L, or platelets $< 100,000/\mu$ L or neutrophils $< 1,500/\mu$ L or hemoglobin < 8.5 g/dL (85 g/L)

19. Active systemic infections during the last two weeks (exception: common cold) prior to randomization

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20. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection
21. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization
22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years
23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
24. Inability or unwillingness to undergo repeated venipuncture
25. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
26. Donation or loss of 400 mL or more of blood within 8 weeks before dosing
27. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
28. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

Trial Population: The study population comprised of male and female patients, 18 years or older, who were diagnosed with moderate to severe AS according to the Modified New York Criteria for AS with prior documented X-ray evidence, BASDAI \geq 4 and spinal pain \geq 4 at baseline. Enrolled patients were to have active disease despite current or previous treatment with NSAIDs, DNARDs, and/or TNF inhibitors.

Treatments in study F2305:

Secukinumab was provided in glass vials containing 150 mg secukinumab as a lyophilized cake. The 150 mg powder for solution was used to prepare both 75 mg and 150 mg subcutaneous doses and IV doses. The color of the caps for the vials of secukinumab for solution was different from the placebo vials. To maintain the blind of the study, an unblinded pharmacist or unblinded qualified site personnel was appointed to prepare the study treatment.

Selection of doses in study F2305: The Applicant used two studies to justify their dose selection. In study A2209, 60 AS patients were treated with two doses of 10 mg/kg secukinumab IV separated by 21 days or placebo. ASAS20 at week 6 was the key endpoint and conclusions were that secukinumab showed evidence of therapeutic benefit in AS patients. 14/23 (60.9%) on secukinumab achieved ASAS20 response compared to 1/6 (16.7%) 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.

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The Applicant used these two studies and dose exposure predictions from pharmacokinetic models to determine their doses. The doses that were selected for study F2305 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.

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Concomitant medications in study F2305:

The patient was to notify the study site of any new medications including over-the-counter drugs, calcium, and vitamins, taken after enrolling in the study. Any concomitant medications were to be listed on the concomitant medication electronic case report form (eCRF). The reason and name of drug were to be listed. Patients on methotrexate were to be on a stable dose during the study and take folic acid supplementation. Patients could take a stable dose of sulfasalazine. Stable doses of systemic corticosteroids were allowed with a maximum dosage equivalent to 10 mg daily of prednisone allowed. Stable doses of NSAIDs or acetaminophen were allowed but could not be taken 24 hours prior to a disease activity assessment.

Prohibited therapies in study F2305:

Table 9 shows the therapies that were not allowed for study F2305 and the required washout period prior to randomization.

Table 9. F2305: Prohibited treatment

Prohibited treatment	Washout period (before randomization)
Biological immunomodulating agent	Not applicable
Etanercept	4 weeks
Infliximab	8 weeks
Adalimumab, golimumab, certolizumab	10 weeks
Unstable dose of MTX or SSZ	4 weeks
Other DMARD	4 weeks
Leflunomide	8 weeks
Leflunomide with choestyramine washout	4 weeks
Unstable dose of NSAIDs (COX-1 or COX-2 inhibitors)	2 weeks
Systemic corticosteroids >10 mg prednisone equivalent	2 weeks
Intra-articular injections up to week 16	4 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives
Analgesics other than acetaminophen and low strength opioids, as needed	4 weeks
Live vaccinations up to week 24	6 weeks

Source: adapted from F2305 clinical study report, p. 65

Patient stopping rules in study F2305:

The following circumstances required study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events:
 - Any severe or serious adverse event that was not compatible with administration of study medication,

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- Onset of lymphoproliferative disease or any malignancy
- Life-threatening infection
- 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 patient's safety

In case of undue safety risk for the patient, the patient was to discontinue study treatment at the discretion of the investigator.

Trial monitoring and evaluations for study F2305:

Table 10. Assessment schedule

	SCR	Treatment Period 1																	Treatment Period 2										Follow up			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30 ^a	F11 ^b	
Week	≤ -4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 ^a Dis- patient ^c	112	
Informed consent / optional PG informed consent	X																															
Inclusion/Exclusion criteria	X	X																														
Relevant medical history, current medical condition	X	X																														
Cardiovascular medical history		X																														
Prior medication	X	X																														
AS assessment and history of extra-axial involvement	X																															
Demography	X																															
Smoking History		X																														
Physical Exam ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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							X														X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test ^e or QuantiFERON TB-Gold test	X																															
Chest X-ray	X ^f																															
Hematology, blood chemistry, urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	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		X			X		X	X		X		X		X		X		X		X		X		X		X		X		X	X	
ECG		X						X									X														X	
Randomisation		X						X ^g		X ^g																						
Administration of iv study treatment		X		X	X																											

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	SCR	Treatment Period 1																Treatment Period 2										Follow up			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30 ¹	F112 ²
Week	±-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 ¹ Disc. patient ³	112
Administration of 1st study treatment						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication / non drug therapy	Update as necessary																														
Adverse Events / SAE (incl. injection site reactions)	Update as necessary																														
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	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's assessment of Spinal pain (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BASFI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BASDAI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spinal mobility (BASMI Linear- chest expansion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WPAI-GH questionnaire		X							X	X							X														
SF-36 v2 questionnaire		X			X	X	X	X	X								X														
FACT-Fatigue questionnaire		X			X	X	X	X	X								X														
ASQoL		X			X	X	X	X	X								X														
EQ-5D		X			X	X	X	X	X								X														
44 tendons and swollen joint count		X				X	X	X	X								X														
Expanded MASES (Osteostrict AS Embolic Score)		X				X	X	X	X								X														
MBI (spine and sacralis count)		X						X									X														
X-Ray (cervical + thoracic + lumbar) for m-ASSS		X																													
DNA (spine and hip)		X															X														
Erythrocyte Sedimentation Rate (ESR)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X	X

	SCR	Treatment Period 1																Treatment Period 2										Follow up				
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30 ¹	F112 ²	
Week	±-4	BSL	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104 ¹ Disc. patient ³	112	
HLA-B*27		X																														
Immunogenicity		X						X	X								X															
PK assessments (at pre-dose)		X			X			X	X								X															
Lipids ⁴		X				X		X	X								X						X									
Cardiovascular panel		X						X	X								X						X									
Cartilage and Bone markers ⁵		X						X									X															
Serum Biomarkers		X						X									X															
Pharmacogenetics ⁶		X																														
Treatment Phase 1 completion form ⁷																	X															
Treatment Phase 2 completion form																															X	
Study completion form																																X

¹ In case of premature discontinuation, assessments to be done 4 weeks after last study treatment administration. In case of premature discontinuation before week 52, the Treatment Phase 1 completion form needs to be completed as well.

² These assessments are source documentation only and will not be entered into the eCRF

³ The PPD skin test can be performed at any time during the screening period but it has to be read within 72 hrs and before randomization.

⁴ Based on Week 16 assessment, subjects will be re-randomized or re-assigned and at Week 24, all remaining placebo subjects will be randomized to active treatment

⁵ Pharmacogenetic sample should only be collected after separate consent is signed

⁶ Unless X-ray was taken within the past 3 months prior Screening

⁷ Only done in a sub-population of selected centers

⁸ Sample must be obtained fasting

⁹ Follow-up visit to be done 12 weeks after last study treatment administration for subjects who early terminated the study or for subjects who completed the study but do not enter the extension study

Source: F2305 clinical study report, p. 7357-7359

Efficacy endpoints

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Primary Efficacy Endpoint: The primary efficacy endpoint for F2305 was response to ASAS20 criteria at week 16 using the full analysis set.

The ASAS Response Criteria (ASAS 20) was defined as an improvement of $\geq 20\%$ and ≥ 1 unit on a scale of 10 in at least three of the four main domains and no worsening of $\geq 20\%$ and ≥ 1 unit on a scale of 10 in the remaining domain.

The four main domains are:

1. Patient's global assessment of disease activity measured on a VAS scale (0-100 mm)
2. Patient's assessment of spinal pain, represented by either total or nocturnal back pain scores, both measured on a VAS scale (0-100 mm)
3. Function represented by the Bath Ankylosing Spondylitis Functional Index (BASFI), the average of 10 questions regarding ability to perform specific tasks as measured by VAS scale (0-10 cm)
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale (0-10 cm)

In addition, the following domains are assessed:

5. Spinal mobility represented by the BASMI lateral spinal flexion assessment
6. C-reactive protein (acute phase reactant)

The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem), which was used to answer 6 questions pertaining to the 5 major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Joint pain / swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness severity
6. Morning stiffness duration

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness was taken (questions 5 and 6). The resulting 0 to 10 score was added to the scores for questions 1 through 4. The resulting 0 to 50 score was divided by 5 to give a final 0 – 10 BASDAI score.

The ranked secondary variables analyzed were the following:

- Response to treatment at week 16 according to ASAS 40 criteria
- Change from baseline in hsCRP at week 16
- Response to treatment at week 16 according to the ASAS 5/6 criteria
- Change from baseline in total BASDAI score at week 16
- Change in SF-36 PCS from baseline at week 16
- Change in ASQoL from baseline at week 16

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- Response to week 16 according to the ASAS partial remission criteria

ASAS 40 response is defined as an improvement of $\geq 40\%$ and ≥ 2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain.

ASAS 5/6 response is an improvement of $\geq 20\%$ in at least five domains.

ASAS partial remission is defined as a value of ≤ 2 units in each of the 4 core domains on a scale of 10.

The ASQoL is a self-administered questionnaire designed to assess disease-specific health related quality of life in adult patients with AS, with an established MCID for the ASQoL being a change of 1.8. The ASQoL contains 18 items with dichotomous yes/no response options, assessing whether the patient experiences limitations on life quality due to negative experiences with mobility/energy, self-care and mood/emotion. A single point is assigned for each "yes" response and no points for each "no" response, resulting in an overall score that ranges from 0 to 18. As such, a lower score indicates a better quality of life (less negative impact on quality of life). The recall period is "at the moment," and the measure requires approximately 6 minutes to be completed.

The SF-36 is an instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role- Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed.

Statistics in study F2305:

Populations: The populations specified in the statistical analysis plan were:

- Randomized set comprised randomized patients
- FAS comprised all patients who were randomized and to whom study treatment had been assigned. Efficacy analyses are based on the FAS.
- Safety set comprised all patients who received at least one dose of study treatment during the treatment period. Safety analyses are based on the safety set.
- Per-protocol set included all patients who completed the study without a major protocol deviation.

Database locks: The database was locked after all patients completed week 52 and there will be another lock of the database upon all patients completing study F2305.

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Methods for the primary efficacy endpoint: The analysis of the primary variable was based on the FAS. The statistical hypothesis for ASAS20 was that there was no difference in the proportion of patients fulfilling the ASAS20 criteria at week 16 in any of the secukinumab arms versus placebo. The primary analysis was conducted via logistic regression with treatment and TNF inhibitor status as factors and weight as a covariate. Odds ratios and 95% confidence intervals were compared between secukinumab arms and placebo.

Handling of missing data for the primary endpoint: The impact of missing data on the results of ASAS20 response was assessed by repeating logistic regression model using different ways to handle missing data such as multiple imputation and observed data analysis.

Methods for the 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 is not different to placebo regimen with respect to signs and symptoms (ASAS 20 response) at Week 16

H2: secukinumab 150 mg is not different to placebo regimen with respect to signs and symptoms (ASAS 20 response) at Week 16

Secondary objectives:

H3: secukinumab 75 mg is not different to placebo regimen with respect to signs and symptoms (ASAS 40 response) at Week 16

H4: secukinumab 150 mg is not different to placebo regimen with respect to signs and symptoms (ASAS 40 response) at Week 16

H5: secukinumab 75 mg is not different to placebo regimen with respect to hsCRP at Week 16

H6: secukinumab 150 mg is not different to placebo regimen with respect to hsCRP at Week 16

H7: secukinumab 75 mg is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H8: secukinumab 150 mg is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H9: secukinumab 75 mg is not different to placebo regimen with respect to total BASDAI at Week 16

H10: secukinumab 150 mg is not different to placebo regimen with respect to total BASDAI at Week 16

H11: secukinumab 75 mg is not different to placebo regimen with respect to SF-36 PCS at Week 16

H12: secukinumab 150 mg is not different to placebo regimen with respect to SF-36 PCS at Week 16

H13: secukinumab 75 mg is not different to placebo regimen with respect to ASQoL at Week 16

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H14: secukinumab 150 mg is not different to placebo regimen with respect to ASQoL at Week 16

H15: secukinumab 75 mg is not different to placebo regimen with respect to ASAS partial remission at Week 16

H16: secukinumab 150 mg is not different to placebo regimen with respect to ASAS partial remission at Week 16

The family-wise error was set to $\alpha=5\%$ and it was controlled with the proposed hierarchical testing strategy. Each of the hypotheses (H1 and H2) for the primary objective (ASAS 20 at Week 16) for each secukinumab regimen versus placebo was tested simultaneously at $\alpha/2$. Then based on the rejection of one or both (of H1 and H2), the ASAS 40 at Week 16 endpoint was tested hierarchically for each dose (through H3 and/or H4). This procedure was continued (pending rejection of the null hypotheses) until H15 and/or H16 were/was rejected, then the respective $\alpha/2$ could be passed on to the other secukinumab regimen's hierarchy of hypotheses, if they were not already rejected at $\alpha/2$.

Definitions of safety endpoints in Study F2305:

AE definition

The Applicant defined an adverse event as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing the informed consent form even if the event is not considered to be related to study treatment.

SAE definition

The Applicant defined an SAE as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study treatment
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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Coding dictionaries

The Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 was utilized for coding of AEs and conditions in the medical history.

5.3.4 CAIN457F2310 (F2310)

The following description of the protocol for the study comes from the applicant's clinical study report dated November 26, 2014.

Title: A randomized, double-blind, placebo-controlled phase 3 multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active Ankylosing Spondylitis

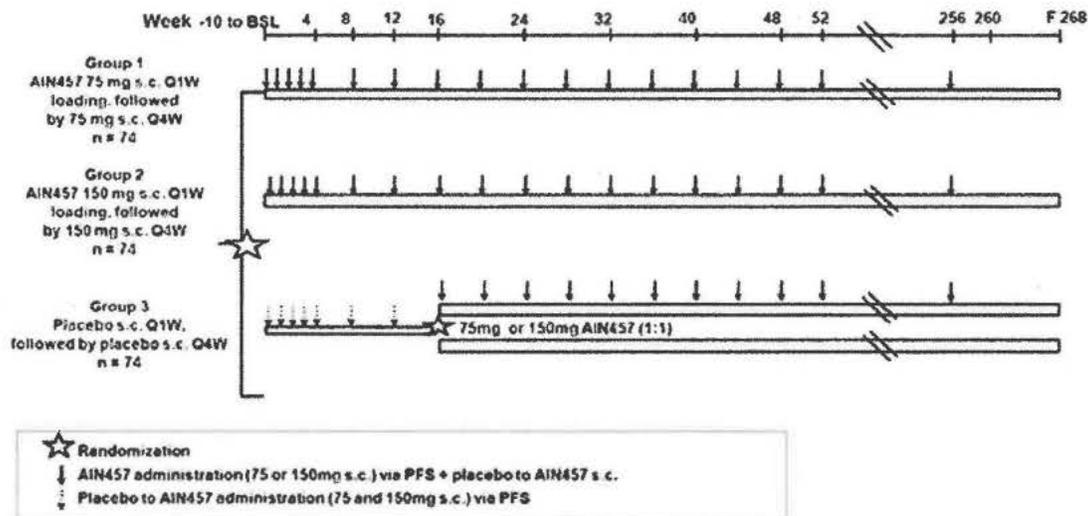
Study dates: The first patient's first visit was October 18, 2013 and the last patient's last 52 week visit was August 4, 2014. The study is ongoing.

Study sites: Patients were enrolled in 54 centers from 13 countries. The countries were Austria, Canada, Czech Republic, Finland, Germany, Italy, Netherlands, Russian Federation, Singapore, Spain, Switzerland, United Kingdom, and United States.

Objectives of study F2310: The primary objective of this study was to demonstrate that the efficacy of secukinumab 75 mg s.c. or 150 mg s.c. at Week 16 was superior to placebo in subjects with active AS based on the proportion of subjects achieving an ASAS 20 (Assessment of SpondyloArthritis International Society criteria) response.

Overall design: Study F2310 was a randomized, double-blind, placebo-controlled Phase 3 multicenter study of subcutaneous secukinumab to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active Ankylosing Spondylitis.

Figure 3. F2310: Study design



Source: F2310 clinical study report, p. 48

Patient selection for study F2310: Study F2310 randomized patients who met the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Patients were required to be able to understand and communicate with the investigator and comply with the requirements of the study and had to give a written, signed and dated informed consent before any study assessment was performed
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. At Baseline: Diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI ≥ 4 (0-10) and spinal pain as measured by VAS ≥ 4 cm (BASDAI question #2)
4. Patients had to be on NSAIDs at the highest recommended dose for at least 3 months prior to randomization with an inadequate response or failure to respond, or less than 3 months if therapy was withdrawn due to intolerance, toxicity or contraindications
5. Patients who were regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy were required to be on a stable dose for at least 2 weeks before randomization
6. Patients who have been on a TNF α inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNF α agent
7. Patients who have previously been on a TNF α inhibitor were allowed entry into study after wash-out period prior to randomization.

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8. Patients taking MTX (7.5 to 25 mg/week) or sulfasalazine (≤ 3 g/day) were allowed to continue their medication and must have taken it for at least 3 months and had to be on a stable dose for at least 4 weeks prior to randomization
9. Patients on MTX must be on stable folic acid supplementation before randomization
10. Patients who were on a DMARD other than MTX or sulfasalazine must have discontinued the DMARD 4 weeks prior to randomization, except for leflunomide, which had to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout had been performed
11. Patients taking systemic corticosteroids had to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization

Exclusion criteria:

1. Chest x-ray or magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
2. Patients with total ankylosis of the spine
3. Patients who were taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
5. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever was longer
6. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
8. Any intramuscular corticosteroid injection within 2 weeks before randomization
9. Patients previously treated with any biological immunomodulating agents except for those targeting TNF α
10. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
11. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
12. Women of child-bearing potential, were defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment.
13. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis
14. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the

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investigator immunocompromised the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy

15. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension ($\geq 160/95$ mmHg), congestive heart failure [New York Heart Association status of class III or IV], uncontrolled diabetes, or very poor functional status unable to perform self-care

16. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin.

17. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dl (132.6 $\mu\text{mol/L}$)

18. 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 (85 g/L)

19. Active systemic infections during the last two weeks (exception: common cold) prior to randomization

20. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection

21. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization

22. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that had been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that had been removed)

23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator rendered the patient unsuitable for the trial

24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)

25. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol

26. Donation or loss of 400 mL or more of blood within 8 weeks before dosing

27. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization

28. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

Trial Population: The study population comprised of male and female patients, 18 years or older, who were diagnosed with moderate to severe AS according to the Modified New York Criteria for AS with prior documented X-ray evidence, BASDAI ≥ 4 and spinal pain ≥ 4 at baseline. Enrolled patients were to have active disease despite current or previous treatment with NSAIDs, DNARDs, and/or TNF inhibitors.

Treatments in study F2310:

The Applicant supplied treatments as follows:

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- Investigational Treatment: Secukinumab 75 mg/150 mg provided in 0.5/1.0 ml PFS for s.c. injection.
- Reference Therapies: Secukinumab placebo provided in 0.5/1.0 ml PFS for s.c. injection.

Subjects were instructed how to self-administer the s.c. injections. The pre-filled syringes were packed in double blinded fashion for the double blind portion of the study. During the double blind portion of the study the study medications were labeled as AIN457 75mg/0.5ml/Placebo and AIN457 150mg/1.0ml/Placebo

Selection of doses in study F2310:

Selection of doses in study F2305: The Applicant used two studies to justify their dose selection. In study A2209, 60 AS patients were treated with two doses of 10 mg/kg secukinumab IV separated by 21 days or placebo. ASAS20 at week 6 was the key endpoint and conclusions were that secukinumab showed evidence of therapeutic benefit in AS patients. 14/23 (60.9%) on secukinumab achieved ASAS20 response compared to 1/6 (16.7%) 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 F2310 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.
- Placebo at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4.

At week 16, all placebo patients 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 F2310:

The patient was to notify the study site of any new medications including over-the-counter drugs, calcium, and vitamins, taken after enrolling in the study. Any concomitant medications were to be listed on the concomitant medication electronic case report form (eCRF). The reason and name of drug were to be listed. Patients on methotrexate

were to be on a stable dose during the study and take folic acid supplementation. Patients could take a stable dose of sulfasalazine. Stable doses of systemic corticosteroids were allowed with a maximum dosage equivalent to 10 mg daily of prednisone allowed. Stable doses of NSAIDs or acetaminophen were allowed but could not be taken 24 hours prior to a disease activity assessment.

Prohibited therapies in study F2310:

The same therapies prohibited in study F2305 were prohibited in study F2310 as shown in Table 9. The same washout periods used in study F2305 were also used in study F2310.

Patients stopping rules in study F2310:

The following circumstances required study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events:
 - Any severe or serious adverse event that was not compatible with administration of study medication,
 - Onset of lymphoproliferative disease or any malignancy
 - Life-threatening infection
 - 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 patient's safety

In case of undue safety risk for the patient, the patient was to discontinue study treatment at the discretion of the investigator.

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Trial monitoring and evaluations for study F2310:

Table 11 shows the schedule of assessments that were conducted through week 52 in study F2310.

Table 11. F2310: Schedule of Assessments

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Week	Screening ¹		Treatment period 1								Treatment period 2								
	-10 to -4	≤-4	BSL	1	2	3	4	8	12	16*	20	24	28	32	36	40	44	48	52*
Obtain informed consent & Exploratory Biomarker informed consent	X																		
Inclusion/Exclusion criteria ²	X	X	X																
Relevant medical history: current medical condition	X	X	X																
Prior medication	X	X	X																
AS assessment and history of extra-axial involvement	X																		
Demography	X																		
Cardiovascular medical history			X																
Smoking history			X																
Physical Exam ³		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							X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test ⁴ or QuantiFERON TB-Gold test		X																	
Chest x-ray or MRI ⁵		X																	

Week	Screening ¹		Treatment period 1								Treatment period 2								
	-10 to -4	≤-4	BSL	1	2	3	4	8	12	16*	20	24	28	32	36	40	44	48	52*
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			X				X		X	X		X		X		X			X
ECG			X						X										X
Randomization via IRT			X						X*										
Administration of s.c. study treatment via PFS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication / non drug therapy	X	Update as necessary																	
Adverse events / SAE (including injection site reactions) ⁷	X	Update as necessary																	
Cumulative NSAID intake	X	Update as necessary																	
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 assessment of inflammatory back pain intensity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASFI			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASDAI			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spinal mobility (BASMI Linear + chest expansion)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Week	Screening ¹		Treatment period 1								Treatment period 2								
	-10 to -4	≤-4	BSL	1	2	3	4	8	12	16*	20	24	28	32	36	40	44	48	52*
WPAI-GH questionnaire			X							X									X
SF-36 v2 questionnaire			X				X	X	X	X									X
FACT-Fatigue questionnaire			X				X	X	X	X									X
ASQoL			X				X	X	X	X									X
EQ-5D			X				X	X	X	X									X
44 tender and swollen joint count			X					X	X	X									X
Expanded MASES (Maastricht AS Enthesis Score)			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	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
HLA-B27			X																
Immunogenicity			X							X		X							X
PK assessments (at predose)			X				X			X		X							X
Lipids ⁴			X					X		X		X							X
Cardiovascular panel			X							X		X							X
Serum Biomarkers			X							X									X
Pharmacogenetics ⁵			X																

Week	Screening ¹		Treatment period 1								Treatment period 2								
	-10 to -4	≤-4	BSL	1	2	3	4	8	12	16*	20	24	28	32	36	40	44	48	52*
RNA ⁶		X	X	X			X			X									
Treatment period 1 completion form										X									
Treatment period 2 completion form																			X

¹ If the subject's washout period ≥4 weeks, Visit 1 and Visit 2 could be performed on the same day.

² A copy of the x-ray or radiologist's report was kept in the source documentation.

³ These assessments are source documentation only and were not entered into the eCRF.

⁴ The PPD skin test could be performed at any time during the screening period, but it had to be read within 72 hours and before randomization.

⁵ A chest x-ray was required if it was not performed and evaluated within 3 months prior to screening. The x-ray was performed after it was certain the subject met inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The x-ray assessment could be replaced by an MRI assessment.

⁶ Placebo subjects were re-randomized at Week 16 to active treatment.

⁷ AEs / SAEs occurring after the subject had signed the informed consent was captured on the appropriate eCRF page.

⁸ Sample was obtained fasting.

⁹ Pharmacogenetic and RNA samples were only collected after separate Exploratory Biomarker informed consent was signed.

¹⁰ For all subjects who discontinued or withdrew from the study, the investigator ensured that the subject completed an end of treatment visit (corresponds to the last visit for the subject's current period of treatment) 4 weeks after last study treatment, and also returned after an additional 8 weeks for a final follow-up visit, F268 (12 weeks after last study treatment). The final visit was performed before any new treatment was initiated.

Source: F2310 clinical study report, p. 65-68

Efficacy endpoints

Primary efficacy endpoints: The primary efficacy endpoint was response to treatment according to ASAS20 criteria at week 16 in the full analysis set.

The ranked secondary variables were the following:

- ASAS40 response at week 16
- Change from baseline in hsCRP at week 16
- ASAS 5/6 response at week 16
- Change from baseline BASDAI at week 16
- Change from baseline in SF-36 at week 16
- Change in ASQoL at week 16
- ASAS partial response at week 16

Statistics in study F2310:

Populations: The populations specified in the statistical analysis plan were:

- Randomized set comprised randomized patients
- FAS comprised all patients who were randomized and to whom study treatment had been assigned. Efficacy analyses are based on the FAS.
- Safety set comprised all patients who received at least one dose of study treatment during the treatment period. Safety analyses are based on the safety set.
- Per-protocol set included all patients who completed the study without a major protocol deviation.

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Database locks:

The Applicant performed a clinical database lock after all patients completed the week 16 visit to perform the primary efficacy analysis. The Applicant also performed a database lock after all patients completed the week 52 visit. A final database lock will occur after all patients complete study F2310.

Methods for the primary efficacy endpoint: The analysis of the primary variable was based on the FAS. The statistical hypothesis for ASAS20 was that there was no difference in the proportion of patients fulfilling the ASAS20 criteria at week 16 in any of the secukinumab arms versus placebo. The primary analysis was conducted via logistic regression with treatment and TNF inhibitor status as factors and weight as a covariate. Odds ratios and 95% confidence intervals were compared between secukinumab arms and placebo.

Handling of missing data for the primary endpoint: Patients who dropped out of the trial for any reason were considered non-responders from the time that they dropped out until week 52. Subjects who did not have the required data to compute response at baseline and the specific time point were also classified as non-responders.

Methods for secondary endpoints:

The following hypothesis was 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 was not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

H2: secukinumab 150 mg was not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

Secondary objectives:

H3: secukinumab 75 mg was not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H4: secukinumab 150 mg was not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H5: secukinumab 75 mg was not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H6: secukinumab 150 mg was not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H7: secukinumab 75 mg was not different to placebo regimen with respect to ASAS5/6 response at Week 16

H8: secukinumab 150 mg was not different to placebo regimen with respect to ASAS5/6 response at Week 16

H9: secukinumab 75 mg was not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

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H10: secukinumab 150 mg was not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H11: secukinumab 75 mg was not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H12: secukinumab 150 mg was not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H13: secukinumab 75 mg was not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H14: secukinumab 150 mg was not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H15: secukinumab 75 mg was not different to placebo regimen with respect to ASAS partial remission at Week 16

H16: secukinumab 150 mg was not different to placebo regimen with respect to ASAS partial remission at Week 16

The family-wise error was set to $\alpha=5\%$ and it was controlled with the proposed hierarchical testing strategy. Each of the hypotheses (H1 and H2) for the primary objective (ASAS20 at Week 16) for each secukinumab regimen versus placebo was tested simultaneously at $\alpha/2$. Then based on the rejection of one or both (of H1 and H2), the ASAS40 at Week 16 endpoint was tested hierarchically for each dose (through H3 and/or H4). This procedure continued (pending rejection of the null hypotheses) until H15 and/or H16 were/was rejected, then the respective $\alpha/2$ was passed on to the other secukinumab regimen's hierarchy of hypotheses, if they were not already rejected at $\alpha/2$.

Definitions of safety endpoints in Study F2305:

AE definition

The Applicant defined an adverse event as any untoward medical occurrence in a subject or clinical investigation subject after providing written informed consent for participation in the study.

SAE definition

The Applicant defined an SAE as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study treatment

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

6 Review of Efficacy

Efficacy Summary

Trials F2305 and F2310 were submitted as the primary source of efficacy data for secukinumab in the treatment of AS. Both trials consisted of a 16-week double-blind period followed by an open label extension. The Applicant submitted data to Week 52. The primary efficacy analysis was at Week 16. The primary endpoint was the proportion of patients with an ASessment in Ankylosing Spondylitis (ASAS) 20 response. Secondary efficacy analyses were performed at Week 16. The trials were well-controlled and had endpoints that are considered acceptable for efficacy evaluations in AS.

In the pre-specified primary analyses, secukinumab met the primary and secondary endpoints in study F2305. In study F2310, the 150 mg dose of secukinumab met the primary and secondary endpoints while the lower 75 mg maintenance dose did not. A possible explanation for these findings was the different loading doses that were used in study F2305 and study F2310. Study F2305 used a large IV loading dose at the beginning of the study and study F2310 used a SC loading dose that was predicted to give a lower secukinumab exposure. It is suspected that the greater loading dose at the beginning of study F2305 may have had effects on the efficacy endpoints at week 16.

As part of the study design, patients who switched from placebo to secukinumab did not receive a loading dose. 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 F2305 and F2310, the placebo patients who were switched to secukinumab were evaluated for ASAS20 response. Both studies showed that placebo patients, all of whom received no loading dose, were able to achieve ASAS20 responses and maintain ASAS20 responses for 32 weeks.

6.1 Indication

The Applicant proposed secukinumab to be indicated for treatment of adult patients with active ankylosing spondylitis.

6.1.1 Methods

Studies F2305 and F2310 served as the clinical trials for the evaluation of the efficacy of secukinumab in the treatment of ankylosing spondylitis. The trials were well controlled and utilized endpoints used in other programs to support approval for AS. Both studies assessed ASAS20 criteria at week 16. Study F2305 treated patients with 10 mg/kg IV treatment at weeks 0, 2, and 4 or placebo followed by either 75 mg or 150 mg s.c. treatment every 4 weeks or placebo. Study F2310 treated patients with 75 mg or 150 mg s.c. treatment at weeks 0,1,2,3, and 4 followed by the same dose every 4 weeks or placebo.

6.1.2 Demographics

6.1.2.1 F2305 Demographics

Table 12 displays the baseline demographics in study F2305. In the overall AS population, the three treatment arms had similar baseline characteristics. The population studied was predominantly Caucasian males in their forties. All treatment arms had more than 15% Asians who were equally distributed across arms. The percentage of Asians was likely due to enrollment from the Taiwanese study sites.

Table 12. F2305: Baseline demographic characteristics

Demographic variable	AIN457 10 mg/kg-75 mg N=124	AIN457 10 mg/kg-150 mg N=125	Placebo N=122
Age (years)			
Mean±SD	42.3±13.24	40.1±11.61	43.1±12.44
Median (min, max)	41 (18,76)	39 (19,67)	41 (18,74)
Female, n (%)	36 (29)	41 (32.8)	37 (30.3)
Weight (kg)			
Mean±SD	77.7±19.62	74.65±16.16	76.69±14.41
Median (min, max)	73.6 (41, 142)	73.4 (40, 112)	75.25 (48.1, 134)
Height (cm)			
Mean±SD	170.33±10.96	168.11±9.58	170.21±8.81
Median (min, max)	170 (137.6, 196)	168 (146, 192)	170 (150, 192)
Race, n (%)			
White	76 (61.3)	69 (55.2)	81 (66.4)
Black	0 (0)	0 (0)	1 (0.8)
Asian	23 (18.5)	21 (16.8)	19 (15.6)
Native American	3 (2.4)	8 (6.4)	3 (2.5)
Other	22 (17.7)	27 (21.6)	17 (13.9)

Source: adapted from F2305 clinical study report, p. 112-113

Table 13 displays the baseline disease characteristics in study F2305. In general, baseline disease characteristics were similar in the different treatment groups. Most patients enrolled into the study were HLA-B27 positive (69-80%). The baseline disease characteristics were consistent with characteristics of patients who have active AS.

Table 13. F2305: Baseline disease measures

Baseline characteristic	AIN457 10 mg/kg-75 mg N=124	AIN457 10 mg/kg-150 mg N=125	Placebo N=122
Patient global assessment of disease activity (0-100 mm)			
Mean (SD)	60.5 (18.29)	64 (19.42)	66.3 (18.59)
Median (min, max)	62.5 (0,100)	66 (3,96)	68.5 (17,100)
Total spinal pain (0-100 mm)			
Mean (SD)	61.7 (18.87)	64 (18.56)	66.7 (16.45)
Median (min, max)	65 (3,93)	65 (2,98)	69 (18,100)
BASFI (0-10)			
Mean (SD)	5.39 (2.157)	5.64 (2.211)	5.82 (2.034)
Median (min, max)	5.59 (0.4,9.4)	5.81 (0.8,9.8)	6.11 (0.4, 9.8)
BASDAI score			
Mean (SD)	6.05 (1.42)	6.35 (1.58)	6.51 (1.53)
Median (min, max)	6.2 (1.4, 9.1)	6.44 (1.7, 9.4)	6.7 (0.7, 9.4)
BASMI			
n	120	120	119
Mean (SD)	4.21 (1.76)	3.91 (1.79)	4.07 (1.58)
Median (min, max)	4.38 (0.4, 7.8)	3.85 (0.2, 9.2)	4.03 (0.5, 8.4)
hsCRP			
n	124	125	121
Mean (SD)	17.63 (23.82)	17.04 (22.25)	16.91 (22.31)
Median (min, max)	9.2 (0.4, 139.7)	7.4 (0.2, 147.7)	7.9 (0.2, 146.8)
Time since first diagnosis of AS (years)			
n	123	125	122
Mean (SD)	7.94 (9.73)	6.54 (6.93)	8.34 (8.86)
Median (min, max)	4.99 (0-56.82)	4.09 (0-32.65)	5.84 (0-47.18)
HLA-B27 positive, n (%)	99 (79.8)	86 (68.8)	90 (73.8)

Source: adapted from F2305 clinical study report, p. 114-117

Table 14 displays the percent of patients who received medications prior to the start of study F2305. Prior medications were defined as treatments taken and stopped prior to the first dose of treatment. Almost all patients had taken a NSAID in the past and a little over 25% of patients had taken a TNF inhibitor. Approximately 40% of patients in all groups were taking sulfasalazine. Over 10% in each group were taking a systemic glucocorticoid. The number of patients taking each type of prior medication was relatively balanced across groups.

Table 14. F2305: Prior medications

Prior medications n (%)	AIN457 10 mg/kg- 75 mg N=124	AIN457 10 mg/kg- 150 mg N=125	Placebo N=122
Any medication	124 (100)	125 (100)	121 (99.2)
Systemic glucocorticoid	16 (12.9)	21 (16.8)	20 (16.4)
NSAIDs	120 (96.8)	123 (98.4)	115 (94.3)
TNF inhibitor	34 (27.4)	33 (26.4)	33 (27)
Sulfasalazine	53 (42.7)	49 (39.2)	53 (43.4)
Methotrexate	27 (21.8)	18 (14.4)	20 (16.4)
paracetamol	15 (12.1)	14 (11.2)	9 (7.4)

Source: adapted from F2305 clinical study report, p. 296-298

Any medication given at least once between the day of first dose randomized study treatment and the date of the last study visit was defined as a concomitant medication. Table 15 displays the concomitant medications used by patients participating in study F2305. The most frequent concomitant medication was sulfasalazine with over 30% of patients receiving sulfasalazine in each study arm. The concomitant medications used in each study arm were relatively balanced.

Table 15. F2305: Concomitant medications

Concomitant medications	AIN457 10 mg/kg- 75 mg N=124	AIN457 10 mg/kg- 150 mg N=125	Placebo N=122
Any medication	124 (100)	120 (96)	122 (100)
Sulfasalazine	40 (32.3)	43 (34.4)	43 (35.2)
Etoricoxib	29 (23.4)	24 (19.2)	22 (18)
Folic acid	27 (21.8)	16 (12.8)	18 (14.8)
Omeprazole	(21)	(18.4)	(15.6)
Paracetamol	(18.5)	(21.6)	(15.6)
Meloxicam	(13.7)	(13.6)	(17.2)

Source: adapted from F2305 clinical study report, p. 1228-1236

6.1.2.2 F2310 Demographics

Table 16 shows the baseline demographics of patients who participated in study F2310. Most patients who participated in study F2310 were male, in their forties, and Caucasian. The baseline demographic characteristics were similar across the treatment arms. The demographic characteristics were similar to what be expected in an AS population.

Table 16. F2310: Baseline demographics

Demographic variable	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74
Age (years)			
Mean±SD	44.4±13.06	41.9±12.48	43.6±13.17
Median (min, max)	46 (19, 77)	41 (20, 66)	44 (21, 77)
Female, n (%)	22 (30.1)	26 (36.1)	18 (24.3)
Weight (kg)			
Mean±SD	81.5±17.4	82.3±18	80.3±15.2
Median (min, max)	80 (51, 123)	79.8 (50, 134)	79 (47.5, 123.4)
Height (cm)			
Mean±SD	170.6±9	173.4±8.8	172.1±9.3
Median (min, max)	172 (153, 193)	172.3 (151, 189)	173 (150, 190)
Race, n (%)			
White	70 (95.9)	69 (95.8)	70 (94.6)
Asian	3 (4.1)	2 (2.8)	4 (5.4)
Hispanic or Latino	6 (8.2)	5 (6.9)	8 (10.8)
Native American	0 (0)	1 (1.4)	0 (0)

Source: F2310 clinical study report, p. 111

The baseline disease activity measures for study F2310 are shown in Table 17. The mean hsCRP appeared to be lower in the 75 mg AIN457 group. The higher mean hsCRP in the 150 mg AIN457 group was likely due to the maximum value of 237 as median CRP was similar between the AIN457150 mg and placebo groups. Over 70% of the patients who participated in study F2310 were HLA-B27 positive. The baseline disease measurements appeared relatively balance across groups and were consistent with an AS population with active disease.

Table 17. F2310: Baseline disease measures

Baseline characteristic	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74
Patient global assessment of disease activity (0-100 mm)			
Mean (SD)	64.6 (17.9)	67.5 (16.8)	70.5 (15.8)
Median (min, max)	64 (1,99)	68 (31,99)	72 (28,100)
Total spinal pain (0-100 mm)			
Mean (SD)	65.1 (17.7)	66.2 (16.7)	69.2 (18.8)
Median (min, max)	66 (22,97)	68 (22,99)	70 (0,100)
BASFI (0-10)			
Mean (SD)	6.0 (2.1)	6.2 (2.1)	6.1 (2)
Median (min, max)	6.3 (1,9.7)	6.7 (1.4,9.9)	6.3 (0.1,9.5)
BASDAI score			
Mean (SD)	6.6 (1.3)	6.6 (1.5)	6.8 (1.3)
Median (min, max)	6.5 (2.4, 9.6)	6.8 (3.2, 10)	6.9 (4, 9.5)
BASMI (linear)			
n	71	71	70
Mean (SD)	3.9 (1.7)	3.6 (1.9)	3.9 (1.6)
Median (min, max)	3.9 (0.3, 7.8)	3.6 (0.2, 7.8)	4.2 (0.4, 7.2)
hsCRP			
Mean (SD)	15.3 (19.8)	25.8 (50)	15.7 (18.5)
Median (min, max)	5.7 (0.5, 86.2)	7.5 (0.4, 237)	8.3 (0.5, 84.6)
Time since first diagnosis of AS (years)			
n	72	70	73
Mean (SD)	5.3 (7.4)	7 (8.2)	6.4 (8.9)
Median (min, max)	2.7 (0-28.6)	3.8 (0-32.7)	2.8 (0-37.9)
HLA-B27 positive, n (%)	53 (72.6)	57 (79.2)	58 (78.4)

Source: F2310 clinical study report, p. 115-118

Table 18 shows the prior medications used by patients in study F2310. Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Almost all patients (over 98%) took a NSAID. Almost 40% of patients in each treatment group had previous exposure to a TNF inhibitor and over 10% of patients had prior exposure to a systemic glucocorticoid. The prior exposure to medications was relatively balanced across the study groups.

Table 18. F2310: Prior medications

Prior medications	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74
Any medication	72 (98.6)	71 (98.6)	74 (100)
Systemic glucocorticoid	10(13.7)	10 (13.9)	9 (12.2)
NSAIDs	71 (97.3)	71 (98.6)	74 (100)
TNF inhibitor	28 (38.4)	28 (38.9)	29 (39.2)
Sulfasalazine	19 (26)	23 (31.9)	19 (25.7)
Methotrexate	11 (15.1)	12 (16.7)	12 (16.2)
paracetamol	1 (1.4)	3 (4.2)	6 (8.1)

Source: adapted from F2310 clinical study report, p. 277-279

Table 19 shows the concomitant medications that were taken by patients in study F2310. For the most part, the number of patients taking each concomitant medication was balanced. There were numerically higher amount of patients who took diclofenac in the 150 mg secukinumab group.

Table 19. F2310: Concomitant medications

Concomitant medications	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74
Any medication	73 (100)	72 (100)	73 (98.6)
Omeprazole	16 (21.9)	11 (15.3)	14 (18.9)
Sulfasalazine	12 (16.4)	10 (13.9)	9 (12.2)
Diclofenac	9 (12.3)	17 (23.6)	11 (14.9)
Methotrexate	8 (11)	8 (11.1)	8 (10.8)
Folic acid	10 (13.7)	8 (11.1)	10 (13.5)

Source: adapted from F2310 clinical study report, p. 893-897

6.1.3 Subject Disposition

6.1.3.1. F2305: Subject disposition

Table 20 shows the disposition of patients up to week 52 in study F2305. 122 patients were in the original placebo group of which 10 discontinued prior to week 16 and 1 discontinued prior to week 20. 9 additional patients who were non-responders discontinued after receiving AIN457. One of the placebo responders discontinued prior to receiving AIN457 treatment. Of the 122 placebo patients, 77 placebo non-responders and 35 placebo responders were re-randomized to AIN457 treatment at week 16.

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Table 20. F2305: Patient disposition up to week 52

Disposition n (%)	AIN457 10mg/kg -75 mg N=124	AIN457 10mg/kg -150 mg N=125	Placebo N=122	Placebo non-resp AIN457 75 mg N=39	Placebo non-resp AIN457 150 mg N=38	Placebo resp AIN457 75 mg N=17	Placebo resp AIN457 150 mg N=18
Completed week 1-52	111 (89.5)	106 (84.8)	102 (83.6)	34 (87.2)	34 (89.5)	16 (94.1)	18 (100)
Discontinued week 1-52	13 (10.5)	19 (15.2)	20 (16.4)	5 (12.8)	4 (10.5)	1 (5.9)	0 (0)
Adverse event	6 (4.8)	7 (5.6)	7 (5.7)	0 (0)	2 (5.3)	0 (0)	0 (0)
Lack of efficacy	2 (1.6)	6 (4.8)	5 (4.1)	3 (7.7)	1 (2.6)	1 (5.9)	0 (0)
Lost to follow-up	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Non-compliance with study treatment	0 (0)	1 (0.8)	1 (0.8)	1 (2.6)	0 (0)	0 (0)	0 (0)
Physician decision	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pregnancy	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Protocol deviation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No longer requires treatment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Technical problems	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subject/guardian decision	4 (3.2)	3 (2.4)	5 (4.1)	1 (2.6)	1 (2.6)	0 (0)	0 (0)
Death	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)

Source: adapted from F2305 Clinical study report, p. 109

6.1.3.2 F2310: Subject disposition

Table 21 shows the disposition of patients to Week 52 and includes patients who switch from placebo to active therapy. The percent of discontinuations appeared balanced across the placebo and treatment groups. The patients who received 75 mg without a load in the placebo group had 4 discontinuations (12.5%) due to lack of efficacy which was a higher percentage than the other groups.

Table 21. F2310: Patient disposition to Week 52

Disposition n (%)	AIN457 75 mg N=73	AIN457 150 mg N=72	Placebo N=74	Placebo AIN457 75 mg N=32	Placebo AIN457 150 mg N=34
Completed week 1-52	60 (82.2)	61 (84.7)	60 (81.1)	28 (87.5)	32 (94.1)
Discontinued week 1-52	13 (17.8)	11 (15.3)	14 (18.9)	4 (12.5)	2 (5.9)
Adverse event	3 (4.1)	6 (8.3)	4 (5.4)	0 (0)	0 (0)
Lack of efficacy	4 (5.5)	3 (4.2)	6 (8.1)	4 (12.5)	1 (2.9)
Lost to follow-up	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-compliance with study treatment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Physician decision	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)
Pregnancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Protocol deviation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No longer requires treatment	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Technical problems	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subject/guardian decision	5 (6.8)	2 (2.8)	3 (4.1)	0 (0)	1 (2.9)
Death	1 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)

Source: adapted from F2310 clinical study report, p. 108

Reviewer's comments: A relatively similar percent of patients discontinued from each group. Lack of efficacy was the main reason that placebo patients randomized to secukinumab 75 mg every 4 weeks and the percent of patients in this group who discontinued was higher than other groups. This provides additional evidence that the 75 mg dose of secukinumab every 4 weeks does not appear to be a suitable maintenance dose for treatment of ankylosing spondylitis.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 F2305: Analysis of Primary Endpoint

The primary endpoint measured for study F2305 was ASAS20 response using non-responder imputation at week 16. ASAS 20 response was 59.7% for AIN457 10 mg/kg

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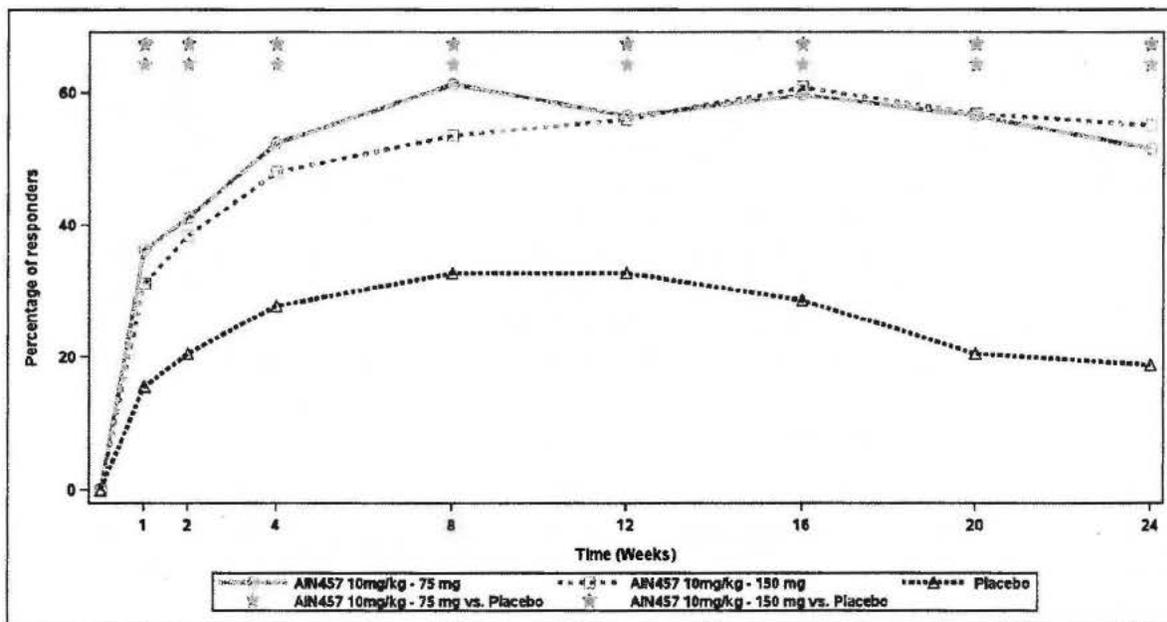
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IV-75 mg SC, 60.8% for AIN457 10 mg/kg IV-150 mg SC, and 28.7% for placebo. Both AIN457 arms performed significantly better than placebo ($p < 0.0001$).

Figure 4 shows the ASAS20 response in study F2305 over a 24 week period. The AIN457 10 mg/kg IV-75 mg and AIN457 10mg/kg IV-150 mg SC study arms were superior to placebo at all the displayed time points in Figure 4.

Figure 4. F2305: ASAS20 response up to week 24



*p-value < 0.05

Source: adapted from F2305 clinical study report, p. 122

6.1.4.2. F2310: Analysis of Primary Endpoint

The primary efficacy variable measured was the response to treatment according to ASAS 20 criteria at week 16. The odds ratio, 95% confidence interval, and p-values were calculated using a logistic regression model with treatment and TNF inhibitor status as factors and baseline weight as a covariate. The secukinumab 150 mg SC group was superior to placebo while the 75 mg secukinumab group was not statistically superior to placebo.

Table 22. F2310: ASAS20 response at week 16

Treatment group	n/M (%)	Odds ratio	95% confidence interval	p-value, unadjusted
AIN457 75 mg	30/73 (41.1)	1.82	(0.9, 3.7)	0.0967
AIN457 150 mg	44/72 (61.1)	4.38	(2.1, 9)	<0.0001
Placebo	21/74 (28.4)			

Source: adapted from F2310 clinical study report, p. 130

Reviewer's comment: Both studies showed that the 150 mg dose was statistically superior to placebo in achieving ASAS20 response. The 75 mg dose in study F2310 did not show a superior response to placebo in ASAS20. One potential explanation is that the IV loading dose in study F2305 had a larger effect on the ASAS20 at week 16. The 150 mg arm in study F2312 received a larger loading dose than the 75 mg arm, so there was continued concern whether the loading dose was affecting the ASAS20 at week 16. Therefore, it was unclear based on the analysis of the primary endpoint, whether the data from the primary efficacy analysis was sufficient to support the use of secukinumab as a therapy that can be used chronically. Additional analyses were performed to assess the efficacy without a loading dose as described in Section 6.1.7.

6.1.5 Analysis of Secondary Endpoints

6.1.5.1 F2305: Analysis of secondary endpoints

Table 23 shows the key secondary endpoints assessed at week 16. In hierarchical testing, both AIN457 treatment arms were significantly superior to placebo for all secondary endpoints at week 16.

Table 23. F2305: Estimates for secondary efficacy endpoints at week 16

Endpoint	AIN457 10 mg/kg-75mg N=124	AIN457 10 mg/kg-150 mg N=125	Placebo N=122
ASAS 40 response	33.1% (p=0.0003)	41.6% (p<0.0001)	13.1%
hsCRP (ratio: post-baseline/baseline)	0.45 (p<0.0001)	0.40 (p<0.0001)	0.97
ASAS 5/6 response	45.3% (p<0.0001)	48.8% (p<0.0001)	13.1%
BASDAI change from baseline	-2.34 (p<0.0001)	-2.32 (p<0.0001)	-0.59
SF-36 PCS change from baseline	5.64 (p<0.0001)	5.57 (p<0.0001)	0.96
ASQoL change from baseline	-3.61 (p<0.0001)	-3.58 (p<0.0001)	-1.04
ASAS partial remission	16.1% (p=0.002)	15.2% (p=0.0033)	3.3%

Source: adapted from F2305 clinical study report, p. 125

6.1.5.2 F2310: Analysis of secondary endpoints (s)

Table 24 shows the results for secondary efficacy endpoints that were assessed in study F2310. The 75 mg of secukinumab was not statistically superior to placebo but the 150 mg dose did show statistically superior responses in comparison to placebo for all endpoints except ASAS partial remission.

Table 24. F2310: Estimates for secondary efficacy endpoints at week 16

Endpoint	AIN457 75mg N=73	AIN457 150 mg N=72	Placebo N=74
ASAS 40 response	26% (p=0.097)	36% (p=0.0008)	11%
hsCRP (ratio: post-baseline/baseline)	0.6 (p=0.097)	0.6 (p=0.0008)	1.1
ASAS 5/6 response	34.2% (p=0.097)	43.1% (p=0.0008)	8.1%
BASDAI change from baseline	-1.92 (p=0.097)	-2.19 (p=0.0008)	-0.85
SF-36 PCS change from baseline	4.77 (p=0.097)	6.1 (p=0.0008)	1.9
ASQoL change from baseline	-3.33 (p=0.097)	-4 (p=0.001)	-1.4
ASAS partial remission	15% (p=0.097)	14% (p=0.094)	4%

Source: adapted from F2310 clinical study report, p. 127-128

Reviewer's comment: While both the 75 mg and 150 mg dose of secukinumab met all primary and secondary endpoints in study F2305, patients received 10 mg/kg IV loading doses at week 0, 2, and 4 which may have led to effects on the primary endpoint at week 16. The large loading doses received at the beginning of the study may have impacted the efficacy results at Week 16.

In study F2310, the 75 mg was not statistically superior to placebo while the 150 mg dose was. The loading dose was higher for the 150 mg dose as compared to the 75 mg dose, so whether the 150 mg dose could maintain efficacy chronically was not certain based on the secondary efficacy analysis. Additional analyses were performed in patients who did not receive a loading dose and the efficacy at week 52 was evaluated to provide support that the efficacy would be maintained. Due to the separation in ability to achieve secondary endpoints, it was concluded that the 150 mg dose was more effective than the 75 mg dose.

6.1.6 Other Endpoints

No additional endpoints were evaluated in this clinical review. Please see the statistical review for additional discussion of other endpoints.

6.1.7 Subpopulations

Table 25 shows ASAS20 responses in the subpopulations by age, gender, and weight. The results are the pooled efficacy results from studies F2305 and F2310. The table shows the difference from placebo in percent responders. The 150 mg dose had a better response to placebo in all subgroups while the 75 mg had a better response than placebo for most dose groups.

Table 25. ASAS20 response at week 16 by age, gender, and weight

Difference from placebo in % responders	placebo	Secukinumab 150 mg every 4 weeks	Secukinumab 75 mg every 4 weeks
Age			
<65 years	--	32%	15%
≥65 years	--	67%	-33%
Gender			
Male	--	34%	14%
Female	--	29%	8%
Weight			
<70 kg	--	45%	25%
70-90 kg	--	31%	16%
>90 kg	--	22%	-7%

Source: adapted from AS summary of clinical efficacy, p. 88

Reviewer's comments: Limited conclusions can be derived from these results. Some subgroups had very small numbers of patients. The two studies had different loading dose regimens further limiting any conclusion from the Week 16 data. White patients comprised a majority of the patients enrolled in studies F2305 and F2310. Small group sizes limited comparisons in racial groups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No additional efficacy data was provided to support dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

6.1.9.1 F2305: Discussion of Persistence of Efficacy and/or Tolerance Effects

Placebo patients classified as ASAS 20 non-responders at Week 16 were re-randomized to secukinumab 75 mg or 150 mg and received the first dose of active treatment at Week 16.

Figure 5 shows ASAS20 response for patients enrolled in study F2305 to week 52. Non-responder imputation was used to account for missing data. The ASAS20

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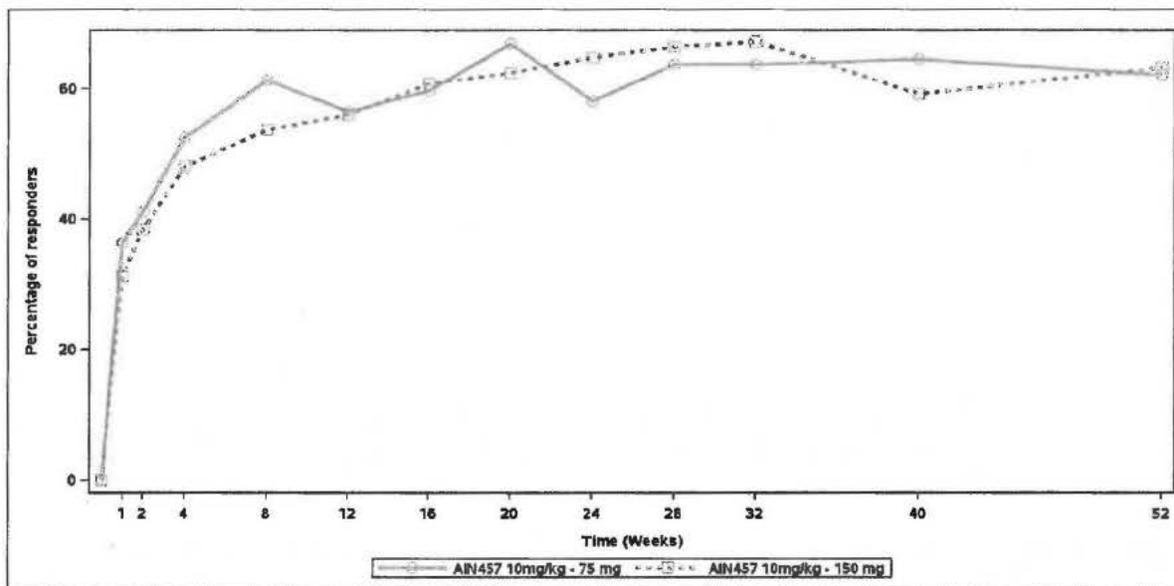
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response approached 60% for both the AIN457 10 mg/kg-75 mg group and 10 mg/kg-150 mg group. No significant differences in ASAS 20 responses were seen between the two dose groups.

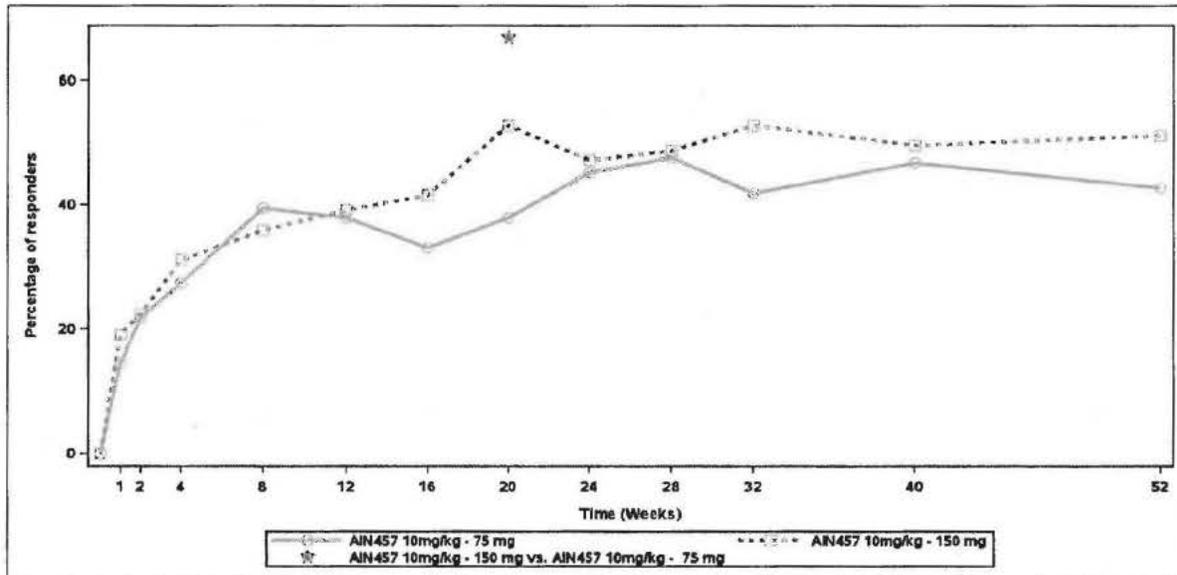
Figure 5. F2305: ASAS20 response to week 52



Source: F2305 clinical study report, p. 130

Figure 6 shows ASAS40 response in study F2305 to week 52. Non-responder imputation was used to account for missing data. The ASAS40 response was relatively similar between both study arms. The patients appeared to maintain response to week 52.

Figure 6. F2305. ASAS40 response to week 52



Source: F2305 clinical study report, p. 131

Following the switch to active treatment, the percent achieving ASAS 20 at Week 20 for the placebo non-responders re-randomized to 75 mg secukinumab was 48.7% (19/39) and 47.4% (18/38) for placebo non-responders re-randomized to 150 mg secukinumab. The percent achieving ASAS 20 response at Week 32 were 56.4% (22/39) for the placebo non-responders on 75 mg and were 50.0% (19/38) for the placebo nonresponders on 150 mg.

The percent achieving ASAS 40 at Week 20 for placebo nonresponders re-randomized to 75 mg was 23.1% (9/39) and 18.4%(7/38) for placebo nonresponders re-randomized to 150 mg secukinumab. The ASAS 40 response rates at Week 32, corresponding to 16 weeks of secukinumab treatment, were 28.2% (11/39) for placebo non-responders on 75 mg and 23.7% (9/38) for placebo non-responders on 150 mg.

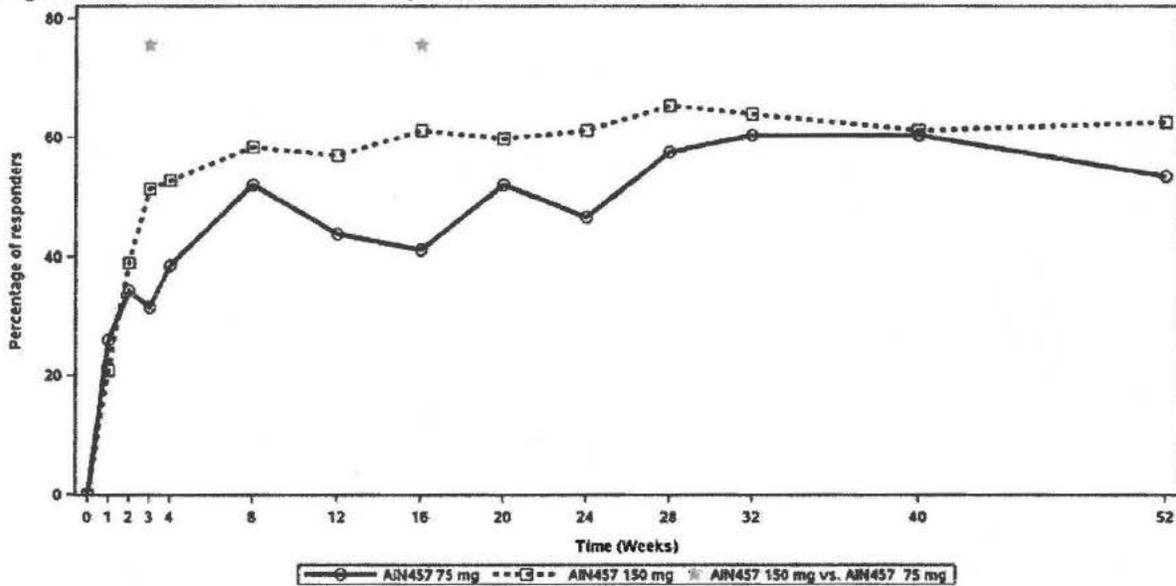
6.1.9.2 F2310: Discussion of Persistence of Efficacy and/or Tolerance Effects

shows ASAS20 response for patients enrolled in study F2310 to week 52. Non-responder imputation was used to account for missing data. The ASAS20 response approached 60% for both the AIN457 150 mg group. At week 16, ASAS20 response with 150 mg of secukinumab was statistically superior to 75 mg of secukinumab.

Figure 7 shows ASAS20 response for patients enrolled in study F2310 to week 52. Non-responder imputation was used to account for missing data. The ASAS20 response approached 60% for both the AIN457 150 mg group. At week 16, ASAS20

response with 150 mg of secukinumab was statistically superior to 75 mg of secukinumab.

Figure 7. F2310: ASAS 20 response to week 52

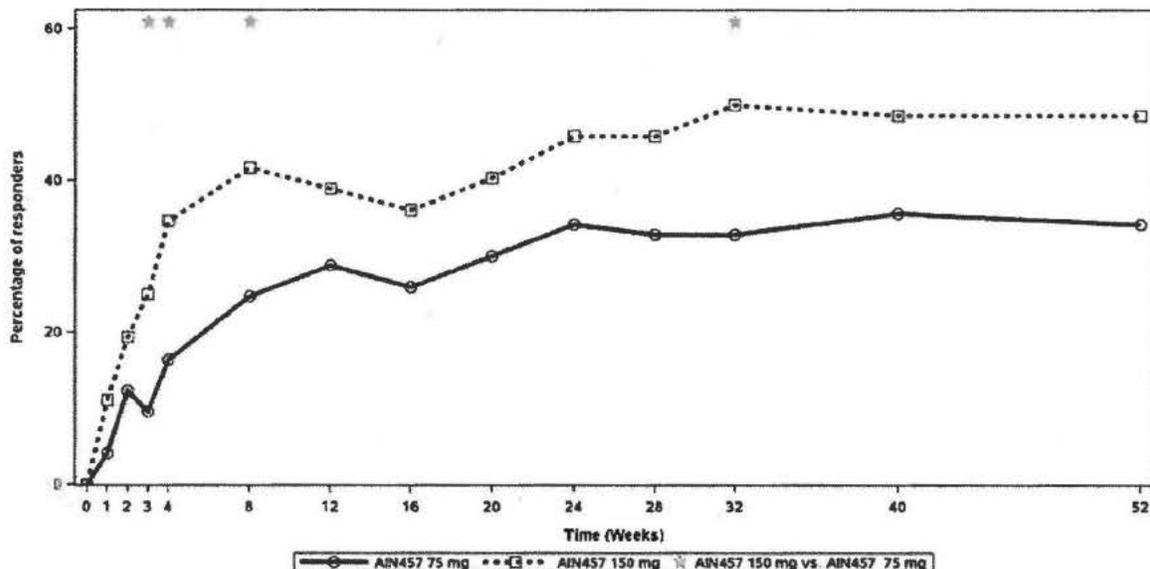


*p<0.05, unadjusted

Source: F2310 Clinical study report, p. 137

Figure 8 shows ASAS40 response in study F2310 to week 52. Non-responder imputation was used to account for missing data. The ASAS40 response was numerically greater with the 150 mg dose as compared to the 75 mg dose and was significantly better as late as week 32 in the study.

Figure 8. F2310: ASAS40 response to week 52



*p<0.05, unadjusted

Source: F2310 clinical study report, p. 140

All placebo patients were re-randomized at Week 16 to either secukinumab 75 or 150 mg and received their first dose of active treatment at Week 16.

Following the switch to active treatment, the ASAS 20 response at the next analysis visit at Week 20 for the placebo patients re-randomized to secukinumab 75 mg sc was 50.0% (16/32). For placebo patients switched to secukinumab 150 mg sc 58.8% (20/34) had ASAS20 response at week 20. At Week 32, 67.6% (23/34) for the placebo -150 mg sc group and 43.8% (14/32) for the placebo -75 mg sc group achieved ASAS20 response.

For ASAS 40, at Week 20 for the placebo patients re-randomized to 75 mg sc, 21.9% (7/32) achieved ASAS40 response and 41.2% (14/34) achieved ASAS40 response in the placebo-150 mg sc secukinumab group. The ASAS 40 response rates at Week 32 were 55.9% (19/34) for the placebo-150 mg sc group and 28.1% (9/32) for the placebo -75 mg sc group.

Reviewer's comment: While there were limitations to the data provided, it appeared that secukinumab was capable of achieving ASAS20 response and maintaining it with or without a loading regimen. Concerns regarding the data provided were that the initial loading doses provided to the patients may have had an effect on efficacy results at the time point of primary assessment and that the data beyond the primary efficacy endpoint was uncontrolled.

The data from the placebo patients who were re-randomized to secukinumab was without a loading dose and the data showed that patients were able to attain and maintain ASAS20 responses without the loading dose. In combination with the 52 week data provided from the active secukinumab arms, it appeared that 150 mg secukinumab every 4 weeks was able to maintain efficacy in the treatment of AS. As placebo patients switched to secukinumab were able to achieve ASAS20 responses in 4 weeks, it was uncertain whether loading doses were necessary for the treatment of AS.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues or analyses were performed as part of the clinical review.

7 Review of Safety

Safety Summary

The safety information for secukinumab in ankylosing spondylitis was obtained from two phase 3 studies during which 571 patients received a dose of secukinumab. The median duration of treatment was 442 days with the minimum amount of days on secukinumab being 8 days and the maximum number was 757 days.

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. A causal relationship with secukinumab could not be established for any of these deaths.

Serious adverse events (SAEs) were low and comparable across dose groups. The most common SAEs by system organ class (SOC) were “gastrointestinal disorders”, “injury, poisoning, and procedural complications”, and “infections and infestations”. There were 3 SAEs related to inflammatory bowel disease in patients taking secukinumab in the phase 3 AS studies.

Overall, the rate of AEs leading to discontinuation was low. The percent of discontinuations was higher in the 150 mg group versus the 75 mg group. The AEs leading to discontinuation that occurred in 2 patients on secukinumab were Crohn’s disease, dyspnea, decreased hemoglobin, increased hepatic enzyme, pregnancy, and transaminases increased.

The most common adverse events by preferred term are nasopharyngitis (18.7%), diarrhea (9.3%), headache (9.3%), upper respiratory tract infection (9.1%), and oropharyngeal pain (6%). These common AEs were very similar to what has been seen in the PsA and psoriasis programs.

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 multiple cases of new onset inflammatory bowel disease and worsening of inflammatory bowel disease. Currently, the prescribing information includes information regarding the risk of exacerbation of Crohn's disease, but it does not describe a risk of inflammatory bowel disease (IBD), including new onset disease. While the safety findings were consistent with the psoriasis and PsA programs, the prescribing information will be updated to reflect the risk of new onset and worsening of IBD. Otherwise, no new safety signals were identified in the phase 3 AS studies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.2 (Review Strategy) for the two phase 3 trials used to evaluate the safety of secukinumab for the treatment of ankylosing spondylitis.

7.1.2 Categorization of Adverse Events

The Applicant's categorization of adverse events with preferred terms is consistent with the investigator's verbatim terms.

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

In this sBLA review, the Applicant submitted safety data on 571 patients with AS who were in studies F2305 and F2310. F2305 and F2310 were ongoing at the time of submission but safety data for at least 52 weeks was submitted for both studies. In addition to the AS studies, the safety data for 38 phase 2 or 3 studies using secukinumab in other indications was provided.

7.2 Adequacy of Safety Assessments

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

The Applicant conducted two phase 3 studies in AS.

Table 26 shows the duration of exposure to treatment arms in the pooled phase 3 AS studies. Patients in the study were exposed to AIN457 for greater lengths of time as compared to placebo (mean 442 days for any AIN457 versus mean 119 days for

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placebo). This is expected as patients who were on placebo were switched to AIN457 as early as week 16 as part of the study design. Due to the difference in exposure time, the comparison between placebo and AIN457 for adverse events, the Applicant calculated incidence rates to account for difference in time that patients were exposed to placebo versus AIN457. The overall exposure, in the context of the known safety profile in plaque psoriasis, is reasonable.

Table 26. Pooled phase 3 AS studies: Duration of exposure

Duration of exposure	Any AIN457 75 mg N=284	Any AIN457 150 mg N=287	Any AIN457 N=571	Placebo N=196
Days				
Mean (SD)	443 (145)	441 (141)	442 (143)	119 (33)
Median (min-max)	469 (8-757)	462 (16-729)	463 (8-757)	113 (1-206)
Patient-years	344.6	346.5	691.1	63.6

Source: adapted from Applicant AS summary of clinical safety, p. 30

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 for 5 weeks (75 mg or 150 mg). In addition, the Applicant searched for differences in AEs based on the dose of secukinumab patients received every 4 weeks (75 or 150 mg) following the loading dose. See section 7.5.1 for results.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

7.2.4.1 F2305: Routine Clinical Testing

Table 27 shows clinical testing performed through week 52 in study F2305. The Applicant conducted regular physical examinations and laboratory evaluations to assess for adverse events. For study F2305, the Applicant also performed radiographic assessments to monitor for disease progression in AS.

Table 27. F2305: Clinical testing to week 52

Evaluation	Frequency (weeks)
Physical examination/Vital Signs	Every visit
Hematology, chemistry, urinalysis	Screening, 0, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 40, 52
Urine pregnancy testing	0, 4, 12, 16, 24, 32, 40, 52
ECG	0, 16, 52
Tb testing	Screening
Immunogenicity	0, 16, 24, 52
MRI (spine and sacroiliac joints)	0, 16, 52
X-ray (cervical+thoracic+lumbar)	0

Source: adapted from clinical study report, p. 69-71

Reviewer's comments: The type and frequency of clinical testing was reasonable to monitor the safety profile of secukinumab in ankylosing spondylitis.

7.2.4.2 F2310: Routine Clinical Testing

Table 28 shows clinical testing performed through week 52 in study F2310. The Applicant conducted regular physical examinations and laboratory evaluations to assess for adverse events.

Table 28. F2310: Clinical testing to week 52

Evaluation	Frequency (weeks)
Physical examination/Vital Signs	Every visit
Hematology, chemistry, urinalysis	Screening, 0, 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 40, 52
Urine pregnancy testing	0, 4, 12, 16, 24, 32, 40, 52
ECG	0, 16, 52
Tb testing	Screening
Immunogenicity	0, 16, 24, 52

Source: adapted from F2310 clinical study report, p. 65-67

Reviewer's comments: The type and frequency of clinical testing was reasonable to monitor the safety profile of secukinumab in ankylosing spondylitis.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific drug-drug interaction, clearance, or interaction studies were performed for secukinumab in this sBLA.

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

Studies F2305 and F2310 incorporated monitoring for toxicities associated with secukinumab, such as infections, tuberculosis, Crohn's disease and hypersensitivity reactions. Details of these analyses are found in section 7.3.5. There are no other FDA approved IL-17A inhibitors at this time. Due to concerns regarding suicidal ideation with the IL-17 inhibitor, brodalumab, the Applicant performed Columbia Classification Algorithm of Suicide Assessment (C-CASA) to determine whether similar symptoms of suicidal ideation occurred in patients taking secukinumab.

7.3 Major Safety Results

7.3.1 Deaths

7.3.1.1 F2305: Deaths

There were two deaths in study F2305: one in the placebo group and one in the secukinumab group. In the placebo group, there was one death by suicide secondary to underlying depression.

In the AIN457 10 mg/kg-75 mg group, a 39 year old man died on Day 706 of the study period. The patient had last received treatment at Day 674 (the week 96 visit). The patient had a history of pulmonary fibrosis and cardiac failure. 8 days after receiving AIN457, the patient developed a dry, irritating cough, joint and muscle pain, general fatigue, and fever. The patient was diagnosed with cardiac failure, bilateral pulmonary fibrosis, and decompensated chronic respiratory insufficiency. The patient was hospitalized and treated for bilateral pneumonia and respiratory failure. The patient developed acute cardiovascular failure and cerebral edema and subsequently died on Day 706.

Reviewer's comments: One patient treated with secukinumab died after approximately 2 years on active treatment. The patient had cardiorespiratory risk factors at Baseline, including 20 year smoking history, hypertension, and dyspnea. A causal relationship with secukinumab could not be established.

7.3.1.2 F2310: Deaths

There was one death in the 75 mg sc dosing group. A 60 year old male with multiple baseline cardiac risk factors died on Day 29 due to an acute myocardial infarction. Autopsy showed 3-vessel cardiac arteriosclerosis, cardiac hypertrophy, recurrent anteroseptal myocardial infarction, chronic pulmonary congestion and emphysema.

Reviewer's comments: One death secondary to cardiovascular disease occurred in the secukinumab treatment group. The patient had an acute myocardial infarction and

multiple baseline cardiac risk factors. Deaths related to cardiovascular disease would be anticipated in the patient population.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 F2305 Nonfatal Serious Adverse Events

Table 29 shows the nonfatal SAEs by preferred term that occurred in the pooled phase 3 AS studies over the entire treatment period more than once. SAEs were infrequent and it was impossible to assess dose dependency due to infrequency of events. Incidence rates are shown by 100 patient-years. The incidence rate of SAEs was 8.2 in the AIN457 75 mg group, 7.5 in the AIN457 150 mg group, and 12.8 in the placebo group. Each of the following SAEs was seen twice in patients who received secukinumab in the pooled phase 3 AS studies: cataract, cholelithiasis, ulcerative colitis, lower limb fracture, myocardial infarction, and rib fracture. MACE events and inflammatory bowel disease will be reviewed in greater detail in section 7.3.5.

Table 29. Pooled phase 3 AS studies: Nonfatal serious adverse events over entire treatment period

Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo up to week 196 N=122 n/EX (IR)
Any preferred term	27/327 (8.2)	25/332 (7.5)	52/660 (7.9)	8/63 (12.8)
Cataract	1/344 (0.3)	1/346 (0.3)	2/690 (0.3)	0/64 (0)
cholelithiasis	1/344 (0.3)	1/345 (0.3)	2/689 (0.3)	0/64 (0)
Ulcerative colitis	1/345 (0.3)	1/346 (0.3)	2/690 (0.3)	0/64 (0)
Lower limb fracture	1/344 (0.3)	1/345 (0.3)	2/690 (0.3)	0/64 (0)
Myocardial infarction	1/345 (0.3)	1/346 (0.3)	2/691 (0.3)	0/64 (0)
Rib fracture	0/345 (0)	2/345 (0.6)	2/690 (0.3)	0/64 (0)

Source: adapted from Applicant AS Summary of clinical safety, p. 75

Reviewer's comments: During the entire treatment period, the incidence rate of serious adverse events was higher in the placebo group than the secukinumab groups. In general, the occurrence of serious adverse events was low. There was no evidence of a dose-response relationship for serious adverse events. No new safety signals were detected for serious adverse events compared to the known safety profile in plaque psoriasis.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 F2305 Dropouts and/or Discontinuations

Table 30 shows the adverse events listed by preferred term that caused discontinuation in the pooled phase 3 AS studies over the entire treatment period. The number of

discontinuations was infrequent but appeared to be slightly higher in the 150 mg group versus the 75 mg group. The adverse events that were reported in all secukinumab groups more than once are listed as follows: Crohn's disease, dyspnea, decreased hemoglobin, increased hepatic enzymes, pregnancy, and transaminases increased. Each of these adverse events was reported twice.

Table 30. Pooled phase 3 AS studies: Adverse events causing discontinuation by preferred term over entire treatment period

Preferred term	Any AIN457 75 mg N=179 n (%)	Any AIN457 150 mg N=181 n (%)	Any AIN457 N=360 n (%)
Any preferred term	11 (3.9)	20 (7)	31 (5.4)
Crohn's disease	2 (0.7)	0 (0)	2 (0.4)
Dyspnea	1 (0.4)	1 (0.3)	2 (0.4)
Hemoglobin decrease	1 (0.4)	1 (0.3)	2 (0.4)
Hepatic enzyme increase	0 (0)	2 (0.7)	2 (0.4)
Pregnancy	0 (0)	2 (0.7)	2 (0.4)
Transaminases increased	1 (0.4)	1 (0.3)	2 (0.4)
Alanine aminotransferase increase	0 (0)	1 (0.3)	1 (0.2)
Anemia	0 (0)	1 (0.3)	1 (0.2)
Ankylosing spondylitis	0 (0)	1 (0.3)	1 (0.2)
Arthralgia	1 (0.4)	0 (0)	1 (0.2)
B-cell lymphoma	1 (0.4)	0 (0)	1 (0.2)
Bladder transitional cell carcinoma	0 (0)	1 (0.3)	1 (0.2)
Blood pressure increase	1 (0.4)	0 (0)	1 (0.2)
Breast cancer	0 (0)	1 (0.3)	1 (0.2)
Colitis	0 (0)	1 (0.3)	1 (0.2)
Headache	1 (0.4)	0 (0)	1 (0.2)
Herpes zoster	0 (0)	1 (0.3)	1 (0.2)
Hyperhidrosis	0 (0)	1 (0.3)	1 (0.2)
Malignant melanoma	0 (0)	1 (0.3)	1 (0.2)
Myocardial infarction	1 (0.4)	0 (0)	1 (0.2)
Nuclear MRI brain abnormal	0 (0)	1 (0.3)	1 (0.2)
Polyneuropathy	0 (0)	1 (0.3)	1 (0.2)
Pulmonary cavitation	0 (0)	1 (0.3)	1 (0.2)
Skin ulcer	1 (0.4)	0 (0)	1 (0.2)
Small intestinal obstruction	0 (0)	1 (0.3)	1 (0.2)

Source: adapted from F2305 clinical study report, p. 163-164

During the 16-week placebo controlled period, the proportion of patients with adverse events causing discontinuation of study treatment was low and not elevated in the secukinumab groups (3%) compared to the placebo groups (5%).

7.3.4 Significant Adverse Events

AEs of interest for this product are discussed in section 7.3.5 (submission specific primary safety concerns). 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 immune/administration reactions that occurred during the entire treatment period for the AS phase 3 studies. Most AEs were mild to moderate with a small percentage being severe. The severe reactions reported in the secukinumab group were AS, dyspnea, application site pain, Crohn's disease and local swelling. There did not appear to be dose dependence for reactions.

Table 31. Pooled phase 3 AS studies: exposure-adjusted incidence of Immune/administration reactions over entire treatment period

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Immune/administration reactions	63/297 (21.2)	68/286 (23.8)	131/583 (22.5)	37/55 (67.6)
Immune/administration reactions (SAEs)	5/342 (1.5)	4/342 (1.2)	9/684 (1.3)	0/64 (0)

Source: adapted from Applicant AS Summary of clinical safety, p. 86

Hypersensitivity

Table 32 shows the hypersensitivity events that occurred during the entire treatment period for the AS phase 3 studies. All AEs were mild to moderate. The common hypersensitivity events were rash, dermatitis, and eczema. No SAEs were recorded. Hypersensitivity did not appear to be dose dependent. No cases of angioedema or anaphylaxis were reported.

Table 32. Pooled phase 3 AS studies: exposure-adjusted incidence of hypersensitivity over entire treatment period

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Hypersensitivity	21/330 (6.4)	22/327 (6.7)	43/657 (6.5)	8/62 (13)
Hypersensitivity (SAEs)	0	0	0	0

Source: adapted from Applicant AS Summary of clinical safety, p. 88

No new safety signals related to hypersensitivity were detected in the AS clinical program. The current prescribing information includes a Warning related to the risk of hypersensitivity with secukinumab treatment.

Inflammatory bowel disease

Table 33 shows the incidence rates of inflammatory bowel disease in studies F2305 and F2310. The incidence rate for an occurrence of inflammatory bowel disease in any patient receiving secukinumab was 1.2 per 100 patient-years. There did not appear to be a dose relationship for the instances of inflammatory bowel disease. Of the 8 cases of inflammatory bowel disease recorded, 3 occurred with the first 16 weeks. The placebo group did not have any events of inflammatory bowel disease over 16 weeks or the entire treatment period.

Over the entire treatment period, 5 cases of Crohn's disease were reported in the secukinumab group of which 4 had a suspected or prior history of Crohn's. The other case was in a patient with history of intestine polyps/adenoma and had been receiving infliximab for over 2 years.

In the first 16 weeks of the studies, one patients who had experienced rectal bleeding prior to randomization to the 75 mg SC group and was diagnosed with Crohn's on Day 45 due to exacerbation of a pre-existing condition. A second patient with 6 year history of Crohn's had disease and colectomy experienced flares on Day 42 and 89 while in the 75 mg IV secukinumab group.

A patient in the 75 mg SC group was reported to have ischemic and ulcerative colitis SAE on Day 48. The patient had not had a previous diagnosis of IBD. The patient had been on a TNF inhibitor in the past.

A patient in the 150 mg SC group experienced colitis on Day 3. The patient had a history of IBD. A colonoscopy was performed on Day 39 for ulcerative colitis assessment but the result was not available at the time of submission.

In addition to the cases that occurred in the first 16 weeks, there were three additional cases of Crohn's and two more cases of ulcerative colitis. One Crohn's case occurred in the 75 mg IV secukinumab group and was an exacerbation on Day 162 in a patient

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with 7 year history of Crohn's. Another case in the 75 mg IV group was in a patient with history of intestinal polyps and colon adenoma who had been treated with infliximab for 2 years prior to stopping 8 months before the start of the trial. The patient was diagnosed with Crohn's on Day 141.

The third case occurred in a patient who switched from placebo to 150 mg of secukinumab and was diagnosed with Crohn's on Day 263 while on secukinumab.

Both of the additional cases of ulcerative colitis occurred in the secukinumab 150 mg SC group. One patient had an exacerbation of ulcerative colitis and the other occurred in a patient with 3 year history of chronic diarrhea but no previous history of inflammatory bowel disease.

Table 33. Pooled phase 3 AS studies: exposure-adjusted incidence of inflammatory bowel disease (IBD) over entire treatment period

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
IBD	5/342 (1.5)	3/344 (0.9)	8/687 (1.2)	0/64 (0)
Colitis ulcerative	1/345 (0.3)	2/345 (0.6)	3/689 (0.4)	0/64 (0)
Crohn's disease	4/343 (1.2)	1/346 (0.3)	5/689 (0.7)	0/64 (0)
IBD	1/345 (0.3)	0/347 (0)	1/691 (0.1)	0/64 (0)

Source: adapted from AS clinical safety summary, p. 93

Reviewer's comments: In addition to exacerbations of existing Crohn's disease, there were patients who had exacerbations of ulcerative colitis. New cases of Crohn's and ulcerative colitis occurred during the exposure to secukinumab and similar results have been seen in the psoriasis and PsA programs.

Further, study A2202 studied the use of secukinumab in Crohn's disease. The primary outcome measure was reduction in Crohn's Disease Activity Index (CDAI) at week 6. The primary endpoint was not met and key secondary endpoints showed statistically significant response rates in favor of placebo. 8 SAEs were noted with 6 worsening of disease occurring with secukinumab treatment and 2 with placebo. 28.2% on secukinumab had severe AEs compared to 10% in the placebo group. The Applicant concluded that secukinumab was not effective treatment for Crohn's and may worsen disease in some patients. In addition, secukinumab was accompanied by higher rates of infections.

Infections

Table 34 shows the incidence rates of infections over time in the pooled phase 3 AS studies. During the first 16 weeks, there was a higher incidence of infections which was mainly attributable to upper respiratory tract infections and candida infections. The one

serious adverse event was a tonsillitis infection in the secukinumab 150 mg IV group. The candida infections were mucosal or cutaneous and mild in severity.

6 cases of candida infections were reported over the entire treatment period and none in the placebo group. There was one case of disseminated cutaneous zoster in a patient who was in the 75 mg group with IV loading dose. There was one event of viral hepatitis in a patient in the 75 mg IV group who did not have a previous history of hepatitis. Secukinumab infections did not appear to be dose dependent.

Table 34. Pooled phase 3 AS studies: exposure-adjusted incidence for infections over entire treatment period

Level 1 HLT	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
AEs				
Infections and infestations	150/217 (68.9)	148/216 (68.6)	298/433 (68.8)	36/56 (63.8)
URI	100/259 (38.7)	102/261 (39.1)	202/520 (38.9)	21/60 (35.3)
Candida infections	4/341 (1.2)	2/346 (0.6)	6/687 (0.9)	0/64 (0)
Opportunistic infections	1/344 (0.3)	0/347 (0)	1/690 (0.1)	0/64 (0)
SAEs				
Infections and infestations	3/342 (0.9)	3/344 (0.9)	6/686 (0.9)	0/64 (0)
URI	1/344 (0.3)	1/346 (0.3)	2/690 (0.3)	0/64 (0)
Candida infections	0/345 (0)	0/347 (0)	0/691 (0)	0/64 (0)
Opportunistic infections	0/344 (0)	0/347 (0)	0/690 (0)	0/64 (0)

Abbreviations: HLT=high level term, URI=upper respiratory tract infection
Source: adapted from AS clinical safety summary, p. 98

Reviewer's comments: The current secukinumab prescribing information includes a Warning and Precaution regarding the risk of infections in patients treated with secukinumab. In addition, the risk of candida and herpetic infections is described. No new safety signals were detected in the AS clinical program.

Malignancy

Table 35 shows the malignancies and skin tumors that occurred over the entire treatment period. During the initial 16 week period, one malignant melanoma was diagnosed in the secukinumab 150 mg group.

There were 3 additional malignancies during the rest of the treatment period. There was one B-cell lymphoma in the IV 75 mg group, one breast cancer in the IV 150 mg

group, and one case bladder transitional cell carcinoma in the IV 150 mg group. Due to the low number of cases, it was impossible to determine whether, dose or route of loading dose administration had any effect on incidence of malignancies.

Table 35. Pooled phase 3 AS studies: exposure adjusted incidence rates for malignancies and skin tumors over entire treatment period

Level 1 Preferred term	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Malignant or unspecified tumors	1/345 (0.3)	3/346 (0.9)	4/690 (0.6)	1/64 (1.6)
B-cell lymphoma	1/345 (0.3)	0/347 (0)	1/691 (0.1)	0/64 (0)
Bladder transitional cell carcinoma	0/345 (0)	1/346 (0.3)	1/691 (0.1)	0/64 (0)
Breast cancer	0/345 (0)	1/346 (0.3)	1/691 (0.1)	0/64 (0)
Lymphoma	0/345 (0)	0/347 (0)	0/691 (0)	1/64 (1.6)
Malignant melanoma	0/345 (0)	1/347 (0.3)	1/691 (0.1)	0/64 (0)

Source: adapted from AS clinical safety summary, p. 102

Reviewer's comments: Overall, the exposure adjusted incidence rate of infections was higher in the placebo group than the secukinumab groups. The types of infections would be anticipated in the patient population. No new safety signals related to malignancy were detected.

Neutropenia

Table 36 shows the events of neutropenia that occurred in the pooled phase 3 studies. There were four CTCAE Grade 3 infections and one Grade 4. None of the CTCAE Grade 3 or 4 events of neutropenia was accompanied by a serious infection.

Table 36. Pooled phase 3 AS studies: exposure adjusted incidence rates for neutropenia over entire treatment period

Applicant MedDRA query	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Neutropenia	15/328 (4.6)	12/335 (3.6)	27/663 (4.1)	1/63 (1.6)

Source: adapted from AS clinical safety summary, p.106

MACE

Table 37 shows the adjudicated MACE that occurred during the pooled phase 3 studies. During the first 16 weeks, one patient in the secukinumab 75 mg group who was a smoker with 3-vessel cardiac arteriosclerosis had a fatal myocardial infarction.

For the entire treatment period, there was one additional myocardial infarction in a patient who was on 75 mg maintenance therapy. This patient received IV load instead

of SC load. Another myocardial infarction was reported in the IV load 150 mg dose group. A cerebrovascular event occurred in a patient who was initially randomized to placebo and then started secukinumab 150 mg SC every 4 weeks. All four cases over the entire treatment period were considered SAEs.

The Adjudication committee considered the case reported in the secukinumab IV load 150 mg group to not meet MACE criteria. ST elevation was seen in inferior leads during a stress echocardiogram test but the troponin I was not elevated. The Adjudication committee considered the event to be angina pectoris.

Table 37. Pooled phase 3 AS studies: exposure adjusted incidence rates for adjudicated MACE over entire treatment period

MACE category	Any AIN457 75 mg N=284 n/EX (IR)	Any AIN457 150 mg N=287 n/EX (IR)	Any AIN457 N=571 n/EX (IR)	Placebo N=196 n/EX (IR)
Myocardial infarction	2 (0.7)	0	2 (0.4)	0
Stroke	0	1 (0.3)	1 (0.2)	0
Cardiovascular death	1 (0.4)	0	0	0
Total number of MACE	2 (0.7)	1 (0.3)	3 (0.6)	0

Source: adapted from AS clinical safety summary, p. 109

Reviewer's comments: While there was a slight imbalance in the number of cases of MACE in the secukinumab group compared to the placebo group, the overall incidence rate was low and the types of adverse events observed would be anticipated in the patient population. During the initial review in the psoriasis program, the Division of Cardiology and Renal Products was consulted and did not feel that the results were suggestive of a safety signal. No new findings were observed in the clinical program in ankylosing spondylitis to suggest a safety signal related to MACE.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 F2305 Common Adverse Events

Table 38 shows the common adverse events listed by preferred term that occurred in study F2305. The table shows the incidence rates of each adverse event by calculating the number of events over time exposed. The highest incidence rates of adverse events for patients who received secukinumab were nasopharyngitis, headache, diarrhea, upper respiratory infection, and dyslipidemia.

Dyslipidemia was noted to be increased in the first 16 weeks of treatment versus placebo with 9.5% occurring in patients in the 75 mg group, 6.1% in the 150 mg secukinumab group, and 4.9% reported in the placebo group. None of the lipid

abnormalities were considered serious or caused study treatment discontinuation. There was no dose-response on any lipid parameter. There were differences in mild elevations of LDL in the secukinumab groups versus placebo. With triglycerides there were differences in mild elevations of triglycerides in the secukinumab groups versus placebo.

Table 38. F2305: Exposure-adjusted incidence rates for common adverse events

Preferred term	Any AIN457 75 mg N=179 n/EX (IR)	Any AIN457 150 mg N=181 n/EX (IR)	Any AIN457 N=360 n/EX (IR)	Placebo up to week 24 N=122 n/EX (IR)
Nasopharyngitis	31/196.2 (15.8)	41/187 (21.9)	72/383.2 (18.8)	9/40.1 (22.5)
Headache	18/208.7 (8.6)	21/197.8 (10.6)	39/406.6 (9.6)	7/40.3 (17.4)
Diarrhea	21/204.6 (10.3)	18/210.9 (8.5)	39/415.6 (9.4)	7/40.2 (17.4)
Upper respiratory infection	20/205.4 (9.7)	15/211.6 (7.1)	35/417 (8.4)	2/41.3 (4.8)
Dyslipidemia	17/201.4 (8.4)	11/207.4 (5.3)	28/408.8 (6.8)	6/40 (15)
Oropharyngeal pain	13/211.3 (6.2)	14/210.5 (6.6)	27/421.9	6/40.5 (14.8)
Pharyngitis	10/215.4 (4.6)	15/213.5 (7)	25/428.9 (5.8)	1/41.6 (2.4)
Leukopenia	11/210 (5.2)	9/213.2 (4.2)	20/423.2 (4.7)	1/41.6 (2.4)
Nausea	8/216.6 (3.7)	9/211.6 (4.3)	17/428.2 (4)	2/41.1 (4.9)
Mouth ulceration	9/212.9 (4.2)	7/214.1 (3.3)	16/427 (3.7)	3/40.8 (7.4)
Arthralgia	9/216.1 (4.2)	7/216.6 (3.2)	16/432.7 (3.7)	4/41.2 (9.7)
Cough	9/215.1 (4.2)	6/215.5 (2.8)	15/430.7 (3.5)	2/41.2 (4.9)
Abdominal pain upper	7/214.9 (3.3)	7/216 (3.2)	14/431 (3.2)	0/41.8 (0)
Gastroenteritis	7/216.6 (3.2)	7/216.9 (3.2)	14/433.5 (3.2)	1/41.5 (2.4)
Hypertension	8/218.1 (3.7)	6/216.9 (2.8)	14/435 (3.2)	0/41.8 (0)
Fatigue	5/217.2 (2.3)	5/216.7 (2.3)	10/433.9 (2.3)	2/41.3 (4.8)
Anemia	4/218.3 (1.8)	4/217.1 (1.8)	8/435.4 (1.8)	1/41.3 (2.4)

Source: adapted from F2305 clinical study report

7.4.1.2 F2310 Common Adverse Events

Table 39 shows the common adverse events listed by preferred term that occurred in study F2310. The table shows the incidence rates of each adverse event by calculating the number of events over time exposed. The highest incidence rates of adverse events for patients who received secukinumab were nasopharyngitis, upper respiratory tract infection, headache, and diarrhea.

Table 39. F2310: Common adverse events

Preferred term n/EX (IR)	Any AIN457 75 mg N=105	Any AIN457 150 mg N=106	Any AIN457 N=211	Placebo N=74
Nasopharyngitis	20/103.7 (19.3)	15/110.6 (13.6)	35/214.4 (16.3)	3/21.4 (14)
Upper respiratory tract infection	10/113.4 (8.8)	7/118.7 (5.9)	17/232.1 (7.3)	2/21.5 (9.3)
Headache	6/116.7 (5.1)	8/115.5 (6.9)	14/232.2 (6)	6/20.3 (29.5)
Diarrhea	6/119 (5)	8/119 (6.7)	14/238 (6)	1/22 (4.6)
Influenza	6/116 (5.2)	6/120 (5)	12/236 (5.1)	0/22 (0)
Hypertension	4/119 (3.4)	8/118 (6.8)	12/237 (5.1)	0/22 (0)
Bronchitis	7/117 (6)	4/121 (3.3)	11/238 (4.6)	1/22 (4.6)
Gastroenteritis	4/119 (3.4)	4/121 (3.3)	8/240 (3.3)	1/22 (4.6)
Oropharyngeal pain	4/119 (3.4)	3/121 (2.5)	7/240 (2.9)	2/22 (9.3)
Fatigue	4/117 (3.4)	3/123 (2.4)	7/240 (2.9)	5/21 (24.3)
Dyspepsia	3/119 (2.5)	4/121 (3.3)	7/240 (2.9)	1/22 (4.6)
Viral infection	2/120 (1.7)	4/119 (3.3)	6/239 (2.5)	2/21 (9.4)
Nausea	2/121 (1.7)	4/121 (3.3)	6/241 (2.5)	3/21 (14.2)
Hypercholesterolemia	2/119 (1.7)	3/121 (2.5)	5/240 (2.1)	3/21 (14.2)
Pain in extremity	0/122 (0)	5/120 (4.2)	5/242 (2.1)	1/22 (4.6)
Injection site pain	0/122 (0)	4/118 (3.4)	4/240 (1.7)	1/22 (4.7)
Hepatic enzyme increase	2/120 (1.7)	2/123 (1.6)	4/243 (1.6)	0/22 (0)

Source: adapted from F2310 clinical study report, p. 163

Reviewer's comment: The adverse reactions that occur in ankylosing spondylitis patients are consistent with the adverse events seen in the US prescribing information. Only dyslipidemia had not been previously seen in the plaque psoriasis studies or psoriatic arthritis studies. The dyslipidemia that occurred in study 2305 was mild in patients with no serious adverse events or discontinuations. A similar finding of dyslipidemia was not seen in study 2310 although hypercholesterolemia was one of the more common AEs.

7.4.2 Laboratory Findings

In the pooled data for the phase 3 AS studies, neutropenia was more common in the secukinumab groups compared to placebo during the first 16 weeks. More cases of neutropenia appeared in patients who received IV loading doses. All cases of neutropenia were Grade 1 or Grade 2. More Grade 1 and Grade 2 decreases in platelets and leukocytes occurred in the secukinumab groups versus the placebo group.

In the entire treatment period, there were 4 cases of Grade 3 neutropenia and 1 case of Grade 4 neutropenia. The events did not appear to be related to the dose of medication received.

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In the first 16 weeks of the phase 3 AS studies, Grade 1 AST and ALT elevations were more frequent than placebo. Grade 1 alkaline phosphatase, cholesterol, and triglycerides appeared more frequently in the IV loading dose groups compared to the SC loading group. No patient fulfilled Hy's Law (ALT or AST > 3*ULN with TBL > 2*ULN and ALP < 2*ULN) during the first 16 weeks of the study.

In the entire treatment period, dose dependent changes between the 75 mg and 150 mg groups were seen in Grade 1 ALT, Grade 2 cholesterol, Grade 2 decreased fasting glucose, and Grade 3 triglycerides.

The only Grade 4 abnormality noted in the entire treatment period for patients on secukinumab was for cholesterol. A patient in the IV load 75 mg group with a baseline cholesterol value of 10 mmol/L (Grade 2) had a measurement of 13.2 (Grade 4) at Week 52. The patient was not on cholesterol lowering therapy.

Liver enzymes were balanced over the entire treatment period. No dose dependent increases in lab abnormalities were noted. One patient with a history of hyperbilirubinemia in the IV load 75 mg group fulfilled criteria for Hy's law but was able to continue in the study. The patient had baseline hyperbilirubinemia. ALT started to rise on Day 366 and on Day 440 the ALT was > 8*ULN. No change was made to study medication. By Day 555, the event had resolved.

7.4.3 Vital Signs

In the pooled phase 3 AS studies, the vital sign results were comparable across treatment arms. No dose dependent findings or worsening with longer term exposure. Although the hypertension AE was seen in 2% of patients of secukinumab versus 0% in placebo, there were no differences in proportion of patients with elevated blood pressure based on the actual vital signs data.

7.4.4 Electrocardiograms (ECGs)

ECG results for the AS population were consistent with the profile observed in the larger psoriasis dataset reported in the original submission. The incidence of QTc prolongation was low and comparable across the treatment groups. There were no patients with QTc > 500 msec across the treatment groups.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 F2305: Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

For studies F2305 and F2310, anti-drug antibodies (ADAs) were measured in 584 patients. Two patients (0.3%) developed ADAs while on secukinumab. Neutralizing antibodies were detected in one of the two patients who developed ADAs. Both patients were on 150 mg of secukinumab at the time of detection. There was no loss of efficacy, no immunoglobulin-related AEs and no alteration in PK.

8 of 584 patients had ADAs measured at baseline prior to receiving secukinumab. 7 patients were positive at baseline only while the one other patient was also positive at week 52. 5 of the 8 patients had neutralizing antibodies. The antibodies did not appear to have any effect clinically or on pharmacokinetics.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

From weeks 0 to 8, a comparison of adverse events during loading dose revealed that AEs were highest in patients receiving the 10 mg/kg IV loading dose (57%) followed by placebo (54.1%), secukinumab 75 mg SC load (46.6%) and then secukinumab 150 mg load (48.6%). The increased number of AEs in the 10 mg/kg IV loading dose group was driven by nausea, mouth ulceration, upper abdominal pain, diarrhea, dyslipidemia, leukopenia, uveitis, dry eye irritation, and eye pain.

Over the entire treatment period, AEs with increased incidence in the 150 mg secukinumab dose group versus the 75 mg group were nausea, nasopharyngitis, pharyngitis, headache, and oral herpes.

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 analyzed safety data based on race. 72% of patients who took secukinumab were white. Analyses by preferred term did not show any differences by race in adverse events. The Applicant performed safety analyses by gender. More adverse events were noted in females than males. This was observed in patients taking secukinumab as well as patients who took placebo. There were too few cases of patients ≥ 65 years or age to make any conclusion in a drug-age effect.

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 AS 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 Applicant is requesting a full waiver of performing studies in juvenile AS. The rationale the Applicant has provided is that spinal features in juvenile AS seldom appear before the age of 16 to 18 years. Therefore, it is difficult to diagnose in children. Because the necessary studies are impossible or highly impracticable as there are too few children to study, a full waiver for juvenile ankylosing spondylitis is reasonable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose have been reported in the AS clinical studies. There is no known potential for abuse of secukinumab and no abuse studies have been performed.

7.7 Additional Submissions / Safety Issues

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

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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.

8 Postmarket Experience

No post-marketing data were submitted in this submission.

9 Appendices

9.1 Literature Review/References

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 AS.

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 AS. Therefore, providers will have the option to start secukinumab for the indication of AS with or without a loading dose.

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

3. In the AS section, additional information on the adverse events that occurred during the AS trials will be provided.

Clinical Studies

4. A statement stating that patients on placebo who received secukinumab without a loading regimen achieved similar ASAS20 responses as patients who received a loading regimen was added.

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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.

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 Secukinumab (Cosentyx) for the treatment of ankylosing spondylitis

Clinical Investigator Financial Disclosure
 Review Template

Application Number: 125504-2

Submission Date(s): March 23, 2015

Applicant: Novartis

Product: secukinumab

Reviewer: Raj Nair

Date of Review: December 14, 2015

Covered Clinical Studies (Name and/or Number): AIN457F2305 and AIN457F2310

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>941</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>0</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: _____</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 type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input 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, F2305 and F2310, 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 941 investigators listed in the study report indicating:

- Certified investigators. A total of 941 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.

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
12/14/2015

JANET W MAYNARD
12/14/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s002

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, 2.2.342.1.2.200.100.1.1-0014137532 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:
125504Orig1s002

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

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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

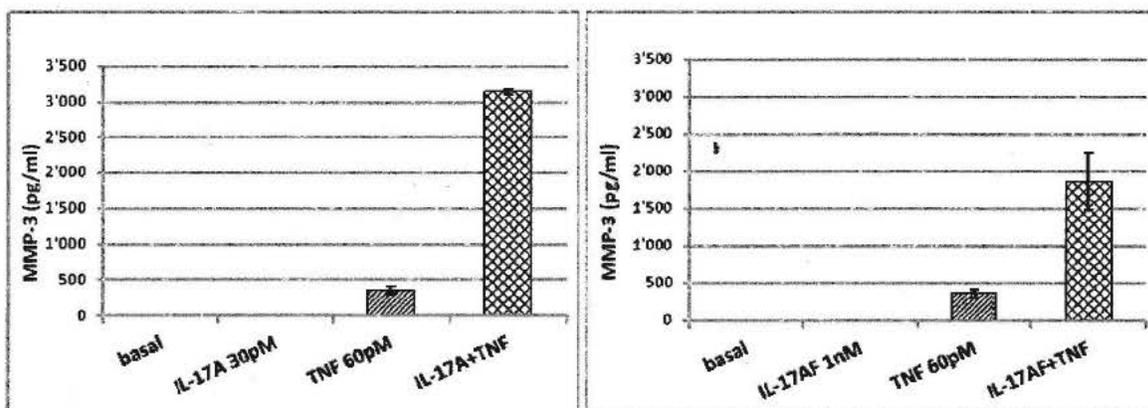
Stimulation of fibroblast-like synoviocytes with 30 pM IL-17A alone had no effect on MMP-3 release. TNF α alone resulted in a small increase in MMP-3. However, the combination of IL-17A with TNF α greatly potentiated (10.7-fold increase) MMP-3 release. The heterodimer, IL-17AF, was less potent than IL-17A 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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MARCIE L WOOD

12/18/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125504Orig1s002

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 125,504/0061

Drug Name: Cosentyx™ (secukinumab) 150 mg s.c.
Indication(s): Treatment of Ankylosing Spondylitis (AS)
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.
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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 ankylosing spondylitis (AS). The applicant submitted the results from two phase 3 clinical trials, CAIN457F2305 and CAIN457F2310 (F2305 and F2310 for short hereafter), to support the efficacy of secukinumab for the treatment of AS. The applicant claims that the results from these trials provide substantial evidence of efficacy by the predefined primary efficacy endpoint ASAS20 at Week 16.

Based on my review of the data from the two phase 3 studies, F2305 and F2310, there is sufficient evidence to support the efficacy of secukinumab 150 mg in treating patients with AS. The analysis of the primary efficacy endpoint, ASAS20 at Week 16, for secukinumab 150 mg was statistically significant in the two studies reviewed. This evidence was further supported by the analyses of secondary endpoints. In these studies, analyses of the key secondary endpoints, ASAS40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, and ASQoL at Week 16, were statistically significantly in favor of secukinumab. 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 ankylosing spondylitis. 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 ankylosing spondylitis. Furthermore higher frequency of IL-17-producing cells was detected in the synovial fluid of patients with ankylosing spondylitis.

The submission included the results from two phase 3, randomized, double-blind, placebo-controlled studies, F2305 and F2310 that were similar in design, but were different in the

placebo escape option. The objective of the phase 3 studies was to evaluate the efficacy and safety of secukinumab 150 mg treatment compared with placebo in patients with AS. In each study, patients were to receive randomized, double-blind study treatment for 52 weeks. The primary efficacy variable was the response rate of ASAS20 at Week 16.

History of Drug Development and Regulatory Interactions

The secukinumab clinical development program for AS 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 AS and psoriatic or 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 secukimumab 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, F2305 and F2310. The design of the two studies is described in Table 1.

Table 1. Clinical Trials Reviewed

Trial	Phase	Design	Treatment Arms	Number of Patients	Dates
-------	-------	--------	----------------	--------------------	-------

No.					
F2305	3	52-week, randomized, double-blind, parallel-group, placebo-controlled	secukinumab 75 mg	124	10/2011-12/2013 (52 weeks cut for interim analysis)
			secukinumab 150 mg	125	
			Placebo	122	
F2310	3	52-week, randomized, double-blind, parallel-group, placebo-controlled	secukinumab 75 mg	73	10/2012-08/2014 (52 weeks cut for interim analysis)
			secukinumab 150 mg	72	
			Placebo	74	

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 plan, 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\ain457f2305\analysis\adam\datasets
\\cdsesub1\evsprod\BLA125504\0060\m5\datasets\ain457f2310\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, F2305 and F2310. 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 placebo escape and subcutaneous (sc) or intravenous (iv) loading. In Study F2305, placebo patients who met non-response criteria at Week 16 were re-randomized to secukinumab 75 mg or 150 mg, but in Study F2310, all placebo patients were re-randomized to secukinumab 75 mg or 150 mg at Week 16. The loading regimen used in Study F2305 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 to as iv-75 mg and iv-150 mg regimens). The loading regimen used in Study F2310 was 4×weekly sc injections of 75 mg or 150 mg at Weeks 0, 1, 2, and 3 followed by 75 mg sc or 150 mg sc, respectively, every 4 weeks (hereafter referred to as 75 mg sc and 150 mg sc regimens).

3.2.1 Study F2305

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 AS. 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 in a ratio of 1:1:1:

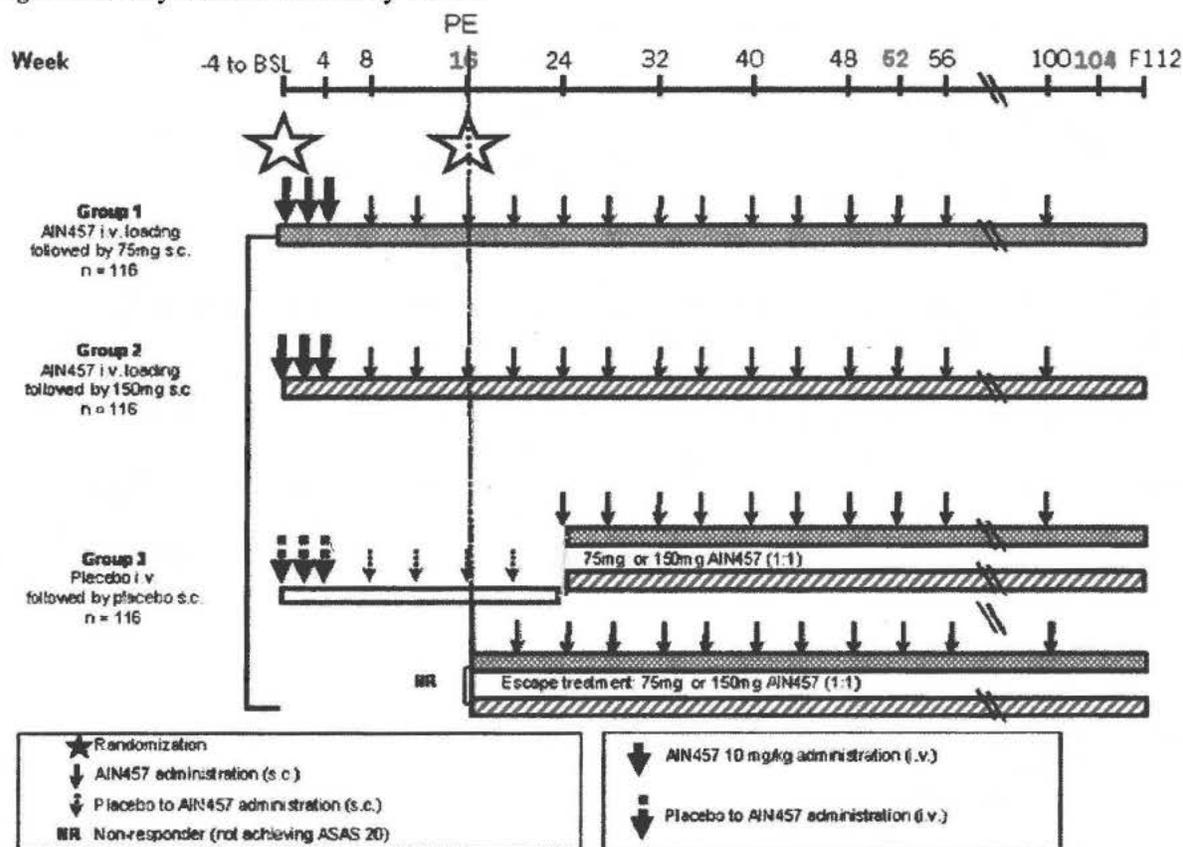
- Group 1: Secukinumab iv (10mg/kg) at BSL, Weeks 2 and 4 then secukinumab 75 mg sc starting at Week 8 and injected every 4 weeks
- Group 2: Secukinumab iv (10mg/kg) at BSL Weeks 2 and 4 then secukinumab 150 mg sc starting at Week 8 and injected every 4 weeks
- Group 3: Placebo iv at BSL Weeks 2 and 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. At Week 16 (Visit 8), all subjects were classified as responders or non-responders (based on ASAS 20 improvement criteria). 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 placebo (Group 3) who were responders remained on placebo at weeks 16 and 20. At Week 24, these subjects received either secukinumab 75 or 150 mg sc every 4 weeks (as dictated by the randomization).
- Subjects on placebo (Group 3) who were non-responders were re-randomized (1:1) at Week 16 to receive either secukinumab 75 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 16. 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 F2305



Source: Excerpted from the Clinical Study Report for Study F2305 (page 7337).

The study population comprised adult patients (aged ≥ 18 years) from 65 centers who were diagnosed with moderate to severe AS according to the Modified New York criteria for AS with prior documented radiological evidence (by X-ray), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 (0-10) and spinal pain as measured by visual analog scale (VAS) ≥ 4 cm (on a scale of 0-10 cm) at baseline. Enrolled patients were to have active disease despite current or previous NSAIDs, DMARDs and/or TNF- α inhibitor therapy.

The primary efficacy endpoint was the Assessment of SpondyloArthritis International Society 20 (ASAS20) response at Week 16. The ASAS Response Criteria (ASAS20) is defined as an improvement of $\geq 20\%$ and ≥ 1 unit on a scale of 10 in at least three of the four main domains and no worsening of $\geq 20\%$ and ≥ 1 unit on a scale of 10 in the remaining domain. The following are the ASAS domains:

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by Bath Ankylosing Spondylitis Functional Index (BASFI) average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

5. Spinal mobility represented by the Bath Ankylosing Spondylitis Metrology Index (BASMI) lateral spinal flexion assessment
6. C-reactive protein (acute phase reactant)

The secondary efficacy variables were ASAS40, high sensitivity C-Reactive Protein (hsCRP), ASAS 5/6, BASDAI, Short Form-36 Physical Component Summary (SF-36 PCS), Ankylosing Spondylitis Quality of Life (ASQoL), and ASAS partial remission at Week 16. The ASAS 40 response is defined as an improvement of $\geq 40\%$ and ≥ 2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain. The ASAS 5/6 improvement criteria is an improvement of $\geq 20\%$ in at least five domains. The ASAS partial remission criteria are defined as a value not above 2 units in each of the domains 1 to 4 on a scale of 10. The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Joint pain / swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity

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 model included terms for treatment regimen, analysis visit, and TNF-alpha inhibitor status as factors, and weight and baseline 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.

Since the primary endpoint and all key secondary endpoints were assessed at Week 16 prior to

escape, there was no impact of the escape to secukinumab in the key statistical analyses.

Missing data for ASAS20/40 response and other binary efficacy variables (e.g. ASAS5/6, etc.) at Week 16 were handled as follows:

1. Subjects who dropped out of the trial for any reason prior to Week 16 were considered non-responders.
2. Subjects who did not have the required data to compute ASAS response (i.e. ASAS components) at baseline and at Week 16 were classified as non-responders.

Therefore, these binary endpoints should in fact be considered composite response endpoints defined by: (1) remaining in the study through Week 16; and (2) achieving a response in the outcome of interest (e.g., ASAS20) at Week 16.

Continuous variables (e.g. ASAS components, BASDAI, 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 as well 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 assess sensitivity of results to violations in the assumption about the missing data mechanism since the method assumed an unverifiable missing at random mechanism. The applicant's observed data analysis used actually assessed data and did not impute missing data after dropout as non-response. However, the observed data analysis was still conducted in the subset of patients who completed Week 16 assessments, thus also relying on an unverifiable missing at random assumption about dropouts.

Therefore, 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 multiple doses and endpoints (Figure 2).

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 (ASAS20 response) at Week 16

H2: secukinumab 150 mg sc is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

Secondary objectives:

H3: secukinumab 75 mg sc is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H4: secukinumab 150 mg sc is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H5: secukinumab 75 mg sc is not different to placebo regimen with respect to hsCRP at Week 16

H6: secukinumab 150 mg sc is not different to placebo regimen with respect to hsCRP at Week 16

H7: secukinumab 75 mg sc is not different to placebo regimen with respect to ASAS5/6 response at Week 16

H8: secukinumab 150 mg sc is not different to placebo regimen with respect to ASAS5/6 response at Week 16

H9: secukinumab 75 mg sc is not different to placebo regimen with respect to total BASDAI at Week 16

H10: secukinumab 150 mg sc is not different to placebo regimen with respect to total BASDAI at Week 16

H11: secukinumab 75 mg sc is not different to placebo regimen with respect to SF-36 PCS at Week 16

H12: secukinumab 150 mg sc is not different to placebo regimen with respect to SF-36 PCS at Week 16

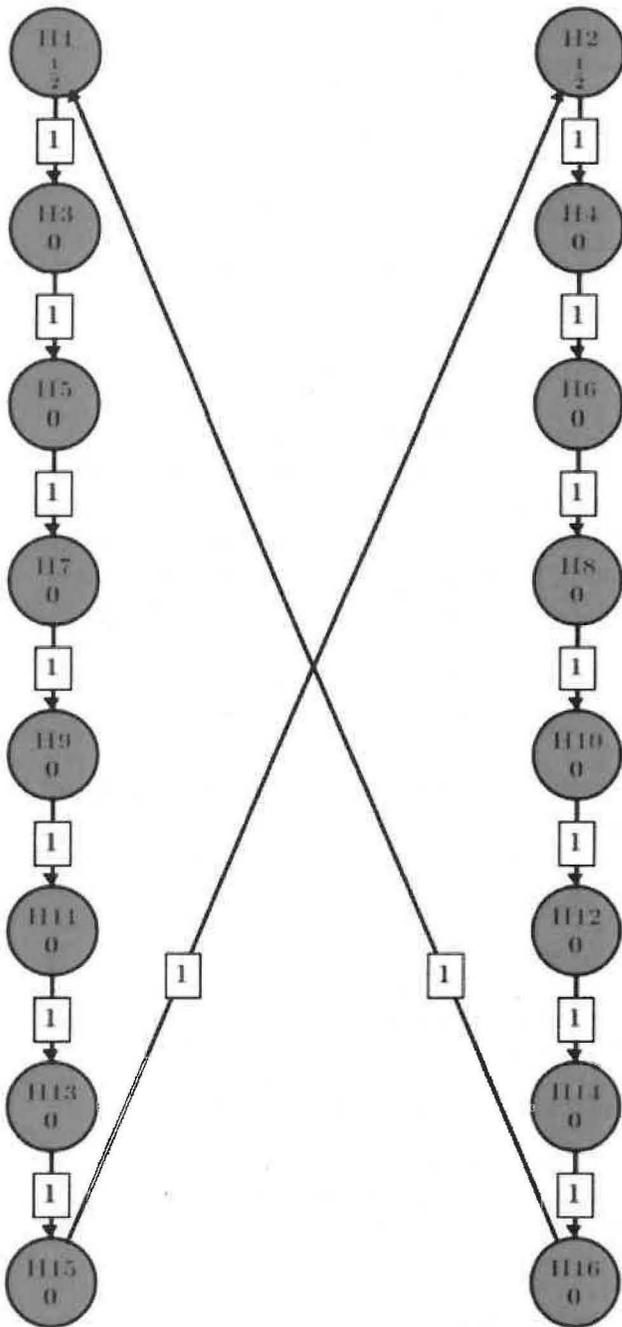
H13: secukinumab 75 mg sc is not different to placebo regimen with respect to ASQoL at Week 16

H14: secukinumab 150 mg sc is not different to placebo regimen with respect to ASQoL at Week 16

H15: secukinumab 75 mg sc is not different to placebo regimen with respect to ASAS partial remission at Week 16

H16: secukinumab 150 mg sc is not different to placebo regimen with respect to ASAS partial remission at Week 16

Figure 2. Multiple testing strategy



Source: Excerpted from the Clinical Study Report for Study F2305 (page 7386).

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. Each of the hypotheses (H1 and H2) for the primary

objective (ASAS20 at Week 16) for each secukinumab regimen versus placebo will be tested simultaneously at $\alpha/2$. Then based on the rejection of one or both (of H1 and H2), the ASAS40 at Week 16 endpoint will be tested hierarchically for each dose (through H3 and/or H4).

This procedure will continue (pending rejection of the null hypotheses) until H15 and/or H16 are/is rejected, then the respective $\alpha/2$ can be passed on to the other secukinumab regimen's hierarchy of hypotheses, if they were 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 (ASAS20 response at Week 16), 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 20% after 14 weeks was assumed based on the results for the AS population in a historical study. The response on secukinumab was assumed to be 60% in the AS population. For the primary endpoint, ASAS20 in the overall population, 116 subjects per group would yield at least 90% power to detect a treatment difference in the response rates between the secukinumab regimens and placebo with the above assumptions using Fisher's exact test.

Changes in the statistical analysis plan

There were three amendments to the original protocol (May 4, 2011), Amendment 1 (August 4, 2011), Amendment 2 (December 10, 2012), and Amendment 3 (November 22, 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 Ankylosing Spondylitis. These endpoints include but are not limited to ASQoL, BASDAI and SF-36. In addition, the analysis was changed to include all patients in the FAS, rather than focusing only on the subset of patients who are TNF α inhibitor naïve, as the FAS would be more representative of the general population of AS patients.
- This protocol amendment is issued to update sections of the data analysis plan, specifically to update how missing values are handled. The guidance language for study treatment interruptions and discontinuation has been clarified.

Patient Disposition, Demographic and Baseline Characteristics

A total of 371 patients were randomized. The majority (86%) of patients completed the 52 weeks of active treatment and 95% of patients completed 16 weeks (Table 2). Slightly more patients in the placebo group discontinued treatment prior to Weeks 16 and 52 compared to the secukinumab treatment groups. The most common reasons for discontinuation at Week 52 were adverse event and lack of efficacy with comparable rates in each treatment group. Of the 122 patients in the placebo group, 112 patients were re-randomized (1:1). Of the

placebo patients who were re-randomized, 77 non-responding patients received secukinumab starting at Week 16 (75 mg: 39 patients and 150 mg: 38 patients), and 35 patients continued on placebo until Week 24 and then received either secukinumab 75 mg (17 patients) or 150 mg (18 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	124 (100)	125 (100)	122 (100)				
Completed Wk16	118 (95)	121 (97)	112 (92)	39 (100)	38 (100)	17 (100)	18 (100)
Non-responder at Wk16	37 (31)	40 (33)	77 (69)				
Re-randomized at Wk16				39 (100)	38 (100)		
Completed Wk24	113 (91)	113 (91)	104 (85)	34 (87)	34 (89)	17 (100)	17 (94)
Completed Wk52	111 (89)	106 (85)	102 (84)				
Discontinued Wk52	13 (11)	19 (15)	20 (16)				
Adverse event	6 (5)	7 (6)	7 (6)				
Lack of efficacy	2 (2)	6 (5)	5 (4)				
Other	5 (4)	6 (4)	8 (6)				

Note: SCK stands for secukinumab.

Source: Reviewer & the Clinical Study Report for Study F2305 (page 109).

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 42 years old, 76 kg in weight, and had 8 years of duration of AS. The majority of patients (69%) were male and approximately 61% of patients were Caucasian. About 73% of patients were naïve to TNF alpha inhibitors and about 15% of patients used methotrexate at baseline.

Table 3. Patients' Demographic and Baseline Characteristics by Treatment

	SCK 75 mg N=124	SCK 150 mg N=125	Placebo N=122
Age (years)			
N	124	125	122
Mean	42	40	43
SD	13	12	12
Median	41	39	41
Min-Max	18-76	19-67	18-74
Gender, n (%)			
Female	36 (29)	41 (33)	37 (30)
Male	88 (71)	84 (67)	85 (70)
Race, n (%)			
White	76 (61)	69 (55)	81 (66)
Black	0 (0)	0 (0)	1 (1)
Asian	23 (19)	21 (17)	19 (16)
Other	25 (20)	35 (28)	21 (17)
Weight (kg)			
N	124	125	122

Mean	78	75	77
SD	20	16	14
Median	74	73	75
Min-Max	41-142	40-112	48-134
BMI (kg/m**2)			
N	124	125	122
Mean	27	26	27
SD	6	5	5
Median	26	26	26
Min-Max	15-46	16-40	18-42
Patients global assessment of disease activity (0-100 mm)			
N	124	125	122
Mean	61	64	66
SD	18	19	19
Median	63	66	69
Min-Max	0-100	3-96	17-100
Total back pain (0-100 mm)			
N	124	125	122
Mean	62	64	67
SD	19	19	16
Median	65	65	69
Min-Max	3-93	2-98	18-100
BASFI			
N	124	125	122
Mean	5.4	5.6	5.8
SD	2.2	2.2	2.0
Median	5.6	5.8	6.1
Min-Max	0.4-9.4	0.8-9.8	0.4-9.7
BASDAI			
N	124	125	122
Mean	6.1	6.4	6.5
SD	1.4	1.6	1.5
Median	6.2	6.4	6.7
Min-Max	1.4-9.1	1.7-9.4	0.7-9.4
BASMI (linear)			
N	120	120	119
Mean	4.2	3.9	4.1
SD	1.8	1.8	1.6
Median	4.4	3.9	4.0
Min-Max	0.4-7.8	0.2-9.2	0.5-8.4
hs CRP (mg/L)			
N	124	125	121
Mean	18	17	17
SD	24	22	22
Median	9	7	8
Min-Max	0-140	0-148	0-147
MTX use, n (%)			
Yes	22 (18)	17 (14)	16 (13)
No	102 (82)	108 (86)	106 (87)
Dose of MTX (mg/week)			
N	22	15	16
Mean	14	14	13
SD	5	6	4
Median	11	10	14
Min-Max	8-25	4-25	8-20
Naive to TNF alpha inhibitors, n (%)			
Yes	90 (73)	92 (74)	89 (73)
No	34 (27)	33 (26)	33 (27)
Number of prior TNF alpha inhibitors, n (%)			
0	90 (73)	92 (74)	89 (73)
1	33 (26)	30 (24)	33 (27)
≥2	1 (1)	30 (2)	0 (0)

Time since first diagnosis of ankylosing spondylitis (years)			
N	123	125	122
Mean	8	7	8
SD	10	7	9
Median	5	4	6
Min-Max	0-57	0-33	0-47

Source: Excerpted from the Clinical Study Report for Study F2305 (pages 112- 118).

Results and Conclusions

Primary Efficacy Endpoint – ASAS20 response at Week 16

The analysis of the primary endpoint showed statistically significantly greater ASAS20 responses at Week 16 for both secukinumab regimens compared to placebo. As pre-specified in the protocol, all dropouts prior to Week 16 were treated as non-responders. There was some dropout prior to Week 16 (4% of active and 8% of placebo).

The applicant conducted sensitivity analyses to handle missing data, mainly due to study dropout, based on multiple imputation and an observed data analysis. However, while the analysis with multiple imputation basically resolved the issue due to a single imputation, it still relied on an unverifiable missing at random assumption. Also the analysis based on observed data was a subset analysis of completers by Week 16. Therefore, it also relies on a missing at random assumption and therefore may not reliably estimate the intention-to-treat (ITT) estimand, i.e., the difference in ASAS20 response at Week 16 in all randomized patients regardless of adherence. To assess robustness of the primary analysis with respect to the ITT estimand, I requested that the applicant conduct additional sensitivity analyses including a tipping point analysis. The tipping point analysis was useful to assess the robustness of the study conclusions.

The applicant's primary and sensitivity analyses appeared to support efficacy of both secukinumab regimens – statistically significant differences in ASAS20 responses at Week 16 between each secukinumab regimen and placebo.

Table 4. Applicant's analyses of ASAS20 response at Week 16

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Primary analysis with NRI	SCK 75mg (N=124)	74/124 (60)	vs. Placebo	3.8	(2.2, 6.4)	<0.0001
	SCK 150mg (N=125)	76/125 (61)	vs. Placebo	3.9	(2.3, 6.6)	<0.0001
	Placebo (N=122)	35/122 (29)				
Sensitivity analysis with multiple imputation	SCK 75mg (N=124)	(63)	vs. Placebo	3.6	(2.1, 6.3)	<0.0001
	SCK 150mg (N=125)	(62)	vs. Placebo	3.4	(2.0, 5.9)	<0.0001
	Placebo (N=122)	(32)				
Sensitivity analysis with observed data	SCK 75mg (N=124)	74/115 (64)	vs. Placebo	3.9	(2.2, 6.8)	<0.0001
	SCK 150mg (N=125)	76/121 (63)	vs. Placebo	3.5	(2.0, 6.2)	<0.0001
	Placebo (N=122)	35/108 (17)				

In the response to FDA’s IR after the filing meeting, the applicant justified that there was no need for tipping point analyses for the primary endpoint (for Studies F2305 and F2310) as follows:

To examine the potential effects of missing data on the results of the primary endpoint ASAS20 at Week 16, a worst-case scenario sensitivity analysis was done. The worst-case scenario was first analyzed to determine if a tipping point analysis is needed for CAIN457F2305 and CAIN457F2310. Since the primary endpoint for AS is at Week 16 there was no rescue penalty applied, but all missing data (regardless of reason for missing) was accounted for in the analysis.

Worst-case scenario analysis imputes the worst response observed (not achieving an ASAS20 response) among the secukinumab group for all missing values, while the missing data in the Placebo group are imputed with the best observed response (achieving an ASAS20 response). The results of the worst-case scenario analysis are summarized in Table 4-7 and Table 4-8, together with the results of the primary and sensitivity analyses that are presented in each pivotal trial CSR.

For CAIN457F2305, using the worst-case scenario, the ASAS20 rate at Week 16 was 60.8% (p=0.0015) for iv-150 mg and 59.7% (p=0.0020) for iv-75 mg versus 40.2% for placebo, demonstrating a clinically meaningful treatment difference in response rate between secukinumab and placebo of approximately 20%. For CAIN457F2310, using the worst-case scenario, the ASAS20 rate at Week 16 was 61.1% (p=0.0234) for 150 mg sc and 41.1% (p=0.8198) for 75 mg sc versus 43.2% for placebo. The results from both these pivotal trials were consistent with the primary analysis using non-responder imputation and the other sensitivity analyses presented in each pivotal trial CSR that demonstrated the efficacy of the 150 mg sc dose and the ineffectiveness of 75 mg sc. Thus, these analyses provide additional evidence of the robust efficacy of secukinumab 150 mg sc in AS, which continually demonstrates greater responses than 75 mg sc, regardless of the statistical methodology employed.

With the results of the worst-case sensitivity analysis demonstrating robust efficacy of the 150 mg sc dose, a tipping point analysis was not needed for either CAIN457F2305 or CAIN457F2310.

Table 4-7 Summary of primary and sensitivity analyses for ASAS20 at Week 16 - CAIN457F2305

Missing Data Handling	iv-75 mg	iv-150 mg	Placebo
Non-responder Imputation	74/124 (59.7%) p<0.0001	76/125 (60.8%) p<0.0001	35/122 (28.7%)
Multiple Imputation	62.9% p<0.0001	61.9% p<0.0001	32.4%
Observed	74/115 (64.3%) p<0.0001	76/121 (62.8%) p<0.0001	35/108 (32.4%)
Worst-Case	74/124 (59.7%) p=0.0020	76/125 (60.8%) p=0.0015	49/122 (40.2%)

P-values are from logistic regression model with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate.

Worst-case scenario analysis imputes the worst response observed (not achieving an ASAS20 response) among the AIN457 group for missing values, while the missing data in the Placebo group are imputed with the best response observed (achieving an ASAS20 response).

Source: Study [CAIN457F2305 CSR:– Table 14.2-1.1], [Table 16.1.9-4.2] and [Table 16.1.9-4.3]

Appendix 5: – Table 3.6-1.1

Table 4-8 Summary of primary and sensitivity analyses for ASAS20 at Week 16 - CAIN457F2310

Missing Data Handling	75 mg sc	150 mg sc	Placebo
Non-responder Imputation	30/73 (41.1%) p=0.0967	44/72 (61.1%) p<0.0001	21/74 (28.4%)
Multiple Imputation	43.2% p=0.1176	62.9% p=0.0001	30.8%
Observed	30/67 (44.8%) p=0.1549	44/66 (66.7%) p<0.0001	21/63 (33.3%)
Worst-Case	30/73 (41.1%) p=0.8198	44/72 (61.1%) p=0.0234	32/74 (43.2%)

P-values are from logistic regression model with treatment and TNF-alpha inhibitor status as factors and baseline weight as a covariate.

Worst-case scenario analysis imputes the worst response observed (not achieving an ASAS20 response) among the AIN457 group for the missing values, while the missing data in the Placebo group are imputed with the best response observed (achieving an ASAS20 response).

Source: [CAIN457F2310 CSR: – Table 14.2-1.1], [Table 16.1.9-5.2] and [Table 16.1.9-5.3]

Appendix 5 – Table 3.6-2.1

In my opinion, the applicant's worst-case analysis and justification to not provide additional tipping point analyses appears reasonable and resolves our concern with the handling of missing data at Week 16 due to dropout.

Components of ASAS20 response at Week 16

I was able to confirm the results of the applicant's analyses of the components of the primary endpoint, ASAS20 response at Week 16. Analyses of all the components of ASAS were statistically significant and there was no single component driving the efficacy in terms of ASAS20 response.

Table 5. Applicant's analysis of ASAS20 main components at Week 16

	Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
Patient's global assessment of disease activity	SCK 75mg (N=124)	116	-25.4	vs. Placebo	-18.8 (2.9)	(-24.5, -13.1)	<0.0001
	SCK 150mg (N=125)	121	-28.0	vs. Placebo	-21.3 (2.9)	(-27.0, -15.7)	<0.0001
	Placebo (N=122)	108	-6.6				
Patient's assessment of total spinal pain	SCK 75mg (N=124)	116	-27.5	vs. Placebo	-20.8 (2.9)	(-26.5, -15.1)	<0.0001
	SCK 150mg (N=125)	121	-27.7	vs. Placebo	-20.9 (2.9)	(-26.6, -15.3)	<0.0001
	Placebo (N=122)	108	-6.8				
Inflammation (mean of questions 5 and 6 of the BASDAI)	SCK 75mg (N=124)	116	-2.6	vs. Placebo	-1.9 (0.3)	(-2.5, -1.4)	<0.0001
	SCK 150mg (N=125)	121	-2.7	vs. Placebo	-2.0 (0.3)	(-2.5, -1.4)	<0.0001
	Placebo	108	-0.7				

	(N=122)						
BASFI	SCK 75mg	116	-1.7	vs. Placebo	-1.4 (0.2)	(-1.8, -0.9)	<0.0001
	(N=124)						
	SCK 150mg	121	-1.8	vs. Placebo	-1.5 (0.2)	(-1.9, -1.0)	<0.0001
	(N=125)						
	Placebo	108	-0.4				
	(N=122)						

Source: Excerpted from the Clinical Study Report for Study F2305 (pages 666, 689, 712, 735).

Note: LSmeans and 95% CIs were based on the MMRM analysis.

In summary, the study showed statistically significant evidence in favor of the secukinumab 75 mg and 150 mg dosing regimens for the ASAS20 response at Week 16 (primary efficacy endpoint). Several sensitivity analyses were conducted on the primary efficacy endpoint 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 continuous responder analyses on the continuous endpoints to assess the impact of missing data due to dropout. All p-values for the secondary endpoints presented here are nominal.

Key Secondary Endpoints – ASAS40 response at Week 16

The applicant's results of ASAS40 analyses are summarized in Table 6. The same statistical method in the ASAS20 analysis was employed for this endpoint. Treatment with the secukinumab regimens resulted in statistically significantly higher ASAS40 response rates than treatment with placebo.

Table 6. Applicant's analyses of ASAS40 response at Week 16

Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
SCK 75mg (N=124)	41/124 (33)	vs. Placebo	3.4	(1.8, 6.4)	0.0003
SCK 150mg (N=125)	52/125 (42)	vs. Placebo	4.9	(2.6, 9.3)	<0.0001
Placebo (N=122)	16/122 (13)				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 383).

Key Secondary Endpoints - change from baseline in hsCRP at Week 16

The mean change in hsCRP at Week 16 in patients treated with the secukinumab regimens was statistically significantly lower compared to patients treated with placebo (Table 7). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab regimens and placebo (Figure 3).

Table 7. Applicant's analysis of change from baseline in hsCRP at Week 16

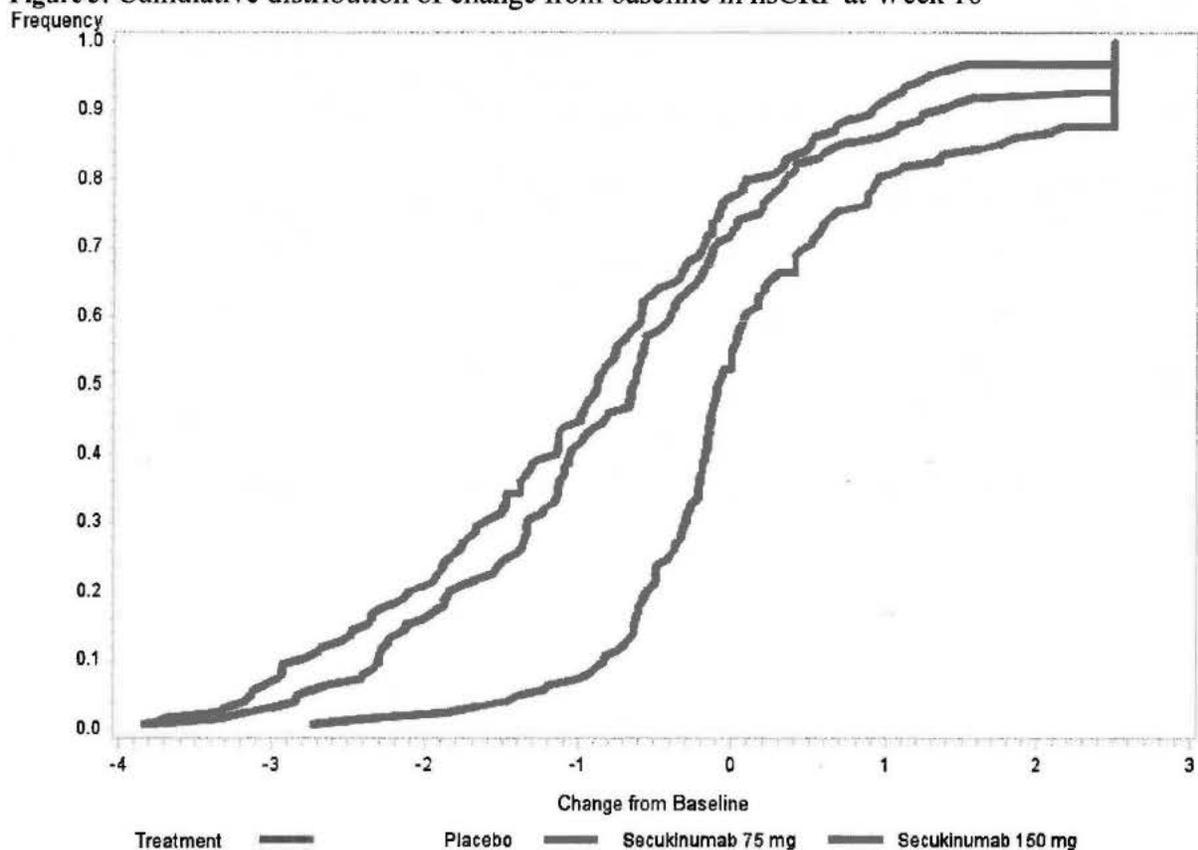
Treatment Group	n	Exp (LS Mean Change)	Comparison	Ratio	95% Confidence Interval	p-value
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SCK 75mg (N=124)	115	0.45	vs. Placebo	0.46	(0.36, 0.59)	<0.0001
SCK 150mg (N=125)	121	0.40	vs. Placebo	0.41	(0.32, 0.52)	<0.0001
Placebo (N=122)	107	0.97				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 451).

Note: $\log(\text{hsCRP})$ was used in the MMRM analysis and the LSmean difference were back-transformed (exponentiation) to the ratio between treatment groups.

Figure 3. Cumulative distribution of change from baseline in hsCRP at Week 16



Note: Missing data were imputed with the worst score.

Source: Reviewer

Key Secondary Endpoints – ASAS5/6 response at Week 16

The applicant's results of ASAS5/6 analyses are summarized in Table 8. The same statistical method in the ASAS20 analysis was employed for this endpoint. Treatment with the secukinumab regimens resulted in statistically significantly higher ASAS5/6 response rates than treatment with placebo.

Table 8. Applicant's analyses of ASAS5/6 response at Week 16

Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
SCK 75mg (N=124)	56/124 (45)	vs. Placebo	5.6	(3.0, 10.6)	<0.0001

SCK 150mg (N=125)	61/125 (49)	vs. Placebo	6.5	(3.5, 12.4)	<0.0001
Placebo (N=122)	16/122 (13)				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 434).

Key Secondary Endpoints - change from baseline in BASDAI at Week 16

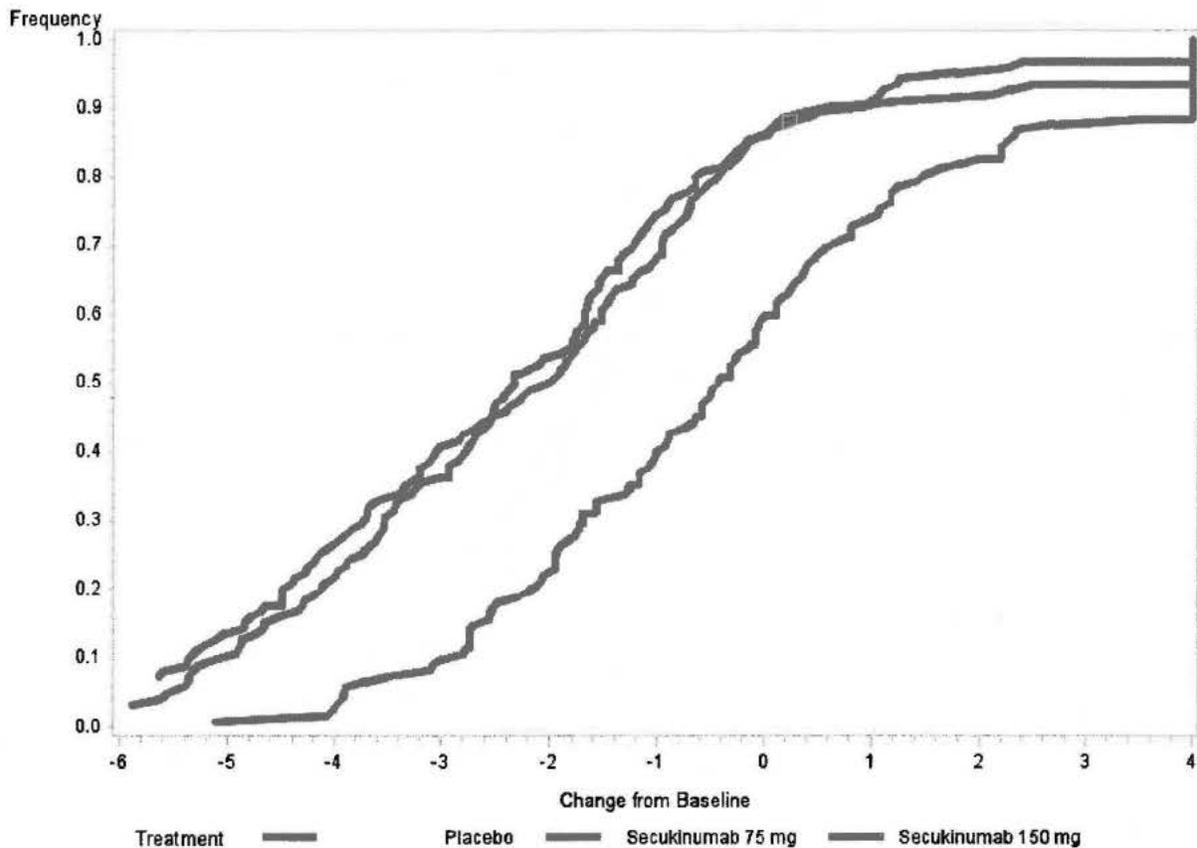
The mean change in BASDAI at Week 16 in patients treated with the secukinumab regimens was statistically significantly greater compared to patients treated with placebo (Table 9). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab regimens and placebo (Figure 4).

Table 9. Applicant's analysis of change from baseline in BASDAI at Week 16

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=124)	116	-2.34	vs. Placebo	-1.75 (0.25)	(-2.23, -1.27)	<0.0001
SCK 150mg (N=125)	121	-2.32	vs. Placebo	-1.74 (0.24)	(-2.22, -1.26)	<0.0001
Placebo (N=122)	108	-0.59				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 400).

Figure 4. Cumulative distribution of change from baseline in BASDAI at Week 16



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 16

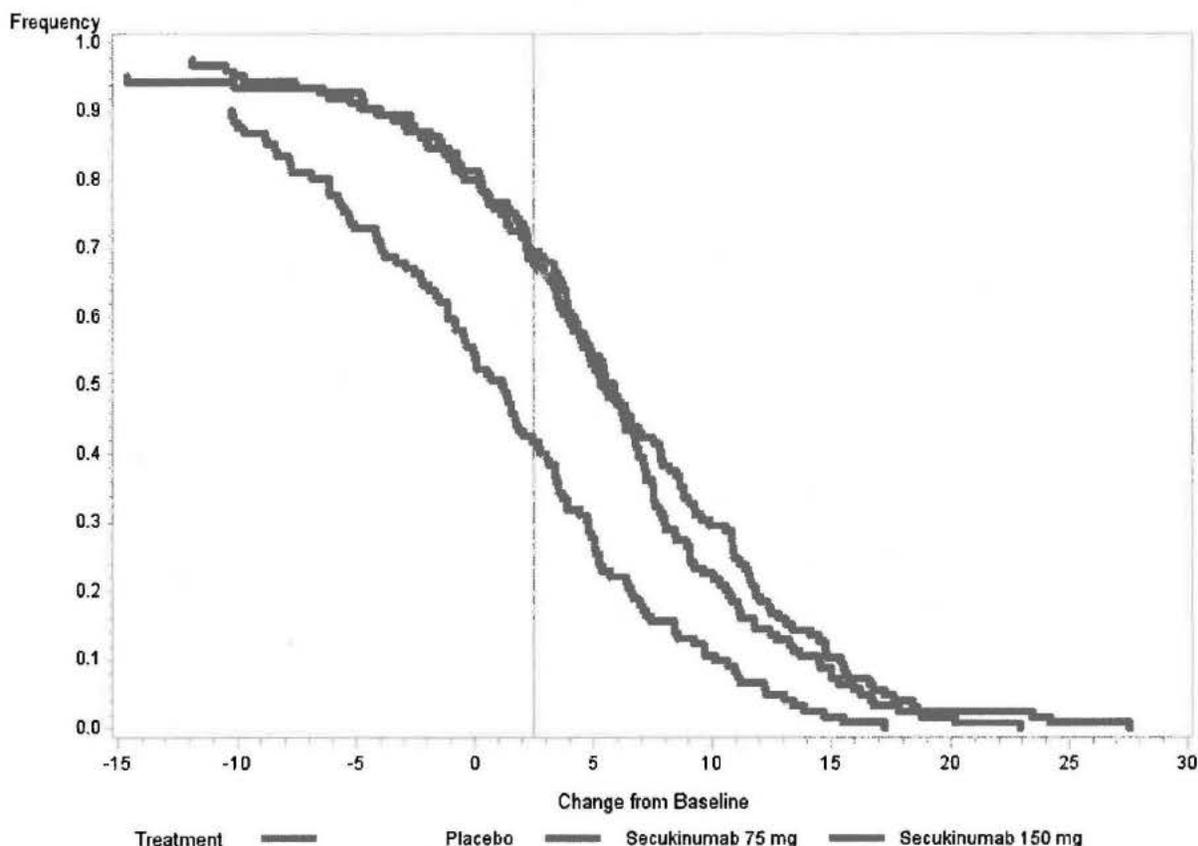
The mean change in SF36-PCS at Week 16 in patients treated with the secukinumab regimens was statistically significantly greater compared to patients treated with placebo (Table 10). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab regimens and placebo (Figure 5).

Table 10. Applicant’s analysis of change from baseline in SF36-PCS at Week 16

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=124)	118	5.64	vs. Placebo	4.68 (0.83)	(3.05, 6.30)	<0.0001
SCK 150mg (N=125)	122	5.57	vs. Placebo	4.61 (0.82)	(2.99, 6.22)	<0.0001
Placebo (N=122)	111	0.96				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 504).

Figure 5. Cumulative distribution of change from baseline in SF36-PCS at Week 16



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 ASQoL at Week 16

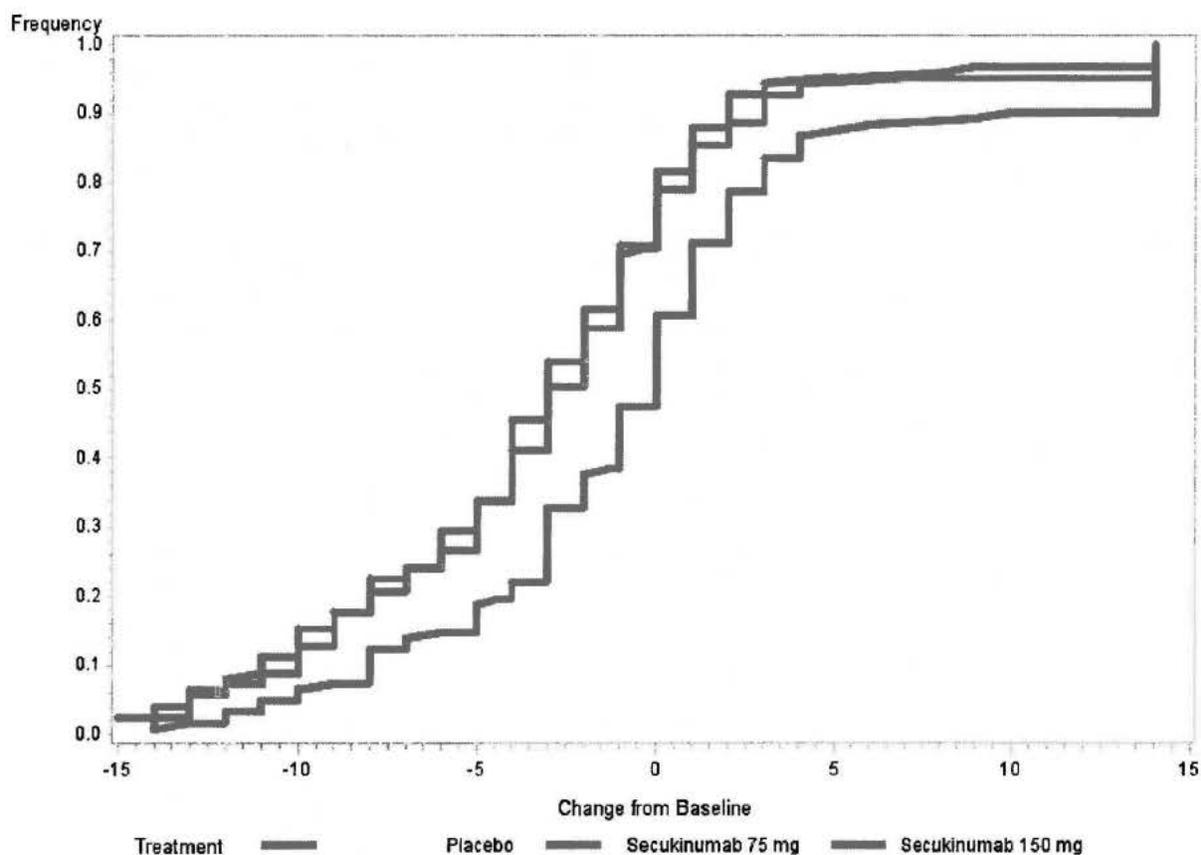
The mean change in ASQoL at Week 16 in patients treated with the secukinumab regimens was statistically significantly greater compared to patients treated with placebo (Table 11). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab regimens and placebo (Figure 6).

Table 11. Applicant’s analysis of change from baseline in ASQoL at Week 16

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=124)	118	-3.61	vs. Placebo	-2.57 (0.59)	(-3.7, -1.4)	<0.0001
SCK 150mg (N=125)	121	-3.58	vs. Placebo	-2.54 (0.59)	(-3.7, -1.4)	<0.0001
Placebo (N=122)	111	-1.04				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 646).

Figure 6. Cumulative distribution of change from baseline in ASQoL at Week 16



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 – ASAS partial remission at Week 16

The applicant's results of ASAS partial remission analyses are summarized in Table 12. The same statistical method in the ASAS20 analysis was employed for this endpoint. Treatment with the secukinumab regimens resulted in statistically significantly higher ASAS partial remission rates than treatment with placebo.

Table 12. Applicant's analyses of ASAS partial remission at Week 16

Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
SCK 75mg (N=124)	20/124 (16)	vs. Placebo	5.8	(1.9, 17.5)	0.0020
SCK 150mg (N=125)	19/125 (15)	vs. Placebo	5.3	(1.7, 16.1)	0.0033
Placebo (N=122)	4/122 (3)				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 488).

Long-term efficacy analysis – observed ASAS20 response over 52 weeks

I conducted a descriptive analysis to numerically compare the secukinumab 75 mg and 150 mg dosing regimens with regard to ASAS20 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 ASAS20 responses over time on the two dosing regimens were similar.

Table 13. Reviewer’s analysis of observed ASAS20 response over 52 weeks

Week	SCK 75 mg	SCK 150 mg
	n/N (%)	n/N (%)
1	45/118 (38)	39/120 (33)
2	51/119 (43)	48/121 (40)
4	65/120 (54)	60/124 (48)
8	76/120 (63)	67/124 (54)
12	70/119 (59)	70/121 (58)
16	74/115 (64)	76/121 (63)
20	83/116 (72)	78/120 (65)
24	72/113 (64)	81/113 (72)
28	79/111 (71)	83/110 (75)
32	79/112 (71)	84/116 (72)
40	80/112 (71)	74/111 (67)
52	77/108 (71)	79/103 (77)

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 ASAS20 response at Week 16 and all the secondary endpoints at Week 16 in the multiplicity adjustment hierarchy – ASAS40 response, hsCRP, ASAS5/6 response, BSADAI, SF-36 PCS, ASQoL, and ASAS partial remission. Analyses of all the endpoints remained statistically significant in sensitivity analyses using different approaches to handle missing data due to dropout.

3.2.2 Study F2310

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 AS. Patients were to receive randomized study treatment in a double-blind manner for 52 weeks.

Study Design and Endpoints

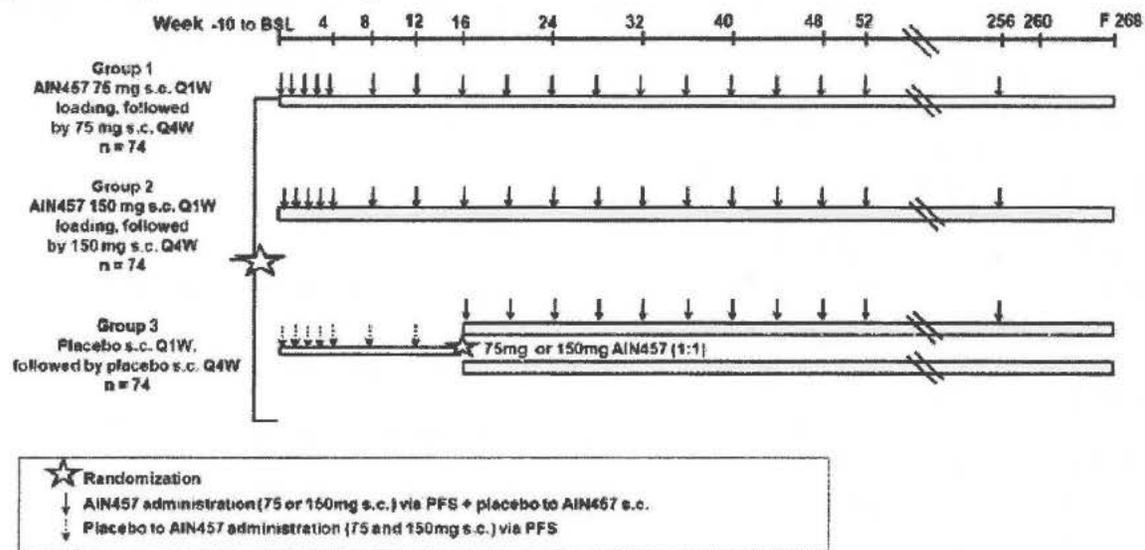
The study used a double-blind, randomized, parallel-group, placebo-controlled design. A screening period running up to 10 weeks before randomization was used to assess eligibility followed by 52 weeks of treatment and 4 years of additional long-term treatment, see Figure 7. At baseline (BSL), subjects whose eligibility was confirmed were randomized to one of three treatment groups:

- Group 1: Secukinumab 75 mg sc plus placebo 150 mg sc at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4
- Group 2: Secukinumab 150 mg sc plus placebo 75 mg sc at BSL, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks starting at Week 4
- Group 3: Placebo 75 mg sc and placebo 150 mg sc 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 132 TNF- α inhibitor naïve patients and 90 TNF α -IR patients. At Week 16, subjects who had been randomized to placebo at baseline were re-randomized by the Interactive Response Technology to receive secukinumab 75 mg plus placebo 150 mg or secukinumab 150 mg plus placebo 75 mg (1:1) every 4 weeks for up to 256 weeks.

Rescue medication was not allowed until Week 20. 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 F2310



Source: Excerpted from the Clinical Study Report for Study F2310 (page 48).

The study population comprised adult patients (aged ≥ 18 years) from 65 centers who were

diagnosed with moderate to severe AS according to the Modified New York criteria for AS with prior documented radiological evidence (by X-ray), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 (0-10) and spinal pain as measured by visual analog scale (VAS) ≥ 4 cm (on a scale of 0-10 cm) at baseline. Enrolled patients were to have active disease despite current or previous NSAIDs, DMARDs and/or TNF- α inhibitor therapy.

The primary efficacy endpoint was the ASAS20 response at Week 16. The secondary efficacy variables were ASAS40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission at Week 16.

Statistical Methodologies

The statistical methods including the analysis set, models, and the handling of missing data due to dropout were the same as in Study F2305.

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 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 multiple doses and endpoints (Figure 8). The following primary and secondary hypotheses were included in the sequential testing strategy:

Primary objective:

H1: secukinumab 75 mg is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

H2: secukinumab 150 mg is not different to placebo regimen with respect to signs and symptoms (ASAS20 response) at Week 16

Secondary objectives:

H3: secukinumab 75 mg is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H4: secukinumab 150 mg is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) at Week 16

H5: secukinumab 75 mg is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H6: secukinumab 150 mg is not different to placebo regimen with respect to change from baseline in hsCRP at Week 16

H7: secukinumab 75 mg is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H8: secukinumab 150 mg is not different to placebo regimen with respect to ASAS 5/6 response at Week 16

H9: secukinumab 75 mg is not different to placebo regimen with respect to change from

baseline in total BASDAI at Week 16

H10: secukinumab 150 mg is not different to placebo regimen with respect to change from baseline in total BASDAI at Week 16

H11: secukinumab 75 mg is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

H12: secukinumab 150 mg is not different to placebo regimen with respect to change from baseline in SF-36 PCS at Week 16

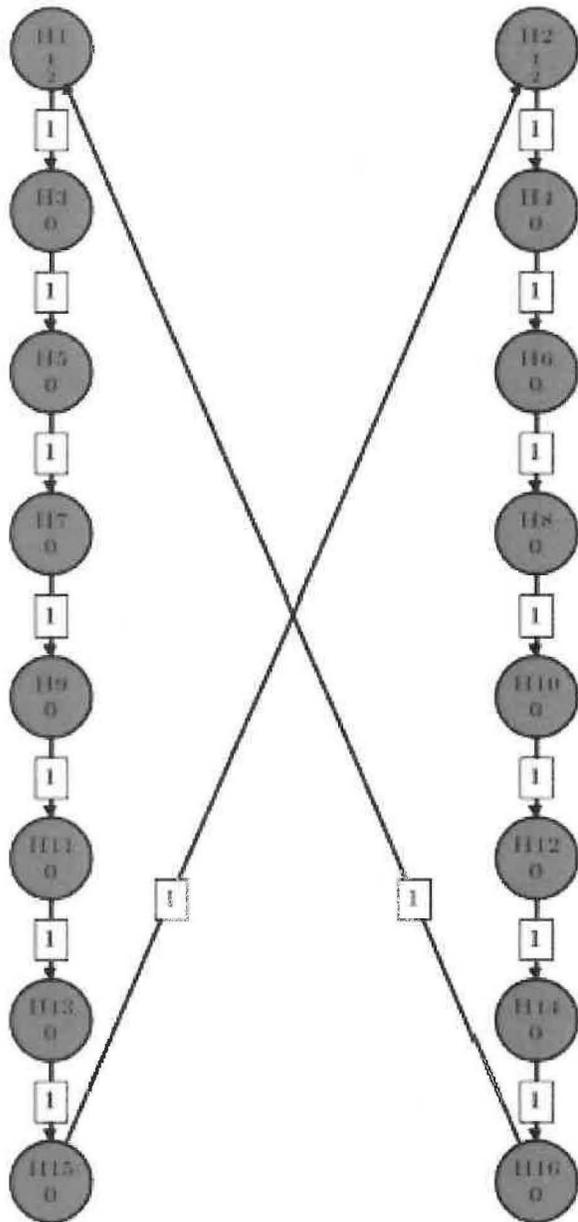
H13: secukinumab 75 mg is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H14: secukinumab 150 mg is not different to placebo regimen with respect to change from baseline in ASQoL at Week 16

H15: secukinumab 75 mg is not different to placebo regimen with respect to ASAS partial remission criteria at Week 16

H16: secukinumab 150 mg is not different to placebo regimen with respect to ASAS partial remission criteria at Week 16

Figure 8. Multiple testing strategy



Source: Excerpted from the Clinical Study Report for Study F2310 (page 3858).

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. Each of the hypotheses (H1 and H2) for the primary objective (ASAS20 at Week 16) for each secukinumab regimen versus placebo will be tested simultaneously at $\alpha/2$. Then based on the rejection of one or both (of H1 and H2), the ASAS40 at Week 16 endpoint will be tested hierarchically for each dose

(through H3 and/or H4). This procedure will continue (pending rejection of the null hypotheses) until H15 and/or H16 are/is rejected, then the respective $\alpha/2$ can be passed on to the other secukinumab regimen's hierarchy of hypotheses, if they were 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 (ASAS20 response at Week 16), 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 20% after 14 weeks was assumed based on the results for the AS population in a historical study. The response on secukinumab was assumed to be 60% in the AS population. For the primary endpoint, ASAS20 in the overall population, 74 subjects per group would yield at least 90% power to detect a treatment difference in the response rates between the secukinumab regimens and placebo with the above assumptions using Fisher's exact test.

Changes in the statistical analysis plan

There was one amendment to the original protocol (May 31, 2013), Amendment 1 (November 22, 2013). The applicant claimed that this amendment was 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 Ankylosing Spondylitis. These endpoints include but are not limited to ASQoL, BASDAI and SF-36. In addition, the analysis was changed to include all patients in the FAS, rather than focusing only on the subset of patients who are TNF α inhibitor naïve, as the FAS would be more representative of the general population of AS patients.

Patient Disposition, Demographic and Baseline Characteristics

A total of 219 patients were randomized and 200 (91%) of patients completed the 16 weeks of active treatment (Table 14). More patients in the placebo group (11%) discontinued treatment compared with the secukinumab treatment groups (7%-8%). The most common reasons for discontinuation were adverse events, which occurred at a slightly higher rate in the placebo group compared with the secukinumab groups. Subject/guardian decision was the second most common reason for discontinuing treatment.

Table 14. Patients' Accountability, N (%) (All Randomized Patients)

Disposition/Reason	SCK	SCK	Placebo n (%)
	75 mg n (%)	150 mg n (%)	

Randomized	73 (100)	72 (100)	74 (100)
Completed Wk16	68 (93)	66 (92)	66 (89)
Discontinued Wk16	5 (7)	6 (8)	8 (11)
Adverse event	2 (3)	5 (7)	4 (6)
Lack of efficacy	0 (0)	0 (0)	1 (1)
Subject/guardian decision	2 (3)	1 (1)	2 (3)
Other	1 (1)	0 (0)	1 (1)

Note: SCK stands for secukinumab.

Source: Reviewer & the Clinical Study Report for Study F2310 (page 107).

The demographic and baseline disease characteristics were generally balanced and comparable between the treatment groups (Table 15). Overall, the average patient in the study was 43 years old, 81 kg in weight, and had 6 years of duration of AS. The majority of patients (96%) were Caucasian and approximately 70% of patients were male. About 61% of patients were naïve to TNF alpha inhibitors and about 12% of patients used methotrexate at baseline.

Table 15. Patients' Demographic and Baseline Characteristics by Treatment

	SCK 75 mg N=73	SCK 150 mg N=72	Placebo N=74
Age (years)			
N	73	72	74
Mean	44	42	44
SD	13	13	13
Median	46	41	44
Min-Max	19-77	20-66	21-77
Gender, n (%)			
Female	22 (30)	26 (36)	18 (24)
Male	51 (70)	46 (64)	56 (76)
Race, n (%)			
White	70 (96)	69 (96)	70 (95)
Black	0 (0)	1 (1)	4 (5)
Asian	3 (4)	2 (3)	0 (0)
Weight (kg)			
N	73	72	74
Mean	81	82	80
SD	17	18	15
Median	80	80	79
Min-Max	51-123	50-134	48-123
BMI (kg/m²)			
N	73	72	73
Mean	28	27	27
SD	6	6	6
Median	28	27	26
Min-Max	17-45	18-44	18-55
Patients global assessment of disease activity (0-100 mm)			
N	73	72	74
Mean	65	68	71
SD	18	17	16
Median	64	68	72
Min-Max	1-99	31-99	28-100
Total back pain (0-100 mm)			
N	73	72	74
Mean	65	66	69
SD	18	17	19
Median	66	68	70
Min-Max	22-97	22-99	0-100

BASFI			
N	73	72	73
Mean	6.0	6.2	6.1
SD	2.1	2.1	2.0
Median	6.3	6.7	6.3
Min-Max	1.0-9.7	1.4-9.9	0.1-9.5
BASDAI			
N	73	72	74
Mean	6.6	6.6	6.8
SD	1.3	1.5	1.3
Median	6.5	6.8	6.9
Min-Max	2.4-9.6	3.2-10.0	4.0-9.5
BASMI (linear)			
N	71	71	70
Mean	3.9	3.6	3.9
SD	1.7	1.9	1.6
Median	3.9	3.6	4.2
Min-Max	0.3-7.8	0.2-7.8	0.4-7.2
hs CRP (mg/L)			
N	73	72	74
Mean	15	26	16
SD	20	50	33
Median	6	8	8
Min-Max	1-86	0-237	1-85
MTX use, n (%)			
No	64 (88)	64 (89)	65 (88)
Yes	9 (12)	8 (11)	9 (12)
Dose of MTX (mg/week)			
N	9	7	9
Mean	13	15	14
SD	3	3	4
Median	15	15	13
Min-Max	10-15	10-20	10-20
Naive to TNF alpha inhibitors, n (%)			
No	28 (38)	28 (39)	29 (39)
Yes	45 (62)	44 (61)	45 (61)
Number of prior TNF alpha inhibitors, n (%)			
0	45 (62)	44 (61)	45 (61)
1	28 (38)	27 (38)	29 (39)
≥2	0 (0)	1 (1)	0 (0)
Time since first diagnosis of ankylosing spondylitis (years)			
N	72	70	73
Mean	5	7	6
SD	7	8	9
Median	3	4	3
Min-Max	0-29	0-33	0-38

Source: Excerpted from the Clinical Study Report for Study F2310 (pages 111- 118).

Results and Conclusions

Primary Efficacy Endpoint – ASAS20 response at Week 16

The analysis of the primary endpoint showed statistically significantly greater ASAS20 responses at Week 16 for the secukinumab 150 mg dosing regimen, but not for the secukinumab 75 mg dosing regimen, compared to placebo. As pre-specified in the protocol, all dropouts prior to Week 16 were treated as non-responders.

There was some dropout prior to Week 16 (8% of active and 11% of placebo) calling for some sensitivity analysis to assess impact of non-responder imputation. But since there were similar number of dropouts due to adverse events (3-7% for active and 6% for placebo), the penalizing non-responder imputation did not seem to give a bias in favor of active arm in the primary analysis. The applicant conducted sensitivity analyses to handle missing data based on multiple imputation and an observed data analysis as in Study F2305. My comments on these analyses in Study F2305 also apply for this study. To assess robustness of the primary analysis with respect to an ITT estimand, I requested that the applicant conduct additional sensitivity analyses including a tipping point analysis. In my opinion, the applicant's worst-case analysis and justification to not provide additional tipping point analyses appears reasonable and resolves our concern with the handling of missing data at Week 16 due to dropout.

The applicant's primary and sensitivity analyses appeared to support efficacy of the secukinumab 150 mg dosing regimen only – there was a statistically significant difference in ASAS20 responses at Week 16 between the secukinumab 150 mg dosing regimen and placebo, but there was not a statistically significant difference between the secukinumab 75 mg dosing regimen and placebo.

Table 16. Applicant's analyses of ASAS20 response at Week 16

	Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
Primary analysis with NRI	SCK 75mg (N=73)	30/73 (41)	vs. Placebo	1.8	(0.9, 3.7)	0.0967
	SCK 150mg (N=72)	44/72 (61)	vs. Placebo	4.4	(2.1, 9.0)	<0.0001
	Placebo (N=74)	21/74 (28)				
Sensitivity analysis with multiple imputation	SCK 75mg (N=73)	(43)	vs. Placebo	1.8	(0.9, 3.6)	0.1176
	SCK 150mg (N=72)	(63)	vs. Placebo	4.2	(2.0, 8.6)	0.0001
	Placebo (N=74)	(31)				
Sensitivity analysis with observed data	SCK 75mg (N=73)	30/67 (45)	vs. Placebo	1.7	(0.8, 3.5)	0.1549
	SCK 150mg (N=72)	44/66 (67)	vs. Placebo	4.5	(2.1, 9.6)	<0.0001
	Placebo (N=74)	21/63 (33)				

Source: Excerpted from the Clinical Study Report for Study F2310 (pages 130, 6264, 6265).

Components of ACR20 response at Week 16

I was able to confirm the results of the applicant's analyses of the components of the primary endpoint, ASAS20 response at Week 16. Analyses of all the components of ASAS were statistically significant for the secukinumab 150 mg regimen compared to placebo and there was no single component driving the efficacy in terms of ASAS20 response.

Table 17. Applicant's analysis of ASAS20 components at Week 16

	Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
Patient's global	SCK 75mg (N=73)	67	-20.9	vs. Placebo	-8.0 (4.1)	(-16.1, 0.0)	0.0506

assessment of disease activity	SCK 150mg (N=72)	67	-27.7	vs. Placebo	-14.8 (4.0)	(-22.8, -6.9)	0.0003
	Placebo (N=74)	64	-12.9				
Patient's assessment of total spinal pain	SCK 75mg (N=73)	67	-19.4	vs. Placebo	-8.4 (4.1)	(-16.4, -0.5)	0.0384
	SCK 150mg (N=72)	67	-28.5				
	Placebo (N=74)	64	-10.9				
Inflammation (mean of questions 5 and 6 of the BASDAI)	SCK 75mg (N=73)	67	-2.2	vs. Placebo	-1.4 (0.4)	(-2.2, -0.6)	0.0007
	SCK 150mg (N=72)	67	-2.5				
	Placebo (N=74)	64	-0.8				
BASFI	SCK 75mg (N=73)	67	-1.7	vs. Placebo	-1.0 (0.3)	(-1.6, -0.3)	0.0029
	SCK 150mg (N=72)	67	-2.2				
	Placebo (N=74)	64	-0.7				

Source: Excerpted from the Clinical Study Report for Study F2310 (pages 533, 549, 565, 581).

Note: LSmeans and 95% CIs were based on the MMRM analysis.

In summary, the study showed statistically significant evidence in favor of the secukinumab 150 mg dosing regimen for the ASAS20 response at Week 16 (primary efficacy endpoint), but did not show statistically significant evidence in favor of secukinumab 75 mg. Several sensitivity analyses were conducted on the primary efficacy endpoint 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 continuous responder analyses on the continuous endpoints to assess the impact of missing data due to dropout. All p-values for the secondary endpoints presented here are nominal. Although some nominal p-values for secondary endpoints in the hierarchy comparing the secukinumab 75 mg dosing regimen vs. placebo were smaller than 0.025, after adjusting for multiplicity, none of these analyses were statistically significant.

Key Secondary Endpoints – ASAS40 response at Week 16

The applicant's results of ASAS40 analyses are summarized in Table 18. The same statistical method in the ASAS20 analysis was employed for this endpoint. Treatment with the secukinumab 150 mg dosing regimen resulted in a statistically significantly higher ASAS40 response rate than treatment with placebo.

Table 18. Applicant's analyses of ASAS40 response at Week 16

Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
SCK 75mg (N=73)	19/73 (26)	vs. Placebo	3.0	(1.2, 7.5)	0.0194
SCK 150mg (N=72)	26/72 (36)	vs. Placebo	5.1	(2.1, 12.4)	0.0004
Placebo (N=74)	8/74 (11)				

Source: Excerpted from the Clinical Study Report for Study F2310 (page 333).

Key Secondary Endpoints - change from baseline in hsCRP at Week 16

The mean change in hsCRP at Week 16 in patients treated with the secukinumab 150 mg dosing regimen was statistically significantly lower compared to patients treated with placebo (Table 19). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg dosing regimen and placebo (Figure 9).

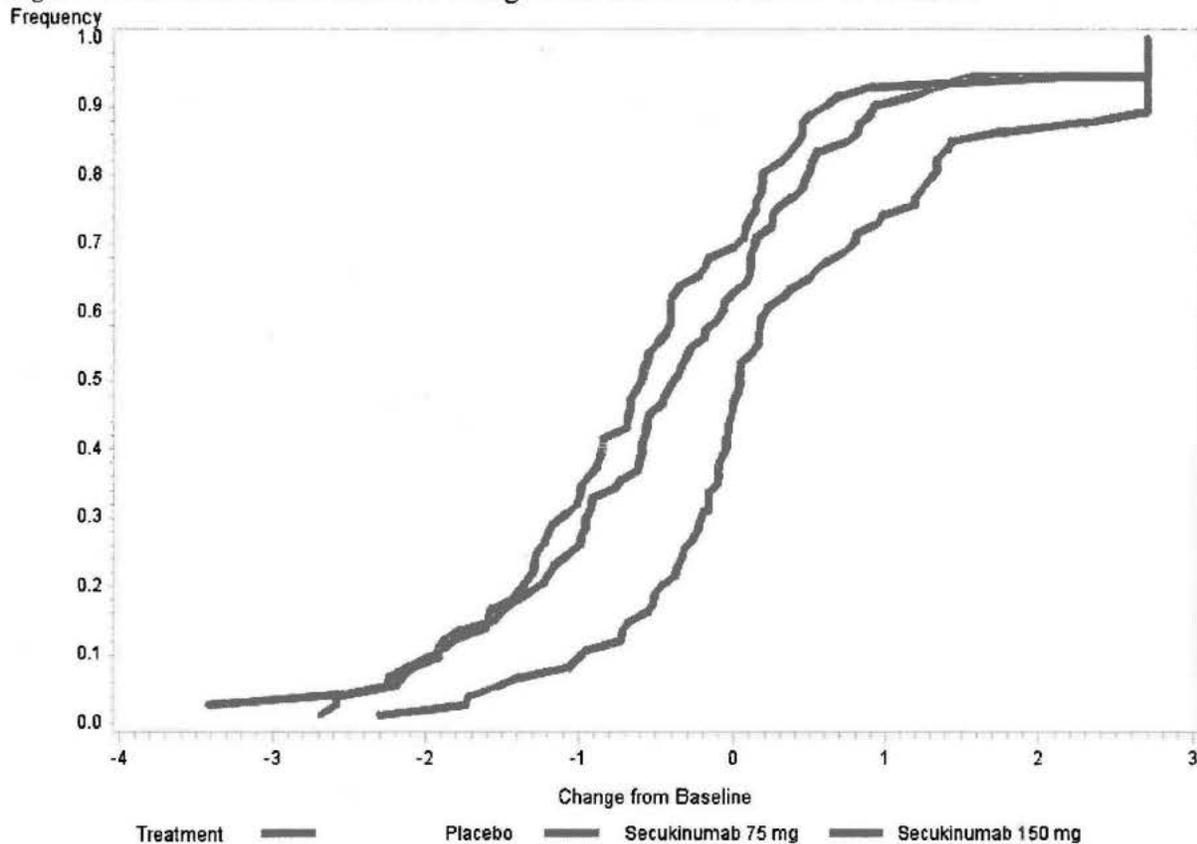
Table 19. Applicant's analysis of change from baseline in hsCRP at Week 16

Treatment Group	n	Exp (LS Mean Change)	Comparison	Ratio	95% Confidence Interval	p-value
SCK 75mg (N=73)	69	0.61	vs. Placebo	0.54	(0.41, 0.71)	<0.0001
SCK 150mg (N=72)	68	0.55	vs. Placebo	0.49	(0.37, 0.64)	<0.0001
Placebo (N=74)	66	1.13				

Source: Excerpted from the Clinical Study Report for Study F2310 (page 385).

Note: log(hsCRP) was used in the MMRM analysis and the LSmean difference were back-transformed (exponentiation) to the ratio between treatment groups.

Figure 9. Cumulative distribution of change from baseline in hsCRP at Week 16



Note: Missing data were imputed with the worst score.
Source: Reviewer

Key Secondary Endpoints – ASAS5/6 response at Week 16

The applicant’s results of ASAS5/6 analyses are summarized in Table 20. The same statistical method in the ASAS20 analysis was employed for this endpoint. Treatment with the secukinumab 150 mg dosing regimen resulted in a statistically significantly higher ASAS5/6 response rate than treatment with placebo.

Table 20. Applicant’s analyses of ASAS5/6 response at Week 16

Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
SCK 75mg (N=73)	25/73 (34)	vs. Placebo	6.1	(2.3, 16.3)	0.0003
SCK 150mg (N=72)	31/72 (43)	vs. Placebo	9.2	(3.5, 24.1)	<0.0001
Placebo (N=74)	6/74 (8)				

Source: Excerpted from the Clinical Study Report for Study F2305 (page 434).

Key Secondary Endpoints - change from baseline in BASDAI at Week 16

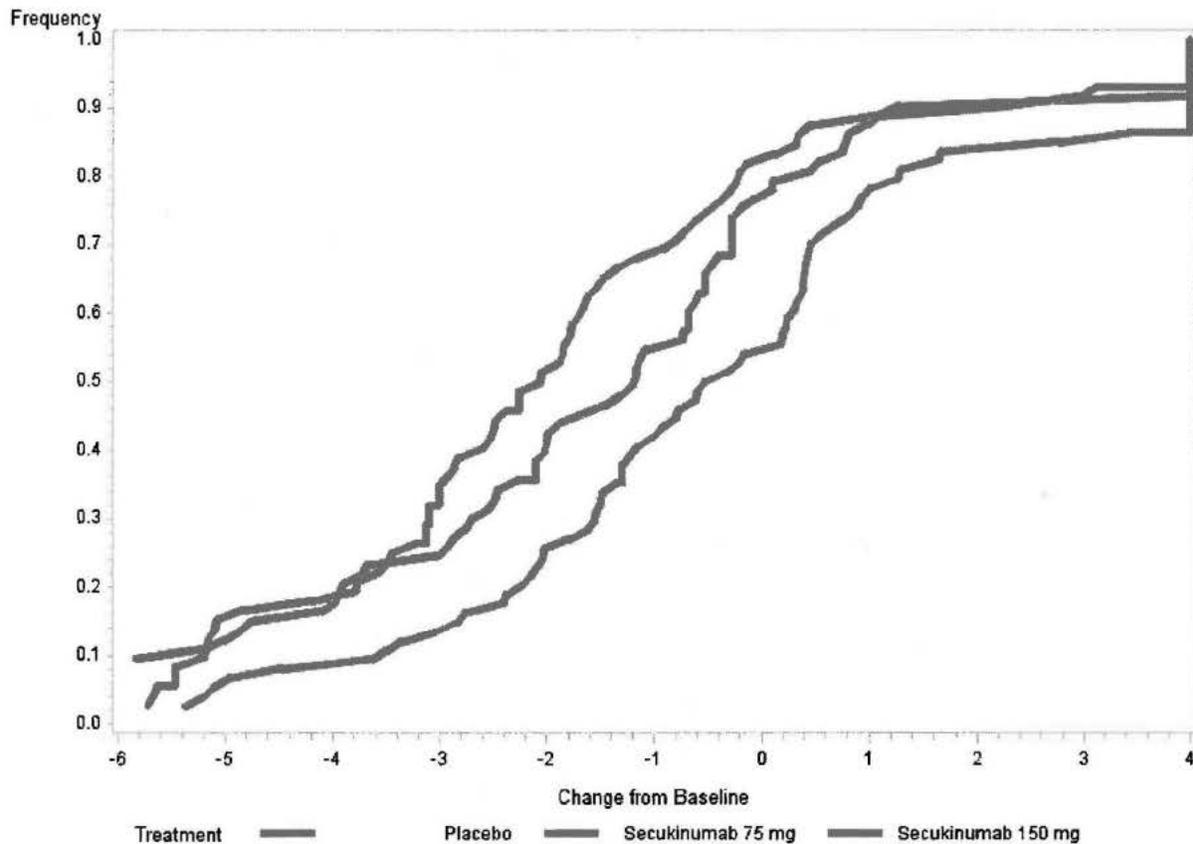
The mean change in BASDAI at Week 16 in patients treated with the secukinumab 150 mg dosing regimen was statistically significantly lower compared to patients treated with placebo (Table 21). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg dosing regimen and placebo (Figure 10).

Table 21. Applicant’s analysis of change from baseline in BASDAI at Week 16

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=73)	67	-1.92	vs. Placebo	-1.07 (0.35)	(-1.77, -0.37)	0.0028
SCK 150mg (N=72)	67	-2.19	vs. Placebo	-1.34 (0.35)	(-2.04, -0.65)	<0.0001
Placebo (N=74)	64	-0.85				

Source: Excerpted from the Clinical Study Report for Study F2310 (page 347).

Figure 10. Cumulative distribution of change from baseline in BASDAI at Week 16



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 16

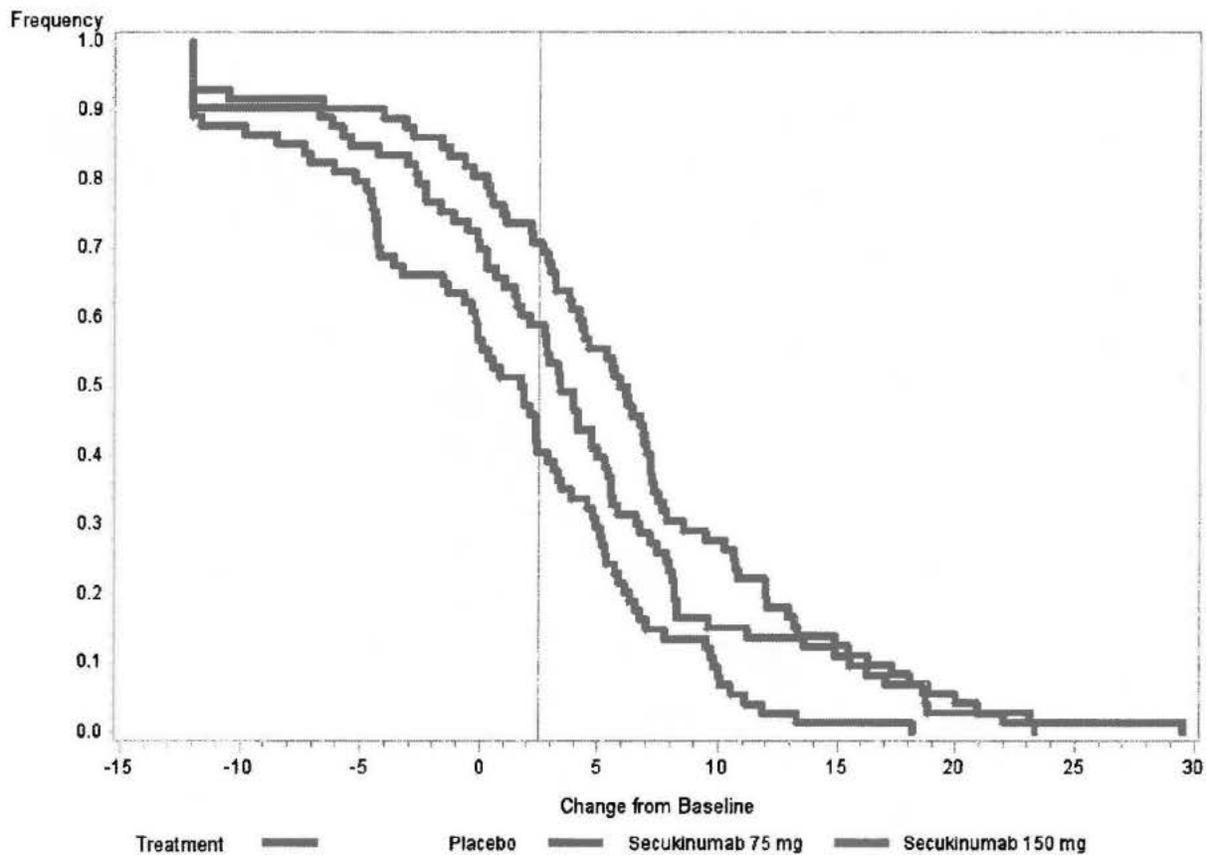
The mean change in SF36-PCS at Week 16 in patients treated with the secukinumab 150 mg dosing regimen was statistically significantly lower compared to patients treated with placebo (Table 22). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg dosing regimen and placebo (Figure 11).

Table 22. Applicant’s analysis of change from baseline in SF36-PCS at Week 16

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=73)	66	4.77	vs. Placebo	2.84 (1.11)	(0.66, 5.03)	0.0110
SCK 150mg (N=72)	67	6.06	vs. Placebo	4.14 (1.11)	(1.96, 6.32)	0.0002
Placebo (N=74)	66	1.92				

Source: Excerpted from the Clinical Study Report for Study F2310 (page 423).

Figure 11. Cumulative distribution of change from baseline in SF36-PCS at Week 16



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 ASQoL at Week 16

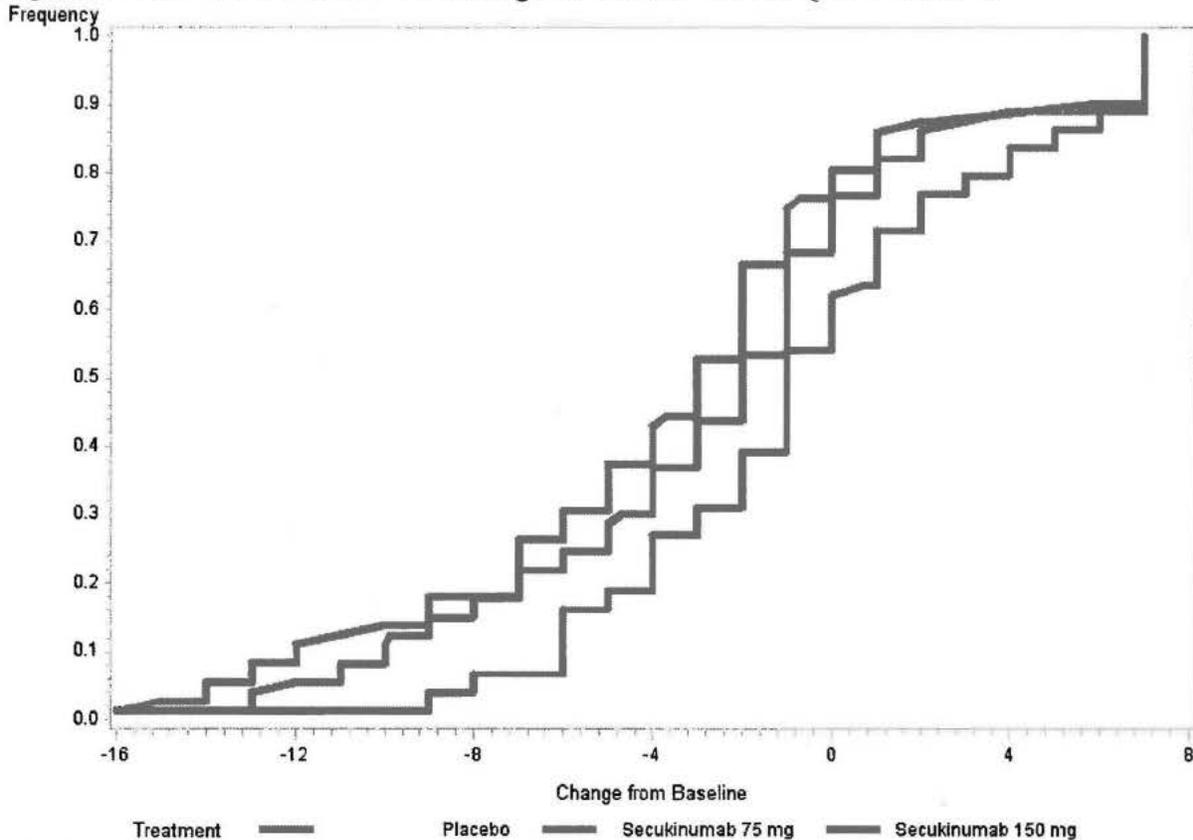
The mean change in ASQoL at Week 16 in patients treated with the secukinumab 150 mg dosing regimen was statistically significantly lower compared to patients treated with placebo (Table 23). My cumulative distribution curves with worst score imputation for missing data showed separation of the curves between the secukinumab 150 mg dosing regimen and placebo (Figure 12).

Table 23. Applicant's analysis of change from baseline in ASQoL at Week 16

Treatment Group	n	LS Mean Change	Comparison	Mean Difference (SE)	95% Confidence Interval	p-value
SCK 75mg (N=73)	66	-3.33	vs. Placebo	-1.96 (0.75)	(-3.43, -0.48)	0.0096
SCK 150mg (N=72)	66	-4.00	vs. Placebo	-2.63 (0.74)	(-4.09, -1.16)	0.0005
Placebo (N=74)	66	-1.37				

Source: Excerpted from the Clinical Study Report for Study F2310 (page 519).

Figure 12. Cumulative distribution of change from baseline in ASQoL at Week 16



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 – ASAS partial remission at Week 16

The applicant’s results of ASAS partial remission analyses are summarized in Table 24. The same statistical method in the ASAS20 analysis was employed for this endpoint. Treatment with the secukinumab regimens failed to show statistically significantly higher ASAS partial remission rate than treatment with placebo (p-value > 0.025), although there were favorable trends.

Table 24. Applicant’s analyses of ASAS partial remission at Week 16

Treatment Group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
SCK 75mg (N=73)	11/73 (15)	vs. Placebo	4.3	(1.1, 16.2)	0.0325
SCK 150mg (N=72)	10/74 (14)	vs. Placebo	3.9	(1.0, 15.0)	0.0471
Placebo (N=74)	3/74 (4)				

Source: Excerpted from the Clinical Study Report for Study F2310 (page 410).

Long-term efficacy analysis – observed ASAS20 response over 52 weeks

I conducted a descriptive analysis to numerically compare the secukinumab 75 mg and 150 mg dosing regimens with regard to ASAS20 over 52 weeks without statistical hypothesis testing. Observed ASAS20 responses on the two dosing regimens were similar over time, with slightly greater response rates on the 150 mg dose.

Table 25. Reviewer’s analysis of observed ASAS20 response over 52 weeks

Week	SCK 75 mg	SCK 150 mg
	n/N (%)	n/N (%)
1	19/68 (28)	15/70 (21)
2	25/67 (37)	28/70 (40)
4	23/66 (35)	37/70 (53)
8	28/71 (39)	38/70 (54)
12	38/69 (55)	42/71 (59)
16	32/67 (48)	41/69 (59)
20	30/67 (45)	44/66 (67)
24	38/68 (56)	43/65 (66)
28	34/67 (51)	44/65 (68)
32	42/68 (62)	47/62 (76)
40	44/66 (67)	46/63 (73)
52	44/64 (69)	44/63 (70)

Source: Reviewer

In summary, study data demonstrated that the secukinumab 150 mg was superior compared to placebo with respect to the primary endpoint of ASAS20 response at Week 16 and most of the secondary endpoints at Week 16 in the multiplicity adjustment hierarchy – ASAS40 response, hsCRP, ASAS5/6 response, BSADAI, SF-36 PCS, and ASQoL. However, study data failed to demonstrate that secukinumab 75 mg was superior compared to placebo with respect to the primary endpoint and all the secondary endpoints at Week 16. Analyses of these endpoints for the secukinumab 150 mg dose compared to placebo remained statistically significant in sensitivity analyses using different approaches to handle missing data due to dropout.

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 ASAS20 response at Week 16, based on integrated data from Studies F2305 and F2310, for the secukinumab 150 mg dose. The subgroup analyses were largely consistent with the results from the overall population in terms of ASAS20 response, although there was some evidence of a quantitative interaction between treatment and race subgroup –Whites showed smaller, though still statistically significant, effects of secukinumab treatment relative to Non-Whites (Table 26 & Figure 13).

Table 26. Reviewer's Subgroup Analyses on ASAS20 response at Week 16 – Studies F2305 and F2310 pooled

	SCK 150mg		Placebo		
	N	n(%)	N	n(%)	Odds ratio (95% CI)
Overall ($p < 0.001$)^a					
	197	120(61)	196	56(29)	4.0 (2.6, 6.2)
Sex ($p = 0.60$)^b					
Male	130	78(60)	141	38(27)	4.3 (2.6, 7.4)
Female	67	42(63)	55	18(33)	3.3 (1.6, 7.2)
Age ($p = 0.12$)^b					
<40 yrs	101	67(66)	88	24(27)	5.7 (3.0, 10.8)
≥40 yrs	96	53(55)	108	32(30)	2.9 (1.6, 5.3)
Region ($p = 0.25$)^b					
ROW ^c	182	112(62)	183	55(30)	3.8 (2.4, 5.9)
USA	15	8(53)	13	1(8)	17.0 (1.5, 188.1)
Race ($p = 0.02$)^b					
White	138	79(57)	151	47(31)	3.1 (1.9, 5.0)
N-White	59	41(69)	45	9(20)	10.2 (3.8, 27.0)
TNF-naive ($P = 0.75$)^b					
Y	136	91(67)	134	43(32)	4.2 (2.6, 7.1)
N	61	29(48)	62	13(21)	4.1 (1.8, 9.3)
Time Since AS Diagnosis ($P = 0.36$)^b					
<5 yrs	138	87(63)	130	36(28)	4.6 (2.7, 7.8)
≥5 yrs	59	33(56)	66	20(30)	3.0 (1.4, 6.4)

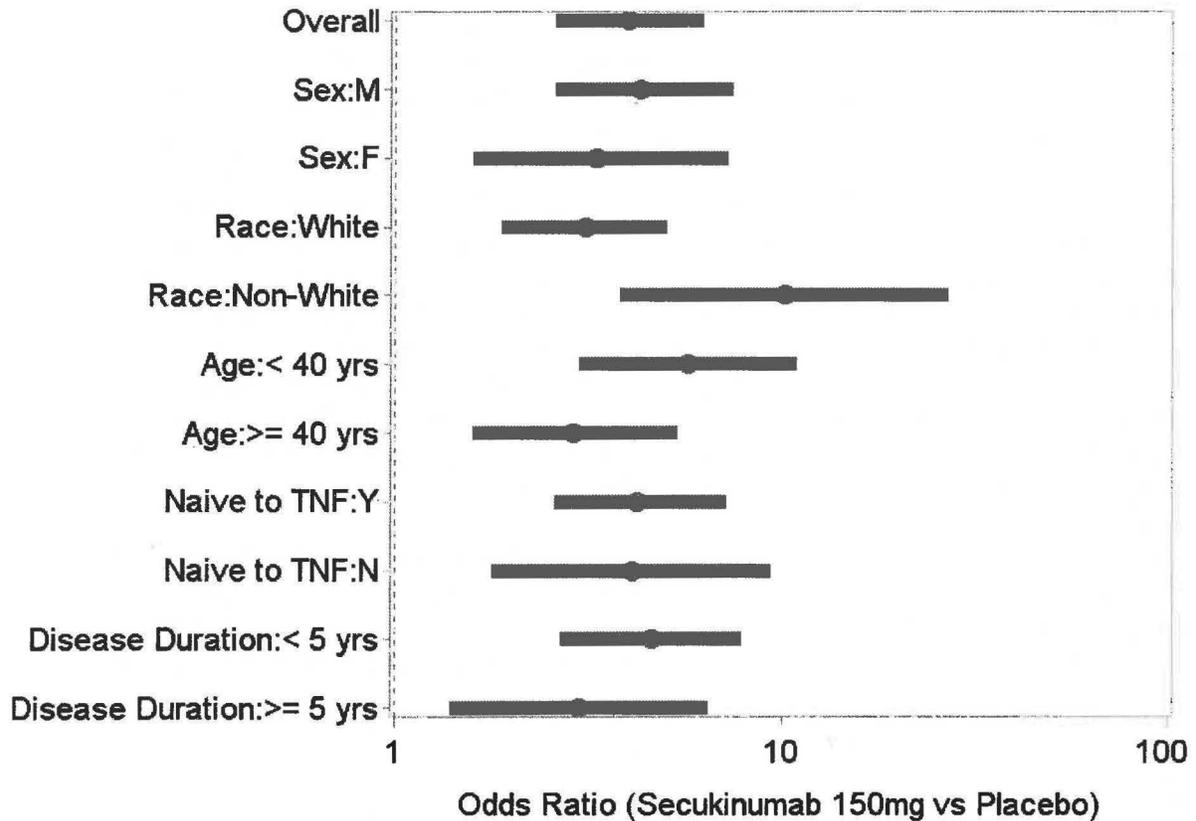
Source: Reviewer

[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 Austria, Belgium, Bulgaria, Canada, Czech Rep, Finland, France, Germany, Italy, Mexico, Netherlands, Peru, Russian Federation, Singapore, Spain, Switzerland, Taiwan, Turkey, and United Kingdom.

Figure 13. Reviewer’s Subgroup Analyses on ASAS20 response at Week 16 – Studies F2305 and F2310 pooled



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During my review of the application, several potential statistical issues were identified:

- Potential Effect of Missing Data on Reliability of Efficacy Results
- Efficacy of Proposed Maintenance Doses Given the Presence of Loading Doses
- Evidence to Support Proposed Dosing Recommendations

The first issue was the potential effect of missing data. For the analysis of the primary endpoint, the applicant pre-specified an approach that considered patients who dropped out to be non-responders. The use of non-responder imputation for patients who discontinued study

treatment prior to Week 16 implies that the primary analysis evaluated a composite endpoint defined by staying on treatment and achieving an ASAS20 response at Week 16. However, it is also important to evaluate the ITT estimand, i.e., the difference in ASAS20 response at Week 16 *regardless of adherence*. Therefore, the applicant conducted a sensitivity analysis with missing-at-random multiple imputation, an analysis with observed data, and a worst case analysis in response to an FDA request for tipping point analyses. Results from the sensitivity analyses suggested that secukinumab is efficacious notwithstanding missing data due to dropout.

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 16 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 ASAS20 responses as the secukinumab treatment groups (see figures in the Appendix).

Finally, I believe that there is sufficient evidence of efficacy to support the proposed 150 mg dose of secukinumab. The 150 mg dose demonstrated benefit with respect to the primary endpoint ASAS20 and several important secondary endpoints in two independent placebo-controlled clinical trials. The applicant is proposing recommended dosing with the 150 mg dose in AS patients.

5.2 Collective Evidence

In the two phase 3 studies F2305 and F2310 reviewed, the analysis of the predefined primary efficacy endpoint, ASAS20 at Week 16, was statistically significant for the secukinumab 150 mg dose. In Study F2305, the ASAS20 response rates were 60%, 61%, and 29% for secukinumab 75 mg, 150 mg, and placebo, respectively. In Study F2310, which included the proposed SC loading dose (rather than the IV loading dose used in Study F2305), the response rates were 41%, 61%, and 28% for secukinumab 75 mg, 150 mg, and placebo, respectively.

More specifically, the efficacy data from Study F2305 provided statistical evidence of efficacy for the secukinumab 75 mg and 150 mg doses for treatment of AS based on ASAS20, the primary endpoint, and all the key secondary endpoints, including ASAS40, hsCRP, ASAS5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission. The efficacy data from Study F2310 provided statistical evidence of efficacy for the secukinumab 150 mg dose based on the primary endpoint of ASAS20 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 the primary endpoint and any of the secondary endpoints. With the secukinumab 150 mg dose, analyses of

ASAS40, hsCRP, ASAS5/6, BASDAI, SF-36 PCS, and ASQoL were statistically significant, but analysis of ASAS partial remission was 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 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 dose for treating AS.

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. I recommend the removal of (b) (4)

[Redacted]

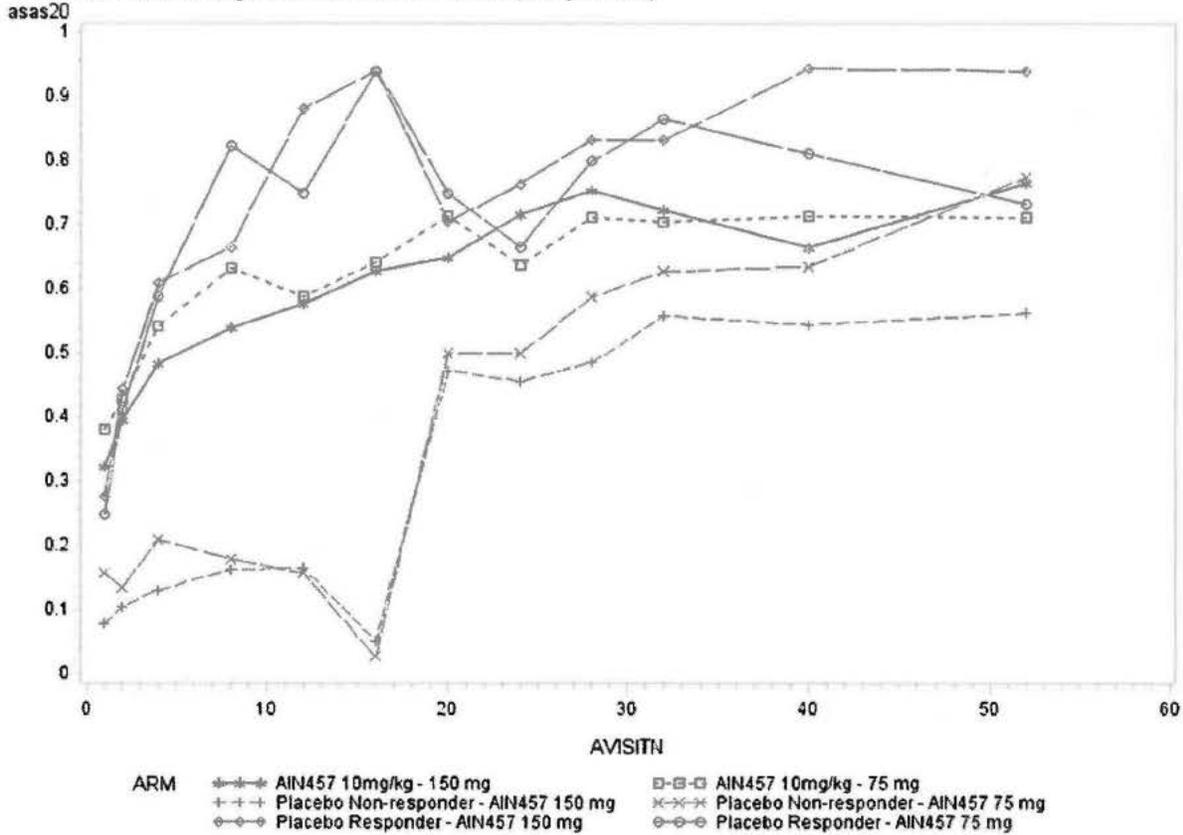
[Large Redacted Block] (b) (4)

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APPENDICES

Exploration for loading dose effects:

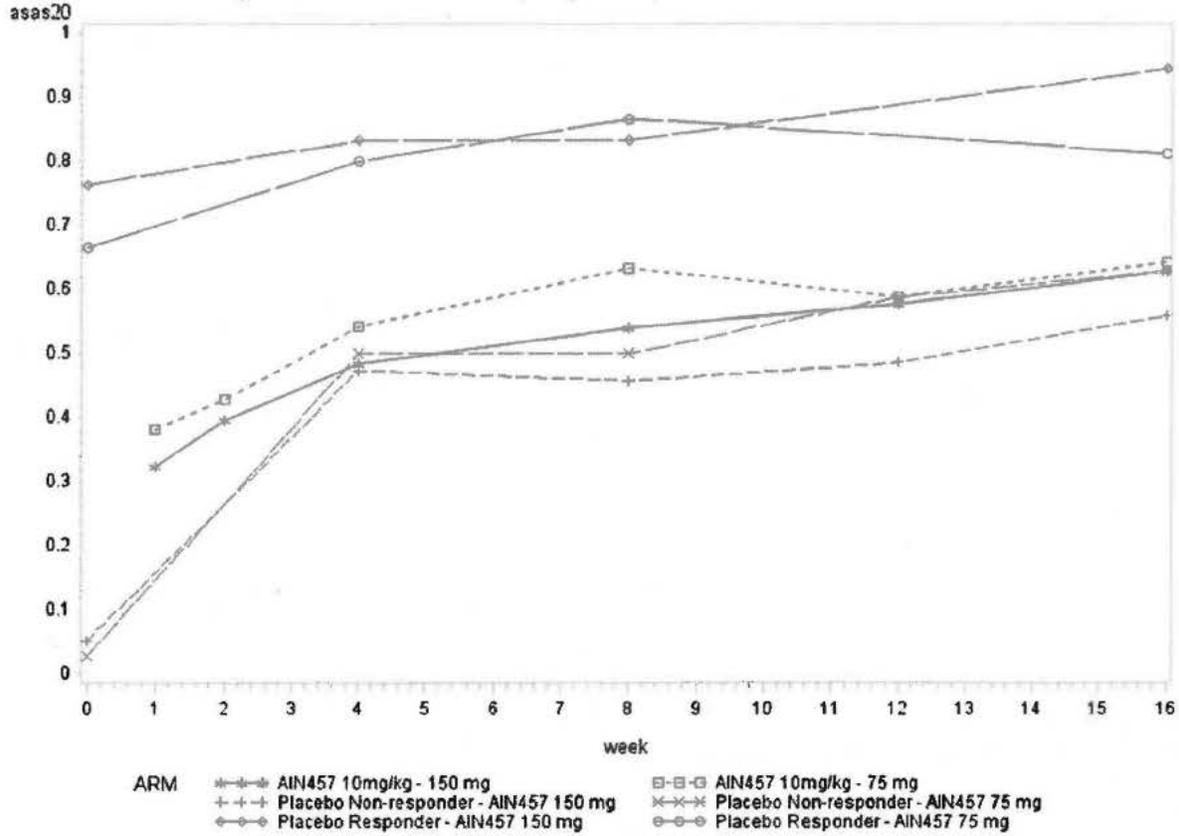
Observed ASAS20 response rates over 52 weeks (Study F2305)



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	39/120 (33)	45/118 (38)	3/38 (8)	6/38 (16)	5/18 (28)	4/16 (25)
2	48/121 (40)	51/119 (43)	4/38 (11)	5/37 (14)	8/18 (44)	7/17 (41)
4	60/124 (48)	65/120 (54)	5/38 (13)	8/38 (21)	11/18 (61)	10/17 (59)
8	67/124 (54)	76/120 (63)	6/37 (16)	7/39 (18)	12/18 (67)	14/17 (82)
12	70/121 (58)	70/119 (59)	6/36 (17)	6/38 (16)	15/17 (88)	12/16 (75)
16	76/121 (63)	74/115 (64)	2/38 (5)	1/36 (3)	16/17 (94)	16/17 (94)
20	78/120 (65)	83/116 (72)	18/38 (47)	19/38 (50)	12/17 (71)	12/16 (75)
24	81/113 (72)	72/113 (64)	16/35 (46)	18/36 (50)	13/17 (76)	5/15 (67)
28	83/110 (75)	79/111 (71)	17/35 (49)	20/34 (59)	15/18 (83)	12/15 (80)
32	84/116 (72)	79/112 (71)	19/34 (56)	22/35 (63)	15/18 (83)	13/15 (87)

40	74/111 (67)	80/112 (71)	18/33 (55)	21/33 (64)	17/18 (94)	13/16 (81)
52	79/103 (77)	77/108 (71)	18/32 (56)	24/31 (77)	16/17 (94)	11/15 (73)

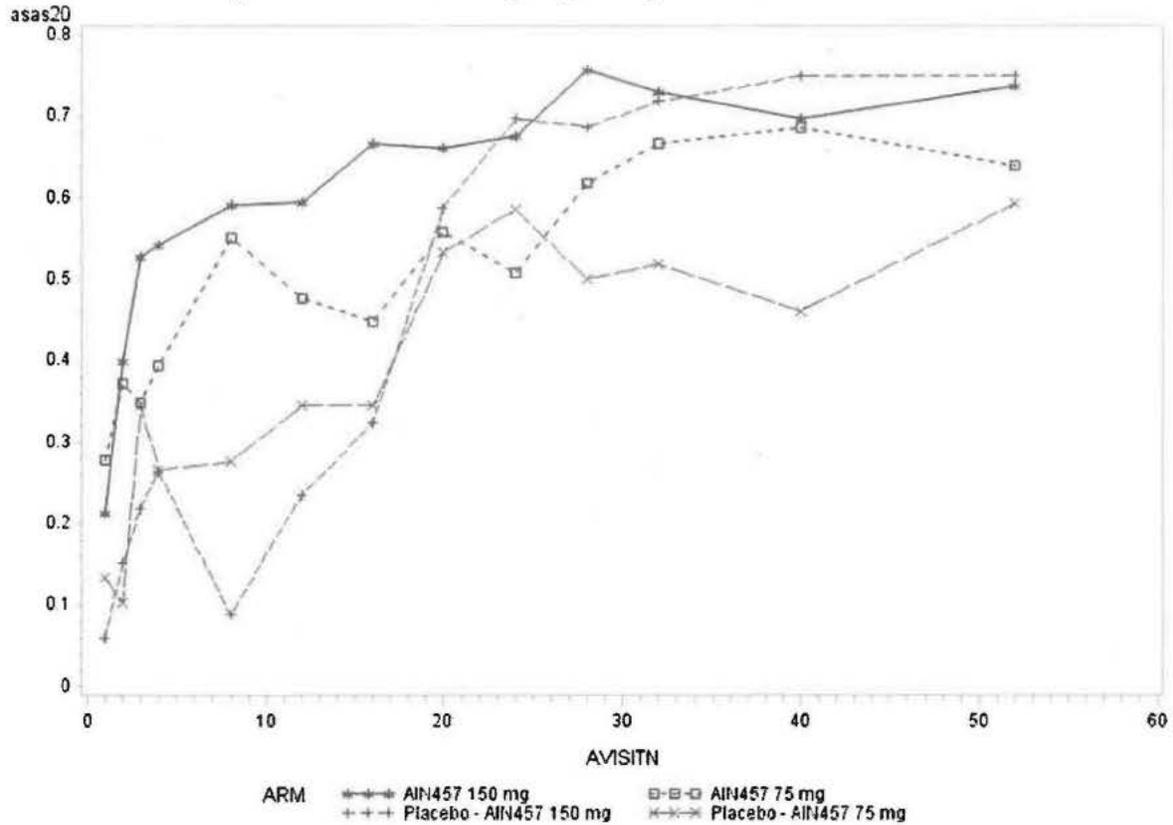
Observed ASAS20 response rates over 16 weeks (Study F2305)



Note: Data for the placebo group were shifted 16 weeks to the left.

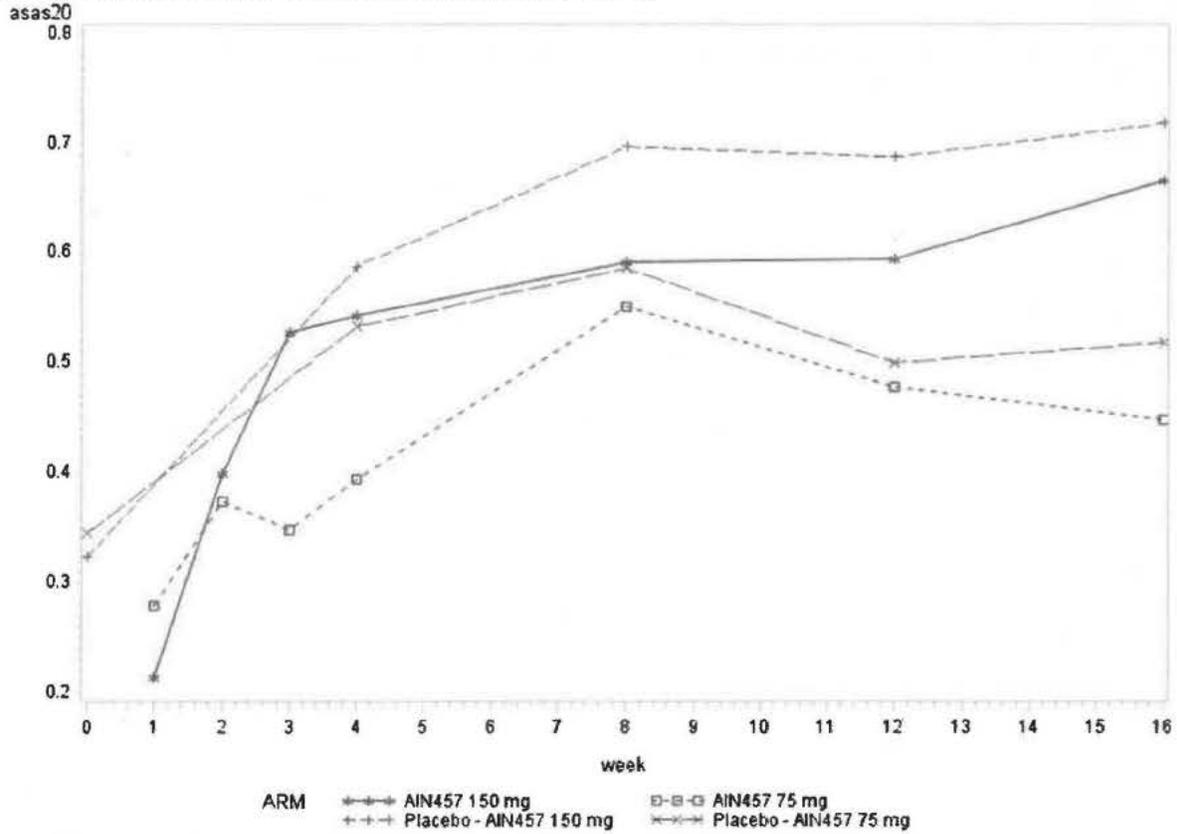
WEEK	AIN457 10mg/kg - 150 mg n/N (%)	AIN457 10mg/kg - 75 mg n/N (%)	Placebo Non-responder - AIN457 150 mg n/N (%)	Placebo Non-responder - AIN457 75 mg n/N (%)	Placebo Responder - AIN457 150 mg n/N (%)	Placebo Responder - AIN457 75 mg n/N (%)
0	-	-	2/38 (5)	1/36 (3)	13/17 (76)	10/15 (67)
1	39/120 (33)	45/118 (38)	-	-	-	-
2	48/121 (40)	51/119 (43)	-	-	-	-
4	60/124 (48)	65/120 (54)	18/38 (47)	19/38 (50)	15/18 (83)	12/15 (80)
8	67/124 (54)	76/120 (63)	16/35 (46)	18/36 (50)	15/18 (83)	13/15 (87)
12	70/121 (58)	70/119 (59)	17/35 (49)	20/34 (59)	-	-
16	76/121 (63)	74/115 (64)	19/34 (56)	22/35 (63)	17/18 (94)	13/16 (81)

Observed ASAS20 response rates over 52 weeks (Study F2310)



AVISITN	AIN457 150 mg n/N (%)	AIN457 75 mg n/N (%)	Placebo - AIN457 150 mg n/N (%)	Placebo - AIN457 75 mg n/N (%)
1	15/70 (21)	19/68 (28)	2/33 (6)	4/30 (13)
2	28/70 (40)	25/67 (37)	5/33 (15)	3/29 (10)
3	37/70 (53)	23/66 (35)	7/32 (22)	10/29 (34)
4	38/70 (54)	28/71 (39)	9/34 (26)	8/30 (27)
8	42/71 (59)	38/69 (55)	3/34 (9)	8/29 (28)
12	41/69 (59)	32/67 (48)	8/34 (24)	10/29 (34)
16	44/66 (67)	30/67 (45)	11/34 (32)	10/29 (34)
20	43/65 (66)	38/68 (56)	20/34 (59)	16/30 (53)
24	44/65 (68)	34/67 (51)	23/33 (70)	17/29 (59)
28	47/62 (76)	42/68 (62)	22/32 (69)	15/30 (50)
32	46/63 (73)	44/66 (67)	23/32 (72)	14/27 (52)
40	44/63 (70)	44/64 (69)	24/32 (75)	12/26 (46)
52	45/61 (74)	39/61 (64)	24/32 (75)	19/27 (59)

Observed ASAS20 response rates over 16 weeks (Study F2310)



Note: Data for the placebo group were shifted 16 weeks to the left.

WEEK	AIN457 150 mg n/N (%)	AIN457 75 mg n/N (%)	Placebo - AIN457 150 mg n/N (%)	Placebo - AIN457 75 mg n/N (%)
0	-	-	11/34 (32)	10/29 (34)
1	15/70 (21)	19/68 (28)	-	-
2	28/70 (40)	25/67 (37)	-	-
3	37/70 (53)	23/66 (35)	-	-
4	38/70 (54)	28/71 (39)	20/34 (59)	16/30 (53)
8	42/71 (59)	38/69 (55)	23/33 (70)	17/29 (59)
12	41/69 (59)	32/67 (48)	22/32 (69)	15/30 (50)
16	44/66 (67)	30/67 (45)	23/32 (72)	14/27 (52)

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/s/

YONGMAN KIM
12/11/2015

GREGORY P LEVIN
12/11/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125504Orig1s002

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA	125504 Supplement-02
Submission Date	03/23/2015
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)(1); 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	Ankylosing Spondylitis (AS)
Dosage Regimen	The recommended dosing regimen is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4.

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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-02 on 03/23/2015 seeking the approval of COSENTYX for the treatment of ankylosing spondylitis (AS) with the proposed dosing regimen of “150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4”.

A total of three clinical trials in AS patients have been submitted. Study A2209 is a Phase 2, randomized, double-blind, placebo controlled, proof-of-concept study in AS patients. Studies F2305 and F2310 are Phase 3, randomized, double-blind, placebo-controlled, multicenter studies in AS patients to demonstrate the efficacy of secukinumab at Week 16.

1.1 Recommendations

From a Clinical Pharmacology perspective, the application is acceptable for approval for the treatment active AS 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-02 on 03/23/2015 seeking the approval of COSENTYX for the treatment of AS with the proposed dosing regimen of “150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4”.

The AS clinical development program includes one Phase 2 proof-of-concept study and two Phase 3 confirmatory studies in AS patients.

Pharmacokinetics

The PK properties of secukinumab in AS patients were similar to those in PsO and plaque psoriasis (PsA) patients.

Population PK analysis indicated that body weight is the only significant covariate (absolute change > 20%) affecting secukinumab PK in AS, which was consistent with the findings in PsO and PsA. Methotrexate did not appear to influence secukinumab PK significantly.

Exposure-Response Relationship for Efficacy

The efficacy of secukinumab in AS was evaluated in the two pivotal, placebo-controlled Phase 3 studies (Studies F2310 and F2305). Following SC150mg-SC150mg, the ASAS20 response rates at Week 16 are significantly higher than placebo, while SC75mg-SC75 mg did not produce significantly higher response rate. Comparable response rates between IV loading regimen and SC 75 or 150 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 C_{min} at Week 16 in Study F2310, the exposure-response curve flattens at C_{min} levels that are higher than 25 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC150 mg-SC150 mg dosing regimen at Week 16. Increase of the C_{min} beyond 25 mcg/mL induces limited improvement in ASAS20 response rates. A trend was observed for increased responses with higher C_{min} concentrations for ASAS40/5-6 response rates, BASDAI and SF36-PCS.

Exposure-Response Relationship for Safety

Exposure-response relationships from Phase 3 studies (Studies F2310 and F2305) showed no effect of exposure on the occurrence of any AE, any SAE, and upper respiratory tract infections. A trend for increased rates of for infections and infestations, nasopharyngitis and oral herpes with higher C_{min} was observed.

Dose Selection

During the clinical development of secukinumab, the SC or IV loading doses followed by SC maintenance doses were evaluated in AS 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 ~16 weeks or longer. The anti-secukinumab antibody rate appeared comparable in patients with loading doses (n=1) and without loading doses (patients who switched from placebo to secukinumab, n=2). The placebo patients who were randomized to secukinumab treatment (without loading doses) appeared to have similar responses in ASAS20 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 16 (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

The incidence of immunogenicity was low (<1%) 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

Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the proinflammatory cytokine 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-02 on 03/23/2015 seeking the approval of COSENTYX for the treatment of AS with the proposed dosing regimen of “150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing 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	A2209	AS (n=60)	Randomized, two-part, double-blind, placebo controlled	Part 1: 2×IV 10 mg/kg 2×IV Placebo Part 2: 2×IV 0.1 mg/kg 2×IV 1.0 mg/kg 2×IV 10 mg/kg
	A2209 E1	AS (n=39)	Non-randomized, open label, extension study	IV 3 mg/kg q4w until Week 52
Pivotal Phase 3 studies	F2305	AS (n=371)	Randomized, double-blind, placebo control	IV 10 mg/kg at Wks 0, 2 and 4, then SC 75 or 150 mg q4w at Wk 8

(primary endpoint analysis at Wk 16)				Placebo at Wks 0, 2 and 4, then SC q4w at Wks 8 and 12; non-responders 75 mg or 150 mg SC q4w
	F2310	AS (n=219)	Randomized, double-blind, placebo control	SC 75 or 150 mg at Wks 0, 1, 2 and 3, then q4w at Wk 4 SC placebo at Wks 0, 1, 2 and 3 then q4w at Wk 4; At week 16 start 75 mg or 150 mg SC q4w.

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 AS.

2.3.3 What are the proposed dosages and routes of administration?

The proposed dosage for the treatment of AS is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4.

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 AS patients.

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 A2209, the primary efficacy endpoint is ASAS20 response (Part 1) and BASDAI score (Part 2) at Week 6. In the Phase 3 confirmatory studies, Studies F2305 and F2310, the primary efficacy endpoint is ASAS20 response at Week 16 and the secondary efficacy endpoints are ASAS 40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission at Week 16. Study F2305 also includes analysis of MRIs of the sacroiliac joints on a subset of TNF-naïve patients.

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 AS. 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 effectiveness?

There appears a dose/exposure-response relationship for ASAS20 response rate of secukinumab in AS patients.

The efficacy of secukinumab in AS was evaluated in the two pivotal, placebo-controlled Phase 3 studies (Studies F2310 and F2305) (Figure 1). In Study F2310, the ASAS 20 response rates at Week 16 for SC150mg-SC150 mg are significantly higher than placebo, while SC75mg-SC75 mg did not produce significantly higher response rate: 61.1% for SC150mg-SC150 mg ($p=0.0001$ vs placebo); 41.1% for SC75mg-SC75 mg ($p=0.0967$ vs placebo); 28.4% for placebo. In Study F2305, both dosing regimens produced significantly higher ASAS 20 response rates compared with placebo at Week 16: 60.8% for IV10 mg/kg-SC150mg and 59.7% for IV10 mg/kg-SC75 mg vs 28.7% for placebo ($p<0.0001$ for both comparisons vs placebo). Comparable response rates between IV 10 mg/kg-SC 150mg and IV10 mg/kg-SC75 mg should be due to the high exposure from the IV loading regimen given during the first month. Similar ASAS20 response rates of IV loading dose regimen and SC150mg-SC150 mg regimen indicated that additional exposure did not lead to clinically meaningful increases in efficacy.

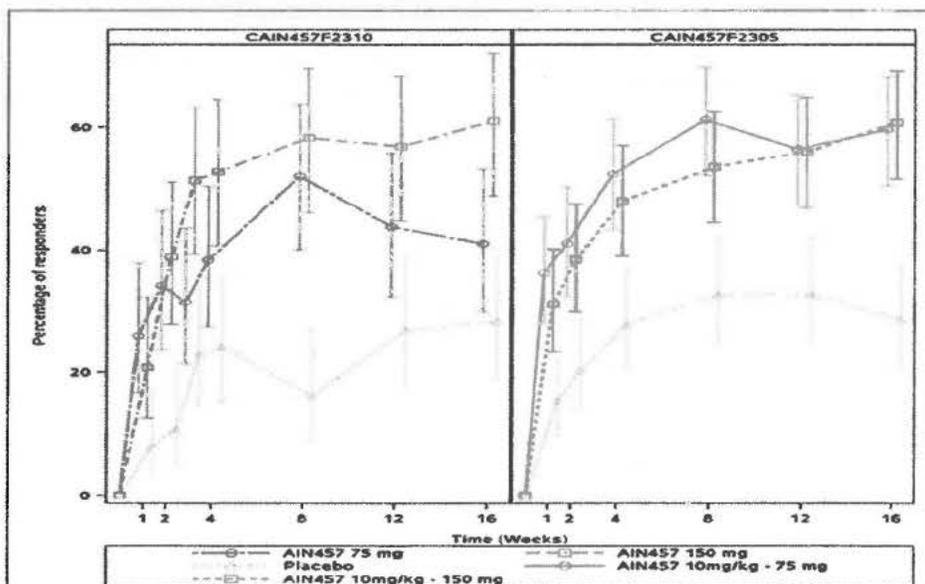


Figure 1. Time course of ASAS 20 response (estimate and 95% CI) using nonresponder imputation by study and treatment up to Week 16 for Studies F2310/F2305
(Source: Figure 3-2, Summary of Clinical Efficacy for AS)

Exploratory exposure-response analyses were also performed based on the response rate and trough concentration (C_{min}) at Week 16. The exposure-response curve flattens at C_{min} levels that are higher than 25 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC150 mg-SC150 mg dosing regimen at Week 16. Increase of the C_{min} beyond 25 mcg/mL induces limited improvement in ASAS20 response rates (Figure 2). A trend was observed for increased responses with higher C_{min} concentrations for ASAS40/5-6 response rates, BASDAI and SF36-PCS (Figure 3).

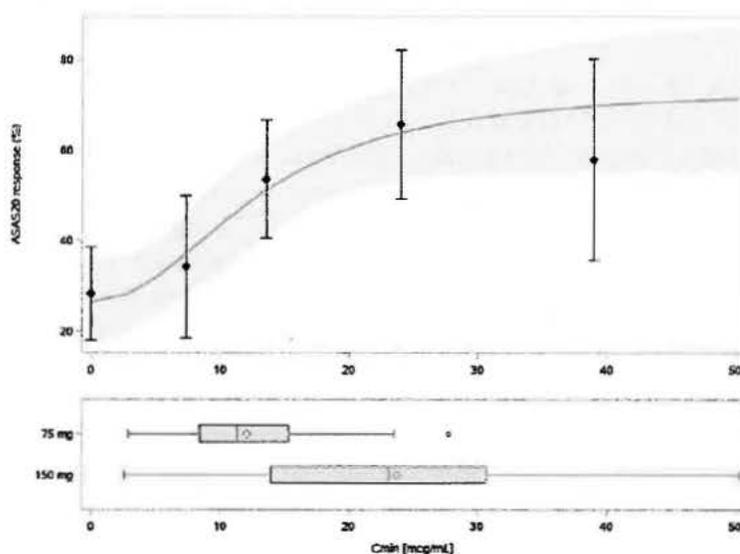


Figure 2. ASAS20 response rate versus C_{min} concentration at Week 16
 (Source: Figure 4-1, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy and adverse events in AS patients)

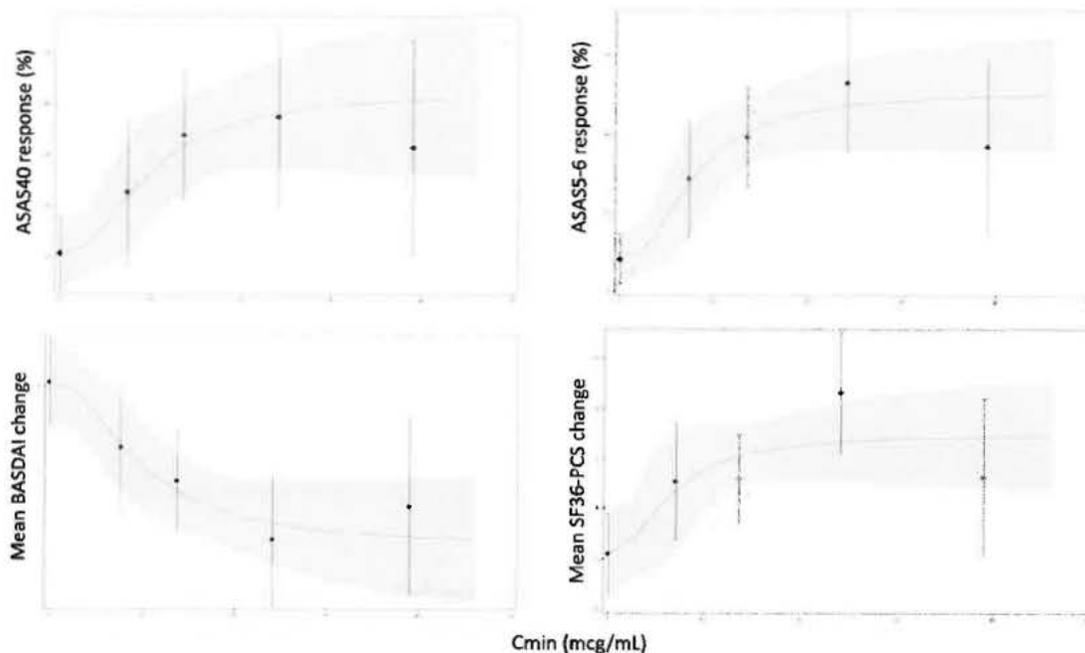


Figure 3. ASAS40/5-6 response rates, BASDAI and SF36-PCS versus Cmin concentration following the administration of SC75 mg-SC75 mg or SC150 mg-SC150 mg dosing regimens at Week 16

(Adapted from Figures 4-2 to 4-5, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in ankylosing spondylitis 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 4 shows the exposure-response relationships for the following categories of AEs: any AE, any SAE, infections and infestations, upper respiratory tract infections, nasopharyngitis, and oral herpes, respectively. No evidence of an effect of Cmin was observed on AE rates for the following categories: any AE, any SAE, and upper respiratory tract infections. A trend for increased rates of for infections and infestations, nasopharyngitis and oral herpes with higher Cmin was observed.

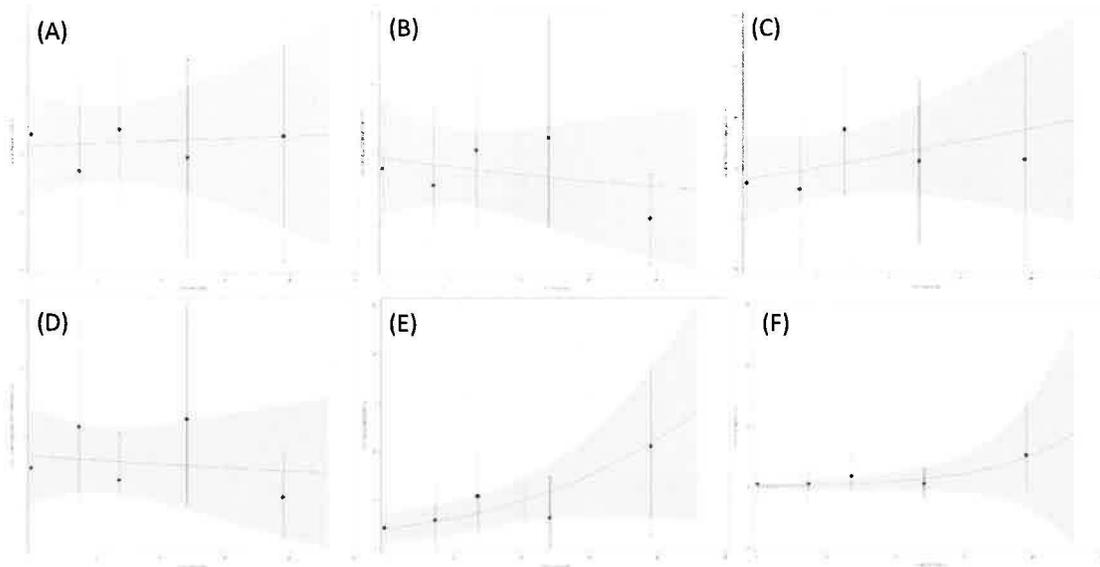


Figure 4. Occurrence of any AE (A), any SAE (B), any infections and infestations (C), upper respiratory tract infections (D), nasopharyngitis (E), oral Herpes (F) versus Cmin concentration at Week 16
 (Adapted from Figures 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in ankylosing spondylitis patients)

2.5.3 Is the proposed dosing regimen for COSENTYX appropriate?

The two Phase 3 confirmatory studies in AS patients were randomized, double-blind, placebo-controlled, multicenter studies in AS to demonstrate the efficacy of secukinumab at Week 16 (Studies F2305 and F2310). The dosing regimens assessed in these two Phase 3 program include:

Study F2305

- IV10 mg/kg-SC75mg: IV 10 mg/kg at Weeks 0, 2 and 4, then SC 75 mg q4w starting at Week 8
- IV10 mg/kg-SC150mg: 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 F2310

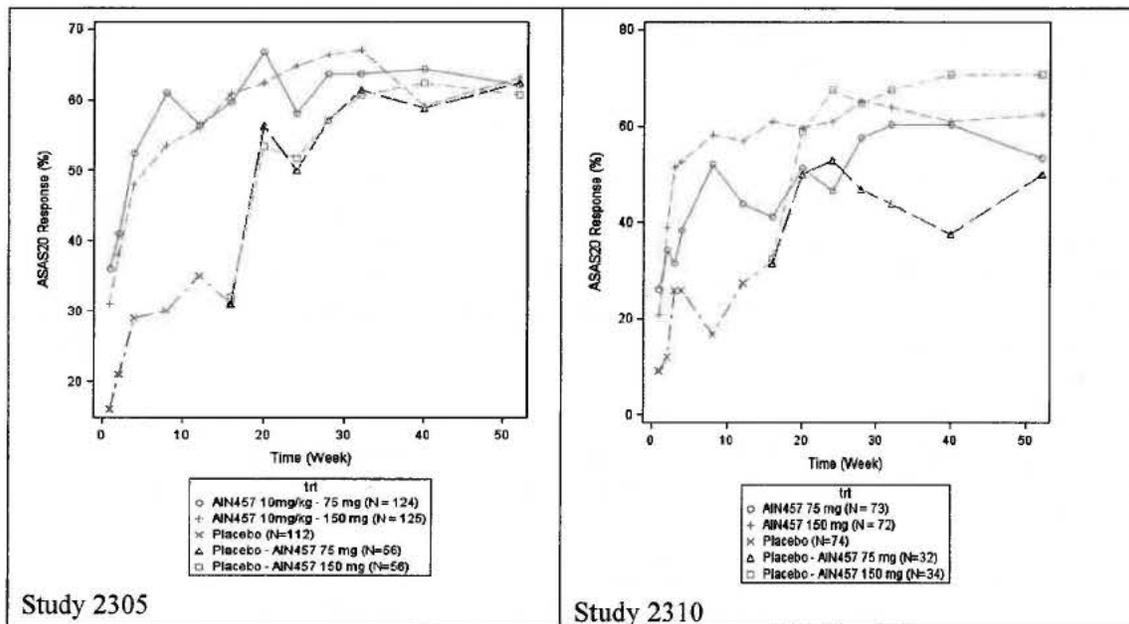
- SC75 mg-SC75 mg: SC 75 mg at Weeks 0, 1, 2 and 3, then SC 75 mg q4w starting at Week 4
- SC150 mg-SC75 mg: SC 150 mg at Weeks 0, 1, 2 and 3, then SC 150 mg q4w starting at Week 4
- Placebo: placebo at Weeks 0, 1, 2, 3 and 4, followed by SC 75 mg or 150 mg (1:1) q4w starting at Week 16

The proposed dosing regimen in AS patients is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4.

The proposed dosing regimen was investigated in the confirmative Phase 3 study F2310. 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 150 mg showed statistical significance over placebo for the primary endpoint ASAS20 at Week 16, while SC75mg-SC75 mg did not produce significantly higher response rate (Figure 1). After switching to secukinumab, the response rate in the placebo group was about the same over time as the treatment groups in both Phase 3 studies F2310 and F2305 (Figure 5). 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).



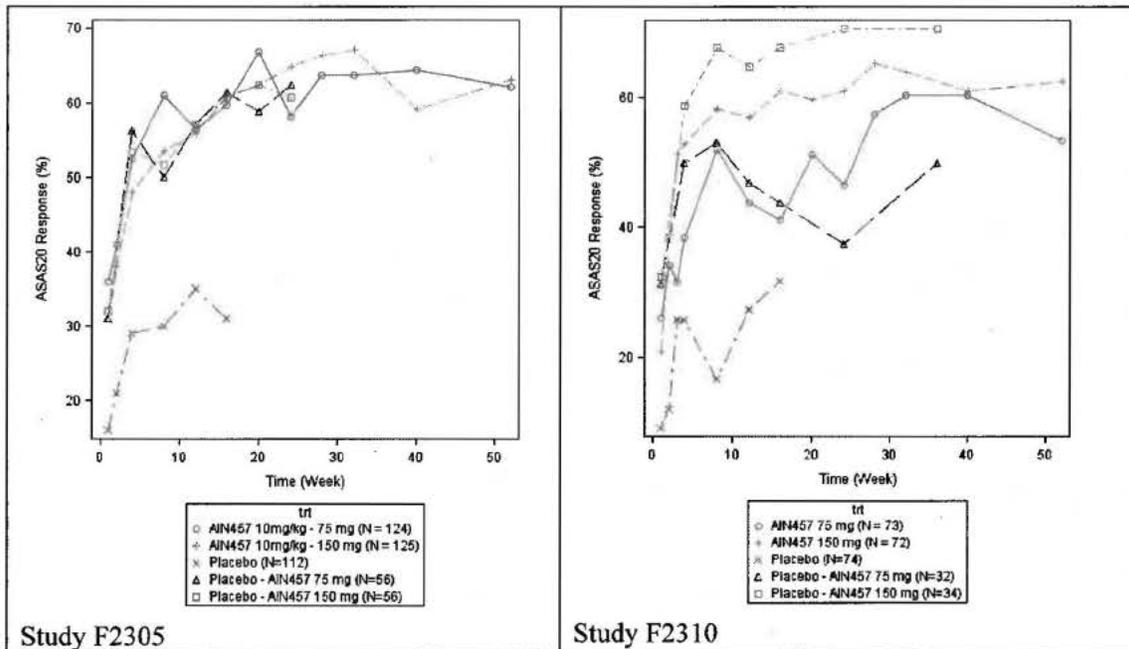


Figure 5. ASAS20 response rate over time in Studies F2305 and F2310

Note: all the time points in the Placebo-AIN457 75 mg and Placebo-AIN457 150 mg groups were adjusted according to the switching time.

(Data source: Table 14.2-1.2 Page 369, CSR F2305 and Table 14.2-1.2 Page 320, CSR 2310)

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 F2305, Table 2). With the loading doses of SC 75 and 150 mg once a week for three weeks, the trough concentrations up to Week 16 appeared higher than those in Week 24 (Study F2310, Table 3). Therefore, the steady state concentrations did not appear to reach until 16 weeks or later.

Table 2. Secukinumab trough concentrations by treatment and visit in Study F2305

Visit	10 mg/kg-75 mg		Placebo non-responders 75 mg		Placebo responders 75 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	116	132 ± 37.9	--	--	--	--
Week 16	112	37.1 ± 17.6	--	First dose	--	--
Week 24	110	17.2 ± 9.06	35	8.92 ± 4.25	--	First dose
Week 52	93	10.9 ± 4.88	28	11.4 ± 5.03	14	11.7 ± 5.25
Visit	10 mg/kg-150 mg		Placebo non-responders 150 mg		Placebo responders 150 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	111	131 ± 38.5	--	--	--	--
Week 16	117	43.6 ± 18.8	--	First dose	--	--
Week 24	112	25.5 ± 11.7	35	13.7 ± 5.57	--	First dose
Week 52	96	20.0 ± 7.92	28	17.2 ± 6.65	17	18.2 ± 6.19

(Source: Table 11-9, Study AIN457F2305 report)

Table 3. Secukinumab trough concentrations by treatment and visit in Study F2310

Visit	75 mg		150 mg		Placebo → 75 mg		Placebo → 150 mg	
	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)
Week 4	56	25.4 ± 9.42	63	52.9 ± 17.9	--	Placebo	--	Placebo
Week 16	52	13.0 ± 5.35	56	23.0 ± 10.8	--	First dose	--	First dose
Week 24	50	11.3 ± 4.63	55	20.3 ± 9.98	18	8.37 ± 3.38	25	15.5 ± 4.79
Week 52	47	10.8 ± 5.15	48	20.7 ± 8.63	15	11.0 ± 6.70	17	18.8 ± 5.70

Conc = secukinumab concentration.
(Source: Table 11-11, Study CAIN457F2310 report)

Immunogenicity

The immunogenicity data showed that 3 out of 371 patients in Study F2305 and none of 210 patients in Study F2310 were positive for anti-secukinumab antibodies post dose (Tables 4 and 5). In Study F2305, 2 placebo patients developed ADA after switching to secukinumab treatments and one patient with IV10 mg/kg-SC150 mg developed ADA. The anti-secukinumab antibody rate appeared comparable in patients with the loading doses (n=1) and in patients who switched from placebo to secukinumab without a load (n=2). 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 F2305

Patient ID (F2305-)	Group	Prior biologics	ADA ¹ (titer) /N-Ab	Impact on efficacy ²	AE possibly IG related ³	PK ⁴
Patients with treatment emergent ADA (n=2)						
(b) (6)	AIN457 10mg/kg -150 mg	None	Week 52 (2.39) / Yes	No	None	Normal
	Placebo non- responder - AIN457 150 mg	None	Week 52 (10.61) / No	No	None	Normal
Patients with baseline and post-baseline persistent ADA (n=1)						
(b) (6)	Placebo non- responder - AIN457 150 mg	None	BL (no titer) / Yes Week 16 (no titer) / Yes	n/e	None	Normal
Patients with only baseline ADA (n=3)						
(b) (6)	AIN457 10mg/kg - 75 mg	infliximab	BL (7.81) / Yes	n/e	None	Normal
	AIN457 10mg/kg - 150 mg	None	BL (2.80) / Yes	n/a	None	Normal
	Placebo responder - 75 mg	None	BL (2.05) / Yes	n/e	None	n/e (only one PK time point during treatment)

ADA=anti-drug antibodies; BL=baseline; IG=immunogenicity; N-Ab=neutralizing antibodies; n/a=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Only applicable to patients with treatment emergent ADAs. For patients who newly develop post-baseline ADA, loss of efficacy is defined as failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits at any time prior to first detection of ADA

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: Table 12-22, Study AIN457F2305 report)

Table 5. Overview of patients with anti-drug antibodies (ADA) in Study F2310

Patient ID	Group	Prior biologics	ADA ¹ (titer)/ N-Ab	Impact on efficacy ²	AE possibly IG related ³ (Day of onset)	PK ⁴
Patients with only baseline ADA (n=4)						
(b) (6)	Placebo - AIN457 75 mg	None	Baseline (1.98)/ No	n/a	No	NA, Only 1 PK result available
	Placebo - AIN457 150 mg	ETANERCEPT	Baseline (No titer)/ No	n/a	Seasonal allergy /Day-45 /Non-SAE	NA, Only 1 PK result available
	AIN457 150 mg	None	Baseline (2.03)/ No	n/a	No	Normal*
	AIN457 150 mg	INFLIXIMAB	Baseline (No titer)/ YES	n/a	No	Normal

¹ADA=anti-drug antibodies; BL=baseline; IG=immunogenicity; N-Ab=neutralizing antibodies; n/a=not applicable; PK=pharmacokinetics

²Only positive ADA results at the respective study week are shown

³Only applicable to patients with treatment emergent ADAs. For patients who newly develop post-baseline ADA, loss of efficacy is defined as failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits prior to first detection of ADA

⁴IG-related AEs refers to preferred terms in the SMQ hypersensitivity

*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

* Patient (b) (6) did not show steady state behavior.

n/a = not available

(Source: Table 12-8, Study CAIN457F2310 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	Cmax (mcg/mL)	Tmax (day)	T1/2 (day)	CL (L/d)	Vz (L)	F
A2106	HVs	300 mg SC (PFS) 300 mg SC (LYO)	43.2 42.0	5.0 5.0	25.9 26.6	-- --	-- --	-- --
A2104	HVs	10 mg/kg IV	255	0.09	29.8	0.12	5.05	--
A2103	PsO	1 mg/kg IV 150 mg SC	24.1 11.8	0.09 8.50	27.1 22.2	0.22 --	7.10 --	0.60
A2206	PsA	2×10 mg/kg IV	424	0.09	29.8	0.161	6.81	--
A2209	AS	2×10 mg/kg IV 2×1 mg/kg IV 2×0.1 mg/kg IV	364 33.1 5.51	21.08 21.08 21.12	28.1 27.3 34.3	0.157 0.172 0.118	6.06 6.48 5.83	-- -- --

(Adapted from Table 3-1, Addendum to Summary of Clinical Pharmacology)

2.6.3 What are the characteristics of drug absorption?

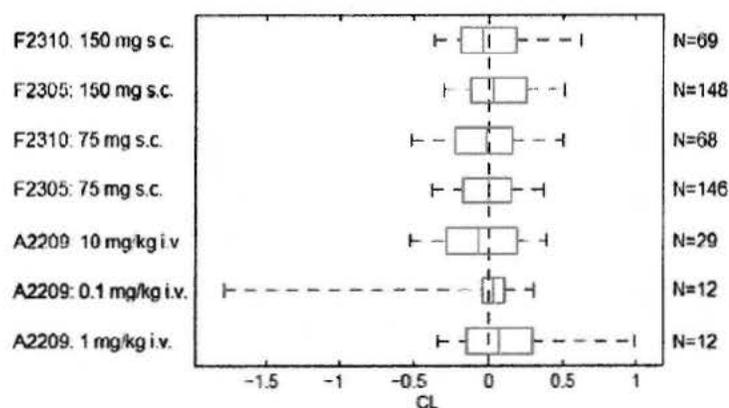
Based on population PK analysis, the bioavailability of secukinumab is 79% following SC administration in AS patients.

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 F2310, following SC 75 or 150 mg at Weeks 0, 1, 2 and 3, then SC 75 or 150 mg q4w starting from Week 4, the pre-dose concentrations increased in a dose-proportional manner: at Week 4, the mean C_{min} levels are 25.4 µg/mL and 52.9 µg/mL in 75 mg and 150 mg arms, respectively. At Week 52, the mean C_{min,ss} levels are 10.8 µg/mL (47.8% CV) and 20.7 µg/mL (41.7% CV) in 75 mg and 150 mg arms, respectively.

In population PK analysis, the estimates of CL of secukinumab in AS were consistent across studies and dose levels suggesting the dose-proportionality of secukinumab PK (Figure 6).



Legend: 'Relative clearance' indicates relative to the clearance of CL=0.16 L/Day in a 'typical' AS patient of 77 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 represents 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 6. Relative clearance by treatment group for secukinumab in AS patients (after adjusting for bodyweight)

(Source: Figure 5-10, Population PK of secukinumab in AS 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 7).

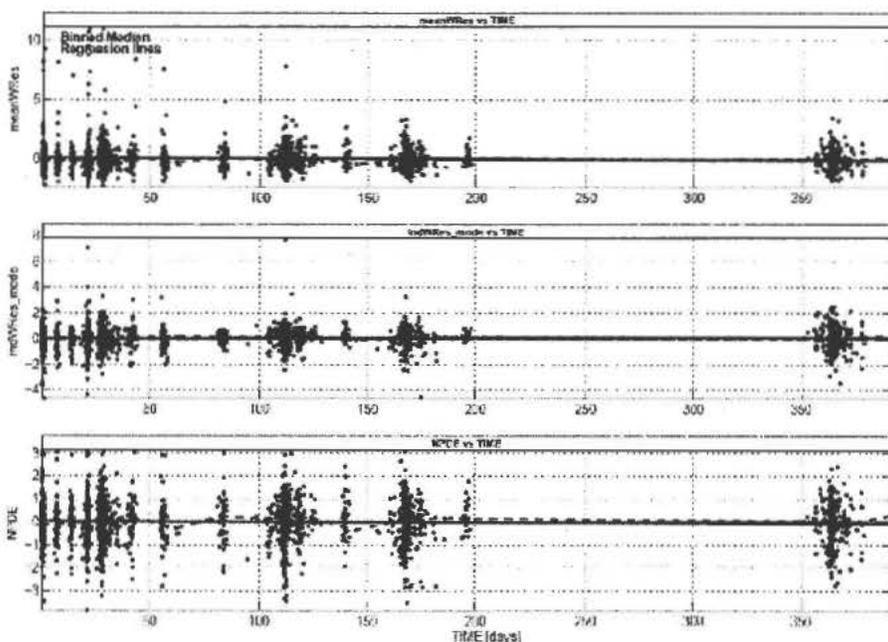


Figure 7. Model-based weighted residuals vs. time: No trend in residuals over time
 (Source: Figure 5-11, Population PK of secukinumab in AS modeling report)

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 as the significant intrinsic factor contributing the inter-subject variability in secukinumab exposure in AS patients. The inter-subject variability on CL is 32.8%.

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?

No dose adjustments are recommended.

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 indicated the co-administration of methotrexate does not affect the disposition of secukinumab. Please refer to the Pharmacometrics Review in Appendix 4.1 for more details.

2.8.8 Does the label specify co-administration of another drug?

No, the label does not specify co-administration of another drug.

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 AS 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 AS

Study	Number of subject with ADA+	Subject ID			Cmin (µg/mL)	Responder (Y/N)
		Treatment-emergent ADA+ and nAb+	Treatment-emergent ADA+ and nAb-	Non-treatment emergent ADA+ and nAb-		
F2209	0/60	NA	NA	NA	NA	NA
F2305	3/371	(b) (6)		-	26.6	Y
			(b) (6)		16.5	Y
		-	-	(b) (6)	9.99	Y
F2310	0/210	NA		NA	NA	NA

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.

3 out of 641 (0.47%) AS patients were detected positive for anti-secukinumab antibodies and only 1 of the 3 patients had neutralizing antibodies. At Week 16, the secukinumab Cmin in these patients are comparable to the Cmin of all tested AS patients (Mean 20

mcg/mL (SD 9.1 mcg/mL) [Range 9.7-39 mcg/mL]). By Week 16, all these 3 patients were treatment responder. No immunogenicity related AEs were reported.

APPEARS THIS WAY IN
ORIGINAL

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.

7 DRUG INTERACTIONS

Drug interaction trials have not been conducted with COSENTYX.

(b) (4)

(b) (4)

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.

12.3 Pharmacokinetics

The PK properties of secukinumab observed in 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 and ankylosing spondylitis. Subjects who are 65 years or older had apparent clearance of secukinumab similar to subjects less than 65 years old.

4. Appendix

4.1 Appendix –PM Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

BLA Number	125504 Supplement-02
Brand Name	COSENTYX
Drug Components	Secukinumab
Indication	Ankylosing Spondylitis (AS)
Dosing Regimen	The proposed dosing regimen is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4.
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 AS. A total of 2138 secukinumab serum concentrations of 484 patients from Studies A2209, F2305 and F2310 were used in the population PK analysis. The developed 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 AS?

The influence of various covariates on secukinumab PK in AS has been evaluated in the population model development (Table 4-1).

Only bodyweight 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 1.2, respectively.

The co-medication of methotrexate was found not to influence secukinumab PK significantly.

Table 1. Candidate covariates

Covariate	Model parameters
Bodyweight	CL, V _c , Q ₁ , V _{p1}
Age	CL
Gender	CL
Asian / non-Asian	CL
Time since first diagnosis of AS	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
BASDAI score at baseline	CL

(Source: Table 4-2, Population PK of secukinumab in AS modeling report)

2. What are the characteristics of the dose/exposure-response relationship for efficacy?

There appears a dose/exposure-response relationship for ASAS20 response rate of secukinumab in AS patients.

The efficacy of secukinumab in AS was evaluated in the two pivotal, placebo-controlled Phase 3 studies (Studies F2310 and F2305) (Figure 4-1). In Study F2310, the ASAS 20 response rates at Week 16 for SC150mg-SC150 mg are significantly higher than placebo, while SC75mg-SC75 mg did not produce significantly higher response rate: 61.1% for SC150mg-SC150 mg ($p=0.0001$ vs placebo); 41.1% for SC75mg-SC75 mg ($p=0.0967$ vs placebo); 28.4% for placebo. In Study F2305, both dosing regimens produced significantly higher ASAS 20 response rates compared with placebo at Week 16: 60.8% for IV10 mg/kg-SC150mg and 59.7% for IV10 mg/kg-SC75 mg vs 28.7% for placebo ($p<0.0001$ for both comparisons vs placebo). Comparable response rates between IV 10 mg/kg-SC 150mg and IV10 mg/kg-SC75 mg should be due to the high exposure from the IV loading regimen given during the first month. Similar ASAS20 response rates of IV loading dose regimen and SC150mg-SC150 mg regimen indicated that additional exposure did not lead to clinically meaningful increases in efficacy.

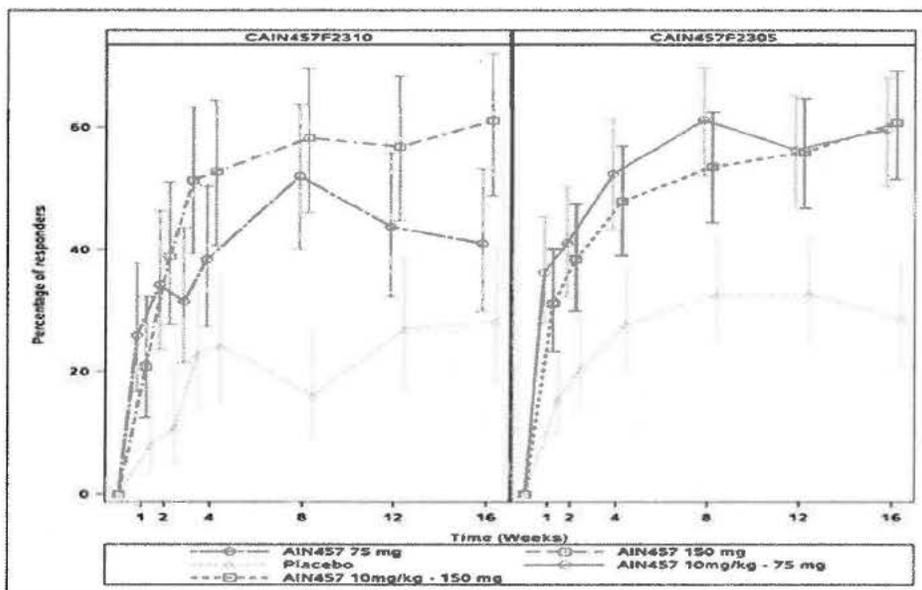


Figure 4-1. Time course of ASAS 20 response (estimate and 95% CI) using nonresponder imputation by study and treatment up to Week 16 for Studies F2310/F2305 (Source: Figure 3-2, Summary of Clinical Efficacy for AS)

Exploratory exposure-response analyses were also performed based on the response rate and trough concentration (C_{min}) at Week 16. The exposure-response curve flattens at C_{min} levels that are higher than 25 mcg/mL, which approximately correspond to the mean steady state levels that are achieved following a SC150 mg-SC150 mg dosing regimen at Week 16. Increase of the C_{min} beyond 25 mcg/mL induces limited improvement in ASAS20 response rates (Figure 4-2). A trend was observed for increased responses with higher C_{min} concentrations for ASAS40/5-6 response rates, BASDAI and SF36-PCS (Figure 4-3).

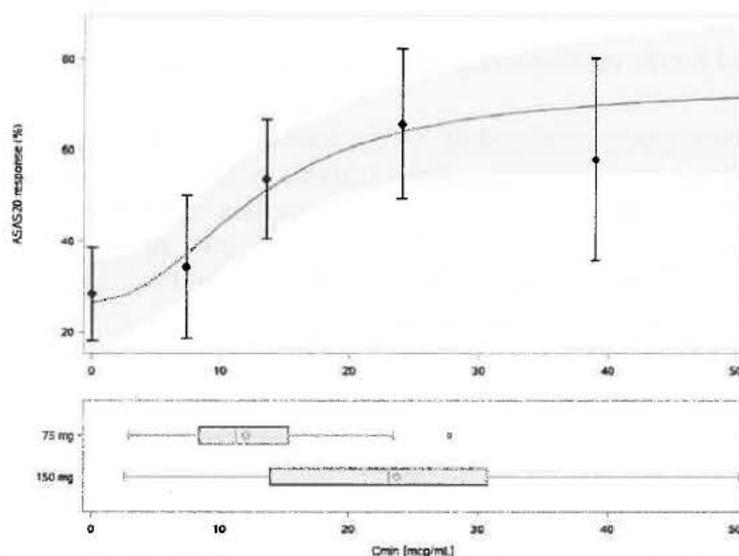


Figure 4-2. ASAS20 response rate versus C_{min} concentration at Week 16

(Source: Figure 4-1, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy and adverse events in AS patients)

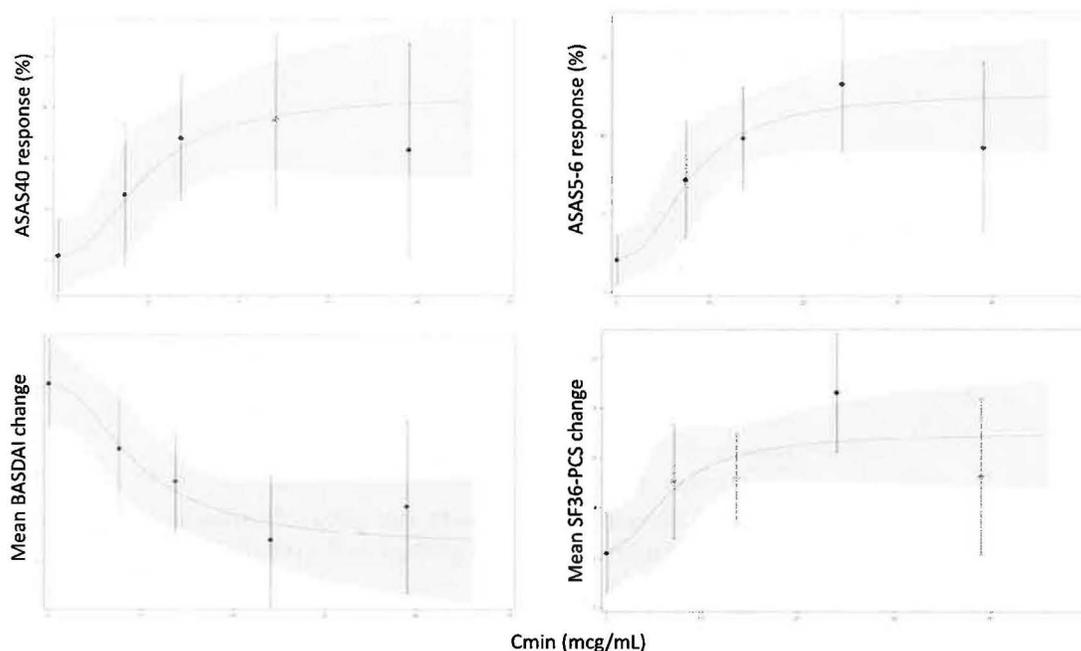


Figure 4-3. ASAS40/5-6 response rates, BASDAI and SF36-PCS versus Cmin concentration following the administration of SC75 mg-SC75 mg or SC150 mg-SC150 mg dosing regimens at Week 16

(Adapted from Figures 4-2 to 4-5, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in ankylosing spondylitis 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 4-4 shows the exposure-response relationships for the following categories of AEs: any AE, any SAE, infections and infestations, upper respiratory tract infections, nasopharyngitis, and oral herpes, respectively. No evidence of an effect of Cmin was observed on AE rates for the following categories: any AE, any SAE, and upper respiratory tract infections. A trend for increased rates of for infections and infestations, nasopharyngitis and oral herpes with higher Cmin was observed.

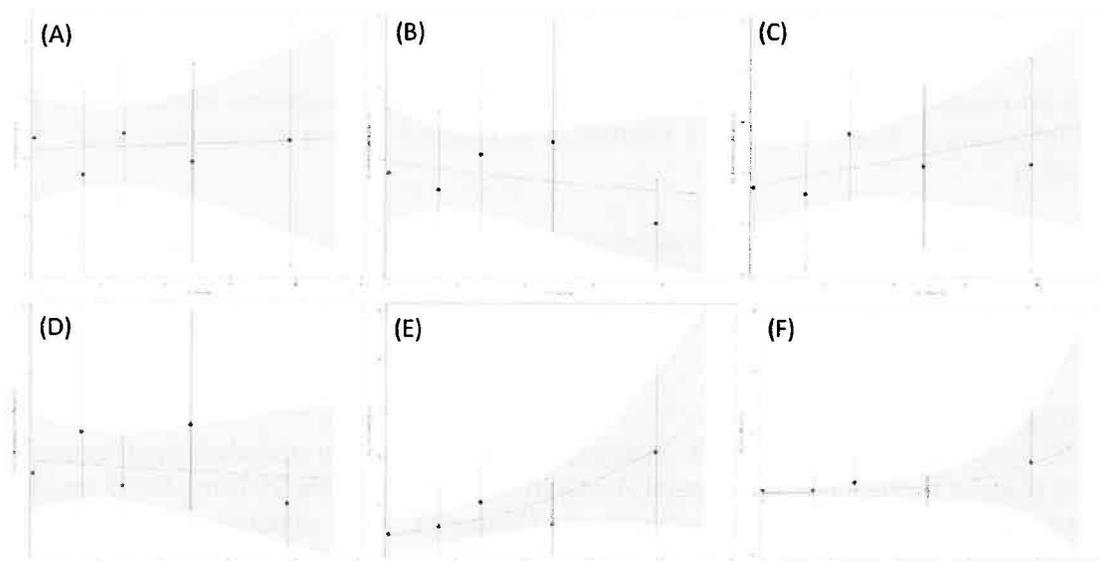


Figure 4-4. Occurrence of any AE (A), any SAE (B), any infections and infestations (C), upper respiratory tract infections (D), nasopharyngitis (E), oral Herpes (F) versus Cmin concentration at Week 16

(Adapted from Figures 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy, adverse events and radiographic assessments in ankylosing spondylitis patients)

2.5.3 Is the proposed dosing regimen for COSENTYX appropriate?

The two Phase 3 confirmatory studies in AS patients were randomized, double-blind, placebo-controlled, multicenter studies in AS to demonstrate the efficacy of secukinumab at Week 16 (Studies F2305 and F2310). The dosing regimens assessed in these two Phase 3 program include:

Study F2305

- IV10 mg/kg-SC75mg: IV 10 mg/kg at Weeks 0, 2 and 4, then SC 75 mg q4w starting at Week 8
- IV10 mg/kg-SC150mg: 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 F2310

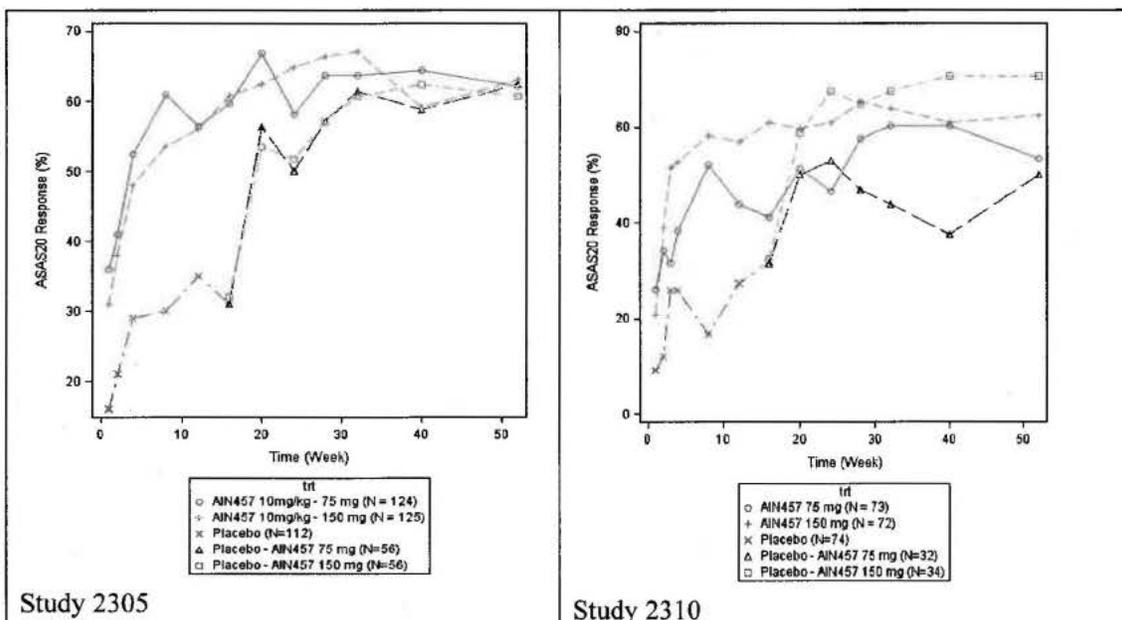
- SC75 mg-SC75 mg: SC 75 mg at Weeks 0, 1, 2 and 3, then SC 75 mg q4w starting at Week 4
- SC150 mg-SC75 mg: SC 150 mg at Weeks 0, 1, 2 and 3, then SC 150 mg q4w starting at Week 4
- Placebo: placebo at Weeks 0, 1, 2, 3 and 4, followed by SC 75 mg or 150 mg (1:1) q4w starting at Week 16

The proposed dosing regimen in AS patients is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4.

The proposed dosing regimen was investigated in the confirmative Phase 3 study F2310. 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 150 mg showed statistical significance over placebo for the primary endpoint ASAS20 at Week 16, while SC75mg-SC75 mg did not produce significantly higher response rate (Figure 1). After switching to secukinumab, the response rate in the placebo group was about the same over time as the treatment groups in both Phase 3 studies F2310 and F2305 (Figure 5). 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).



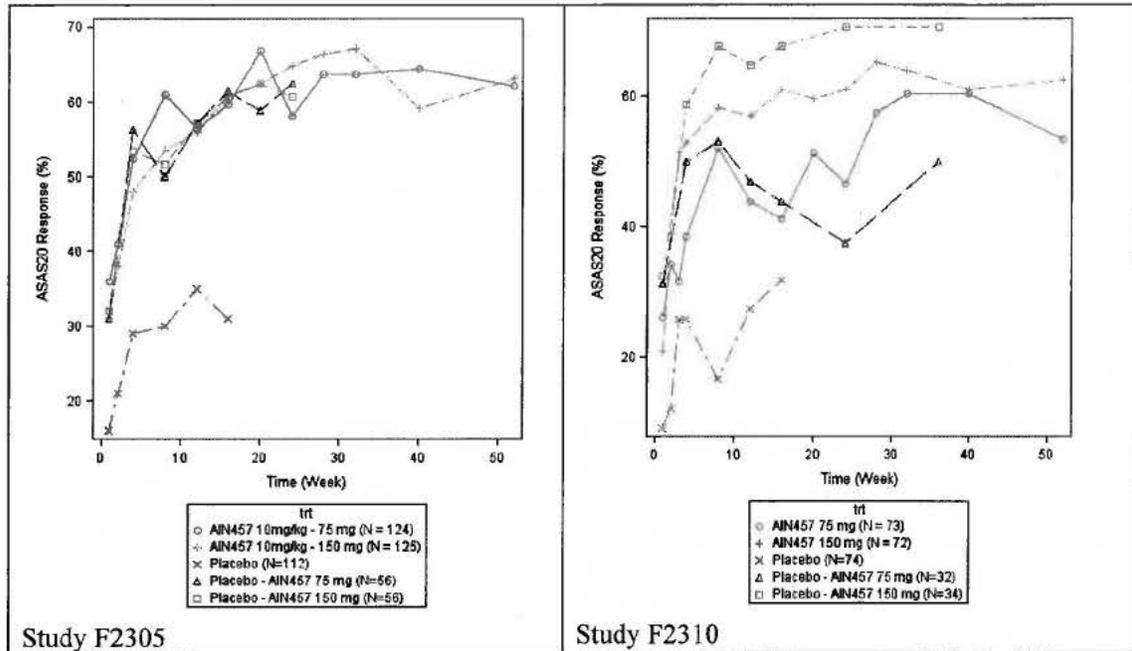


Figure 5. ASAS20 response rate over time in Studies F2305 and F2310

Note: all the time points in the Placebo-AIN457 75 mg and Placebo-AIN457 150 mg groups were adjusted according to the switching time.

(Data source: Table 14.2-1.2 Page 369, CSR F2305 and Table 14.2-1.2 Page 320, CSR 2310)

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 F2305, Table 2). With the loading doses of SC 75 and 150 mg once a week for three weeks, the trough concentrations up to Week 16 appeared higher than those in Week 24 (Study F2310, Table 3). Therefore, the steady state concentrations did not appear to reach until 16 weeks or later.

Table 2. Secukinumab trough concentrations by treatment and visit in Study F2305

Visit	10 mg/kg-75 mg		Placebo non-responders 75 mg		Placebo responders 75 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	116	132 ± 37.9	--	--	--	--
Week 16	112	37.1 ± 17.6	--	First dose	--	--
Week 24	110	17.2 ± 9.06	35	8.92 ± 4.25	--	First dose
Week 52	93	10.9 ± 4.86	28	11.4 ± 5.03	14	11.7 ± 5.25
Visit	10 mg/kg-150 mg		Placebo non-responders 150 mg		Placebo responders 150 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	111	131 ± 38.5	--	--	--	--
Week 16	117	43.6 ± 18.8	--	First dose	--	--
Week 24	112	25.5 ± 11.7	35	13.7 ± 5.57	--	First dose
Week 52	96	20.0 ± 7.92	28	17.2 ± 6.65	17	18.2 ± 6.19

(Source: Table 11-9, Study AIN457F2305 report)

Table 3. Secukinumab trough concentrations by treatment and visit in Study F2310

Visit	75 mg		150 mg		Placebo → 75 mg		Placebo → 150 mg	
	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)
Week 4	56	25.4 ± 9.42	63	52.9 ± 17.9	--	Placebo	--	Placebo
Week 16	52	13.0 ± 5.35	56	23.0 ± 10.8	--	First dose	--	First dose
Week 24	50	11.3 ± 4.63	55	20.3 ± 9.98	18	8.37 ± 3.38	25	15.5 ± 4.79
Week 52	47	10.8 ± 5.15	48	20.7 ± 8.63	15	11.0 ± 6.70	17	18.8 ± 5.70

Conc = secukinumab concentration.
(Source: Table 11-11, Study CAIN457F2310 report)

Immunogenicity

The immunogenicity data showed that 3 out of 371 patients in Study F2305 and none of 210 patients in Study F2310 were positive for anti-secukinumab antibodies post dose (Tables 4 and 5). In Study F2305, 2 placebo patients developed ADA after switching to secukinumab treatments and one patient with IV10 mg/kg-SC150 mg developed ADA. The anti-secukinumab antibody rate appeared comparable in patients with the loading doses (n=1) and in patients who switched from placebo to secukinumab without a load (n=2). 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 F2305

Patient ID (F2305-)	Group	Prior biologics	ADA ¹ (titer) / N-Ab	Impact on efficacy ²	AE possibly IG related ³	PK ⁴
Patients with treatment emergent ADA (n=2)						
(b) (6)	AIN457 10mg/kg -150 mg	None	Week 52 (2.39) / Yes	No	None	Normal
	Placebo non- responder - AIN457 150 mg	None	Week 52 (10.61) / No	No	None	Normal
Patients with baseline and post-baseline persistent ADA (n=1)						
(b) (6)	Placebo non- responder - AIN457 150 mg	None	BL (no titer) / Yes Week 16 (no titer) / Yes	n/e	None	Normal
Patients with only baseline ADA (n=3)						
(b) (6)	AIN457 10mg/kg - 75 mg	infliximab	BL (7.81) / Yes	n/e	None	Normal
	AIN457 10mg/kg - 150 mg	None	BL (2.80) / Yes	n/e	None	Normal
	Placebo responder - 75 mg	None	BL (2.05) / Yes	n/e	None	n/e (only one PK time point during treatment)

ADA=anti-drug antibodies; BL=baseline; IG=immunogenicity; N-Ab=neutralizing antibodies; n/e=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Only applicable to patients with treatment emergent ADAs. For patients who newly develop post-baseline ADA, loss of efficacy is defined as failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits at any time prior to first detection of ADA

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: Table 12-22, Study AIN457F2305 report)

Table 5. Overview of patients with anti-drug antibodies (ADA) in Study F2310

Patient ID	Group	Prior biologics	ADA ¹ (titer)/ N-Ab	Impact on efficacy ²	AE possibly IG related ³ (Day of onset)	PK ⁴
Patients with only baseline ADA (n=4)						
(b) (6)	Placebo - AIN457 75 mg	None	Baseline (1.98)/ No	n/a	No	NA, Only 1 PK result available
	Placebo - AIN457 150 mg	ETANERCEPT	Baseline (No titer)/ No	n/a	Seasonal allergy /Day-45 /Non-SAE	NA, Only 1 PK result available
	AIN457 150 mg	None	Baseline (2.03)/ No	n/a	No	Normal*
	AIN457 150 mg	INFLIXIMAB	Baseline (No titer)/ YES	n/a	No	Normal

¹ADA=anti-drug antibodies; BL=baseline; IG=immunogenicity; N-Ab=neutralizing antibodies; n/a=not applicable; PK=pharmacokinetics

²Only positive ADA results at the respective study week are shown

³Only applicable to patients with treatment emergent ADAs. For patients who newly develop post-baseline ADA, loss of efficacy is defined as failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits prior to first detection of ADA

⁴IG-related AEs refers to preferred terms in the SMQ hypersensitivity

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

* Patient (b) (6) did not show steady state behavior.

n/a = not available

(Source: Table 12-8, Study CAIN457F2310 report)

INDIVIDUAL STUDY REVIEW

4.1.1 Population Pharmacokinetics of Secukinumab (AIN457) in Ankylosing Spondylitis

Objectives

- To describe the PK of secukinumab in patients with AS, 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 AS patients as summarized below. Study A2209 provides dense samples within hours and/or days after dose, and Studies F2305 and F2310 provide only pre-dose trough samples (Table 4-2).

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 2138 secukinumab serum concentrations from 484 patients (Table 4-3).

Table 4-2 Summary of clinical studies to be used in the population pharmacokinetic analyses

Study	Description	Regimens	Note
A2209	PoC PD study of efficacy of AIN457	<ul style="list-style-type: none"> • 2 x 0.1 mg/kg i.v. q3w • 2 x 1 mg/kg i.v. q3w • 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, 12, 16, 20, 24 and 28/end of study
F2305*	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 pre-dose samples in weeks 0, 4, 16, 24 and 52. For premature discontinuation, samples at 4 weeks after last dose.
F2310**	Phase III efficacy, safety and tolerability	<ul style="list-style-type: none"> • 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4 • 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4 • placebo + 150 mg s.c. q4w from week 16 • placebo + 75 mg s.c. q4w from week 16 • placebo 	PK pre-dose samples in weeks 0, 4, 16

* F2305: Week 52 interim lock

** F2310: Week 16 interim lock

(Source: Table 3-1, Population PK of secukinumab in AS modeling report)

Table 4-3 Summary table of PK analysis set by treatment group

Group	N	records	active doses	PK observations
A2209: 2 x 0.1 mg/kg i.v. q3w	12	220	24	196
A2209: 2 x 1 mg/kg i.v. q3w	12	223	24	199
A2209: 2 x 10 mg/kg i.v. q3w	29	542	57	485
F2305: 3 x 10 mg/kg q2w + 150 mg s.c. q4w from week 8	119	2127	1692	435
F2305: 3 x 10 mg/kg + 75 mg s.c. q4w from week 8	116	2111	1682	429
F2305: placebo + 150 mg s.c. q4w from week 16	28	473	275	58
F2305: placebo + 75 mg s.c. q4w from week 16	28	474	278	56
F2305: placebo + 150 mg s.c. q4w from week 24	1	17	8	2
F2305: placebo + 75 mg s.c. q4w from week 24	2	34	16	4
F2310: 4 x 150 mg s.c. q1w + 150 mg s.c. q4w from week 4	69	671	533	138
F2310: 4 x 75 mg s.c. q1w + 75 mg s.c. q4w from week 4	68	662	526	136
TOTAL	484	7554	5115	2138

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 AS 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 AS.

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 AS 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 4-4;
- . 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 4-4 Considered candidate covariates

Covariate	Model parameters
Bodyweight	CL, V _c , Q ₁ , V _{p1}
Age	CL
Gender	CL
Asian / non-Asian	CL
Time since first diagnosis of AS	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
BASDAI score at baseline	CL

(Source: Table 4-2, Population PK of secukinumab in AS 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 4-5.

- . 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 4-5 Parameters of final PK model

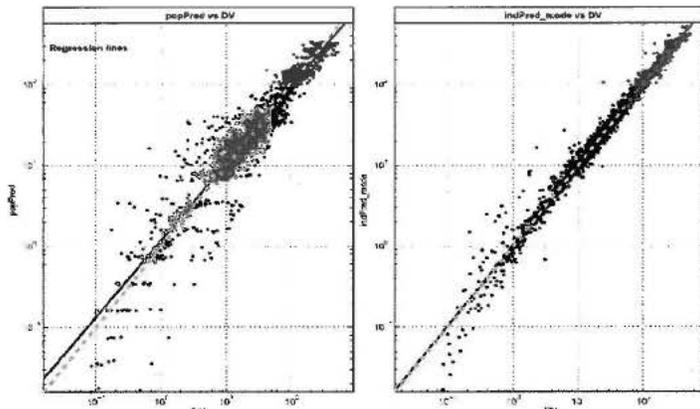
Name	Value	%RSE	Shrinkage (%)
<i>Structural parameters</i>			
CL [L/day]	0.16	2	
V_c [L]	3.09	3	
Q_1 [L/day]	0.41	9	
V_{p1} [L]	2.38	4	
k_a [1/day]	0.18 (fixed)	-	
F_{abs1} (bioavailability)	79%	2	
<i>Covariate effect</i>			
WT0 on CL	0.83	9	
WT0 on V_c	1.24	11	
<i>Inter-individual variability(std)</i>			
IIV on CL	0.32	4	6.5
IIV on V_c	0.3	9	34
IIV on Q_1	-	-	-
IIV on V_{p1}	0.3	11	42
IIV on k_a	-	-	-
IIV on F_{abs1}	-	-	-
<i>Covariance</i>			
CL- V_c (corr)	0.62	13	
CL- V_{p1} (corr)	0.28	39	
V_c - V_{p1} (corr)	0.3	53	
<i>Residual variability</i>			
Additive Error (std)	0.49	7	
Proportional error (std)	0.16	3	
Objective Function Value (BIC)	14904		
Objective Function Value (-2xLL)	14811		

Source: Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/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 AS modeling report)

Final Model Evaluation

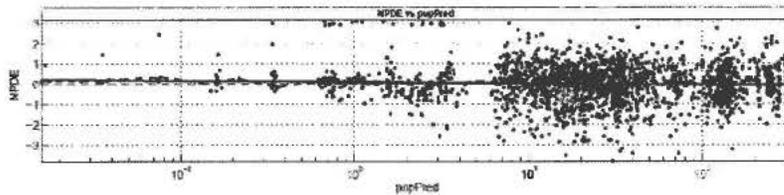
Goodness-of-fit: the diagnostic plots of the final model were shown in Figure 4-1. Overall, the 2-compartment model fit the PK data well, with a tendency to under-predict the higher concentration. Normalized prediction distribution errors (NPDE) versus population predictions show no evident trends (Figure 4-2).



Source: Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/RESULTS/GOF_OUTPUT_1_Cc/GOF_1_Cc_03_GOF_plots.pdf

Figure 4-1 Goodness-of-fit diagnostics for PK model

(Source: Figure 5-7, Population PK of secukinumab in AS modeling report)

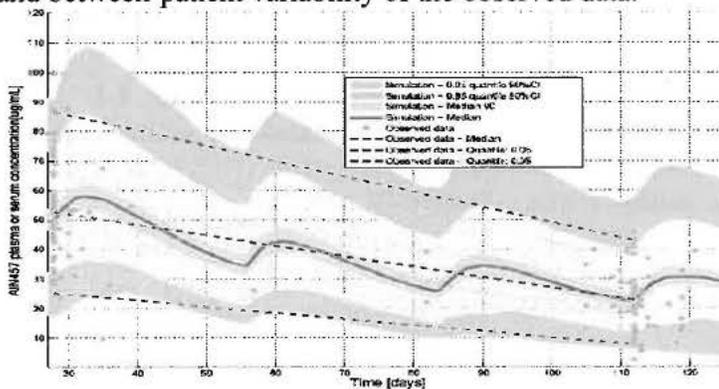


Source: Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/RESULTS/GOF_OUTPUT_1_Cc/GOF_1_Cc_03_GOF_plots.pdf

Figure 4-2 NPDE over population prediction

(Source: Figure 5-8, Population PK of secukinumab in AS modeling report)

Predictive Performance: Predictive performance of the models was assessed using visual predictive check (VPC). Figure 4-3 shows visual predictive checks for the 150 mg treatment group in study F2310. The model-based prediction matches the time course and between-patient variability of the observed data.



Source: Models/PK_FINAL_MODEL/PK_FINAL_MODEL_MONOLIX/RESULTS/GOF_OUTPUT_1_Cc/GOF_1_Cc_07_VPC_inY_PhIII.pdf

Dashed black lines represent the mean data and 95% CI, the grey circles represent the observed data, the red line represents the mean predictions and the shaded area represents the 95% confidence interval of the mean prediction of 500 simulations.

Figure 4-3 Visual predictive check for 4x150 mg SC q1w followed by 150 mg SC q4w from week 4 in study F2310

(Source: Figure 5-9, Population PK of secukinumab in AS 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 4-4 and 4-5.

Due to the linear PK, the simulated secukinumab exposure levels increased in a 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.

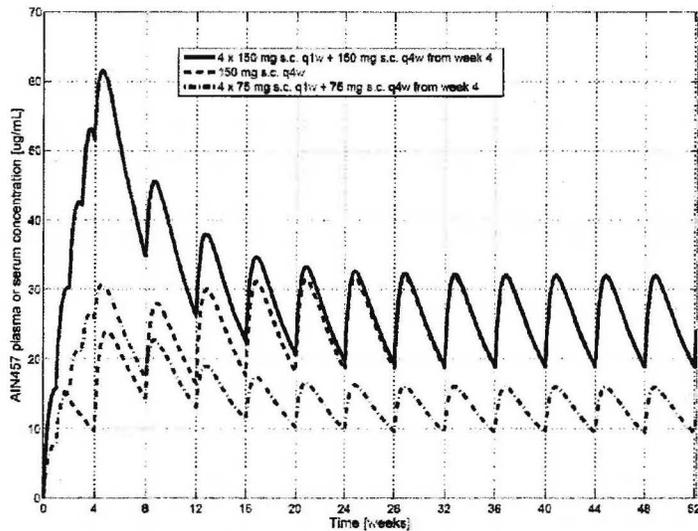
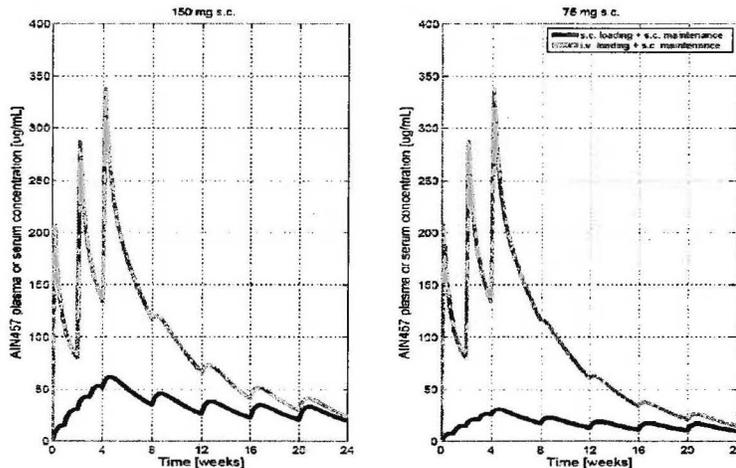


Figure 4-4 Simulated concentration profiles of SC loading + SC maintenance 150 mg and 75 mg dosing regimens and regular Q4W dosing regimen
(Source: Figures 5-12, Population PK of secukinumab in AS modeling report)



Source: Output/Simulations/SIM_03_all_phases/II_regimens.pdf
i.v. loading refers to 3 x 10 mg/kg i.v. q2w; s.c. loading is 4 x s.c. dose (150 mg or 75 mg, respectively for each panel) q1w; s.c. maintenance is s.c. dose (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 4-5 Simulated concentration profiles with IV and SC loading dosing regimens
(Source: Figure 5-13, Population PK of secukinumab in AS modeling report)

4.1.2 Graphical Exploratory Analysis of Secukinumab (AIN457) Exposure-Response of Efficacy and Adverse Events in Ankylosing Spondylitis Patients

Objective

Secukinumab exposure response relationships for efficacy and adverse events in study CAIN457F2310

Software

All analyses were performed with SAS version 9.4, using the SGPLOT and SG PANEL procedures for plotting purposes, and the NLMIXED procedure for model fitting.

Data Source

A total of 216 patients from Study F2310 contributed to the exposure-response analyses.

- Efficacy endpoints: ASAS (20/40/5-6) response, BASDAI, and SF36-PCS at Week 16
- Safety: Crude incidence rates for the following treatment emergent adverse events up to Week 16
- Exposure: trough concentration (C_{min}) at Week 16

Results

Exposure-response for efficacy

The exposure-response relationship for ASAS20/40/5-6 response rates, BASDAI, and SF36-PCS at Week 16 are shown in Figures 4-1 and 4-2. The exposure-response curve for ASAS20 flattens at C_{min} levels that are higher than 25 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 C_{min} concentrations at Week 16 in the different arms. A trend was observed for increased responses with higher C_{min} concentrations for ASAS40/5-6 response rates, BASDAI and SF36-PCS.

Exposure-response for safety

Figure 4-3 shows the exposure-response relationships for the following categories of AEs: any AE, any SAE, infections and infestations, upper respiratory tract infections, nasopharyngitis and oral herpes, respectively. No evidence of an effect of C_{min} was observed on AE rates for the following categories: any AE, any SAE, and upper respiratory tract infections. A trend for increased rates of for infections and infestations, nasopharyngitis and oral herpes with higher C_{min} was observed.

4.2. Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

Phase 2 Proof-of-Concept Study in AS

Study A2209

Title: Randomized, placebo controlled, double blind, multi-center Phase 2 proof-of-concept study to assess the efficacy of AIN457 in patients with moderate to severe ankylosing spondylitis.

Objectives

Primary:

- Part 1: To evaluate the efficacy of AIN457 at 6 weeks based on the proportion of patients achieving an ASAS20 response
- Part 2: To evaluate the efficacy of lower doses of AIN457 at 6 weeks based on the change in BASDAI score

Secondary:

- Efficacy at other time points
- PK
- Safety and tolerability

Exploratory:

- Model free IL-17 levels in AS patients
- Build preliminary AIN457 concentration-IL-17 inhibition-ASAS response-time model
- Exploratory genetic and other biomarkers studies

Study Design and Treatment Schedule: This was a 2-part multi-center PoC study of two doses of either 10 mg/kg, 1.0 mg/kg or 0.1 mg/kg of AIN457 (2 infusions 3 weeks apart) for the treatment of patients with a diagnosis of moderate to severe AS with or without previous TNF antagonist therapy.

The study consisted of 3 periods: a screening period of 4 weeks; a treatment period of 3 weeks, and a follow-up period of 25 weeks. AIN457 or placebo was administered on Day 1 and Day 22.

- Part 1: Subjects were randomized to receive two IV doses of either AIN457 10 mg/kg or placebo (2 infusions 3 weeks apart) in a ratio of 4:1.
- Part 2: Subjects were randomized to two IV doses of either 10 mg/kg, 1.0 mg/kg or 0.1 mg/kg of AIN457, respectively (2 infusions 3 weeks apart) in a ratio of 2:2:1.

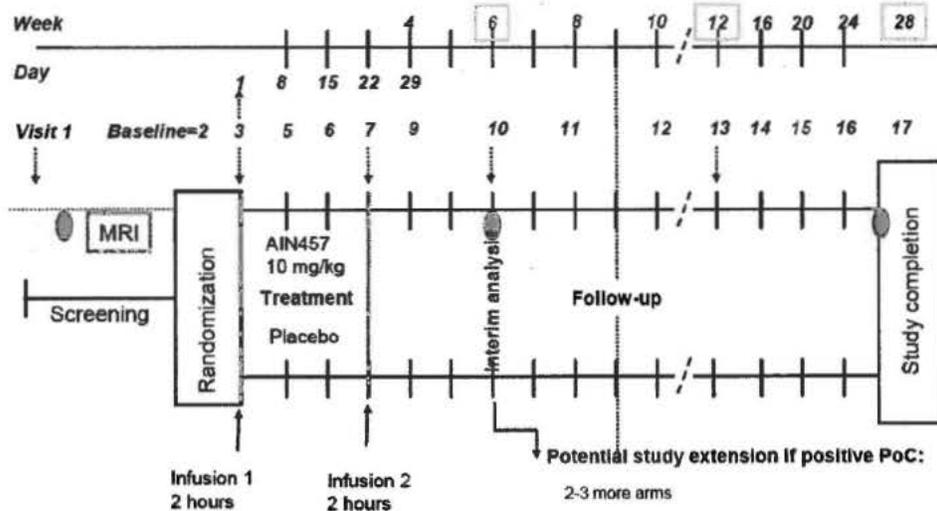


Figure 1. Study Design
(Source: Figure 9-1, Study AIN457A2209 report)

Test product

Study drug and strength	Formulation control number	Batch number
AIN457 50 mg	LYVI 7005405.005	Y017 0208 Y071 0409
Placebo	LYVI 7005406.004	Y021 0208

(Source: Table 9-1, Study AIN457A2209 report)

PK Assessment

Blood samples were collected: pre-dose, 2, 3, 4 and 24 hours after initiation of the infusions (Days 1 and 22), Weeks 1, 2, 4, 6, 8, 12, 16, 20, 24 and end of study/Week 28.

An ELISA method was used for bioanalytical analyses and the LLOQ of 80 ng/mL.

Immunogenicity Assessment

Blood samples were collected at baseline, and Weeks 12 and 28 (EOS).

Results

PK Results

The PK profiles and PK parameters are shown in Figure 2 and Tables 1 and 2. Following IV infusion at doses ranged 0.1-10 mg/kg, the mean clearance was 0.12-0.17 L/day and the apparent elimination half-life was 25-34 days.

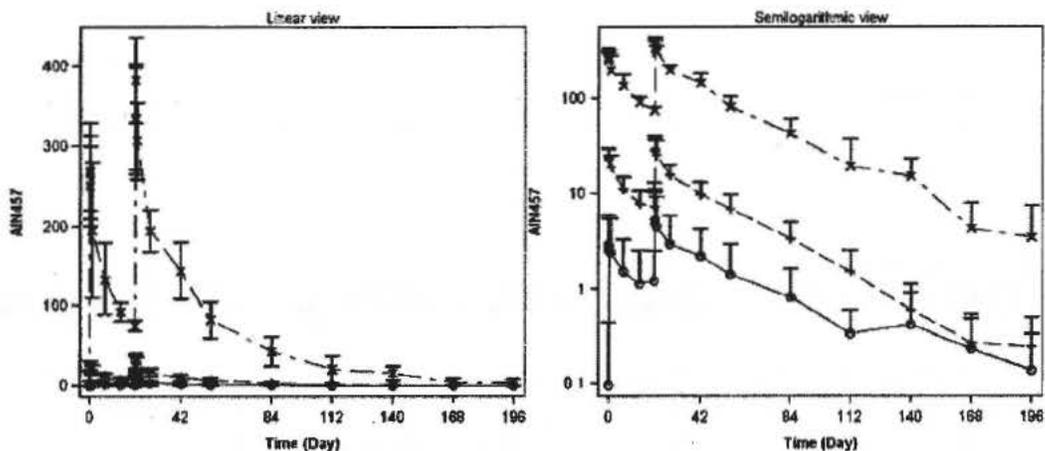


Figure 2. Arithmetic mean (SD) AIN457 serum concentration-time profile (Part 1 and 2 combined)

(Source: Figure 11-18, Study AIN457A2209 report)

Table 1. Pharmacokinetic parameters in Part 1

	Cmax (µg/mL)	Tmax * (day)	AUCinf (day*µg/mL)	AUClast (day*µg/mL)	Cl (L/day)	Vz (L)	T1/2 (day)
n	23	23	20	20	20	20	20
Mean (SD)	357.7 (87.74)	21.07 (0.083 - 21.9)	10510 (3036)	10310 (2869)	0.1594 (0.04998)	6.121 (0.999)	27.95 (5.624)
CV% mean	24.5	-	28.9	27.8	31.4	16.3	20.1

Source: PT-Table 14.2-10.1.a * Median (range) is given for Tmax.

(Source: Table 11-18, Study AIN457A2209 report)

Table 2. Summary of pharmacokinetic parameters Part 1 and 2 combined

	Cmax (µg/mL)	Tmax * (day)	AUCinf (day*µg/mL)	AUClast (day*µg/mL)	Cl (L/day)	Vz (L)	T1/2 (day)
2 x 10 mg/kg							
n	28	28	25	25	25	25	25
Mean (SD)	363.9 (82.30)	21.08 (0.083 - 22.2)	10880 (2983)	10630 (2818)	0.1571 (0.04734)	6.055 (0.943)	28.09 (5.994)
CV%	22.6		27.4	26.5	30.1	15.6	21.3
2 x 1 mg/kg							
n	12	12	11	11	11	11	11
Mean (SD)	33.13 (9.828)	21.08 (0.125 - 23.0)	1025 (276.0)	993.0 (279.5)	0.1718 (0.04942)	6.481 (1.701)	27.32 (7.234)
CV%	29.7		26.9	28.1	28.8	26.2	26.5
2 x 0.1 mg/kg							
n	12	12	11	11	11	11	11
Mean (SD)	5.509 (5.418)	21.12 (19.1 - 22.1)	198.0 (195.5)	187.7 (190.7)	0.1182 (0.05474)	5.827 (2.887)	34.31 (6.656)
CV%	98.3		98.8	101.6	46.3	49.5	19.4

Source: PT-Table 14.2-10.1.ab and PT-Table 14.2-10.2.ab *Median (range) is given for Tmax.

(Source: Table 11-19, Study AIN457A2209 report)

Immunogenicity Results

None of the patients tested for anti-AIN457 antibodies showed persistent, treatment-related immunogenicity.

Phase 3 Efficacy Study in AS

Study F2305

Title: A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis.

Objectives

Primary: to demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 20.

Secondary:

- Efficacy at Week 16: ASAS40, hsCRP, ASAS 5/6 response, BASDAI, PCS, ASQoL, ASAS partial remission
- Safety and tolerability

Exploratory:

- Efficacy at Week 16 and other time points
- Immunogenicity
- PK/PD

Study Design and Treatment Schedule: This is a double-blind, randomized, parallel-group, placebo controlled study. A screening period running 4 weeks before randomization was used to assess eligibility, followed by a treatment period of 2 years.

Eligible patients were randomized to one of three treatment groups:

- Group 1 (IV 75 mg-SC 75 mg): Secukinumab IV (10 mg/kg) at baseline, Week 2 and Week 4, and then secukinumab 75 mg SC starting at Week 8 and injected every 4 weeks
- Group 2 (IV150 mg-SC 150 mg): Secukinumab IV (10 mg/kg) at baseline, Week 2 and Week 4, and then secukinumab 150 mg SC starting at Week 8 and injected every 4 weeks
- Group 3 (Placebo): Placebo IV at baseline, Week 2 and Week 4, and then placebo SC at Week 8 and Week 12

At Week 16, the efficacy of secukinumab treatment was assessed based on ASAS 20 improvement criteria and all patients were classified as responders or non-responders.

Patients who had been randomized to placebo (Group 3) at baseline were to be re-randomized to receive double-blind treatment up to 2 years:

- Placebo non-responders were re-randomized to receive secukinumab 75 mg or 150 mg SC (1:1) injected every 4 weeks
- Placebo responders remained on placebo SC at Weeks 16 and 20. At Week 24, these patients received secukinumab 75 mg SC or 150 mg SC (1:1) injected every 4 weeks, regardless of responder status, as dictated by the re-randomization.

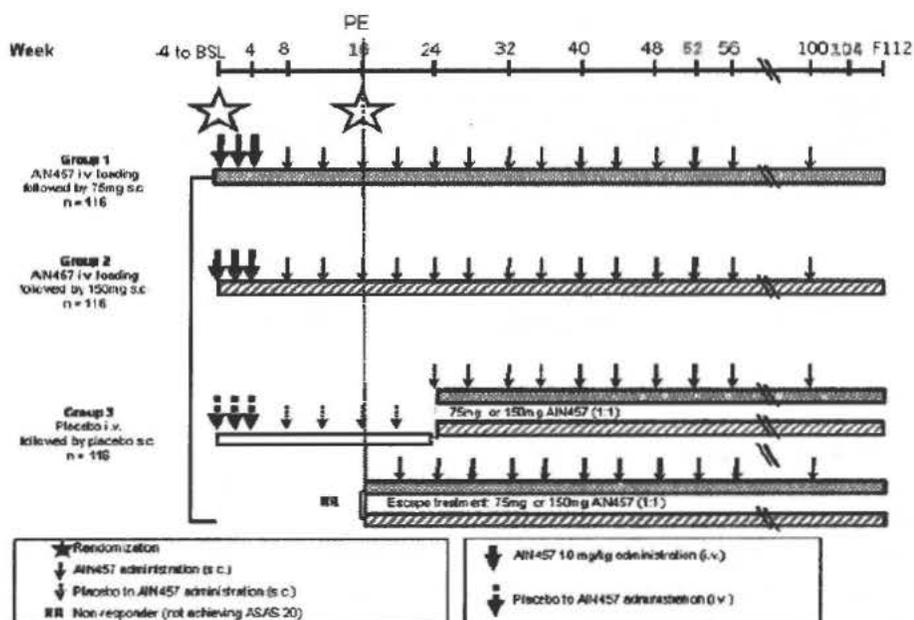


Figure 3. Study Design

(Source: Figure 9-1, Study AIN457F2305 report)

Test product

Study drug and strength	Formulation control number	Batch number
Secukinumab 150 mg Powder for Solution	7006580.010	S0006
		S0007
		S0012
		S0016
Placebo matching secukinumab	7005406.005	Y055 0511
		Y131 0609
		Y136 1110

(Source: Table 9-1, Study AIN457F2305 report)

PK Assessment

PK blood samples were collected pre-dose at baseline, Weeks 4, 16, 24, and 52.

Serum secukinumab concentrations were analyzed by an ELISA assay with the LLOQ of 80 ng/mL.

Immunogenicity Assessment

Blood samples for immunogenicity assessment were collected pre-dose at baseline, Weeks 16, 24, 52, 104, and 112.

Anti-AIN457 antibodies were assessed in serum using an electrochemiluminescence method.

Results

PK results

The serum concentrations of secukinumab by treatment at each visit were summarized in the Table below.

Table 3. Secukinumab concentrations by treatment and visit

Visit	10 mg/kg-75 mg		Placebo non-responders 75 mg		Placebo responders 75 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	116	132 ± 37.9	--	--	--	--
Week 16	112	37.1 ± 17.6	--	First dose	--	--
Week 24	110	17.2 ± 9.06	35	8.92 ± 4.25	--	First dose
Week 52	93	10.9 ± 4.88	28	11.4 ± 5.03	14	11.7 ± 5.25

Visit	10 mg/kg-150 mg		Placebo non-responders 150 mg		Placebo responders 150 mg	
	n	Conc (µg/mL)	n	Conc (µg/mL)	n	Conc (µg/mL)
Week 4	111	131 ± 38.5	--	--	--	--
Week 16	117	43.6 ± 18.8	--	First dose	--	--
Week 24	112	25.5 ± 11.7	35	13.7 ± 5.57	--	First dose
Week 52	96	20.0 ± 7.92	28	17.2 ± 6.65	17	18.2 ± 6.19

(Source: Table 11-9, Study AIN457F2305 report)

Immunogenicity

The incidence of anti-secukinumab antibody was summarized in the Table as below. Overall, the ADA incidence is low and there is no evidence of the impact of ADA formation on PK, efficacy and safety.

Table 4. Overview of patients with anti-drug antibodies (ADAs)

Patient ID (F2305-)	Group	Prior biologics	ADA ¹ (titer) /N-Ab	Impact on efficacy ²	AE possibly IG related ³	PK ⁴
Patients with treatment emergent ADA (n=2)						
(b) (6)	AIN457 10mg/kg -150 mg	None	Week 52 (2.39) / Yes	No	None	Normal
(b) (6)	Placebo non-responder - AIN457 150 mg	None	Week 52 (10.61) / No	No	None	Normal
Patients with baseline and post-baseline persistent ADA (n=1)						
(b) (6)	Placebo non-responder - AIN457 150 mg	None	BL (no titer) / Yes Week 16 (no titer) / Yes	n/a	None	Normal
Patients with only baseline ADA (n=3)						
(b) (6)	AIN457 10mg/kg - 75 mg	infliximab	BL (7.81) / Yes	n/a	None	Normal
(b) (6)	AIN457 10mg/kg - 150 mg	None	BL (2.80) / Yes	n/a	None	Normal
(b) (6)	Placebo responder - 75 mg	None	BL (2.05) / Yes	n/a	None	n/a (only one PK time point during treatment)

ADA=anti-drug antibodies; BL=baseline; IG=immunogenicity; N-Ab=neutralizing antibodies; n/a=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Only applicable to patients with treatment emergent ADAs. For patients who newly develop post-baseline ADA, loss of efficacy is defined as failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits at any time prior to first detection of ADA

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: Table 12-22, Study AIN457F2305 report)

Phase 3 Efficacy Study in AS

Study F2310

Title: A randomized, double-blind, placebo-controlled Phase 3 multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active Ankylosing Spondylitis.

Objectives

Primary: to demonstrate that the efficacy of secukinumab 75 mg s.c. or 150 mg s.c. at Week 16 was superior to placebo in subjects with active AS based on the proportion of subjects achieving an ASAS 20 response.

Secondary:

- Efficacy of at least one dose of secukinumab at Week 16 was superior to placebo in patients with active AS based on ASAS 40, hsCRP, ASAS 5/6 response, etc.
- Safety and tolerability

Exploratory:

- The efficacy of secukinumab at other time points
- Immunogenicity
- PK/PD relationship of secukinumab
- Pharmacogenetic assessments

Study Design and Treatment Schedule: The study used a randomized, double-blind, double-dummy, placebo controlled, parallel-group design. A screening period running 4-10 weeks before randomization was used to assess patient's eligibility followed by 52 weeks of blinded treatment and 4 years of additional long-term treatment. A total of 222 eligible patients were randomized at baseline (BSL), to one of three treatment groups (1:1:1).

- Group 1 (SC 75 mg-SC-75 mg): secukinumab 75 mg plus placebo 150 mg once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4
- Group 2 (SC 150 mg-SC150 mg):: secukinumab 150 mg plus placebo 75 mg once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4
- Group 3 (Placebo): placebo 75 mg and placebo 150 mg once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 16

At Week 16, subjects who had been randomized to placebo at baseline were re-randomized to receive secukinumab 75 mg plus placebo 150 mg or secukinumab 150 mg plus placebo 75 mg (1:1) every 4 weeks up to 256 weeks.

After the Week 52 analysis was conducted, site personnel and the subject were unblinded to the subject's treatment regimen in order to eliminate the placebo injection (i.e. only 75 mg or 150 mg secukinumab were dispensed). The subjects continued to receive the same active dose of secukinumab as open-label treatment until Week 256, and the subjects no longer received the placebo PFS, which had been administered to maintain the dose double-blind.

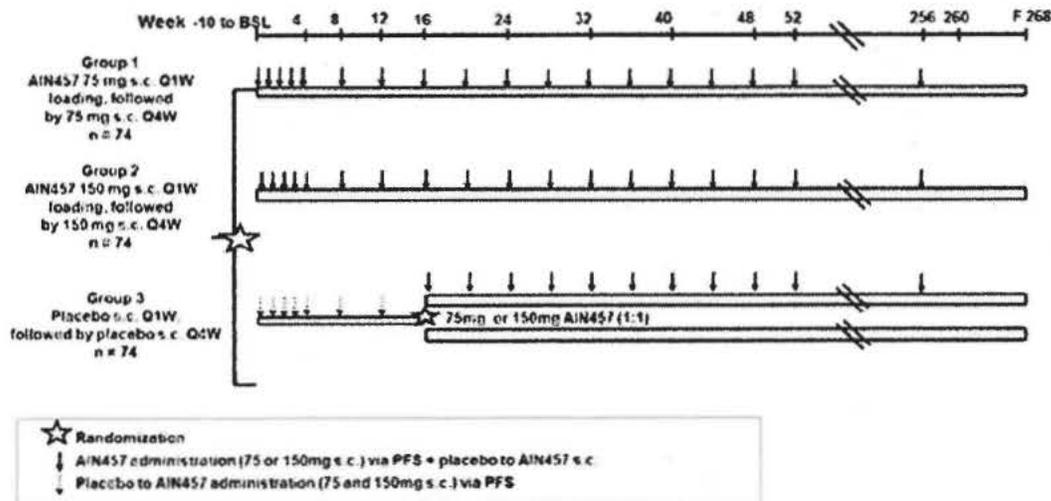


Figure 4. Study Design
(Source: Figure 9-1, Study CAIN457F2310 report)

Test Product

Study drug and strength	Formulation control number	Batch number
AIN457 150mg/1ml PFS	7007916.002	U003 0711
	7007916.008	S0005
AIN457 75mg/0.5ml PFS	7007917.008	U004 0711
	7007917.011	S0004
AIN457 Placebo/0.5ml PFS	7008332.001	Y067 0711
	7008332.002	Y104 1012
AIN457 Placebo/1ml PFS	7008333.003	Y093 0911
	7008333.004	Y118 1212

(Source: Table 9-1, Study CAIN457F2310 report)

PK Assessment

The PK samples were collected pre-dose at baseline and Weeks 4, 16*, 24, 52*, 104*, 156*, 208*, 260*, and 268*.

(*For all subjects who discontinued or withdrew from the study, the investigator ensured that the subject completed an end of treatment visit (corresponded to the last visit for the subject's current period of treatment) 4 weeks after last study treatment, and also returned after an additional 8 weeks for a final follow-up visit, F268 (12 weeks after last study treatment). The final visit was performed before any new treatment was initiated.)

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 16*, 24, 52*, 104*, 156*, 208*, 260*, 268*.

(*For all subjects who discontinued or withdrew from the study, the investigator ensured that the subject completed an end of treatment visit (corresponded to the last visit for the subject's current period of treatment) 4 weeks after last study treatment, and also returned after an additional 8 weeks for a final follow-up visit, F268 (12 weeks after last study treatment). The final visit was performed before any new treatment was initiated.)

An electrochemiluminescence method was used for the detection of potential anti-secukinumab antibody formation.

Results

PK results

All mean trough serum concentrations by treatment and visit are summarized in Table 5. At Week 52, the steady state was reached and the mean serum concentrations are in dose-proportional manner.

Table 5. Secukinumab concentrations by treatment and visit

Visit	75 mg		150 mg		Placebo → 75 mg		Placebo → 150 mg	
	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)	N	Conc (ug/mL)
Week 4	56	25.4 ± 9.42	63	52.9 ± 17.9	--	Placebo	--	Placebo
Week 16	52	13.0 ± 5.35	56	23.0 ± 10.8	--	First dose	--	First dose
Week 24	50	11.3 ± 4.63	55	20.3 ± 9.98	18	8.37 ± 3.38	25	15.5 ± 4.79
Week 52	47	10.8 ± 5.15	48	20.7 ± 8.63	15	11.0 ± 6.70	17	18.8 ± 5.70

Conc = secukinumab concentration.
(Source: Table 11-11, Study CAIN457F2310 report)

Immunogenicity results

The incidence of anti-secukinumab antibody was summarized in the Table as below. Overall, the ADA incidence is low and there is no evidence of the impact of ADA formation on PK, efficacy and safety.

Table 6. Overview of patients with anti-drug antibodies (ADAs)

Patient ID	Group	Prior biologics	ADA ¹ (titer)/ N-Ab	Impact on efficacy ²	AE possibly IG related ³ (Day of onset)	PK ⁴
Patients with only baseline ADA (n=4)						
(b) (6)	Placebo - AIN457 75 mg	None	Baseline (1.98)/ No	n/a	No	NA, Only 1 PK result available
	Placebo - AIN457 150 mg	ETANERCEPT	Baseline (No titer)/ No	n/a	Seasonal allergy /Day-45 /Non-SAE	NA, Only 1 PK result available
	AIN457 150 mg	None	Baseline (2.03)/ No	n/a	No	Normal*
	AIN457 150 mg	INFLIXIMAB	Baseline (No titer)/ YES	n/a	No	Normal

*ADA=anti-drug antibodies; BL=baseline; IG=immunogenicity; N-Ab=neutralizing antibodies; n/a=not applicable; PK=pharmacokinetics

¹ Only positive ADA results at the respective study week are shown

² Only applicable to patients with treatment emergent ADAs. For patients who newly develop post-baseline ADA, loss of efficacy is defined as failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits prior to first detection of ADA

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"

* Patient (b) (6) did not show steady state behavior.

n/a = not available

(Source: Table 12-8, Study CAIN457F2310 report)

4.3. Appendix – New Drug Application Filing and Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	125504 Supplement-02	SDN	168
Applicant	Novartis	Submission Date	03/23/2015
Generic Name	Secukinumab (AIN457, NVP-AIN457)	Brand Name	COSENTYX
Drug Class	Recombinant human IgG1κ monoclonal antibody against interleukin (IL)-17A		
Indication	Ankylosing Spondylitis (AS)		
Dosage Regimen	The proposed dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly 150 mg dosing starting at Week 4.		
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	5/22/2015	74-Day Letter Date	5/29/2015
Review Due Date	12/11/2015	PDUFA Goal Date	1/23/2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
<input checked="" type="checkbox"/> Yes			
<input type="checkbox"/> No			
If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			
If yes list comment(s)			

Is there a need for clinical trial(s) inspection?		
<input type="checkbox"/> Yes		
<input checked="" type="checkbox"/> No		
If yes explain		
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 CAIN457A2209 (AS); Study CAIN457F2201 (RA);

		Study CAIN457F2310 (AS); Study CAIN457F2305 (AS). Bioanalytical Assay Reports (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		Population pharmacokinetics of secukinumab (AIN457) in ankylosing spondylitis Modeling Report	
<input checked="" type="checkbox"/> Exposure-Efficacy		Graphical exploratory analysis of secukinumab (AIN457) exposure-response of efficacy and adverse events in ankylosing spondylitis patients	
<input type="checkbox"/> Exposure-Safety			
Total Number of Studies	In Vitro	In Vivo	4
Total Number of Studies to be Reviewed			14

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/s/

LEI HE
12/15/2015

PING JI
12/15/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s002

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.

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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
11467775
11467879
11475682
11482158
11486080
11486261
11486750
11486840
11487399
11487598
11490219
11491815

11493235
11497114
11497164
11510710
11510809
11512372
11514435
11514437
11528221
11528516
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
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

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 (DPAAP) 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