CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA125504Orig1s063

Name: Cosentyx (secukinumab) injection

Sponsor: Novartis Pharmaceuticals Corporation.

Approval Date: October 10, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s073

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s063

APPROVAL LETTER

BLA 125504/S-063

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Gaelle Enderlin
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936

Dear Gaelle Enderlin:

Please refer to your supplemental biologics license application (sBLA), dated and received September 30, 2022, submitted under section 351(a) of the Public Health Service Act for Cosentyx (secukinumab) injection, for subcutaneous use.

We acknowledge receipt of your major amendment dated July 10, 2023, which extended the goal date by three months.

This Prior Approval supplemental biologics license application provides support for the use of Cosentyx for the treatment of adult patients with moderate to severe hidradenitis suppurativa.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

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 FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also, within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 ages <12 years because necessary studies are impossible or highly impracticable as HS typically starts after puberty, and there is a rarity of diagnosis in children aged <12 years of age.

We are deferring submission of your pediatric study for ages 12 to <17 years for this application because this product is ready for approval for use in adults and the adolescent studies (i.e., PK-based extrapolation) have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

#4543 Conduct an open-label study to evaluate the pharmacokinetics (PK) and safety in the adolescent population 12 to less than 17 years of age with moderate to severe hidradenitis suppurativa who are candidates for systemic treatment. Evaluate at least 80 subjects exposed to the highest approved dosage of subcutaneous secukinumab (300 mg every 2 weeks) for a minimum of 52 weeks.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Draft Protocol Submission: 07/2024
Final Protocol Submission: 01/2025
Study Completion: 08/2029
Final Report Submission: 02/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol to your IND 100418, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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 Sascha Randolph, Regulatory Project Manager, at Sascha.Randolph@fda.hhs.gov or at (301)796-8546.

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[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TATIANA OUSSOVA
11/01/2023 03:43:27 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s063

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 or intravenous use

Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.6)	10/2023
Dosage and Administration (2.2, 2.3, 2.4, 2.7, 2.10)	5/2023
Dosage and Administration (2.2, 2.4, 2.5, 2.6, 2.7, 2.9, 2.11)	10/2023
Warnings and Precautions (5.4)	10/2023
Warnings and Precautions (5.5)	7/2023

----------INDICATIONS AND USAGE----------

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

- moderate to severe **plaque psoriasis (PsO)** in patients 6 years and older who are candidates for systemic therapy or phototherapy. (1.1)
- active **psoriatic arthritis (PsA)** in patients 2 years of age and older. (1.2)
- adults with **active ankylosing spondylitis (AS)**. (1.3)
- adults with active **non-radiographic axial spondyloarthritis (nr-axSpA)** with objective signs of inflammation. (1.4)
- active **enthesitis-related arthritis (ERA)** in pediatric patients 4 years of age and older. (1.5)
- adults with moderate to severe **hidradenitis suppurativa (HS)** (1.6)

----------DOSAGE AND ADMINISTRATION----------

- Prior to COSENTYX initiation, complete all age-appropriate vaccinations, evaluate patients for tuberculosis (TB). (2.1). See Full Prescribing Information for instructions on preparation and administration of COSENTYX. (2.2, 2.9, 2.10)
- **Administration of Intravenous Formulation:** COSENTYX for intravenous use must be diluted prior to administration. Administer as an intravenous infusion after dilution over a period of 30 minutes. (2.10)
- **Plaque Psoriasis:**
  - *Subcutaneous Dosage in Adults:* 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. (2.3)
  - *Subcutaneous Dosage in Pediatric Patients 6 Years and Older:* Recommended weight-based dosage is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
    - For patients < 50 kg (at the time of dosing), the dose is 75 mg.
    - For patients ≥ 50 kg (at the time of dosing), the dose is 150 mg. (2.3)
- **Psoriatic Arthritis:**

  Adult Patients

  Subcutaneous Dosage:
  - For PsA patients with coexistent moderate to severe PsO, use the dosage and administration for PsO. (2.3)
  - For other PsA patients, administer with or without a loading dosage.
    - With a loading dosage: 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter
    - Without a loading dosage: 150 mg every 4 weeks
    - If a patient continues to have active PsA, consider a dosage of 300 mg every 4 weeks. (2.4)

  Intravenous Dosage:

  The recommended intravenous dosages are:
  - With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (max. maintenance dose 300 mg per infusion).
  - Without a loading dosage: 1.75 mg/kg every 4 weeks (max. maintenance dose 300 mg per infusion). (2.4)

  Pediatric Patients 2 Years and Older

  Subcutaneous Dosages: Administer by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter:
  - For patients ≥ 15 kg and < 50 kg the dose is 75 mg.
  - For patients ≥ 50 kg the dose is 150 mg. 2.5)
- **Ankylosing Spondylitis:**

  Subcutaneous Dosage:

  Administer with or without a loading dosage.

  The recommended dosages are:
  - With a loading dosage: 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
  - Without a loading dosage: 150 mg every 4 weeks.
  - If a patient continues to have active ankylosing spondylitis, consider a dosage of 300 mg every 4 weeks. (2.6)

  Intravenous Dosage:

  The recommended intravenous dosages are:
  - With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (max. maintenance dose 300 mg per infusion).
  - Without a loading dosage: 1.75 mg/kg every 4 weeks (max. maintenance dose 300 mg per infusion). (2.6)
- **Non-Radiographic Axial Spondyloarthritis:**

  Subcutaneous Dosage:

  Administer with or without a loading dosage. The recommended dosage is:
  - With a loading dosage: 150 mg at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
  - Without a loading dosage: 150 mg every 4 weeks. (2.7)

  Intravenous Dosage:

  The recommended intravenous dosages are:
  - With a loading dosage: 6 mg/kg given at Week 0 as a loading dose, followed by 1.75 mg/kg every 4 weeks thereafter (max. maintenance dose 300 mg per infusion).
  - Without a loading dosage: 1.75 mg/kg every 4 weeks (max. maintenance dose 300 mg per infusion). (2.7)
- **Enthesitis-Related Arthritis:** Recommended weight-based dosage is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
  - For patients ≥ 15 kg and < 50 kg the dose is 75 mg.
  - For patients ≥ 50 kg the dose is 150 mg. 2.8)
- **Hidradenitis Suppurativa:** Recommended dosage is 300 mg administered by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 and every 4 weeks thereafter. If a patient does not adequately respond, consider increasing the dosage to 300 mg every 2 weeks. (2.9)

----------DOSAGE FORMS AND STRENGTHS----------

Subcutaneous Injection

- Injection: 300 mg/2 mL solution in a single-dose UnoReady® pen and in a single-dose prefilled syringe. (3)
- Injection: 150 mg/mL solution in a single-dose Sensoready® pen and in a single-dose prefilled syringe. (3)
- Injection: 75 mg/0.5 mL solution in a single-dose prefilled syringe (for pediatric patients). (3)

Intravenous Infusion

- Injection: 125 mg/5 mL solution in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

Serious hypersensitivity to secukinumab or any excipients in COSENTYX. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Serious infections have occurred. Exercise caution 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)
- Hypersensitivity Reactions: If an anaphylactic reaction or other serious allergic reaction occurs, discontinue COSENTYX immediately and initiate appropriate therapy. (5.2)
- Tuberculosis (TB): Prior to initiating treatment with COSENTYX, evaluate for TB. (5.3)
- Inflammatory Bowel Disease (IBD): Cases of IBD were observed in clinical trials. Exercise caution when prescribing COSENTYX to patients with IBD. (5.4)
- Eczematous Eruptions: Cases of severe eczematous eruptions have occurred in patients receiving COSENTYX. (5.5)
- Immunizations: Avoid use of live vaccines in patients treated with COSENTYX. (5.7)

----------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.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

COSENTYX® is indicated for the treatment of moderate to severe plaque psoriasis (PsO) in patients 6 years and older who are candidates for systemic therapy or phototherapy.

1.2 Psoriatic Arthritis

COSENTYX is indicated for the treatment of active psoriatic arthritis (PsA) in patients 2 years of age and older.

1.3 Ankylosing Spondylitis

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

1.4 Non-Radiographic Axial Spondyloarthritis

COSENTYX is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

1.5 Enthesitis-Related Arthritis

COSENTYX is indicated for the treatment of active enthesitis-related arthritis (ERA) in pediatric patients 4 years of age and older.

1.6 Hidradenitis Suppurativa

COSENTYX is indicated for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).

2 DOSAGE AND ADMINISTRATION

2.1 Testing and Procedures Prior to Treatment Initiation

Perform the following evaluations prior to COSENTYX initiation:

- Evaluate for active or latent tuberculosis (TB). COSENTYX initiation is not recommended in patients with active TB infection. Initiate treatment of latent TB prior to initiation of COSENTYX *[see Warnings and Precautions (5.3)]*.
- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with COSENTYX *[see Warnings and Precautions (5.7)]*.

2.2 Important Administration Instructions

- COSENTYX is for use under the guidance and supervision of a healthcare provider.
- UnoReady pens, Sensoready pens, and prefilled syringes are for subcutaneous use only.
- Solution in vials is for intravenous use in adult patients only.

Important Subcutaneous Administration Instructions

Adult patients may self-administer COSENTYX or be injected by a caregiver after proper training in subcutaneous injection technique.

Pediatric patients should not self-administer COSENTYX. An adult caregiver should prepare and inject COSENTYX after proper training in subcutaneous injection technique.

Administer each subcutaneous 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 subcutaneous COSENTYX in the upper, outer arm may be performed by a caregiver or healthcare provider.

The COSENTYX "Instructions for Use" for each presentation and strength contains more detailed instructions on the preparation and administration of COSENTYX for patients and caregivers *[see Instructions for Use]*.

Important Intravenous Infusion Instructions

Intravenous infusion is only for use by a healthcare professional in a healthcare setting. Prepare COSENTYX intravenous infusion by diluting COSENTYX injection in vial(s) and administering based on patient body weight *[see Dosage and Administration (2.10)]*. Intravenous infusion may be administered only in adults with PsA, AS, and nr-axSPA.

2.3 Recommended Dosage in Plaque Psoriasis

Recommended Subcutaneous Dosage in Adults with PsO

The recommended dosage in adults with PsO is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. Each 300 mg dosage is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

For some patients, a dosage of 150 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter may be acceptable.

Recommended Subcutaneous Dosage in Pediatric Patients 6 Years of Age and Older with PsO

The recommended weight-based dosage in pediatric patients 6 years of age and older with PsO is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.

- For patients < 50 kg (at the time of dosing), the recommended dose is 75 mg.
- For patients ≥ 50 kg (at the time of dosing), the recommended dose is 150 mg.

2.4 Recommended Dosage in Adults with Psoriatic Arthritis

COSENTYX may be administered with or without methotrexate.

Recommended Subcutaneous Dosage

For adult patients with PsA and with coexistent moderate to severe PsO, use the dosage and administration recommendations for adults with PsO *[see Dosage and Administration (2.3)]*.

For other adult patients with PsA, administer COSENTYX with or without a loading dosage by subcutaneous injection.

The recommended dosage in adults with PsA:

- 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 PsA, consider increasing the dosage to 300 mg by subcutaneous injection every 4 weeks. Each 300 mg dosage is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Recommended Intravenous Dosage

COSENTYX injection for intravenous use (solution in vials) requires dilution prior to intravenous administration. The recommended intravenous dosage regimen in adults with PsA:

- With a loading dosage is 6 mg/kg loading dose given at Week 0, followed by 1.75 mg/kg every 4 weeks thereafter (maintenance dosage).
- Without a loading dosage is 1.75 mg/kg every 4 weeks.

Administer as an intravenous infusion over a period of 30 minutes *[see Dosage and Administration (2.10)]*.

Total doses exceeding 300 mg per infusion are not recommended for the 1.75 mg/kg maintenance dose in adults with PsA *[see Dosage and Administration (2.10)]*.

2.5 Recommended Dosage in Pediatric Patients 2 Years of Age and Older with Juvenile Psoriatic Arthritis

COSENTYX may be administered with or without methotrexate.

The recommended weight-based subcutaneous dosage in pediatric patients 2 years of age and older with PsA at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter is as follows:

- For patients ≥ 15 kg and < 50 kg, the recommended dose is 75 mg.
- For patients ≥ 50 kg, the recommended dose is 150 mg.

2.6 Recommended Dosage in Adults with Ankylosing Spondylitis

Recommended Subcutaneous Dosage

Administer COSENTYX with or without a loading dosage by subcutaneous injection in adult patients with active AS. 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 AS, consider increasing the dosage to 300 mg every 4 weeks by subcutaneous injection. Each 300 mg dosage is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Recommended Intravenous Dosage

COSENTYX injection for intravenous use (solution in vials) requires dilution prior to intravenous administration. The recommended intravenous dosage regimen in adult patients with active AS:

- With a loading dosage is 6 mg/kg loading dose given at Week 0, followed by 1.75 mg/kg every 4 weeks thereafter (maintenance dosage).
- Without a loading dosage is 1.75 mg/kg every 4 weeks.

Administer as an intravenous infusion over a period of 30 minutes *[see Dosage and Administration (2.10)]*.

Total doses exceeding 300 mg per infusion are not recommended for the 1.75 mg/kg maintenance dose in patients with AS *[see Dosage and Administration (2.10)]*.

2.7 Recommended Dosage in Adults with Non-Radiographic Axial Spondyloarthritis

Recommended Subcutaneous Dosage

Administer COSENTYX with or without a loading dosage by subcutaneous injection in adult patients with active nr-axSpA. 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.

Recommended Intravenous Dosage

COSENTYX injection for intravenous use (solution in vials) requires dilution prior to intravenous administration. The recommended intravenous dosage regimen in adult patients with active nr-axSpA:

- With a loading dosage is 6 mg/kg loading dose given at Week 0, followed by 1.75 mg/kg every 4 weeks thereafter (maintenance dosage).
- Without a loading dosage is 1.75 mg/kg every 4 weeks.

Administer as an intravenous infusion over a period of 30 minutes *[see Dosage and Administration (2.10)]*.

Total doses exceeding 300 mg per infusion are not recommended for the 1.75 mg/kg maintenance dose in patients with nr-axSpA *[see Dosage and Administration (2.10)]*.

2.8 Recommended Dosage in Enthesitis-Related Arthritis

COSENTYX may only be administered as a subcutaneous injection in pediatric patients aged 4 years and older with active ERA.

The recommended weight-based dosage in pediatric patients 4 years of age and older with ERA is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter:

- For patients ≥ 15 kg and < 50 kg, the recommended dose is 75 mg.
- For patients ≥ 50 kg, the recommended dose is 150 mg.

2.9 Recommended Dosage in Hidradenitis Suppurativa

The recommended dose in adult patients with moderate to severe HS is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 and every 4 weeks thereafter.

If a patient does not adequately respond, consider increasing the dosage to 300 mg every 2 weeks. Each 300 mg dosage is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

2.10 Preparation for Use of COSENTYX UnoReady Pen, Sensoready Pen and Prefilled Syringes

COSENTYX UnoReady pens, Sensoready pens and prefilled syringes are for subcutaneous injection only.

Before subcutaneous injection, remove COSENTYX from the refrigerator and allow COSENTYX to reach room temperature (15 to 30 minutes for the Sensoready pen, the 150 mg/mL and 75 mg/0.5 mL prefilled syringes; 30 to 45 minutes for the UnoReady pen and the 300 mg/2 mL prefilled syringe) without removing the needle cap.

The removable cap of the COSENTYX 150 mg/mL Sensoready pen and the COSENTYX prefilled syringes (150 mg/mL, 75 mg/0.5 mL) contain natural rubber latex and should not be handled by latex-sensitive individuals *[see Warnings and Precautions (5.6)]*.

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. Discard any unused product.

2.11 Preparation and Administration of COSENTYX for Intravenous Use

COSENTYX (for intravenous use) must be diluted prior to infusion. Using aseptic technique, prepare COSENTYX (for intravenous use) as follows:

Step 1. Volume Calculation

- Calculate the total volume of COSENTYX for intravenous use solution (in mL) required based on the patient's actual body weight as follows:
    - Loading dose (6 mg/kg) is 0.24 mL/kg
    - Maintenance dose (1.75 mg/kg) is 0.07 mL/kg
- Use the number of vials based on total volume needed (one vial contains 5 mL of COSENTYX solution).

Step 2. Dilution

- Before dilution, allow the COSENTYX solution in vial(s) to sit for approximately 20 minutes at room temperature 20ºC to 25ºC (68ºF to 77ºF).
- Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulates or discolorations are noted.
- Follow Table 1 for recommended infusion bag size based on patient's body weight.

Table 1: Recommended Infusion Bags for Dilution and Preparation of COSENTYX for Intravenous Use Based on Body Weight and Dose

Body weight at time of dosing	For the loading dose (6 mg/kg) recommended infusion bag	For maintenance dose (1.75 mg/kg) recommended infusion bag
Greater than 52 kg	100 mL	100 mL
Less than or equal to 52 kg	100 mL	50 mL*

*If a 50 mL infusion bag is unavailable, then use a 100 mL infusion bag and withdraw and discard 50 mL of saline using aseptic technique and continue to follow the preparation and administration steps.

- From the infusion bag, withdraw and discard a volume of 0.9% Sodium Chloride Injection, USP, equal to the calculated volume of the COSENTYX solution required for the patient's dose *[see Dosage and Administration (2.4, 2.6, 2.7)]*.
- From the vial(s), withdraw the calculated volume (mL) of COSENTYX solution and add slowly into the 0.9% Sodium Chloride Injection, USP infusion bag. To mix the solution, gently invert the bag to avoid foaming. Do not shake.
- Discard unused COSENTYX product in vials because it does not contain preservatives.

Administer the diluted COSENTYX solution for infusion as soon as possible. If not administered immediately, store the diluted solution either:

- At room temperature 20ºC to 25ºC (68ºF to 77ºF) for no more than 4.5 hours from the start of the preparation (piercing the first vial) to the completion of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours, from the start of the time of the preparation (piercing the first vial) to the completion of infusion. This time includes the refrigeration of the diluted solution and the time to allow the diluted solution to warm to room temperature. Protect the diluted solution from light during storage under refrigeration.

Step 3. Administration

- Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
- Administer the infusion at a flow rate of about 3.3 mL/minute for a 100 mL bag or 1.7 mL/min for a 50 mL bag (total administration time: 30 minutes).
- When administration is complete, flush the line with at least 50 mL of 0.9% Sodium Chloride Injection, USP to guarantee that all the COSENTYX solution for infusion in the line has been administered.
- Do not infuse COSENTYX concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the IV coadministration of COSENTYX with other drugs.

3 DOSAGE FORMS AND STRENGTHS

Injection for subcutaneous use:

- 300 mg/2 mL as a clear to opalescent, colorless to slightly yellowish solution in a single-dose UnoReady pen
- 300 mg/2 mL as a clear to opalescent, colorless to slightly yellowish solution in a single-dose prefilled syringe
- 150 mg/mL as a clear to opalescent, colorless to slightly yellowish solution in a single-dose Sensoready pen
- 150 mg/mL as a clear to opalescent, colorless to slightly yellowish solution in a single-dose prefilled syringe
- 75 mg/0.5 mL as a clear to opalescent, colorless to slightly yellowish solution in a single-dose prefilled syringe (for pediatric patients less than 50 kg)

Injection for intravenous use:

- 125 mg/5 mL as a clear to opalescent, colorless to slightly yellowish solution in a single-dose vial for dilution prior to intravenous infusion (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 in COSENTYX. Cases of anaphylaxis have been reported during treatment with COSENTYX *[see Warnings and Precautions (5.2)]*.

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 subjects with moderate to severe PsO, 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 in subjects treated with COSENTYX compared to placebo-treated subjects. A similar increase in risk of infection in subjects treated with COSENTYX was seen in placebo-controlled trials in subjects with PsA, AS and nr-axSpA. The incidence of some types of infections, including fungal infections, appeared to be dose-dependent in clinical trials *[see Adverse Reactions (6.1)]*.

In the postmarketing setting, serious and some fatal infections have been reported in patients treated with COSENTYX.

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, monitor the patient closely and discontinue COSENTYX until the infection resolves.

5.2 Hypersensitivity Reactions

Anaphylaxis and cases of urticaria occurred in COSENTYX treated subjects in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of COSENTYX should be discontinued immediately and appropriate therapy initiated *[see Contraindications (4)]*.

5.3 Pre-Treatment Evaluation for Tuberculosis

Evaluate patients for active or latent TB infection prior to initiating treatment with COSENTYX. Avoid administration of 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. Monitor patients closely for signs and symptoms of active TB during and after treatment.

5.4 Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) exacerbations, in some cases serious and/or leading to discontinuation of COSENTYX, occurred in COSENTYX treated subjects during clinical trials in PsO, PsA, AS, nr-axSpA, and HS. In adult subjects with HS, the incidence of IBD was higher in subjects who received COSENTYX 300 mg every 2 weeks (Ulcerative Colitis [UC] 1 case, EAIR 0.2/100 subject-years; Crohn`s Disease [CD] 1 case, EAIR 0.2/100 subject-years) compared to subjects who received COSENTYX 300 mg every 4 weeks (IBD 1 case, EAIR 0.2/100 subject-years). In addition, new onset IBD cases occurred in subjects treated with COSENTYX in clinical trials. In an exploratory trial in 59 subjects with active Crohn's disease [COSENTYX is not approved for the treatment of Crohn`s disease], there were trends toward greater disease activity and increased adverse reactions in subjects treated with COSENTYX as compared to placebo-treated subjects.

Exercise caution when prescribing COSENTYX to patients with IBD. Patients treated with COSENTYX should be monitored for signs and symptoms of IBD *[see Adverse Reactions (6.1)]*.

5.5 Eczematous Eruptions

In postmarketing reports, cases of severe eczematous eruptions, including atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma, were reported in patients receiving COSENTYX; some cases resulted in hospitalization. The onset of eczematous eruptions was variable, ranging from days to months after the first dose of COSENTYX.

Treatment may need to be discontinued to resolve the eczematous eruption. Some patients were successfully treated for eczematous eruptions while continuing COSENTYX.

5.6 Risk of Hypersensitivity in Latex-Sensitive Individuals

The removable caps of the COSENTYX 150 mg/mL Sensoready pen and the COSENTYX 1 mL and 0.5 mL prefilled syringes contain natural rubber latex, which may cause a hypersensitivity reaction in latex-sensitive individuals. The safe use of COSENTYX 150 mg/mL Sensoready pen or 1 mL and 0.5 mL prefilled syringes in latex-sensitive individuals has not been studied.

5.7 Immunizations

Prior to initiating therapy with COSENTYX, consider completion of all age-appropriate immunizations according to current immunization guidelines. COSENTYX may alter a patient's immune response to live vaccines. Avoid use of live vaccines in patients treated with COSENTYX *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

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

- Infections *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Inflammatory Bowel Disease *[see Warnings and Precautions (5.4)]*
- Eczematous Eruptions *[see Warnings and Precautions (5.5)]*

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.

Adverse Reactions in Clinical Trials of Subcutaneous COSENTYX

Adverse Reactions from Clinical Trials in Adults with PsO

A total of 3,430 adult subjects with PsO were treated with COSENTYX in controlled and uncontrolled clinical trials. Of these, 1,641 subjects were treated with COSENTYX for at least 1 year.

Four placebo-controlled Phase 3 trials in PsO subjects (Trials PsO1, PsO2, PsO3, and PsO4) were pooled to evaluate the safety of COSENTYX in comparison to placebo up to 12 weeks after treatment initiation. In total, 2,077 subjects were evaluated (691 in the COSENTYX 300 mg group, 692 in the COSENTYX 150 mg group, and 694 in the placebo group). Subjects randomized to COSENTYX received 300 mg or 150 mg doses subcutaneously at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks *[see Clinical Studies (14)]*.

Table 2 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 these trials.

Table 2: Adverse Reactions Reported by Greater Than 1% of Adult Subjects With PsO (and at a Higher Rate in Subjects Treated with COSENTYX) Through Week 12 in Trials PsO1, PsO2, PsO3, and PsO4

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 in subjects treated with COSENTYX at rates less than 1% in the placebo-controlled period of Trials PsO1, PsO2, PsO3, and PsO4 through Week 12 included: sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, impetigo, otitis media, otitis externa, IBD, increased liver transaminases, and neutropenia.

Infections

In the placebo-controlled period of the clinical trials in PsO (a total of 1,382 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.

Over the entire treatment period (a total of 3,430 PsO 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 subject-year of

follow-up) and serious infections were reported in 1.2% of subjects treated with COSENTYX (0.015 per subject-year of follow-up).

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

In the PsO open-label extension of Trials PsO1 and PsO2 (median follow-up of 3.9 years), representing 3,582 subject-years of exposure, 74% of COSENTYX treated subjects reported infections (55 per 100 subject-years) and serious infections were reported in 4.5% of COSENTYX treated subjects (1.4 per 100 subject-years). Sepsis was reported in 5 COSENTYX treated subjects (0.2 per 100 subject-years).

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

In the open-label extension of Trials PsO1 and PsO2, neutropenia (ANC < 1 x 10^9/L) was reported in 1% of COSENTYX treated subjects (0.3 per 100 subject-years). Some cases of serious infections were associated with neutropenia; however, the causal relationship was not established.

Inflammatory Bowel Disease

Cases of IBD, in some cases serious, were observed in subjects treated with COSENTYX in clinical trials. In the PsO program, with 3,430 subjects exposed to COSENTYX over the entire treatment period for up to 52 weeks (2,725 subject-years), there were 3 cases (0.11 per 100 subject-years) of exacerbation of CD, 2 cases (0.08 per 100 subject-years) of exacerbation of UC, and 2 cases (0.08 per 100 subject-years) of new onset UC. There were no IBD cases in placebo-treated subjects (N = 793; 176 subject-years) during the 12-week placebo-controlled period.

One case of exacerbation of Crohn's disease in a subject treated with COSENTYX subject was reported in open-label portions of clinical trials in PsO.

Adverse Reactions from Clinical Trials in Pediatric Subjects with PsO

The safety of COSENTYX was assessed in two Phase 3 trials in pediatric subjects with PsO.

- The first was a randomized, double-blind, placebo and active-controlled, 236-week trial (Trial PsO8) that enrolled 162 pediatric subjects 6 years of age and older, with severe PsO (defined by PASI score ≥ 20, an IGA modified 2011 score of 4, and involving ≥ 10% of the body surface area [BSA]) who were candidates for systemic therapy. The 162 subjects were randomized to receive placebo, a biologic active control, or COSENTYX. In the COSENTYX groups, subjects with body weight (BW) less than 25 kg received 75 mg, subjects with BW 25 to less than 50 kg received either 75 mg or 150 mg (2 times the recommended dose), and subjects with BW of at least 50 kg received either 150 mg or 300 mg (2 times the recommended dose). Subjects were dosed at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
- The second trial was a randomized, open-label, 208-week trial (Trial PsO9; NCT03668613) of 84 pediatric subjects 6 years of age and older with moderate to severe PsO (defined by a PASI score ≥ 12, IGA mod 2011 score of ≥ 3, and BSA involvement of ≥ 10% at randomization) who were randomized into two COSENTYX arms [Arm 1: 75 mg for BW < 50 kg or 150 mg for ≥ 50 kg; and Arm 2: 75 mg for BW < 25 kg, 150 mg for BW ≥ 25 kg and < 50 kg, or 300 mg for BW ≥ 50 kg]. Subjects were dosed at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.

The safety profile of COSENTYX reported in these trials was consistent with the safety profile reported in adult PsO trials.

Infections

One case of methicillin-resistant Staphylococcus aureus (MRSA) toxic shock syndrome (TSS) was reported in a COSENTYX treated pediatric subject during the placebo-controlled period.

In the pediatric safety pool, which includes all subjects who took at least one dose of COSENTYX during the treatment periods [198 subjects (287 subject-years)], 22 (11%) subjects reported ≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 neutropenia (≥ 1,000 to < 1,500 cells/mm^3) with 57% of subjects followed for one year or more and 30% of subjects followed for two years or more. During the placebo-controlled period, which included a total of 80 pediatric subjects treated with COSENTYX and 41 subjects treated with placebo up to 12 weeks, ≥ CTCAE Grade 2

neutropenia was reported in 3 (4%) of the subjects treated with COSENTYX compared with no subjects treated with placebo. No serious infections were associated with cases of neutropenia.

Adverse Reactions from Clinical Trials in Adults with PsA

COSENTYX was studied in two placebo-controlled PsA trials with 1,003 adult 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 PsA, 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 adult patients with PsA treated with COSENTYX is consistent with the safety profile in the PsO trials in adults.

Similar to the clinical trials in patients with PsO, there was an increased proportion of patients with infections in the COSENTYX groups (29%) compared to placebo group (26%).

There were cases of CD and UC in the secukinumab group that included patients who experienced either exacerbations or the development of new disease. There were three cases of IBD, of which two patients received secukinumab and one received placebo.

Adverse Reactions from Clinical Trials in Adults with AS

COSENTYX was studied in two placebo-controlled AS trials with 590 adult 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 AS, 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 AS treated with COSENTYX is consistent with the safety profile in PsO clinical trials. In a third controlled trial of AS (study AS3), the safety profile of the 300 mg dose of COSENTYX was consistent with the safety profile of the 150 mg dose of COSENTYX.

Similar to clinical trials in patients with PsO, there was an increased proportion of patients with infections in the COSENTYX groups (31%) compared to the placebo group (18%).

In the original AS program, with 571 patients exposed to COSENTYX, there were 8 cases of IBD during the entire treatment period [5 cases of Crohn's (0.7 per 100 patient-years) and 3 cases of UC (0.4 per 100 patient-years)]. During the placebo-controlled 16-week period, there were 2 Crohn's disease exacerbations and 1 new onset UC 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 trial when all patients received COSENTYX, 1 patient developed Crohn's disease, 2 patients had Crohn's exacerbations, 1 patient developed UC, and 1 patient had an UC exacerbation.

Adverse Reactions from Clinical Trials in Adults with nr-axSpA

COSENTYX was studied in one randomized, double-blind, placebo-controlled nr-axSpA trial with 555 adult patients (185 patients received a loading COSENTYX dose, 184 patients did not receive a loading COSENTYX dose, and 186 patients received placebo). The safety profile for patients with nr-axSpA treated with COSENTYX was overall similar to the safety profile seen in patients with AS and other previous experience with COSENTYX. Patients in nr-axSpA1 trial who received the loading dosing regimen compared to those without the loading regimen, had higher incidence of infections and infestations (92 per 100 patient-years versus 72 per 100 patient-years), including nasopharyngitis, upper respiratory tract infection and urinary tract infection, and gastrointestinal disorders (27 per 100 patient-years versus 22 per 100 patient-years), including gastritis, lower abdominal pain, colitis, diarrhea, and hematochezia.

Adverse Reactions from Clinical Trials in Pediatric Patients with Juvenile Psoriatic Arthritis (JPsA) and ERA

COSENTYX was studied in one double-blind, placebo-controlled, event-driven, randomized trial in 86 pediatric patients aged 2 to less than 18 years old with JPsA and ERA. The safety profile reported in this trial was consistent with the safety profile of secukinumab.

Adverse Reactions from Clinical Trials in Adults with HS

COSENTYX was studied in two 52-week, randomized, double-blind, placebo-controlled HS trials with 1,084 adult subjects (361 subjects received COSENTYX 300 mg every 2 weeks, 360 subjects received COSENTYX 300 mg every 4 weeks, and 363 subjects received placebo) with a total of 901 subject-years of COSENTYX exposure (the median duration of exposure for subjects treated with COSENTYX was 360 days). The safety profile of COSENTYX observed in these HS trials was consistent with the known safety profile of COSENTYX observed in the PsO trials.

Infections

During the 16-week placebo-controlled period, subjects who received COSENTYX 300 mg every 2 weeks had the highest incidence of fungal infections (5.3%), compared to subjects who received COSENTYX 300 mg every 4 weeks (4.2%) and subjects who received placebo (2.8%). With longer exposure, the rate of fungal infections remained higher for subjects who received COSENTYX 300 mg every 2 weeks (14.7/100 subject-years) compared to subjects who received COSENTYX 300 mg every 4 weeks (10.1/100 subject-years). The majority of the cases were reported as non-serious, non-severe, and resolved with anti-fungal treatment.

Inflammatory Bowel Disease

In the open-labeled portion of HS clinical trials, five (0.7%) IBD adverse reactions were reported, all of which were serious and led to withdrawal of trial drug, and occurred only in subjects treated with COSENTYX 300 mg every 2 weeks. There were no IBD cases in subjects treated with COSENTYX 300 mg every 4 weeks.

Adverse Reactions of Intravenous COSENTYX

The safety of intravenous COSENTYX is based on the pharmacokinetic exposure and extrapolation of the established safety of subcutaneous COSENTYX in PsA, AS and nr-axSpA patients *[see Clinical Pharmacology (12.3)]*.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of COSENTYX. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Eczematous eruptions (atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma) *[see Warnings and Precautions (5.5)]*.

7 DRUG INTERACTIONS

Certain CYP450 Substrates

Increased concentrations of cytokines (e.g., IL-17) during chronic inflammation associated with certain diseases including PsO, PsA, AS, nr-axSpA, ERA, and HS may suppress the formation of CYP enzymes.

Upon initiation or discontinuation of COSENTYX in patients who are receiving concomitant CYP450 substrates, particularly those where minimal decreases in the concentration may reduce CYP substrate effectiveness or minimal increases in the concentration may increase CYP substrate adverse reactions, consider monitoring for therapeutic effect or concentration of the CYP substrate and consider dosage adjustment of the CYP substrate as needed *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available human data with COSENTYX use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. In an embryo-fetal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of secukinumab during organogenesis at doses up to 30 times the maximum recommended human dose (MRHD) *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

An embryo-fetal development study was performed in cynomolgus monkeys with secukinumab. No malformations or embryo-fetal 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 MRHD (on a mg/kg basis at a maternal dose of 150 mg/kg).

A pre- and post-natal 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.

8.2 Lactation

Risk Summary

It is not known whether secukinumab is excreted in human milk or absorbed systemically after ingestion. There are no data on the effects of COSENTYX on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COSENTYX and any potential adverse effects on the breastfed child from COSENTYX or from the underlying maternal condition.

8.4 Pediatric Use

Subcutaneous Administration

Pediatric Plaque Psoriasis

The safety and effectiveness of COSENTYX have been established for the treatment of moderate to severe PsO in pediatric patients aged 6 years and older who are candidates for systemic therapy or phototherapy *[see Adverse Reactions (6.1)* and *Clinical Studies (14.2)]*.

Safety and effectiveness of COSENTYX in pediatric patients with PsO below the age of 6 years have not been established.

Juvenile Psoriatic Arthritis

The safety and effectiveness of COSENTYX have been established for the treatment of active JPsA in pediatric patients aged 2 years and older who weigh 15 kg or more *[see Adverse Reactions (6.1)* and *Clinical Studies (14.6)]*.

The safety and effectiveness of COSENTYX in pediatric patients less than 2 years of age with JPsA or with a body weight less than 15 kg has not been established.

Enthesitis-Related Arthritis

The safety and effectiveness of COSENTYX for the treatment of active ERA in pediatric patients aged 4 years and older who weigh 15 kg or more has been established *[see Adverse Reactions (6.1)* and *Clinical Studies (14.6)]*.

The safety and effectiveness of COSENTYX in pediatric patients below the age of 4 years old or with body weight less than 15 kg have not been established.

Hidradenitis Suppurativa

The safety and effectiveness of COSENTYX in pediatric patients with HS have not been established.

Intravenous Administration

The safety and effectiveness of intravenous COSENTYX in pediatric patients have not been established.

8.5 Geriatric Use

Of the 3,430 PsO subjects exposed to subcutaneous COSENTYX in clinical trials, a total of 230 (7%) were 65 years of age or older, and 32 (1%) subjects were 75 years of age or older. Although no differences in safety or efficacy were

observed between subjects 65 years of age or older and younger adult subjects, the number of subjects 65 years of age and older was not sufficient to determine whether they respond differently from younger adult subjects.

Of the 1,060 subjects with HS exposed to COSENTYX in clinical trials, a total of 14 (1.3%) were 65 years of age and older. Clinical trials in HS did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

10 OVERDOSAGE

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. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Secukinumab, a recombinant human monoclonal IgG1/κ antibody, is an interleukin-17A antagonist. 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 for Subcutaneous Use

COSENTYX injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous use. COSENTYX injection is supplied in a single-dose 300 mg/2 mL UnoReady pen with a 27-gauge fixed ½-inch needle, a single-dose 150 mg/mL Sensoready pen with a 27-gauge fixed ½-inch needle, or a single-dose prefilled syringe (300 mg/2 mL, 150 mg/mL, 75 mg/0.5 mL) with a 27-gauge fixed ½-inch needle. The removable cap of the COSENTYX 150 mg/mL Sensoready pen or 1 mL and 0.5 mL prefilled syringes contains natural rubber latex.

Each COSENTYX 300 mg/2 mL UnoReady pen or 300 mg/2 mL prefilled syringe contains 300 mg of secukinumab formulated in: L-histidine/histidine hydrochloride monohydrate (6.206 mg), L-methionine (1.492 mg), polysorbate 80 (0.4 mg), trehalose dihydrate (151.34 mg), and Sterile Water for Injection, USP, at pH of 5.8.

Each COSENTYX 150 mg/mL Sensoready pen or 150 mg/mL 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.

Each COSENTYX 75 mg/0.5 mL prefilled syringe contains 75 mg of secukinumab formulated in: L-histidine/histidine hydrochloride monohydrate (1.552 mg), L-methionine (0.373 mg), polysorbate 80 (0.1 mg), trehalose dihydrate (37.83 mg), and Sterile Water for Injection, USP, at pH of 5.8.

COSENTYX Injection for Intravenous Use

COSENTYX solution is supplied as a sterile, preservative free, clear to opalescent, colorless to slightly yellowish solution in single-dose vials for intravenous infusion after dilution.

Each COSENTYX vial contains 125 mg of secukinumab formulated in: L-histidine (5.67 mg), L-histidine hydrochloride monohydrate (13.3 mg), L-methionine (3.73 mg), polysorbate 80 (1 mg), trehalose dihydrate (426 mg), and Sterile Water for Injection, USP, at pH of 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 and in HS lesions. 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 trials. 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 PsA and AS. Increased numbers of IL-17A producing lymphocytes have also been found in patients with nr-axSpA.

Immune Response to Non-Live Vaccines During Treatment

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 (5.7)]*.

12.3 Pharmacokinetics

Pharmacokinetics Following Subcutaneous Administration

The observed pharmacokinetics (PK) of secukinumab administered subcutaneously in patients with PsO, PsA, AS and nr-axSpA were similar. The secukinumab PK is also similar in pediatric patients with ERA and PsO for the same weight tiered dosing regimen.

The mean steady-state trough concentration of secukinumab was approximately 26% lower in HS subjects than that of PsO subjects.

Absorption

Following a single subcutaneous dose of either 150 mg or 300 mg (administered as two injections of 150 mg) of COSENTYX in PsO subjects, secukinumab reached peak mean (± 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 COSENTYX (administered as one or two injections of 150 mg), the mean (± 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 approximately 30% higher than those from the prefilled syringe. Following multiple subcutaneous doses of 300 mg administered via the 300 mg/2 mL UnoReady pen, the mean serum trough concentrations of secukinumab were generally consistent with those in the previous Sensoready pen study used to deliver 300 mg.

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

In healthy subjects and subjects with PsO, secukinumab bioavailability ranged from 55% to 77% following subcutaneous COSENTYX dose of 150 mg or 300 mg (administered as two injections of 150 mg).

Following subcutaneous administrations of 300 mg of COSENTYX at Weeks 0, 1, 2, 3, and 4 and then every 2 weeks thereafter, steady-state concentrations of secukinumab were achieved by Week 24 in both HS trials. The mean (± SD) steady-state trough concentrations were 55.7±28.9 mcg/mL and 50.5±28.2 mcg/mL in HS Trial 1 and HS Trial 2, respectively.

Distribution

The mean volume of distribution during the terminal phase (Vz) following a single intravenous administration ranged from 7.10 to 8.60 L in PsO subjects.

Secukinumab concentrations in interstitial fluid in lesional and non-lesional skin of PsO subjects ranged from 27% to 40% of those in serum at 1 and 2 weeks after a single subcutaneous dose of COSENTYX 300 mg (administered as two injections of 150 mg).

Elimination

Metabolism

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

Excretion

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 PsO subjects following intravenous and subcutaneous administration across all PsO trials.

In a population PK analysis, the mean systemic CL in subjects with HS was 0.26 L/day. The mean elimination half-life, as estimated from population PK analysis, was 23 days in HS subjects.

Dose Linearity

Secukinumab exhibited dose-proportional PK in subjects with PsO 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

Patients with Hepatic or Renal Impairment

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

Geriatric Patients

Population PK analysis indicated that the clearance of secukinumab was not significantly influenced by age in adult subjects with PsO, PsA and AS. Subjects who are 65 years or older had apparent clearance of secukinumab similar to subjects less than 65 years old.

Pediatric Patients

In a pool of the two pediatric trials, subjects with moderate to severe PsO (6 years of age and older) were administered subcutaneous COSENTYX at the recommended pediatric dosing regimen. At Week 24, secukinumab steady state mean ± SD serum trough concentrations were 32.6 ± 10.8 mcg/mL (n = 8), 19.8 ± 6.96 mcg/mL (n = 24), and 27.3 ± 10.1 mcg/mL (n = 36), in subjects who weighed less than 25 kg and received 75 mg of subcutaneous COSENTYX, subjects who weighed at least 25 kg and less than 50 kg and received 75 mg of subcutaneous COSENTYX, and subjects who weighed at least 50 kg and received 150 mg of subcutaneous COSENTYX, respectively.

In a pediatric trial, JPsA and ERA patients (2 to less than 18 years of age) were administered subcutaneous COSENTYX at the recommended pediatric dosing regimen. At Week 24, patients who weighed at least 15 kg and less than 50 kg, and patients who weighed at least 50 kg had a mean ± SD steady-state trough concentration of 25.2 ± 5.45 mcg/mL (n = 10) and 27.9 ± 9.57 mcg/mL (n = 19), respectively.

Drug Interactions

Cytochrome P450 Substrates

In adult subjects with PsO, midazolam (CYP3A4 substrate) PK was similar when administered alone, or when administered following either a single or five weekly subcutaneous administrations of 300 mg of COSENTYX *[see Drug Interactions (7)]*.

Pharmacokinetics Following Intravenous Administration

Following an intravenous administration of 1.75 mg/kg maintenance dose every four weeks, with or without a loading dose of 6 mg/kg at Day 0, the secukinumab concentrations [steady state trough secukinumab concentrations ($C_{min,ss}$), mean secukinumab concentrations ($C_{avg,ss}$), and maximum secukinumab concentrations ($C_{max,ss}$)] are estimated to be within the range of the steady state concentrations following subcutaneous administration of 150 mg and 300 mg doses of COSENTYX administered every four weeks.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the trials described below with the incidence of ADA in other trials, including those of COSENTYX (secukinumab).

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.

In up to 52 weeks of treatment in controlled trials in patients with PsO, PsA, AS, nr-axSpA, HS, pediatric PsO, JPsA and ERA *[see Clinical Studies (14)]*, the incidence of anti-secukinumab antibodies (referred as ADA) formation was less than 1% (25 of 6268 total of subjects treated with COSENTYX). Of the subjects treated with COSENTYX who developed ADA, approximately 8% developed neutralizing antibodies. Because of the low occurrence of ADA, the effect of these antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of COSENTYX is unknown.

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 Adult Plaque Psoriasis

Four multicenter, randomized, double-blind, placebo-controlled trials of subcutaneous COSENTYX (Trials PsO1, PsO2, PsO3, and PsO4) enrolled 2,403 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 PsO who had a minimum BSA 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. In these studies, each 300 mg dose was administered as two injections of 150 mg.

- Trial PsO1 (NCT01365455) 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 receive placebo that were non-responders at Week 12 were 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 trial treatment.
- Trial PsO2 (NCT01358578) enrolled 1306 subjects (327 randomized to COSENTYX 300 mg, 327 to COSENTYX 150 mg, 326 to placebo, and 323 to a biologic active control). Subjects received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. Subjects randomized to receive placebo that were non-responders at Week 12 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 trial treatment.
- Trial PsO3 (NCT01555125) 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 PsO4 (NCT01636687) 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 BSA 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 Disease 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 2,077 PsO 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-biologic therapies). Of the subjects 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 PsO1 and PsO2 are presented in Table 3.

Table 3: Clinical Outcomes at Week 12 in Adults With PsO in Trials PsO1 and PsO2 (Subcutaneous Treatment)

	Trial PsO1			**Trial PsO2**		
	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 PsO3 and PsO4 are presented in Table 4.

Table 4: Clinical Outcomes at Week 12 in Adults With PsO in Trials PsO3 and PsO4 (Subcutaneous Treatment)

	Trial PsO3			**Trial PsO4**		
	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)	2 (3)
IGA of clear or almost clear	40 (68)	31 (53)	0 (0)	44 (73)	32 (52)	0 (0)

Examination of age, sex, and racial subgroups did not identify differences in response to COSENTYX among these subgroups. Based on post-hoc subgroup analyses in subjects with moderate to severe PsO, subjects 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 PsO1) and 54% (175/327) and 42% (137/327) versus 2% (5/326) of subjects, respectively (Trial PsO2). Similar results were seen in Trials PsO3 and PsO4.

- With continued treatment over 52 weeks, subjects in Trial PsO1 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 PsO1 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 PsO2, 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 PsO2 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 PsO1 and PsO2) were observed using the Psoriasis Symptom Diary©.

Psoriasis Lesions of Scalp

A randomized, placebo-controlled trial (Trial PsO5; NCT02267135) enrolled 102 subjects with moderate to severe psoriasis lesions of scalp, defined as having a Psoriasis Scalp Severity Index (PSSI) score of greater than or equal to 12, an IGA scalp only score of 3 or greater, and at least 30% of the scalp affected. In this trial, 62% of subjects had at least 50% of scalp surface area affected. In this study, each 300 mg dose was administered as two injections of 150 mg. The proportions of subjects achieving an IGA scalp only score of *0* or *1* (clear or almost clear) were 56.9% and 5.9% for the COSENTYX 300 mg and the placebo groups, respectively.

300 mg/2 mL Pre-filled Syringe and 300 mg/2 mL UnoReady Pen

Two randomized, double-blind, placebo-controlled, 52-week trials (PsO6 and PsO7) enrolled 336 subjects at least 18 years of age with moderate to severe PsO who are candidates for systemic therapy or phototherapy to evaluate the safety and efficacy of COSENTYX 300 mg subcutaneously administered with a single 300 mg/2 mL prefilled syringe (Trial PsO6, NCT02748863, 214 patients) or with a single 300 mg/2 mL UnoReady pen (Trial PsO7, NCT03589885, 122 patients) compared to two subcutaneous injections using a 150 mg/1 mL prefilled syringe. The co-primary endpoints for both trials were the proportion of subjects who achieved a PASI 75 response and IGA mod 2011 ‘clear’ or ‘almost clear’ response with at least a two-grade reduction from baseline at Week 12.

Table 5: Clinical Outcomes at Week 12 in Adults With PsO in Trials PsO6 and PsO7 (Subcutaneous Treatment)

	Trial PsO6			**Trial PsO7**		
	COSENTYX 300 mg			**COSENTYX 300 mg**		
	2 mL PFS (N = 72) %	**Two 1 mL PFS (N = 71) %**	**Placebo (N = 71) %**	**2 mL Pen (N = 41) %**	**Two 1 mL PFS (N = 41) %**	**Placebo (N = 40) %**
IGA of clear or almost clear	76	69	1	76	68	8
PASI 75 response	89	82	2	95	83	10
PASI 90 response	67	70	2	76	62	5

Abbreviation: PFS, prefilled syringe.
Missing data was imputed using multiple imputation.

14.2 Pediatric Plaque Psoriasis

A 52-week, multicenter randomized, double-blind, placebo and active-controlled trial (Trial PsO8; NCT02471144) enrolled 162 pediatric subjects 6 years of age and older, with severe plaque psoriasis (as defined by a PASI score ≥ 20, an IGA modified 2011 score of 4, and involving ≥ 10% of the BSA) who were candidates for systemic therapy.

Subjects were randomized to receive subcutaneous placebo, COSENTYX, or a biologic active control. In the COSENTYX groups, subjects with BW less than 25 kg received 75 mg, subjects with BW 25 to less than 50 kg received either 75 mg or 150 mg (2 times the recommended dose), and subjects with BW at least 50 kg received either 150 mg or 300 mg (2 times the recommended dose). In this study, each 300 mg dose was administered as two subcutaneous injections of 150 mg. Subjects in the COSENTYX and placebo groups received subcutaneous treatment at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks. At Week 12, subjects randomized to placebo who were non-responders were switched to COSENTYX (dose based on body weight) and received COSENTYX at Weeks 12, 13, 14, and 15, followed by the same dose every 4 weeks starting at Week 16.

Baseline Characteristics

Overall, 60% of the subjects were female, 83% were White, the median BW was 50.6 kg, and the mean age was 13.5 years with 23% of the subjects less than 12 years. At baseline, the median PASI score was 26 (ranged from 17 to 60), and 99% of the subjects had an IGA modified 2011 score of 4 ('severe'). Approximately 43% of the subjects had prior exposure to phototherapy, 53% to conventional systemic therapy, 3% to biologics, and 9% had concomitant psoriatic arthritis.

Endpoints

The co-primary 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 the proportion of subjects who achieved an IGA modified 2011 score of 'clear' or 'almost clear' (0 or 1) with at least a 2-point improvement from baseline to Week 12. The key secondary endpoint was the proportion of subjects who achieved a reduction in PASI score of at least 90% (PASI 90) from baseline to Week 12.

Clinical Response

Table 6 presents the efficacy results at Week 12 by baseline weight strata for the approved dosage in Trial PsO8.

Table 6: Clinical Outcomes at Week 12 in Pediatric Subjects With Severe PsO in Trial PsO8 (Subcutaneous Treatment)

	Body weight < 50 kg		**Body weight ≥ 50 kg**		**Total**	
	COSENTYX 75 mg (N = 22) n (%)	**Placebo (N = 20) n (%)**	**COSENTYX 150 mg (N = 21) n (%)**	**Placebo (N = 21) n (%)**	**COSENTYX[a] (N = 43) n (%)**	**Placebo (N = 41) n (%)**
IGA of clear or almost clear	7 (32)	1 (5)	17 (81)	1 (5)	24 (56)	2 (5)
PASI 75 response	12 (55)	2 (10)	18 (86)	4 (19)	30 (70)	6 (15)
PASI 90 response	9 (41)	1 (5)	17 (81)	0 (0)	26 (60)	1 (2)

Non-responder imputation was used to handle missing values.
[a]COSENTYX treated subjects received 75 mg for subjects less than 50 kg and 150 mg for subjects at least 50 kg body weight.

14.3 Adult Psoriatic Arthritis

The safety and efficacy of COSENTYX were assessed in 1,999 patients, in 3 randomized, double-blind, placebo-controlled trials (PsA1, PsA2, and PsA3) in adult patients, age 18 years and older with active PsA (greater than or equal to 3 swollen and greater than or equal to 3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. Patients in these trials had a diagnosis of PsA of at least 5 years across all trials.

- PsA1 Study (NCT 01752634) evaluated 397 patients, who were treated with 75 mg, 150 mg or 300 mg of COSENTYX (administered as two subcutaneous injections of 150 mg) at Weeks 0, 1, 2, 3, and 4, followed by the same subcutaneous dose every 4 weeks. Patients who received placebo were re-randomized to receive subcutaneous 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 (NCT 01392326) evaluated 606 patients, who were treated with intravenous secukinumab 10 mg/kg, or placebo at Weeks 0, 2, and 4, followed by either 75 mg or 150 mg of subcutaneous COSENTYX treatment (or placebo) every 4 weeks. Patients who received placebo were re-randomized to receive subcutaneous COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status.
- PsA3 Study (NCT 02404350) evaluated 996 patients, who were treated with 150 mg or 300 mg of COSENTYX (administered as two subcutaneous injections of 150 mg) at Weeks 0, 1, 2, 3, and 4 followed by the same subcutaneous dose every 4 weeks, or once every 4 weeks of COSENTYX 150 mg. Patients treated with placebo received subcutaneous COSENTYX, either 150 mg or 300 mg, per baseline randomization, at Week 16 or Week 24 based upon responder status. The primary endpoint was ACR20 response at Week 16 with the key secondary endpoint the change from baseline in modified Total Sharp Score (mTSS) at Week 24.

Baseline Disease Characteristics

At baseline, over 61% and 42% of the patients had enthesitis and dactylitis, respectively. Overall, 31% of patients discontinued previous treatment with anti-TNFα agents due to either lack of efficacy or intolerance. In addition,

approximately 53% 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 (63%), distal interphalangeal involvement (58%), spondylitis with peripheral arthritis (20%), and arthritis mutilans (7%).

Clinical Response

In PsA1, patients treated with 150 mg or 300 mg COSENTYX demonstrated a greater clinical response, including ACR20, ACR50, and ACR70 compared to patients treated with placebo at Week 24 (Table 7). Responses were similar in patients regardless of concomitant MTX treatment. Responses were seen regardless of prior anti-TNFα exposure.

In patients with coexistent PsO 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 7: Responses[a] in PsA1 Study at Week 16 and Week 24 (Subcutaneous Treatment)

	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 who achieved a 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 Adult Patients Who Achieved ACR 20 Response[a] in PsA1 Study Through Week 24 (Subcutaneous Treatment)

[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 in the PsA1 study are shown in Table 8.

Table 8: Mean Change From Baseline in ACR Components at Week 16[a] (PsA1 Study) (Subcutaneous Treatment)

	COSENTYX 150 mg (N = 100)	**COSENTYX 300 mg** (N = 100)	**Placebo** (N = 98)
Number 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.

Radiographic Response

In PsA3 Study, inhibition of progression of structural damage was assessed radiographically and expressed by the modified mTSS and its components, the Erosion Score (ES) and Joint Space Narrowing Score (JSN), at Week 24 compared to baseline. Radiographs of hands, wrists, and feet were obtained at baseline, Week 16 and/or Week 24 and scored independently by at least two readers who were blinded to treatment group and visit number. Treatment with subcutaneous COSENTYX 150 mg without a loading dose, 150 mg with a loading dose and 300 mg with a loading dose significantly inhibited progression of peripheral joint damage compared with treatment with placebo as measured by change from baseline in mTSS at Week 24. The percentage of patients with no disease progression (defined as a change from baseline in mTSS of less than or equal to 0.0) from randomization to Week 24 was 75.7%, 70.9%, and 76.5% for COSENTYX 150 mg without a loading dose, 150 mg, 300 mg, respectively versus 68.2% for placebo.

Table 9: Rate of Change per 24 Weeks in Modified Total Sharp Score (Subcutaneous Treatment)

Treatment	N	Rate of change per 24 weeks	Difference from placebo (95% CI)
COSENTYX 150 mg without a loading dose	210	-0.10	-0.61 (-0.95, -0.26)
COSENTYX 150 mg with a loading dose	213	0.14	-0.37 (-0.71, -0.03)
COSENTYX 300 mg with a loading dose	217	0.03	-0.48 (-0.82, -0.14)
Placebo	296	0.51	--

Results from a linear mixed effects model that excluded data after escape for placebo subjects who received escape therapy at Week 16. The model assumes approximately linear progression over time and estimates a difference in rates (slopes) of progression over 24 weeks to compare treatment arms.

Physical Function

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 subcutaneous COSENTYX 150 mg and 300 mg groups compared to the placebo group at Weeks 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.

Treatment of Adult Patients with Active Psoriatic Arthritis with Intravenous COSENTYX

The effectiveness of intravenous COSENTYX in the treatment of adult patients with active PsA was extrapolated from the established effectiveness of subcutaneous COSENTYX in adult patients with active PsA based on pharmacokinetic exposure *[see Clinical Pharmacology (12.3)]*.

14.4 Ankylosing Spondylitis

The safety and efficacy of subcutaneous COSENTYX were assessed in 816 adult patients (18 years of age and older) with active AS in three randomized, double-blind, placebo-controlled trials (AS1, AS2, and AS3). 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.

- AS1 Study (NCT01649375) evaluated 219 patients, who were treated with 75 mg or 150 mg of subcutaneous COSENTYX treatment at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks. At Week 16, patients who received placebo were re-randomized to either 75 mg or 150 mg of subcutaneous COSENTYX every 4 weeks. The primary endpoint was the percentage of patients who achieved an ASAS20 response at Week 16.
- AS2 Study (NCT01358175) evaluated 371 patients, who were treated with intravenous secukinumab 10 mg/kg 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 who received placebo were re-randomized to receive subcutaneous COSENTYX (either 75 mg or 150 mg every 4 weeks) at Week 16 or Week 24 based on responder status.

- AS3 Study (NCT02008916) evaluated 226 patients, who were treated with intravenous secukinumab 10 mg/kg at Weeks 0, 2, and 4 (for both treatment arms) or placebo, followed by either 150 mg or 300 mg subcutaneous COSENTYX treatment every 4 weeks or placebo. Patients who received placebo were re-randomized to receive subcutaneous COSENTYX (either 150 mg or 300 mg every 4 weeks) at Week 16. The primary endpoint was the percentage of patients who achieved an ASAS20 response at Week 16. Patients were blinded to the treatment regimen up to Week 52, and the trial continued to Week 156. In this study, each 300 mg dose was administered as two injections of 150 mg.

Baseline Disease Characteristics

At baseline, approximately 13% and 25% used concomitant MTX or sulfasalazine, respectively. Overall, 29% of patients discontinued previous treatment with anti-TNFα agents due to either lack of efficacy or intolerance.

Clinical Response

In AS1, patients treated with 150 mg COSENTYX demonstrated greater improvements in ASAS20 and ASAS40 responses compared to patients treated with placebo at Week 16 (Table 10). Responses were similar in patients regardless of concomitant therapies.

Table 10: ASAS20 and ASAS40 Responses in All AS Patients at Week 16 in Study AS1 (Subcutaneous Treatment)

	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 11.

Table 11: ASAS20 Components and Other Measures of Disease Activity at Week 16 (AS1 Study) (Subcutaneous Treatment)

	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 score[4]	6.6	-2.2	6.8	-0.9
BASMI[5]	3.6	-0.51	3.9	-0.22
hsCRP[6] (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-assessments 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 percentage of patients who achieved ASAS20 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 (Subcutaneous Treatment)

In AS3 Study, patients treated with subcutaneous COSENTYX (150 mg and 300 mg) demonstrated improved signs and symptoms, and had comparable efficacy responses, regardless of dose, that were superior to placebo at Week 16 for the primary and most secondary endpoints. At Week 16, the ASAS20 and ASAS40 responses were 58.1% and 40.5% for 150 mg and 60.5% and 42.1% for 300 mg, respectively. The percent of patients achieving ASAS20 responses by visit is shown in Figure 3.

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

Figure 3: ASAS20 Responses in All AS3 Study Patients Over Time Up to Week 16 (Subcutaneous Treatment)

Treatment of Adult Patients with Active Ankylosing Spondylitis with Intravenous COSENTYX

The effectiveness of intravenous COSENTYX in the treatment of adult patients with active AS was extrapolated from the established effectiveness of subcutaneous COSENTYX in adult patients with active AS based on pharmacokinetic exposure *[see Clinical Pharmacology (12.3)]*.

14.5 Non-Radiographic Axial Spondyloarthritis

The safety and efficacy of COSENTYX were assessed in 555 adult patients (18 years of age and older) with active nr-axSpA in one randomized, double-blind, placebo-controlled Phase 3 study (nr-axSpA1, NCT02696031). Patients met ASAS criteria for axSpA with objective signs of inflammation and had active disease as defined by a BASDAI greater or equal to 4, a Visual Analogue Scale (VAS) for total back pain greater or equal to 40 (on a scale of 0-100 mm) despite NSAID therapy and no evidence of radiographic changes in the sacroiliac joints that would meet the modified New York criteria for AS. Patients also had to have objective signs of inflammation with a C-reactive protein (CRP) level above the upper limit of normal and/or evidence of sacroiliitis on Magnetic Resonance Imaging (MRI).

Patients were treated with 150 mg of subcutaneous COSENTYX treatment with a loading dosage (Weeks 0, 1, 2, 3, and 4) or without a loading dosage (Weeks 0 and 4) followed by the same dose every 4 weeks or placebo. In the double-blind period, patients (n = 555) received either placebo or COSENTYX for 52 weeks. Starting Week 16, dosage adjustment or addition of concomitant NSAIDs and DMARDs was permitted. Starting at Week 20, patients were allowed to switch to open-label 150 mg of subcutaneous COSENTYX monthly or other biologic at the discretion of the investigator and patient. The primary endpoint was at least 40% improvement in Assessment of Spondyloarthritis International Society (ASAS40) at Week 52.

Baseline Disease Characteristics

Approximately 10% and 15% of patients used concomitant MTX or sulfasalazine, respectively. Overall, 10% of patients had received previous treatment with anti-TNFα agents and discontinued these due to either lack of efficacy or intolerance.

Clinical Response

In nr-axSpA1 Study, treatment with COSENTYX 150 mg resulted in significant improvements in the measure of disease activity compared to treatment with placebo at Week 16 and Week 52 (Table 12).

Table 12: Clinical Response in the nr-axSpA1 Study at Week 16 and Week 52 (Subcutaneous Treatment)

Number of subjects with ASAS40 response (%)	COSENTYX 150 mg without load (n = 184)	COSENTYX 150 mg with load (n = 185)	Placebo (n = 186)	Difference from placebo (95% CI)	
				COSENTYX 150 mg without load	COSENTYX 150 mg with load
Week 16	75 (41)	74 (40)	52 (28)	13 (3, 22)	12 (2, 22)
Week 52	70 (38)	62 (34)	36 (19)	19 (10, 28)	14 (5, 23)

Difference in proportions with 95% CI based on normal approximation.

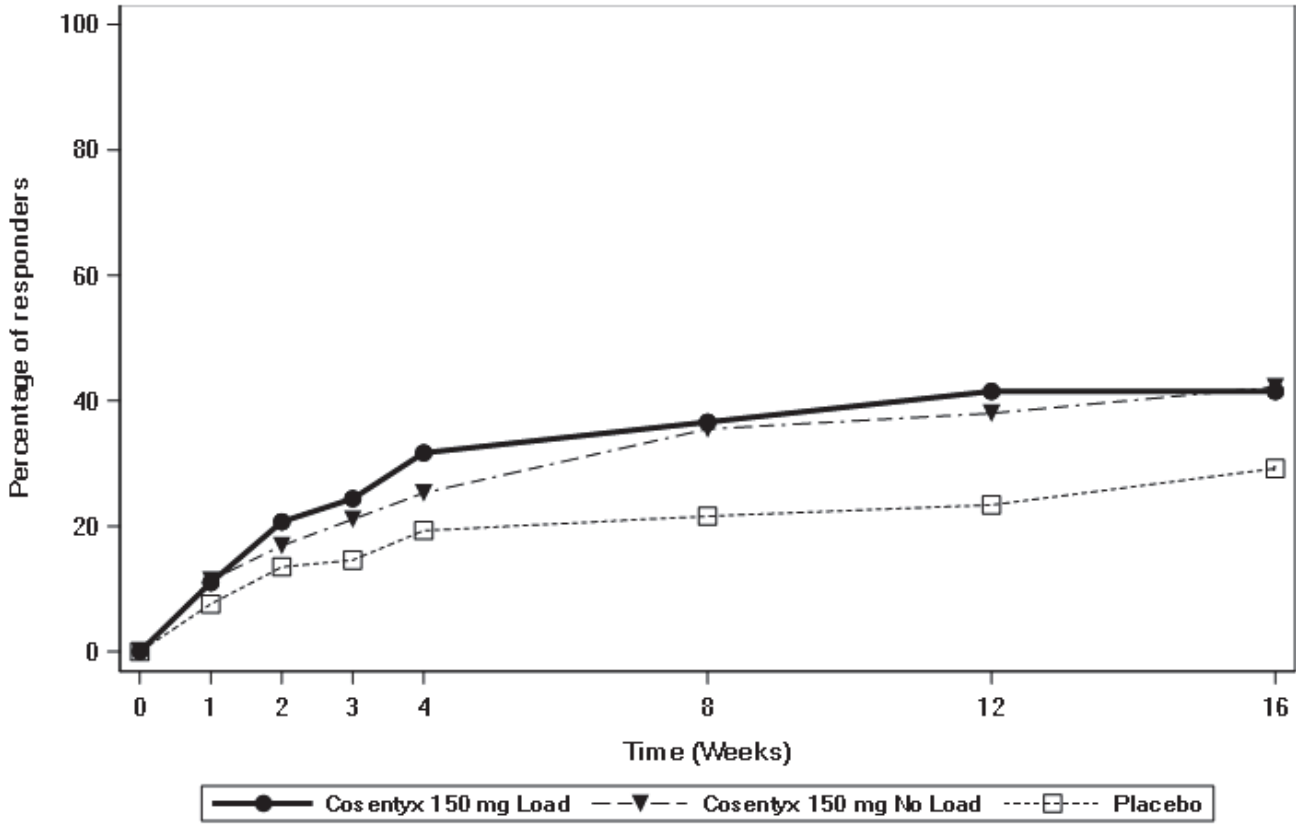
The results of the main components of the ASAS40 response criteria in the nr-axSpA1 Study are shown in Table 13.

Table 13: Main Components of the ASAS40 Response Criteria and Other Measures of Disease Activity in nr-axSpA Patients at Baseline and Week 16 in the nr-axSpA1 Study (Subcutaneous Treatment)

	COSENTYX 150 mg without loading dosage (N = 184)		COSENTYX 150 mg with a loading dosage (N = 185)		Placebo (N = 186)	
	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline
ASAS40 response criteria						
-Patient Global Assessment of Disease Activity (0-100 mm)	71.0	-26.2	72.6	-24.1	68.8	-13.8
-Total back pain (0-100 mm)	72.0	-25.5	73.3	-25.0	70.9	-15.6
-BASFI (0-10)	5.9	-1.6	6.2	-1.8	5.9	-1.0
-Inflammation (0-10)	6.8	-2.8	7.2	-2.8	6.6	-1.7
hsCRP (mg/L) mean change at Week 16	9.8	-4.7	13.4	-7.9	9.2	-2.4
BASDAI (0-10)	6.9	-2.4	7.1	-2.4	6.8	-1.5
-Spinal pain	7.6	-3.0	7.8	-3.0	7.5	-2.0
-Peripheral pain and swelling (0-10)	6.6	-2.4	6.3	-2.3	6.1	-1.6
BASMI	2.8	-0.3	2.9	-0.3	2.8	-0.1

The percentage of patients achieving an ASAS40 response by visit is shown in Figure 4.

Figure 4: ASAS40 Responses in nr-axSpA1 Study Over Time up to Week 16 (Subcutaneous Treatment)



Health-Related Quality of Life

COSENTYX treated patients showed improvement in both loading and without loading doage arms compared to placebo-treated patients at Week 16 in health-related quality of life as measured by ASQoL (LS mean change: Week 16: -3.5 and -3.6 versus -1.8, respectively).

Treatment of Adult Patients with Active Non-radiographic Axial Spondyloarthritis with Intravenous COSENTYX

The effectiveness of intravenous COSENTYX in the treatment of adult patients with active nr-axSpA was extrapolated from the established effectiveness of subcutaneous COSENTYX in adult patients with active nr-axSpA based on pharmacokinetic exposure *[see Clinical Pharmacology (12.3)]*.

14.6 Juvenile Psoriatic Arthritis and Enthesitis-Related Arthritis

The efficacy and safety of subcutaneous secukinumab were assessed in a two-year, 3-part, double-blind, placebo-controlled, event-driven, randomized, Phase 3 study (NCT03031782) in 86 pediatric patients (2 to less than 18 years of age) with active ERA or JPsA as diagnosed based on a modified International League of Associations for Rheumatology (ILAR) Juvenile Idiopathic Arthritis (JIA) classification criteria. The trial consisted of an open-label portion (Part 1) followed by randomized withdrawal (Part 2) followed by open-label treatment (Part 3). Patients were given subcutaneous doses of 75 mg if they weighed less than 50 kg, or subcutaneous doses of 150 mg if they weighed at least 50 kg or greater, administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4, and every 4 weeks thereafter.

The primary endpoint was time to flare in Part 2. Disease flare was defined as at least 30% worsening in at least three of the six JIA ACR response criteria and at least 30% improvement in not more than one of the six JIA ACR response criteria and a minimum of two active joints.

In open-label Part 1, all patients received subcutaneous secukinumab until Week 12. Patients classified as responders (achieving JIA ACR30 response) at Week 12 entered into the Part 2 double-blind phase and were randomized 1:1 to continue treatment with secukinumab or begin treatment with placebo.

Baseline Disease Characteristics

The JIA patient subtypes at study entry were: 60.5% ERA and 39.5% JPsA. In the study, 67.6% of patients with JPsA, and 63.5% of patients with ERA, were treated concomitantly with MTX.

Clinical Response

Similar responses were seen in each JIA subtype (JPsA and ERA). The JIA ACR 30, 50, 70, and 90 responses for patients with JPsA and ERA at Week 12 are presented below in Table 14.

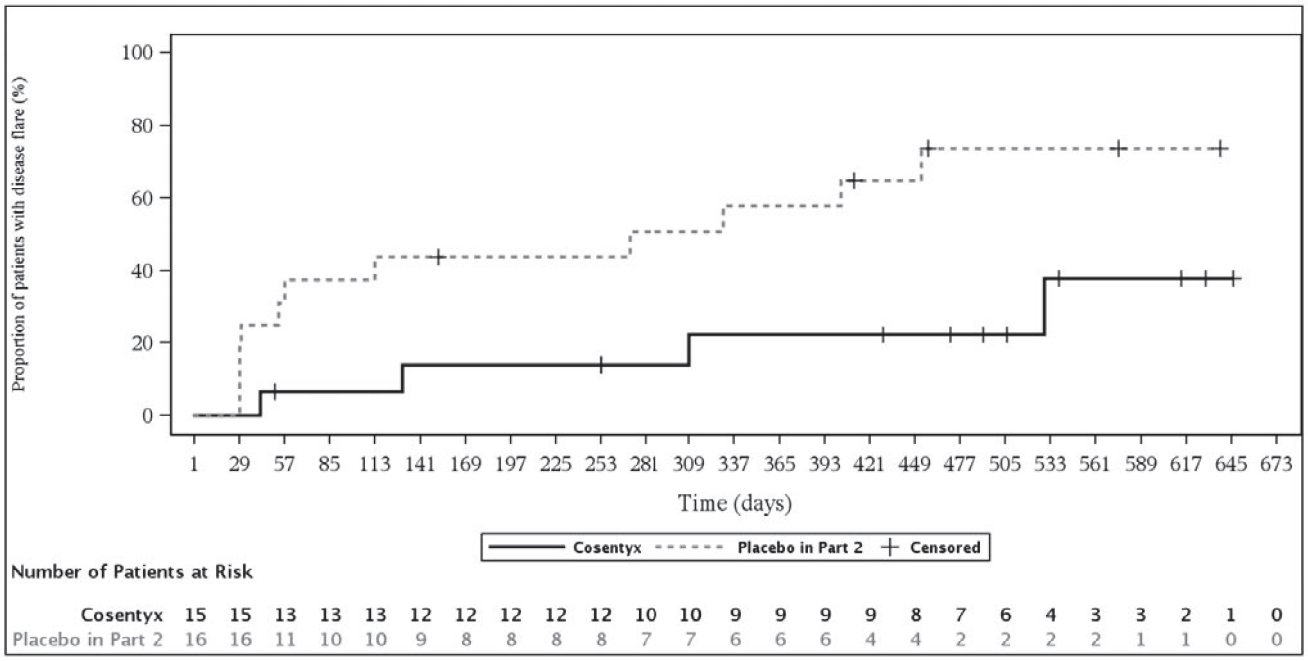
Table 14: JIA ACR 30, 50, 70, and 90 Responses at Week 12 (Subcutaneous Treatment)

Number of subjects with response (%)	JIA ACR 30	JIA ACR 50	JIA ACR 70	JIA ACR 90
JPsA (N = 34)	31 (91)	31 (91)	24 (71)	16 (47)
ERA (N = 52)	44 (85)	41 (79)	34 (65)	17 (33)

Juvenile Psoriatic Arthritis Results

During Part 2, a total of 11 JPsA patients in the placebo group experienced a flare event compared with 4 JPsA patients in the secukinumab group. The risk of flare was reduced by 85% for patients who received secukinumab compared with patients who received placebo (Hazard Ratio = 0.15, 95% CI: 0.04 to 0.56) (Figure 5).

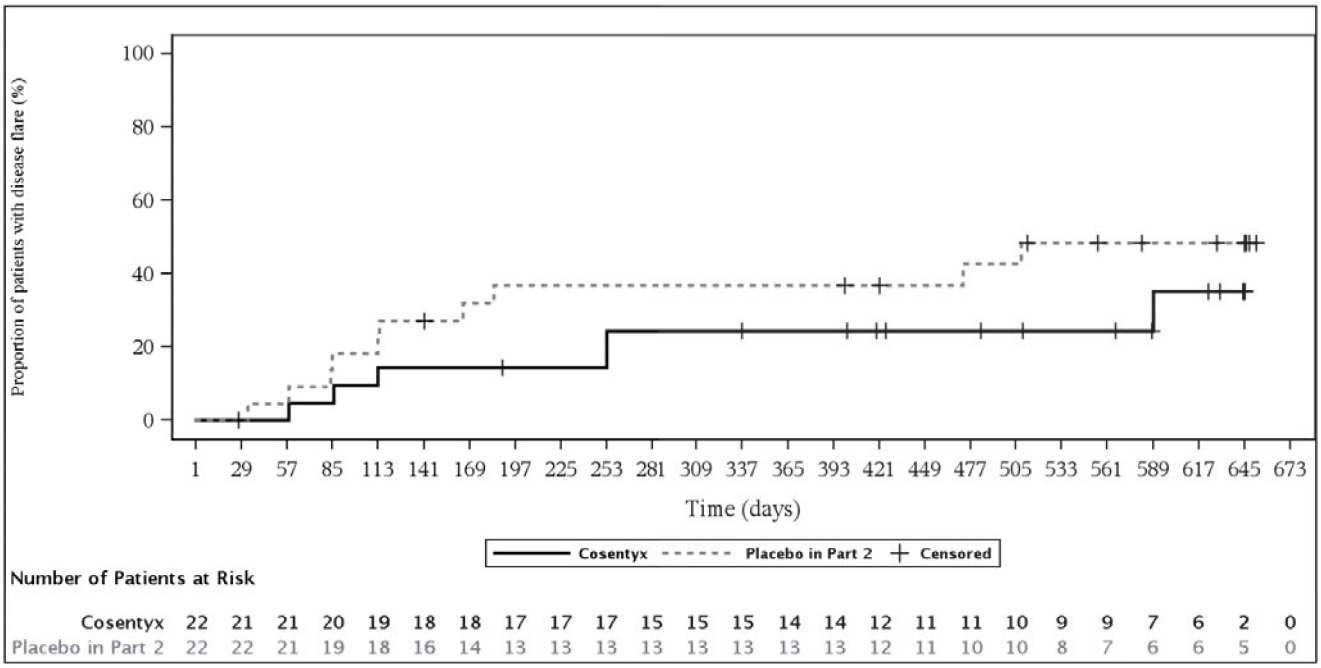
Figure 5: Kaplan-Meier Estimates of the Time to Disease Flare in Part 2 for JPsA Patients (Subcutaneous Treatment)



Enthesitis-Related Arthritis Results

During Part 2, a total of 10 ERA patients in the placebo group experienced a flare event compared with 6 ERA patients in the secukinumab group. The risk of flare was reduced by 53% for patients who received secukinumab compared with patients who received placebo (Hazard Ratio = 0.47, 95% CI: 0.17 to 1.32) (Figure 6). Supplementary analyses provided confirmatory evidence of the treatment effect in ERA.

Figure 6: Kaplan-Meier Estimates of the Time to Disease Flare in Part 2 for ERA Patients (Subcutaneous Treatment)



14.7 Hidradenitis Suppurativa

Two randomized, double-blind, placebo-controlled 52-week Phase 3 trials (i.e., HS Trial 1 [NCT03713619] and HS Trial 2 [NCT03713632]) assessed the efficacy and safety of COSENTYX in the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). In both trials, subjects were randomized to placebo or COSENTYX 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks or every 4 weeks. At Week 16, subjects who were randomized to placebo were reassigned to receive COSENTYX 300 mg at Weeks 16, 17, 18, 19, and 20 followed by either COSENTYX 300 mg every 2 weeks (Q2W) or COSENTYX 300 mg every 4 weeks (Q4W).

Baseline Demographics and Disease Characteristics

HS Trials 1 and 2 included 1,084 adult subjects with moderate to severe HS. HS Trial 1 evaluated 541 subjects and HS Trial 2 evaluated 543 subjects, of whom 13% and 11%, respectively, received concomitant stable dose of systemic antibiotics. In HS Trial 1 and HS Trial 2, 24% and 23% of patients, respectively, were previously treated with a biologic (biologic-exposed patients) and discontinued the biologic agent for either lack of efficacy or intolerance.

Endpoints

The primary endpoint in both trials was the proportion of subjects who achieved a Hidradenitis Suppurativa Clinical Response (HiSCR50) defined as at least a 50% decrease in abscesses and inflammatory nodules (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae relative to baseline at Week 16.

Clinical Response

In HS Trial 1 and HS Trial 2, a statistically significantly higher proportion of subjects treated with COSENTYX 300 mg every 2 weeks (after the first four weeks) achieved a HiSCR50 response at Week 16 compared to patients treated with placebo (see Table 14). In both HS trials, a higher proportion of subjects treated with COSENTYX 300 mg every 4 weeks (after the first four weeks) achieved HiSCR50 at Week 16 compared to subjects treated with placebo (see Table 14), where statistical significance was reached in HS Trial 2. In both trials, the onset of action of COSENTYX occurred as early as Week 2 and the efficacy progressively increased up to Week 16.

For the primary endpoint, HiSCR50, subjects who received any rescue medication or lesion intervention were considered treatment failures and handled as non-responders (n=20 in Placebo, 11 in Q4W, and 8 in Q2W in HS Trial 1; n=23 in Placebo, 17 in Q4W, and 13 in Q2W in HS Trial 2).

Improvements were seen for the primary endpoint in HS subjects regardless of previous or concomitant antibiotic treatment or previous biologic exposure.

Table 14: Clinical Response at Week 16 in Adults with Hidradenitis Suppurativa in HS Trial 1 and HS Trial 2[1]

	HS Trial 1			HS Trial 2		
	Placebo (n=180)	**COSENTYX 300 mg every 4 weeks[2] (n = 180)**	**COSENTYX 300 mg every 2 weeks[2] (n = 181)**	**Placebo (n = 183)**	**COSENTYX 300 mg every 4 weeks[2] (n = 180)**	**COSENTYX 300 mg every 2 weeks[2] (n = 180)**
HiSCR50	29.4%	41.3%	44.5%*	26.1%	42.5%*	38.3%*

[1]Multiple imputation was implemented for missing data.
[2]Subjects received COSENTYX 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks (Q4W) or every 2 weeks (Q2W).
*Statistically significant versus placebo based on the pre-defined hierarchy with overall alpha = 0.05 (two-sided).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

COSENTYX (secukinumab) injection is a clear to opalescent, colorless to slightly yellowish solution available as follows:

COSENTYX injection for subcutaneous use

COSENTYX 300 mg/2 mL UnoReady pen

• NDC 0078-1070-68: Carton of one 300 mg/2 mL (300 mg dose) single-dose UnoReady pen (injection)

COSENTYX 300 mg/2 mL (150 mg/mL) prefilled syringe

• NDC 0078-1070-97: Carton of one 300 mg/2 mL (150 mg/mL) single-dose prefilled syringe (injection)

COSENTYX 150 mg/mL Sensoready pen

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

• NDC 0078-0639-68: Carton of one 150 mg/mL single-dose Sensoready pen (injection)

COSENTYX 150 mg/mL prefilled syringe

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

• NDC 0078-0639-97: Carton of one 150 mg/mL single-dose prefilled syringe (injection)

COSENTYX 75 mg/0.5 mL prefilled syringe (for pediatric patients less than 50 kg)

• NDC 0078-1056-97: Carton of one 75 mg/0.5 mL single-dose prefilled syringe (injection)

The removable cap of the COSENTYX 150 mg/mL Sensoready pen and prefilled syringe, and 75 mg/0.5 mL prefilled syringe contains natural rubber latex. Each 300 mg/2 mL UnoReady pen, 150 mg/mL Sensoready pen and 300 mg/2 mL, 150 mg/mL, and 75 mg/0.5 mL prefilled syringe is equipped with a needle safety guard.

COSENTYX injection for intravenous use

• NDC 0078-1168-61: Carton containing one 125 mg/5 mL (25 mg/mL) solution in a single-dose vial for dilution prior to intravenous infusion.

Storage and Handling

Refrigerate COSENTYX injection for subcutaneous use (300 mg/2 mL UnoReady Pen, 150 mg/mL Sensoready Pens, and 150 mg/mL and 75 mg/0.5 mL Prefilled Syringes), and COSENTYX injection for intravenous use at 2ºC to 8ºC (36ºF to 46ºF). Keep the products 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.

If removed from refrigeration, COSENTYX 150 mg/mL Sensoready Pens, and 150 mg/mL and 75 mg/0.5 mL Prefilled Syringes:

- May be stored for up to 4 days at room temperature not to exceed 30°C (86°F).
- Write the date COSENTYX is removed from and returned to the refrigerator in the space provided on the carton.
- Discard if stored outside of the refrigerator over 4 days.
- May be returned to the refrigerator only one time and must be stored at 2ºC to 8ºC (36ºF to 46ºF) until used or expired.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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 (5.2)]*.

Eczematous Eruptions

Inform patients that skin reactions resembling eczema may occur with the use of COSENTYX. Instruct patients to seek medical advice if they develop signs or symptoms of eczema *[see Warnings and Precautions (5.5)]*.

Risk of Hypersensitivity in Latex-Sensitive Individuals

Advise latex-sensitive patients that the removal caps of the COSENTYX 150 mg/mL Sensoready pen and the COSENTYX 1 mL and 0.5 mL prefilled syringes contain natural rubber latex, which may cause an allergic reaction in latex-sensitive individuals *[see Warnings and Precautions (5.6)]*.

Immunization

Advise patients that vaccination with live vaccines is not recommended during COSENTYX treatment. Instruct patients to inform the healthcare practitioner that they are taking COSENTYX prior to a potential vaccination *[see Warnings and Precautions (5.7)]*.

Instructions on Subcutaneous Injection Technique

If a patient or caregiver is to subcutaneously administer COSENTYX using the UnoReady pen, Sensoready pen, or the prefilled syringe, instruct him/her in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of COSENTYX *[see Dosage and Administration (2.2, 2.9), Medication Guide, and Instructions for Use]*.

For pediatric patients, inform patients and caregivers that pediatric patients should not self-administer COSENTYX.

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 according to the directions provided in the Medication Guide and Instructions for Use.

Storage

Instruct patients to store COSENTYX in a refrigerator at 2°C to 8°C (36ºF to 46ºF) and to discard expired or unused COSENTYX.

Inform patients that if removed from refrigeration, COSENTYX 150 mg/mL Sensoready pens, 150 mg/mL and 75 mg/0.5 mL prefilled syringes may be stored for up to 4 days at room temperature not to exceed 86°F (30°C). Instruct patients to discard if kept outside of the refrigerator over 4 days *[see How Supplied/Storage and Handling (16.2)]*.

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

US License Number 1244

MEDICATION GUIDE

COSENTYX® (koe-sen-tix)

(secukinumab)

injection, for subcutaneous or intravenous use

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. Some people have died from these 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 use 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:

- people 6 years of age and older with moderate to severe plaque psoriasis (PsO) 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)
- people 2 years of age and older with active psoriatic arthritis (PsA)
- adults with active ankylosing spondylitis (AS)
- adults with active non-radiographic axial spondyloarthritis (nr-axSpA) and objective signs of inflammation
- people 4 years of age and older with active enthesitis-related arthritis (ERA)
- adults with moderate to severe hidradenitis suppurativa (HS)

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

- under 6 years of age with PsO
- under 2 years of age and weighing less than 33 pounds (15 kg) with active PsA
- under 4 years of age and weighing less than 33 pounds (15 kg) with active ERA
- with HS

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 using 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 150 mg/mL and 75 mg/0.5 mL prefilled syringes contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who take COSENTYX **should not** receive live vaccines. Children should be brought up to date with all vaccines before starting COSENTYX.
- 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 will I receive COSENTYX?

When administered subcutaneously (under your skin)

Read 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.

- Use COSENTYX exactly as prescribed by your healthcare provider.
- COSENTYX comes in a single-dose UnoReady pen, single-dose Sensoready pen, or single-dose prefilled syringes (300 mg/2 mL, 150 mg/mL, 75 mg/0.5 mL) that you or your caregiver may use at home to give injections.
- Your healthcare provider will decide which type of COSENTYX, and which dose is right for you.
- 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.
- Children should not inject themselves with COSENTYX. An adult caregiver should prepare and inject COSENTYX after receiving training on the right way to prepare and inject COSENTYX.
- **Do not handle the needle cap of the COSENTYX Sensoready pen, or the 75 mg/0.5 mL or 150 mg/mL prefilled syringes if you are sensitive to latex.**
- 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 or healthcare provider 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 Poison Help line at 1-800-222-1222, or go to the nearest emergency room right away.

When administered intravenously (by vein)

- You will be given COSENTYX by a healthcare provider through a needle placed in a vein (infusion). It takes about 30 minutes to give you the full dose of COSENTYX.
- Your healthcare provider will tell you how often you should receive COSENTYX.

- If you miss an appointment to receive COSENTYX, make another appointment as soon as possible.

What are the possible side effects of COSENTYX?

COSENTYX may cause serious side effects, including:

- See **"What is the most important information I should know about COSENTYX?"**
- **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
  - hives (red, itchy bumps)

If you have a severe allergic reaction, do not give another injection of 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.
- **Severe skin reactions that look like eczema** can happen during treatment with COSENTYX from days to months after your first dose and can sometimes lead to hospitalization. Your healthcare provider may temporarily stop treatment with COSENTYX if you develop severe skin reactions. Tell your healthcare provider if you have any of the following signs or symptoms:
  - redness or rash
  - itching
  - small bumps or patches
  - your skin is dry or feels like leather
  - blisters on the hands or feet that ooze or become crusty
  - skin peeling

The most common side effects of COSENTYX include:

- cold symptoms
- diarrhea
- upper respiratory tract 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.
- **If you use COSENTYX Sensoready pen, or COSENTYX 75 mg/0.5 mL or 150 mg/mL prefilled syringe**:
  - It may be stored at room temperature, up to 86°F (30°C), for up to 4 days.
  - Write the date it was removed from and returned to the refrigerator in the space provided on the carton.
  - Throw it away if it has been stored outside of the refrigerator over 4 days.
  - It may be returned to the refrigerator **only 1 time** and must be stored between 36°F to 46°F (2°C to 8°C) until you use it or until it expires.
- Do not freeze COSENTYX.
- Do not shake COSENTYX.
- Throw away any expired or unused 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 pharmacist or healthcare provider for information about COSENTYX that is written for health professionals.

What are the ingredients in COSENTYX?

Active ingredient: secukinumab.

Inactive ingredients:

L-histidine/histidine hydrochloride monohydrate, L-methionine, polysorbate 80, trehalose dihydrate, and sterile water for injection.

Manufactured by: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, U.S. License Number 1244

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 10/2023

INSTRUCTIONS FOR USE

COSENTYX® [koe-sen-tix]

(secukinumab)

injection, for subcutaneous use

300 mg/2 mL single-dose prefilled syringe

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and inject COSENTYX properly using the prefilled syringe before you use it for the first time. Talk to your healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting COSENTYX:

- **Do not use** the COSENTYX prefilled syringe if either the seal on the outside carton or the seal of the blister are broken. Keep the COSENTYX prefilled syringe in the sealed carton until you are ready to use it.
- **Do not use** the COSENTYX prefilled syringe if the syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- **Do not shake** the COSENTYX prefilled syringe.
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the prefilled syringe.
- **Do not** remove the needle cap until just before you give the injection.
- Avoid touching the syringe guard wings before use. Touching them may cause the syringe guard to be activated too early.
- Throw away (dispose of) the used COSENTYX prefilled syringe right away after use. **Do not re-use the COSENTYX prefilled syringe.** See **"How should I dispose of the used COSENTYX prefilled syringe?"** at the end of this Instructions for Use.

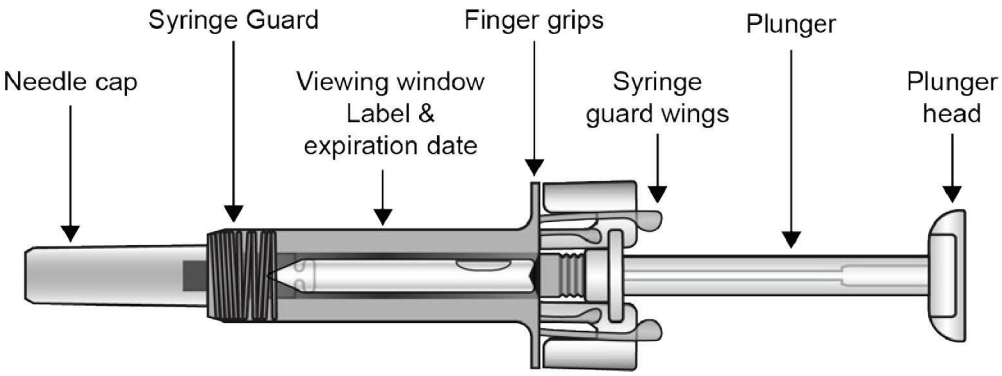
How should I store COSENTYX?

- Store your carton of COSENTYX prefilled syringe in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep the COSENTYX prefilled syringe in the original carton until ready to use to protect from light.
- **Do not** freeze the COSENTYX prefilled syringe.
- Throw away (dispose of) any expired or unused COSENTYX prefilled syringes.

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

COSENTYX prefilled syringe parts (see Figure A):

Figure A



What you need for your injection:

Included in the carton:

A new COSENTYX prefilled syringe.

Each COSENTYX prefilled syringe contains **300 mg** of COSENTYX. Check to make sure that you have the correct medicine and dose.

Not included in the carton **(see Figure B):**

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container

See "**How should I dispose of the used COSENTYX prefilled syringe**?" at the end of this Instructions for Use.

Figure B

Prepare the COSENTYX 300 mg prefilled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the carton containing the COSENTYX prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 30 to 45 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

Step 4. Remove the COSENTYX prefilled syringe from the outer carton and take it out of the blister.

Step 5. Look through the viewing window on the COSENTYX prefilled syringe. The liquid inside should be clear. The color may be colorless to slightly yellow. You may see a small air bubble in the liquid. This is normal. **Do not use** the prefilled syringe if the liquid contains visible particles, or if the liquid is cloudy or discolored.

Step 6. Do not use the COSENTYX prefilled syringe if it is broken. Return the prefilled syringe and the package it came in to the pharmacy.

Step 7. Do not use the COSENTYX prefilled syringe if the expiration date has passed.

Choose and clean the injection site

- Areas of your body that you may use as injection sites include:
  - the front of your thighs **(see Figure C)**
  - the lower stomach-area (abdomen), but **not** the area 2 inches around your navel (belly button) **(see Figure C)**
  - the upper outer arms, if a caregiver or healthcare provider is giving you the injection **(see Figure D)**
- Choose a different site for each injection of COSENTYX.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

Figure C

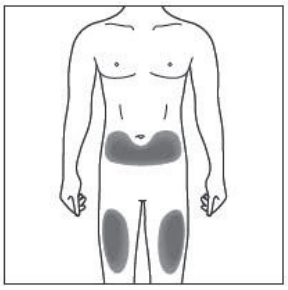
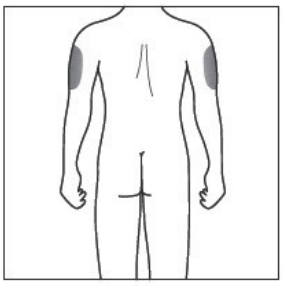


Figure D

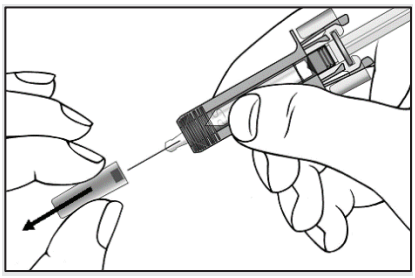


Step 8. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. **Do not** touch the cleaned area again before injecting.

Giving the injection

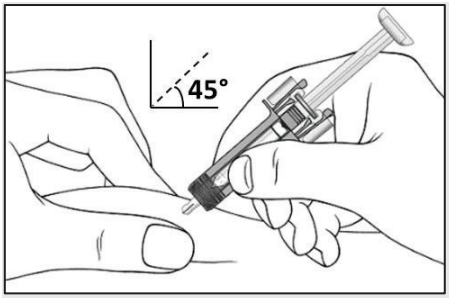
Step 9. Carefully remove the needle cap from the COSENTYX prefilled syringe **(see Figure E)**. Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure E



Step 10. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin at a 45-degree angle as shown **(see Figure F)**. Push the needle all the way in to make sure that you inject your full dose.

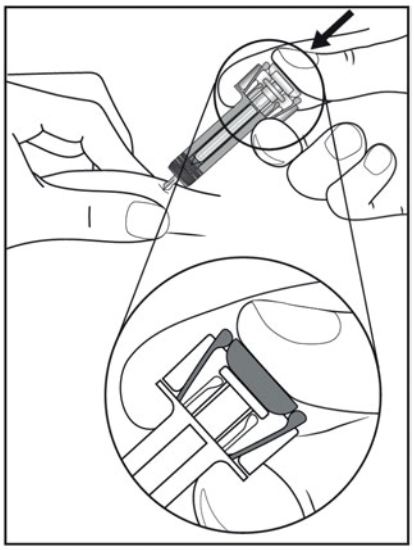
Figure F



Step 11. Hold the COSENTYX prefilled syringe finger grips as shown **(see Figure G)**. Slowly press down on the plunger as far as it will go, so that the plunger head is completely between the syringe guard wings. This will make sure that the syringe guard has been activated.

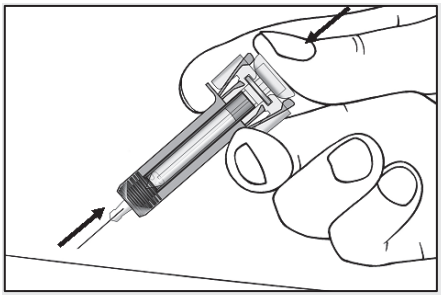
Step 12. Continue to press fully on the plunger for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.

Figure G



Step 13. Keep the plunger fully depressed while you carefully pull the needle straight out from the injection site **(see Figure H)**.

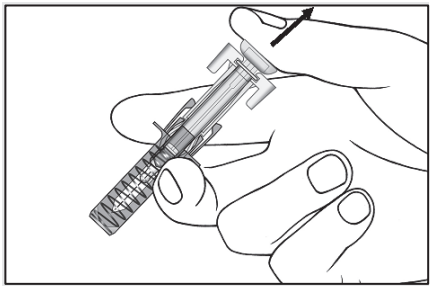
Figure H



Step 14. Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle **(see Figure I)**.

Step 15. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure I



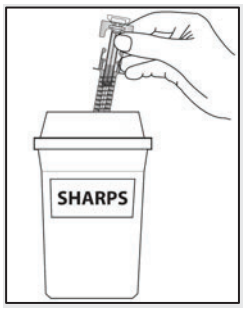
How should I dispose of the used COSENTYX prefilled syringe?

Step 16. Put your used prefilled syringe in an FDA-cleared sharps disposal container right away after use **(see Figure J)**. **Do not throw away (dispose of)** the prefilled syringe in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

Figure J



When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

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

US License Number 1244

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T2023-42

INSTRUCTIONS FOR USE

COSENTYX® [koe-sen-tix]

(secukinumab)

injection, for subcutaneous use

150 mg/mL single-dose prefilled syringe

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and inject COSENTYX properly using the prefilled syringe before you use it for the first time. Children should not inject COSENTYX themselves using the prefilled syringe. An adult caregiver should prepare and inject COSENTYX after receiving proper training in subcutaneous injection technique. Talk to your healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting COSENTYX:

- **Do not use** the COSENTYX prefilled syringe if either the seal on the outside carton or the seal of the blister are broken. Keep the COSENTYX prefilled syringe in the sealed carton until you are ready to use it.
- **Do not use** the COSENTYX prefilled syringe if the syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- **Do not shake** the COSENTYX prefilled syringe.
- **The needle caps of the prefilled syringes contain latex. Do not handle the prefilled syringes if you are sensitive to latex.**
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the prefilled syringe.
- **Do not** remove the needle cap until just before you give the injection.
- Avoid touching the syringe guard wings before use. Touching them may cause the syringe guard to be activated too early.
- Throw away (dispose of) the used COSENTYX prefilled syringe right away after use. **Do not re-use the COSENTYX prefilled syringe.** See **"How should I dispose of used COSENTYX prefilled syringes?"** at the end of this Instructions for Use.

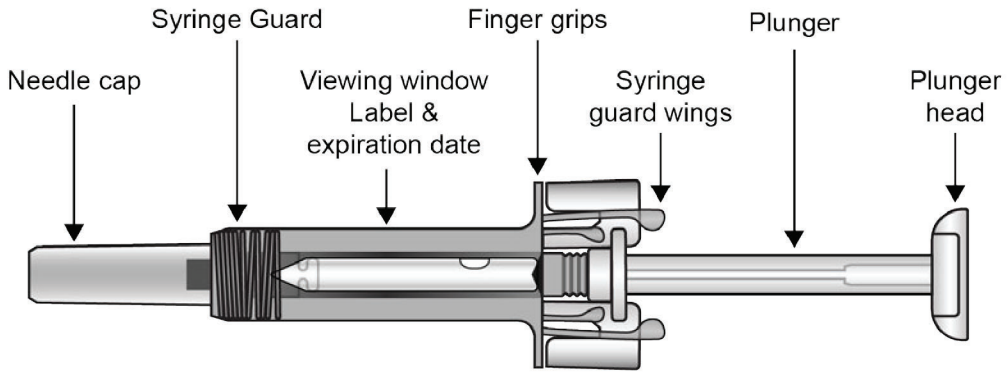
How should I store COSENTYX?

- Store your carton of COSENTYX prefilled syringes in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep the COSENTYX prefilled syringes in the original carton until ready to use to protect from light.
- The COSENTYX prefilled syringes may be stored at room temperature, up to 86°F (30°C), for up to 4 days.
- Write the date the COSENTYX prefilled syringes were removed from and returned to the refrigerator in the space provided on the carton.
- Throw away the COSENTYX prefilled syringe if it has been kept outside of the refrigerator over 4 days.
- COSENTYX prefilled syringe may be returned to the refrigerator **only 1 time** and must be stored between 36°F to 46°F (2°C to 8°C) until you use it or until it expires.
- **Do not** freeze the COSENTYX prefilled syringes.
- Throw away (dispose of) any expired or unused COSENTYX prefilled syringes.

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

COSENTYX prefilled syringe parts (see Figure A):

Figure A



What you need for your injection:

Included in the carton:

A new COSENTYX prefilled syringe.

Each COSENTYX prefilled syringe contains **150 mg** of COSENTYX. Check to make sure that you have the correct medicine and dose.

- If your **prescribed dose** of COSENTYX is **150 mg**, you must give **1 injection**.
- If your **prescribed dose** of COSENTYX is **300 mg**, you must give **2 injections**.

Not included in the carton **(see Figure B)**:

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container

Figure B

See "**How should I dispose of used COSENTYX prefilled syringes**?" at the end of this Instructions for Use.

Prepare the COSENTYX 150 mg prefilled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the carton containing the COSENTYX prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

Step 4. Remove the COSENTYX prefilled syringe from the outer carton and take it out of the blister.

Step 5. Look through the viewing window on the COSENTYX prefilled syringe. The liquid inside should be clear. The color may be colorless to slightly yellow. You may see a small air bubble in the liquid. This is normal. **Do not use** the prefilled syringe if the liquid contains visible particles, or if the liquid is cloudy or discolored.

Step 6. Do not use the COSENTYX prefilled syringe if it is broken. Return the prefilled syringe and the package it came in to the pharmacy.

Step 7. Do not use the COSENTYX prefilled syringe if the expiration date has passed.

Choose and clean the injection site

- Areas of your body that you may use as injection sites include:
  - the front of your thighs **(see Figure C)**
  - the lower stomach-area (abdomen), but **not** the area 2 inches around your navel (belly button) **(see Figure C)**
  - the upper outer arms, if a caregiver or healthcare provider is giving you the injection **(see Figure D)**
- Choose a different site for each injection of COSENTYX.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

Figure C

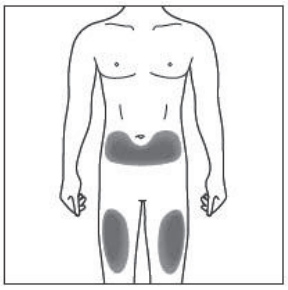
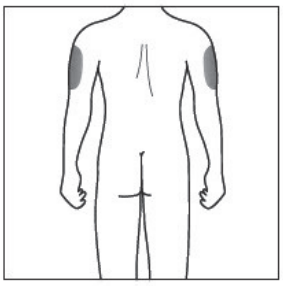


Figure D

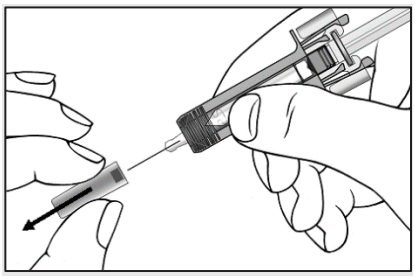


Step 8. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. **Do not** touch the cleaned area again before injecting.

Giving the injection

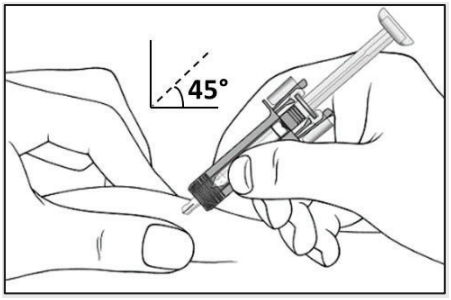
Step 9. Carefully remove the needle cap from the COSENTYX prefilled syringe **(see Figure E)**. Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure E



Step 10. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin at a 45-degree angle as shown **(see Figure F)**. Push the needle all the way in to make sure that you inject your full dose.

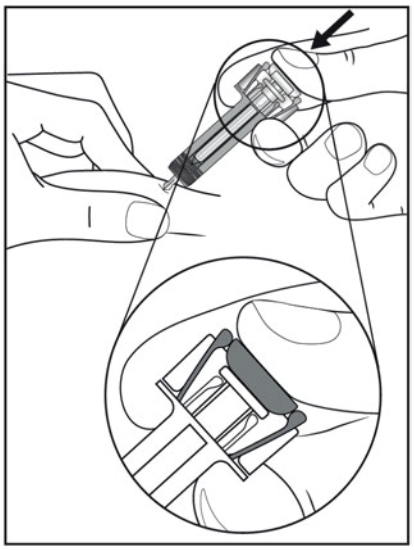
Figure F



Step 11. Hold the COSENTYX prefilled syringe finger grips as shown **(see Figure G)**. Slowly press down on the plunger as far as it will go, so that the plunger head is completely between the syringe guard wings. This will make sure that the syringe guard has been activated.

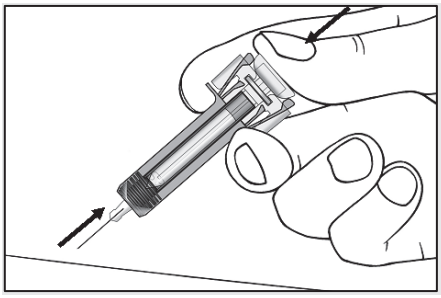
Step 12. Continue to press fully on the plunger for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.

Figure G



Step 13. Keep the plunger fully depressed while you carefully pull the needle straight out from the injection site **(see Figure H)**.

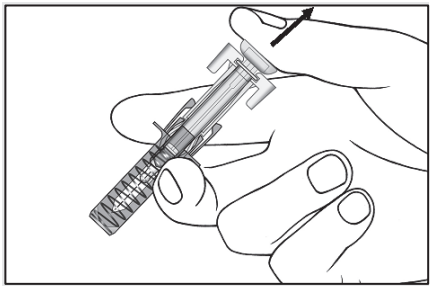
Figure H



Step 14. Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle **(see Figure I)**.

Step 15. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure I



If your prescribed dose of COSENTYX is 300 mg, repeat Steps 4 through 15 with a new COSENTYX prefilled syringe.

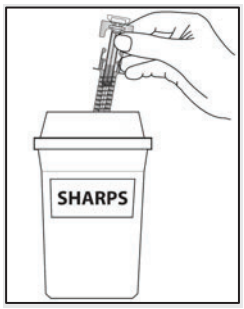
How should I dispose of used COSENTYX prefilled syringes?

Step 16. Put your used prefilled syringes in an FDA-cleared sharps disposal container right away after use **(see Figure J)**. **Do not throw away (dispose of)** the prefilled syringes in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

Figure J



When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

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

US License Number 1244

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: July 2023

T2023-43

INSTRUCTIONS FOR USE

COSENTYX® [koe-sen-tix]

(secukinumab)

injection, for subcutaneous use

75 mg/0.5 mL single-dose prefilled syringe

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and inject COSENTYX properly using the prefilled syringe before you use it for the first time. Children should not inject COSENTYX themselves using the prefilled syringe. An adult caregiver should prepare and inject COSENTYX after receiving proper training in subcutaneous injection technique. Talk to your healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting COSENTYX:

- **Do not use** the COSENTYX prefilled syringe if either the seal on the outside carton or the seal of the blister are broken. Keep the COSENTYX prefilled syringe in the sealed carton until you are ready to use it.
- **Do not use** the COSENTYX prefilled syringe if the syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- **Do not shake** the COSENTYX prefilled syringe.
- **The needle cap of the prefilled syringe contains latex. Do not handle the prefilled syringe if you are sensitive to latex.**
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the prefilled syringe.
- **Do not** remove the needle cap until just before you give the injection.
- Avoid touching the syringe guard wings before use. Touching them may cause the syringe guard to be activated too early.
- Throw away (dispose of) the used COSENTYX prefilled syringe right away after use. **Do not re-use the COSENTYX prefilled syringe.** See "**How should I dispose of the used COSENTYX prefilled syringe?**" at the end of this Instructions for Use.

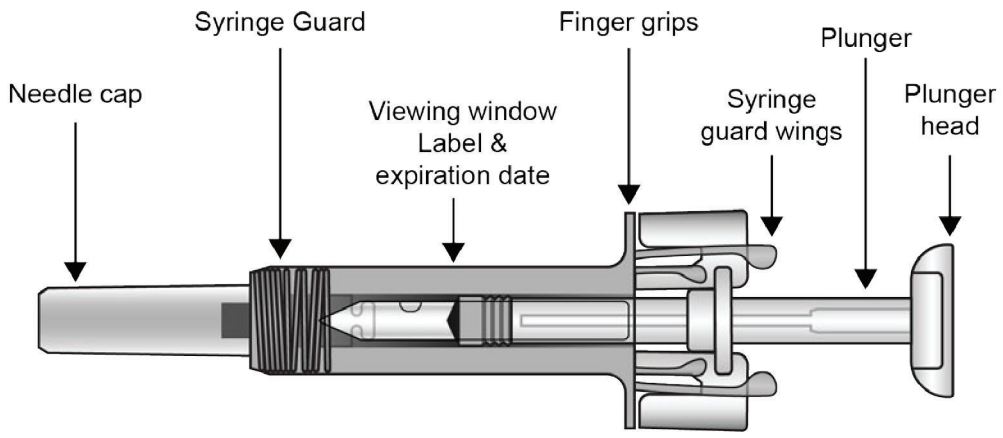
How should I store COSENTYX?

- Store your carton of COSENTYX prefilled syringe in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep the COSENTYX prefilled syringe in the original carton until ready to use to protect from light.
- COSENTYX prefilled syringe may be stored at room temperature, up to 86°F (30°C), for up to 4 days.
- Write the date COSENTYX prefilled syringe was removed from and returned to the refrigerator in the space provided on the carton.
- Throw away COSENTYX prefilled syringe if it has been kept outside of the refrigerator over 4 days.
- COSENTYX prefilled syringe may be returned to the refrigerator only 1 time and must be stored between 36°F to 46°F (2°C to 8°C) until you use it or until it expires.
- **Do not freeze** the COSENTYX prefilled syringe.
- Throw away (dispose of) any expired or unused COSENTYX prefilled syringe.

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

COSENTYX prefilled syringe parts (see Figure A):

Figure A



What you need for your injection:

Included in the carton:

A new COSENTYX prefilled syringe.

Each COSENTYX prefilled syringe contains **75 mg** of COSENTYX. Check to make sure that you have the correct medicine and dose.

Not included in the carton **(see Figure B):**

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container

Figure B

See "**How should I dispose of the used COSENTYX prefilled syringe**?" at the end of this Instructions for Use.

Prepare the COSENTYX 75 mg prefilled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the carton containing the COSENTYX prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for about 15 to 30 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

Step 4. Remove the COSENTYX prefilled syringe from the outer carton and take it out of the blister.

Step 5. Look through the viewing window on the COSENTYX prefilled syringe. The liquid inside should be clear. The color may be colorless to slightly yellow. You may see a small air bubble in the liquid. This is normal. **Do not use** the prefilled syringe if the liquid contains visible particles, or if the liquid is cloudy or discolored.

Step 6. Do not use the COSENTYX prefilled syringe if it is broken. Return the prefilled syringe and the package it came in to the pharmacy.

Step 7. Do not use the COSENTYX prefilled syringe if the expiration date has passed.

Choose and clean the injection site

- Areas of your body that you may use as injection sites include:
  - the front of your thighs **(see Figure C)**
  - the lower stomach-area (abdomen), but **not** the area 2 inches around your navel (belly button) **(see Figure C)**
  - the upper outer arms **(see Figure D)**
- Choose a different site for each injection of COSENTYX.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

Figure C

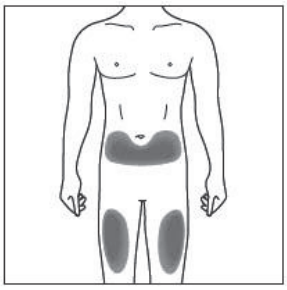
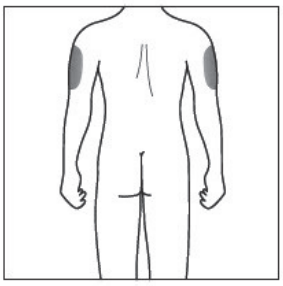


Figure D

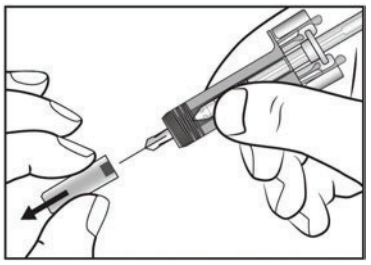


Step 8. Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting. **Do not** touch the cleaned area again before injecting.

Giving the injection

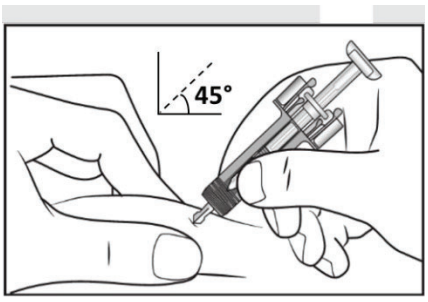
Step 9. Carefully remove the needle cap from the COSENTYX prefilled syringe **(see Figure E)**. Throw away the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Figure E



Step 10. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin at a 45-degree angle as shown **(see Figure F)**. Push the needle all the way in to make sure that you inject your full dose.

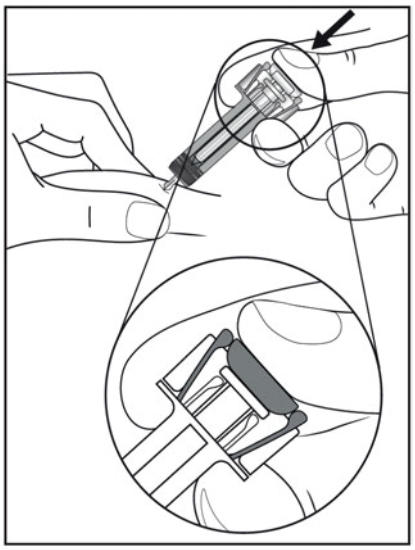
Figure F



Step 11. Hold the COSENTYX prefilled syringe finger grips as shown **(see Figure G)**. Slowly press down on the plunger as far as it will go, so that the plunger head is completely between the syringe guard wings. This will make sure that the syringe guard has been activated.

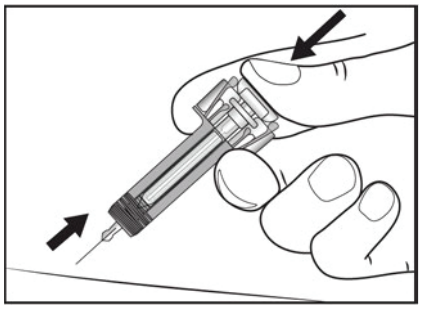
Step 12. Continue to press fully on the plunger for an additional 5 seconds. Hold the syringe in place for the full 5 seconds.

Figure G



Step 13. Keep the plunger fully depressed while you carefully pull the needle straight out from the injection site **(see Figure H)**.

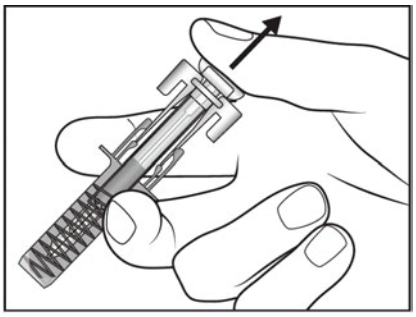
Figure H



Step 14. Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle **(see Figure I)**.

Step 15. There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Figure I



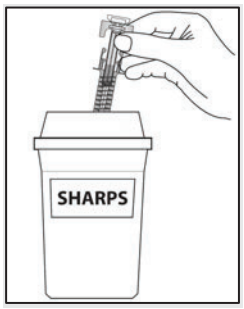
How should I dispose of the used COSENTYX prefilled syringe?

Step 16. Put your used prefilled syringe in an FDA-cleared sharps disposal container right away after use **(see Figure J). Do not throw away (dispose of)** the prefilled syringe in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

Figure J



When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

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

US License Number 1244

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: July 2023

T2023-44

INSTRUCTIONS FOR USE

COSENTYX® [koe-sen-tix]

(secukinumab)

injection, for subcutaneous use

300 mg/2 mL single-dose UnoReady® pen

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and properly inject with the COSENTYX UnoReady pen before you use it for the first time. Talk to your healthcare provider if you have any questions.

Cosentyx UnoReady pen parts

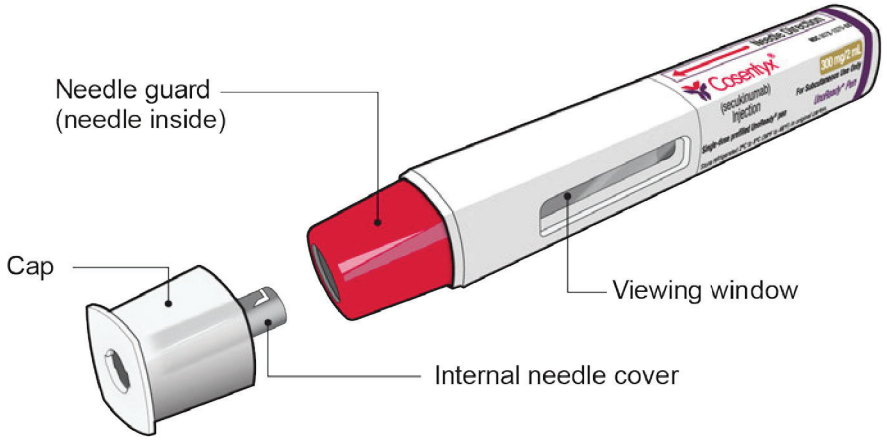


Figure A

The COSENTYX UnoReady pen is shown in **Figure A** with the cap removed.
Do not remove the cap until you are ready to inject.

Important information You Need to Know Before Injecting COSENTYX:

- **Do not** use the COSENTYX UnoReady pen if the seal on the outer carton is broken. Keep the COSENTYX UnoReady pen in the sealed outer carton until you are ready to use it.
- **Do not** shake the COSENTYX UnoReady pen.
- If you drop your COSENTYX UnoReady pen, **do not** use it if it looks damaged, or if you dropped it with the cap removed.
- The needle is covered by the needle guard and the needle will not be seen. **Do not** touch or push the needle guard because you could get a needle stick.
- Throw away (dispose of) the used COSENTYX UnoReady pen right away after use.
- **Do not** re-use the COSENTYX UnoReady pen. See "**Step 9. Disposing of the used COSENTYX UnoReady pen**" at the end of this Instructions for Use.

Storing the COSENTYX UnoReady pen

- Store your carton of COSENTYX UnoReady pen in a refrigerator between 36°F and 46°F (2°C and 8°C).
- Keep the COSENTYX UnoReady pen in the original carton until ready to use to protect from light.
- **Do not** freeze the COSENTYX UnoReady pen.

- Throw away (dispose of) any expired or unused COSENTYX UnoReady pen.

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

What you need for your injection

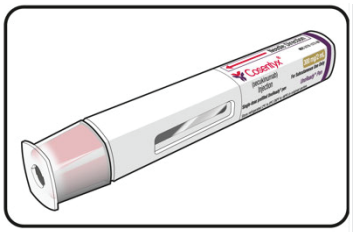


Figure B

Included in the carton (see Figure B)

- A new COSENTYX UnoReady pen

  Each COSENTYX UnoReady pen contains **300 mg** of COSENTYX. Check to make sure that you have the correct medicine and dose.

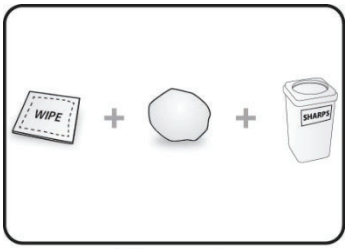


Figure C

Not included in the carton (see Figure C)

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container. See "**Step 9. Disposing of the used COSENTYX UnoReady pen**" at the end of this Instructions for Use.

Prepare to inject

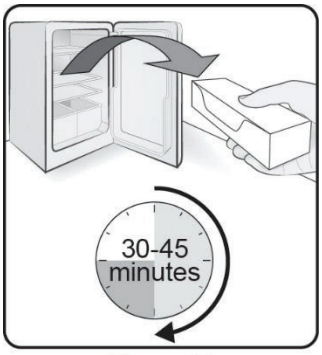


Figure D

Step 1. Bring to room temperature

Take the carton containing the COSENTYX UnoReady pen out of the refrigerator **(see Figure D)** and leave it **unopened for 30 to 45 minutes before injecting** to allow it to reach room temperature.

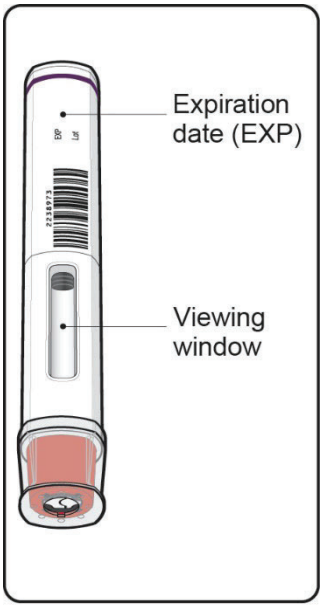


Figure E

Step 2. Important safety checks before you inject (see Figure E)

- Look at the expiration date **(EXP)** on your COSENTYX UnoReady pen. **Do not** use the COSENTYX UnoReady pen if the expiration date has passed.
- Look through the viewing window. The liquid should be clear. Its color may vary from colorless to slightly yellow.
- **Do not** use if the liquid contains visible particles, is cloudy or is discolored. You may see air bubbles, which is normal.

Contact your healthcare provider or pharmacist if the COSENTYX UnoReady pen fails any of these checks.

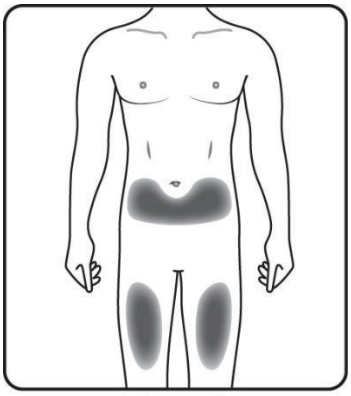


Figure F

Step 3. Choose the injection site

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 2 inches around the navel (belly button) **(see Figure F)**.
- Choose a different site each time you give an injection.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.

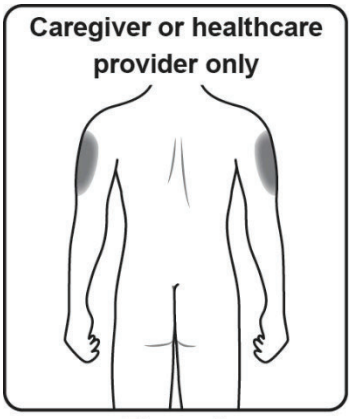


Figure G

- If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your outer upper arm **(see Figure G)**.

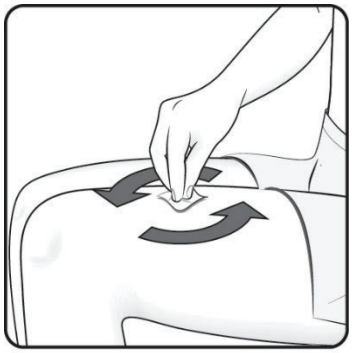


Figure H

Step 4. Clean the injection site

- Wash your hands well with soap and water.
- Using a circular motion, clean the injection site with the alcohol wipe **(see Figure H)**. Leave it to dry before injecting.
- **Do not** touch the cleaned area again before injecting.

Injecting with the COSENTYX UnoReady pen

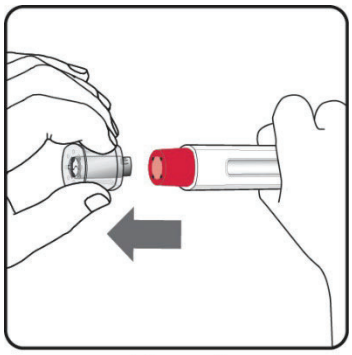


Figure I

Step 5. Remove the cap

- Only remove the cap when you are ready to use the COSENTYX UnoReady pen.
- **Pull** the cap straight off **(see Figure I)**. **Do not** twist the cap.
- Throw away the cap. **Do not** try to re-attach the cap.
- Use the COSENTYX UnoReady pen within 5 minutes of removing the cap.

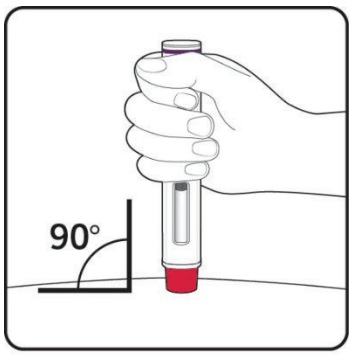


Figure J

Step 6. Position the COSENTYX UnoReady pen
Hold the COSENTYX UnoReady pen at 90 degrees against the cleaned injection site with the viewing window facing you **(see Figure J)**.

Step 7. Injecting with the COSENTYX UnoReady pen as described below **(see Figure K)**

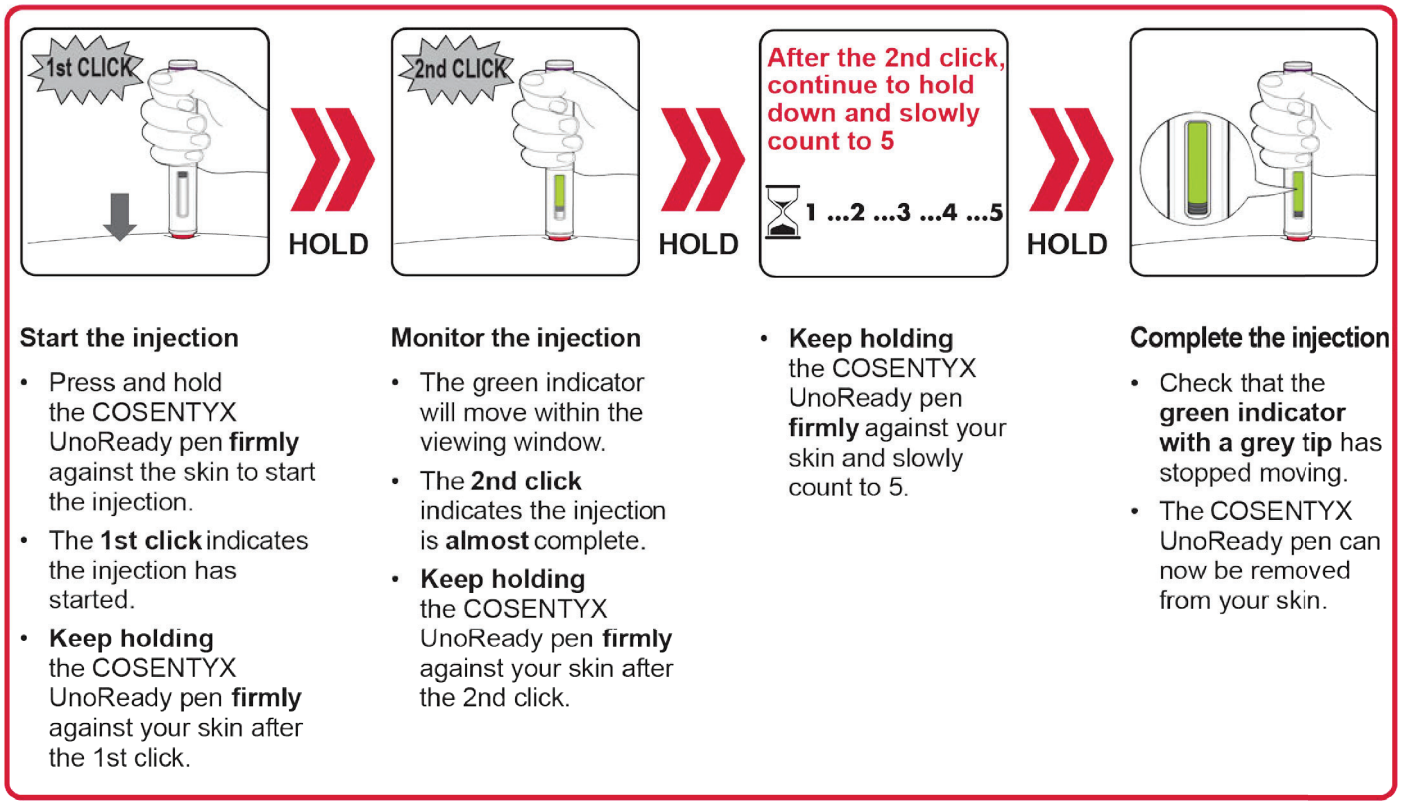


Figure K

After the injection

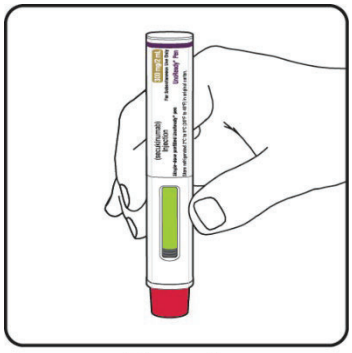


Figure L

Step 8. Check that the green indicator has filled the window (see Figure L)

- This means the medicine has been delivered. Contact your healthcare provider or pharmacist if the green indicator is not visible or does not fill the window.
- There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for a few seconds. **Do not** rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

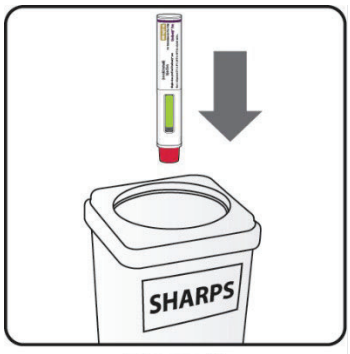


Figure M

Step 9. Disposing of the used COSENTYX UnoReady pen

- Put your used COSENTYX UnoReady pen in an FDA-cleared sharps disposal container right away after use **(see Figure M)**. **Do not throw away (dispose of)** the COSENTYX UnoReady pen in your household trash. If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,

  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and COSENTYX UnoReady pens.

  For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

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

US License Number 1244

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued: July 2023

T2023-45

INSTRUCTIONS FOR USE

COSENTYX® [koe-sen-tix]

(secukinumab)

injection, for subcutaneous use

150 mg/mL single-dose Sensoready® pen

Be sure that you read, understand, and follow this Instructions for Use before injecting COSENTYX. Your healthcare provider should show you how to prepare and inject COSENTYX properly using the Sensoready pen before you use it for the first time. Children should not inject COSENTYX themselves using the Sensoready pen. An adult caregiver should prepare and inject COSENTYX after receiving proper training in subcutaneous injection technique. Talk to your healthcare provider if you have any questions.

Important Information You Need to Know Before Injecting COSENTYX:

- **Do not use** the COSENTYX Sensoready pen if either the seal on the outer carton or the seal on the pen is broken. Keep the COSENTYX Sensoready pen in the sealed outer carton until you are ready to use it.
- **Do not shake** the COSENTYX Sensoready pen.
- The caps of the Sensoready pens contain latex. **Do not handle the Sensoready pens if you are sensitive to latex**.
- If you drop your COSENTYX Sensoready pen, **do not use** it if the Sensoready pen looks damaged, or if you dropped it with the cap removed.
- Throw away (dispose of) the used COSENTYX Sensoready pen right away after use. **Do not re-use the COSENTYX Sensoready pen.** See "**How should I dispose of used COSENTYX Sensoready pens?"** at the end of this Instructions for Use.

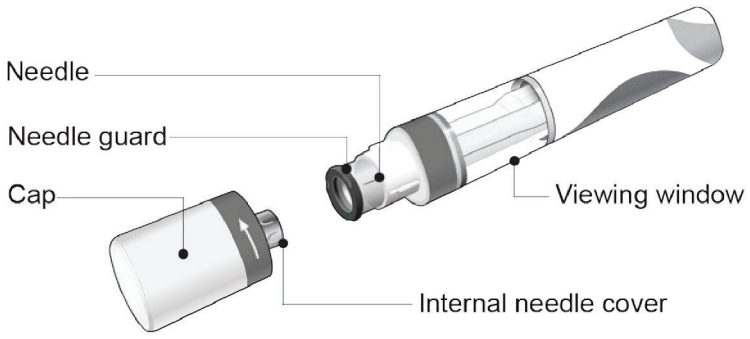
How should I store COSENTYX?

- Store your carton of COSENTYX Sensoready pens in a refrigerator, between 36°F to 46°F (2°C to 8°C).
- Keep the COSENTYX Sensoready pens in the original carton until ready to use to protect from light.
- The COSENTYX Sensoready pens may be stored at room temperature, up to 86°F (30°C), for up to 4 days.
- Write the date the COSENTYX Sensoready pens were removed from and returned to the refrigerator in the space provided on the carton.
- Throw away the COSENTYX Sensoready pen if it has been kept outside of the refrigerator over 4 days.
- COSENTYX Sensoready pen may be returned to the refrigerator **only 1 time** and must be stored between 36°F to 46°F (2°C to 8°C) until you use it or until it expires.
- **Do not** freeze the COSENTYX Sensoready pens.
- Throw away (dispose of) any expired or unused COSENTYX Sensoready pens.

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

COSENTYX Sensoready pen parts (see Figure A):

Figure A



The COSENTYX Sensoready pen is shown above with the cap removed. **Do not** remove the cap until you are ready to inject.

What you need for your injection:

Included in the carton:

A new COSENTYX Sensoready pen **(see Figure B)**.

Each COSENTYX Sensoready pen contains **150 mg** of COSENTYX. Check to make sure that you have the correct medicine and dose.

Figure B

- If your **prescribed dose** of COSENTYX is **150 mg**,

  you must give **1 injection.**

- If your **prescribed dose** of COSENTYX is **300 mg**,

  you must give **2 injections**.

Not included in the carton **(see Figure C)**:

Figure C

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container.

See "**How should I dispose of used COSENTYX Sensoready pens**?" at the end of this Instructions for Use.

Before your injection:

Take the carton containing the COSENTYX Sensoready pen out of the refrigerator and leave it **unopened for about 15 to 30 minutes before injecting** to allow it to reach room temperature.

Step 1. Important safety checks before you inject **(see Figure D)**:

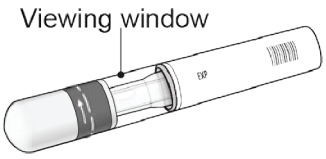
- Look through the viewing window. The liquid should be clear. Its color may vary from colorless to slightly yellow.

  Do not use if the liquid contains visible particles, is cloudy or is discolored. You may see a small air bubble, which is normal.

- Look at the **expiration date (EXP)** on your Sensoready pen. **Do not use** your COSENTYX Sensoready pen if the expiration date has passed.

Contact your pharmacist if the COSENTYX Sensoready pen fails any of these checks.

Figure D



Step 2. Choose the injection site:

- The recommended site is the front of the thighs. You may also use the lower abdomen, but **not** the area 2 inches around the navel (belly button) **(see Figure E)**.
- Choose a different site each time you give an injection.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard, or in an area of skin that is affected by psoriasis. Avoid areas with scars or stretch marks.
- If a **caregiver** or **healthcare provider** is giving you your injection, they may also inject into your outer upper arm **(see Figure F)**.

Figure E

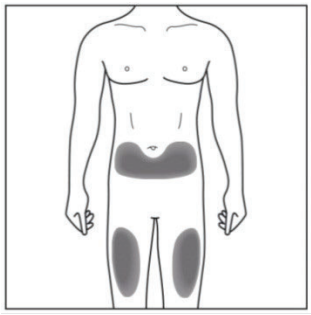
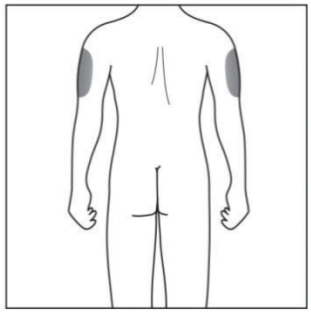


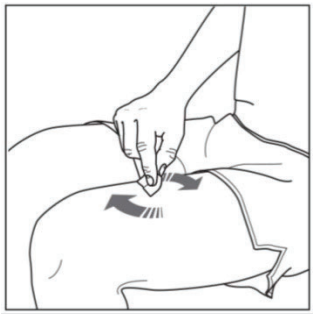
Figure F



Step 3. Cleaning the injection site:

- Wash your hands well with soap and water.
- Using a circular motion, clean the injection site with the alcohol wipe. Leave it to dry before injecting **(see Figure G)**.
- **Do not** touch the cleaned area again before injecting.

Figure G

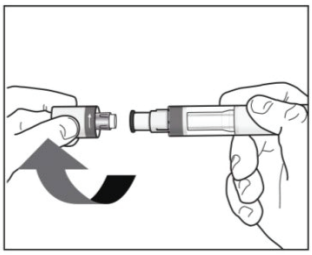


Your injection:

Step 4. Removing the cap:

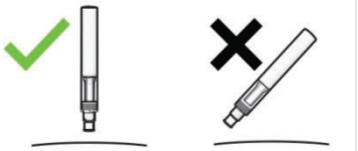
- Only remove the cap when you are ready to use the COSENTYX Sensoready pen.
- Twist off the cap in the direction of the arrow **(see Figure H)**.
- Throw away the cap. **Do not try to re-attach the cap.**
- Use the COSENTYX Sensoready pen within 5 minutes of removing the cap.

Figure H



Step 5. Holding the COSENTYX Sensoready pen:

- Hold the COSENTYX Sensoready pen at 90 degrees to the cleaned injection site **(see Figure I)**.



Correct Incorrect

Figure I

Important: During the injection you will hear **2 loud clicks**:

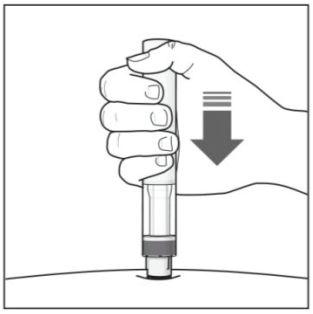
- The **1st click** indicates that **the injection has started**.
- Several seconds later a **2nd click** will indicate that **the injection is almost finished**.

You must keep holding the COSENTYX Sensoready pen firmly against the skin until you see a **green indicator** fill the window and stop moving.

Step 6. Starting the injection:

- Press the COSENTYX Sensoready pen firmly against the skin to start the injection **(see Figure J)**.
- The **1st click** indicates the injection has started.
- **Keep holding** the COSENTYX Sensoready pen firmly against the skin.
- The **green indicator** shows the progress of the injection.

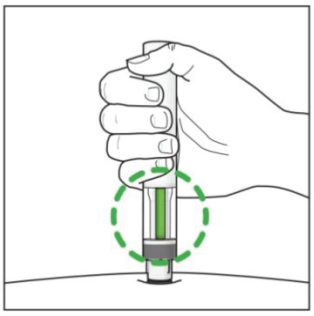
Figure J



Step 7. Completing the injection:

- Listen for the **2nd click**. This indicates the injection is **almost** complete.
- Check the **green indicator** fills the window and has stopped moving **(see Figure K)**.
- The COSENTYX Sensoready pen can now be removed.

Figure K

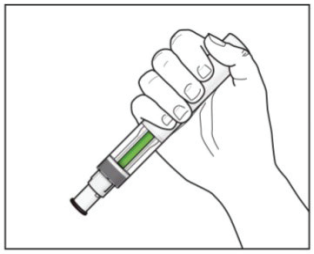


After the injection:

Step 8. Check the green indicator fills the window **(see Figure L)**:

- This means the medicine has been delivered. Contact your healthcare provider if the green indicator is not visible.
- There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

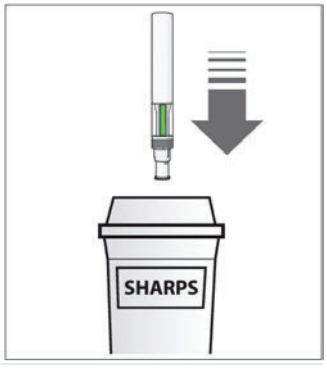
Figure L



If your prescribed dose of COSENTYX is 300 mg, repeat Steps 1 through 8 with a new COSENTYX Sensoready pen.

How should I dispose of used COSENTYX Sensoready pens?

Figure M



Step 9. Put your used Sensoready pen in an FDA-cleared sharps disposal container right away after use **(see Figure M). Do not throw away (dispose of)** the Sensoready pens in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and Sensoready pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

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

US License Number 1244

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: July 2023

T2023-46

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s063

MULTIDISCIPLINE REVIEW(s)

BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement (SE1)
Application Number	BLA 125504/S-063
Priority or Standard	Standard
Submit Date	30 September 2022
Received Date	30 September 2022
PDUFA Goal Date	30 July 2023
Division/Office	Division of Dermatology and Dentistry (DDD)/Office of Immunology and Inflammation (OII)
Review Completion Date	30 October 2023
Established/Proper Name	Secukinumab
Trade Name	Cosentyx
Pharmacologic Class	Human interleukin-17A antagonist
Code name	Not Applicable
Applicant	Novartis Pharmaceuticals Corporation
Dosage form	Injection
Applicant proposed Dosing Regimen	300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks
Applicant Proposed Indication/Population	For the treatment of adults with moderate to severe hidradenitis suppurativa (HS)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	59393003 - Hidradenitis suppurativa (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults with moderate to severe hidradenitis suppurativa (HS)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	59393003 - Hidradenitis suppurativa (disorder)
Recommended Dosing Regimen	300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. If a patient does not adequately respond, consider increasing the dosage to 300 mg every 2 weeks

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sascha Randolph
Nonclinical Reviewer	Review not required
Nonclinical Team Leader	Review not required
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Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer	Maryjoy Mejia
Clinical Team Leader	Amy Woitach
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Deputy Director for Safety (DDD)	Tatiana Oussova

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OSE/DEPI	Benjamin Booth
OSE/DMEPA	Madhuri Patel
OSE/SRPM	Tri Bui-Nguyen
ADL	Matthew White

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology and Pharmacometrics Reviewer	Selim Fakhruddin, Ph.D.	OCP/DIIP	Section: 6 and 19.4	**Select one:** __X_ Authored ___ Approved
	Signature:			
Clinical Pharmacology Team Leader	Chinmay Shukla, Ph.D.	OCP/DIIP	Section: 6 and 19.4	**Select one:** ___ Authored _X__ Approved
	Signature:			
Pharmacometrics Team Leader	Youwei Bi, Ph.D.	OCP/DPM	Section: 6 and 19.4	**Select one:** ___ Authored _X__ Approved
	Signature:			
Clinical Reviewer	Maryjoy Mejia, M.D.	OII/DDD	Sections: 1, 2, 3, 4, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.2	**Select one:** __X_ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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	Signature:			
Statistical Reviewer	**Guoying Sun, PhD**	OTS/OB/DBVIII	Sections: 8.1, 8.3	**Select one:** ___ Authored _x__ Approved
	Signature:			
Statistical Team Leader	Wanjie Sun, PhD	OTS/OB/DBVIII	Sections: 8.1, 8.3	**Select one:** ___ Authored _x__ Approved
	Signature:			
Deputy Director for Safety	Tatiana Oussova, MD		Sections:	**Select one:** ___ Authored ___ Approved
	Signature:			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Secukinumab is a human monoclonal IgG1κ antibody that selectively binds to the pro-inflammatory cytokine interleukin-17A (IL-17A) and blocks its interaction with the IL-17 receptor. Secukinumab is considered to inhibit the release of proinflammatory cytokines, chemokines, and mediators of tissue damage resulting from IL-17A mediated autoimmune and inflammatory diseases. It is marketed under the trade name COSENTYX and received initial approval for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy on January 21, 2015.

The recommended dose of secukinumab for the treatment of psoriasis in adults is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some subjects, a dose of 150 mg may be acceptable. For the treatment of children greater than 6 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, secukinumab is approved at 75 mg or 150 mg every 4 weeks depending on body weight. Secukinumab is also approved for active psoriatic arthritis and active ankylosing spondylitis, in adults at a dose of 150 mg every 4 weeks and if a patient continues to have active disease, a dosage of 300 mg every 4 weeks may be considered. Additionally, secukinumab is approved in adults for the treatment of active non-radiographic axial spondyloarthritis at 150 mg every 4 weeks and for active enthesitis-related arthritis in patients 4 years of age and older at doses of 75 mg or 150 mg every 4 weeks based on body weight strata.

In the efficacy supplement that is the subject of this review (BLA 125504/S-063), the Applicant proposes a new indication, the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS), and a new proposed dosing regimen of 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks.

Approval of supplement 63 would introduce the second FDA approved medication for the treatment of HS in the United States, as well as a new dosage regimen for COSENTYX.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from two identical, adequate and well-controlled trials, CAIN457M2301 (M2301) and CAIN457M2302 (M2302), that evaluated secukinumab 300 mg every 2 weeks and 300 mg every 4 weeks versus placebo in 1084 adult subjects with moderate to severe HS. Primary efficacy was assessed at Week 16 by the proportion of subjects who achieved a Hidradenitis Suppurativa Clinical Response, HiSCR50, defined as at least a 50% reduction in total abscess and inflammatory nodule count (AN count), with no increase in abscess count, and no increase in draining fistula count relative to baseline.

While the effectiveness standard was met, the results on the primary efficacy endpoint were inconsistent across the two trials. In both trials, the secukinumab Q2W dose regimen showed statistically significantly higher response rates with clinically meaningful differences compared to placebo. However, the secukinumab Q4W dose regimen showed a statistically significantly higher response rate with a clinically meaningful difference compared to placebo in trial M2302 but not in trial M2301. Moreover, the Q4W regimen in Trial M2302 had the highest response rate (46.1%) compared to the Q2W regimen in both trials (45.0% in Trial M2301 and 41.8% in Trial M2302).

To understand these results, analyses of response rates based on disease severity (measured by Hurley staging) were conducted by the review team as there was an imbalanced distribution of subjects with baseline Hurley stage III severity among the three treatment arms across both trials, and baseline Hurley stage appeared to be the only significant variable in the multivariate logistic regression analysis. Additionally, the submitted data demonstrated a positive correlation between disease severity and drug clearance which corresponded to lower systemic exposures in subjects with worse disease severity.

Although both trials were randomized, the placebo group in Trial M2301 had a significantly smaller proportion of subjects with Hurley stage III disease (28.3%) compared to the placebo group in Trial M2302 (38.3%)—this difference significantly impacted treatment effect. In Trial M2301, because more subjects in the placebo group had milder disease, a higher response rate was observed (33.7%) compared to the response rate for the placebo group in Trial M2302 (31.2%) which had 10% more subjects with Hurley stage III severity. The difference in response rates between the placebo groups explains the lower treatment effect observed for the Q4W group relative to placebo in Trial M2301 compared to the treatment effect for the Q4W group in Trial M2302.

The imbalanced distribution of subjects with Hurley stage III also helps to explain why the secukinumab Q4W regimen in Trial M2302 had the highest response rate. In both Trials M2301 and M2302, the Q2W group was comprised of a larger proportion of subjects with more severe disease (i.e., Hurley stage III) at baseline. The submitted data also demonstrated that secukinumab clearance increases with increasing HS severity, and subjects with Hurley stage III disease severity had worse exposure-response (E-R) relationships than those with Hurley stages I and II. Additionally, the E-R curve plateaued at high exposures achieved with the Q2W regimen. These findings provide a reasonable scientific rationale as to why the Q2W groups in both trials had a lower response rate compared to the Q4W group in Trial M2302.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Hidradenitis suppurativa (HS) is a chronic, recurrent suppurative disease that manifests with inflamed skin lesions, with or without skin tunnels or scarring, which primarily affect intertriginous areas, such as the axillae, groin, and anogenital regions, and may be associated with pain, pruritis, malodor, drainage, and disfigurement. The extent or severity of disease is often characterized by the Hurley staging system, which divides patients with HS into three groups: Stage I – abscess(es) without skin tunnels or scarring; Stage II – recurrent single or multiple widely separated abscesses with skin tunnels and scarring; and Stage III – multiple interconnected skin tunnels and abscesses across an entire area

Secukinumab is a human monoclonal IgG1κ antibody that selectively binds to the pro-inflammatory cytokine interleukin-17A (IL-17A) and blocks its interaction with the IL-17 receptor. Secukinumab is considered to inhibit the release of proinflammatory cytokines, chemokines, and mediators of tissue damage resulting from IL-17A mediated autoimmune and inflammatory diseases. It is marketed under the trade name COSENTYX and initially received approval for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy on January 21, 2015. Since that time, secukinumab has been approved for the treatment of multiple chronic inflammatory conditions all of which have a recommended maintenance dosage frequency of every 4 weeks.

Currently, the only FDA-approved therapy for HS is Humira (adalimumab), a tumor necrosis factor blocker, which is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older. The labeling for Humira contains a boxed warning for malignancy, as well as serious infections, including active tuberculosis (TB) and reactivation of latent TB that frequently have frequently presented as disseminated or extrapulmonary disease, invasive fungal infections, and opportunistic. Other labeled adverse reactions include anaphylaxis, nervous system demyelinating diseases, cytopenias, and heart failure.

Off-label treatment options for HS include topical and systemic antibiotics, oral retinoids, antiandrogenic agents, metformin, biological products other than adalimumab, intralesional corticosteroids, incision and drainage of cysts, surgical excision, grafting, and laser ablation. Success with these approaches is variable and may be limited by side effect profiles, disease severity, concomitant medical conditions, and patient preference.

Substantial evidence of effectiveness of secukinumab for the treatment of adult patients with moderate to severe HS was provided from two

identical, randomized, double-blind, placebo-controlled, 52-week phase 3 trials, CAIN457M2301 and CAIN457M2302 (hereafter referred to M2301 and M2302, respectively), that evaluated secukinumab 300 mg every 2 weeks and 300 mg every 4 weeks versus placebo in 1084 adult subjects with moderate to severe HS. Primary efficacy was assessed at Week 16 by the proportion of subjects who achieved a Hidradenitis Suppurativa Clinical Response, HiSCR50, defined as at least a 50% reduction in total abscess and inflammatory nodule count (AN count), with no increase in abscess count, and no increase in draining fistula count relative to baseline.

The results on the primary efficacy endpoint were inconsistent across the two trials.
Based on the Applicant's strategies for handling intercurrent events, the secukinumab Q2W dosage regimen showed statistically significantly higher response rates with clinically meaningful differences compared to placebo in both trials (45.0% in vs. 33.7% in M2301, two-sided p=0.0140 < pre-specified alpha 0.04 and 42.3% vs. 31.2% in M2302, two-sided p=0.0299 < 0.04). The secukinumab Q4W dose regimen showed a statistically significantly higher rate with clinically meaningful differences compared to placebo in Trial M2302 (46.1% vs. 31.2%, two-sided p=0.0044 < pre-specified alpha 0.01) but not in Trial M2301 (41.8% vs. 33.7%, two-sided p=0.0835). Moreover, the Q4W regimen in Trial M2302 had the highest response rate (46.1%) compared to the Q2W regimen in both trials (45.0% in Trial M2301 and 41.8% in Trial M2302).

Based on further analyses wherein subjects who received any rescue medication or underwent lesion intervention were considered treatment failures and handled as non-responders, the results were in general similar to that of the Applicant's aforementioned analyses except that all the p-values were smaller (i.e., more statistically significant). In particular, the statistical significance of the secukinumab Q4W vs. placebo in Study M2301 considerably improved (41.3% vs. 29.4%, p=0.0123 > pre-specified alpha 0.01).

Extensive analyses to understand the inconsistent efficacy results showed that baseline Hurley stage appeared to be the only significant variable in the multivariate logistic regression analysis, and despite randomization, there was an imbalanced distribution of subjects with more severe disease (i.e., Hurley stage III) at baseline among all the three treatment arms across both trials. Additionally, the submitted data demonstrated a positive correlation between disease severity and drug clearance which corresponded to lower systemic exposures in subjects with worse disease severity.

Although both trials were randomized, the placebo group in Trial M2301 had a notably smaller proportion of subjects with Hurley stage III disease (28.3%) compared to the placebo group in Trial M2302 (38.3%)—this difference significantly impacted treatment effect. In Trial M2301, because more subjects in the placebo group had milder disease, a higher response rate was observed (33.7%) compared to the response rate for the placebo group in Trial M2302 (31.2%). The difference in response rates between the placebo groups explains the lower treatment effect observed for the Q4W group relative to placebo in Trial M2301 compared to the treatment effect for the Q4W group in Trial M2302.

In attempts to ascertain why the secukinumab Q4W regimen in Trial M2302 had the highest response rate, the impact of the imbalanced distribution of subjects with Hurley stage III was further assessed. In both trials, the Q2W group was comprised of a larger proportion of subjects with more severe disease (i.e., Hurley stage III) at baseline. Although serum exposure of secukinumab was approximately 2-fold higher with a 300 mg Q2W regimen at maintenance compared to a 300 mg Q4W regimen, secukinumab clearance is expected to be increased in this group with worse HS severity. Additionally, efficacy (as measured by HiSCR50) plateaued at higher exposures achieved with the Q2W regimen. These findings altogether provide a reasonable scientific rationale as to why the response rates for the Q2W groups in both trials were lower than that of the Q4W group in Trial M2302.

The safety of secukinumab for the treatment of adults with moderate to severe HS was assessed primarily using data from Trials M2301 and M2302. The safety review was also supported by a dossier summarizing data from an ongoing, 4-year randomized withdrawal extension trial, CAIN457M2301E1 (M2301E1), which included information from 700 subjects who completed trials M2301 and M2302 and who wished to continue treatment.

The size of the overall database from Trials M2301 and M2302 included 1060 subjects exposed to at least one dose of secukinumab, 527 of which received secukinumab Q2W and 533 subjects who received secukinumab Q4W, with approximately half of the subjects in each group exposed to trial drug for at least 1 year. In addition to primary safety analyses [i.e., treatment emergent adverse events (TEAEs), deaths, serious adverse events (SAEs), AEs leading to discontinuation, and immunogenicity], additional analyses of AEs of special interest based on prior experience with secukinumab, consisted of infections (including opportunistic infections), hypersensitivity, suicidal ideation and behavior (SIB), inflammatory bowel disease (IBD), neutropenia, major adverse cardiovascular events (MACE), and malignancy.

The size of the safety database and the safety evaluations were adequate to identify treatment-emergent adverse reactions. The total exposure at 52 weeks is reasonable to characterize the safety of the product and two dosage regimens over longer treatment periods. While the demographics of the trial population reasonably represented the target population, the safety database is considered insufficient to assess the risks of secukinumab in the pediatric population with moderate to severe HS as these patients were excluded from the clinical trials. To determine benefit-risk in the pediatric population, a postmarketing assessment will be required.

Overall, the safety profile observed in subjects with moderate to severe HS through Week 52 treated with secukinumab 300 mg Q2W and 300 mg Q4W was similar to the safety profile in subjects with psoriasis.
During the placebo-controlled period, the most common adverse reactions (ARs) reported in at least 1% of subjects treated with secukinumab Q2W or Q4W and at least 1% more frequently than subjects who received placebo included headache, dental caries, oropharyngeal pain, eczema, lipase increased, and conjunctivitis. With longer exposure through 52 weeks, the types of adverse reactions were similar to those

observed during the first 16 weeks of treatment, and the frequencies of ARs between the Any secukinumab Q2W and Q4W groups were comparable.
During the HS program, there were two deaths among subjects receiving secukinumab; both were in the secukinumab Q4W group. Neither of the deaths were assessed as probably related to the drug product.

The review team also evaluated the comparative safety of secukinumab 300 mg Q2W and 300 mg Q4W. The proportion of subjects with SAEs or who discontinued due to AEs was similar across secukinumab and placebo groups during the placebo-controlled period and comparable between the Any secukinumab Q2W and Any secukinumab Q4W groups with longer exposure through 52 weeks. However, more severe clinical courses and unfavorable outcomes were generally observed for subjects in the secukinumab Q2W who experienced SAEs. Additionally, fungal infections, hypersensitivity, and inflammatory bowel disease, were reported more frequently in subjects treated with secukinumab 300 mg Q2W than 300 mg Q4W. The review team considered these findings in the assessment of benefit-risk and in determining the recommended dosage regimen.

While the secukinumab Q2W dosage regimen demonstrated statistically significant superiority over placebo for HiSCR50 in both trials, the Applicant's analyses showed that the secukinumab Q4W dosage regimen had the highest response rate across all treatment groups and was statistically significant in Trial M2302. This outcome was explained by the uneven distribution of baseline disease severity among the three treatment arms in both trials. The findings were also supported by PK results that showed subjects with Hurley stage III disease severity had worse exposure-response (E-R) relationships than those with Hurley stages I and II due to increased secukinumab clearance with increasing HS severity and efficacy plateaued at higher exposures achieved with Q2W dosing.

The results of the extensive subgroup efficacy analyses and findings of the comparative safety assessments between secukinumab Q2W and Q4W dosing support the Applicant's proposed indication, treatment of adult patients with moderate to severe HS. However, the findings do not support the Applicant's proposed dosage regimen of 300 mg every 2 weeks for all adults with moderate to severe HS. The higher rate of fungal infections, IBD, and hypersensitivity events coupled with modest efficacy on the primary endpoint (HISCR50 response) for the Q2W dosage regimen, generates a risk-benefit profile that favors a recommended dose of secukinumab 300 mg dosed every 4 weeks in adults with moderate to severe HS. The review team therefore determined that labeling reflect a recommended dosage regimen of 300 mg every 4 weeks, and for some patients who fail to improve with secukinumab 300 mg every 4 weeks, a dosage of 300 mg every 2 weeks may be acceptable for the treatment of moderate to severe HS.

HS is a serious condition with limited available treatment modalities. The safety and efficacy data submitted by the Applicant support approval of this sBLA for COSENTYX (secukinumab) 300 mg administered subcutaneously every 4 weeks for the treatment of adults with moderate to

severe HS. For adults who continue to have active disease, 300 mg administered subcutaneously every 2 weeks may be acceptable. The extension of the indication addresses an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hidradenitis suppurativa (HS) is a chronic, recurrent suppurative disease that is clinically diagnosed based on characteristic inflamed skin lesions primarily affecting intertriginous areas. Clinical manifestations may include recurrent abscesses and inflamed nodules, draining skin tunnels (also known as sinus tracts or fistulae), and bands of scar, all of which may be associated with pain, pruritis, malodor, drainage, and disfigurement. • The exact prevalence in the United States, as well as worldwide is not clear and has ranged from 0.05% to 4.1%. The disease occurs in adolescents and adults, and rarely begins before puberty suggesting that hormones play a role in the pathophysiology of HS. In the United States, hidradenitis suppurativa occurs with higher incidence in women and blacks. • Multiple complications associated with chronic, poorly controlled HS have been reported in the literature which include contractures, lymphatic obstruction, fistulae into the urethra, bladder, rectum, and peritoneum, infections, anemia, and depression, as well as suicide.	HS is a chronic disease that has a significant impact on how patients feel and function, and has the potential for associated comorbities. Moderate to severe HS has considerable negative effects on quality of life and emotional well-being.
Current Treatment Options	• There is no cure and only one FDA-approved treatment (adalimumab) for HS. • There are a number of treatments used off-label to manage HS. The selection of treatment depends on the severity of disease. For limited disease, the most common treatment is antibiotics, applied topically or administered orally. • Other treatment options include oral retinoids, antiandrogenic	There is a significant unmet medical need for effective treatment of patients with HS. There are limited approved therapies, and existing therapies that are used off-label do not adequately manage the condition for many patients with moderate to severe HS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	agents, metformin, biological products other than adalimumab, intralesional corticosteroids, incision and drainage of cysts, surgical excision, grafting, and laser ablation. • Systemic therapies and surgical interventions are considered for patients who have more severe and/or recalcitrant disease.	
Benefit	• Data from two identical, 52-week, adequate and well-controlled clinical trials, CAIN457M2301 and CAIN457M2302, provided evidence of the effectiveness of secukinumab in adults with moderate to severe HS, defined as ≥5 abscess and inflammatory nodules affecting ≥2 distinct anatomic areas for ≥ 1 year. • A total of 1084 adult subjects were randomized to receive COSENTYX 300 mg every 2 weeks (N =361), COSENTYX 300 mg every 4 weeks (N= 360), and placebo (N= 363), with a total of 901 subject-years of COSENTYX exposure and median duration of exposure for COSENTYX-treated subjects of 360 days. • Primary efficacy was assessed at Week 16 by the proportion of subjects who achieved a Hidradenitis Suppurativa Clinical Response, HiSCR50, defined as at least a 50% reduction in total abscess and inflammatory nodule count (AN count), with no increase in abscess count, and no increase in draining fistula count relative to baseline. • In both trials, a statistically significantly higher proportion of subjects treated with COSENTYX 300 mg every 2 weeks achieved a HiSCR50 response at Week 16 compared to subjects treated with placebo. • In both trials, a higher proportion of subjects treated with COSENTYX 300 mg every 4 weeks achieved a HiSCR50 response at Week 16 compared to subjects treated with placebo at Week 16; however, a statistical significance was only reached in Trial M2302. • Although both trials were randomized, an imbalanced distribution of subjects with Hurley stage III at baseline among all the three	The submitted data has met the evidentiary standard for providing substantial evidence of effectiveness in subjects with moderate to severe HS. Treatment effect was impacted by the difference in the proportion of subjects in the placebo groups with baseline Hurley stage III between trials wherein Trial M2302 had 10% more subjects with Hurley stage III severity. The higher response rate for the placebo group in Trial M2301 compared to the response rate for the placebo group in Trial M2302 corresponded to a lower treatment effect observed for the Q4W group relative to placebo in Trial M2301 compared to the treatment effect for the Q4W group in Trial M2302. Additionally, because the secukinumab Q2W group was comprised of a larger proportion of subjects with more severe disease at baseline in both Trials M2301 and M2302 and submitted data demonstrated a positive

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment arms across both trials was identified and appeared to affect efficacy. • The proportion of subjects in the placebo groups with baseline Hurley stage III differed between trials (28.3% in Trial M2301 and 38.3% in Trial M2302), which corresponded to a higher response rate of 33.7% for the placebo group in Trial M2301 compared to a response rate of 31.2% for the placebo group in Trial M2302. • The secukinumab Q2W group was comprised of a larger proportion of subjects with more severe disease (i.e., Hurley stage III) at baseline in both Trials M2301 and M2302. This imbalance coupled with the submitted pharmacokinetic data, which demonstrated that secukinumab clearance increases with increasing HS severity, and subjects with Hurley stage III disease severity had worse exposure-response (E-R) relationships than those with Hurley stages I and II, may explain the discrepant response rates of Q2W and Q4W dosing between the two trials. • Improvements of HiSCR50 were observed regardless of previous or concomitant antibiotic treatment or previous biologic exposure. • The E-R analysis for the HiSCR50 endpoint using pooled HS data showed an approximately 3% higher response rate for the Q2W over the Q4W regimen at Week 16 which was sustained at Week 52 at which time an approximately 5% higher response rate was observed. However, the E-R relationship was shallow, and there was significant overlap of exposures between both regimens. Furthermore, the exposure-response curve plateaued at high exposures achieved with the Q2W regimen.	correlation between disease severity and drug clearance which corresponded to lower systemic exposures in subjects with worse disease severity, the lower response rate in both Q2W groups compared to the Q4W group in Trial M2302 is understandable. The data suggest that a patient with moderate-to severe HS treated with secukinumab 300 mg at Weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter is likely to achieve at least a 50% reduction in total AN count, with no increase in abscess count, and no increase in draining fistula count by Week 16, and is also likely maintain these results by Week 52. Whille the E-R results for the primary endpoint, HiSCR50, demonstrated a numerically higher response rate for the Q2W regimen, the difference compared to the Q4W regimen is marginal (3 – 5%). Furthermore, because efficacy (as measured by HiSCR50) plateaued at the higher exposures, further increase in dose strength or dosing frequency will unlikely provide additional benefit. Secukinumab will provide patients with an approved therapeutic option that has adequately characterized benefits.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety database, which consisted of data from the pooled phase 3 trials M2301 amd M2302, is adequate to characterize the safety profile of secukinumab 300 mg by subcutaneous injection in the treatment of HS. The size of the overall safety database was considered adequate and in line with the principles of ICH E1. The database includes a total of 1060 subjects exposed to at least 1 dose of secukinumab with 257 subjects receiving at least 1 dose of secukinumab 300 mg Q2W and 246 subjects receiving at least 1 dose of secukinumab 300 mg Q2W for ≥ 1 year. • Two deaths were reported among subjects receiving secukinumab; both were in the secukinumab Q4W group. Neither of the deaths were assessed as probably related to the drug product. • Serious adverse events (SAEs) were reported in 3.0% of subjects treated with secukinumab 300 mg Q2W, secukinumab 300 mg Q4W, and placebo during the first 16 weeks of treatment. No SAE was reported with greater than 1% frequency. The most common SAEs were worsening hidradenitis and sweat gland infection. • Adverse events leading to discontinuation occurred in 1.7% of subjects treated secukinumab 300 mg Q2W, 1.7% treated with secukinumab 300 mg Q4W, and 1.4% treated with placebo. • Fungal infections were reported more frequently for the secukinumab Q2W group (5.3%) compared to the secukinumab Q4W (3.9%) and placebo (2.8%) groups during the first 16 weeks of treatment. After 52 weeks of exposure, more infections by SOC were reported for the Any secukinumab Q2W group (94.5/100 PY) compared to the Any secukinumab Q4W group (87.9/100 PY); this difference was due to a higher rate of fungal infections. • Hypersensitivity events were highest for the secukinumab Q2W group (5.3%) compared to the secukinumab Q4W (3.3%) and placebo	The data provided in this supplement from adult subjects with moderate to severe HS demonstrated a safety profile for both dosage regimens that is similar to what has been established for the psoriasis population. Treatment with secukinumab 300 mg Q2W and Q4W in subjects with moderate to severe HS was not associated with an increased risk of mortality. Evaluation of the comparative safety of secukinumab 300 mg Q2W and 300 mg Q4W demonstrated that the proportion of subjects with SAEs or who discontinued treatment due to AEs was similar across secukinumab and placebo groups during the first 16 weeks of treatment, and was comparable between the Any secukinumab Q2W and Any secukinumab Q4W groups with longer exposure through 52 weeks. However, more severe clinical courses and unfavorable outcomes were generally observed for subjects in the secukinumab Q2W who experienced SAEs. The higher dosing frequency of secukinumab Q2W did not appear to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(3.9%) groups during the first 16 weeks of treatment. Similar findings after 52 weeks of exposure were observed wherein the rate of hypersensitivity AEs remained higher for the Any secukinumab Q2W group (5.1%) compared to the Any secukinumab Q4W group (3.4%). A positive association between the incidence of these hypersensitivity events and more frequent dosing cannot be ruled out and is concerning for potentially more severe immune reactions and/or escalation of an immune response with repeated dosing beyond the recommended 300 mg every 4 weeks. • Events of inflammatory Bowel Disease (IBD) were reported more frequently in subjects receiving secukinumab Q2W during the HS development program, in particular during the randomized withdrawal extension trial (M2301E1), which included information from 700 subjects who completed trials M2301 and M2302 and who wished to continue treatment. Five (0.7%) subjects out of 700 total subjects in the ongoing extension trial were documented to have experienced events of new IBD. All of the subjects were receiving secukinumab 300 mg Q2W at the time of their diagnoses. All IBD events were serious and led to withdrawal of trial drug. • The number of suicidal ideation and behavior (SIB) cases were small, and the difference in exposure adjusted incidence rates (0.4/100 PY for the Any secukinumab Q2W group compared to 0.2/100 PY for the Any secukinumab Q4W group) was not significant. • The overall number of serious cardiovascular AEs was relatively small, and the incidence of major adverse cardiovascular events (MACE) was low. • The number of malignancy events was relatively small, and most subjects had underlying risk factors that could possibly explain their cancers, although a synergistic effect by secukinumab cannot be	impact the rate or type of AEs that led to treatment drug discontinuation. The AESIs, fungal infections, hypersensitivity, and inflammatory bowel disease, were reported more frequently in subjects treated with secukinumab 300 mg Q2W than 300 mg Q4W. To convey the higher rate of fungal infections observed with increased dose frequency in the HS population, inclusion of language in Warnings and Precautions and Adverse Reactions is recommended. Hypersensitivity is labeled under Contraindications and Warning and Precautions in the current Cosentyx USPI. While no further updates to the labeling regarding hypersensitivity are indicated at this time, ongoing postmarketing surveillance of hypersensitivity events is necessary. IBD is labeled under the Warnings and Precautions and Adverse Reactions sections of the current secukinumab USPI. Modifications of these sections to include the increased rate of new, serious IBD events in the HS population who were administered

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	excluded. • During the 16-week placebo-controlled period, the most common ARs reported in at least 1% of subjects treated with secukinumab Q2W or Q4W and at least 1% more frequently than subjects who received placebo included headache, dental caries, oropharyngeal pain, eczema, lipase increased, and conjunctivitis. With longer exposure through 52 weeks, the types of adverse reactions were similar to those observed during the first 16 weeks of treatment, and the frequencies of ARs between the Any secukinumab Q2W and Q4W groups were comparable. • Pregnant and breastfeeding women were excluded from participating in the trials. Five pregnancies were reported in subjects who received secukinumab during the HS development program. All subjects were discontinued from the trials as per protocol. • The safety database did not allow for assessment of the risks of secukinumab use in children as they were excluded from the clinical trials.	secukinumab Q2W compared to those who received secukinumab Q4W is recommended. There is insufficient evidence of an increased risk of SIB with more frequent dosing of secukinumab to recommend updating the labeling. While the reported events of self-harm in the trials do not alter the current recommendations for use of secukinumab, continued postmarket monitoring of SIB especially for this population and this drug class is recommended. An increased risk of serious CV events, including MACE, with either dosage regimen of secukinumab cannot be concluded. Incorporation of CV risk to the current labeling of COSENTYX is not indicated at this time. An increase in overall malignancy risk cannot be concluded in the HS population for either dosage regimen. Given the short duration of the trials and the long latency of malignancy, the absence of a clear safety signal is not in itself reassuring. Routine postmarketing monitoring is necessary to assess the risk of malignancy in patients with moderate to severe HS receiving secukinumab 300 mg every 2 or 4 weeks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		The available data are insufficient to inform secukinumab-associated risk in pregnant women and children. Pregnancy exposure will be assessed through evaluation of data from the long-term extension trial and reports of post-marketing events. Evaluation of the benefit-risk in the pediatric population, specifically in those 12 to ≤17 years of age, will be required as a postmarketing assessment. Assessment of pediatric patients with HS aged < 12 years is impossible or highly impracticable as HS typically starts after puberty, and there is a rarity of diagnosis in children aged <12 years of age. A REMS is not recommended for this supplement. Prescription labeling, patient labeling and routine pharmacovigilance, in conjunction with the pediatric post marketing requirement, are adequate to manage the risks of secukinumab 300 mg Q2W and Q4W in the HS population.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		8.1
		x	Patient reported outcome (PRO)	8.1
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	8.1
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Hidradenitis suppurativa (HS) is a chronic, recurrent suppurative disease that is clinically diagnosed based on characteristic inflamed skin lesions primarily affecting intertriginous areas, such as the axillae, groin, and anogenital regions. Clinical manifestations may include recurrent abscesses and inflamed nodules, draining skin tunnels (also known as sinus tracts or fistulae), and bands of scar, all of which may be associated with pain, pruritis, malodor, drainage, and disfigurement.[1]

The extent or severity of disease is often characterized by the Hurley staging system, which divides patients with HS into three groups: Stage I – abscess(es) without skin tunnels or scarring; Stage II – recurrent single or multiple widely separated abscesses with skin tunnels and scarring; and Stage III – multiple interconnected skin tunnels and abscesses across an entire area.[2]

Although the cause of HS is unknown, factors that may be associated with the development (or exacerbation) of HS have been identified and include genetic susceptibility, mechanical stress (pressure or friction) on the skin, obesity, hormones, bacteria, and drugs (e.g., contraceptives containing androgenic progestins, lithium and some tumor necrosis factor (TNF) antagonists).[1] The pathogenesis of HS is not yet fully understood but is thought to involve follicular hyperkeratosis with subsequent occlusion and dilatation of the hair follicle, leading to rupture, inflammation, abscess formation, and dermal contractures.[3]

The exact prevalence in the United States (U.S.), as well as worldwide is not clear and has ranged from 0.05% to 4.1%. This wide variation is suspected to be due to the different data sources (e.g., insurance claims and healthcare system databases) and methods of data collection (e.g., cross-sectional studies using surveys about skin boils, diagnostic codes, or in-person examinations by dermatologists).[4] The disease occurs in adolescents and adults, and rarely begins before puberty suggesting that hormones play a role in the pathophysiology of HS. In the United States, hidradenitis suppurativa occurs with higher incidence in women and blacks.

Several complications have been reported with chronic, poorly controlled HS, which include contractures, lymphatic obstruction, fistulae into the urethra, bladder, rectum, and

[1] Ingram J. Hidradenitis suppurativa: Pathogenesis, clinical features, and diagnosis. UpToDate. Accessed May 26, 2023
[2] Wieczorek M et al. Hidradenitis suppurativa - known and unknown disease. Reumatologia. 2018;56(6):337-339.
[3] Dylan E. Lee et al. Dermatology (2018) 233 (6): 456–461.
[4] Ingram JR. The epidemiology of hidradenitis suppurativa. Br J Dermatol. 2020 Dec;183(6):990-998

peritoneum, infections, anemia, and depression, as well as suicide.[5,6]

2.2. Analysis of Current Treatment Options

Currently, the only FDA-approved therapy for HS is Humira (adalimumab), a tumor necrosis factor blocker, which was approved for the treatment of adults with chronic moderate to severe hidradenitis suppurativa on January 18, 2008. The recommended subcutaneous dosage of Humira for adults with HS is an initial dose of 160 mg, followed by 80 mg two weeks later, then 40 mg weekly or 80 mg every other week dosing two weeks later. The indication for Humira was expanded to adolescents 12 years and older who weigh greater than 30 kg on October 16, 2018. The labeling for Humira contains a boxed warning for serious infections, including active tuberculosis (TB) and reactivation of latent TB that frequently presented as disseminated or extrapulmonary disease, invasive fungal infections, and opportunistic infections. A boxed warning for malignancy is also described in labeling. Other adverse reactions include anaphylaxis, nervous system demyelinating diseases, cytopenias, and heart failure.

Off-label treatment options for HS include topical and systemic antibiotics, oral retinoids, antiandrogenic agents, metformin, biological products other than adalimumab, intralesional corticosteroids, incision and drainage of cysts, surgical excision, grafting, and laser ablation. Success with these approaches is variable and may be limited by side effect profiles, disease severity, concomitant medical conditions, and patient preference.

While all patients with HS generally require patient education and support, wound management, and pain control, targeted treatment interventions based on the severity of HS are usually necessary. Healthcare providers generally tailor therapies with specific goals to i) treat existing lesions and reduce associated symptoms like pain and drainage, ii) decrease formation of new abscesses/nodules, skin tunnels, and scarring, and iii) minimize the psychologic impact of the disease.

To reduce disease burden in patients with mild HS (i.e., Hurley stage I), treatments that are often used include topical clindamycin, oral tetracyclines, antiandrogenic agents, and metformin. Patients with mild HS who fail to improve with these therapies are often treated with interventions used for more severe disease, such as clindamycin and rifampin combination therapy, acitretin, and dapsone. Laser therapy has also been used in this setting. For relief of acute symptomatic lesions, warm compresses plus intralesional corticosteroid injections, deroofing, and topical resorcinol have been used.

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[5] Thorlacius L et al. "Increased Suicide Risk in Patients with Hidradenitis Suppurativa." *J Invest Dermatol*. 2018 Jan;138(1):52-57.
[6] Yuan JT et al. "Complications of hidradenitis suppurativa." *Semin Cutan Med Surg*. 2017 Jun;36(2):79-85.

Treatment of moderate to severe HS (Hurley stage II or III,) also includes medical and surgical interventions to reduce disease burden and improve acute, symptomatic lesions. Combination therapy is often required. The initial course of treatment to reduce disease burden consists of oral antibiotics, usually tetracyclines or a combination of clindamycin and rifampin, with antiandrogenic agents (for female patients) or metformin commonly used as adjunctive therapies. When adequate disease control is not achieved with these therapies, other interventions, such as biologic products (adalimumab and infliximab), oral retinoids, dapsone, or alternative antibiotic therapy are used. Wide local excision may be beneficial for severe, refractory disease that cannot be controlled with medical therapy.

HS is a serious condition with limited available treatment modalities. The proposed product addresses an unmet medical need.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Secukinumab (COSENTYX) received initial approval for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy on January 21, 2015. The product was later approved for the treatment of adults with active psoriatic arthritis (PsA) or active ankylosing spondylitis (AS) in 2016, and adults with active non-radiographic axial spondyloarthritis (nr-AxSpA) with objective signs of inflammation in 2020.

On May 28, 2021, the first pediatric indication for secukinumab, moderate to severe plaque psoriasis in patients 6 years of age and older, was approved in the United States. Other pediatric indications including treatment of active enthesitis-related arthritis (ERA) in patients 4 years of age and older and treatment of PsA 2 years of age and older were approved in December 2022.

3.2. Summary of Presubmission/Submission Regulatory Activity

During a Type C guidance meeting on September 18, 2017 to discuss the development program of secukinumab for the treatment of HS, the Applicant proposed to conduct two phase 3 trials although they had not conducted any phase 2 trials with secukinumab in subjects with HS. The Applicant had conducted a randomized, double-blind, placebo-controlled phase 2 trial (CCJM112X2202) in 66 subjects with moderate to severe HS with a different IL-17A antagonist (CJM112) and stated that early clinical evidence of the effects of an anti-IL-17 antibody, CJM112, supports the potential of an anti-IL-17 antibody as an effective therapy for patients with HS.

During the meeting, the Applicant proposed a simplified version of Hidradenitis Suppurativa Clinical Response (HiSCR) as the primary endpoint: a reduction of at least 50% in the AN (abscesses and inflammatory nodules) counts and no increase in draining fistula count related to baseline. The Agency pointed out that no preliminary data with secukinumab had been submitted to date, exploratory trials with secukinumab in subjects with HS to evaluate the potential endpoints for the phase 3 trials had not been conducted, proposed changes to the outcome scales were primarily based on expert opinion interviews, and protocols for the proposed phase 3 trials were not provided. The Agency recommended that the primary efficacy endpoint be the proportion of subjects that achieve HiSCR, defined as at least 50% reduction in inflammatory lesion count with no increase in abscess count and no increase of draining fistula count.

On September 20, 2018, the Applicant submitted protocols for the identically designed phase 3 trials, CAIN457M2301 (M2301) and CAIN457M2302 (M2302), in subjects with HS which included the Agency's recommended primary endpoint. Upon review of the protocols, the

Agency i) reiterated the importance of phase 2 investigations with secukinumab, ii) recommended a secondary pain endpoint of the proportion of subjects who achieve a clinically meaningful change, and iii) challenged whether the assessment of at least one flare over 16 weeks was clinically meaningful, given the risk of flare during the adalimumab program (the only program which has yielded an Agency-approved drug product for the treatment of HS) was assessed upon discontinuation or upon decreased dosing frequency of adalimumab.

On July 24, 2020, amended protocols for the phase 3 trials (M2301 and M2302) were submitted as the Applicant intended to introduce a level of flexibility in drug dispensation, protocol assessments and visit schedule due to the COVID-19 pandemic. Advice regarding these submissions was sent to the Applicant to i) encourage using assessments collected at randomization to define baseline for the primary endpoint of HiSCR instead of using a weighted average of screening and randomization visits, ii) convey the need for clinical data to support the relevancy and clinical meaningfulness of the minimum 2-unit reduction of pain on the NRS, and emphasize the requirement that all efficacy analyses be conducted at the individual study level with control of the Type I error rate at the study level for replication of study findings.

On January 15, 2021, amended protocols and SAPs of the phase 3 trials (M2301 and M2302) were submitted wherein the Applicant accepted most of the Agency's recommendations and modified the definition of baseline, as well as informed the Agency that they would submit the data and analysis results justifying the clinical relevance of the minimum 2-unit reduction on the pain NRS when available. However, they insisted on pooling data from the two phase 3 trials to assess statistical significance and clinical relevance of pain (i.e., proportion of subjects with NRS30 at Week 16). In an advice letter dated July 22, 2021, the Agency, reiterated disagreement with Novartis's plan to pool the two phase 3 trials to make such assessments. The Applicant submitted results of all efficacy analyses at the individual study level.

Additionally, in the amended protocols, a new secondary efficacy endpoint, percent change from baseline in AN count at Week 16, was added. The Agency conveyed that a mere change (and percent change) from baseline in AN count at Week 16 may not translate to a clinically meaningful improvement and therefore, may not be appropriate for labeling and that their approach for addressing control of the Type I error rate should be modified to account for clinically meaningful endpoints that are expected for labeling. Following receipt of the FDA Advice letter dated July 22, 2021, Novartis updated the secondary endpoints to replace "percentage change from baseline in AN count at Week 16" to "achievement of AN50 at Week 16" in the SAP amendments submitted to the Agency on September 23, 2021.

After review of the amended SAPs, the Agency did not agree with the proposed handling of intercurrent events and recommended i) a composite strategy to handle intercurrent events of intake of rescue medication and permanent discontinuation of study treatment due to adverse events or lack of efficacy for the primary and secondary estimands where subjects will be defined as non- responders, and ii) a treatment policy strategy for COVID-19 related intercurrent events, where all observations after such an event would be discarded and

imputed via multiple imputation. The Applicant subsequently modified the SAPs according to the Agency's recommended strategies.

In addition to trials M2301 and M2302, the Applicant submitted a protocol for a phase 3 extension trial (CAIN457M2301E1) on November 11, 2019 which would enroll subjects who complete trials M2301 and M2302. The Applicant stated that the purpose of this extension trial is to evaluate the maintenance of response in either continuous or interrupted therapy (using a randomized withdrawal period) of secukinumab (300 mg Q4W or 300 mg Q2W) and to assess long-term efficacy, safety and tolerability of secukinumab. On March 6, 2020, the Applicant submitted the statistical analysis plan (SAP) for the phase 3 extension trial (CAIN457M2301E1). For each dose frequency (300 mg Q2W and 300 mg Q4W), the Applicant described a plan to compare two treatment groups (secukinumab and placebo). However, the Agency did not consider such a comparison to be clinically meaningful and provided advice that information about the proportion of subjects who maintain their response over the maintenance period and the time to loss of response after treatment withdrawal is informative and could be described in labeling.

Upon review of the Type B Pre-sBLA meeting package submitted December 22, 2021, the Agency did not initially agree with the proposed safety database. The Applicant planned to submit an sBLA with 300 mg Q2W as the proposed dosing regimen for the treatment of moderate to severe HS in adult patients; however, the safety database included only 200 subjects who would have received Q2W dosing for 52 weeks. Following further discussion, the Agency agreed that safety data for approximately 250 subjects who receive Q2W dosing for 52 weeks plus data on approximately 160 cross-over subjects who receive Q2W dosing for 36 weeks would be adequate to initiate review of the 300 mg Q2W dose. The Applicant provided the agreed upon safety database with the sBLA submission.

Another issue that arose during review of sBLA-63 centered around the to-be-marketed product for the treatment of HS. Novartis had developed four different presentations of secukinumab [1 mL pre-filled syringe (PFS), 2mL PFS, 1 mL autoinjector (AI), and 2 mL AI)] with the 2 mL PFS used during the phase 3 trials in HS. However, only the 1 mL formulation(s) and device(s) were approved at the time of submission of sBLA-063. On May 11, 2023, efficacy supplement sBLA-44, which sought the approval for the 300 mg/2 mL PFS and 300 mg/2 mL AI presentations, was approved. Data from sBLA-44 demonstated that bioavailability for the secukinumab 2 mL PFS was similar to that of the 2x1 mL PFS. Because the safety and PK profile of 300 mg/2mL formulation and 150 mg/mL appeared relatively comparable to each of the respective presentations (PFS to PFS, as well as AI to AI), the use of and data from the 2 mL PFS in the phase 3 HS development program was determined to be acceptable.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division requested and collaborated with the Office of Scientific Investigations (OSI) to select sites for clinical inspections. Two clinical investigators, Dr. Maryam Alam (site # 4022 in Canada) and Dr. Melody Stone (site # 5028 in the United States), as well as the Applicant, Novartis, were inspected in an attempt to account for the differences in the active treatment arms and to possibly gain an understanding of the trial conduct.

Site 4022 had a large difference in treatment effect (100 % for the Q4W group and 50% for the Q2W group); however, the inspection found no regulatory violations at the site.

The inspection of Site 5028 observed unreported protocol deviations in five subjects: Subjects # (b) (6) had no full physical exams performed at week 16 and subjects (b) (6) at week 52. Dr. Stone, who had had serious Good Clinical Practice (GCP) issues reported against her, was unable to provide reasons why the physical exams were not performed and/or documented. OSI reviewer, Lee Pai-Scherf, MD noted that subject (b) (6) was lost to follow-up by Week 16, and subject (b) (6) was lost to follow-up by week 52. Source records indicated that all other protocol specified assessments, including primary and secondary efficacy measures, AE results, and laboratory tests were assessed as per protocol and were found to be consistent with the data submitted to the sBLA. There were no significant AEs or laboratory abnormalities noted at week 16 for subjects (b) (6) and week 52 for subjects (b) (6) (b) (6) According to Dr. Pai-Scherf, notwithstanding the above protocol deviation, there was no evidence of subject harm based on the lack of significant AEs and/or laboratory test abnormalities collected at Weeks 16 and 52; therefore, data generated by the site appeared acceptable in support of the proposed indication.

The inspection of Novartis found no regulatory violations, and their monitoring as well as oversight of Trials M2301 and M2302 appeared adequate.

Based on the results of these inspections, the OSI reviewer, Lee Pai-Scherf, MD, considered that despite the aforementioned protocol deviation, the trials overall appear to have been conducted adequately, and the data generated by the sites appear to be acceptable in support of sBLA 125504/S-063 (Review dated July 17, 2023).

4.2. Product Quality

In both Trial M2301 and Trial M2302, secukinumab 300 mg was administered using a 300 mg/2 mL pre-filled syringe (PFS), a drug product presentation approved in the United States on

May 11, 2023 under BLA 125504/S-044. Supplement 44 provided data to support the approval of two new, additional product presentations:

- 300 mg/2 mL solution for injection in pre-filled syringe (PFS)
- 300 mg/2 mL solution for injection in pre-filled pen/autoinjector (AI)

The BLA 125504/S-044 application initially received a Complete Response on November 15, 2021 due to several identified deficiencies including, but not limited to, dose accuracy testing, audible design inputs, as well as needle safety device and cap removal forces for the AI that remained unresolved despite a review extension.
There were no product quality issues found for the 300 mg/2 mL PFS or AI products and the quality section of the BLA remains unchanged.

The Office of Biotechnology Products (OBP) has no objection to the approval of this efficacy supplement.

Novartis requested a categorical exclusion from the preparation of an environmental assessment for secukinumab according to 21 CFR Part 25.31. This is acceptable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

As described under section 4.2. Product Quality, BLA 125504/S-044 provided data to support the approval of two additional product presentations (300 mg/2mL PFS and AI) and initially received a Complete Response due to several identified deficiencies related to device constituent parts and manufacturing issues.

The Office of Product Evaluation and Quality (OPEQ) in the Center for Device and Radiological Health (CDRH) concluded that all Complete Response deficiencies (nine to Novartis and three Master Files for Devices (MAF) to Ypsomed manufacturer that were identified during the initial review cycle) were adequately addressed upon resubmission of supplement 44. The 2 mL PFS and 2 mL autoinjector/pen presentations were approved on May 11, 2023. The reader is referred to the OPEQ review by Dunya Karimi dated May 2, 2023 for details.

5 Nonclinical Pharmacology/Toxicology

No new non-clinical data was submitted for this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Novartis Pharmaceuticals submitted an efficacy supplement (Supplement 63, SDN 4557) under BLA125504 on 09/30/2022, seeking the approval for a new indication of Cosentyx (Secukinumab) to treat the adult patients with moderate to severe hidradenitis suppurativa (HS). The proposed dosing regimen is 300 mg at Week 0, 1, 2, 3, 4 (as loading doses) and then once every 2 weeks (Q2W).

Of note, secukinumab was first approved on 01/21/2015 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Subsequently, it was also approved to treat other conditions in adults: active psoriatic arthritis (2016), active ankylosing spondylitis (2016), and active non- radiographic axial spondyloarthritis with objective signs of inflammation (2020). Pediatric approval was also granted for moderate to severe psoriasis (6 years and older), active psoriatic arthritis (2 years and older), and active enthesitis-related arthritis (ERA) (4 years and older). Approved dose and dosing regimen were different across indications, adult, and pediatric patients. Body weight was an influential covariate based on which dose adjustment was recommended in different approved indications.

To support the current supplement, the Applicant submitted data from two identical clinical studies presented in **Table 1**.

Table 1: Clinical studies conducted to support efficacy supplement 63 of BLA125504

Study ID	Objectives	Study design	Study treatment	Remark
M2301 & M2302	Primarily to evaluate the efficacy of secukinumab at week 16. Exploratorily to evaluate the PK, immunogenicity, safety, and tolerability of secukinumab over 52 weeks	Phase 3, randomized, MC, DB, PC, PG study in adult patients with moderate to severe HS (N = 541 and 543 in study M2301 and M2302, respectively). - Period 1: 16 weeks placebo-controlled treatment - Period 2: 36 weeks active treatment - 8 weeks follow-up PK samples were collected as follows: Baseline, Week 16, 24, 52, and 60 (at pre-dose only). Immunogenicity samples were taken at the	<u>Period 1</u>: Patients were randomized in a 1:1:1 ratio to receive 300 mg at week 0, 1, 2, 3, and 4 for induction, then - secukinumab 300 mg Q2W or - secukinumab 300 mg Q4W or - placebo to blind 2 treatment arms <u>Period 2</u>: At the end of week 16 in period 1, treatments were continued as follows: - secukinumab 300 mg Q2W - secukinumab 300 mg Q4W	Formulation: secukinumab 300 mg and placebo for s.c. injection in 2 mL PFS The applicant conducted popPK analyses to evaluate the PK and E-R relationship of secukinumab in HS patients and assess the effect of drug-device combination on its PK.

		same timepoints as the PK samples except at Week 24	- subjects of placebo arm were re-randomized in 1:1 ratio to receive either 300 mg Q2W or Q4W regimen with loading dose of 300 mg at week 16, 17, 18, 19, 20.	

MC: multicenter; DB: double-blind; PC: placebo-controlled; PG: parallel group; s.c.: subcutaneous. Note that the dosage regimen of secukinumab 300 mg q2w and q4w in HS studies will be abbreviated as Q2W and Q4W regimen throughout the Clinical Pharmacology review.

As mentioned in the **Table 1**, the Applicant only collected sparse pharmacokinetic (PK) samples in the two phase 3 studies conducted in HS patients. The Applicant characterized the PK of secukinumab in HS patients by pooling data from M2301, M2302, and 11 more PK studies conducted in patients with moderate to severe plaque psoriasis. All PsO studies were reviewed under original BLA125504 or its different supplements, therefore will not be reviewed under the current supplement.

The clinical pharmacology review team will focus on currently submitted two HS studies along with the adequacy of the population PK (popPK) and exposure-response (E-R) analyses.

In the two HS studies submitted under the current supplement, the Applicant used a 2 mL pre-filled syringe (PFS). The 2 mL PFS and 2 mL autoinjector/pen presentation were approved on 05/11/2023 under Supplement 44. Under Supplement 44, the Applicant established a PK bridge between the 1mL PFS, 2 mL PFS (the same device used in HS studies), and 1 mL PFS and 2 mL AI presentations based on data from studies A2323 and A2325 which were submitted and reviewed under supplement 44 of this BLA. Under this submission, the Applicant also submitted additional popPK analysis report to support the PK exposures from different drug-device combination products (DDCP).

The review of supplement-44 indicates that relative bioavailability was similar for the secukinumab 2-mL PFS when compared to 2×1-mL PFS as a reference. Per the review, the 90% CI for the ratios of geometric means of AUC84-112d and Cmax were within the no-effect boundary (0.80 to 1.25), indicating that these two presentations (2-mL PFS vs 2x1-mL PFS) were comparable. However, for the 2-mL AI device when compared to the 2x1-mL PFS as a reference, both AUC84-112d and Cmax values were higher by 32% and 33%, respectively. The increase in exposures of secukinumab resulting from one injection via 2-mL AI was recommended to be included in the label. Of note, there was no change in the to-be-marketed formulation.

Recommendations

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the clinical pharmacology data submitted under the supplement-63 of BLA125504 supplement. The proposed dosing regimen of 300 mg secukinumab subcutaneous injection at Week 0, 1, 2, 3, 4 and then every 2 weeks is recommended for approval from a clinical pharmacology perspective for the treatment of hidradenitis suppurativa (HS) in adults. Also, the exposure-response (E-R) analyses show that there is no difference between the Q2W and Q4W maintenance dose in terms of efficacy and even the Q4W maintenance dose is reasonable from a clinical Pharmacology perspective.

Post-Marketing Requirements and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 2: Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
General dosing instructions	Recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks for the treatment of hidradenitis suppurativa (HS) in adults. Since exposure-response analyses also support maintenance dosing regimen of 300 mg every 4 weeks, the Clinical Pharmacology review team is in agreement with the Clinical and Statistics review teams to recommend 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks for the treatment of HS in adults. If a patient continues to have active HS, the maintenance dosage can be increased to 300 mg every 2 weeks.
Pharmacokinetics	• Following subcutaneous administrations of 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 2 weeks, steady-state concentrations of secukinumab were achieved by Week 24 in both HS studies. The mean (± SD) steady-state trough concentrations were 55.7 ± 28.9 mcg/mL and 50.5 ± 28.2 mcg/mL in HS study 1 and HS study 2, respectively. • Based on the two HS studies, serum exposure of secukinumab was approximately 2-fold higher with a 300 mg Q2W regimen at maintenance compared with a 300 mg Q4W

	regimen. This implies that the exposure of secukinumab in HS patients is dose proportional. • A cross-study comparison between the serum exposure of patients with PsO and HS indicates that the mean steady state Ctrough at Week 52 was approximately 26 % lower in HS patients than that observed in PsO patients (e.g., 26 vs 35 µg/mL), regardless of drug-device combination used. • In a population pharmacokinetic analysis, the mean systemic CL following subcutaneous administrations of 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 2 weeks to patients with HS was 0.26 L/day. The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 23 days in HS patients. • The popPK analysis demonstrated that disease severity of HS as defined by hurley stages and baseline high-sensitive C-reactive protein (hsCRP) levels were significant covariates affecting the PK exposure of secukinumab. The clearance of secukinumab was estimated 22% and 43% higher in HS subjects with Hurley stage I-II and stage III, respectively, compared with PsO subjects. The popPK analysis also estimated a 9% lower Cavg,ss in HS patients when the body weight, disease severity is the same but hsCRP value was 2-fold higher at baseline. • Based on popPK, there was no relevant effect of concomitant use of antibiotics on secukinumab exposure in HS subjects.
Exposure-Response Analyses	• The E-R analyses were performed on the following: primary endpoint, HiSCR50 (hidradenitis suppurativa clinical response 50), and secondary endpoints include AN50 response (abscesses and inflammatory nodules 50 response), NRS30 (numerical rating scale 30), and proportion of subjects with flares. Other exploratory endpoints were also considered for E-R analyses. • The E-R analysis for the primary (e.g., HiSCR50) and secondary (e.g., NRS30, AN50 response, and flares) endpoints showed that, at Week 16, there was a large overlap of exposures between the two dose regimens and a numerical increase of ~2-3% in response rate was estimated for Q2W over Q4W. This numerical increment in response rate was sustained beyond Week 16 (~4-5% at Week 52). At the individual level, this analysis showed an incremental benefit for subjects achieving high exposure compared to low exposure.

	• At Week 52, the plateau achieved at high exposure for HiSCR50 and AN50 indicated that additional clinical benefit is unlikely to be achieved by increasing the dose strength or the frequency of administration beyond 300 mg Q2W. • These conclusions held when analyses were performed by the different subgroups, for example body weight. In particular, the exposure-response analysis demonstrated similar relationships between subjects weighing <90 kg and ≥90 kg at Week 16 and 52. • The exposure-response analyses showed no meaningful differentiation between Q2W and Q4W regimens for the other efficacy endpoints considered. • In addition, exposure-safety analysis conducted on infections and infestations (SOC) and Candida infections (HLT) for the pooled data of M2301 and M2302 on subjects randomized to secukinumab 300 mg Q2W or Q4W (n = 721) showed comparable incidence rates across the concentration groups (e.g., Cavg,ss of >0-20, >20-40, >40-60, >60-80, and >80 µg/mL). The relationship between Cavg,ss and the incidence of the selected AEs for one year was further modeled using logistic regression. The predicted incidence rates of both Infections and infestations (SOC) and Candida infections (HLT) remained overall stable with increasing Cavg,ss.
Immunogenicity Potential	The incidence of treatment-emergent anti-drug antibodies (TE-ADAs) was below 1% in both M2301 and M2302 studies throughout the 52 weeks period. TE-ADAs were also not associated with altered PK profiles. For example, the PK profiles of subjects with positive TE-ADAs appear comparable to the overall study population).
Bridge between the "to-be- marketed" and clinical trial formulations	• As noted, the Applicant used a 2-mL PFS in the two HS clinical studies, which was approved on 05/11/2023 under supplement 44 of this BLA. In this supplement, the Applicant established a PK bridge between the 2-mL PFS, 2×1-mL PFS and 2-mL AI based on the data from PsO clinical studies A2323 and A2325, which were submitted and reviewed under supplement 44 of this BLA. The summary review of the PK bridging studies is as follows: – The relative bioavailability was similar for the secukinumab 2-mL PFS when compared to 2×1-mL PFS as a reference. Per the review, the 90% CI for the ratios of geometric means of AUC84-112d and Cmax were within the no-effect boundary (0.80 to 1.25), indicating that these two presentations (2-mL PFS vs 2x1-mL PFS) were comparable. However, for the 2-mL AI device when compared to the 2x1-mL PFS as a reference,

	both AUC84-112d and Cmax were higher by 32% and 33%, respectively. The 90% CI for the ratios of geometric means of AUC84-112d and Cmax were consistently greater than 1 (ranging from 1.15 to 1.52), and the upper limit of the 90% CI ranged from 1.51 to 1.52, indicating that the trough concentrations obtained from the two products (2-mL AI vs 2x1-mL PFS) cannot be considered comparable if the no-effect boundary of 0.80 to 1.25 for 90% CI is applied. • The popPK analysis of different DDCP conducted by pooling data from PsO, PsA, and HS studies also supported that the PK exposures were comparable between 2-mL PFS and 2×1-mL PFS. Furthermore, statistical analysis performed on the pooled PsO and PsA data demonstrated comparable PK exposure (only Cmin,ss at pre-dose was considered) across 2-mL PFS, 2×1-mL PFS, 2×1-mL AI, 2-mL AI. • The popPK analysis in HS patients also indicated that among Q2W and Q4W regimens simulated, the use of 2 x 1 mL AI device compared to a 2 mL PFS device resulted in an increase not exceeding 10% for all relevant PK metrics at steady state demonstrating generally comparable serum exposure between the two devices in HS population.
Drug Interactions with Cytochrome P450 Substrates	• The Applicant did not conduct any new drug interaction studies.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Secukinumab (Cosentyx) was first approved in 2015 at the recommended dosing regimen of 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Consentyx was later approved to treat other indications which will not be summarized in this review. Approved dose and dosing regimen were different

across indications, adult, and pediatric patients. Body weight was an influential covariate based on which dose adjustment was recommended in different approved indications.
In the current supplement, the Applicant is proposing the following treatment regimens:

- Recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks for the treatment of moderate to severe hidradenitis suppurativa (HS) in adults.

The clinical pharmacology data submitted under the current supplement supports the proposed dosing regimen for the treatment of moderate to severe HS in adults.

Based on the efficacy results from the two phase 3 HS studies, secukinumab Q2W dose regimen met the primary endpoint (e.g., HiSCR50) at Week 16 in both studies, while Q4W was deemed significant only in study M2302. The Q2W regimen showed statistically significant higher rates with clinically meaningful differences (>10%) compared to placebo in both studies (45.0% vs. 33.7% in M2301, one-sided p=0.0070; 42.3% vs. 31.2% in M2302, one-sided p=0.0149). Conversely, the Q4W regimen showed a statistically significant higher rate with a clinically meaningful difference compared to placebo in M2302 (46.1% vs.31.2%, one-sided p=0.0022) but not in M2301 (41.8% vs. 33.7%, one-sided p=0.0418).

When the efficacy analysis was performed with respect to secondary endpoints (AN50, NRS30 response, and proportion of subjects experiencing flares) at Week 16, Q2W regimen met AN50 and flares in M2301 and AN50 in M2302 while Q4W met AN50 and flares in only M2302. Neither secukinumab dosing regimens achieved statistical significance over placebo with respect to the secondary endpoint of NRS30 response at Week 16; however, a clinically meaningful improvement (>10% difference vs. placebo) was observed only with the Q2W dose regimen in pooled data (12%).

However, the adequacy of the proposed dosing regimen (300 mg Q2W) will further be discussed in section 8.

Therapeutic Individualization
From a clinical pharmacology perspective, no therapeutic individualization is needed for the proposed indication to treat HS in adults based on the submitted clinical pharmacology and popPK data.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Secukinumab is a human interleukin-17A antagonist. 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. Cosentyx has been approved for the treatment of several indications including PsO, PsA, AS, nr-axSpA, and ERA across different age groups. Refer to the approved labeling of COSENTYX regarding secukinumab PK characteristics in subjects with the approved indications.

To support the current supplement, the Applicant submitted the data and report from two identical phase 3 studies (M2301, M2302) conducted in HS patients. Of note, sparse predose PK samples were collected at Week 16, 24, 52, and 60 to evaluate the PK profile of secukinumab in HS patients. Refer to **Table 1** for detailed study design of both studies.

Since the pivotal HS studies had few PK samples, the Applicant adopted a popPK approach to adequately characterize the PK profile of secukinumab in HS patients. Hence, a popPK model was developed by pooling data from the two HS studies along with 11 PsO studies to describe the PK in HS patients and its comparison across indications. The study design of 11 PsO clinical studies are compiled in the **Table 3**.

In a separate popPK analysis, the Applicant also compared the PK exposures resulting from different DDCPs across the PsO, PsA, and HS indications. In this analysis, the data from PsO, PsA, and HS studies were pooled to extrapolate the DDCP impact on PK exposures to the HS population. Refer to pharmacometrics review in OCP appendix for popPK model assessment and E-R analysis.

Table 3: Clinical studies in patients with moderate to severe plaque psoriasis used in popPK analyses to characterize the PK of secukinumab in HS patients and its comparison across PsO and HS indications

Study ID	Objectives	Study design	Study treatment	Formulation
A2102	Primarily efficacy. Safety, tolerability and PK/PD	Phase 2a, randomized, DB, PC, proof-of-concept study in patients with PsO	Single dose (SD): 3 mg/kg IV infusion	Lyophilized powder
A2103	Absolute bioavailability	Phase 1, multiple dose, open-label, cross-over study in patients with PsO (N = 28).	Randomized in a 1:1 ratio to 1 mg/kg IV or 150 mg SC on Day 1, then crossed over on Day 29	Lyophilized powder

A2211	Efficacy (induction dose ranging)	Randomized, PG, PC, DB study in patients with PsO	Single induction: 150 mg SC at Week 1; Monthly induction: 150 mg SC at Weeks 1, 5, and 9; Early induction: 150 mg SC at Week 1, 2, 3, and 5 or placebo	Lyophilized Powder
A2212	Efficacy at 12 weeks for each loading-dose regimen compared to placebo	Phase 2, randomized, DB, PC, multiple-loading dose regimen study in patients with PsO	N=100, randomized in 3:3:3:1 ratio to receive 3 mg/kg IV on Day 1; 10 mg/kg IV on Day 1; 10 mg/kg IV on Day 1, 15, and 29; or Placebo	Lyophilized Powder
A2220	Dose-ranging	Phase 2, randomized, DB, PC, PG, dose-ranging study in PsO patients	150 mg SC, 75 mg SC, 25 mg SC at Weeks 1, 5, and 9; 25 mg SC at Week 1, or Placebo	Lyophilized powder
A2302	Efficacy/safety	Phase 3, randomized, DB, PC, PG study in PsO patients	SC doses: 150, 300 mg, or placebo at Week 0, 1, 2, 3 then every 4 Week (Q4W) up to Week 48. At week 12, placebo rerandomized based on PASI 75 to 150 mg or 300 mg, injections at weeks 12, 13, 14, 15, then q4w to week 48	Lyophilized Powder
A2303	Efficacy/Safety	Phase 3, randomized, DB, DD, PC study in PsO patients	SC doses: 150, 300 mg or placebo at weeks 0, 1, 2, 3, 4, and then q4w; etanercept 50 mg twice weekly from weeks 0 to 12, then once a week from week 12 to week 51. PBO non-responders up to week 12 was re-randomized at week 12 to 150 or 300 mg qw × 5 doses then q4w up to week 48. PBO responders continued to receive PBO.	Lyophilized Powder
A2308	Efficacy/safety	Phase 3, randomized, DB, PC study in PsO patients	SC doses: 150, 300 mg, or placebo at weeks 0, 1, 2, 3, 4, and then q4w until week 48. At week 12, placebo group was rerandomized to either 150 mg or 300 mg based on PASI 75 response to placebo at week 12	150 mg/1 mL prefilled syringes
A2310	Efficacy/safety	Randomized, DB, PC, AC study in PSO patients aged 6 to <18 yo	BW ≥50kg: 150 mg (low dose) and 300 mg (high dose). BW 25 to <50kg: 75 mg and 150 mg. BW <25kg: 75 mg for both dose groups. Regimen (both low and high dose): Day 0, weeks 1, 2, 3, 4 then q4w3, 4 then q4w until week 232, for placebo until week 8, then re-randomized at week 12 per PASI 75 response. Placebo non-responders receive secukinumab at weeks 12, 13, 14, 15, and 16, then q4w until week 232. Etanercept weekly from Week 0 (Day 1) to Week 51	150 mg/1 mL and 75 mg/0.5 mL prefilled syringes

A2311	Efficacy/safety	Randomized, open-label study in PsO patients aged 6 to <18 yo	BW ≥50kg: 150 mg (low dose) and 300 mg (high dose). BW 25 to <50kg: 75 mg and 150 mg. BW <25kg: 75 mg for both dose groups. Regimen: Day 0, weeks 1, 2, 3, 4 then q4w3, 4 then q4w until week 204	150 mg/1 mL and 75 mg/0.5 mL prefilled syringes
A2324	Efficacy	Randomized, DB study in PsO patients weighing ≥90 kg	300 mg at week 0 (randomization), 1, 2, and 3 then Q2W up to week 48; 300 mg at week 0 (randomization), 1, 2, and 3 then Q4W up to week 48	150 mg/1 mL prefilled syringes

DD: double-dummy, PG: parallel-group

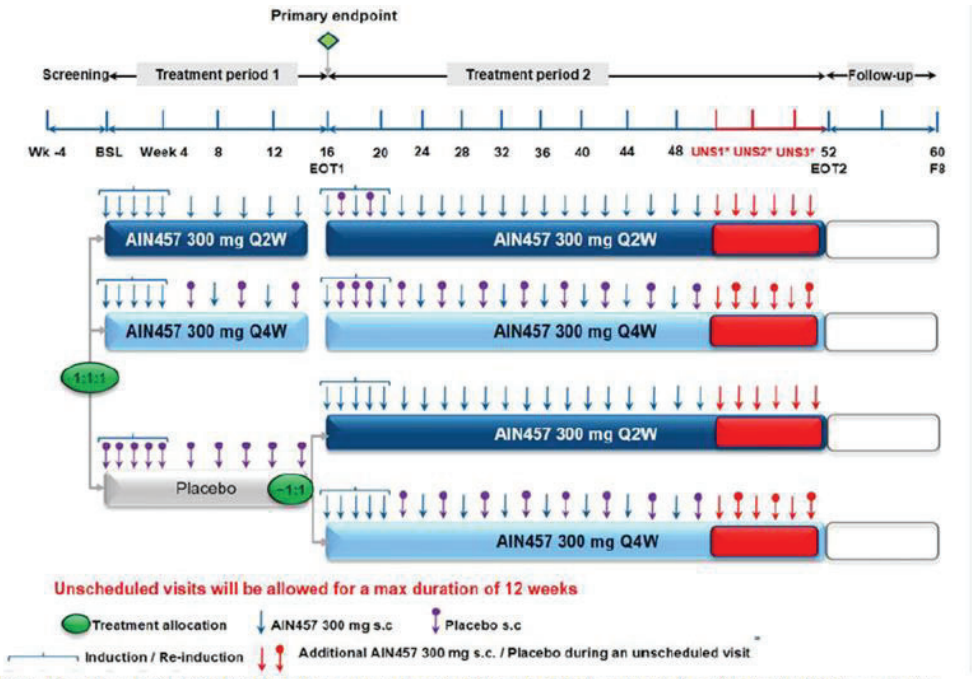
Pharmacokinetics of secukinumab in HS patients

The PK of secukinumab was derived based on two HS studies (M2301 and M2302) and a popPK analysis. Refer to **Table 1** for detailed study design of these studies. Of note, only pre-dose PK samples at Weeks 16, 24, 52, and 60 were collected in M2301 and M2302 studies, which are not adequate to fully characterize the PK of secukinumab in HS patients. However, the popPK approach used in this submission aids in characterizing the full PK profile of secukinumab in HS patients. In the 2 HS studies, the Applicant used a validated ELISA bioanalytical method with a lower limit of quantitation (LLOQ) of 160 ng/mL to measure serum concentrations of secukinumab. Of note, in the previously used bioanalytical method, the LLOQ was 80 ng/mL. At the LLOQ of 80 ng/mL, a plate effect was observed in the bioanalytical study CAIN457M2302-CBA-02, hence the Applicant amended the bioanalytical method to increase LLOQ to 160 ng/mL (see bioanalytical review in section 19.4).

HS Studies (M2301 and 2302):

Both HS studies were identically designed phase 3 studies entitled 'A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa'. The efficacy of two dosing regimens (secukinumab 300 mg Q2W and Q4W, abbreviated as Q2W and Q4W regimen throughout the Clinical Pharmacology review) were evaluated in a placebo-controlled period up to week 16 and active maintenance treatment up to week 52. The study design and randomization process are schematically presented in the **Figure 1**.

Figure 1: The schema of study design for M2301 and M2302 studies conducted in HS patients (Source: **CSR of M2301 and 2302, Figure 9-1)**



BSL: Baseline; EOT1/EOT2: End of treatment 1 or 2; F8: End of Follow-up visit at Week 60; Q2W: every two weeks; Q4W: every four weeks.
*UNS = Unscheduled; UNS1, UNS2 and UNS3 corresponded to three possible additional IRT calls at which 2 doses were dispensed if COVID related occurrences required it.
Treatment allocation for placebo arm switching to secukinumab arms at Week 16 was performed at the Randomization visit in 1:1 ratio and did not account for potential discontinuations during Treatment Period 1.
Follow-up: only subjects who prematurely discontinued treatment during Treatment Period 1 or 2 or subjects who did not enroll in the extension study entered Follow-up.

After meeting the eligibility criteria, the number of patients randomized (in 1:1:1 ratio at baseline) to Q2W, Q4W, and placebo were 181, 180, and 180 in M2301, and 180, 180, and 183 in M2302 study, respectively. The placebo group was re-randomized at Week 16 in 1:1 ratio to receive either Q2W or Q4W regimen preceded by the loading doses of 300 mg QW from Week 16 – 20.

The major baseline demographic and disease characteristics of patients for each of the studies and dosing regimens are provided in the **Table 4 and Table 5, respectively**.

Table 4: Baseline demographic characteristics of M2301 and M2302

Study M2301							
Characteristic	**Q2W N=181**	**Q4W N=180**	**Any secukinumab N=361**	**Placebo N=180**	**PBO-Q2W N=90**	**PBQ-Q4W N=90**	**Total N=541**
Age group in years, n (%)							
<30	58 (32.0)	69 (38.3)	127 (35.2)	51 (28.3)	27 (30)	24 (26.7)	178 (32.9)
30-<40	56 (30.9)	45 (25.0)	101 (28.0)	70 (38.9)	38 (42.2)	32 (35.6)	171 (31.6)
40-<65	64 (35.4)	63 (35.0)	127 (35.2)	58 (32.2)	25 (27.8)	33 (36.7)	185 (34.2)
≥65	3 (1.7)	3 (1.7)	6 (1.7)	1 (0.6)	0 (0)	1 (1.1)	
Age (years)							
Mean (SD)	37.1 (12.53)	35.7 (11.71)	36.4 (12.14)	35.5 (10.75)	34.3 (9.7)	36.8 (11.6)	36.1 (11.69)

Gender, n (%)							
Male	79 (43.6)	80 (44.4)	159 (44.0)	78 (43.3)	33 (36.7)	45 (50)	237 (43.8)
Female	102 (56.4)	100 (55.6)	202 (56.0)	102 (56.7)	57 (63.3)	45 (50)	304 (56.2)
Weight (Kg)							
Mean (SD)	95.9 (25.0)	95.4 (25.9)	95.7 (25.4)	92.9 (22.1)	90.2 (21.8)	95.5 (22.2)	94.73 (24.4)
Median (min-max)	92 (51-205)	92.35 (43-201.6)	92 (43-205)	92 (47.4-159.2)	92 (47.4-155)	92.8 (58-159.2)	92 (43-205)
Weight groups (kg), n (%)							
<90 kg	82 (45.3)	80 (44.4)	162 (44.9)	83 (46.1)	41 (45.6)	42 (46.7)	245 (45.3)
≥90 kg	99 (54.7)	100 (55.6)	199 (55.1)	97 (53.9)	49 (54.4)	48 (53.3)	296 (54.7)
Study M2302	**N=180**	**N=180**	**N=360**	**N=183**	**N=90**	**N=93**	**N=543**
Age group in years, n (%)							
<30	52 (28.9)	60 (33.3)	112 (31.1)	57 (31.1)	24 (26.7)	33 (35.5)	169 (31.1)
30-<40	48 (26.7)	61 (33.9)	109 (30.3)	65 (35.5)	40 (44.4)	25 (26.9)	174 (32.0)
40-<65	77 (42.8)	57 (31.7)	134 (37.2)	59 (32.2)	26 (28.9)	33 (35.5)	193 (35.5)
≥65	3 (1.7)	2 (1.1)	5 (1.4)	2 (1.1)	0 (0)	2 (2.2)	7 (1.3)
Age (years)							
Mean (SD)	37.3 (11.5)	35.5 (11.4)	36.4 (11.47)	36.2 (11.3)	35.6 (9.52)	36.9 (12.73)	36.3 (11.38)
Gender, n (%)							
Male	82 (45.6)	77 (42.8)	159 (44.2)	78 (42.6)	32 (35.6)	46 (49.5)	237 (43.6)
Female	98 (54.4)	103 (57.2)	201 (55.8)	105 (57.4)	58 (64.4)	47 (50.5)	306 (56.4)
Weight (Kg)							
Mean (SD)	92.7 (24.3)	93.1 (22.3)	92.9 (23.3)	91.0 (22.0)	91.5 (22.0)	90.5 (22.2)	92.25 (22.84)
Median (min-max)	90 (50-181.9)	90 (50-152)	90 (50-181.9)	89.4 (49.8-157)	89.1 (53.8-157)	90 (49.8-141)	90 (49.8-181.9)
Weight groups (kg), n (%)							
<90 kg	85 (47.2)	89 (49.4)	175 (48.6)	92 (50.3)	46 (51.1)	46 (49.5)	267 (49.2)
≥90 kg	95 (52.8)	91 (50.6)	185 (51.4)	91 (49.7)	44 (48.9)	47 (50.5)	276 (50.8)

Table 5: Baseline disease characteristics of M2301 and M2302

Study M2301							
Characteristic	**Q2W N=181**	**Q4W N=180**	**Any secukinumab N=361**	**Placebo N=180**	**PBO-Q2W N=90**	**PBQ-Q4W N=90**	**Total N=541**
Baseline Hurley stage, n (%)							
I	7 (3.9)	10 (5.6)	17 (4.7)	8 (4.4)	5 (5.6)	3 (3.3)	25 (4.6)

II	104 (57.5)	107 (59.4)	211 (58.4)	121 (67.2)	59 (65.6)	62 (68.9)	332 (61.4)
III	70 (38.7)	63 (35.0)	133 (36.8)	51 (28.3)	26 (28.9)	25 (27.8)	184 (34.0)
Baseline CRP levels in mg/L							
Mean (SD)	16.9 (21.8)	16.6 (27.1)	16.7 (24.6)	13.2 (21.4)	12.2 (17.9)	14.2 (24.5)	15.5 (23.6)
Median (min-max)	7.7 (0.31-103.6)	6.6 (0.29-152.6)	7.1 (0.29-152.6)	6.5 (0.17-159.4)	6.4 (0.17-97)	6.7 (0.21-159.35)	6.7 (0.17-159.4)
CRP groups in mg/L, n (%)							
<5	65 (35.9)	76 (42.2)	141 (39.1)	79 (43.9)	41 (45.6)	38 (42.2)	220 (40.7)
5-<10	37 (20.4)	37 (20.6)	74 (20.5)	39 (21.7)	19 (21.1)	20 (22.2)	113 (20.9)
≥10	79 (43.6)	67 (37.2)	146 (40.4)	62 (34.4)	30 (33.3)	32 (35.6)	208 (38.4)
Baseline AN count							
Mean (SD)	12.9 (9.60)	12.6 (8.38)	12.7 (9.00)	12.8 (8.15)	13.0 (7.8)	12.5 (8.5)	12.8 (8.72)
Baseline inflammatory nodule count							
Mean (SD)	10.1 (7.8)	9.9 (7.6)	10.0 (7.69)	10.1 (7.0)	9.9 (6.2)	10.4 (7.7)	10.0 (7.46)
Baseline NRS							
n	163	163	326	162	83	79	488
Mean (SD)	4.5 (2.5)	4.2 (2.51)	4.4 (2.51)	4.3 (2.50)	4.1 (2.6)	4.4 (2.4)	4.3 (2.51)
Study M2302	**N=180**	**N=180**	**N=360**	**N=183**	**N=90**	**N=93**	**N=543**
Baseline Hurley stage, n (%)							
I	6 (3.3)	6 (3.3)	12 (3.3)	3 (1.6)	NA	3 (3.2)	15 (2.8)
II	92 (51.1)	105 (58.3)	197 (54.7)	110 (60.1)	61 (67.8)	49 (52.7)	307 (56.5)
III	82 (45.6)	69 (38.3)	151 (41.9)	70 (38.3)	29 (32.2)	41 (44.1)	221 (40.7)
Baseline CRP levels in mg/L							
Mean (SD)	20.4 (30.1)	15.2 (28.1)	17.8 (29.2)	15.7 (23.4)	14.5 (19.2)	16.8 (26.9)	17.1 (27.4)
Median (min-max)	8.7 (0.19-171.57)	6.6 (0.33-213.9)	7.97 (0.19-213.93)	7.4 (0.34-138.78)	8.7 (0.43-126.9)	5.9 (0.34-138.8)	7.73 (0.19-213.93)
CRP groups in mg/L, n (%)							
<5	59 (32.8)	74 (41.1)	133 (36.9)	71 (38.8)	31 (34.4)	40 (43.0)	204 (37.6)
5-<10	38 (21.1)	41 (22.8)	79 (21.9)	44 (24.0)	20 (22.2)	24 (25.8)	123 (22.7)
≥10	83 (46.1)	65 (36.1)	148 (41.1)	68 (37.2)	39 (43.3)	29 (31.2)	216 (39.8)
Baseline AN count							
Mean (SD)	13.9 (9.9)	13.2 (8.8)	13.6 (9.4)	12.3 (8.5)	12.9 (8.6)	12.8 (8.4)	13.3 (9.1)

Baseline inflammatory nodule count							
Mean (SD)	10.0 (7.7)	10.3 (7.6)	10.2 (7.7)	9.6 (6.8)	10.0 (6.3)	9.3 (7.2)	10.0 (7.4)
Baseline NRS							
n	166	163	329	166	84	82	495
Mean (SD)	4.8 (2.4)	4.6 (2.5)	4.7 (2.4)	4.7 (2.4)	4.9 (2.2)	4.5 (2.6)	4.7 (2.4)

Based on the data from two HS studies, the PK profile of secukinumab was evaluated by summarizing pre-dose (Cmin) concentrations from the available measured PK samples over the entire sampling time period (**Table 6**). The mean Cmin-time profiles for each study with respect to each treatment group are presented in the **Figure 2**. The PK profiles show that, for subjects who started treatment at the beginning of the study, steady-state Cmin levels were observed for both secukinumab Q4W and Q2W regimens at Week 24 and Week 52. It was observed that mean Cmin concentrations at Weeks 16, Week 24, and Week 52 were approximately 2-fold higher in the Q2W group than that in the Q4W group.

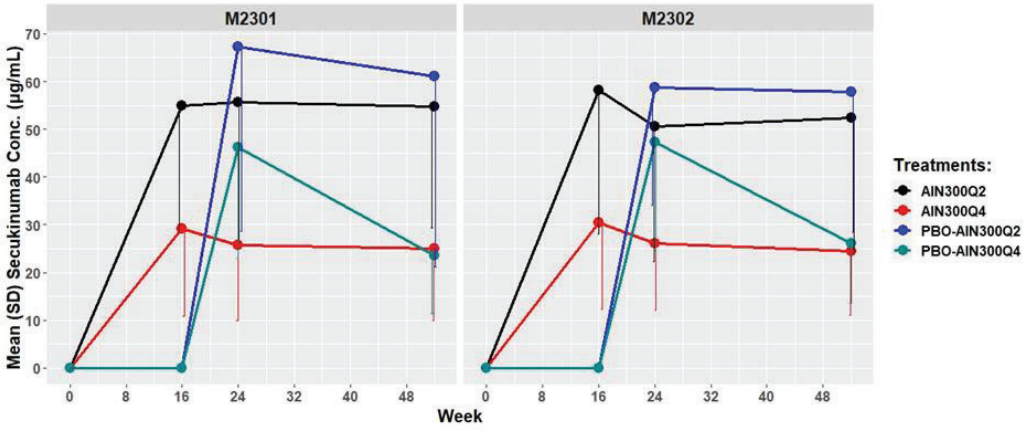
Of note, for placebo switched to 300 mg Q2W regimen at Week 16, the Cmin at Week 24 was similar to that of Week 52 (steady state). Conversely, the Cmin was much higher at Week 24 compared to that of Week 52 for placebo switched to 300 mg Q4W (**Figure 2**). This discrepancy can be explained by the more prominent impact of loading doses (QW doses from Week 16-20) on Q4W regimen than Q2W regimen.

Table 6: Mean (SD) secukinumab Cmin (at Week 16) and Cmin,ss (at Weeks 24 and 52) serum concentrations from study M2301 and M2302

Study	Visit	300 mg Q2W		300 mg Q4W		Placebo-Q2W		Placebo-Q4W	
		n	Mean (SD) in µg/mL	n	Mean (SD) in µg/mL	n	Mean (SD) in µg/mL	n	Mean (SD) in µg/mL
M2301	Week 16	150	55.0 (26.1)	163	29.2 (18.3)	83	1.08 (9.67)*	77	0 (0)
	Week 24	133	55.7 (28.9)	132	25.7 (15.7)	71	67.2 (38.6)	70	46.2 (23.2)
	Week 52	89	54.8 (25.5)	85	25.0 (15.0)	43	61.1 (40.0)	50	23.5 (12.2)
M2302	Week 16	152	58.1 (30.1)	152	30.4 (18.0)	74	0.094 (0.73)#	78	0.007 (0.066)#
	Week 24	136	50.5 (28.2)	132	26.0 (13.9)	63	58.8 (24.6)	64	47.3 (22.7)
	Week 52	98	52.4 (27.9)	89	24.6 (13.5)	46	57.8 (29.3)	43	26.0 (12.4)

*Due to two measurable pre-dose concentration at Week 16 in the Placebo–Q2W group, the mean concentration was not zero at this time point.
#Due to a few measurable pre-dose concentrations at Week 16 in the groups of placebo switchers, i.e., 2 in placebo – secukinumab Q2W and 1 in placebo – secukinumab Q4W, mean concentrations were not zero at this timepoint.
n = number of evaluable subjects
Source: m2.7.2, summary of clinical pharmacology studies – Hidradenitis Suppurativa, page 10. The reviewer's independent analysis based on adpc.xpt dataset corresponding to m2301 and m2302 studies confirmed the results.

Figure 2: Serum concentration (Cmin)-time profiles for secukinumab



Note: SD bars (only lower half) were jittered for better visualization. **Source:** Reviewer's independent analysis based on dataset adpc.xpt corresponding to study m2301 and m2302.

A cross-study comparison between the serum exposure in PsO (data from A2302, A2308, and A2323) and HS patients indicates that the mean steady state Ctrough at Week 52 was approximately 26 % lower in HS patients than that observed in PsO patients (e.g., 26 vs 35 µg/mL), regardless of drug-device combination used (see **Table 7**).

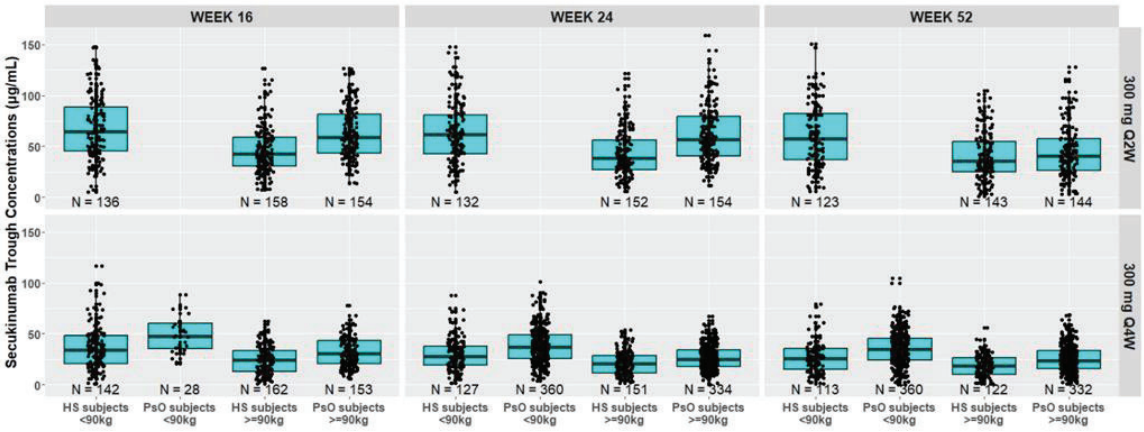
Table 7: Steady state trough serum concentrations (µg/mL) of secukinumab with a 300 mg Q4W maintenance regimen in HS and PsO patients

	M2301, HS (2 mL PFS)		M2302, HS (2 mL PFS)		A2302, PsO (2 x 1 mL LYO)		A2308, PsO (2 x 1 mL PFS)		A2323* PsO (2 x 1 mL PFS		A2323* PsO (2 mL PFS)	
Visit	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
W24	118	25.9 (15.8)	124	26.4 (13.8)	211	34.4 (16.6)	52	33.2 (14.9)	65	33.6 (13.9)	59	36.3 (18.4)
W52	71	25.2 (14.1)	76	25.7 (13.4)	177	32.7 (14.4)	45	30.6 (13.1)	48	37.2 (14.5)	50	38.5 (16.3)

*Trough serum concentrations in A2323 were not at Week 24, but at Week 28. Week 24 and Week 28 are both steady-state concentrations during maintenance.

Similarly, popPK analyses conducted on pooled data from PsO and HS studies supported the lower exposure in HS compared to PsO patients, which was due to an increase in clearance of around 30% (0.256 L/d) in HS compared to 0.198 L/d in PsO. Though body weight was a significant covariate for increase in CL, the exposure is consistently lower (23%) in HS compared to PsO patients for the same body weight (**Figure 3**). Hence, the lower exposure in HS patients cannot be explained by body weight only.

Figure 3: Distribution of observed trough concentration in HS and PsO adult patients, by visit and treatment (Source: Reviewer's analysis based on popPK dataset, mt92534_PK.csv).



Dots: Observed trough secukinumab concentrations from subjects from Phase 3 PsO studies A2302, A2303, A2308, A2324 and Phase 3 HS studies M2301 and M2302. Placebo-switchers are not included in the figure. Dots are horizontally jittered to ensure legibility.
N represents the number of observed trough concentrations. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box.

However, in popPK model, disease severity of HS as defined by hurley stages and baseline high-sensitive C-reactive protein (hsCRP) levels were identified as significant covariates affecting the PK exposure of secukinumab. For example, popPK analysis revealed that the clearance of secukinumab was estimated 22% and 43% higher in HS subjects with Hurley stage I-II and stage III, respectively, compared to that of PsO subjects. Due to this, Q2W dosing in subjects with Hurley stage III may be of added benefit compared to Q4W dosing. This corresponds to clearance values of 0.242 L/d and 0.283 L/d in HS subjects with Hurley stage I/II and III, respectively, compared to 0.198 L/d in PsO subjects. Due to increased clearance, the terminal half-life (T1/2) in the overall HS population (irrespective of Hurley stage) was estimated to be 23 days, compared to 27 days in PsO subjects.

The popPK analysis also estimated a 9% lower Cavg,ss in HS patients when the body weight, disease severity is the same but hsCRP value was 2-fold higher at baseline. Moreover, the Cavg,ss was 15% lower in HS patients with Hurley stage III when compared to Hurley stages I and II with the same body weight and same hsCRP value at baseline. This implies that hurley stages and hsCRP levels played a significant role to increase secukinumab clearance in HS patients. Historical and emerging data from M2301/2302 studies showed that baseline hsCRP values are higher in HS patients compared to PsO patients (median value: 7.2 vs 2.52 mg/L), further supporting lower systemic exposure of secukinumab in HS patients.

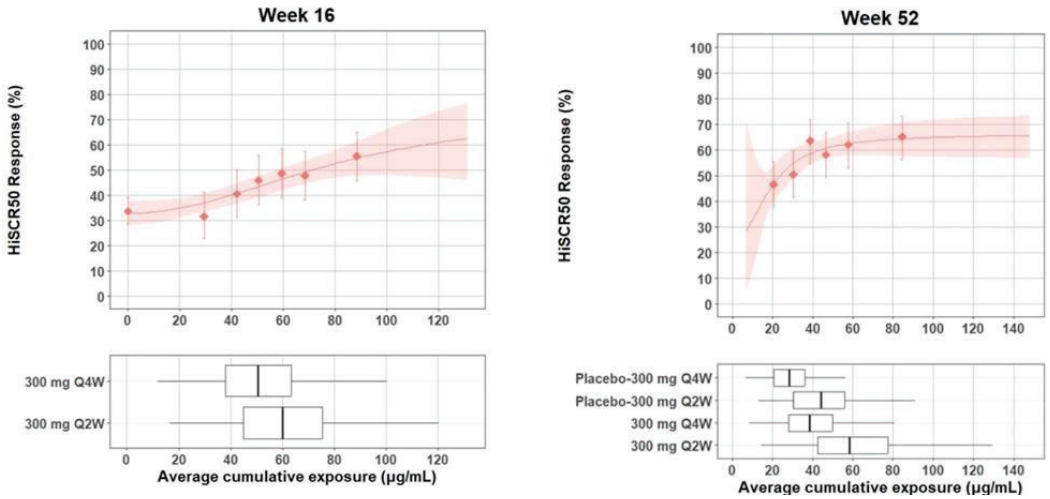
The lower exposure of monoclonal antibody in HS patients is not only specific to secukinumab, but it was also observed for other mAbs such as adalimumab and bimekizumab. Hence, the fact

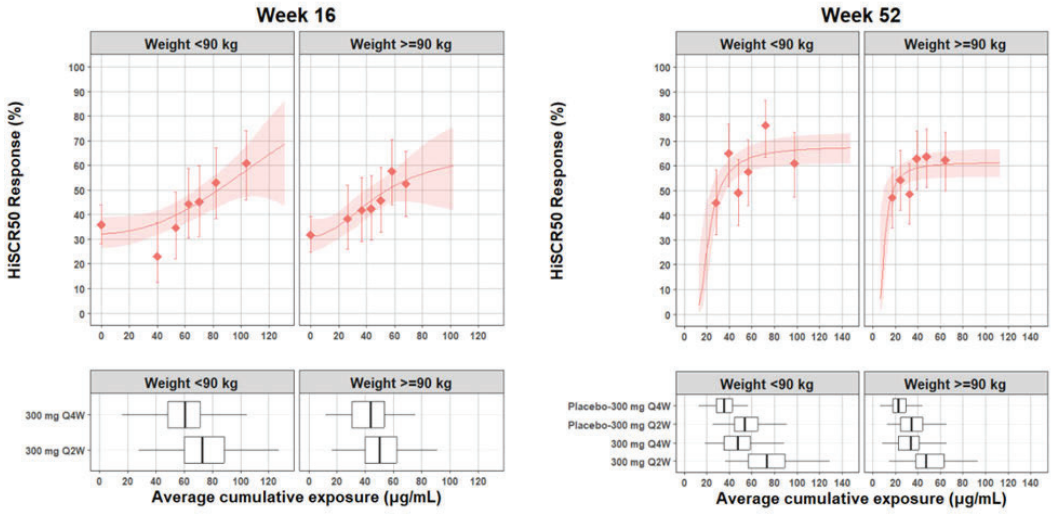
that secukinumab exposure decreases with HS severity and hsCRP levels supports the rationale that the lower exposure observed in HS is disease related.

Exposure-Response Relationship

Exposure-response analyses were performed on the two HS studies with respect to the primary and secondary endpoints at relevant timepoints (Weeks 16, 24, 40, and 52) using a logistic regression model for binary endpoints. The analyses were performed on all subjects as well as in subgroups defined based on concomitant use of antibiotics, previous exposure to biologics, baseline disease status (Hurley stages I and II vs. III), body weight (<90 kg versus >= 90 kg) and study. The E-R analysis on HiSCR50 endpoint using pooled HS data showed a numerical increase of ~3% in response rate for Q2W over Q4W regimen at Week 16 beyond which the effect was sustained (~5% increment in response rate at Week 52). Similar E-R relationship was demonstrated when analysis was performed on the body weight strata (<90 kg vs ≥90 kg) for Q2W and Q4W regimens at Week 16 and 52 (**Figure 4**). Of note, though E-R curve at the individual level showed an incremental benefit for higher exposure from Q2W regimen, it reached plateau at certain point, therefore, further increase in dose or dosing frequency beyond 300 mg Q2W is unlikely to provide any additional clinical benefit.

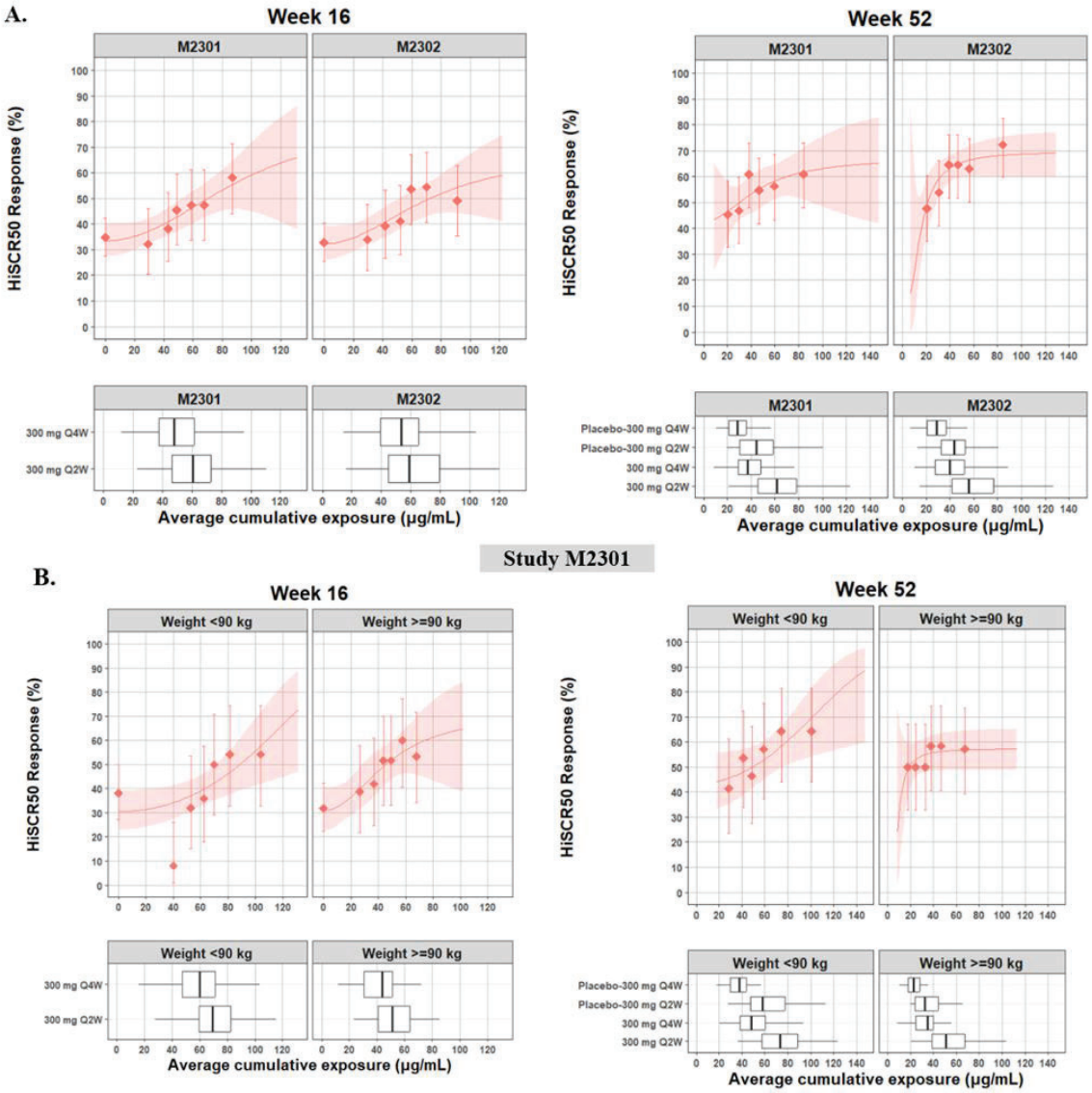
Figure 4: Exposure-response analysis performed on HiSCR50 response vs average cumulative exposure at Week 16 and Week 52 based on the pooled data from two HS studies. Lower panel presents HiSCR50 vs exposure analysis stratified by body weight. The primary endpoint, HiSCR50 response was defined as at least a 50% reduction in abscess and inflammatory nodule (AN) count)

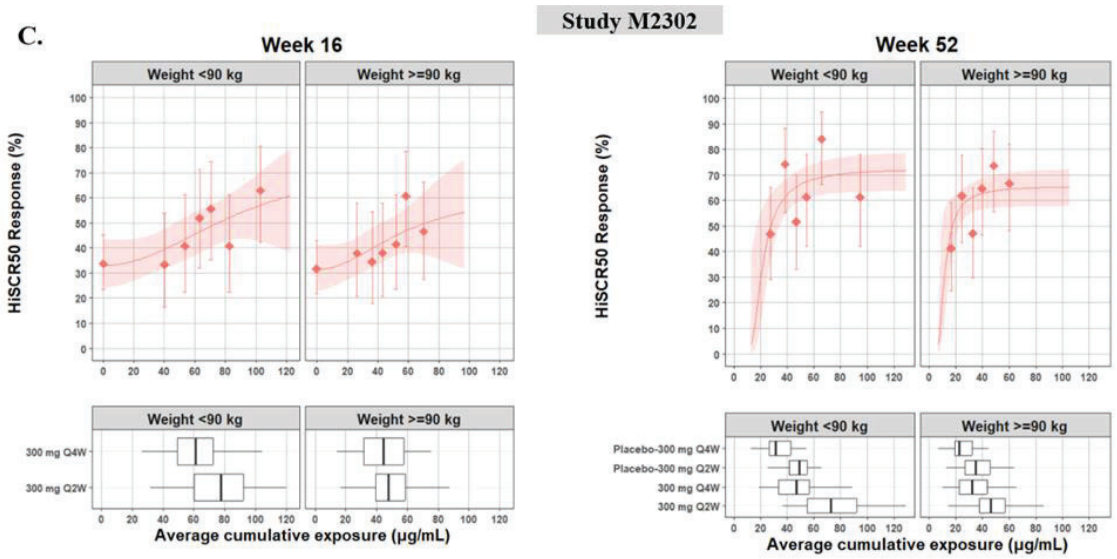




Though the Q2W regimen showed a statistically and clinically significant effect with respect to the primary endpoint in both studies, Q4W showed greater response rates in study M2302, reversing the trend in efficacy. Hence, further E-R subgroup analysis was performed on HiSCR50 response for individual study and body weight strata. This analysis did not show different E-R relationship than what was observed based on pooled HS data. Regardless of individual study and body weight groups, a 2-5% increase in response rate for Q2W over Q4W regimen still holds true (**Figure 5A, B, and C**). However, it should be noted that the exposure between Q2W and Q4W regimens is very close in M2302, specifically for hurley stage III subgroup, hence the response is indistinguishable between two regimens (see pharmacometrics review). The negligible difference in exposure between Q2W and Q4W regimen can be attributed to increased CL of secukinumab in severe patients, who are more abundant in Q2W arm of study M2302 (45.6% vs 38.3%).

Figure 5: Exposure-response analysis performed on HiSCR50 response vs average cumulative exposure at Week 16 and Week 52 for: A) individual studies, B) Study M2301 stratified by body weight, and C) Study M2302 stratified by body weight.





It should be noted that the popPK estimated exposure (average cumulative exposure [Cavg,cum]) in Q2W is not ~2-fold higher than that in Q4W group as observed in the HS studies for PK parameter, Cmin. However, popPK estimated Cmin values from Q2W regimen were approximately 2~fold higher than those from Q4W regimen. The reason of this discrepancy between the popPK estimated two PK parameters (Cavg,cum vs Cmin) is not clear.

The difference in Cavg,cum is further narrow in subgroup of hurley stages. The exploratory analyses of PK exposure for hurley stages of HS studies, however, still demonstrates a ~2-fold higher Cmin values in Q2W group than that of Q4W group. Additionally, the Cmin values are consistently lower in patients with hurley stage III, thereby supporting the increase clearance of secukinumab in this severe patient (**Table 8**). It should be noted that when Cmin is considered for E-R analyses, a further numerical increment (2-8%) in response rate for Q2W over Q4W regimen appears to be possible depending on the timepoints and endpoints (data not shown). It may be due to the maintained 2-fold higher Cmin values for Q2W compared to that of Q4W regimen.

Table 8: The mean Cmin (µg/mL) with the corresponding response rate on HiSCR50 response for the hurley stages in the HS studies

Week	Hurley	300 mg Q2W			300 mg Q4W			PBO-Q2W			PBO-Q4W		
		n	Cmin	%RR	n	Cmin	%RR	n	Cmin	%RR	n	Cmin	%RR
M2301													
W16	I&II	93	58.2	51.6	107	33.1	40.2	58	-	34.5	56	-	41.1
	III	56	49.7	37.5	55	21.9	32.7	25	-	16.0	21	-	28.6
W52	I&II	51	61.4	45.1	57	27.7	56.1	29	66.1	51.7	37	26.1	56.8
	III	38	45.9	55.3	28	19.4	64.3	14	50.6	50.0	13	16.2	38.5
M2302													

W16	I&II	81	69.0	46.9	94	33.9	48.9	49	-	34.7	41	-	19.5
	III	71	45.8	32.4	57	24.9	40.4	23	-	39.1	35	-	34.3
W52	I&II	54	62.8	64.8	59	26.8	67.8	31	61.4	61.3	25	29.8	64.0
	III	44	39.6	65.9	30	20.2	46.7	14	49.7	50.0	18	20.8	38.9

Reviewer's analysis based on adsl.xpt, adhiscr.xpt, and adpc.xpt datasets for the corresponding studies.

E-R analysis was also conducted on AN50 (defined as a ≥50% decrease in abscess and inflammatory nodule) and NRS30 (defined as a ≥30% reduction and ≥2-unit reduction from baseline in patient's global assessment of skin pain – at worst) as secondary endpoints.

A numerical increase of 2 – 3% at Week 16 and 4% at Week 52 in response rates were observed at other secondary endpoints (e.g., AN50 and NRS30 response) for Q2W over Q4W regimen. The body weight-based strata also provided similar incremental benefit. Similar results hold true for other subgroup-based E-R analysis indicating that the difference in response for Q2W over Q4W was consistent across subgroups. The exposure-response analyses showed no meaningful differentiation for the other efficacy endpoints considered. In summary, the Q2W regimen can provide a marginal increase in efficacy (only 2-3% and 4-5% higher efficacy at Week 16 and Week 52, respectively) over the Q4W regimen regardless of demographic and disease characteristics of HS patients and clinical endpoints considered.

It is to note that a disagreement between ADHiSCR.XPT and ADCM.XPT was identified by Stat review team during late cycle review. Hence, an initial IR was sent on 6/30/2023 seeking clarification for the data discrepancy and updated efficacy analyses to which the Applicant responded on 7/10/2023. As the response was unsatisfactory, another IR was sent on 7/17/2023 to address unresolved issues, one of which was the reevaluation of E-R relationship based on the updated dataset. To this IR, a final response was provided on 7/31/2023 which included E-R analyses based on updated data for major efficacy endpoints. The review of the updated E-R analyses report showed that there was no change in E-R relationship compared to what was documented above, hence the conclusion drawn above is still valid.

Exposure-safety analyses:
Exposure-safety analyses conducted on Infections and infestations (SOC) and Candida infections (HLT) for the pooled data of M2301 and M2302 on subjects randomized to secukinumab 300 mg Q2W or Q4W (n=721) showed comparable incidence rates across the concentration groups (**see Pharmacometrics Review in OCP appendix**).

Immunogenicity Potential:
The incidence of treatment-emergent anti-drug antibody (TE-ADA) was below 1% in both M2301 and M2302 studies throughout the 52 weeks period. The development of TE-ADA was not associated with any injection site reactions, nor with serious or severe administration reactions. TE-ADA were also not associated with altered PK profiles in TE-ADA positive subjects, in whom PK profiles appear comparable to the overall study population.

Table 9: Summary of ADA incidence in the two HS studies

Study M2301					
Treatments	**ADA characteristics**	**Baseline**	**Week 16**	**Week 52**	**Week 60**
Secukinumab 300 mg Q2W	Total subjects with ADA samples	178	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	10 (5.6)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	0 (0)	0 (0)
Secukinumab 300 mg Q4W	Total subjects with ADA samples	173	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	5 (2.9)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	0 (0)	1 (0.6)
Placebo – 300 mg Q2W	Total subjects with ADA samples	85	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	6 (7.1)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	0 (0)	0 (0)
Placebo – 300 mg Q4W	Total subjects with ADA samples	85	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	4 (4.7)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	0 (0)	0 (0)
	Study M2302				
Secukinumab 300 mg Q2W	Total subjects with ADA samples	175	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	5 (2.9)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	1 (0.6)	0 (0)	1 (0.6)
Secukinumab 300 mg Q4W	Total subjects with ADA samples	172	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	4 (2.3)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	1 (0.6)	0 (0)
Placebo – 300 mg Q2W	Total subjects with ADA samples	79	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	0 (0)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	0 (0)	0 (0)
Placebo – 300 mg Q4W	Total subjects with ADA samples	84	-	-	-
	No. of ADA positive subjects at baseline (%)[1]	4 (4.8)	-	-	-
	No. of subjects with TE-ADA (%)[2]	-	0 (0)	0 (0)	0 (0)

[1]No. of ADA positive subjects at baseline/Total number of subjects with samples measured at baseline x 100%

[2]No. of ADA positive subjects at Week x / Total number of ADA negative subjects measured at baseline x 100%
Source: Study reports of CAIN457M2301-52 week (page 83) and CAIN457M2302-52 week (page 84). Confirmed by the reviewer's independent analysis based on adis.xpt dataset corresponding to M2301 and M2302 studies.

Non-treatment-emergent ADA were also observed in both studies. In Study M2301, 5.6% and 2.9% of secukinumab naïve subjects were ADA positive at baseline only in the Q2W and Q4W arms, respectively. In Study M2302, 2.9% and 2.3% of secukinumab naïve subjects were ADA positive at baseline only in the Q2W and Q4W arms, respectively.

Dose-Safety relationship for common adverse effects:

The most common treatment-emergent adverse event by system organ class (SOC) was infections and infestations observed in HS studies. However, the incidence of rate of infections and infestations was comparable across the treatment arms (30.7% in secukinumab Q2W, 30.6% in secukinumab Q4W, 31.7% in placebo) during treatment period 1. Similarly, AEs in the Infections and infestations (SOC) during the Entire Treatment Period occurred at similar rates in the any of the secukinumab groups (51.2% in Q2W and 48.8% in Q4W, **Table 10**).

The major infections and infestations incidence using preferred terms (PTs) includes nasopharyngitis, upper respiratory tract infection, and urinary tract infection.

On the other hand, hypersensitivity reactions were commonly observed with secukinumab treatment. In a previous supplement (s-47) review, hypersensitivity reaction rate was reported to have increased dose dependently (8.5% in Q2W and 4.5% in Q4W regimen). However, pooled HS studies showed that incidence rates of Hypersensitivity (SMQ, narrow) were comparable in the secukinumab and placebo groups (5.3% in Q2W, 3.9% in Q4W, 4.4% in placebo) and mainly consisted of the PTs of eczema, (contact or atopic) dermatitis, (pruritic) rash, and urticaria (<1.5% in all groups). No cases of anaphylaxis were reported in Treatment Period 1. Analysis of entire study period also showed comparable hypersensitivity incidence rates between any secukinumab Q2W and Q4W regimen (**Table 10**). See Section 8.2for further assessment of safety.

Table 10: Treatment-emergent adverse events, by primary system organ class (Safety Set)

Treatment Period 1 (pooled HS data)				
Primary system organ class	**AIN457 Q2W N=361 n (%)**	**AIN457 Q4W N=360 n (%)**	**Any AIN457 N=721 n (%)**	**Placebo N=363 n (%)**
Infections and infestations	111 (30.7)	110 (30.6)	467 (64.8)	115 (31.7)
Hypersensitivity (SMQ) (narrow)	19 (5.3)	14 (3.9)	33 (4.6)	16 (4.4)
Entire Treatment Period (pooled HS data)				
	AIN457 Q2W N=361 n (%)	**AIN457 Q4W N=360 n (%)**	**Any AIN457 Q2W; N=527 n (%)**	**Any AIN457 Q4W; N=533 n (%)**
Infections and infestations	194 (53.7)	187 (51.9)	270 (51.2)	260 (48.8)
Hypersensitivity (SMQ) (narrow)	51 (14.1)	43 (11.9)	62 (11.8)	55 (10.3)

Bioanalytical Method
The bioanalytical method validation is acceptable. See Section 19.4 for details.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of secukinumab for the treatment of patients with moderate to severe HS was demonstrated in two pivotal phase 3 studies. Though two dosing regimens (Q2W and Q4W) were evaluated for efficacy up to Week 52, Q2W regimen demonstrated better efficacy. In exposure-response analyses, Q2W regimen consistently provided a numerically higher response rate of 2 – 5% over Q4W regimen, depending on endpoints and timepoints. Though Q4W regimen failed the primary endpoint in M2301, it showed higher placebo-adjusted response rate (14.9% and 11.1% for Q4W and Q2W, respectively) than that of Q2W regimen in M2302. Q4W regimen also showed greater effect on AN50 response (**Table 10**). The reason of higher response rate in Q4W regimen of M2302 appears to be due to an imbalance in disease severity (having a relatively smaller number of severe patient than Q2W arm) may have played a role.

However, E-R analysis for different subgroups still retains the conclusion that Q2W regimen can provide a numerically 2 – 5% higher response rate over Q4W regimen, notwithstanding an indistinguishable response seen between 2 regimens for hurley stage III in M2302. Based on totality of evidence, the clinical pharmacology data supports the proposed dosing regimen of secukinumab 300 mg SC injection at Week 0, 1, 2, 3, 4 and Q2W or Q4W thereafter. See Section 8.1 of the review for further information on efficacy.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Although, the Applicant's proposed dosing regimen for the treatment of adults with moderate to severe HS appears reasonable from the Clinical Pharmacology standpoint; maintenance dose of Q4W could be considered based on E-R analysis. Refer to section 1.3 for the benefit-risk assessment to aid dose selection.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimen or management strategy is required based on intrinsic (e.g., age, race, gender, body weight) and extrinsic factors (e.g., current systemic antibiotic use, previous exposure to biologics).

Exposure-response analyses indicated that Q2W regimen performed better as it provided 2-5% higher response over Q4W consistently across all subgroups. However, the E-R analysis of hurley stage III in study m2302 at Week 16 did not show any difference in response between two regimens, though showed higher response at Week 52. Conversely, in clinical study, Q4W regimen showed better response than Q2W at Week 16. This is supported by the exploratory analyses of hurley stage III for HiSCR50 response at Week 16 of M2302 (**Table 8**). The favorable responses resulting from Q4W seen at only Week 16 of M2302 trial can though be attributed to disproportionate number of severe patients between Q2W and Q4W, it can't be explained by E-

R analyses. Moreover, Week 52 of M2302 showed favorable benefit for Q2W regimen in E-R and exploratory analyses (**Table 8**). Hence, we will defer to clinical and statistical reviewer if there is a need to recommend lower dosing regimen (Q4W) for less severe patients defined by hurley stage I and II.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?
The Applicant did not conduct any new drug interaction studies. Food-drug interaction is not relevant for secukinumab is it is intended to be administered subcutaneously.

The current approved label of secukinumab indicates that increased cytokine levels during chronic inflammation may alter the expression of CYP450 enzymes. The label mentioned that midazolam (CYP3A4 substrate) pharmacokinetics in adults with PsO was similar when administered alone, or when administered following either a single or five weekly subcutaneous administrations of 300 mg secukinumab. However, the approved label provided a statement to monitor for therapeutic effect or drug concentration in patients who are receiving concomitant CYP450 substrates with narrow therapeutic index.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support of BLA 125504/S-063, the Applicant submitted data from the following 3 clinical trials:

- Two ongoing identical, 52-week, phase 3 controlled trials in subjects with hidradenitis suppurativa:
  - CAIN457M2301 (M2301)
  - CAIN457M2302 (M2302)
- One ongoing, 4-year, randomized withdrawal extension trial of M2301 and M2302 with blinded (up to 52 weeks) and open-label periods
  - CAIN457M2301E1 (M2301E1)

Table 11 provides a summary of the aforementioned trials submitted for secukinumab 300 mg every 2 weeks and 300 mg every 4 weeks to treat moderate to severe hidradenitis suppurativa in adults.

Table 11: Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
CAIN457 M2301	NCT03713619	Phase 3, randomized, DB, PBO controlled	Secukinumab 300 mg/2 mL by SC injection via PFS at Weeks 0, 1, 2, 3 and 4, followed by 300 mg Q2W Secukinumab 300 mg/2 mL by SC injection via PFS at Weeks 0, 1, 2, 3 and 4, followed by 300 mg Q4W PBO 2 mL by SC injection via PFS at Weeks 0, 1, 2, 3 and 4, followed by 300 mg Q2W	Primary: Achievement of HiSCR50[a] at Week 16. Secondary: ● Achievement of AN50[b] at Week 16 ● Flares up to Week 16 ● Achievement of NRS30[c] in HS-related skin pain at Week 16, among subjects with baseline NRS ≥3	PBO-controlled treatment - 16 weeks Total treatment - 52 weeks Follow-up - 8 weeks	541*	Subjects with moderate-to-severe HS (defined as ≥5 AN affecting ≥2 distinct anatomic areas for ≥ 1 year; males and females ≥ 18 years of age	113 sites Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Korea, Mexico, Philippines, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States
CAIN457 M2302	NCT03713632	Phase 3, randomized, DB, PBO controlled	Secukinumab 300 mg/2 mL by SC injection via PFS at Weeks 0, 1, 2, 3 and 4, followed by 300 mg Q2W Secukinumab 300 mg/2 mL by SC injection via PFS at Weeks 0, 1, 2, 3 and 4,	Primary: Achievement of HiSCR50[a] at Week 16. Secondary: ● Achievement of AN50[b] at Week 16	PBO-controlled treatment - 16 weeks; Total treatment - 52 weeks;	543*	Subjects with moderate-to-severe HS (defined as ≥5 AN affecting ≥2 distinct anatomic	114 sites Argentina, Belgium, Bulgaria, Canada, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Greece, Guatemala,

			followed by 300 mg Q4W PBO 2 mL by SC injection via PFS at Weeks 0, 1, 2, 3 and 4, followed by 300 mg Q2W	● Flares up to Week 16 ● Achievement of NRS30[c] in HS-related skin pain at Week 16, among subjects with baseline NRS ≥3	Follow-up - 8 weeks		areas for ≥ 1 year; males and females ≥ 18 years of age	Hungary, India, Israel, Italy, Lebanon, Lithuania, Malaysia, Netherlands, Philippines, Poland, Russia, Singapore, Slovakia, South Africa, Spain, Switzerland, Turkey, United Kingdom, United States, Vietnam
CAIN457 M2301E1	NCT04179175	Phase 3, DB randomized withdrawal (up to Week 104 or LOR) extension trial of M2301 and M2302 plus OL portion HiSCR responders in trials M2301/M2302 randomized in a 2:1 ratio to continue same dose up to Week 258 or PBO up to Week 104 (or	<u>Secukinumab</u> 300 mg/2 mL by SC injection via PFS Q2W <u>Secukinumab</u> 300 mg/2 mL by SC injection via PFS Q4W PBO 2 mL by SC injection via PFS Q2W	<u>Primary</u>: Time to LOR[d] up to Week 104 (Randomized Withdrawal period) in subjects who were HiSCR responders at Week 52 in the trials M2301/M2302 <u>Secondary</u>: Adverse events, laboratory values, vital signs	Treatment duration up to 4 years	700	Subjects with moderate-to-severe HS (defined as ≥5 AN affecting ≥2 distinct anatomic areas for ≥ 1 year; males and females ≥ 18 years of age	As per M2301 and M2302

		until LOR) Open label at Week 104 or if LOR before Week 104 HiSCR non-responders at Week 52 of M2301/M2302 receive OL 300 mg SC Q2W						

Abbreviations: AN= abscess and inflammatory nodule; DB=double blind; HiSCR=Hidradenitis Suppurativa Clinical Response; LOR=Loss of Response; PBO=placebo; SC=subcutaneous; Q2W=every 2 weeks; Q4W=every 4 weeks

[a]HiSCR50 is defined as ≥ 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae.

[b]AN50 is defined as a reduction of at least 50% in the number of abscesses and/or inflammatory nodules

[c]NRS30 is defined as 30% reduction in Patient's Global Assessment of Skin Pain Numeric Rating Scale

[d]LOR is defined as a 50% or greater increase in the abscess and/or inflammatory nodule (AN) count at a regular or unscheduled visit compared to the average AN count from the 3 previous visits (including visits from trials M2301 and M2302) or Week 52, whichever was lower, and the increase is of at least 3 AN.

*Three subjects in Study M2301 were excluded from the randomized set statistical analysis plan: 1 subject mis-randomized in Interactive Response Technology (IRT), 1 subject with severe GCP violation, and 1 subject with serious breach. One subject in Study M2302 was excluded from the randomized set per SAP; mis-randomized in IRT.

7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety for the proposed indication included trial reports submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)]. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included protocols, statistical analysis plans (SAPs), clinical trial reports, SAS transport datasets in Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format. The datasets were in the following network path:

Original Submission: \\cdsesub1\evsprod\BLA125504\0378\m5\datasets

120-day safety update: \\cdsesub1\evsprod\BLA125504\0402\m5\datasets

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CAIN457M2301 and Study CAIN457M2302

Trial Design

Study CAIN457M2301 and Study CAIN457M2302 were identically designed multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials that evaluated the efficacy and safety of two subcutaneous dose regimens of secukinumab 300 mg, once every 2 weeks (Q2W) and once every 4 weeks (Q4W) in comparison with placebo for the indication of hidradenitis suppurative (HS) in adult patients with moderate to severe HS. Both studies were comprised of following phases: Screening (up to 4 weeks), Placebo-controlled Treatment Period 1 (16 weeks), and Treatment Period 2 (36 weeks). Subjects who completed Treatment Period 2 had an option to enter an extension study. Subjects who prematurely discontinued the study, or who completed the study but could not or did not wish to continue in the optional extension study, were required to complete a post-treatment follow-up period (8 weeks).
Subjects with moderate to severe HS (541 subjects in M2301 and 543 subjects in M2302) were randomized to secukinumab 300 mg Q2W, secukinumab 300 mg Q4W, placebo Q2W, or placebo Q4W in 1:1:0.5:0.5 ratio. Randomization was stratified by region, current antibiotic use (yes vs. no) and body weight (<90 kg vs. ≥90 kg).

Subjects who completed Treatment Period 1 entered Treatment Period 2. At the Week 16 visit, subjects initially randomized to placebo were switched to one of the two active dose regimens (secukinumab 300 mg Q2W or Q4W), whereas subjects randomized to secukinumab 300 mg (Q2W or Q4W) during Treatment Period 1 continued on the same dose regimen.

The end of Treatment Period 2 visit (EOT 2) was performed at Week 52. For subjects rolling over to the optional extension study, Week 52 was the end of study visit. The subjects who prematurely discontinued study treatment in Treatment Periods 1 or 2 for any reason, or subjects who did not enroll in the optional extension study, entered the post-treatment Follow-Up period, and the visit at Week 60 was the end of study visit.

Study Endpoints

The primary efficacy endpoint was HiSCR50 response at Week 16, which was defined as at least a 50% decrease in abscess and inflammatory nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae from baseline to Week 16.

The applicant specified three secondary efficacy endpoints: 1) AN50 response at Week 16. AN50 is defined as at least a 50% decrease in AN count. 2) Flare over Week 16. Flare was

defined as at least a 25% increase in AN count with a minimum increase of at least 2 AN relative to baseline. 3) NRS30 (skin pain) response at Week 16, among subjects with baseline NRS ≥ 3. NRS30 was defined as at least a 30% reduction and at least a 2-unit reduction from baseline in Patient's Global Assessment of Skin Pain - at worst.

Statistical Analysis Plan

Analysis Populations

- The Randomized Analysis Set (RAS): consisted of all randomized subjects. Subjects were analyzed according to the treatment they are assigned to at randomization. Unless otherwise specified, mis-randomized patients (mis-randomized in the Interactive response technology (IRT)) were excluded from the randomized set. Mis-randomized patients are patients who were screen-failures, but had been randomized by the investigator before eligibility was finally assessed, however had not been treated.
- The Full Analysis Set (FAS): comprised all subjects to whom study treatment was assigned. Subjects were analyzed according to the treatment assigned to at randomization. Misrandomized subjects (mis-randomized in IRT) and subjects with serious good clinical practices (GCP) violation were excluded from FAS. If the actual stratum (e.g., use of antibiotic, and baseline body weight) was different to the assigned stratum in IRT, the actual stratum was used in the analyses.

The RAS and FAS were identical within each trial. All efficacy analyses were based on the FAS.

Primary Estimand for the Primary Efficacy Endpoint

The SAP specified the following estimand framework for the primary efficacy endpoint:

1. **Population**: Subjects with moderate to severe hidradenitis suppurativa who had a total of at least 5 inflammatory lesions, i.e. abscessed and/or inflammatory nodules, affecting at least 2 distinct anatomic areas, and who had HS diagnosed ≥ 1 years defined through appropriate inclusion/exclusion criteria.

Statistical reviewers' comment:

- *This is the same as the FAS.*

2. **Endpoint**: HiSCR response at Week 16.
3. **Treatment of interest**: The randomized study treatment (secukinumab 300 mg in two different dosing regimens Q2W or Q4W vs. placebo) with or without rescue medication, regardless of discontinuation due to AE or lack of efficacy.
4. **Summary measure**: odds ratio of secukinumab dose regimen (Q2W or Q4W) vs. placebo.

5. Intercurrent Events (ICEs):

For the primary efficacy endpoint, the SAP listed the following ICEs along with the primary method for handling these ICEs:

ICE #1) Intake of prohibited medication/treatment (medication/treatment with possible confounding effect defined as biologics if taken more than once, antibiotics in the nonantibiotic stratum if taken over a period of more than 14 days, or any major HS-related surgery for HS other than allowed as a rescue therapy). A ***treatment policy*** strategy was applied in any case of prohibited medication. Such events were ignored, and all observed values were considered.
ICE #2) Intake of rescue medication: a ***composite*** strategy was applied. If such an event (intake of rescue antibiotics) occurred, the subject was considered as a non-responder.
ICE #3) Permanent discontinuation of study treatment due to adverse events or lack of efficacy: a ***composite*** strategy was applied, and the subject was considered as a non-responder.
ICE #4) Permanent discontinuation of study treatment due to reasons other than adverse events or lack of efficacy: a ***hypothetical*** strategy was applied. Any observation after such an event was discarded and imputed via multiple imputation under the MAR assumption.
ICE #5) COVID-19 related intercurrent events:
a. missed at least one dose prior to Week 16 due to COVID-19;
b. discontinued treatment prior to Week 16 due to COVID-19.
A ***treatment policy*** strategy was applied in the same way as described under intercurrent event #1.

Sensitivity Analysis for the Primary Estimand of Primary Efficacy Endpoint:
The SAP specified conducting a sensitivity analysis using the weighted average across the screening and baseline assessments as the baseline value;

Supplementary Analysis for the Primary Estimand of Primary Efficacy Endpoint:
The SAP also specified conducting a supplementary analysis where all of the above intercurrent events were handled using a ***treatment policy*** strategy.

Secondary Estimands for the Secondary Efficacy Endpoints

For Secondary Efficacy Endpoints Based on AN Counts:
The estimand framework for the secondary efficacy endpoint of AN50 at Week 16 and flare over 16 weeks was specified to be the same as the primary efficacy endpoint. For these two endpoints, the SAP specified using the same approaches to handling the intercurrent events as the primary efficacy endpoint.

For Secondary Efficacy Endpoint Based on Pain:
The SAP specified the following estimand framework for the secondary efficacy endpoint of NRS30 at Week 16:

1. **Population**: Subjects with moderate to severe hidradenitis suppurativa who had a total of at least 5 inflammatory lesions, i.e. abscesses and/or inflammatory nodules and Inflammatory lesions should affect at least 2 distinct anatomic areas, and who had HS diagnosed ≥ 1 years defined through appropriate inclusion/exclusion criteria. Only subjects with baseline NRS ≥ 3 were considered.

2. **Endpoint**: NRS30 at Week 16, which was defined as at least a 30% reduction and at least 2 unit reduction from baseline in Patient's Global Assessment of Skin Pain at worst and without confounding prohibited medication opioid analgesics intake within 2 days of the assessment and without two or more major surgeries up to Week 16.
3. **Treatment of interest**: The randomized study treatment (secukinumab 300 mg in two different dosing regimens Q2W or Q4W vs. placebo) with or without rescue medication, regardless of discontinuation due to AE or lack of efficacy.
4. **Summary measure**: odds ratio of secukinumab dose regimens versus placebo.
5. **ICE**:

For this secondary efficacy endpoint, the SAP specified using the same approaches to handling the intercurrent events **ICE #2- #5** as the primary efficacy endpoint. For the intercurrent event **ICH #1**: Intake of prohibited medication, it was specified as following:

Intake of prohibited medication (medications with possible confounding effect defined as opioid analgesics taken for HS within 2 days of Week 16 assessment or any major surgery for HS other than allowed as a rescue therapy): A **composite** strategy was applied where subjects taking such medications were defined as non-responders.

Sensitivity Analysis for the Secondary Estimands of Secondary Efficacy Endpoints:

For secondary efficacy endpoints, the SAP specified conducting a sensitivity analysis using the weighted average across the screening and baseline assessments as the baseline value.

Statistical Reviewers' Comment on Rescue Medication (ICE #2) and Information Request:

The statistical reviewers found that there were only 2 subjects in Study M2301 and no subjects in Study M2302 classified as on rescue medication (ICE #2) and were treated as 'non-responders' in the applicant's submitted efficacy data set ADHiSCR.xpt/ADHSRMI.xpt. However, there were 37 more subjects in Study M2301 and 53 more subjects in Study M2302 who were either on rescue medication or on rescue therapy according to the applicant's submitted data sets ADCM.xpt/ADPR.xpt.

On 6/30/2023, FDA sent an IR letter to the applicant and requested the applicant to provide clarification on the discrepancy in identifying subjects who used the rescue medication/therapy between two sets of submitted data sets; provide corrected data sets with a consistent approach for handling rescue medication/therapy as "non-responders"per SAP; and submit analysis results for the primary and secondary endpoints and all the related analyses based on the corrected data sets.

On 7/10/2023, in respond to the Agency's 6/30/2023 IR letter, the applicant "acknowledged there are differences between the datasets" but each data served "different purposes". The datasets were "programmed as per the submitted study protocols and statistical analysis plan

(SAP), as well as the programming data set specifications (PDS) document." ADCM.xpt captured any rescue medication use. For HiSCR.xpt/HiSCRMI.xpt, "Only the use of selected rescue medications (oral minocycling or doxycycline up to 100 mg bid) was considered as an intercurrent event, as pre-specified in the study protocols, SAPs and PDS. Per the PDS, use of rescue medication during Treatment Period 1 was considered as an intercurrent event on the next day of its occurring and all subsequent days, only if there was an increase of 150% in AN count and a minimum increase of 3 lesions." Regarding rescue therapy, the applicant stated that "a single lesion intervention was not considered an intercurrent event as it was not a systemic therapy that could affect HS lesions in other areas of the body" and "therefore, single lesion intervention was considered unlikely to impact the assessment of the primary endpoint of HiSCR".

As requested by the Agency, the applicant submitted "additional analyses which considered all subjects who used rescue medication and underwent a single lesion intervention as non-responders in Treatment Period 1", but in these analyses the MI data sets for handling missing data were not regenerated to incorporate the change in defining the response data.

On 7/16/2023, the Agency sent another IR letter to the applicant indicating that "the detailed definition of 'rescue medication'" as defined in the applicant's PDS document "was not submitted to the Agency" in the original submission. The Agency also expressed disagreement with the proposed definition for rescue medication. In particular, for a single lesion intervention, the Agency "considers that an excision, drainage, or corticosteroid injection of a single lesion may significantly impact the primary endpoint analysis" and "suggest that single lesion intervention should qualify for "rescue medication" and "Non-responder" should be imputed for the primary endpoint and related secondary endpoints for those underwent single lesion intervention".

The Agency requested the applicant to a) provide corrected data sets with single lesion intervention added to their original definition of 'rescue medication' in their internal document and handle the updated rescue medication/therapy as "non-responders" per SAP; b) regenerate 100 MI data sets based on the corrected response data; c) submit analysis results for the primary and secondary endpoints and all the related analyses based on the corrected data sets.

On 7/31/2023, the applicant submitted updated response data sets in which any use of rescue medication or lesion intervention was considered a treatment failure and the updated multiple imputation datasets were based on the updated response data. The applicant also submitted the "FDA-requested post-hoc analyses for the primary and secondary endpoints and all the related analyses based on the updated datasets.

The resulting difference in the primary endpoint HiSCR Response between the applicant's analysis and FDA-requested analysis is summarized in Table 1A for Study M2301 and Table 1B in Study M2302.

*For Study M2301 (**Table 12**), there were a total of 37 subjects (secukinumab Q2W: 8, secukinumab Q4W: 9, Placebo: 20) who had either a rescue medication according to ADCM.xpt (n=19) or a single lesion intervention done during Treatment Period 1 according to ADPR.xpt (n=19), however, were not considered as ICE #2 for "intaking of rescue medication" in the efficacy data ADHiSCR.xpt/ADHSCMI.xpt (note that one subject had both an intake of rescue medication and a single lesion intervention). Among the 37, 8 subjects (secukinumab Q2W: 1, secukinumab Q4W: 0, Placebo: 7) were counted as HiSCR responders according to the applicant's primary analysis, but were counted as non-responders in the FDA-requested analysis; 6 subjects (secukinumab Q2W: 2, secukinumab Q4W: 2, Placebo: 2) had missing response status in the applicant's primary analysis, but were counted as non-responders in the FDA-requested analysis; the remaining 23 subjects (secukinumab Q2W: 5, secukinumab Q4W: 7, Placebo:11) were non-responders in the applicant's primary analysis and remained to be non-responders in the FDA-requested analysis. Therefore, there were a total of 8+6=14 subjects whose HiSCR response status that were changed in Study M2301.*

Table 12: Change in HiSCR Response Status from Applicant's Primary Analysis to FDA-requested Analysis for Subjects with Rescue Medication/Therapy Use in Study M2301

Pre-specified	New definition	AIN457 Q2W (N=8)	AIN457 Q4W (N=9)	Placebo (N=20)
HiSCR responders (n)	Switch to non-responders (n)	1	0	7
HiSCR non-responders (n)	Remain non-responders (n)	5	7	11
Missing responder status (n)	Define as non-responders (n)	2	2	2

Source: Applicant's response (7/10/2023) to the agency's 6/30/2023 IR letter

*Likewise, for Study M2302 (**Table 13**), there were a total of 53 subjects (secukinumab Q2W: 13, secukinumab Q4W: 17, Placebo: 23) who had either a rescue medication according to ADCM.xpt (n=36) or a single lesion intervention done during Treatment Period 1 according to ADPR.xpt (n=20), however, were not considered as ICE #2 for "intaking of rescue medication" in the efficacy data ADHiSCR.xpt/ADHiSCRMI.xpt (note that three subject had both an intake of rescue medication and a single lesion intervention). Among the 53, 22 subjects (secukinumab Q2W: 7, secukinumab Q4W: 6, Placebo: 9) were counted as HiSCR responders according to the applicant's primary analysis, but were counted as non-responders in the FDA-requested analysis; 2 subjects (secukinumab Q2W: 0, secukinumab Q4W: 1, Placebo: 1) had missing response status in the applicant's primary analysis, but were counted as non-responders in the FDA-requested analysis; the remaining 29 subjects (secukinumab Q2W: 6, secukinumab Q4W: 10, Placebo:13) were non-responders in the applicant's primary analysis and remained to be non-*responders in the *FDA-requested analysis. Therefore, there were a total of 22+2=24 subjects whose HiSCR response status that were changed in Study M2302.*

Table 13: Change in HiSCR Response Status from Applicant's Primary Analysis to FDA-requested Analysis for Subjects with Rescue Medication/Therapy Use in Study M2302

Pre-specified	New definition	AIN457 Q2W (N=13)	AIN457 Q4W (N=17)	Placebo (N=23)
HiSCR responders (n)	Switch to non-responders (n)	7	6	9
HiSCR non-responders (n)	Remain non-responders (n)	6	10	13
Missing responder status (n)	Define as non-responders (n)	0	1	1

Source: Applicant's response (7/10/2023) to the agency's 6/30/2023 IR letter

Handling Missing Data

The protocol/SAP specified that for all missing values not related to intercurrent events, the primary method for handling missing data was the multiple imputation with the fully conditional specification (FCS) approach, following an MAR assumption for the missing data mechanism.

For the endpoints based on AN count, the SAP specified imputing the individual components (i.e., number of inflammatory nodules, number of abscesses, and the number of draining fistulas). In addition, the SAP specified that missing pain NRS scores were imputed rather than the binary endpoint (i.e., NRS30).

Missing data was imputed 100 times using linear regression models for continuous variables and logistic regression models for categorical variables. The imputation was done separately for each treatment group. The SAP specified that the model included corresponding baseline value, geographical region, Hurley stage, use of antibiotic (yes and no), and body weight (< 90 kg and ≥ 90 kg).

A tipping point analysis was conducted as a sensitivity analysis to assess the robustness of the multiple imputation approach.

Efficacy Analyses:

The protocol/SAP specified that the primary analysis was a logistic regression with treatment group, Hurley stage, and baseline AN count as explanatory variables. Geographical region, use of antibiotic, and baseline body weight (categorized as stratified) were also included as explanatory variables. Odds ratios were computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted.

The analysis method for all secondary endpoints (AN50, flare over 16 weeks, and NRS30 at Week 16) was a logistic regression. Odds ratios were computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted.

For AN50 and flare over 16 weeks: A logistic regression was utilized with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotic, and baseline body weight (categorized as stratified) in the model as explanatory variables.

For Skin Pain/NRS30 at Week 16: A logistic regression was conducted with treatment group, Hurley stage, and baseline NRS, geographical region, use of antibiotic, baseline body weight (categorized as stratified) in the model as explanatory variables.

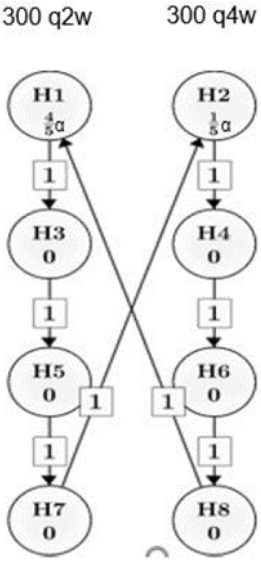
Subgroup Analysis

Subgroup Analysis for the primary and the secondary efficacy endpoints was carried out by the current antibiotic use (Yes/No), body weight stratum (< 90kg, ≥ 90kg), geographical region, age (<65 or ≥65 years), gender, race, disease duration (<2 years, 2 to <5 years, 5 to <10 years, ≥10 years), previous exposure to biologics, baseline AN count (≤10, >10), and Hurley stage.

Multiplicity

According to the protocol/SAP, the primary endpoint and all secondary endpoints were tested as follows. In order to control for the type-I error rate ("false positive rate"), the sequence of the multiplicity testing strategy illustrated in Figure 6 was implemented. The alpha level assigned to the secukinumab Q2W vs. placebo testing was and that to the secukinumab Q4W vs. placebo testing was . For example, for a two-sided test with a significance level 0.05, the alpha level assigned to secukinumab Q2W vs. placebo was 0.04 and that for secukinumab Q4W vs placebo was 0.01.

Figure 6. Multiplicity Testing Strategy



Source: applicant's study report

The sequence of hypotheses included in the multiplicity test procedure are as follows:

Primary endpoint:

H_1: secukinumab 300 mg Q2W s.c. is not different to placebo regimen w.r.t HiSCR at Week 16.
H_2: secukinumab 300 mg Q4W s.c. is not different to placebo regimen w.r.t HiSCR at Week 16.

Secondary endpoints:

H_3: secukinumab 300 mg Q2W s.c. is not different to placebo regimen w.r.t AN50 at Week 16.
H_4: secukinumab 300 mg Q4W s.c. is not different to placebo regimen w.r.t AN50 at Week 16.
H_5: secukinumab 300 mg Q2W s.c. is not different to placebo regimen w.r.t flare over 16 weeks.

H_6: secukinumab 300 mg Q4W s.c. is not different to placebo regimen w.r.t flare over 16 weeks.
H_7: secukinumab 300 mg Q2W s.c. is not different to placebo regimen w.r.t NRS30 at Week 16.
H_8: secukinumab 300 mg Q4W s.c. is not different to placebo regimen w.r.t NRS30 at Week 16.

Source: applicant's study report**Protocol Amendments**

The original study protocol was amended twice. The Amendment 01 was dated on June 17, 2020 and Amendment 02 was dated on January 8, 2021. Details are attached below.

Version and date	Summary of key changes
Amendment 02 (08-Jan-2021)	The purpose of this amendment was to update the statistical analysis section including adjusting the split of the overall alpha level allocating 80% to testing the high dose secukinumab regimen (300 mg Q2W) versus placebo, based on the recent findings from Study CAIN457A2324 demonstrating an improved benefit of secukinumab 300 mg Q2W when used in subjects with psoriasis over 90 kg. These data were not available at the time of the initial production of the protocol. In addition, following the FDA feedback this amendment introduced the value of the individual lesion count assessed at the randomization visit only to be used as 'baseline' in the statistical analyses, instead of the weighted average across the two screening visits and the baseline (randomization) visit. Moreover, a secondary endpoint evaluating only the abscesses and inflammatory nodules (AN) count was added. Analyzing AN count on the original, continuous scale, enabled a more sensitive and granular approach to summarizing the clinical effect of treatment (Revuz 2009, Kimball et al 2018). Lastly, the exploratory objective section has been updated to include a specific analysis to evaluate the benefit of secukinumab in the bio-naive population and in the subjects with body weight above and below 90 kg, and to explore treatment effect with regard to inflammatory markers (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)).
Amendment 01 (17-Jun-2020)	The rationale for the amendment reflects the guidance released from several Health Authorities (FDA, EMA, MHRA) to introduce a level of flexibility in drug dispensation, protocol assessments and visit schedule if a major health care event requires it (i.e., COVID-19 pandemic). While adherence to protocol procedure and GCPs remains mandatory, Novartis has edited the wording in some sections of the protocol to allow the subjects in the trial to continue treatment while being monitored for safety in these situations. These changes were introduced to reduce the risk of exposure for subjects and study staff, and potentially the risk for transmission of infectious diseases (e.g., COVID-19).

Version and date	Summary of key changes
	In addition, a 'special scenario' was added to the study design to ensure a careful, on site assessment of lesions at Week 52, by allowing for the possibility to perform up to 3 unscheduled visits in case lockdowns or mobility restriction would impede the subject or the site to perform the visit on site. In case of a global health crisis impeding the subjects (or the sites) to attend (or perform) Week 52 study visit on site, the subjects in the study were allowed to receive additional study treatment up to 12 weeks after Week 50, or until they could return to the study site to perform the Week 52 assessment (whichever occurs first). This additional, optional phase permitted the subjects to be assessed for eligibility to roll over to the 4-year long-term extension study. During this period, the subjects were continuously monitored for safety. Lastly, the Amendment 01 allowed for an increase in the number of randomized subjects up to 15% to account for the disruptive impact of the COVID-19 pandemic.

Source: applicant's study report

8.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attested to conducting clinical trials M2301 and M2302 in compliance with good clinical practices (GCPs), including study design, monitoring, conduct, and ethical principles.

Financial Disclosure

Refer to Section 19.2

Patient Disposition

A total of 1084 subjects, 541 subjects in study M2301 and 543 subjects in Study M2302, were randomized to secukinumab Q2W, secukinumab Q4W, placebo Q2W or placebo Q4W in a 1:1:0.5:0.5 ratio and were included in the Randomized Analysis Set. Three subjects in M2301 (1 mis-randomized in IRT, 1 at a site closed due to serious GCP violation and 1 with ICF related serious breach) and one subject in M2302 (mis-randomized in IRT) were excluded from the RAS.

Treatment Period 1

Table 14 reports the subject disposition during Treatment Period 1 in Study M2301 and Study M2302. Overall, most subjects (509 subjects, 94.1% in M2301 and 506 subjects, 93.2% in M2302) completed the first 16 weeks of the study treatment (Treatment Period 1) in both studies. Of the 32 (5.9%) subjects in M2301 and the 37 (6.8%) subjects in M2302 who discontinued the study treatment, the primary reason for discontinuing study treatment was subject decision in both studies (18 subjects, 3.3% in M2301 and 20 subjects, 3.7% in M2302). Discontinuation of study treatment due to AEs was low in both studies (5 subjects, 0.9% in M2301, and 9 subjects, 1.7% in M2302). No subject in M2301 and two subjects (one each in the secukinumab Q2W dose regimen and placebo) in M2302 discontinued study treatment due to lack of efficacy. There was no meaningful difference in subject disposition across the treatment groups in both studies.

Table 14: Subject Disposition by Study – Treatment Period 1 (Randomized Analysis Set)

	M2301				M2302			
Disposition/Reason	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=180 n (%)	Total N=541 n (%)	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=183 n (%)	Total N=543 n (%)
Completed Treatment period 1	168 (92.8)	169 (93.9)	172 (95.6)	509 (94.1)	170 (94.4)	169 (93.9)	167 (91.3)	506 (93.2)
Discontinued treatment	13 (7.2)	11 (6.1)	8 (4.4)	32 (5.9)	10 (5.6)	11 (6.1)	16 (8.7)	37 (6.8)
Primary reason for treatment discontinuation								
Adverse event	4 (2.2)	0 (0.0)	1 (0.6)	5 (0.9)	1 (0.6)	4 (2.2)	4 (2.2)	9 (1.7)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.5)	2 (0.4)
Lost to follow-up	3 (1.7)	1 (0.6)	1 (0.6)	5 (0.9)	1 (0.6)	1 (0.6)	1 (0.5)	3 (0.6)
Physician decision	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (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 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.6)	0 (0.0)	1 (0.5)	2 (0.4)
Subject decision	4 (2.2)	9 (5.0)	5 (2.8)	18 (3.3)	6 (3.3)	6 (3.3)	8 (4.4)	20 (3.7)
Discontinued study	13 (7.2)	11 (6.1)	8 (4.4)	32 (5.9)	10 (5.6)	11 (6.1)	16 (8.7)	37 (6.8)

- All percentages were computed using N as denominator.
- N = Number of subjects randomized and included in the randomized set.
- Three subjects in M2301 were excluded from the randomized set per SAP: 1 subject mis-randomized in IRT, 1 subject with severe GCP violation, and 1 subject with serious breach.
- One subject in M2302 was excluded from the randomized set per SAP: mis-randomized in IRT.

Source: [Study M2301 Week 16-Table 14.1-1.2], [Study M2302 Week 16-Table 14.1-1.2], [SCS Appendix 1-Table 1.1-1.1]

Entire Study Period

Table 15 reports the subject disposition during the entire study period (52 weeks of study treatment). Overall, 71.3% of the subjects in M2301 and 72.4% in M2302 completed 52 weeks of study treatment. In Study M2301, proportion of treatment completion was comparable between the secukinumab dose regimens (69.1% in Q2W vs. 70.0% in Q4W) whereas slightly more subjects completed the study treatment in secukinumab Q2W (77.2%) than in Q4W (69.4%) in Study M2302. The most frequently reported primary reason for discontinuing study treatment was subject decision in both studies (14.2% in M2301 and 12.3% in M2302), which was comparable between the secukinumab dose regimens in M2301, but slightly lower in secukinumab Q2W (8.3%) than in secukinumab Q4W (12.8%) in M2302. The proportion of subjects who discontinued study treatment due to AEs (3.5% in M2301 and 3.9% in M2302) and lack of efficacy (1.1% in M2301 and 2.0% in M2302) was low in both studies. Of the 373 subjects who completed Study M2301 and 390 who completed Study M2302, 321 in M2301 and 336 in M2302 entered the extension study. The disposition of subjects was similar between the two studies.

Table 15: Subject Disposition by Study – Entire Study Period (Randomized Analysis Set)

	M2301			M2302			Pooled data		
Disposition/Reason	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 N=541 n (%)	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 N=543 n (%)	AIN457 Q2W N=361 n (%)	AIN457 Q4W N=360 n (%)	Any AIN457 N=1084 n (%)
Completed treatment	125 (69.1)	126 (70.0)	386 (71.3)	139 (77.2)	125 (69.4)	393 (72.4)	264 (73.1)	251 (69.7)	779 (71.9)
Discontinued treatment	49 (27.1)	43 (23.9)	127 (23.5)	31 (17.2)	46 (25.6)	123 (22.7)	80 (22.2)	89 (24.7)	250 (23.1)
Primary reason for treatment discontinuation									
Adverse event	10 (5.5)	5 (2.8)	19 (3.5)	7 (3.9)	7 (3.9)	21 (3.9)	17 (4.7)	12 (3.3)	40 (3.7)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.1)
Lack of efficacy	1 (0.6)	2 (1.1)	6 (1.1)	4 (2.2)	3 (1.7)	11 (2.0)	5 (1.4)	5 (1.4)	17 (1.6)
Lost to follow-up	6 (3.3)	4 (2.2)	15 (2.8)	2 (1.1)	9 (5.0)	13 (2.4)	8 (2.2)	13 (3.6)	28 (2.6)
Physician decision	1 (0.6)	3 (1.7)	7 (1.3)	1 (0.6)	2 (1.1)	5 (0.9)	2 (0.6)	5 (1.4)	12 (1.1)
Pregnancy	1 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.6)	2 (0.4)	1 (0.3)	1 (0.3)	4 (0.4)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (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 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	1 (0.6)	0 (0.0)	1 (0.2)	2 (1.1)	0 (0.0)	3 (0.6)	3 (0.8)	0 (0.0)	4 (0.4)
Subject decision	29 (16.0)	29 (16.1)	77 (14.2)	15 (8.3)	23 (12.8)	67 (12.3)	44 (12.2)	52 (14.4)	144 (13.3)
Completed study	120 (66.3)	123 (68.3)	373 (68.9)	141 (78.3)	124 (68.9)	390 (71.8)	261 (72.3)	247 (68.6)	763 (70.4)
Moved to extension study	107 (59.1)	103 (57.2)	321 (59.3)	126 (70.0)	104 (57.8)	336 (61.9)	233 (64.5)	207 (57.5)	657 (60.6)
Discontinued study	52 (28.7)	45 (25.0)	136 (25.1)	28 (15.6)	46 (25.6)	123 (22.7)	80 (22.2)	91 (25.3)	259 (23.9)

- All percentages were computed using N as denominator.
- N = Number of subjects randomized and included in the randomized set.
- Three subjects in M2301 were excluded from the randomized set per SAP: 1 subject mis-randomized in IRT, 1 subject with severe GCP violation, and 1 subject with serious breach.
- One subject in M2302 was excluded from the randomized set per SAP: mis-randomized in IRT.

Source: [Study M2301 Week 52-Table 14.1-1.3], [Study M2302 Week 52-Table 14.1-1.3], [SCS Appendix 1-Table 1.1-2.1]

Protocol Violations/Deviations

A total of 173 (32%) subjects in M2301 and 158 (29.1%) subjects had at least one protocol deviation during Treatment Period 1 with no meaningful differences observed across treatment arms (Table 3). The most common categories of protocol deviations were “treatment deviation” (18.1% in M2301 and 15.3% in M2302), mainly related to home vs. site drug administration and similar across groups, “other” (10.5% in M2301 and 7.9% in M2302), and “prohibited concomitant medication” (7.0% in M2301, and 7.6% in M2302). All other protocol deviations were minor and did not impact the overall analysis and study conclusion (Table 16).

Table 16: Protocol Deviations by Study – Treatment Period 1 (Full Analysis Set)

Protocol Deviation	Study M2301				Study M2302			
	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=180 n (%)	Total N=541 n (%)	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=183 n (%)	Total N=543 n (%)
Subjects with at least one protocol deviation	59 (32.6)	53 (29.4)	61 (33.9)	173 (32.0)	48 (26.7)	49 (27.2)	61 (33.3)	158 (29.1)
Selection criteria not met	8 (4.4)	8 (4.4)	4 (2.2)	20 (3.7)	8 (4.4)	13 (7.2)	8 (4.4)	29 (5.3)
Subject not withdrawn as per protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment deviation	33 (18.2)	27 (15.0)	38 (21.1)	98 (18.1)	23 (12.8)	29 (16.1)	31 (16.9)	83 (15.3)
Prohibited concomitant medication	12 (6.6)	12 (6.7)	14 (7.8)	38 (7.0)	14 (7.8)	7 (3.9)	20 (10.9)	41 (7.6)
Other*	20 (11.0)	18 (10.0)	19 (10.6)	57 (10.5)	15 (8.3)	11 (6.1)	17 (9.3)	43 (7.9)

- A subject with multiple occurrences of a protocol deviation category was counted only once in the protocol deviation category.

*Category "Other" covers protocol deviations that do not fall into the previous categories (selection criteria not met, subject withdrawal as per protocol, treatment deviation or prohibited concomitant medication) and impact the completeness, accuracy, and/or reliability of study data or subject's rights, safety, and well-being; e.g., procedure was performed after the subject withdrew consent, GCP non-compliance of study site, or missed primary endpoint assessment.
- Subjects may have protocol deviations in more than one protocol deviation category.
Source: Study M2301 Week 16 Table 14.1-2.1 and Study M2302 Week 16 Table 14.1-2.1

Table of Demographic Characteristics

The demographic characteristics were generally balanced across the treatment groups in each study and consistent between the two studies, with some minor differences in the age group and smoking status being noted (Table 17). Overall, the mean age of subjects was 36.1 years in Study M2301 and 36.3 years in Study M2302. In Study M2301, subjects in secukinumab Q2W (mean age 37.1) were slightly older than those in the other two groups (35.7 in secukinumab QW4 and 35.5 in placebo), likewise in Study M2302 (mean age 37.3 in secukinumab Q2W, 35.5 in secukinumab Q4W, and 36.2 in placebo. The proportion of female subjects was 56.2% in M2301 and 56.4% in M2302. A majority of the subjects were White (79.5% in M2301 and 76.4% in M2302). The proportion of subjects weighing ≥ 90 kg was 54.7% in M2301 and 50.8% in M2302. More than half of the subjects were current smokers in both studies (54.0% each). The proportion of never smokers in M2301 was slightly higher in the secukinumab Q2W (33.1%) and Q4W (31.1%) dose regimens compared to placebo (27.2%) and that proportion in M2302 was slightly higher in secukinumab Q4W dose regimen (36.1%) compared to secukinumab Q2W dose regimen (28.3%) and placebo (29.0%) (Table 17).

Table 17: Demographic Characteristics by Study (Full Analysis Set)	**M2301**				**M2302**			
Characteristic	**AIN457 Q2W N=181**	**AIN457 Q4W N=180**	**Placebo N=180**	**Total N=541**	**AIN457 Q2W N=180**	**AIN457 Q4W N=180**	**Placebo N=183**	**Total N=543**
Age group in years, n (%)								
< 30	58 (32.0)	69 (38.3)	51 (28.3)	178 (32.9)	52 (28.9)	60 (33.3)	57 (31.1)	169 (31.1)
30-<40	56 (30.9)	45 (25.0)	70 (38.9)	171 (31.6)	48 (26.7)	61 (33.9)	65 (35.5)	174 (32.0)
40-<65	64 (35.4)	63 (35.0)	58 (32.2)	185 (34.2)	77 (42.8)	57 (31.7)	59 (32.2)	193 (35.5)
≥65	3 (1.7)	3 (1.7)	1 (0.6)	7 (1.3)	3 (1.7)	2 (1.1)	2 (1.1)	7 (1.3)
Age (years)								
Mean (SD)	37.1 (12.53)	35.7 (11.71)	35.5 (10.75)	36.1 (11.69)	37.3 (11.48)	35.5 (11.41)	36.2 (11.25)	36.3 (11.38)
Median (min-max)	35.0 (18-73)	34.0 (18-67)	33.5 (19-65)	34.0 (18-73)	37.0 (18-67)	33.5 (18-71)	34.0 (18-71)	35.0 (18-71)
Gender, n (%)								
Male	79 (43.6)	80 (44.4)	78 (43.3)	237 (43.8)	82 (45.6)	77 (42.8)	78 (42.6)	237 (43.6)
Female	102 (56.4)	100 (55.6)	102 (56.7)	304 (56.2)	98 (54.4)	103 (57.2)	105 (57.4)	306 (56.4)
Race, n (%)								
White	145 (80.1)	146 (81.1)	139 (77.2)	430 (79.5)	133 (73.9)	139 (77.2)	143 (78.1)	415 (76.4)
Black or	15 (8.3)	10 (5.6)	12 (6.7)	37 (6.8)	18 (10.0)	19 (10.6)	12 (6.6)	49 (9.0)

African American								
Asian	19 (10.5)	23 (12.8)	24 (13.3)	66 (12.2)	16 (8.9)	16 (8.9)	19 (10.4)	51 (9.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
American Indian or Alaska native	1 (0.6)	1 (0.6)	2 (1.1)	4 (0.7)	7 (3.9)	5 (2.8)	8 (4.4)	20 (3.7)
Multiple	1 (0.6)	0 (0.0)	3 (1.7)	4 (0.7)	4 (2.2)	1 (0.6)	1 (0.5)	6 (1.1)
Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Ethnicity, n (%)								
Hispanic or Latino	18 (9.9)	21 (11.7)	22 (12.2)	61 (11.3)	35 (19.4)	30 (16.7)	33 (18.0)	98 (18.0)
Not Hispanic or Latino	157 (86.7)	152 (84.4)	157 (87.2)	466 (86.1)	136 (75.6)	144 (80.0)	143 (78.1)	423 (77.9)
Not Reported	4 (2.2)	6 (3.3)	0 (0.0)	10 (1.8)	8 (4.4)	6 (3.3)	7 (3.8)	21 (3.9)
Unknown	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Weight (kg)								
Mean (SD)	95.87 (25.032)	95.43 (25.894)	92.88 (22.098)	94.73 (24.387)	92.57 (24.308)	93.13 (22.271)	90.96 (22.020)	92.21 (22.861)
Median (min-max)	92.00 (51.0-205.0)	92.35 (43.0-201.6)	92.00 (47.4-159.2)	92.00 (43.0-205.0)	90.00 (50.0-181.9	90.00 (50.0-152.0)	89.40 (49.8-157.0)	90.00 (49.8-181.9)
Weight groups (kg), n (%)								
<90	82 (45.3)	80 (44.4)	83 (46.1)	245 (45.3)	86 (47.8)	89 (49.4)	92 (50.3)	267 (49.2)
≥90	99 (54.7)	100 (55.6)	97 (53.9)	296 (54.7)	94 (52.2)	91 (50.6)	91 (49.7)	276 (50.8)
BMI (kg/m²)								
n	181	179	180	540	180	180	183	543
Mean (SD)	32.64 (7.904)	32.78 (7.897)	31.97 (7.053)	32.46 (7.622)	31.90 (7.788)	31.98 (7.478)	31.42 (7.382)	31.76 (7.540)
Median (min-max)	31.79 (14.7-59.0)	31.83 (18.3-61.8)	31.30 (16.8-51.3)	31.57 (14.7-61.8)	31.75 (16.9-64.3)	31.08 (19.3-56.9)	30.35 (18.2-52.2)	31.09 (16.9-64.3)
Smoking Status, n (%)								
Never	60 (33.1)	56 (31.1)	49 (27.2)	165 (30.5)	51 (28.3)	65 (36.1)	53 (29.0)	169 (31.1)
Current	95 (52.5)	96 (53.3)	101 (56.1)	292 (54.0)	97 (53.9)	90 (50.0)	106 (57.9)	293 (54.0)
Former	26 (14.4)	28 (15.6)	30 (16.7)	84 (15.5)	32 (17.8)	25 (13.9)	24 (13.1)	81 (14.9)

- Weight and height are taken from baseline visit.
- Race 'Multiple' means multiple entries are selected in the eCRF.

Source: [Study M2301 Week 16-Table 14.1-5], [Study M2302 Week 16-Table 14.1-5]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease history and baseline disease characteristics were generally balanced across the treatment groups in each study and consistent between the studies (Table 18). In both studies, most subjects presented with Hurley stage II at baseline (61.4% in M2301 and 56.7% in M2302, respectively). Of note, the secukinumab Q2W dose regimen in both studies were comprised of more severe subjects (i.e., more subjects with Hurley stage III, having higher abscess and fistulae count) compared to the other two treatment groups: In M2302, 45.6% subjects had baseline Hurley Stage III in secukinumab Q2W compared to 37.8% in secukinumab Q4W and 38.3% in placebo; In M 2301, 38.7% subjects in the secukinumab Q2W and 35.0% in the secukinumab Q4W had baseline Hurley Stage III compared to 28.3% in placebo. Accordingly, the number of baseline AN count, inflammatory nodule count, abscesses count, and fistulae count were also slightly higher in the secukinumab Q2W dose regimen compared to the other treatment groups.
The proportion of subjects with previous exposure to systemic biologic therapy was 23.8% in M2301 and 23.2% in M2302, and most of these subjects received adalimumab (22.6% in M2301, 21.4% in M2302). Most subjects received previous systemic antibiotics (82.3% in M2301, 83.6% in M2302), which had been mostly discontinued by the time of study entry for the predominant reason of lack of efficacy (approximately 60%).The proportion of subjects who had undergone surgical intervention for HS prior to study entry was 39.9% in M2301 and 41.6% in M2302 (Table 18).

Table 18: Disease history and baseline disease characteristics by Study (Full Analysis Set)

Background characteristic	M2301				M2302			
	AIN457 Q2W N=181	AIN457 Q4W N=180	Placebo N=180	Total N=541	AIN457 Q2W N=180	AIN457 Q4W N=180	Placebo N=183	Total N=543
Baseline Hurley stage, n (%)								
I	7 (3.9)	10 (5.6)	8 (4.4)	25 (4.6)	6 (3.3)	6 (3.3)	3 (1.6)	15 (2.8)
II	104 (57.5)	107 (59.4)	121 (67.2)	332 (61.4)	92 (51.1)	106 (58.9)	110 (60.1)	308 (56.7)
III	70 (38.7)	63 (35.0)	51 (28.3)	184 (34.0)	82 (45.6)	68 (37.8)	70 (38.3)	220 (40.5)
Family history of HS, n (%)								
Yes	35 (19.3)	52 (28.9)	55 (30.6)	142 (26.2)	39 (21.7)	42 (23.3)	41 (22.4)	122 (22.5)
No	146 (80.7)	128 (71.1)	125 (69.4)	399 (73.8)	141 (78.3)	138 (76.7)	142 (77.6)	421 (77.5)
Baseline AN count								
Mean (SD)	12.9 (9.60)	12.6 (8.38)	12.8 (8.15)	12.8 (8.72)	13.9 (9.93)	13.3 (8.77)	12.8 (8.45)	13.3 (9.06)
Median (min-max)	10.0 (3-81)	10.0 (5-63)	10.0 (5-42)	10.0 (3-81)	11.0 (4-60)	11.0 (5-51)	10.0 (5-45)	11.0 (4-60)

Baseline inflammatory nodule count								
Mean (SD)	10.1 (7.80)	9.9 (7.60)	10.1 (6.99)	10.0 (7.46)	10.0 (7.71)	10.4 (7.60)	9.6 (6.77)	10.0 (7.36)
Median (min-max)	8.0 (0-53)	8.0 (0-62)	8.0 (1-36)	8.0 (0-62)	8.0 (0-50)	8.0 (0-43)	8.0 (0-41)	8.0 (0-50)
Baseline abscess count								
Mean (SD)	2.9 (4.26)	2.7 (3.96)	2.7 (3.76)	2.7 (3.99)	3.9 (5.41)	2.9 (4.13)	3.2 (4.96)	3.3 (4.87)
Median (min-max)	1.0 (0-30)	1.0 (0-31)	1.0 (0-21)	1.0 (0-31)	2.0 (0-45)	1.0 (0-26)	1.0 (0-32)	2.0 (0-45)
Baseline draining fistulae count								
Mean (SD)	2.9 (3.41)	2.5 (3.52)	2.4 (3.16)	2.6 (3.37)	3.0 (3.63)	2.5 (3.50)	2.6 (3.24)	2.7 (3.46)
Median (min-max)	2.0 (0-17)	1.0 (0-16)	1.0 (0-17)	1.0 (0-17)	2.0 (0-17)	1.0 (0-19)	2.0 (0-19)	1.0 (0-19)
Baseline total fistulae count								
Mean (SD)	5.3 (5.57)	4.4 (5.24)	4.7 (5.25)	4.8 (5.36)	5.1 (4.99)	4.7 (5.26)	4.6 (4.90)	4.8 (5.05)
Median (min-max)	4.0 (0-26)	2.0 (0-19)	3.0 (0-19)	3.0 (0-26)	4.0 (0-19)	2.5 (0-20)	3.0 (0-20)	3.0 (0-20)
Prior surgery for HS, n (%)								
Yes	71 (39.2)	73 (40.6)	72 (40.0)	216 (39.9)	78 (43.3)	70 (38.9)	78 (42.6)	226 (41.6)
No	110 (60.8)	107 (59.4)	108 (60.0)	325 (60.1)	102 (56.7)	110 (61.1)	105 (57.4)	317 (58.4)
Previous exposure to systemic biologic therapy, n (%)								
Yes	44 (24.3)	39 (21.7)	46 (25.6)	129 (23.8)	36 (20.0)	42 (23.3)	48 (26.2)	126 (23.2)
No	137 (75.7)	141 (78.3)	134 (74.4)	412 (76.2)	144 (80.0)	138 (76.7)	135 (73.8)	417 (76.8)
Previous exposure to adalimumab, n (%)								
Yes	41 (22.7)	38 (21.1)	43 (23.9)	122 (22.6)	34 (18.9)	38 (21.1)	44 (24.0)	116 (21.4)
No	140 (77.3)	142 (78.9)	137 (76.1)	419 (77.4)	146 (81.1)	142 (78.9)	139 (76.0)	427 (78.6)
Previous exposure to systemic antibiotics, n (%)								
Yes	146 (80.7)	149 (82.8)	150 (83.3)	445 (82.3)	151 (83.9)	152 (84.4)	151 (82.5)	454 (83.6)
No	35 (19.3)	31 (17.2)	30 (16.7)	96 (17.7)	29 (16.1)	28 (15.6)	32 (17.5)	89 (16.4)
Previous exposure to non- biologic and non-antibiotic systemic therapy, n (%)								
Yes	64 (35.4)	66 (36.7)	62 (34.4)	192 (35.5)	63 (35.0)	54 (30.0)	62 (33.9)	179 (33.0)
No	117 (64.6)	114 (63.3)	118 (65.6)	349 (64.5)	117 (65.0)	126 (70.0)	121 (66.1)	364 (67.0)

Source: [Study M2301 Week 16-Table 14.1-6], [Study M2302 Week 16-Table 14.1-6]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Table 19 reports the event rate of intercurrent events (ICE) for the primary and secondary efficacy endpoints in Treatment Period 1 by treatment arms in the two studies according to the applicant's analysis and Table 6B reports the corresponding event rate according to the FDA-requested analysis (see Section 8.1.1 Statistical Analysis Plan for details).

Table 19 shows that according to the applicant's analysis, the ICE event rate was low in both studies: 8.0% (43 subjects) for AN count-related endpoints (including the primary endpoint HiSCR50 and Secondary endpoints AN50 and Flare) and 8.9% (48 subjects) for the secondary endpoint NRS30 in Study M2301; 8.7% (47 subjects) for AN count-related endpoints and 10.5% (57 subjects) for NRS30 in Study M2302. The ICE event rate was generally balanced across treatment groups in both studies. Of note, placebo had slightly higher rate of ICE for NRS30 than the two secukinumab dose regimens in Study M2302 (10.9% in placebo vs. 7.8% in

secukinumab Q2W and 7.2% in secukinumab Q4W for AN-related endpoints; 13.1% in placebo vs. 8.9% in secukinumab Q2W and 9.4% in secukinumab Q4W for NRS30); In Study 2301, secukinumab Q2W had slightly higher rate of ICE (9.9% for AN count-related endpoints and 10.5% for NRS30) than secukinumab Q4W (7.8% for AN count-related endpoints and 8.3% for NRS30 and placebo (6.1% for AN count-related endpoints and 7.8% for NRS30). For AN count-related endpoints, the most frequent ICE types were ICE #4 permanent discontinuation of treatment due to other reasons (3.3% in Study #2301 and 3.7% in Study #2302) and ICE #5 Missed doses due to COVID19 (3.0% in both Study #2301 and study #2302). For NRS30, the most frequent ICE types were also ICE #4 permanent discontinuation of treatment due to other reasons (2.8% in Study #2301 and 3.3% in Study #2302) and ICE #5 Missed doses due to COVID19 (3.0% in Study #2301 and 3.1% in study #2302).

Table 19: Applicant's Intercurrent Events in Treatment Period 1 by Study For Applicant's Analysis (Full Analysis Set)

Protocol Deviation	Study M2301				Study M2302			
	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=180 n (%)	Total N=541 n (%)	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=183 n (%)	Total N=543 n (%)
Primary endpoint HiSCR50, secondary endpoint AN50, and flares over 16 weeks								
W/O ICE	163 (90.1)	166 (92.2)	169 (93.9)	498 (92.0)	166 (92.2)	167 (92.8)	163 (89.1)	496 (91.3)
W/ ICE	18 (9.9)	14 (7.8)	11 (6.1)	43 (8.0)	14 (7.8)	13 (7.2%)	20 (10.9)	47 (8.7)
ICE reasons								
ICE1: take prohibited mediation	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
ICE2: take rescue medication*	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ICE3: permanent discontinuation of treatment due to AE or LOE	3 (1.7)	0 (0.0)	1 (0.6)	4 (0.7)	2 (1.1)	4 (2.2)	4 (2.2)	10 (1.8)
ICE4: permanent discontinuation of treatment due to other reasons	7 (3.9)	7 (3.9)	4 (2.2)	18 (3.3)	4 (2.2)	6 (3.3)	10 (5.5)	20 (3.7)
ICE5: COVID19-related reasons								
Missed doses due to COVID19	8 (4.4)	3 (1.7)	5 (2.8)	16 (3.0)	7 (3.9)	3 (1.7)	6 (3.3)	16 (3.0)
Treatment discontinuation due to COVID19	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Secondary endpoint NRS30								
W/O ICE	162 (89.5)	165 (91.7)	166 (92.2)	493 (91.1)	164 (91.1)	163 (90.6)	159 (86.9)	486 (89.5)
W/ ICE	19 (10.5)	15 (8.3)	14 (7.8)	48 (8.9)	16 (8.9)	17 (9.4)	24 (13.1)	57 (10.5)
ICE reasons								

ICE1: take prohibited mediation	1 (0.6)	1 (0.6)	5 (2.8)	7 (.13)	3 (1.7)	4 (2.2)	4 (2.2)	11 (2.0)
ICE2: take rescue medication*	0 (0.0)	2 (1.1)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.4)
ICE3: permanent discontinuation of treatment due to AE or LOE	4 (2.2)	0 (0.0)	1 (0.6)	5 (0.9)	2 (1.1)	4 (2.2)	5 (2.7)	11 (2.0)
ICE4: permanent discontinuation of treatment due to other reasons	6 (3.3)	6 (3.3)	3 (1.7)	15 (2.8)	4 (2.2)	5 (2.8)	9 (4.9)	18 (3.3)
ICE5: COVID19-related reasons								
Missed doses due to COVID19	7 (3.9)	4 (2.2)	5 (2.8)	16 (3.0)	7 (3.9)	4 (2.2)	6 (3.3)	17 (3.1)
Treatment discontinuation due to COVID19	1 (0.6)	2 (1.1)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

Table 20: Applicant's Intercurrent Events in Treatment Period 1 by Study for FDA-Requested Analysis (Full Analysis Set)

Protocol Deviation	Study M2301				Study M2302			
	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=180 n (%)	Total N=541 n (%)	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Placebo N=183 n (%)	Total N=543 n (%)
Primary endpoint HiSCR50, secondary endpoint AN50, and flares over 16 weeks								
W/O ICE	156 (86.2)	158 (87.8)	150 (83.3)	464 (85.8)	153 (85.0)	152 (84.4)	143 (78.1)	448 (82.5)
W/ ICE	25 (13.8)	22 (12.2)	30 (16.7)	77 (14.2)	27 (15.0)	28 (15.6)	40 (21.9)	95 (17.5)
ICE reasons								
ICE1: take prohibited mediation	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
ICE2: take rescue medication*	8 (4.4)	11 (6.1)	20 (11.0)	39 (7.2)	13 (7.2)	17 (9.4)	22 (12.0)	52 (9.6)
ICE3: permanent discontinuation of treatment due to AE or LOE	3 (1.7)	0 (0.0)	1 (0.6)	4 (0.7)	2 (1.1)	4 (2.2)	4 (2.2)	10 (1.8)
ICE4: permanent discontinuation of treatment due to other reasons	6 (3.3)	6 (3.3)	3 (1.7)	15 (2.8)	4 (2.2)	5 (2.8)	8 (4.4)	17 (3.1)
ICE5: COVID19-related reasons								
Missed doses due to COVID19 Treatment	8 (4.4)	3 (1.7)	5 (2.8)	16 (3.0)	7 (3.9)	2 (1.1)	6 (3.3)	15 (2.8)
discontinuation due to COVID19	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Secondary endpoint NRS30								
W/O ICE	155 (85.6)	157 (87.2)	147 (81.7)	459 (84.8)	151 (83.9)	150 (83.3)	139 (76.0)	440 (81.0)
W/ ICE	26 (14.4)	23 (12.8)	33 (18.3)	82 (15.2)	29 (16.1)	30 (16.7)	44 (24.0)	103 (19.0)
ICE reasons								
ICE1: take prohibited mediation	1 (0.6)	1 (0.6)	5 (2.8)	7 (.13)	3 (1.7)	2 (1.1)	4 (2.2)	9 (1.7)

ICE2: take rescue medication*	8 (4.4)	11 (6.1)	20 (11.1)	39 (7.2)	13 (7.2)	17 (9.4)	23 (12.6)	53 (9.8)
ICE3: permanent discontinuation of treatment due to AE or LOE	4 (2.2)	0 (0.0)	1 (0.6)	5 (0.9)	2 (1.1)	4 (2.2)	4 (2.2)	10 (1.8)
ICE4: permanent discontinuation of treatment due to other reasons	5 (2.8)	5 (2.8)	2 (1.1)	12 (2.2)	4 (2.2)	4 (2.2)	7 (3.8)	15 (2.8)
ICE5: COVID19-related reasons								
Missed doses due to COVID19	7 (3.9)	4 (2.2)	5 (2.8)	16 (3.0)	7 (3.9)	3 (1.7)	6 (3.3)	16 (2.9)
Treatment discontinuation due to COVID19	1 (0.6)	2 (1.1)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

However, in the FDA-requested analysis as previously discussed in Section 8.1.1 Statistical Analysis Plan, 37 more subjects (8 in secukinumab Q2W, 9 in secukinumab Q4W, 20 in placebo) in Study M2301 and 53 more subjects (13 in secukinumab Q2W, 17 in secukinumab Q4W, 23 in placebo) in Study M2302 who were on any rescue medication or a single lesion intervention were classified as ICE2: taking rescue medication. In the FDA-requested analysis, the ICE #2 taking rescue medication became the most frequent ICE category for both AN-related endpoints and NRS30 in both studies. Of note, more subjects from the placebo arm were on rescue medication (ICE #2) than the two secukinumab dose regimens in both studies, which is expected.

Table 21: Concomitant Antibiotics in Treatment Period 1 by Study (Randomized Analysis Set)

	M2301				M2302			
Medication /Therapy	**AIN457 Q2W N=181**	**AIN457 Q4W N=180**	**Placebo N=180**	**Total N=541**	**AIN457 Q2W N=180**	**AIN457 Q4W N=180**	**Placebo N=183**	**Total N=543**
Current antibiotic use, n (%)								
Yes	26 (14.4)	25 (13.9)	18 (10.0)	69 (12.8)	18 (10.0)	21 (11.7)	19 (10.4)	58 (10.7)
No	155 (85.6)	155 (86.1)	162 (90.0)	472 (87.2)	162(90.0)	159 (88.3)	164 (89.6)	495 (89.3)

Source: [SCS Appendix 1-Table 1.4-1.4]

Table 21 reports the use of concomitant antibiotics in Treatment Period 1 in the two studies. The proportion of subjects who entered the studies on a stable dose of systemic antibiotics was similar between the treatment groups in both studies (Table 7): 14.4% in the secukinumab Q2W dose regimen, 13.9% in the secukinumab Q4W dose regimen, 10.0% in placebo in M2301; 10.0% in the secukinumab Q2W dose regimen, 11.7% in the secukinumab Q4W dose regimen, 10.4% in placebo in M2302.

Efficacy Results – Primary Endpoint

Table 22 reports the primary analysis result of the applicant's analysis vs. the FDA-requested analysis for the primary efficacy endpoint of HiSCR50 response rate at Week 16 among the FAS in the two studies, which was based on the primary estimand and missing data was imputed by 100 MI data sets as described in Section 8.1.1 Statistical Analysis Plan.

For the primary endpoint, according to the applicant's ICE handling strategies, the secukinumab Q2W dose regimen showed statistically significantly higher rate compared to placebo in both studies (45.0% in secukinumab Q2W vs. 33.7% in placebo in M2301, two-sided p=0.0140 < pre-specified alpha 0.04; 42.3% in secukinumab Q2W vs. 31.2% in placebo in M2302, two-sided p=0.0299 < 0.04). The secukinumab Q4W dose regimen showed a statistically significantly higher rate compared to placebo in M2302 (46.1% in secukinumab Q4W vs. 31.2% in placebo, two-sided p=0.0044 < pre-specified alpha 0.01), but not in M2301 (41.8% in secukinumab Q4W vs. 33.7% in placebo, two-sided p=0.0835).

According to the FDA-requested ICE handling strategies, the results were in general similar to that of the applicant's analysis except that all the p values were smaller, i.e., more statistically significant. In particular, the statistically significance of the secukinumab Q4W vs. placebo in Study M2301 improved greatly compared to that based on the applicant's analysis (p=0.0835, 41.8% in secukinumab Q4W vs. 33.7% in placebo): the p value of the FDA-requested analysis just slightly missed the pre-specified alpha for Q4W: p=0.0123 > pre-specified alpha 0.01 (41.3% in secukinumab Q4W vs. 29.4% in placebo). This is expected given that seven more subjects in the placebo arm than the secukinumab Q4W arm were taking rescue medication or intervention and were imputed as non-responders according to the FDA-requested analysis (Table 1A). Similarly, the other p values were also reduced in the FDA-requested analysis due to more placebo subjects than the secukinumab subjects taking rescue medication/intervention and being treated as non-responders: p=0.0014 for secukinumab Q2W vs. placebo in Study M2301 (44.9% in secukinumab Q2W vs. 29.4% in placebo) compared to p value of 0.0140 in the applicant's analysis (45.0% in secukinumab Q2W vs. 33.7% in placebo); Likewise, in Study M2302, the p value was 0.0145 for secukinumab Q2W vs. placebo in the FDA-requested analysis compared to p value of 0.0299 in the applicant's analysis; and the p value was 0.0015 for secukinumab Q4W vs. placebo in the FDA-requested analysis compared to p value of 0.0044 in the applicant's analysis.

Table 22: Primary Analysis Results of the Primary Efficacy Endpoint HiSCR50 at Week 16 (Primary Estimand, Multiple Imputation) For Study M2301 (Full Analysis Set) by Applicant's Analysis vs. FDA-Requested Analysis

Applicant's Analysis				**FDA-Requested Analysis**		
Study M2301: HiSCR Response at Week 16						
	Q2W (N=181)	Q4W (N=180)	Placebo (N=180)	Q2W (N=181)	Q4W (N=180)	Placebo (N=180)
Rate[1]	45.0%	41.8%	33.7%	44.5%	41.3%	29.4%

OR (95% CI)[2]	1.75 (1.12, 2.73)	1.48 (0.95, 2.32)	-	2.10 (1.33, 3.22)	1.79 (1.14, 2.83)	-
Two-sided P-value[2]	**0.0140**	0.0835	-	**0.0014**	0.0123	-
Study M2302: HiSCR Response at Week 16						
	Q2W (N=180)	QW4 (N=180)	Placebo (N=183)	Q2W (N=180)	QW4 (N=180)	Placebo (N=183)
Rate[1]	42.3%	46.1%	31.2%	38.3%	42.5%	26.1%
OR (95% CI)[2]	1.64 (1.05, 2.55)	1.90 (1.22, 2.96)	-	1.77 (1.12, 2.80)	2.10 (1.33, 3.32)	-
Two-sided P-value[2]	**0.0299**	**0.0044**	-	**0.0145**	**0.0015**	-

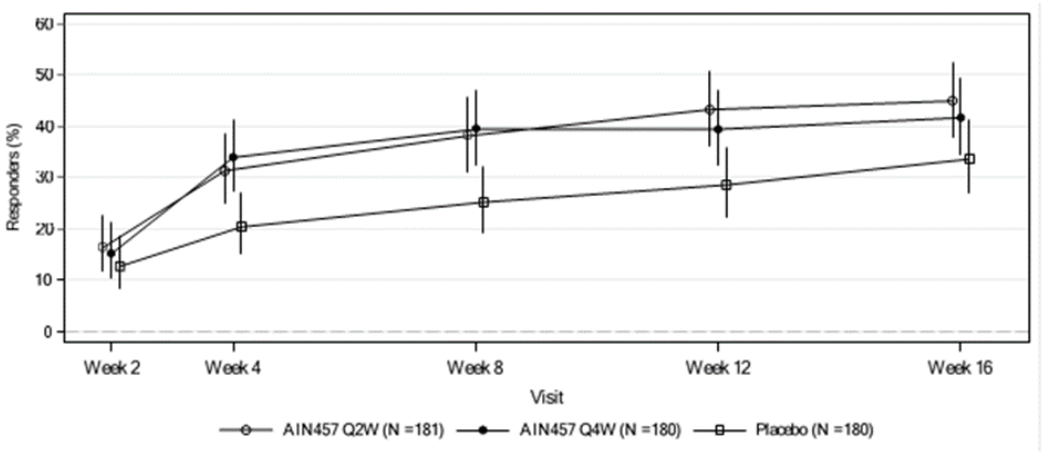
[1] Average over the 100 imputed datasets.
[2] OR (95% CI) and p-value based on logistic regression with treatment group, Hurley stage, geographical region, use of antibiotic, baseline body weight, and baseline AN count [HiSCR response].
Source: Table 14.2-1.1, in Study M2301 Week 16, appendix-M2301, Study M2302 Week 16, appendix-M2302 Table 14.2-1.1and reviewer's analysis

Figure 7 reports the trajectory of HiSCR50 in three treatment arms up to Week 16 in the two studies according to the applicant's analysis. In both studies, a rapid HiSCR50 response was observed as early as Week 2 for both secukinumab dose regimens. In M2301, secukinumab Q2W and secukinumab Q4W had similar response rate, both higher than placebo at all time points from Week 2 up to Week 16 (Figure 7A). In M2302, secukinumab Q4W had the highest response rate, followed by secukinumab Q2W and then placebo from Week 2 to Week 16 (Figure 7B). The FDA-requested analysis showed a similar trajectory (not shown).

Figure 7: HiSCR50 responders up to Week 16 (mean response rate with 95% CI) Primary Estimand, Multiple Imputation) by Study (Full Analysis Set)

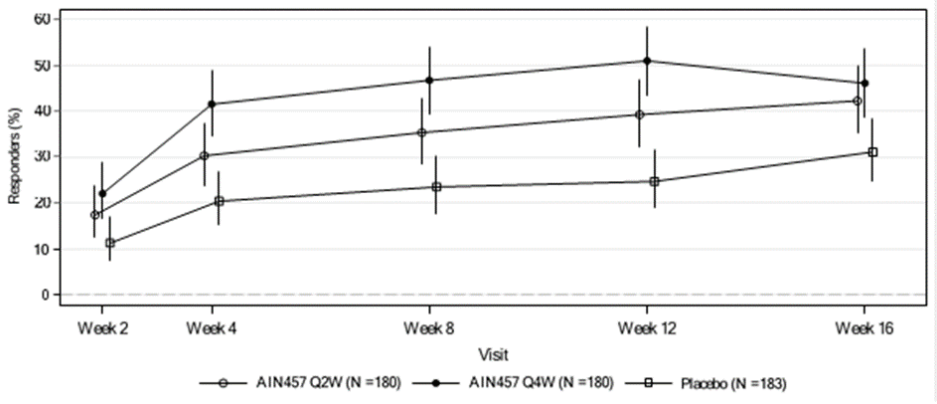
Applicant's Analysis

7A. Study M2301



Source: Study M2301 Figure 14.2-1.1.

7B. Study M2302:



Source: Study M2302 Figure 14.2-1.1.

Sensitivity Analysis Result for the Primary Efficacy Endpoint

Table 9 reports the sensitivity and supplementary analysis results of the applicant's analysis vs. the FDA-requested analysis for the primary efficacy endpoint HiSCR50 at Week 16 in the two studies. Table 9 shows that the applicant's sensitivity analysis for the primary endpoint using the weighted average across the screening and baseline visit assessments as the baseline value demonstrated similar results as the applicant's primary analysis (Table 8): both secukinumab dose regimens demonstrated a higher response (41.9% in the secukinumab Q2W and 38.3% in the secukinumab Q4W in M2301; 41.1% in the secukinumab Q2W and 44.4% in the secukinumab Q4W in M2302) compared to placebo (31.8% in M2301, and 28.7% in M2302) in both studies. However, similar to the result of the applicant's primary analysis (Table 7), secukinumab Q2W demonstrated statistical signific in both studies whereas Q4W only showed significance in Study M2302.

The FDA-requested sensitivity analysis results were similar to that of the applicant's analysis, however, same as the trend observed in the primary analysis (Table 8) for the same reason as

previously discussed, all the p values of the FDA-requested analysis were smaller than that of the applicant's analysis: In Study M2301, for secukinumab Q2W vs. placebo, p=0.0062 for the FDA-requested sensitivity analysis vs. p=0.031 in the applicant's sensitivity analysis; for secukinumab Q4W vs. placebo, p=0.0410 for the FDA-requested sensitivity analysis vs. p=0.167 in the applicant's sensitivity analysis. In Study 2302, for secukinumab Q2W vs. placebo in Study M2301, p=0.0060 for the FDA-requested sensitivity analysis vs. p=0.0128 in the applicant's sensitivity analysis; for secukinumab Q4W vs. placebo, p=0.0012 for the FDA-requested sensitivity analysis vs. p=0.0024 in the applicant's sensitivity analysis.

Supplementary Analysis Result for the Primary Efficacy Endpoint

The applicant specified supplementary analysis for the primary endpoint where all the intercurrent events were handled using a treatment policy strategy (Table 9). Table 9 shows that the applicant's supplementary analysis reported consistent results as the applicant's primary analysis for the primary endpoint (Table 8) except that the p value for secukinumab Q2W vs placebo in Study M2302 changed to 0.0456, which was slightly more than the pre-specified alpha for the Q2W vs placebo comparison 0.04.

The statistical reviewers also conducted supplementary analysis based on the applicant's primary analysis by handling ICE #1 (intake of prohibited medication/treatment) on a case-by-case basis where the clinical reviewer reviewed each event and recommended a specific strategy accordingly rather than the treatment policy strategy as in the applicant's primary analysis; in addition, for ICE #5 (permanent discontinuation of study treatment due to reasons other than adverse events or lack of efficacy), the statistical reviewer used the treatment policy strategy instead of the hypothetical strategy as in the applicant's primary analysis. Table 23 shows that the statistical reviewer's supplementary analysis also revealed a similar result as the applicant's primary analysis (Table 22).

Table 23: Sensitivity and Supplementary Analyses Results of the Primary Efficacy Endpoints HiSCR50 at Week 16 by Study (Full Analysis Set) by Applicant's Analysis vs. FDA-Requested Analysis

	Applicant's Analysis			**FDA Requested/ Reviewer**		
	Secukinumab			**Secukinumab**		
	Q2W (N=181)	**Q4W (N=180)**	**Placebo (N=180)**	**Q2W (N=181)**	**Q4W (N=180)**	**Placebo (N=180)**
			Study CAIN457M2301			
Sensitivity Analysis						
Rate[1]	41.9%	38.3%	31.8%	41.4%	38.0%	28.3%
OR (95% CI)[2]	1.64 (1.05, 2.57)	1.38 (0.87, 2.17)	-	1.89 (1.20, 2.99)	1.61 (1.02. 2.55)	
Two-sided P-value	**0.031**	0.167		**0.0062**	0.0410	

Supplementary Analysis (Applicant)						
Rate[1]	45.9%	41.2%	33.6%	46.0%	41.1%	33.7%
OR (95% CI)[2]	1.82 (1.17, 2.91)	1.45 (0.93, 2.27)	-	1.82 (1.17, 2.84)	1.44 (0.92, 2.26)	
Two-sided P-value	**0.0084**	0.1002		**0.0082**	0.1082	
Study CAIN457M2302						
	Q2W (N=180)	**QW4 (N=180)**	**Placebo (N=183)**	**Q2W (N=180)**	**QW4 (N=180)**	**Placebo (N=183)**
Sensitivity Analysis						
Rate[1]	41.1%	44.4%	28.7%	37.5%	40.7%	24.1%
OR (95% CI)[2]	1.77 (1.13, 2.79)	2.00 (1.28, 3.13)	-	1.92 (1.21, 3.07)	2.16 (1.35, 3.44)	
Two-sided P-value	**0.0128**	**0.0024**		**0.0061**	**0.0012**	
Supplementary Analysis (Applicant)						
Rate[1]	42.0%	46.1%	31.7%	42.1%	46.1%	31.8%
OR (95% CI)[2]	1.57 (1.01, 2.44)	1.85 (1.19, 2.88)	-	1.58 (1.02, 2.45)	1.84 (1.19, 2.87)	
Two-sided P-value	**0.0456***	**0.0061**		**0.0427**	**0.0064**	

[1] Average over the 100 imputed datasets.
[2] OR (95% CI) based on logistic regression with treatment group, Hurley stage, geographical region, use of antibiotic, baseline body weight,
and baseline AN count [HiSCR response].
*significant based on two-sided alpha 0.05 w/o multiplicity adjustment but not significant based on pre-specified two-sided alpha 0.04 for Q2W vs. placebo comparison w/ multiplicity adjustment for approval of only secukinumab dose regimen.
Source: Table 14.2-1.7, Table 14.2-1.6, in Study M2301 Week 16, appendix-M2301, Study M2302 Week 16, appendix-M2302, and reviewer's analysis

Data Quality and Integrity

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of Secukinumab (AIN457). We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Efficacy Results – Secondary and other relevant endpoints

Secondary Endpoints

Table 10 reports the primary analysis result of the applicant's analysis and the FDA-requested analysis for the secondary efficacy endpoints in Treatment Period 1 among the FAS in the two studies. According to the applicant's analysis, among the three secondary endpoints, based on the pre-specified multiplicity testing procedures, the secukinumab Q2W dose regimen met two secondary endpoints (AN50: p=0.0060, flare: p=0.0020) in M2301, and one secondary endpoint (AN50: p=0.0132) in M2302 (pre-specified two-sided alpha = 0.04 for the secukinumab Q2W vs. placebo comparison); The secukinumab Q4W dose regimen met two secondary endpoints

(AN50: p=0.0003, flare: p=0.0098) in M2302; However, despite showing a trend of higher response rates than placebo, secukinumab Q4W failed to meet the primary (p=0.0420, Table 8) or secondary endpoints (AN50: p=0.0119, Table 10) in M2301 based on the pre-specified alpha level for the secukinumab Q4W vs. placebo comparison: two-sided alpha 0.01.

According to the FDA-requested analysis, the results for the secondary endpoints were similar to the applicant's analysis except that all the p values were smaller as previously observed in Tables 8 and 9. Same as in the applicant's analysis, the secukinumab Q2W dose regimen also met two secondary endpoints (AN50: p=0.0009, flare: p=0.0003) in M2301 and one secondary endpoint (AN50: p=0.0072) in M2302 (pre-specified two-sided alpha = 0.04 for the secukinumab Q4W vs. placebo comparison); For the secukinumab Q4W dose regimen, it also met one secondary endpoint (AN50: p=0.0004) in Study M2302 (pre-specified two-sided alpha = 0.01). For Study M2301, even though the p value of the secukinumab Q4W vs. placebo comparison (p=0.0018) for AN50 at Week 16 in the FDA-requested analysis was improved compared to the applicant's analysis result (p=0.0119) and is less than the pre-specified alpha 0.01, according to the multiplicity testing sequence, the secukinumab Q4W dose regimen still did not meet secondary endpoint AN50 in M2301 because of the failing of the primary endpoint (p=0.0123 > pre-specified alpha 0.01, Table 8).

In details, according to the applicant's analysis, the secukinumab Q2W dose regimen showed statistically significant improvements compared to placebo with a higher rate of AN50 response in both studies (54.7% vs. 40.6%, two-sided p=0.0060 in M2301; 51.9% vs. 38.8%, two-sided p=0.0132 in M2302) and a lower cumulative proportion of subjects experiencing flares in M2301 (15.4% vs. 29.0%, two-sided p=0.0020 in M2301) after 16 weeks of treatment. The secukinumab Q4W dose regimen showed statistically significant improvements compared to placebo for these endpoints in M2302 (58.5% vs. 38.8%, two-sided p=0.0003 for AN50; 15.6% vs. 27.0%, two-sided p=0.0098 for flares), and showed a trend of improvement over placebo in these endpoints but did not meet the pre-specified statistical significance in M2301 (53.9% vs. 40.6%, p=0.0119 for AN50; 23.2% vs. 29.0%, two-sided p=0.1853 for flares). Both secukinumab dose regimens showed a higher rate of NRS30 response at Week 16 compared to placebo in both studies but statistical significance over placebo was not achieved (35.0% in Q2W and 34.6% in Q4W vs. 26.9% in placebo with two-sided p=0.1717 and 0.1931, respectively, in M2301; 42.3% in Q2W and 37.4% in Q4W vs. 26.8% in placebo with two-sided p=0.0149 and 0.1174, respectively, in M2302). (Table 9)

Likewise, according to the FDA-requested analysis, the secukinumab Q2W dose regimen showed statistically significant improvements compared to placebo with a higher rate of AN50 response in both studies (52.4% vs. 35.5%, two-sided p=0.0009 in M2301; 47.3% vs. 33.0%, two-sided p=0.0072 in M2302) and a lower cumulative proportion of subjects experiencing flares in M2301 (19.2% vs. 36.1%, two-sided p=0.0003 in M2301) after 16 weeks of treatment. The secukinumab Q4W dose regimen showed statistically significant improvements compared to placebo for AN50 in both studies(51.6% vs. 35.5%, two-sided p=0.0018 in M2301; 52.0% vs. 33.0%, two-sided p=0.0004 in M2302), and a lower cumulative proportion of subjects experiencing flares but did not meet the pre-specified statistical significance in either study

(24.8% vs. 36.1%, p=0.0152 in M2301; 24.3% vs. 35.2%, two-sided p=0.0275 in M2302). Both secukinumab dose regimens showed a higher rate of NRS30 response at Week 16 compared to placebo in both studies but statistical significance over placebo was not achieved (33.0% in Q2W and 31.8% in Q4W vs. 19.0% in placebo with two-sided p=0.0102 and 0.0190, respectively, in M2301; 36.9% in Q2W and 31.1% in Q4W vs. 18.1% in placebo with two-sided p=0.0011 and 0.0209, respectively, in M2302). (Table 24)

Table 24: Primary Analysis Results of the Secondary Efficacy Endpoints (Secondary Estimand, Multiple Imputation) in Treatment Period 1 by Study (Full Analysis Set)

by Applicant's Analysis vs. FDA-requested Analysis

	Applicant's Analysis			**FDA-Requested Analysis**		
	Secukinumab			**Secukinumab**		
	Q2W (N=181)	**Q4W (N=180)**	**Placebo (N=180)**	**Q2W (N=181)**	**Q4W (N=180)**	**Placebo (N=180)**
Study CAIN457M2301						
Secondary Endpoints:						
AN50 at Week 16						
Rate[1]	54.7%	53.9%	40.6%	52.4%	51.6%	35.5%
OR (95% CI)[2]	1.83 (1.19, 2.83)	1.74 (1.13, 2.69)	-	2.11 (1.36, 3.27)	2.01 (1.30, 3.12)	-
Two-sided P-value[2]	**0.0060**	0.0119	-	**0.0009**	**0.0018**	-
Flares over 16 weeks						
Rate[1]	15.4%	23.2%	29.0%	19.2%	24.8%	36.1%
OR (95% CI)[2]	0.42 (0.25, 0.73)	0.71 (0.43, 1.17)	-	0.39 (0.24, 0.65)	0.55 (0.34, 0.89)	-
Two-sided P-value[2]	**0.0020**	0.1853	-	**0.0003**	0.0152	-
Skin Pain/NRS30 Response at Week 16						
N[3]	110	107	110	131	123	119
Rate[1]	35.0%	34.6%	26.9%	33.0%	31.8%	19.0%
OR (95% CI)[2]	1.55 (0.83, 2.92)	1.54 (0.80, 2.93)	-	2.32 (1.22, 4.40)	2.19 (1.14, 4.20)	-
Two-sided P-value[2]	0.1717	0.1931	-	0.0102	0.0190	-

Study CAIN457M2302

	Q2W (N=180)	**Q4W (N=180)**	**Placebo (N=183)**	**Q2W (N=180)**	**Q4W (N=180)**	**Placebo (N=183)**
Secondary Endpoints:						

AN50 at Week 16						
Rate[1]	51.9%	58.5%	38.8%	47.3%	52.0%	33.0%
OR (95% CI)[2]	1.74	2.26		1.83	2.22	
	(1.12, 2.68)	(1.46, 3.50)	-	(1.18, 2.85)	(1.43, 3.46)	-
Two-sided P-value[2]	**0.0132**	**0.0003**	-	**0.0072**	**0.0004**	-
Flares over 16 weeks						
Rate[1]	20.1%	15.6%	27.0%	25.0%	24.3%	35.2%
OR (95% CI)[2]	0.68	0.49		0.63	0.59	
	(0.41, 1.14)	(0.29, 0.84)	-	(0.39, 1.01)	(0.37, 0.94)	-
Two-sided P-value[2]	0.1464	**0.0098**	-	0.0537	0.0275	-
Skin Pain/NRS30 Response at Week 16						
N[3]	123	115	120	135	129	132
Rate[1]	42.3%	37.4%	26.8%	36.9%	31.1%	18.1%
OR (95% CI)[2]	2.06	1.61		2.75	2.10	
	(1.15, 3.68)	(0.89, 2.93)	-	(1.50, 5.04)	(1.12, 3.94)	-
Two-sided P-value[2]	0.0149	0.1174		0.0011	0.0209	-

[1] Average over the 100 imputed datasets.
[2] OR (95% CI) and p-value based on logistic regression with treatment group, Hurley stage, geographical region, use of antibiotic, baseline body weight, and baseline AN count
[AN50, and Flare endpoints] or baseline Pain NRS score [NRS30 endpoint].
[3] Subjects with a baseline Pain NRS score ≥ 3.
Source: Table 14.2-2.1b, Table 14.2-3.1, Table 14.2-5.1 in Study M2301 Week 16, Appendix- M2301, Study M2302 Week16, and Appendix_M2302, and Reviewer's analysis

Sensitivity Analysis for Secondary Endpoints

The sensitivity analysis of the applicant's analysis and the FDA-requested analysis for the secondary endpoints using the weighted average across screening and baseline visit assessments as baseline value demonstrated similar results as the primary analysis (result not shown).

Dose/Dose Response

Table 25 summarizes the primary analysis results of the applicant's analysis and the FDA-requested analysis for the primary and secondary efficacy endpoints in the two studies as follows.

Table 25: Summary of Primary Analysis Results for Primary and Secondary Efficacy Endpoints in Treatment Period 1 by Study (Full Analysis Set)

by Applicant's Analysis and FDA-Requested Analysis

	Applicant's Analysis			FDA-Requested Analysis		
	Secukinumab			Secukinumab		
	Q2W (N=181)	Q4W (N=180)	Placebo (N=180)	Q2W (N=181)	Q4W (N=180)	Placebo (N=180)
Study CAIN457M2301						
Primary Endpoint:						
HiSCR Response at Week 16						
Rate[1]	45.0%	41.8%	33.7%	44.5%	41.3%	29.4%
OR (95% CI)[2]	1.75 (1.12, 2.73)	1.48 (0.95, 2.32)	-	2.10 (1.33, 3.22)	1.79 (1.14, 2.83)	-
Two-sided P-value[2]	**0.0140**	0.0835	-	**0.0014**	0.0123	-
Secondary Endpoints:						
AN50 at Week 16						
Rate[1]	54.7%	53.9%	40.6%	52.4%	51.6%	35.5%
OR (95% CI)[2]	1.83 (1.19, 2.83)	1.74 (1.13, 2.69)	-	2.11 (1.36, 3.27)	2.01 (1.30, 3.12)	-
Two-sided P-value[2]	**0.0060**	0.0119	-	**0.0009**	0.0018	-
Flares over 16 weeks						
Rate[1]	15.4%	23.2%	29.0%	19.2%	24.8%	36.1%
OR (95% CI)[2]	0.42 (0.25, 0.73)	0.71 (0.43, 1.17)	-	0.39 (0.24, 0.65)	0.55 (0.34, 0.89)	-
Two-sided P-value[2]	**0.0020**	0.1853	-	**0.0003**	0.0152	-
Skin Pain/NRS30 Response at Week 16						
N[3]	110	107	110	131	123	119
Rate[1]	35.0%	34.6%	26.9%	33.0%	31.8%	19.0%
OR (95% CI)[2]	1.55 (0.83, 2.92)	1.54 (0.80, 2.93)	-	2.32 (1.22, 4.40)	2.19 (1.14, 4.20)	-
Two-sided P-value[2]	0.1717	0.1931	-	0.0102	0.0190	-

Study CAIN457M2302						
	Q2W (N=180)	Q4W (N=180)	Placebo (N=183)	Q2W (N=180)	Q4W (N=180)	Placebo (N=183)
HiSCR Response at Week 16						
Rate[1]	42.3%	46.1%	31.2%	38.3%	42.5%	26.1%
OR (95% CI)[2]	1.64 (1.05, 2.55)	1.90 (1.22, 2.96)	-	1.77 (1.12, 2.80)	2.10 (1.33, 3.32)	-

Two-sided P-value[2]	**0.0299**	**0.0044**	-	**0.0145**	**0.0015**	-
Secondary Endpoints:						
AN50 at Week 16						
Rate[1]	51.9%	58.5%	38.8%	47.3%	52.0%	33.0%
OR (95% CI)[2]	1.74 (1.12, 2.68)	2.26 (1.46, 3.50)	-	1.83 (1.18, 2.85)	2.22 (1.43, 3.46)	-
Two-sided P-value[2]	**0.0132**	**0.0003**	-	**0.0072**	**0.0004**	-
Flares over 16 weeks						
Rate[1]	20.1%	15.6%	27.0%	25.0%	24.3%	35.2%
OR (95% CI)[2]	0.68 (0.41, 1.14)	0.49 (0.29, 0.84)	-	0.63 (0.39, 1.01)	0.59 (0.37, 0.94)	-
Two-sided P-value[2]	0.1464	**0.0098**	-	0.0537	0.0275	-
Skin Pain/NRS30 Response at Week 16						
N[3]	123	115	120	135	129	18.1%
Rate[1]	42.3%	37.4%	26.8%	36.9%	31.1%	
OR (95% CI)[2]	2.06 (1.15, 3.68)	1.61 (0.89, 2.93)	-	2.75 (1.50, 5.04)	2.10 (1.12, 3.94)	-
Two-sided P-value[2]	0.0149	0.1174		0.0011	0.0209	-

[1] Average over the 100 imputed datasets.
[2] OR (95% CI) and p-value based on logistic regression with treatment group, Hurley stage, geographical region, use of antibiotic, baseline body weight, and baseline AN count [HiSCR response, AN50, and Flare endpoints] or baseline Pain NRS score [NRS30 endpoint].
[3] Subjects with a baseline Pain NRS score ≥ 3.
Source: Table 14.2-1.1, Table 14.2-2.1b, Table 14.2-3.1, Table 14.2-5.1 in Study M2301 Week 16, Appendix-M2301, Study M2302 Week 16, Appendix-M2302, and Reviewer's analysis

Table 25 shows that,

1. According to both the applicant's analysis and the FDA-requested analysis, the secukinumab Q2W dose regimen met the primary (HiSCR50) and two secondary endpoints (AN50 and flare) in M2301, and primary (HiSCR50) and one secondary endpoint (AN50) in M2302 based on the pre-specified alpha level for the secukinumab Q2W vs. placebo comparison (alpha=0.04); The secukinumab Q4W dose regimen met the primary (HiSCR50) and two secondary endpoints (AN50 and flare) in M2302 but failed to meet the primary or secondary endpoints in M2301 based on the pre-specified alpha level for the secukinumab Q4W vs. placebo comparison (alpha=0.01) despite showing a trend of higher response rates than placebo.

However, in the FDA-requested analysis, the p value of the secukinumab Q4W vs. placebo comparison for the primary endpoint (HiSCR50: p=0.0123) just missed the pre-specified alpha (0.01) slightly; and the p value of the secukinumab Q4W vs. placebo comparison for the first secondary endpoint AN50 at Week 16 (p=0.0018) was smaller than the pre-specified alpha (0.01).

2. Between the secukinumab Q2W and Q4W dose regimens, according to both the applicant's analysis and the FDA-requested analysis, secukinumab Q2W had slightly better response rates than secukinumab Q4W in Study M2301 (*HiSCR50*: 45.0% in Q2W vs. 41.8% in Q4W for the applicant's analysis, 44.5% in Q2W vs. 41.3% in Q4W for the FDA-requested analysis – higher is better; *AN50*: 54.7% in Q2W vs. 53.9% in Q4W for the applicant's analysis; 52.4% in Q2W vs. 51.6% in Q4W for the FDA-requested analysis – higher is better; *Flares*: 15.4% in Q2W vs. 23.2% in Q4W for the applicant's analysis, 19.2% in Q2W vs. 24.8% in Q4W for the FDA-requested analysis – lower is better);

On the other hand, Q4W had slightly better response rates than Q2W in Study M2302 based to both the applicant's analysis and the FDA-requested analysis: (***HiSCR50***: 42.3% in Q2W vs. 46.1% in Q4W for the applicant's analysis, 38.3% in Q2W vs. 42.5% in Q4W for the FDA-requested analysis – higher is better; ***AN50***: 51.9% in Q2W vs. 58.5% in Q4W for the applicant's analysis, 47.3% in Q2W vs. 52.0% in Q4W for the FDA-requested analysis – higher is better; ***Flares***: 20.1% in Q2W vs. 15.6% in Q4W for the applicant's analysis, 25.0% in Q2W vs. 24.3% in Q4W for the FDA-requested analysis – lower is better).

Statistical Reviewers' Comment on Observed Lower Efficacy of Secukinumab Q4W vs. Placebo in Study M2301 than in Study M2302

The observed lower efficacy of secukinumab Q4W vs. placebo in Study M2301 (p=0.0835 in the applicant's analysis and p=0.0123 in the FDA-requested analysis) than that in Study M2302 (p=0.0044 in the applicant's analysis and p=0.0015 in the FDA-requested analysis) are likely due to the following reasons.

- *Between the two studies, subjects in the placebo arm of Study M2301 were milder (28.3% with baseline Hurley Stage III) than those in Study M2302 (38.3% with baseline Hurley Stage III) (Table 5). Accordingly, the response rate of the placebo group in Study M2301 was slightly higher (33.7% in the applicant's analysis, 29.4% in the FDA-requested analysis) than that in Study M2302 (31.2% in the applicant's analysis, 26.1% in the FDA-requested analysis) (Table 11), likely due to the higher placebo effect in the former with milder subjects. This made it harder to meet statistical significance for secukinumab Q4W in Study M2301 than in Study M2302.*

- *In Study M2302, secukinumab Q4W and placebo had similar severity level at baseline: baseline Hurley Stage III 37.8% in secukinumab Q4W vs. 38.3% in placebo (Table 4); However, in Study M2301, secukinumab Q4W was comprised of more severe subjects than placebo: baseline Hurley Stage III 35.0% in secukinumab Q4W vs. 28.3% in placebo. Note that baseline Hurley Stage III was highly significantly associated with the HiSCR50 response rate based on reviewers' additional multivariate regression analysis (p<.0001, result not shown): those with more severe Hurley stages were associated with lower HiSCR50 response. The more severe subjects of secukinumab Q4W than those of placebo in Study M2301 made it harder to establish efficacy for secukinumab Q4W in Study 2301 than in Study M2302 where the two were balanced.*

Statistical Reviewers' Comment on the Observed Inconsistent Trend of Efficacy for Secukinumab Q2W vs. Q4W in Study M2301 (Q2W is Better) vs. Study M2302 (Q4W is Better)

As discussed above, in Study M2301, secukinumab Q2W seemed to have a better efficacy than secukinumab Q4W whereas in Study M2302, secukinumab Q4W seemed to have a better efficacy than secukinumab Q2W. The observed inconsistent trend of efficacy for secukinumab Q2W vs. Q4W between the two studies can be explained by the following considerations.

- *In Study M2301, secukinumab Q2W had slightly more severe level at baseline than secukinumab Q4W: baseline Hurley Stage III of 38.7% in secukinumab Q2W vs. 35.0% in secukinumab Q4W; however, in Study M2302, secukinumab Q2W had much more severe level than secukinumab Q4W: baseline Hurley Stage III of 45.6% in Q2W vs. 37.8% in Q4W, which made it harder for secukinumab Q2W to be more efficacious than Q4W in Study M2302 (Table 5).*

- *Secukinumab Q2W seemed to have reached plateau in efficacy: according to the applicant's analysis, the response rate for HiSCR50 in secukinumab Q2W in Study M2301 (45.0%) was similar to that of secukinumab Q4W in Study M2302 (46.1%) whereas the response rate for HiSCR50 in secukinumab Q4W in Study M2301 (41.8%) was close to that of secukinumab Q2W in Study M2302 (42.3%). (Table 11)*

Statistical Reviewers' Comment on Clinical Reviewer's Recommendation to Use Q4W first and then increase to Q2W if not adequately responding

Between the two secukinumab dose regimens, the clinical reviewers recommended to use the secukinumab 300 mg every 4 weeks (Q4W) first, and if a patient does not adequately respond, then consider increasing the secukinumab dosage to every 2 weeks (Q2W).

Statistical reviewers agree with the clinical reviewers' recommendation from the following statistical perspective.
1) The efficacy results for the two secukinumab doses (Q2W and Q4W) are close to each other for the primary and secondary points (Table 11);

2)The statistical significance of the FDA-requested analysis for HiSCR50 (p=0.0123) is only slightly greater than the pre-specified alpha of 0.01 for the Q4W vs. placebo comparison. For AN50, the FDA-requested analysis had a p value (p=0.0018) that is much smaller than the pre-specified alpha 0.01.

3) The lower efficacy result for secukinumab Q4W vs. placebo in Study M2301 than in Study 2302 is likely due to the imbalanced distribution of baseline severity level between secukinumab Q4W and placebo among the two studies, i.e., the milder placebo subjects (subject to higher

placebo effect) in Study M2301 than in Study M2302 and the more severe baseline level in the secukinumab Q4W subjects than the placebo subjects in Study 2301 (Table 5);

4) The observed inconsistent trend of efficacy for secukinumab Q2W vs. Q4W in Study M2301 (Q2W is better than Q4W) and Study M2302 (Q4W is better than Q2W) can be explained by the plateau effect of secukinumab Q2W and the more severe baseline level in the secukinumab Q2W subjects than the secukinumab Q4W subjects in Study M2302.

Therefore, the Statistical reviewers agree with the clinical reviewers' recommendation to use the secukinumab 300 mg every 4 weeks (Q4W) first, and if a patient does not adequately respond, then consider increasing the secukinumab dosage to every 2 weeks (Q2W).

Persistence of Effect

The applicant's long-term response rate of the primary endpoint HiSCR50 up to Week 52 was reported in Table 26. It shows that the primary endpoint HiSCR50 demonstrated persistent efficacy for both secukinumab dose regimens from Week 16 through Week 52: At Week 16, 47.9% with Q2W and 42.1% with Q4W in Study M2301, 42.5% with Q2W and 47.6% with Q4W in M2302; At Week 52, 55.4% with Q2W and 55.9% with Q4W in Study M2301; 66.3% with Q2W and 64.9% with Q4W in Study 2302). In addition, a trend for an increase in HiSCR50 response was seen over time in both the secukinumab dose groups in both studies (e.g., 47.9% at Week 16 vs. 55.4% at Week 52 for Q2W in Study M2301, 55.9% at Week 16 vs. 64.9% at Week 52 for Q4W in Study M2302).

Table 26: Number (%) of subjects with HiSCR Response by Visit Up to Week 52 by Study (Full Analysis Set)

	M2301 AIN457 Q2W N=181		AIN457 Q4W N=180		M2302 AIN457 Q2W N=181		AIN457 Q4W N=180	
Visit	n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Week 2	29/174	(16.7)	26/170	(15.3)	30/174	17.2	39/176	22.2
Week 4	55/172	(32.0)	59/173	(34.1)	53/175	30.3	74/176	42.0
Week 8	66/171	(38.6)	67/170	(39.4)	62/175	35.4	81/172	47.1
Week 12	74/167	(44.3)	65/167	(38.9)	67/170	39.4	88/170	51.8
Week 16	78/163	(47.9)	69/164	(42.1)	71/167	42.5	79/166	47.6
Week 18	83/158	(52.5)	75/155	(48.4)	69/148	46.6	80/150	53.3
Week 20	88/155	(56.8)	82/159	(51.6)	83/158	52.5	77/153	50.3
Week 24	93/158	(58.9)	80/159	(50.3)	67/147	45.6	84/147	57.1
Week 28	88/154	(57.1)	84/152	(55.3)	76/135	56.3	75/142	52.8
Week 32	93/145	(64.1)	83/148	(56.1)	84/135	62.2	76/131	58.0
Week 36	87/139	(62.6)	81/139	(58.3)	69/124	55.6	72/120	60.0
Week 40	83/134	(61.9)	78/139	(56.1)	71/124	57.3	66/113	58.4
Week 44	79/137	(57.7)	74/136	(54.4)	77/116	66.4	60/111	54.1
Week 48	78/131	(59.5)	77/129	(59.7)	74/114	64.9	60/101	59.4

Week 52	62/112	(55.4)	66/118	(55.9)	65/98	66.3	61/ 94	64.9

- n = number of subjects with observed response.
- m = number of subjects evaluable.
Source: Source:[Study 2301 Week 52 Table 14.2-1.4] [Study 2302 Week 52 Table 14.2-1.4]

Similar persistent efficacy was demonstrated for secondary endpoints AN50 (Table 27) and flares (Table 28) through Week 52 for both secukinumab regimens in both studies. Similar to HiSCR50, AN50 also showed a trend for an improvement up to Week 52 in general.

Table 27: Number (%) of subjects with AN50 Response by Visit Up to Week 52 by Study (Full Analysis Set)

	M2301 AIN457 Q2W N=181		AIN457 Q4W N=180		M2302 AIN457 Q2W N=181		AIN457 Q4W N=180	
Visit	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**
Week 2	33/174	19.0	29/170	17.1	36/174	(20.7)	46/176	(26.1)
Week 4	61/172	35.5	69/173	39.9	66/175	(37.7)	79/176	(44.9)
Week 8	80/171	46.8	78/170	45.9	79/175	(45.1)	90/172	(52.3)
Week 12	88/167	52.7	83/167	49.7	85/170	(50.0)	104/170	(61.2)
Week 16	93/163	57.1	90/164	54.9	87/167	(52.1)	99/166	(59.6)
Week 18	98/158	62.0	92/155	59.4	82/149	(55.0)	98/150	(65.3)
Week 20	111/155	71.6	96/159	60.4	102/162	(63.0)	92/156	(59.0)
Week 24	114/158	72.2	95/159	59.7	90/157	(57.3)	110/155	(71.0)
Week 28	106/154	68.8	97/152	63.8	99/150	(66.0)	104/154	(67.5)
Week 32	112/145	77.2	102/148	68.9	103/153	(67.3)	105/149	(70.5)
Week 36	102/139	73.4	91/139	65.5	98/146	(67.1)	94/137	(68.6)
Week 40	104/134	77.6	93/139	66.9	107/149	(71.8)	91/133	(68.4)
Week 44	97/137	70.8	89/136	65.4	103/147	(70.1)	90/136	(66.2)
Week 48	89/131	67.9	92/129	71.3	104/147	(70.7)	86/128	(67.2)
Week 52	78/112	69.6	85/118	72.0	90/127	(70.9)	84/119	(70.6)

- n = number of subjects with observed response.
- m = number of subjects evaluable.
Source: Source:[Study 2301 Week 52 Table 14.2-2.4b] [Study 2302 Week 52 Table 14.2-2.4b]

Table 28: Number (%) of subjects with Flares by Visit Up to Week 52 by Study (Full Analysis Set)

	M2301 AIN457 Q2W N=181		AIN457 Q4W N=180		M2302 AIN457 Q2W N=181		AIN457 Q4W N=180	
Visit	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**	**n/m**	**(%)**
Week 2	13/104	(12.5)	12/105	(11.4)	17/116	(14.7)	22/111	(19.8)
Week 4	31/101	(30.7)	17/97	(17.5)	29/115	(25.2)	24/106	(22.6)
Week 8	35/98	(35.7)	21/92	(22.8)	39/109	(35.8)	30/99	(30.3)
Week 12	42/97	(43.3)	29/86	(33.7)	44/106	(41.5)	33/90	(36.7)

Week 16	33/91	(36.3)	29/81	(35.8)	47/110	(42.7)	35/91	(38.5)
Week 18	49/102	(48.0)	42/101	(41.6)	55/117	(47.0)	48/109	(44.0)
Week 20	45/101	(44.6)	39/96	(40.6)	50/115	(43.5)	44/100	(44.0)
Week 24	45/96	(46.9)	39/98	(39.8)	55/112	(49.1)	46/94	(48.9)
Week 28	49/96	(51.0)	39/97	(40.2)	53/107	(49.5)	52/97	(53.6)
Week 32	43/91	(47.3)	38/91	(41.8)	55/106	(51.9)	48/93	(51.6)
Week 36	49/86	(57.0)	37/83	(44.6)	56/103	(54.4)	44/89	(49.4)
Week 40	47/81	(58.0)	40/81	(49.4)	57/101	(56.4)	46/85	(54.1)
Week 44	49/83	(59.0)	37/78	(47.4)	56/97	(57.7)	40/81	(49.4)
Week 48	44/80	(55.0)	38/76	(50.0)	56/94	(59.6)	39/80	(48.8)
Week 52	40/76	(52.6)	33/68	(48.5)	51/90	(56.7)	43/75	(57.3)

- n = number of subjects observed response.
- m = number of subjects evaluable.
- NRS is the numeric rating scale of the Patient's Global Assessment of Skin Pain - at worst
- Only subjects with a baseline NRS ≥ 3 are included.

Source: Study 2301 Week 52 Table 14.2-5.4, Study 2302 Week 52 Table 14.2-5.4.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses of Primary Endpoint

Subgroup Analyses based on the applicant's analysis and the FDA-requested analysis for the primary and the secondary efficacy endpoints was carried out by stratification variables (current antibiotic use (Yes/No), body weight stratum (< 90kg, ≥ 90kg), geographical region, and other subgroups like age (<65 or ≥65 years), gender, race, disease duration (<2 years, 2 to <5 years, 5 to <10 years, ≥10 years), previous exposure to biologics, baseline AN count (≤10, >10), and baseline Hurley stage for both studies (Tables 16 and 17).

According to both the applicant's analysis and the FDA-requested analysis, subgroup analyses performed on the primary endpoint showed that HiSCR50 response rates were generally higher in the secukinumab Q2W and secukinumab Q4W groups compared to the placebo group across all stratification factors (geographical region, concomitant antibiotic treatment, and baseline body weight) and other subgroups in both studies (Tables 29 and 30). Note that some subgroups had limited number of subjects and results of these subgroups should be interpreted with caution. For example, regions AMEA, LaCAN, and US had small sample sizes (<30 subjects in each treatment group) and the observed effect and the variation in placebo response should be interpreted with caution. In addition, statistical reviewers' additional exploratory analyses shows that the imbalanced distribution of the baseline severity level (Hurley stage) among the three treatment groups in regions with a small sample size also helped to explain the observed variation in the treatment effect in these regions.

Table 29: Subgroup Analysis for Primary Endpoint HiSCR50 Response at Week 16 in Study M2301 (Full Analysis Set) by Applicant's Analysis vs. FDA-Requested Analysis

		Applicant's Analysis				FDA-Requested Analysis			
Subgroup	Treatment	Response Rate	Comparator	Odds Ratio	95% CI for Odds Ratio	Response Rate	Comparator	Odds Ratio	95% CI for Odds Ratio
Current antibiotic use									
N	AIN457 Q2W (m=155)	45.4	Placebo	1.51	(0.95, 2.40)	45.4	Placebo	1.88	(1.17, 3.02)
	AIN457 Q4W (m=155)	42.0	Placebo	1.31	(0.82, 2.09)	41.5	Placebo	1.60	(0.99, 2.58)
	Placebo (m=162)	35.4				30.6			
Y	AIN457 Q2W (m=26)	42.7	Placebo	3.34	(0.75, 14.76)	39.0	Placebo	2.84	(0.64, 12.65)
	AIN457 Q4W (m=25)	40.0	Placebo	3.63	(0.79, 16.60)	40.0	Placebo	3.54	(0.78, 16.19)
	Placebo (m=18)	18.2				18.6			
Weight									
< 90 kg	AIN457 Q2W (m=82)	38.4	Placebo	1.03	(0.54, 1.96)	37.1	Placebo	1.23	(0.64, 2.38)
	AIN457 Q4W (m=80)	38.3	Placebo	1.03	(0.53, 1.99)	37.4	Placebo	1.25	(0.64, 2.45)
	Placebo (m=83)	36.9				31.7			
>= 90 kg	AIN457 Q2W (m=99)	50.6	Placebo	2.34	(1.28, 4.27)	50.6	Placebo	2.78	(1.50, 5.15)
	AIN457 Q4W (m=100)	44.5	Placebo	1.81	(1.00, 3.29)	44.5	Placebo	2.15	(1.17, 3.95)
	Placebo (m=97)	30.9				27.4			
Region									
AMEA	AIN457 Q2W (m=29)	48.3	Placebo	2.95	(0.96, 9.06)	48.3	Placebo	3.62	(1.14, 11.56)
	AIN457 Q4W (m=30)	40.0	Placebo	2.27	(0.73, 7.03)	40.0	Placebo	2.74	(0.85, 8.78)
	Placebo (m=31)	22.6				19.4			
RE	AIN457 Q2W (m=111)	44.9	Placebo	1.66	(0.94, 2.91)	43.9	Placebo	1.87	(1.05,3.33)
	AIN457 Q4W (m=111)	43.0	Placebo	1.53	(0.87, 2.69)	42.3	Placebo	1.75	(0.99, 3.10)
	Placebo (m=112)	33.1				29.7			
LaCAN	AIN457 Q2W (m=11)	45.5	Placebo	1.77	(0.28, 11.16)	45.5	Placebo	3.05	(0.42, 22.19)
	AIN457 Q4W (m=12)	25.0	Placebo	0.66	(0.09, 4.74)	25.0	Placebo	1.13	(0.14, 9.31)
	Placebo (m=10)	30.0				20.0			
US	AIN457 Q2W (m=30)	42.4	Placebo	0.67	(0.22, 2.03)	42.7	Placebo	0.92	(0.30, 2.82)
	AIN457 Q4W (m=27)	45.9	Placebo	0.77	(0.25, 2.39)	45.9	Placebo	1.03	(0.33, 3.23)
	Placebo (m=27)	50.2				43.0			
Hurley Stage									
Stage I	AIN457 Q2W (m=7)	71.4	Placebo	1.99	(0.18, 21.75)	71.4	Placebo	3.85	(0.35, 42.79)
	AIN457 Q4W (m=10)	61.7	Placebo	1.08	(0.11, 10.69)	61.6	Placebo	2.23	(0.24, 20.70)
	Placebo (m=8)	57.9				43.6			
Stage II	AIN457 Q2W (m=104)	50.1	Placebo	1.71	(0.99, 2.96)	49.2	Placebo	1.96	(1.13, 3.40)
	AIN457 Q4W (m=107)	45.2	Placebo	1.40	(0.81, 2.41)	45.0	Placebo	1.65	(0.95, 2.85)
	Placebo (m=121)	36.9				33.1			
Stage III	AIN457 Q2W (m=70)	34.8	Placebo	1.80	(0.77, 4.22)	34.8	Placebo	2.33	(0.95, 5.71)
	AIN457 Q4W (m=63)	32.8	Placebo	1.52	(0.63, 3.68)	31.8	Placebo	1.87	(0.74, 4.70)
	Placebo (m=51)	22.2				18.2			
Age group									

	AIN457 Q4W (m=69)	44.2	Placebo	1.40	(0.64, 3.06)	44.3	Placebo	1.62	(0.73, 3.60)
	Placebo (m=51)	35.4				32.3			
30-<40	AIN457 Q2W (m=56)	44.2	Placebo	2.03	(0.96, 4.29)	48.6	Placebo	2.95	(1.35, 6.44)
	AIN457 Q4W (m=45)	48.7	Placebo	1.08	(0.48, 2.45)	33.9	Placebo	1.57	(0.87, 3.66)
	Placebo (m=70)	31.9				24.4			
≥40	AIN457 Q2W (m=67)	35.0	Placebo	1.09	(0.51, 2.32)	35.0	Placebo	1.18	(0.55, 2.53)
	AIN457 Q4W (m=66)	44.5	Placebo	1.54	(073, 3.24)	43.3	Placebo	1.58	(0.75, 3.36)
	Placebo (m=59)	34.3				32.7			
Gender									
M	AIN457 Q2W (m=79)	49.3	Placebo	2.39	(1.20, 4.79)	49.2	Placebo	2.80	(1.39, 5.64)
	AIN457 Q4W (m=80)	35.0	Placebo	1.32	(0.65, 2.66)	35.0	Placebo	1.55	(0.76, 3.14)
	Placebo (m=78)	29.7				26.5			
F	AIN457 Q2W (m=102)	41.7	Placebo	1.23	(0.69, 2.18)	40.8	Placebo	1.49	(0.83, 2.68)
	AIN457 Q4W (m=100)	47.2	Placebo	1.55	(0.87, 2.78)	46.4	Placebo	1.90	(1.05, 3.44)
	Placebo (m=102)	36.7				31.5			
Race									
White	AIN457 Q2W (m=145)	46.5	Placebo	1.99	(0.18, 21.75)	45.8	Placebo	2.14	(1.28, 3.56)
	AIN457 Q4W (m=146)	41.7	Placebo	1.08	(0.11, 10.69)	41.2	Placebo	1.75	(1.05, 2.92)
	Placebo (m=139)	32.8				28.7			
Black or Africa American	AIN457 Q2W (m=15)	54.2	Placebo	1.79	(034, 9.41)	54.2	Placebo	2.37	(0.44, 12.90)
	AIN457 Q4W (m=10)	42.1	Placebo	1.06	(0.17, 6.63)	42.7	Placebo	149	(0.23, 9.48)
	Placebo (m=12)	41.7				33.3			
Other	AIN457 Q2W (m=21)	28.6	Placebo	0.59	(0.17, 2.09)	28.6	Placebo	0.72	(0.20, 256)

	AIN457 Q4W (m=24)	41.7	Placebo	1.25	(0.38, 4.06)	41.7	Placebo	1.47	(0.45, 4.81)
	Placebo (m=29)	34.5				31.0			
Previous Exposure to Biologics									
N	AIN457 Q2W (m=137)	49.0	Placebo	1.74	(1.55, 2.08)	49.0	Placebo	2.19	(1.31, 3.66)
	AIN457 Q4W (m=141)	44.1	Placebo	1.42	(0.86, 2.35)	44.0	Placebo	1.78	(1.07, 2.98)
	Placebo (m=134)	35.6				30.5			
Y	AIN457 Q2W (m=44)	32.8	Placebo	1.27	(0.51, 3.19)	30.6	Placebo	1.30	(0.51, 3.31)
	AIN457 Q4W (m=39)	33.2	Placebo	1.28	(0.50, 3.29)	31.7	Placebo	1.33	(0.51, 3.46)
	Placebo (m=36)	28.3				26.1			
Disease duration									
<2	AIN457 Q2W (m=10)	40.0	Placebo	0.37	(0.04, 3.38)	40.0	Placebo	0.51	(0.05, 5.35)
	AIN457 Q4W (m=4)	100.0	Placebo			100.0	Placebo		
	Placebo (m=8)	50.0				37.5			
2- <5	AIN457 Q2W (m=28)	53.5	Placebo	2.21	(0.72, 6.82)	53.1	Placebo	2.70	(0.87, 8.36)
	AIN457 Q4W (m=28)	47.3	Placebo	1.72	(0.54, 5.41)	47.4	Placebo	2.14	(0.68, 6.74)
	Placebo (m=35)	31.2				27.4			
5 - <10	AIN457 Q2W (m=46)	44.0	Placebo	1.04	(0.44, 2.45)	44.0	Placebo	1.43	(0.60, 3.44)
	AIN457 Q4W (m=53)	48.9	Placebo	1.26	(0.55, 2.89)	47.6	Placebo	1.65	(0.71, 3.83)
	Placebo (m=45)	43.1				35.5			
≥ 10	AIN457 Q2W (m=97)	43.6	Placebo	1.91	(1.02, 3.54)	42.7	Placebo	2.09	(1.11, 3.92)
	AIN457 Q4W (m=95)	33.7	Placebo	1.19	(0.63, 2.25)	33.6	Placebo	1.33	(0.70, 2.54)
	Placebo (m=92)	28.6				26.4			
Baseline AN Count									
≤10	AIN457 Q2W (m=100)	52.9	Placebo	1.68	(0.95, 2.99)	52.9	Placebo	1.97	(1.11, 3.49)
	AIN457 Q4W (m=97)	43.8	Placebo	1.16	(0.65, 2.08)	43.2	Placebo	1.32	(0.73, 2.37)
	Placebo (m=103)	40.2				36.7			
>10	AIN457 Q2W (m=81)	35.3	Placebo	1.62	(0.79, 3.33)	34.3	Placebo	2.10	(0.98, 4.48)
	AIN457 Q4W (m=83)	39.3	Placebo	1.96	(0.97, 3.97)	28.7	Placebo	2.69	(1.28, 5.64)
	Placebo (m=77)	24.9				19.6			

- m = number of subjects evaluable.
- The model contains the following covariates: treatment group, weight (excluded in the analysis of the weight subgroup), baseline AN count.
- Japan is combined with AMEA region.
- Source: [Study 2301 Week16 Table 14.2-7.1b] [Appendix-M2301 Table 14.2-7.1b]

Table 30: Subgroup Analysis for HiSCR50 Response at Week 16 in Study M2302 (Full Analysis Set) by Applicant's Analysis vs. FDA-Requested Analysis

		Applicant's Analysis				FDA-Requested Analysis			
Subgroup	**Treatment**	**Response rate**	**Comparator**	**Odds ratio**	**95% CI for odds ratio**	**Response rate**	**Comparator**	**Odds ratio**	**95% CI for odds ratio**
Current antibiotic use									
N	AIN457 Q2W (m=162)	40.2	Placebo	1.39	(0.87, 2.21)	35.7	Placebo	1.51	(0.93, 2.45)
	AIN457 Q4W (m=159)	49.7	Placebo	2.04	(1.29, 3.25)	45.7	Placebo	2.29	(1.42, 3.69)
	Placebo (m=164)	32.7				27.0			
Y	AIN457 Q2W (m=18)	61.4	Placebo	6.52	(1.31, 32.42)	61.6	Placebo	6.53	(1.31, 32.50)
	AIN457 Q4W (m=21)	19.2	Placebo	1.03	(0.18, 5.95)	18.4	Placebo	0.98	(0.17, 5.58)
	Placebo (m=19)	17.9				18.1			
Body weight									
<90 kg	AIN457 Q2W (m=86)	45.5	Placebo	1.82	(0.97, 3.41)	40.8	Placebo	1.88	(0.99, 3.58)
	AIN457 Q4W (m=89)	47.0	Placebo	1.93	(1.04, 3.58)	45.0	Placebo	2.22	(1.18, 4.16)
	Placebo (m=92)	31.5				27.1			
≥90 kg	AIN457 Q2W (m=94)	39.4	Placebo	1.46	(0.78, 2.73)	36.0	Placebo	1.68	(0.88, 3.22)
	AIN457 Q4W (m=91)	45.3	Placebo	1.86	(0.99, 3.49)	40.0	Placebo	1.99	(1.03, 3.84)
	Placebo (m=91)	30.9				25.0			
Geographical region									
AMEA	AIN457 Q2W (m=27)	52.9	Placebo	1.22	(0.39, 3.80)	49.2	Placebo	1.25	(0.40, 3.92)
	AIN457 Q4W (m=26)	30.8	Placebo	0.48	(0.14, 1.57)	30.8	Placebo	0.57	(0.17, 1.87)
	Placebo (m=24)	46.6				42.1			
RE	AIN457 Q2W (m=111)	45.3	Placebo	1.87	(1.07, 3.29)	40.7	Placebo	1.93	(1.08, 3.44)
	AIN457 Q4W (m=111)	45.6	Placebo	1.90	(1.08, 3.34)	42.6	Placebo	2.09	(1.17, 3.74)
	Placebo (m=114)	30.6				26.1			
LaCAN	AIN457 Q2W (m=16)	25.0	Placebo	0.88	(0.18, 4.31)	25.0	Placebo	1.20	(0.23, 6.23)
	AIN457 Q4W (m=16)	81.3	Placebo	11.78	(2.09, 66.42)	81.3	Placebo	16.24	(2.71, 97.15)
	Placebo (m=17)	29.4				23.5			
US	AIN457 Q2W (m=26)	29.4	Placebo	1.62	(0.42, 6.17)	25.1	Placebo	2.31	(0.50, 10.55)
	AIN457 Q4W (m=27)	42.4	Placebo	2.77	(0.78, 9.80)	30.1	Placebo	2.88	(0.65, 12.74)
	Placebo (m=28)	21.4				13.5			
Hurley Stage									
Stage I	AIN457 Q2W (m=6)	33.3	Placebo	0.04	(0.00, 4.21)	33.3	Placebo	0.01	(0.00, 3.53)
	AIN457 Q4W (m=6)	66.7	Placebo	0.85	(0.04, 19.56)	50.0	Placebo	0.27	(0.01, 8.78)
	Placebo (m=3)	66.7				66.7			
Stage II	AIN457 Q2W (m=92)	47.1	Placebo	2.13	(1.17, 3.88)	43.7	Placebo	2.63	(1.40, 4.95)
	AIN457 Q4W (m=106)	48.3	Placebo	2.25	(1.26, 3.99)	44.6	Placebo	2.79	(1.52, 5.15)
	Placebo (m=110)	29.2				22.6			
Stage III	AIN457 Q2W (m=82)	37.6	Placebo	1.26	(0.64, 2.49)	32.6	Placebo	1.15	(0.57, 2.32)
	AIN457 Q4W (m=68)	41.0	Placebo	1.42	(0.69, 2.92)	38.4	Placebo	1.47	(0.71, 3.05)
	Placebo (m=70)	32.7				29.8			
Age group									
<30	AIN457 Q2W (m=52)	46.0	Placebo	2.25	(0.99, 5.08)	41.8	Placebo	2.30	(0.99, 5.33)
	AIN457 Q4W (m=60)	50.9	Placebo	1.40	(0.64, 3.06)	46.7	Placebo	2.78	(1.23, 6.27)
	Placebo (m=57)	27.6				23.9			
30-<40	AIN457 Q2W (m=48)	40.4	Placebo	1.05	(0.48, 2.29)	36.2	Placebo	1.14	(0.51, 2.53)
	AIN457 Q4W (m=61)	43.3	Placebo	1.17	(0.57, 2.42)	38.5	Placebo	1.27	(0.60, 2.69)
	Placebo (m=65)	39.9				33.6			
≥40	AIN457 Q2W (m=80)	41.1	Placebo	2.09	(0.98, 4.45)	37.3	Placebo	2.41	(1.08, 5.34)
	AIN457 Q4W (m=59)	44.3	Placebo	2.34	(1.05, 5.22)	42.2	Placebo	2.91	(1.26, 6.74)
	Placebo (m=61)	25.3				20.1			
Gender									
M	AIN457 Q2W (m=88)	43.4	Placebo	1.74	(0.89, 3.40)	40.9	Placebo	1.67	(0.85, 3.29)
	AIN457 Q4W (m=77)	38.1	Placebo	1.37	(0.69, 2.73)	37.9	Placebo	1.46	(0.73, 2.91)
	Placebo (m=78)	31.0				29.4			
F	AIN457 Q2W (m=98)	41.4	Placebo	1.58	(0.88, 2.85)	36.2	Placebo	1.91	(1.02, 3.57)
	AIN457 Q4W (m=103)	52.1	Placebo	2.39	(1.33, 4.27)	45.9	Placebo	2.77	(1.50, 5.11)
	Placebo (m=105)	31.3				23.6			
Race									
White	AIN457 Q2W (m=133)	44.0	Placebo	2.18	(1.29, 3.66)	40.1	Placebo	2.35	(1.37, 4.04)
	AIN457 Q4W (m=139)	45.3	Placebo	2.28	(1.36, 3.81)	42.2	Placebo	2.55	(1.49, 4.36)
	Placebo (m=143)	26.6				22.2			
Black or Africa American	AIN457 Q2W (m=18)	34.7	Placebo	0.95	(0.18, 4.90)	29.2	Placebo	1.14	(0.20, 6.62)
	AIN457 Q4W (m=19)	47.8	Placebo	1.97	(0.39, 9.92)	35.5	Placebo	1.87	(0.33, 10.46)
	Placebo (m=12)	33.3				25.0			
Other	AIN457 Q2W (m=29)	39.1	Placebo	0.54	(0.18, 1.62)	35.9	Placebo	0.63	(0.21, 1.91)
	AIN457 Q4W (m=22)	50.0	Placebo	0.81	(0.26, 2.56)	50.0	Placebo	1.11	(0.35, 3.49)
	Placebo (m=28)	53.6				46.4			
Previous Exposure to Biologics									
N	AIN457 Q2W (m=144)	42.4	Placebo	1.54	(0.93, 2.54)	39.4	Placebo	1.68	(1.01, 2.82)
	AIN457 Q4W (m=138)	46.8	Placebo	1.82	(1.10, 3.02)	43.7	Placebo	2.00	(1.19, 3.36)

	Placebo (m=135)	32.9				28.2			
Y	AIN457 Q2W (m=36)	42.1	Placebo	2.01	(0.76, 5.30)	33.9	Placebo	2.11	(0.74, 6.02)
	AIN457 Q4W (m=42)	44.0	Placebo	2.27	(0.89, 5.78)	38.3	Placebo	2.68	(0.98, 7.29)
	Placebo (m=48)	26.4				20.1			
Disease Duration									
<2	AIN457 Q2W (m=11)	54.5	Placebo	14.95	(0.46, 487.60)	54.5	Placebo	16.12	(0.48, 542.42)
	AIN457 Q4W (m=9)	38.6	Placebo	7.87	(0.24, 252.85)	38.6	Placebo	8.50	(0.25, 286.22)
	Placebo (m=6)	3.5				2.5			
2 - <5	AIN457 Q2W (m=37)	44.5	Placebo	1.41	(0.52, 3.80)	44.2	Placebo	1.60	(0.59, 4.33)
	AIN457 Q4W (m=25)	60.0	Placebo	2.66	(0.90, 7.83)	52.0	Placebo	2.25	(0.77, 6.60)
	Placebo (m=36)	35.5				31.9			
5 - <10	AIN457 Q2W (m=33)	36.1	Placebo	1.25	(0.46, 3.38)	29.5	Placebo	0.98	(0.35, 2.73)
	AIN457 Q4W (m=44)	45.8	Placebo	1.76	(0.72, 4.27)	42.3	Placebo	1.65	(0.68, 4.02)
	Placebo (m=45)	33.6				31.4			
≥10	AIN457 Q2W (m=99)	42.2	Placebo	1.76	(0.96, 3.25)	37.3	Placebo	2.08	(1.08, 4.00)
	AIN457 Q4W (m=102)	43.6	Placebo	1.81	(0.99, 3.32)	40.6	Placebo	2.34	(1.23, 4.47)
	Placebo (m=96)	30.2				22.8			
Baseline AN Count									
≤10	AIN457 Q2W (m=89)	37.9	Placebo	1.60	(0.83, 3.06)	32.2	Placebo	1.49	(0.76, 2.94)
	AIN457 Q4W (m=86)	46.3	Placebo	2.21	(1.16, 4.21)	42.8	Placebo	2.30	(1.18, 4.47)
	Placebo (m=93)	28.0				24.5			
>10	AIN457 Q2W (m=91)	46.4	Placebo	1.67	(0.90, 3.08)	44.3	Placebo	2.12	(1.12, 3.99)
	AIN457 Q4W (m=94)	46.0	Placebo	1.60	(0.87, 2.95)	42.2	Placebo	1.92	(1.02, 3.61)
	Placebo (m=90)	34.5				27.6			

- m = number of subjects evaluable.
- The model contains the following covariates: treatment group, weight (excluded in the analysis of the weight subgroup), baseline AN count.
Source: [Study 2302 Week16 Table 14.2-7.1b] [Appenix-M2302 Table 14.2-7.1b]

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

The efficacy analysis result was consistent for the secukinumab Q2W dose regimen across the two pivotal trials; however, for the secukinumab Q4W dose regimen, efficacy achieved statistical significance in Study M2302 but not in Study M2301 according to the pre-specified alpha for multiplicity control despite a trend of improvement over placebo. This result was also consistent between the applicant's analysis and the FDA-requested analysis (where subjects on any rescue medication or intervention were counted as non-responders) despite that the FDA-requested analysis had smaller p values for all of the endpoints.

Primary Endpoints

The two identical Phase 3 studies, M2301 and M2302, demonstrated efficacy of both secukinumab dose regimens over placebo in the treatment of subjects with moderate to severe HS, with sustained efficacy through Week 52. Of the two secukinumab dosing regimens evaluated, the secukinumab Q2W dose regimen consistently demonstrated superiority with a clinically meaningful difference over placebo in both pivotal studies, with respect to the primary endpoint of HiSCR50 response at Week 16. The secukinumab Q4W dose regimen demonstrated efficacy with statistical significance in Study M2302 but not in Study M2301 despite a trend of improvement over placebo. In particular, based on the FDA-requested analysis for the secukinumab Q4W vs placebo comparison, the primary endpoint HiSCR50 just missed the pre-specified alpha in Study M2301. Of note, there was an imbalanced distribution of subjects with baseline Hurley stage III severity among the three treatment arms between the two studies. In particular, the secukinumab Q4W treatment group was comprised a more severe study population compared to the placebo group in Study M2301; The placebo group in Study M2301 was comprised a milder study population compared to that in Study M2302; The secukinumab

Q2W treatment group was comprised a more severe study population compared to other treatment groups in both studies.

Secondary and Other Endpoints

The secukinumab Q2W dose regimen showed efficacy over placebo with respect to the secondary endpoints of AN50 response at Week 16 in both studies and flares over 16 weeks in M2301. The secukinumab Q4W dose regimen showed statistically significant efficacy over placebo with respect to the secondary endpoints of AN50 and flares in M2302, but not in M2301 despite a trend of improvement over placebo. Of note, the secukinumab Q4W dose regimen had a p value smaller than the pre-specified alpha for the secondary endpoint of AN50, but failed to declare statistical significance due to the failed primary endpoint based on the pre-specified multiplicity testing sequence.

Subpopulations

Subgroup analyses performed on the primary endpoint showed that HiSCR50 response rates were generally higher in the secukinumab Q2W and secukinumab Q4W groups compared to the placebo group across all stratification factors (geographical region, concomitant antibiotic treatment, and baseline body weight) and other subgroups like age, gender, race, disease duration, previous exposure to biologics, baseline AN count, and baseline Hurley stage for both studies. Note that some subgroups had limited number of subjects and results of these subgroups should be interpreted with caution.

8.1.4. Integrated Assessment of Effectiveness

Studies M2301 and M2302 demonstrate the rapid response of both secukinumab dose regimens vs. placebo across multiple efficacy parameters (HiSCR50, AN50, flares and NRS30) in subjects with moderate to severe HS, and their sustained efficacy through Week 52. The secukinumab Q2W dose regimen demonstrated superiority over placebo in both studies with respect to the primary endpoint of HiSCR50 response at Week 16. The secukinumab Q4W dose regimen demonstrated statistically significant superiority vs. placebo with respect to HiSCR50 in Study M2302 but not in Study M2301 despite a trend of improvement over placebo.

Statistical Reviewers' Comment

Between the two secukinumab dose regimens, the clinical reviewers recommended to use the secukinumab 300 mg every 4 weeks (Q4W) first, and if a patient does not adequately respond, then consider increasing the secukinumab dosage to every 2 weeks (Q2W). Statistical reviewers agree with the clinical reviewers' recommendation from the statistical perspective as discussed, which is also copied below.

1) The efficacy results for the two secukinumab doses (Q2W and Q4W) are close to each other for the primary and secondary points (Table 11);

2)The statistical significance of the FDA-requested analysis for HiSCR50 (p=0.0123) is only slightly greater than the pre-specified alpha of 0.01 for the Q4W vs. placebo comparison. For AN50, the FDA-requested analysis had a p value (p=0.0018) that is much smaller than the pre-specified alpha 0.01.

3) The lower efficacy result for secukinumab Q4W vs. placebo in Study M2301 than in Study M2302 is likely due to the imbalanced distribution of baseline severity level between secukinumab Q4W and placebo among the two studies, i.e., the milder placebo subjects (subject to higher placebo effect) in Study M2301 than in Study M2302 and the more severe baseline level in the secukinumab Q4W subjects than the placebo subjects in Study 2301 (Table 5);

4) The observed inconsistent trend of efficacy for secukinumab Q2W vs. Q4W in Study M2301 (Q2W is better than Q4W) and Study M2302 (Q4W is better than Q2W) can be explained by the plateau effect of secukinumab Q2W and the more severe baseline level in the secukinumab Q2W subjects than the secukinumab Q4W subjects in Study M2302.

Therefore, the Statistical reviewers agree with the clinical reviewers' recommendation to use the secukinumab 300 mg every 4 weeks (Q4W) first, and if a patient does not adequately respond, then consider increasing the secukinumab dosage to every 2 weeks (Q2W).

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety focused on pooled data from 2 identical phase 3 trials, CAIN457M2301 (M2301) and CAIN457M2302 (M2302), which were conducted in adult subjects with moderate to severe HS.

All safety analyses were based on the Safety set, which included all subjects who received at least one dose of trial drug. The short-term safety of the two secukinumab dose regimens versus placebo was evaluated based on data from Treatment Period 1 (Weeks 0-16). Long-term safety of the two secukinumab dose regimens was evaluated based on the data available from the Entire Study Period at the time of the Week 52 interim analysis data cut-off date in subjects who were initially randomized to either the secukinumab Q2W or Q4W dose regimens, and is supported by data from subjects who were initially randomized to placebo then switched to either secukinumab Q2W or Q4W at Week 16.

The main analysis dataset for the review of safety was comprised of pooled data from the 16-week placebo-controlled period of Trials M2301 and M2302 which included 361 subjects treated with secukinumab Q2W, 360 subjects treated with secukinumab Q4W, and 363 subjects treated with placebo. Long-term, 52-week safety assessments were conducted using the same analysis dataset for the following four groups: 361 subjects originally randomized to

secukinumab 300 mg Q2W, 360 subjects originally randomized to secukinumab 300 mg Q4W), 527 subjects randomized to secukinumab 300 mg Q2W at trial entry plus subjects who switched from placebo to Q2W at Week 16 (i.e., Any secukinumab Q2W), and 533 subjects randomized to secukinumab 300 mg Q4W at trial entry plus subjects who switched from placebo to Q4W at Week 16 (i.e., Any secukinumab Q4W).

The safety review was also supported by a dossier summarizing data from the ongoing, 4-year randomized withdrawal extension trial, CAIN457M2301E1 (M2301E1), which included information from 700 subjects who completed trials M2301 and M2302 and who wished to continue treatment.

The trials designs for all ongoing phase 3 trials, M2301, M2302, and M2301E1, are summarized in Section 7.1 Table of Clinical Studies.

Additionally, data from Trial CAIN457A2324 (A2324), a phase 3 trial in 331 adult subjects with moderate to severe plaque psoriasis weighing ≥ 90 kg were included to support the evaluation of safety and tolerability of the Q2W regimen (b) (4)

Primary safety analyses included treatment-emergent adverse events (TEAEs), deaths, serious AEs (SAEs), AEs leading to discontinuation, laboratory abnormalities, vital signs, physical examinations, and immunogenicity in the phase 3 trials.

Additional analyses of AEs of special interest based on prior experience with secukinumab, consists of infections (including opportunistic infections), hypersensitivity, suicidal ideation and behavior (SIB), inflammatory bowel disease (IBD), neutropenia, major adverse cardiovascular events (MACE), and malignancy.

8.2.2. Review of the Safety Database

Overall Exposure

Exposure to trial drug is summarized for the pooled data from both trials M2301 and M2302 in which 1060 were exposed to at least one dose of secukinumab.

During Treatment Period 1 (Weeks 0-16), 721 subjects received secukinumab (361 in the Q2W group and 360 in the Q4W group) and 363 subjects received placebo. The mean duration of exposure was comparable between treatment groups (112 days for secukinumab Q2W, 111 days for secukinumab Q4W, and 112 days for placebo). The median duration of exposure was also similar across all groups (112 days).

During the Entire Trial Period, 527 subjects received Any secukinumab Q2W and 533 subjects received Any secukinumab Q4W, with approximately half of the subjects in each group exposed to trial drug for at least 1 year as shown in Table 31 below. Cumulative exposure (patient-years) was similar between the secukinumab Q2W (338.0) and Q4W (334.3) groups and similar

between the Any secukinumab Q2W group (451.2) and Any secukinumab Q4W group (449.7). The overall subject exposure during the Entire Trial period to secukinumab comprised 900.9 patient-years of exposure from studies M2301 and M2302 in adults with moderate to severe HS.

Table 31: Duration of Exposure to Trial Drug – Entire Trial Period (Safety set)

Duration of exposure	Secukinumab Q2W N=361	Secukinumab Q4W N=360	Any Secukinumab Q2W N=527	Any Secukinumab Q4W N=533	Any Secukinumab N=1060
Any exposure, n(%)	**361 (100.0)**	**360 (100.0)**	**527 (100.0)**	**533 (100.0)**	**1060 (100.0)**
>= 52 weeks	257 (71.2)	246 (68.3)	257 (48.8)	246 (46.2)	503 (47.5)
Days					
n	361	360	527	533	1060
Mean	342.0	339.1	312.7	308.2	310.4
SD	81.71	85.96	84.84	89.31	87.10
Median	365.0	365.0	363.0	347.0	360.0
Min - Max	1 - 450	16 - 464	1 - 450	16 - 464	1 - 464
Subject-time (subject years)	338.1	334.3	451.2	449.7	900.9

Subject-time in subject-years is calculated as a sum of individual subject durations in days divided by 365.25.
For placebo-secukinumab switchers, exposure after the first intake of secukinumab is considered into any secukinumab groups.
Source: Modified Applicant's SCS Table 1-6

The size of the overall safety database was considered adequate and in line with ICH E1 principles.

Relevant characteristics of the safety population

More females (56%) were enrolled relative to males (44%). The majority of subjects were white (78%) and less than 65 years of age (99%). The subjects were balanced across treatment groups with regard to gender, race, and weight. However, there was a slight imbalance of age as the secukinumab Q2W group had slightly more subjects over the age of 40 years (147, 41%) compared to the Q4W (125, 35%) and placebo (120, 33%) groups. Additionally, the secukinumab Q2W comprised a greater number of subjects with more severe disease by Hurley staging and baseline lesion counts.

As discussed in more detail under Section 8.2.7 Safety Analyses by Demographic Subgroups, the population appeared to be representative of the United States target population based on sex and age, but not by race as the prevalence of HS in the United States appears to be higher among African Americans.

Adequacy of the safety database:

The total subject exposure to secukinumab Q2W and Q4W for the treatment of moderate to severe HS provides adequate data for the evaluation of safety. The demographics of the trial population reasonably represent the target population. The total exposure at 52 weeks is sufficient to characterize the safety of the product over longer treatment periods.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

During the review of this sBLA, the Applicant informed the Agency on March 15, 2023 that data discrepancies were identified for the secondary endpoint, NRS30/Skin pain, impacting both trials M2301 and M2302. According to the Applicant, "due to a human error, the variables 'average pain' and 'worst pain' were inadvertently transposed at the time of the creation of the Study Data Model Tabulation (SDTM) datasets, resulting in the incorrect NRS pain variable used for the analysis of the NRS30/Skin pain endpoint." These data discrepancies were identified internally following a bioresearch monitoring (BIMO) inspection conducted from February 21 to 24, 2023, by the Agency at a Canadian clinical research site which participated in Trial M2302. Novartis stated that the conclusions on the NRS30/Skin pain endpoint included in the dossier submitted to the Agency were not impacted and "while the test decisions based on the testing hierarchy were not affected, there was a slight increase in the estimated treatment effects (odds ratios) of both secukinumab dose regimens versus placebo in both studies." This determination was confirmed by the Biostatistical team upon on evaluation of corrected outputs and datasets affected by the pain data discrepancies in trials M2301 and M2302. The Applicant also confirmed that there was no issue at the data collection level (i.e., the source data accurately reflected subjects' pain levels).
There appeared to be no impact on patient safety during the conduct of the trials.

No other deficiencies were identified that hindered a thorough analysis of the data presented by the Applicant. Overall, the quality of the data submitted is adequate.

Categorization of Adverse Events

According to the Applicant, an adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a subject after providing written informed consent for participation in the trials. Therefore, an AE may or may not be temporally associated with the use of trial drug.

For Trials M2301, M2302, and M2301E, the Applicant defined treatment emergent adverse events (TEAEs) as events that started after the first dose of trial drug and within 84 days after last dose, or events present prior to the first dose of trial drug but increased in severity based on preferred term within 84 days after last dose. This is not unreasonable given the known half-life ranged from 22 to 31 days in plaque psoriasis subjects following intravenous and subcutaneous administration across all psoriasis trials. Nevertheless, analysis of the entire database beyond this defined scope was assessed for AEs.

Investigators were responsible for determining whether a TEAE had a reasonable possibility of being related to trial drug, considering the disease, concomitant treatment, or other pathologies.

An SAE was defined as any adverse event [appearance of (or worsening of any pre-existing)], undesirable sign(s), symptom(s) or medical conditions(s) which met any one of the following criteria:

- fatal
- life-threatening (refers to a reaction in which the subject was at risk of death at the time of the reaction
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above per ICHE2D Guidelines

All malignant neoplasms were assessed as serious under "medically significant" if other seriousness criteria were not met.
Any suspected transmission via a medicinal product of an infectious agent was also considered a serious adverse reaction.
All reports of intentional misuse and abuse of the product were also considered serious adverse events irrespective if a clinical event occurred.

Adverse events were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities MedDRA) version 24.1 for outputs based on primary endpoint analysis (Week 16) data. MedDRA version 25.0 was used for outputs based on Week 52 interim analysis data. Severity of the AEs was assessed using Common Terminology Criteria for Adverse Events (CTCAE) criteria version 4.3.

The definitions of AE, TEAE, and SAE are acceptable. The method of categorizing severity, as well as assessment of causality were adequate. The coding of adverse events in the sBLA submission appeared adequate. The Applicant's identification and presentation of AEs of special interest were reasonable.

Routine Clinical Tests

Safety analyses included reporting of AEs, laboratory (screening for tuberculosis, screening for pregnancy, hematology, clinical chemistry, and urinalysis), physical examination (including vital signs), and local tolerability. The severity of the laboratory test values was assessed using CTCAE version 4.03

For vital signs, the change from baseline for each subsequent visit was calculated and summarized. Additionally, the number and percentage of subjects with newly occurring abnormal (i.e., out-of-range) vital signs were listed by treatment group for Treatment Period 1 and the Entire Trial Period.

For hematology and clinical chemistry results, the change from baseline to each trial

visit was reported and summarized by treatment group. The number and percentage of subjects with a new or worsening CTCAE grade after baseline were delineated by laboratory test and treatment group.

Safety monitoring and the Applicant's evaluation of routine clinical tests were adequate.

8.2.4. Safety Results

Deaths

The Applicant defined a fatal event as a death if it occurred after written informed consent to participate in the trials was obtained, through to 10 weeks after the final dose of the study treatment. Understanding that the known PK characteristics of secukinumab includes a mean half-life of 22 to 31 days in *plaque psoriasis* subjects following intravenous and subcutaneous administration across all psoriasis trials, a conservative approach to interpreting treatment-related safety observations (including deaths) would translate to a washout period of 155 days or 22 weeks. Ideally, any fatal event reported in a subject administered a trial drug should be considered a death, therefore, analysis of the submitted data in its entirety and beyond the Applicant's defined scope was conducted. One additional subject (M2301-2061-008) in the placebo group was identified to have died during Treatment Period 1.

As of the 120-day safety update a total of 3 deaths were identified in the moderate to severe hidradenitis suppurativa development program for secukinumab. Two subjects were receiving secukinumab Q4W at the time of their deaths, and one was receiving placebo as mentioned above.

The subject in the placebo group was a 65-year-old White male with a history of chronic tobacco use, peripheral arterial disease requiring bypass, and severe HS with an HS-PGA score of 5, Hurley stage of III, total AN count of 18, and 9 draining fistulae, who was diagnosed with metastatic lung adenocarcinoma approximately 12 weeks after starting placebo. He died 10 weeks later.

The other deaths occurred in a 31-year-old male with aortic valve stenosis who had a fatal myocardial infarction (MI) 29 weeks after starting secukinumab Q4W and in a 71-year-old female with multiple duodenal ulcers (DUs), a history of NSAID use, and Crohn's disease whose death (after receiving secukinumab Q4W for 35 weeks) was reported to be due to an upper gastrointestinal bleed (UGIB). Summaries of these two deaths are provided below.

Subject (b) (6) Myocardial Infarction (29 weeks)
A 31-year-old White male with a past medical history of aortic valve stenosis, depression, and herpes zoster was diagnosed with a myocardial infarction (MI) approximately 29 weeks after starting secukinumab Q4W and died the same day. The subject was not a smoker. His concomitant medications included Stellisept (antimicrobial wash), ibuprofen, and as-needed

oral magnesium. At baseline his HS-PGA score was 3 (moderate), Hurley stage was II, total AN count was 30, and he had no draining fistulae. No autopsy was performed.
Full details were not available regarding this subject's coronary risk factors (i.e., a family history of premature cardiovascular disease, the severity of his aortic valve stenosis, and his left ventricular function were not specified). According to the case report form, his BMI was 27.9 kg/m^2. Laboratory data at baseline and at Week 16 demonstrated total cholesterol (5.23 mmol/L; upper limit normal range = 5.17 mmol/L) and LDL levels (3.5 mmol/L; upper limit normal range = 3.36) that were not reflective of significant underlying hyperlipidemia.

There have been few literature reports of acute MI resulting solely from severe aortic stenosis[7], but silent ischemic necrosis has been observed.[8] Although the risk of cardiovascular events among patients with HS is not well established, literature suggests that patients with HS may be at higher risk of MI and stroke.[9] This subject's aortic valve stenosis plus underlying moderate HS serve as potential alternative explanations for his MI; however, given the temporal relationship and no other traditional coronary risk factors, it is possible that the fatal MI was related to secukinumab 300 mg Q4W use.

Subject (b) (6) **Gastrointestinal hemorrhage (19 weeks)**
A 71-year-old White female with a past medical history of Crohn's disease (since 2006) treated with mesalazine; gastric bypass (1975); gastroesophageal reflux disease treated with famotidine; osteoporosis (since 2017) treated with alendronate; nephrectomy (1979); recurrent urinary tract infections; hypertension; chronic kidney disease (since 2015); and anemia (since 2017), presented to the hospital with an acute gastrointestinal bleed 15 weeks after starting secukinumab 300 mg Q4W. The subject initially received placebo during Treatment Period 1 and transitioned to secukinumab Q4W at Week 16. At baseline, her HS-PGA score was 5 (very severe), Hurley stage was III, total AN count was 24, and she had 4 draining fistulae.
Her spouse reported that the subject took ibuprofen several times a day for several days although the reason for her frequent nonsteroidal anti-inflammatory drug (NSAID) use was not specified. Four weeks after being hospitalized, she died of "gastrointestinal hemorrhage with cardiorespiratory arrest and multiple duodenal ulcers."

The subject had multiple risk factors for gastrointestinal hemorrhage which were more likely to have contributed to the cause of death than the trial drug.

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[7] Jondeau G et al. Acute myocardial infarction in a patient with severe aortic stenosis and normal coronary arteries. Eur Heart J 1994; 15: 715 – 717.
[8] Sarda L, et al. Acute diffuse myocyte necrosis evidenced with ^{111}Inantimyosin antibody scintigraphy in a patient with aortic stenosis. JNucl Cardiol 1997; 4: 426 – 427.
[9] Reddy S, Strunk A, Jemec GBE, Garg A. Incidence of Myocardial Infarction and Cerebrovascular Accident in Patients With Hidradenitis Suppurativa. JAMA Dermatol. 2020;156(1):65–71.

Based on the information provided, treatment with secukinumab 300 mg Q4W and Q2W in subjects with moderate to severe HS was not associated with an increased risk of mortality. The deaths reported in the two subjects receiving secukinumab Q4W were not deemed to have been probably related to the drug product.

Serious Adverse Events

Following administration of Any secukinumab dose, 112 serious adverse events (SAEs) were reported in 82 of 1060 (8%) subjects. Most of these SAEs belonged to the Infections and infestations SOC followed by the Skin and subcutaneous tissue disorders SOC.
The majority of subjects with SAEs who received Any secukinumab had outcomes reported as recovered/resolved (67, 82 %) or recovering/resolving (8, 10 %), and did not require a change in dose (47, 57 %). However, two subjects experienced fatal SAEs, and several had outcomes of not recovered/not resolved (8, 10 %), recovered/resolved with sequelae (2, 2 %), or required drug withdrawal (14, 17 %). This section will discuss SAEs by trial periods (Treatment Period 1 and Entire Trial Period) providing relevant, comparative analyses between treatment groups to gauge short- and long-term risks for these outcomes.

Treatment Period 1 (up to 16 weeks)
During the placebo-controlled period, the proportion of subjects with SAEs was the same across secukinumab and placebo groups (3.0 % for both secukinumab Q2W and Q4W and for placebo). Of the subjects who experienced SAEs, the number who required cessation of treatment drug was the same between the secukinumab groups (3/10, 30%) and lowest for the placebo group (1/18, 9%). The single placebo-treated subject with an SAE who had trial drug withdrawn was previously described under the section, Deaths.

Q2W Group
In the secukinumab Q2W group, trial drug was withdrawn for three subjects due to SAEs of attempted suicide (b) (6) ulcerative colitis ((b) (6) and worsening HS (b) (6)). The SAE of attempted suicide was reported as *recovering/resolving*, but the outcome for the latter two subjects was *not recovered/not resolved* at the time of trial discontinuation. Narratives of these 3 subjects are provided below.

Subject (b) (6): Attempted Suicide; recovering/resolving
A 23-year-old White female with a history of depression treated with fluoxetine and alprazolam, active tobacco use, and severe HS (HS-PGA score of 5, Hurley stage of III, total AN count of 12, and 9 draining fistulae), attempted suicide by mixing drugs with alcohol approximately 15 weeks after starting secukinumab 300 mg Q2W. She was hospitalized, treated with alprazolam and paracetamol, and secukinumab was discontinued. The subject withdrew from the trial and was reported to be recovering at the time of database lock.

With a reasonable time relationship to drug intake on the backdrop of depression and severe HS, it is possible that the subject's suicide attempt was related to secukinumab Q2W use.

Subject (b) (6): Ulcerative colitis; not recovered/not resolved
A 43-year-old White male with a history of pyoderma gangrenosum, developed bloody diarrhea approximately 3 weeks after starting secukinumab Q2W. He was hospitalized and diagnosed with ulcerative colitis via colonoscopic biopsies. Despite cessation of secukinumab and a trial of mesalazine, the subject's symptoms persisted. Bloody diarrhea eventually slowed following treatment with aminosalicylic acid, prednisolone, pantoprazole and metamizole.

Given the reasonable time relationship and no other plausible explanations, even in the setting of a negative dechallenge, it is possible ulcerative colitis was related to secukinumab Q2W use.

Subject (b) (6): Hidradenitis, not recovered/not resolved
A 28-year-old White female with a past medical history of chronic tobacco use and axillary plus inguinal abscess excisions (2009) presented with "worsening hidradenitis" manifested as purulent drainage, abscess formation, and severe pain involving both axillae approximately 10 weeks after starting secukinumab Q2W. At baseline, her HS-PGA score was 5 (very severe), Hurley stage was II, total AN count was 15, and she had 9 draining fistulae. She required hospitalization during which she received rifampicin and clindamycin and underwent lesion excisions, as well as skin grafting of the left and right axillae. The trial medication and trial were permanently discontinued reportedly due to the patient's decision ("lack of efficacy").

Although there is not a consensus regarding tobacco use and the occurrence or severity of HS, literature suggests that smoking is associated with weaker response to treatmen.[10] It is possible that this subject's active tobacco use contributed to her worsening hidradenitis.

Q4W Group
In the Q4W group, three subjects had secukinumab withdrawn due to SAEs of acute bacterial meningitis (b) (6), amyloidosis (b) (6)), and inflammatory bowel disease (b) (6). The subject diagnosed with acute bacterial meningitis had an outcome of *recovering/resolving*; however, according to the 120-day safety update report, the other two subjects had not recovered at the time of trial discontinuation. Details of these 3 subjects are provided in the following narratives.

Subject (b) (6) acute bacterial meninningitis; recovering/resolving
56-year-old Asian (Indian) female with severe HS (HS-PGA score of 4, Hurley stage of III, total AN count of 58, and 9 draining fistulae) and no other significant past medical history, was diagnosed with type 2 diabetes mellitus during her initial screening visit. Approximately 4 weeks after starting secukinumab Q4W, the subject developed moderate, nonserious acute left ear otitis media requiring interruption of trial drug. The subject was treated with amoxicillin-clavulanic acid, ibuprofen-paracetamol, cetirizine-phenylephrine, and xylometazoline for acute otitis media. Six days later the subject was diagnosed with severe,

[10] Bukvić Mokos Z, Miše J, Balić A, Marinović B. Understanding the Relationship Between Smoking and Hidradenitis Suppurativa. Acta Dermatovenerol Croat. 2020 Jul;28(1):9-13.

serious bacterial meningitis via lumbar puncture manifesting as headache and vomiting. She was hospitalized, received ceftriaxone, acyclovir, vancomycin, dexamethasone, levetiracetam, sodium chloride, and clotrimazole, and trial drug was discontinued. The subject also withdrew from the trial due to the AE of bacterial meningitis.

Given the reasonable temporal relationship and alternative explanation of acute otitis media with a history of type 2 diabetes mellitus (although control of blood glucose was not specified), it is possible that the event of acute bacterial meningitis was related to secukinumab Q4W use.

Subject (b) (6) **amyloidosis; not recovered/not resolved**
A 54-year-old White male with a history of active tobacco use and severe HS (HS-PGA score of 5, Hurley stage of III, total AN count of 9, and 3 draining fistulae), was documented to have low serum albumin and low total protein at baseline. At subsequent time points within the following 7 weeks, the subject presented persistent low levels of serum albumin, calcium, total protein, hemoglobin, haematocrit, and red blood cells with elevation of eosinophils, as well as albuminuria and bilateral lower limb edema. He was hospitalized and diagnosed with nephrotic syndrome and moderate, serious amyloidosis related to familial Mediterranean fever. Treatment with colchicine was started. Trial drug was permanently discontinued due to amyloidosis and the subject withdrew from the trial.

Signs and symptoms of amyloidosis were present at baseline; therefore, the timing to drug intake makes a relationship to secukinumab Q4W less probable.

Subject (b) (6) **inflammatory bowel disease; not recovered/not resolved**
A 48-year-old White female with no prior medical history aside from severe HS (HS-PGA score of 5, Hurley stage of III, total AN count of 8, and 2 draining fistulae), was diagnosed via colonoscopy with severe, serious inflammatory bowel disease (IBD) which manfested as fever and diarrhea approximately 10 weeks after starting secukinumab Q4W. She required hospitalization during which trial drug was interrupted then permanently stopped due to her IBD. The subject ultimately withdrew from the trial. The event was ongoing at the time of the trial discontinuation despite treatment with mesalazine.

Literature suggests there is an epidemiological association between HS and IBD and also describes histological features that are shared between the two diseases.[11] Based on no other alternative explanation and the reasonable temporal relationship, despite the negative dechallenge, it is possible that subject's serious IBD and secukinumab Q4W use are related, i.e., secukinumab may have potentiated gastrointestinal inflammation in this subject with already severe HS.

Other cases of IBD are discussed in section 8.2.5.5 Inflammatory Bowel Disease and support

[11] Ingram J. Hidradenitis suppurativa: Pathogenesis, clinical features, and diagnosis. UpToDate. Accessed May 16, 2023

changes to COSENTYX's labeling to include the increased rate of new serious IBD events in the HS population who were administered secukinumab every 2 weeks compared to those who received secukinumab every 4 weeks.

Entire Trial Period

After 52 weeks of exposure, the proportion of subjects with SAEs remained comparable between the secukinumab Q2W (39, 7.4%) and secukinumab Q4W (42, 7.7%). Infections and skin disorders continued to be the most common SAEs reported. While the incidence of *infections* was higher for the secukinumab Q4W group and a greater number of *skin and subcutaneous disorders* were reported for the Q2W group, there was significant overlap of these categories as all of the skin/subcutaneous disorders were HS-related (i.e., exacerbation of HS, worsening HS, or abscess from HS) and required systemic antibiotics.
These SAEs will be discussed in more detail within this section.

Serious Infections and Infestations

The higher rate of infectious SAEs in the Q4W group was primarily driven by sweat gland infections (4 compared to 2 in the Q2W group).

All four cases of sweat gland infections in the Q4W group had outcomes of recovered/resolved. Trial drug was interrupted for one subject but there were no subjects who required withdrawal of trial drug due to sweat gland infection. One case described development of a serious sweat gland infection 5 weeks after completion of treatment with secukinumab Q4W.

The 2 AEs of serious sweat gland infections reported for the Q2W group also resulted in outcomes of recovered/resolved; however, one case required interruption of dosing and the other necessitated withdrawal of trial drug. This latter case (b) (6) was reported in a 39-year-old Asian female with a history of insulin-dependent diabetes mellitus, asthma treated with inhaled steroids, iron deficient anemia, and an HS-PGA score of 5 (very severe), Hurley stage of III, total AN count of 7, and 2 draining fistulae at baseline. Prior non-drug HS therapies included incisional drainage of the left groin (2013, 2018) and buttock (2013); saucerization of the lower abdominal wall (2013), right thigh (2013), right gluteal region (2016), and left and right groin (both in 2016). After 46 weeks of treatment with secukinumab Q2W, the subject was hospitalized for "worsening of HS due to infection" involving the left anterior abdomen, bilateral groin areas, and intergluteal cleft. Her wounds grew multiple bacteria including *Peptoniphilus asaccharolyticus, Streptococcus agalactiae, Prevotella bivia, Actinomyces turicensis, Klebsiella pneumoniae, Escherichia coli,* and *Escherichia faecium*. It was reported that the HS flare was likely a result of infection of the HS lesions. Extensive debridement, vacumn assisted dressings, and eventual wide excision of the natal cleft and bilateral gluteal lesions were performed. Trial medication was permanently discontinued. Her hospital course was complicated by sepsis and acute kidney injury. After a 6-week hospitalization she improved and was discharged.
While this subject's comorbid conditions might have contributed to her severe course, the additive role of secukinumab administered at a higher frequency of every 2 weeks cannot be excluded.

Other infections that occurred in more than one subject who received Q4W dosing were cellulitis and pneumonia (2 subjects each). These types of infections for both secukinumab Q4W and Q2W groups are comparatively discussed below.

Both cases of cellulitis (b) (6) in the secukinumab Q4W group recovered/resolved without change in trial drug dosing and occurred in subjects with underlying diabetes mellitus, obesity, and active tobacco use. It is not clear from the narratives and CRFs for either case whether some areas of cellulitis also included HS lesions.
One subject in the Q2W group (b) (6) experienced an SAE of cellulitis. He was a 45-year-old Asian male with eczema treated with topical chlorpheniramine-lidocaine, as well as salicylic and benzoic acid; pyoderma; chronic tinea infection treated with fenticonazole; and chronic tobacco, use who developed severe left buttock cellulitis after 25 weeks of treatment with secukinumab Q2W. He was hospitalized, received IV antibitoics, and required left buttock fasciotomy and debridement. Methicillin resistant Staphylococcus aureus and Streptococcus were isolated from his wound culture. Trial drug was permanently discontinued one week later although the reason for discontinuation was reportedly due to the patient's assessment of "poor efficacy".
Although there were numerically more SAEs of cellulitis for the Q4W group, the severity of the SAE was worse for the subject who received secukinumab every 2 weeks and was associated with discontinuation of trial drug. The adverse impact of more frequent dosing in this case cannot be excluded.

The two events of serious pneumonia (b) (6)) in the secukinumab Q4W group were reported in relatively young subjects (38 and 51 years of age) with histories of >10 years of prior tobacco use. Both subjects required brief (1 to 6 days) hospitalizations for intravenous antibiotics. Trial drug was temporarily interrupted for both events and restarted soon following discharge from the hospital. The outcome for each case was reported as recovered/resolved. There were no SAEs of pneumonia in the Q2W group.

Serious Skin and Subcutaneous Tissue Disorders
The higher rate of serious skin disorders for the secukinumab Q2W group was driven by a greater number of *worsening hidradenitis* events (9 compared to 4 in the Q4W group) as shown below in Table 32. Although the Applicant's datasets reflected that none of the subjects in the Q2W group with SAEs of hidradenitis required withdrawal of trial drug, upon review of the CRFs and narratives, it was ascertained that 7 of the 9 subjects had trial drug discontinued in association with worsening HS.
Furthermore, upon review of the narrative details for the 4 subjects in the secukinumab Q4W group who reported SAEs of hidradenitis, it was determined that 3, not 4, experienced these SAEs and all 3 had outcomes of recovered/resolved without change in dose.

Given that the Q2W group was comprised of subjects with more severe disease (based on Hurley staging), the higher rate of worsening hidradenitis SAEs in this group might be related to lower systemic exposure as PK data demonstrated that drug clearance is increased with more

severe disease (Refer section 6.3.1 General Pharmacology and Pharmacokinetic Characteristics).

Table 32: Exposure-adjusted incidence rates of Treatment emergent SAEs by Preferred Term - Entire Trial Period (Safety Set)

Preferred term	Secukinumab Q2W N=541 n/EX (IR)	Secukinumab Q4W N=543 n/EX (IR)	Placebo N=363 n/EX (IR)
Any preferred term	39/4.37 (8.9)	42/4.33 (9.7)	11/1.09 (10.1)
Hidradenitis	9/4.49 (2.0)	4/4.48 (0.9)	2/1.11 (1.8)
Sweat gland infection	2/4.51 (0.4)	4/4.48 (0.9)	0/1.11 (0.0)
Acute kidney injury	2/4.51 (0.4)	0/4.50 (0.0)	0/1.11 (0.0)
Pyrexia	2/4.51 (0.4)	1/4.49 (0.2)	1/1.11 (0.9)
Abscess	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Appendicitis	1/4.51 (0.2)	1/4.49 (0.2)	0/1.11 (0.0)
Arrhythmia	1/4.50 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Breast cancer	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
COVID-19	1/4.51 (0.2)	1/4.49 (0.2)	0/1.11 (0.0)
Cellulitis	1/4.51 (0.2)	2/4.48 (0.4)	0/1.11 (0.0)
Cholecystitis	1/4.50 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Cholecystitis acute	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Cholelithiasis	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Colitis ulcerative	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Foot deformity	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Gastrointestinal disorder	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Hypotension	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Inguinal hernia	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Injection site abscess	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Large intestine infection	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Localized infection	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Lower limb fracture	1/4.51 (0.2)	1/4.50 (0.2)	0/1.11 (0.0)
Meniscus injury	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Muscle spasms	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Nephrolithiasis	1/4.50 (0.2)	1/4.50 (0.2)	0/1.11 (0.0)
Non-small cell lung cancer metastatic	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Osteoarthritis	1/4.50 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Pelvi-ureteric obstruction	1/4.50 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Pulmonary embolism	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Pyelonephritis	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Sciatica	1/4.51 (0.2)	1/4.50 (0.2)	0/1.11 (0.0)
Skin candida	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Sleep apnea syndrome	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Suicidal ideation	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Suicide attempt	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)

Systemic inflammatory response syndrome	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Thrombosis	1/4.51 (0.2)	0/4.50 (0.0)	0/1.11 (0.0)
Urinary tract infection	1/4.50 (0.2)	1/4.50 (0.2)	1/1.11 (0.9)
Abdominal pain	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Abscess limb	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Amyloidosis	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Ankle fracture	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Asthma	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)
Basal cell carcinoma	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Breast cellulitis	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
C3 glomerulopathy	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
COVID-19 pneumonia	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)
Clostridium difficile colitis	0/4.51 (0.0)	1/4.50 (0.2)	1/1.11 (0.9)
Colonic abscess	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Confusional state	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Constipation	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Dermatitis infected	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Diarrhea hemorrhagic	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)
Dizziness	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Enterocolitis infectious	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Fatigue	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Fibula fracture	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Foot fracture	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)
Gastrointestinal hemorrhage	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Glomerular vascular disorder	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)
Headache	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Hypertensive emergency	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Infection	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Inflammatory bowel disease	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Influenza	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Intentional overdose	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Intervertebral disc protrusion	0/4.51 (0.0)	2/4.49 (0.4)	0/1.11 (0.0)
Joint dislocation	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Lung cancer metastatic	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)
Myocardial infarction	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Otitis externa	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Pericarditis	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Peritonsillar abscess	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Pneumonia	0/4.51 (0.0)	2/4.49 (0.4)	0/1.11 (0.0)
Post procedural infection	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Scrotal infection	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Scrotal inflammation	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Sepsis	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Skull fracture	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Soft tissue infection	0/4.51 (0.0)	1/4.50 (0.2)	0/1.11 (0.0)
Tachycardia	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Ureterolithiasis	0/4.51 (0.0)	0/4.50 (0.0)	1/1.11 (0.9)

Viral upper respiratory tract infection	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)
Vomiting	0/4.51 (0.0)	1/4.49 (0.2)	0/1.11 (0.0)

Source: Modified Applicant SCS Table 2-11
- Preferred terms are sorted in descending order of IR in Any secukinumab Q2W column
- A subject with multiple adverse events with the same preferred term is counted only once for that preferred term.
- EX = Exposure per 100 subject-years. IR = Incidence rate per 100 subject-years. For subjects with multiple events within the preferred term, exposure time is censored at time of first event.

In the 120-day safety update, for trials M2301 and M2302 there were no new SAEs reported in the secukinumab Q4W group. Two subjects in the secukinumab Q2W group reported 3 new SAEs [goiter; depression and obsessive-compulsive disorder (OCD)]. The subject with an SAE of goiter (b) (6)) had an outcome of "resolved" following a hemithyroidectomy. The subject with depression and OCD (b) (6)) had reported worsening of these SAEs that were ongoing at the time of data cut-off although no action was taken with the trial medication and no treatment was reported.

Overall, the majority of SAEs were consistent with those expected for a population of patients with moderate to severe HS treated with an immunosuppressive biologic. Although the incidence rates of SAEs were generally comparable between the secukinumab Q2W and secukinumab Q4W groups, the nature of the events differed. In general, more severe clinical courses and unfavorable outcomes were observed with subjects in the secukinumab Q2W who experienced SAEs. Therefore, increased risk might be incurred with more frequent dosing of secukinumab.

Dropouts and/or Discontinuations Due to Adverse Effects

Treatment Period 1 (up to 16 weeks)
The rate of discontinuations due to an AE appeared comparable across treatment groups up to 16 weeks as shown in Table 33 (6, 1.7% subjects were reported to have discontinued for both Q2W and Q4W groups and 5, 1.4% for the placebo group).

Table 33: Treatment-Emergent Adverse Events leading to Treatment discontinuation by Preferred Term - Treatment Period 1 (Safety set)

	Secukinumab Q2W N=361 n (%)	Secukinumab Q4W N=360 n (%)	Placebo N=363 n (%)
Any preferred term	**6 (1.7)**	**6 (1.7)**	**5 (1.4)**
Amyloidosis	0 (0.0)	1 (0.3)	0 (0.0)
Arthralgia	1 (0.3)	0 (0.0)	0 (0.0)
Bacterial meningitis	0 (0.0)	1 (0.3)	0 (0.0)
Colitis ulcerative	1 (0.3)	0 (0.0)	0 (0.0)

Inflammatory bowel disease	0 (0.0)	1 (0.3)	0 (0.0)
Psoriasis	0 (0.0)	1 (0.3)	0 (0.0)
Rheumatoid arthritis	1 (0.3)	0 (0.0)	0 (0.0)
Sinusitis	1 (0.3)	0 (0.0)	0 (0.0)
Suicide attempt	1 (0.3)	1 (0.3)	0 (0.0)
Urticarial dermatitis	1 (0.3)	0 (0.0)	0 (0.0)
Vulval cancer	0 (0.0)	1 (0.3)	0 (0.0)
Hematuria	0 (0.0)	0 (0.0)	1 (0.3)
Hidradenitis	0 (0.0)	0 (0.0)	1 (0.3)
Human chorionic gonadotropin increased	0 (0.0)	0 (0.0)	1 (0.3)
Pruritus	0 (0.0)	0 (0.0)	1 (0.3)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.3)

Source: Modified Applicant SCS Table 2-12
-A subject with multiple AEs with the same preferred term is counted only once for that preferred term.

Q2W group
In the Q2W group, 3 subjects who had secukinumab withdrawn due to SAEs of attempted suicide, ulcerative colitis, and worsening HS were discussed under the section, Serious Adverse Events. It must be noted again that the action taken with study drug for the SAE of worsening HS was "dose not changed" in the adverse event (ADAE) dataset; however, treatment drug was in fact discontinued when acute worsening of HS requiring hospitalization occurred. The reason for discontinuation in the subject narrative was "patient's decision (lack of efficacy)".

The other TEAEs (rheumatoid arthritis, arthralgia, sinus infection, and urticaria) that led to discontinuation of secukinumab Q2W were not considered serious by the Applicant.
The AE of rheumatoid arthritis (RA) was reported in a 73-year-old female 1 week after starting treatment with secukinumab Q2W. Sinus infection was reported in a 37-year-old female with a history of hypertension and migraine approximately 2 weeks after starting secukinumab Q2W. The event of sinusitis was of moderate severity and required outpatient treatment with acetaminophen-dextromethorphan-phenylephrine, prednisone, cefdinir, and benzonatate. The AE of moderate arthralgia was reported by a 34-year-old Black female approximately 4 weeks after starting secukinumab Q2W; no treatment was reported for the AE.
The AE of urticarial dermatitis was reported in a 28-year-old white female with a history of obesity. After receiving the second dose of secukinumab the subject ((b) (6) developed "injection site rash, rhinorrhoea, and urticarial dermatitis" (location of urticaria was not specified). According to the narrative, trial drug was discontinued 6 weeks later due to urticarial dermatitis which was ongoing at the time of trial discontinuation (Week 16).

Q4W group
In the Q4W group, 3 subjects who had secukinumab withdrawn due to SAEs of acute bacterial meningitis, amyloidosis, and inflammatory bowel disease were discussed under the section, Serious Adverse Events. The other 3 TEAEs that led to discontinuation of secukinumab Q4W (plantar psoriasis, stage 1 vulvar cancer, suicide attempt) were not considered serious by the Applicant. The events of plantar psoriasis and vulvar cancer due to human papillomavirus (HPV

diagnosed 3 years prior) were reported 15 weeks and 10 weeks after starting secukinumab, respectively. Both were mild in severity and reported as ongoing at the time of study discontinuation. There were no new details provided in the safety update report for these events.
Although the event of suicide attempt was described as "suicidal ideation" and not indicated as serious within the Applicant's database, a review of the narrative advocates for a more accurate assessment of *attempted suicide by intentional overdose of psychiatric medications* in a 33-year-old Black female with a history of hypertension, as well as anxiety, depression, and insomnia who was taking numerous psychotropic agents and experiencing a "stressful life event". The subject was observed in the hospital setting for less than 24 hours and her "suicidal ideation" was reported as having resolved after completing "psychological group and individualized therapy". After a total of 17 weeks of taking secukinumab Q4W, trial drug was permanently discontinued.

Although the Applicant did not consider the events of urticarial dermatitis or suicide attempt serious, these events are nonetheless concerning and are regarded as adverse events of special interest (AESI). These AESIs are further discussed in Section 8.2.5 Analysis of Submission-specific Safety Issues.

Entire Trial Period
With longer exposure, the rate of discontinuation due to an AE remained comparable between the Any secukinumab Q2W group (20/527, 3.8%) and Any secukinumab Q4W group (18/533, 3.4%). AEs leading to treatment discontinuation in more than one subject included worsening HS and abdominal pain.

Q2W Group
After Week 16, AEs leading to discontinuation of treatment drug in the Any secukinumab Q2W group that were also SAEs were large intestine infection (b) (6)), skin candida (b) (6)), sweat gland infection (b) (6) breast cancer (b) (6), and muscle spasms (b) (6)). Select events are discussed in more detail below. The event of sweat gland infection (b) (6) was detailed in the section of Serious Adverse Events.

Subject (b) (6): large intestine infection
A 38-year-old female with a history of active tobacco use, overweight status, and gastrointestinal (GI) motility disorder developed a large intestine infection 44 weeks after starting secukinumab Q2W. An abdominal scan and proctosigmoidoscopy showed colitis and moderate rectosigmoiditis, with rare erosions. Intestinal biopsies showed an infectious colitis. Tests for *Clostridium difficile* and parasites were negative. Treatment for the event included narcotic analgesics, anti-spasmodic agents, loperamide, mesalamine, ofloxacin, and metronidazole. At Week 52, the subject discontinued the trial due to the large intestinal infection, which was ongoing at the time of trial discontinuation.

This is a confirmed case of infectious colitis based on intestinal biopsies. The causality in this

case is assessed as possible based on the reasonable time relationship. However, the information on drug withdrawal is unclear. Additionally, the subject's underlying gut motility disorder might have contributed to the development of the AE.

Subject (b) (6) skin candida
A 33-year-old White female with a history of hypothyroidism and polycystic ovaries developed a severe inquinal candida infection approximately 13 weeks after starting secukinumab Q2W. The subject initially received placebo during Treatment Period 1 and transitioned to secukinumab Q2W at Week 16. The subject had mild inguinal candida intertrigo on Day 1 upon randomization to the placebo group. Although skin candida was reportedly resolved, trial medication was discontinued during Week 28. At Week 29 (approximately 2 weeks following the last dose of secukinumab), inguinal intertrigo worsened requiring a punch biopsy, fluconazole, and zinc oxide. Bacteriological, mycological, and parasitological exams were negative. At Week 35, the subject was reported to have recovered from skin candida.

The worsening candidal skin infection is assessed to be probably related to secukinumab use given the temporal relationship, positive dechallenge, and biological plausibility as IL-17A plays a functional role in antifungal responses.[12]

Subject (b) (6): breast cancer
A 50-year-old White female with a history of active tobacco use (34-pack years) was diagnosed with "breast cancer" 45 weeks after starting secukinumab Q2W. Shortly thereafter, treatment drug was discontinued due to this AE and the subject withdrew from the trial. She was started on docetaxel, pertuzumab, and trastuzumab and was reported as recovering from breast cancer at the time of trial discontinuation.

Causality is difficult to assess given the lack of details regarding the pathology, staging, and the subject's breast cancer risk factors (e.g., family history of breast cancer, personal history of atypical hyperplasia, age of menarche, etc.).

Q4W Group
After Treatment Period 1, AEs leading to discontinuation of treatment drug in the Any secukinumab Q4W group that were also SAEs were myocardial infarction (b) (6) pericarditis (b) (6)), scrotal infection ((b) (6), and nephrolithiasis (b) (6). The subject who suffered an MI was discussed under Deaths. Other select serious AEs that led to discontinuation of trial drug are detailed below.

Subject (b) (6): pericarditis and hypertensive emergency
A 20-year-old White male with a history of attention deficit hyperactivity disorder treated with amphetamine salts, obesity, depression on duloxetine; glucose

[12] Song, Xinyang et al. "The roles and functional mechanisms of interleukin-17 family cytokines in mucosal immunity." Cellular & molecular immunology vol. 13,4 (2016): 418-31

intolerance on metformin, and hypertension treated with guanfacine and diltiazem was diagnosed with “myopericarditis” 18 weeks after starting secukinumab Q4W. The subject was hospitalized for four days due to shortness of breath and chest pain in the setting of “hypertensive emergency”. Diagnostic evaluation excluded acute coronary syndrome and pulmonary embolism. A transthoracic echocardiogram showed an ejection fraction 60%, no pericardial effusion, and no obvious left ventricular wall motion abnormalities. Trial medication was temporarily interrupted, and the subject was treated with colchicine, amlodipine, heparin, lisinopril, pantoprazole, ibuprofen, morphine, ondansetron, diphenhydramine, ketorolac, potassium chloride, glyceryl trinitrate, paracetamol, and labetalol. He was discharged with diagnoses of myopericarditis and hypertensive emergency. His condition was reported as recovered at Week 24. At Week 37, the subject was hospitalized again due to recurrent pericarditis. Treatment drug was discontinued. At Week 62, the subject completed the trial. The event was ongoing despite discontinuation of secukinumab and treatment with colchicine, morphine, ketorolac, ibuprofen, glyceryl trinitrate, pantoprazole, ondansetron, and oxycodone.

Despite the negative dechallenge, causality is possible given the reasonable time relationship and no other plausible explanations.

Subject (b) (6): scrotal infection
A 50-year-old White male with a past medical history of diabetes mellitus, hypertension, and active tobacco use, developed paraphimosis, penile edema, and mild scrotal infection 18 weeks after starting secukinumab Q4W. Dosing of trial drug was interrupted and ceftriaxone was administered. In less than a week, the infection improved and trial drug was restarted.
At Week 19, recurrent scrotal infection was diagnosed but was described as severe in nature and considered serious. Trial medication was discontinued and the subject was treated with ceftriaxone, clindamycin, and amoxicillin-clavulanic acid in the hospital setting.
During Week 27, the subject developed a third severe scrotal infection requiring hospitalization and systemic antimicrobial agents. At Week 56, the subject completed the trial with the events of acquired phimosis and scrotal pain reported as ongoing.

Although the time relationship was reasonable for the first and second scrotal infections, the subject developed a third infection 8 weeks after discontinuation of secukinumab. His underlying comorbid conditions may have contributed to his recurrent infections. Causality is hence assessed as possible.

Based on the reported cases, it does not appear that the increased frequency of secukinumab dosing (Q2W instead of Q4W) significantly impacted the rate or type of AEs that led to treatment drug discontinuation.

While the clinical trial experience for the Q4W dosing has extensively evaluated safety in various patient populations with different chronic inflammatory conditions, the Q2W dosage regimen has not been as comprehensively studied. Other than the safety results from trials M2301 and M2302, data from a registrational trial, CAIN457A2324 (A2324) in which subjects with psoriasis were administered secukinumab every 2 weeks has been collected. During trial

A2324, an increased hypersensitivity risk was observed with secukinumab Q2W dosing compared to Q4W dosing. Given that hypersensitivity often worsens in severity with increased exposure, it would not be unexpected that they would lead to discontinuation of secukinumab use.

Significant Adverse Events

Refer to Section 7.2.5 "Analysis of Submission-specific Safety Issues".

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent AEs (TEAEs) were defined as any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) with onset after the first dose of trial drug and within 84 days after the last dose, or events present prior to the first dose of trial drug but increased in severity within 84 days after the last dose.

Adverse events were summarized as both subject incidence rates and exposure-adjusted event rates (EAIR) per 100 patient-years (PYs). The former provided the basis of assessment for the initial placebo-controlled period up to Week 16 (Treatment Period 1), while the latter provided for a more adequate assessment of the long term safety data (i.e., data from all subjects up to the data cut-off date) given the varied duration of exposure across different treatment groups. The exposure adjusted rates also allowed for comparison of data across the short-term and long-term analysis sets.

In the first 16 weeks of treatment, the number and proportion of subjects with TEAEs was similar among treatment groups: 239 (66%) in the secukinumab Q2W group, 236 (66%) in the secukinumab Q4W group, and 236 (65%) in the placebo group. Most TEAEs were mild or moderate in severity. Severe TEAEs were reported more commonly in subjects randomized to the placebo group (19/363, 5.2%) than those treated with either dose of secukinumab (10/361, 2.8% in the secukinumab Q2W and 11/360, 3.0% in the secukinumab Q4W group). The severe TEAEs that occurred in more than 1 subject in any secukinumab group were worsening hidradenitis suppurativa, which was reported in 3 subjects all of whom received secukinumab Q4W; inflammatory bowel disease which was reported in 2 subjects, one in the Q2W group and one in the Q4W group; and self harm, which also occurred in 2 subjects, one attempted suicide in the secukinumab Q2W group and one intentional overdose in the secukinumab Q4W group. Inflammatory bowel disease (IBD) and suicidal ideation and behavior (SIB) are adverse events of special interests (AESIs) and are discussed in Section 8.2.5 of this review.

The review team conducted an analysis wherein preferred terms (PT) for clinically similar AEs were grouped to give a more accurate assessment of their overall frequency. The preferred terms included in the AE pooling are presented in table footnotes.

Additionally, in attempts to determine which TEAEs may be related to secukinumab use, those reported in ≥ 1% of subjects in either secukinumab group and at least 1% more frequently than in the placebo group were evaluated. These TEAEs are presented in Table 34 below.

Table 34: Treatment Emergent Adverse Events Reported in ≥1% in Any Secukinumab Group and ≥1% More Frequently Than Placebo, 16-Week Placebo Controlled Period

Preferred Term	Secukinumab 300 mg Q2W (N=361) n (%)	Secukinumab 300 mg Q4W (N=360) n (%)	Placebo (N=363) n (%)
Upper respiratory infections*	100 (27.7)	82 (22.8)	96 (26.4)
Headache*	65 (18.0)	60 (16.7)	52 (14.3)
Eczema	18 (5.0)	11 (3.1)	7 (1.9)
Abdominal pain*	16 (4.4)	24 (6.7)	14 (3.9)
Dental caries*	16 (4.4)	14 (3.9)	8 (2.2)
Oropharyngeal pain	15 (4.2)	13 (3.6)	8 (2.2)
Folliculitis	13 (3.6)	6 (1.7)	9 (2.5)
Intertrigo	12 (3.3)	11 (3.1)	8 (2.2)
Vulvovaginal candidiasis*	12 (3.3)	9 (2.5)	5 (1.4)
Psoriasis	10 (2.8)	9 (2.5)	2 (0.6)
Lipase increased	10 (2.8)	11 (3.1)	6 (1.7)
Conjunctivitis	9 (2.5)	10 (2.8)	4 (1.1)
Gastroenteritis	9 (2.5)	5 (1.4)	5 (1.4)
Oral candidiasis	8 (2.2)	3 (0.8)	1 (0.3)
Cough	8 (2.2)	15 (4.2)	11 (3.0)
Fungal skin infection	7 (1.9)	2 (0.6)	0 (0.0)
Ligament sprain	7 (1.9)	7 (1.9)	3 (0.8)
Ear infection	6 (1.7)	4 (1.1)	1 (0.3)
Dermatitis contact	5 (1.4)	9 (2.5)	3 (0.8)
Hyperuricaemia	5 (1.4)	4 (1.1)	1 (0.3)
Dermatitis psoriasiform	4 (1.1)	1 (0.3)	0 (0.0)
Hyperkeratosis	4 (1.1)	1 (0.3)	0 (0.0)
Hypertriglyceridemia*	4 (1.1)	9 (2.5)	5 (1.4)
Haemorrhoids	2 (0.6)	6 (1.7)	1 (0.3)
Chest pain	1 (0.3)	6 (1.7)	0 (0.0)
Seasonal allergy	1 (0.3)	4 (1.1)	0 (0.0)
Skin infection	0 (0.0)	4 (1.1)	0 (0.0)

Source: Clinical Reviewer's Table, OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q2W); TRT01A = "Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Upper respiratory infections* includes: Laryngitis, Nasopharyngitis, Pharyngitis, Pharyngitis bacterial, Pharyngitis streptococcal, Pharyngotonsillitis, Respiratory tract infection viral, Rhinitis, Sinusitis, Sinusitis bacterial, Tonsillitis, Tonsillitis bacterial, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Upper respiratory tract inflammation, Viral rhinitis, Viral tonsillitis, Viral upper respiratory tract infection.
Abdominal pain* includes: Abdominal pain, Abdominal pain upper
Dental caries* includes: Dental caries, Toothache.
Headache* includes: Headache, Migraine.
Vulvovaginal candidiasis* includes: Vulvovaginal candidiasis, Vulvovaginal mycotic infection
Hypertriglyceridemia* includes: Blood triglycerides increased, Hypertriglyceridaemia.

The TEAEs reported more commonly in subjects treated with secukinumab Q2W and at a significantly higher rate (i.e., >1%) compared to subjects treated with secukinumab Q4W

include upper respiratory infections, headache, eczema, folliculitis, gastroenteritis, oral candidiasis, and fungal skin infection. Because IL-17A has a functional role in mucosal integrity[13], as well as anti-extracellular bacterial and antifungal responses[14], it is reasonable to consider that increased dose frequency of secukinumab every 2 weeks incurs a higher risk for these adverse events.

Table 35 shows adverse reactions (ARs) some of which warrant eventual incorporation into product labeling because of the imbalance of incidence rates observed during the HS trials but also due to biological plausibility. For example, eczema occurred at a higher rate in subjects with HS in the secukinumab groups (5.0% for the secukinumab Q2W group and 3.1% for the secukinumab Q4W group) compared to the placebo group (1.9%). In the postmarketing setting, there have also been cases of eczematous eruptions thought to be possible paradoxical reactions related to secukinumab use. These cutaneous ARs are the subject of an ongoing safety labeling change review in which eczematous eruptions are planned for inclusion under the Warning and Precautions, as well as Adverse Reactions sections of the full prescribing information (FPI). Additionally, based on reviews of postmarketing cases, labeling updates are planned to describe opportunistic infections, including fungal infections. As shown in the following table, fungal infections (i.e., vulvovaginal candidiasis, oral candidiasis, and fungal skin infections) occurred at higher rates in the secukinumab groups relative to placebo. The imbalance supported by postmarketing findings underscore the significant immunosuppressive impact of IL-17 inhibition and warrant updates to the Warning and Precautions, as well as Adverse Reactions sections of labeling. These issues are discussed in further detail within this review under 8.2.5.2 Infections, as well as 8.2.10. Safety in the Postmarket Setting.

Also worth comment is the increased incidence of dental caries and oropharyngeal pain in the secukinumab groups compared to placebo as demonstrated in Table – below. An increased risk of dental caries has been correlated with tobacco use[15] and most (54.0%) randomized subjects were current smokers. However, the proportion of smokers across treatment groups was comparable. According to published literature , Candida albicans is often detected in dental plaque biofilms and has the capability to cause caries.[16,17] These findings further support labeling updates to emphasize the occurrence of fungal infections associated with secukinumab use and underscore the possible dose dependent risk.

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[13] Ma Wen-Tao et. al The protective and pathogenic roles of IL-17 in viral infections: friend or foe? Open Biol. 2019; 9: 190109.
[14] Song, Xinyang et al. “The roles and functional mechanisms of interleukin-17 family cytokines in mucosal immunity.” Cellular & molecular immunology vol. 13,4 (2016): 418-31.
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[17] Gregoire S, Xiao J, Silva BB, Gonzalez I, Agidi PS, Klein MI, Ambatipudi KS, Rosalen PL, Bauserman R, Waugh RE, Koo H. Role of glucosyltransferase B in interactions of Candida albicans with Streptococcus mutans and with an experimental pellicle on hydroxyapatite surfaces. Appl Environ Microbiol. 2011 Sep;77(18):6357-67.

Table 35: Adverse Reactions reported in ≥1% in Any Secukinumab Group and More Frequently Than Placebo, 16-Week Placebo Controlled Period

Preferred Term	Secukinumab 300 mg Q2W (N=361) n (%)	Secukinumab 300 mg Q4W (N=360) n (%)	Placebo (N=363) n (%)
Upper respiratory infections*	100 (27.7)	82 (22.8)	96 (26.4)
Headache*	65 (18.0)	60 (16.7)	52 (14.3)
Eczema	18 (5.0)	11 (3.1)	7 (1.9)
Abdominal pain*	16 (4.4)	24 (6.7)	14 (3.9)
Dental caries*	16 (4.4)	14 (3.9)	8 (2.2)
Oropharyngeal pain	15 (4.2)	13 (3.6)	8 (2.2)
Folliculitis	13 (3.6)	6 (1.7)	9 (2.5)
Intertrigo	12 (3.3)	11 (3.1)	8 (2.2)
Vulvovaginal candidiasis*	12 (3.3)	9 (2.5)	5 (1.4)
Psoriasis	10 (2.8)	9 (2.5)	2 (0.6)
Lipase increased	10 (2.8)	11 (3.1)	6 (1.7)
Conjunctivitis	9 (2.5)	10 (2.8)	4 (1.1)
Gastroenteritis	9 (2.5)	5 (1.4)	5 (1.4)
Oral candidiasis	8 (2.2)	3 (0.8)	1 (0.3)
Cough	8 (2.2)	15 (4.2)	11 (3.0)
Fungal skin infection	7 (1.9)	2 (0.6)	0 (0.0)
Ear infection	6 (1.7)	4 (1.1)	1 (0.3)
Dermatitis contact	5 (1.4)	9 (2.5)	3 (0.8)
Dermatitis psoriasiform	4 (1.1)	1 (0.3)	0 (0.0)
Hypertriglyceridemia*	4 (1.1)	9 (2.5)	5 (1.4)

Source: Clinical Reviewer's Table, OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q2W); TRT01A = "Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 1%.

Upper respiratory infections* includes: Laryngitis, Nasopharyngitis, Pharyngitis, Pharyngitis bacterial, Pharyngitis streptococcal, Pharyngotonsillitis, Respiratory tract infection viral, Rhinitis, Sinusitis, Sinusitis bacterial, Tonsillitis, Tonsillitis bacterial, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Upper respiratory tract inflammation, Viral rhinitis, Viral tonsillitis, Viral upper respiratory tract infection.
Abdominal pain* includes: Abdominal pain, Abdominal pain upper
Dental caries* includes: Dental caries, Toothache.
Headache* includes: Headache, Migraine.
Vulvovaginal candidiasis* includes: Vulvovaginal candidiasis, Vulvovaginal mycotic infection
Hypertriglyceridemia* includes: Blood triglycerides increased, Hypertriglyceridaemia.

After 52 weeks of exposure, the overall incidence rate of TEAEs was comparable between the Any secukinumab Q2W group and the Any secukinumab Q4W group (81.4% and 82.7%, respectively). Following adjustment for exposure-time, the overall incidence rate of TEAEs was numerically lower in Any secukinumab Q2W (274.9/100 PY) compared to Any secukinumab Q4W (299.3/100 PY), with no apparent AE driving the difference. The types of TEAEs reported for the Entire Treatment Period were similar to those observed during the first 16 weeks of treatment. The most frequently reported AEs (≥ 2%) were headache, upper respiratory tract infection (including nasopharyngitis), (worsening of) hidradenitis, and diarrhea, with generally similar frequencies between the Any secukinumab Q2W and Q4W groups as shown in Table 36 below.

Table 36: Exposure-adjusted incidence rates of most frequent (greater than or equal to 2% in any treatment group) treatment-emergent adverse events, by preferred term - Entire Trial Period (Safety set)

Preferred term	Sec Q2W N=361 n/EX	Sec Q4W N=360 n/EX (IR)	Any Sec Q2W N=527 n/EX (IR)	Any Sec Q4W N=533 n/EX (IR)	Any Sec N=1060 n/EX (IR)	Placebo N=363 n/EX (IR)
Any preferred term	**301/1.08 (278.6)**	**304/1.05 (290.9)**	**429/1.56 (274.9)**	**441/1.47 (299.3)**	**870/3.03 (286.7)**	**236/0.57 (412.4)**
Headache	64/2.92 (21.9)	58/2.93 (19.8)	78/3.99 (19.5)	82/3.97 (20.7)	160/7.96 (20.1)	30/1.05 (28.7)
Nasopharyngitis	53/3.03 (17.5)	42/3.06 (13.7)	68/4.08 (16.7)	54/4.17 (13.0)	122/8.25 (14.8)	29/1.06 (27.4)
Hidradenitis	41/3.15 (13.0)	43/3.13 (13.7)	59/4.22 (14.0)	61/4.20 (14.5)	120/8.42 (14.2)	38/1.04 (36.5)
Diarrhea	24/3.22 (7.4)	30/3.12 (9.6)	31/4.34 (7.1)	43/4.22 (10.2)	74/8.56 (8.6)	22/1.06 (20.7)
Upper respiratory tract infection	22/3.23 (6.8)	20/3.23 (6.2)	28/4.33 (6.5)	27/4.35 (6.2)	55/8.68 (6.3)	11/1.09 (10.1)
Pyrexia	22/3.24 (6.8)	16/3.26 (4.9)	27/4.35 (6.2)	25/4.39 (5.7)	52/8.74 (6.0)	6/1.10 (5.5)
Arthralgia	17/3.27 (5.2)	10/3.30 (3.0)	24/4.37 (5.5)	18/4.43 (4.1)	42/8.80 (4.8)	13/1.09 (11.9)
COVID-19	16/3.32 (4.8)	10/3.31 (3.0)	20/4.43 (4.5)	22/4.43 (5.0)	42/8.86 (4.7)	3/1.10 (2.7)
Back pain	11/3.32 (3.3)	20/3.22 (6.2)	14/4.44 (3.2)	26/4.35 (6.0)	40/8.79 (4.5)	12/1.09 (11.0)
Urinary tract infection	16/3.29 (4.9)	15/3.26 (4.6)	18/4.41 (4.1)	22/4.38 (5.0)	40/8.79 (4.5)	8/1.10 (7.3)
Eczema	21/3.28 (6.4)	12/3.28 (3.7)	23/4.41 (5.2)	16/4.42 (3.6)	39/8.82 (4.4)	2/1.11 (1.8)
Nausea	10/3.30 (3.0)	13/3.26 (4.0)	18/4.40 (4.1)	20/4.39 (4.6)	38/8.78 (4.3)	11/1.09 (10.1)
Pruritus	18/3.27 (5.5)	9/3.28 (2.7)	25/4.36 (5.7)	12/4.43 (2.7)	37/8.79 (4.2)	7/1.09 (6.4)
Fatigue	10/3.29 (3.0)	17/3.22 (5.3)	15/4.40 (3.4)	21/4.36 (4.8)	36/8.76 (4.1)	10/1.09 (9.2)
Oropharyngeal pain	17/3.27 (5.2)	13/3.25 (4.0)	19/4.39 (4.3)	16/4.39 (3.6)	35/8.78 (4.0)	4/1.10 (3.6)
Abdominal pain	11/3.34 (3.3)	13/3.26 (4.0)	13/4.46 (2.9)	21/4.38 (4.8)	34/8.84 (3.8)	3/1.10 (2.7)
Hypertension	16/3.30 (4.9)	10/3.29 (3.0)	21/4.40 (4.8)	12/4.43 (2.7)	33/8.83 (3.7)	4/1.10 (3.6)
Cough	9/3.33 (2.7)	15/3.24 (4.6)	13/4.45 (2.9)	19/4.38 (4.3)	32/8.82 (3.6)	4/1.10 (3.6)
Intertrigo	13/3.31 (3.9)	12/3.28 (3.7)	16/4.43 (3.6)	16/4.42 (3.6)	32/8.84 (3.6)	2/1.11 (1.8)
Lipase increased	11/3.31 (3.3)	14/3.26 (4.3)	13/4.43 (2.9)	16/4.41 (3.6)	29/8.83 (3.3)	3/1.10 (2.7)
Pharyngitis	10/3.30 (3.0)	11/3.27 (3.4)	12/4.42 (2.7)	16/4.41 (3.6)	28/8.83 (3.2)	4/1.11 (3.6)
Toothache	13/3.31 (3.9)	11/3.28 (3.4)	16/4.43 (3.6)	12/4.43 (2.7)	28/8.85 (3.2)	4/1.10 (3.6)
Abdominal pain upper	7/3.34 (2.1)	14/3.25 (4.3)	8/4.47 (1.8)	19/4.39 (4.3)	27/8.86 (3.0)	2/1.11 (1.8)
Dizziness	10/3.31 (3.0)	10/3.26 (3.1)	13/4.43 (2.9)	13/4.40 (3.0)	26/8.83 (2.9)	6/1.10 (5.5)
Bronchitis	10/3.33 (3.0)	11/3.29 (3.3)	10/4.46 (2.2)	15/4.43 (3.4)	25/8.89 (2.8)	5/1.10 (4.5)

Source: Modified Applicant SCS Table 2-4
Preferred terms are sorted in descending order of IR in Any Sec group.
A subject with multiple adverse events with the same preferred term is counted only once for that preferred term.
EX = Exposure in 100 subject years. IR = Incidence rate per 100 subject years. Sec=secukinumab
For subjects with multiple events within the preferred term, exposure time is censored at time of first event.

Overall, the adverse reactions observed in subjects with moderate to severe HS treated with secukinumab Q2W or Q4W were generally consistent with the adverse reactions in patients with psoriasis.

Laboratory Findings

Clinical safety laboratory evaluations were performed at Screening, Baseline, Week 2, Week 4, and then every 4 weeks through the end of Treatment Period 1 followed by assessments at Weeks 18, 20, 28, 44, 52, and 60 during trials M2301 and M2302. During the extension trial, M2301E1, clinical chemistry and hematology were assessed at every visit.

Hematology
Overall, there were infrequent hematological CTCAE grade shifts throughout the trials. During Treatment Period 1, the majority of new or worsening CTCAE grade abnormalities after baseline assessment were Grade 1. There were no Grade 4 abnormalities reported.

Grade 1 and 2 abnormalities in hemoglobin were most common in the placebo group compared to both secukinumab groups. Single events of Grade 3 (< 80 g/L) hemoglobin abnormalities were reported in two subjects, one in the secukinumab Q4W group and one in the placebo group. There were no Grade 3 abnormalities in the secukinumab Q2W group. The subject in the secukinumab Q4W group had a normal baseline hemoglobin level and discontinued trial drug due to an AE of Inflammatory Bowel Disease. The subject in the placebo group had grade 2 hemoglobin values at baseline.

Similar to the hemoglobin abnormalities, most cases of low neutrophil counts were Grade 1 or 2 and also single events. Grade 1 and 2 low neutrophil counts were collectively most common in the secukinumab Q4W group (12/354, 3.4%) compared to both the secukinumab Q2W (7/357, 2.0%) and placebo (8/358, 2.2%) groups. Two cases of Grade 3 neutropenia (<1.0 - 0.5 x 10E9/L) were single events with one occurring in a subject receiving secukinumab Q2W and one reported in a subject receiving placebo. Both subjects had normal baseline values. The subject in the secukinumab Q2W group improved to grade 2 and 1 at subsequent visits. The neutrophil count in the placebo-treated subject returned to normal at a subsequent visit. Both subjects completed treatment and their respective trials per protocol.

After 52 weeks of exposure, two additional subjects, one in each Any secukinumab Q2W group and Any secukinumab Q4W group had Grade 3 anemia. Both subjects had grade 1 hemoglobin abnormalities at baseline and low hemoglobin levels throughout the trials. Both withdrew from the trials reportedly due to lack of efficacy.

One additional subject in the Any secukinumab Q2W group had Grade 3 neutropenia, and two subjects in the Any secukinumab Q4W group had Grade 4 neutropenia. All three subjects had normal absolute neutrophil counts at baseline. All of the abnormalities were isolated, single events that returned to normal at subsequent visits. Each subject completed treatment and the trials per protocol.

Based on the infrequent occurrence of hematological abnormalities and absence of clinically significant sequelae, as well as lack of an imbalance in neutropenia AEs (as described in Section 8.2.5.6. Neutropenia), an update to the COSENTYX labeling which currently describes neutropenia in Section 6.1 in both adult and pediatric patients, is not warranted at this time.

Chemistry
The majority of new or worsening chemistry laboratory abnormalities over the Entire Trial Period were CTCAE Grade 1 or 2 and occurred at generally comparable rates across treatment arms as shown in Table 37. Given the differences in treatment exposures over the 52 week period, comparisons of secukinumab to placebo for the Entire Trial Period should be made and interpreted with caution.

Table 37: Number (%) of Subjects with New or Worsening CTCAE grade Chemistry Abnormalities after Baseline - Entire Trial Period (Safety set)

Laboratory Parameter	CTCAE	Criteria	Any AIN457 Q2W (N=527) n/m (%)	Any AIN457 Q4W (N=533) n/m (%)	Placebo (N=363) n/m (%)
Alanine Aminotransferase (U/L)	Grade 1	> ULN - 3.0 x ULN	92/ 522 (17.6)	90/ 527 (17.1)	43/ 359 (12.0)
	Grade 2	> 3.0 - 5.0 x ULN	5/ 522 (1.0)	4/ 527 (0.8)	3/ 359 (0.8)
	Grade 3	> 5.0 - 20.0 x ULN	3/ 522 (0.6)	2/ 527 (0.4)	0/ 359 (0.0)
	Grade 4	> 20.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
Alkaline Phosphatase (U/L)	Grade 1	> ULN - 2.5 x ULN	30/ 522 (5.7)	35/ 527 (6.6)	16/ 359 (4.5)
	Grade 2	> 2.5 - 5.0 x ULN	1/ 522 (0.2)	1/ 527 (0.2)	1/ 359 (0.3)
	Grade 3	> 5.0 - 20.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
	Grade 4	> 20.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
Aspartate Aminotransferase (U/L)	Grade 1	> ULN - 3.0 x ULN	52/ 522 (10.0)	60/ 527 (11.4)	31/ 359 (8.6)
	Grade 2	> 3.0 - 5.0 x ULN	4/ 522 (0.8)	3/ 527 (0.6)	1/ 359 (0.3)
	Grade 3	> 5.0 - 20.0 x ULN	3/ 522 (0.6)	2/ 527 (0.4)	0/ 359 (0.0)
	Grade 4	> 20.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
Bilirubin (umol/L)	Grade 1	> ULN - 1.5 x ULN	7/ 522 (1.3)	6/ 527 (1.1)	2/ 359 (0.6)
	Grade 2	> 1.5 - 3.0 x ULN	0/ 522 (0.0)	3/ 527 (0.6)	0/ 359 (0.0)
	Grade 3	> 3.0 - 10.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
	Grade 4	> 10.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
Creatinine (umol/L)	Grade 1	> ULN - 1.5 x ULN	50/ 522 (9.6)	53/ 527 (10.1)	22/ 359 (6.1)
	Grade 2	> 1.5 - 3.0 x ULN	2/ 522 (0.4)	2/ 527 (0.4)	2/ 359 (0.6)
	Grade 3	> 3.0 - 6.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
	Grade 4	> 6.0 x ULN	0/ 522 (0.0)	0/ 527 (0.0)	0/ 359 (0.0)
Gamma Glutamyl Transferase (U/L)	Grade 1	> ULN - 2.5 x ULN	44/ 522 (8.4)	52/ 527 (9.9)	27/ 359 (7.5)
	Grade 2	> 2.5 - 5.0 x ULN	15/ 522 (2.9)	9/ 527 (1.7)	4/ 359 (1.1)
	Grade 3	> 5.0 - 20.0 x ULN	1/ 522 (0.2)	3/ 527 (0.6)	1/ 359 (0.3)
	Grade 4	> 20.0 x ULN	0/ 522 (0.0)	1/ 527 (0.2)	0/ 359 (0.0)

Source: Modified Applicant SCS Tables 3.3 and 3.4

Four subjects (2 in each secukinumab arm) reported Grade 3 ALT values during the Entire Trial

Period. All but one subject had ALT values that improved or returned to reference range at subsequent visits despite no change in dosing. One subject in the Any secukinumab Q4W group was in the trial at the time of data cut-off, but there were no data from a subsequent visit.

Five subjects (3 in the secukinumab Q2W group and 2 in the Q4W group) reported Grade 3 AST values during the Entire Trial Period. Similar to the subjects with Grade 3 ALT values, all but one subject had AST values that improved or returned to reference range at subsequent visits despite no change in the dosage regimen. One subject in the Any secukinumab Q4W group remained in the trial, but there were no data from a subsequent visit as of the database lock.

One subject in the Any secukinumab Q4W group with a history of non-alcoholic steatohepatitis (NASH) and a baseline Grade 2 GGT level, experienced an isolated Grade 4 GGT abnormality that was reported at the Week 52 visit. The subject's GGT levels were high throughout the trial and occurred in the setting of an AE of worsening of NASH; however, the subject completed the trial per protocol and transitioned to the extension trial.

Vital Signs

There were no clinically meaningful changes in vital sign parameters (sitting pulse rate and blood pressure) between treatment groups during the controlled period, Entire Trial Period, or safety update reporting period. A higher incidence of hypertension PT in the secukinumab Q2W group compared to the secukinumab Q4W and placebo groups was observed; however, there was no clinically meaningful change from baseline in blood pressure observed in any treatment group as further discussed in Section 8.2.5.7. Cardiovascular (CV) events including Major CV events (MACE).

Electrocardiograms (ECGs)

ECGs were not obtained during trials M2301, M2302, and M2301E1.

QT

Large monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study was not necessary to conduct for this supplement.

Immunogenicity

Potential risks based on class of drug (anti-cytokine) and of the drug substance (foreign protein) were considered. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site reactions and immunogenicity.
Four subjects with Treatment-emergent anti-drug-antibodies (TE-ADA) were observed in trials M2301 and M2302.

In Trial M2301, one subject receiving secukinumab Q4W had TE-ADA with no neutralizing antibodies noted. The TE-ADA incidence in the trial was 0.2% (1 of 491 subjects who were ADA

negative at baseline).

In Trial M2302, three subjects developed TE-ADA, two in the secukinumab Q2W group (one at Week 16 and one during the follow-up period) and one in the secukinumab Q4W group. None of these 3 cases showed neutralizing antibodies, and none were observed in subjects who switched from placebo to secukinumab at Week 16. The TE-ADA incidence in the trial was 0.6% (3 of 492 subjects who were ADA negative at baseline).

The overall TE-ADA incidence was <1% in the HS trial population. The development of TE-ADA was not associated with any injection site reactions, nor with serious or severe administration reactions.

As previously discussed under Section 8.2.5.3. Hypersensitivity, the incidence of hypersensitivity was highest in the secukinumab Q2W group compared to the secukinumab Q4W and placebo groups. Although the review team assessed causality as possible in only one case and determined that there were no cases of probable causality, the overall imbalance is concerning. A positive association between the incidence of these hypersensitivity events and more frequent dosing cannot be ruled out.

This higher rate of hypersensitivity coupled with marginally better efficacy on the primary endpoint (HISCR50 response), generates a less favorable risk-benefit profile for secukinumab 300 mg dosed every 2 weeks in adults with moderate to severe HS. Therefore, the review team determined that labeling should reflect that for some patients who fail to improve with secukiniumab 300 mg every 4 weeks, a dosage of 300 mg every 2 weeks may be acceptable for the treatment of moderate to severe HS.

Hypersensitivity is labeled under Contraindications and Warning and Precautions in the current secukinumab USPI. While no further updates to these sections regarding hypersensitivity are indicated at this time, ongoing postmarketing surveillance of these events is necessary.

8.2.5. Analysis of Submission-Specific Safety Issues

Due to the various inflammatory processes that are thought to play a role in the pathogenesis of HS and because of the recalcitrant nature of moderate to severe disease, rescue medical and surgical interventions for worsening of disease were allowed during the course of the trials. The event of *worsening HS* requiring rescue therapies (e.g., oral antibiotics) was an area of safety interest that will be discussed in this section.

Safety considerations that have arisen from prior experience with secukinumab will also be discussed here. These adverse events of special interest (AESIs) include infections, hypersensitivity, suicidal ideation and behavior (SIB), inflammatory bowel disease (IBD), neutropenia, major adverse cardiovascular events (MACE), and malignancy.
The incidences of these AESIs during the placebo-controlled period are shown in Table 38 and reflect comparable rates for overall infections, notable imbalances of fungal infections and

hypersensitivity events, as well as no reported MACE across treatment groups during the first 16 weeks. Further details on each of these AESIs are discussed in subsections to follow.

Table 38: Incidence Rates of AESIs – Treatment Period 1 (Safety Set)

AESI	Secukinumab Q2W N=361 n (%)	Secukinumab Q4W N=360 n (%)	Secukinumab Any N=721 n (%)	Placebo N=363 n (%)
Infections and infestations (SOC)	111 (30.7)	111 (30.8)	222 (30.8)	115 (31.7)
Infective pneumonia (SMQ) (broad)	8 (2.2)	6 (1.7)	14 (1.9)	12 (3.3)
Fungal infectious disorders (HLGT)	19 (5.3)	14 (3.9)	33 (4.6)	10 (2.8)
Herpes viral infections (HLT)	5 (1.4)	3 (0.8)	8 (1.1)	4 (1.1)
Infections of skin structures (NMQ)	47 (13.0)	51 (14.2)	98 (13.6)	64 (17.6)
Staphylococcal infections (HLT)	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Hypersensitivity (SMQ) (narrow)	19 (5.3)	14 (3.9)	33 (4.6)	16 (4.4)
Suicidal ideation and behavior (SMQ)	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Inflammatory Bowel Disease (FMQ Broad)	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Neutropenia (FMQ Broad)	1 (0.3)	2 (0.6)	3 (0.4)	0 (0.0)
MACE (NMQ)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant or unspecified tumors (SMQ)	0 (0.0)	2 (0.6)	2 (0.3)	2 (0.6)

Source: Modified Applicant's SCS Table 2-14

8.2.5.1. Worsening hidradenitis

During Treatment Period 1, the AE of worsening hidradenitis was one of the most commonly reported AEs by PT. Not surprisingly, the the placebo group had the highest reported rate (71, 19.6%) as shown in Table 39 below. Although one might expect the rate for the secukinumab Q2W group to be higher compared to that of the secukinumab Q4W group given the former was comprised of more subjects with greater baseline disease severity based on Hurley staging, the rate of worsening HS was comparable between the two secukinumab arms.

Table 39: Treatment-emergent Worsening Hidradenitis Suppurativa – Treatment Period 1 (Safety Set)

Grouped Term	Secukinumab 300 mg Q2W (N=361) n (%)	Secukinumab 300 mg Q4W (N=360) n (%)	Placebo (N=363) n (%)
Worsening HS	44 (12.2)	47 (13.1)	71 (19.6)

Source: Clinical Reviewer's Table, OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q2W); TRT01A = "Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).
Worsening HS includes: Hidradenitis, Sweat gland infection.

With longer exposure, the incidence of worsening hidradenitis was consistent with the findings of Treatment Period 1.

Table 40: Treatment-emergent Worsening Hidradenitis Suppurativa – Entire Trial Period (Safety Set)

Grouped Term	Any secukinumab 300 mg Q2W (N=527) n (%)	Any secukinumab 300 mg Q4W (N=533) n (%)	Placebo (N=363) n (%)
Worsening HS	79 (15.0)	79 (14.8)	71 (19.6)

Source: Clinical Reviewe's Table, OCS Analysis Studio, Safety Explorer.
Filters: TRTSEQA = "Secukinumab 300 mg every 2 weeks" or "Placebo - Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Any secukinumab 300 mg Q2W); TRTSEQA = "Secukinumab 300 mg every 4 weeks" or "Placebo - Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Any secukinumab 300 mg Q4W); TRTSEQA = "Placebo" or "Placebo - Secukinumab 300 mg every 4 weeks" or "Placebo - Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).
Worsening HS includes: Hidradenitis, Sweat gland infection.

As noted during the review of Serious Adverse Events, the higher rate of serious skin disorders for the secukinumab Q2W group was driven by a greater number of worsening hidradenitis events, and the higher rate of serious infections in the secukinumab Q4W group was primarily driven by sweat gland infections. Given HS-related AEs span both the Infectious and Skin/Subcutaneous SOCs, it is understandable that the overall rate of worsening hidradenitis was similar between the secukinumab groups.

During the placebo-controlled period, rescue medications (i.e., stable doses of doxycycline and minocycline) were permitted for an increase in AN count of at least 3 lesions, and lesion interventions (i.e., incision, drainage, intralesional corticosteroid injections) were allowed in case one single lesion required immediate intervention. After Week 16, antibiotic use and surgical interventions were allowed in case of HS worsening regardless of the increase in the number of AN or the lesions needing intervention.

In the first 16 weeks of treatment, a greater proportion of subjects in the placebo group (7.1%) required rescue medications compared to 6.1% in the secukinumab Q2W group and 4.5% in the secukinumab Q4W group. Similarly, a larger proportion of subjects in the placebo group (11.0%)

required lesion intervention compared to the secukinumab groups (4.4% in secukinumab Q2W and 6.1% in secukinumab Q4W).

With longer exposure, the findings were similar to those from Treatment Period 1. A higher proportion of subjects in the Any secukinumab Q2W group (13.7%) required rescue medications compared to the Any secukinumab Q4W group (12.4%); and a greater proportion of subjects in the Any secukinumab Q4W group (15.4%) necessitated rescue interventions compared to the Any secukinumab Q2W group (9.1%). While the findings are not unexpected for the use of rescue medications, it is not clear why, despite a more severe population enrolled in the secukinumab Q2W arm, more subjects receiving secukinumab Q4W required rescue interventions.

8.2.5.2. Infections

Given the functional role that IL-17A plays in mucosal integrity, antiviral immunity[18], as well as anti-extracellular bacterial and antifungal responses[19], infections (including serious infections, opportunistic infections, tuberculosis, fungal infections, herpes zoster, and hepatitis B reactivation) is considered an area of safety interest for secukinumab. Additionally, the moderate to severe HS population often have chronic, ruptured HS lesions and skin tunnels that contain a variety of gram positive cocci, gram negative rods, and anaerobic bacteria which have been theorized to promote an inflammatory response[20] and may also increase the risk for secondary infection.

In the first 16 weeks of treatment, the rate of overall infections (by SOC) appeared comparable between treatment groups (30.7% for the secukinumab Q2W group, 30.8% for the secukinumab Q4W group, and 31.7% for the placebo group). However, upon further analyses of more narrowed infection categories, fungal infections were reported more frequently for the secukinumab Q2W group (19, 5.3%) compared to the secukinumab Q4W (14, 3.9%) and placebo (10, 2.8%) groups as shown in Table 41 below. The table also shows a higher incidence of infections involving skin structures for subjects in the placebo (64, 17.6%) and relatively comparable rates for the secukinumab Q4W (51, 14.2%) group compared to the secukinumab Q2W group (47, 13.0%), which is not unexpected for this population with deep inflammatory skin lesions comprised mostly of inflammatory nodules and abscesses. As described in the section, Serious Adverse Events, the secukinumab Q2W group was comprised of subjects with more severe disease at baseline (based on Hurley staging) and there was a higher rate of worsening hidradenitis SAEs in this group possibly related to lower systemic exposure as PK data demonstrated that drug clearance is increased with more severe disease. The slight

[18] Ma Wen-Tao et. al The protective and pathogenic roles of IL-17 in viral infections: friend or foe? Open Biol. 2019; 9: 190109.
[19] Song, Xinyang et al. “The roles and functional mechanisms of interleukin-17 family cytokines in mucosal immunity.” Cellular & molecular immunology vol. 13,4 (2016): 418-31.
[20] Ingram J. Hidradenitis suppurativa: Pathogenesis, clinical features, and diagnosis. UpToDate. Accessed May 11, 2023

numerical difference in the rates of skin infections between the secukinumab groups might be related to a difference in systemic exposure.

Table 41: Incidence Rates of Infections – Treatment Period 1 (Safety Set)

AESI	Secukinumab Q2W N=361 n (%)	Secukinumab Q4W N=360 n (%)	Secukinumab Any N=721 n (%)	Placebo N=363 n (%)
Infections and infestations (SOC)	111 (30.7)	111 (30.8)	222 (30.8)	115 (31.7)
Infective pneumonia (SMQ) (broad)	8 (2.2)	6 (1.7)	14 (1.9)	12 (3.3)
Fungal infectious disorders (HLGT)	19 (5.3)	14 (3.9)	33 (4.6)	10 (2.8)
Herpes viral infections (HLT)	5 (1.4)	3 (0.8)	8 (1.1)	4 (1.1)
Infections of skin structures (NMQ)	47 (13.0)	51 (14.2)	98 (13.6)	64 (17.6)
Staphylococcal infections (HLT)	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)

Source: Modified Applicant's SCS Table 2-14

After 52 weeks of exposure, the rate of overall infections was highest for the placebo group (127.6/100 PY) and appeared to be driven by skin infections; however, comparisons of secukinumab to placebo for the Entire Trial Period should be interpreted with caution as AE rates may not be constant over time. As shown in Table 42 more infections by SOC were reported for the Any secukinumab Q2W group (94.5/100 PY) compared to the Any secukinumab Q4W group (87.9/100 PY), and this difference appeared to be due to the higher rate of fungal infections.

Table 42: Incidence Rates of Infections – Entire Trial Period (Safety Set)

Risk Category Risk Name	Any secukinumab Q2W N=527 n/EX (IR)	Any secukinumab Q4W N=533 n/EX (IR)	Any secukinumab N=1060 n/EX (IR)	Placebo N=363 n/EX (IR)
Infections and infestations (SOC)	273/2.89 (94.5)	261/2.97 (87.9)	534/5.86 (91.1)	115/0.90 (127.6)
Infective pneumonia (SMQ) (broad)	51/4.27 (11.9)	54/4.29 (12.6)	105/8.56 (12.3)	12/1.09 (11.0)
Opportunistic infections (CMQ)	2/4.51 (0.4)	1/4.50 (0.2)	3/9.00 (0.3)	0/1.11 (0.0)
Central nervous system infections and inflammations (HLGT)	1/4.51 (0.2)	0/4.50 (0.0)	1/9.01 (0.1)	0/1.11 (0.0)
Fungal infectious disorders (HLGT)	62/4.23 (14.7)	43/4.27 (10.1)	105/8.50 (12.4)	10/1.10 (9.1)
Herpes viral infections (HLT)	11/4.46	15/4.42	26/8.88	4/1.10

	(2.5)	(3.4)	(2.9)	(3.6)
Mycobacterial infectious disorders	2/4.51	0/4.50	2/9.01	0/1.11
(HLGT)	(0.4)	(0.0)	(0.2)	(0.0)
Esophageal candidiasis (NMQ)	0/4.51	1/4.50	1/9.01	0/1.11
(narrow)	(0.0)	(0.2)	(0.1)	(0.0)
Infections of skin structures (NMQ)	154/3.72	148/3.72	302/7.44	64/0.99
	(41.4)	(39.8)	(40.6)	(64.6)
Staphylococcal infections (HLT)	6/4.48	3/4.48	9/8.96	0/1.11
	(1.3)	(0.7)	(1.0)	(0.0)

Source: Modified Applicant's SCS Table 2-15

Within the safety update, one new infection (COVID-19) was reported in a subject receiving 49 weeks of secukinumab Q2W in Trial M2301. The subject recovered without treatment and received the last dose of secukinumab per protocol.

Over the entire HS program, 50% of subjects who received Any secukinumab dose reported infection AEs (91.1/100 PY). The majority of these infections were mild or moderate and nonserious.

Serious Infections

In the first 16 weeks of treatment, the secukinumab Q4W group comprised the most subjects who experienced a serious infection (5, 1.4%) compared to 1 (0.3%) in the secukinumab Q2W group and 3 (0.8%) in the placebo group. The serious infections in the Q4W group included acute bacterial meningitis, cellulitis, sweat gland infection, appendicitis, and otitis externa, all of which recovered/resolved or were recovering. The events of cellulitis, sweat gland infection, and otitis externa did not require change in dosage regimen. For the case of appendicitis, drug was interrupted. However, in the case of bacterial meningitis, drug was withdrawn as described in section, Serious Adverse Events. The serious infection reported for the subject in the Q2W group was a urinary tract infection that required interruption of drug and resolved. The 3 subjects in the placebo group reported serious Clostridium difficile colitis, Covid pneumonia, and urinary tract infection.

After 52 weeks of exposure, a higher incidence of serious infections was reported for the secukinumab Q4W group (24/533, 4.5%) compared to the secukinumab Q2W group (12/527, 2.3%). As detailed under serious adverse events, this higher rate was primarily driven by the skin or subcutaneous infections (e.g., sweat gland infections, cellulitis, buttock abscess) most of which were HS-related. Refer to section, Serious Adverse Events, for a more comprehensive discussion of serious infections.
As of the safety update, there were no new serious infections reported.

Opportunistic Infections and Infections of Interest

To evaluate opportunistic infections (OIs), the Applicant used a customized MedDRA query (CMQ) that included tuberculosis, invasive fungal infections, and other OIs. Their data appeared acceptable and will be discussed in this subsection.
Additionally, a list of "definite and probable" OIs (Table 43) which was created via a systematic review by Winthrop and colleagues and published in a consensus statement (2015), was referenced and relied upon for this review as it specifies pathogens or specific presentations of pathogens that should be considered as opportunistic (or "indicator") infections in the setting of biologic therapy.[21]

Table 43: Pathogens or infections to be considered Opportunistic or Indicator Infections in the Setting of Biologic Therapy with Associated Levels of Evidence

Definite[*†]	**Probable**[‡]
Pneumocystis jirovecii (II)	Paracoccidioides infections (V)
BK virus disease including PVAN (V)	*Penicillium marneffei* (V)
Cytomegalovirus disease (V)	*Sporothrix schenckii* (V)
Post-transplant lymphoproliferative disorder (EBV) (V)	Cryptosporidium species (chronic disease only) (IV)
Progressive multifocal leucoencephalopathy (IV)	Microsporidiosis (IV)
Bartonellosis (disseminated disease only) (V)	Leishmaniasis (Visceral only) (IV)
Blastomycosis (IV)	Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only) (V)
Toxoplasmosis (IV)	Campylobacteriosis (invasive disease only) (V)
Coccidioidomycosis (II)	Shigellosis (invasive disease only) (V)
Histoplasmosis (II)	Vibriosis (invasive disease due to *Vibrio vulnificus*) (V)
Aspergillosis (invasive disease only) (II)	HCV progression (V)
Candidiasis (invasive disease or pharyngeal) (II)	
Cryptococcosis (II)	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii*, *Fusarium* (II)	
Legionellosis (II)	
Listeria monocytogenes (invasive disease only) (II)	
Tuberculosis (I)	
Nocardiosis (II)	
Non-tuberculous mycobacterium disease (II)	
Salmonellosis (invasive disease only) (II)	
HBV reactivation (IV)	
Herpes simplex (invasive disease only) (IV)	
Herpes zoster (any form) (II)	
Strongyloides (hyperinfection syndrome and disseminated forms only) (IV)	

[21] Winthrop KL, Novosad SA, Baddley JW et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015; 74:2107-16.

* Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity.
† Can occur in patients without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.
‡ Published data is currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.
EBV=Epstein-Barr virus; HBV=Hepatitis B virus; HCV=Hepatitis C virus; PVAN=polyomavirus-associated nephropathy

Source: OSE Pharmacovigilance Review of IL-17 monoclonal antibtodies and OIs dated November 10, 2022

In Trials M2301 and M2302, persons with active tuberculosis (TB), human immunodeficiency virus (HIV), and hepatitis B or C (except for successfully treated and cured hepatitis C) were excluded. Subjects with latent TB were allowed to participate if sufficient treatment was completed at least four weeks prior to randomization.

Treatment Period 1

During the first 16 weeks of treatment, there were no reported TEAEs of active or latent TB in any treatment arm.

The rate of fungal infections was highest for the secukinumab Q2W group. A total of 48 events of "fungal", "candida", "tinea", and "mycotic" infections were reported in 44 subjects: 19 (5.3%) in the secukinumab Q2W group, 15 (4.2%) in the secukinumab Q4W group, and 10 (2.8%) in the placebo group. All of these fungal infections were nonserious, mild to moderate in severity, and did not require change in dosage regimen. All but one subject had an outcome of recovering/recovered/resolved; subject (b) (6) in the secukinumab Q2W group had an event of active vaginal mycosis that had not recovered at the time of database lock although she remained on trial drug. Systemic candida infections including esophageal candidiasis were not reported.

There were no invasive herpes simplex events in any treatment arm. A single case of herpes zoster was reported in one subject in the placebo group. No other OIs, specifically those listed in Table 43, were noted.

Entire Trial Period

After 52 weeks of exposure, a case of "unconfirmed" TB was reported in a subject at a German site receiving secukinumab Q2W (b) (6). According to the submitted datasets and CRF, the subject was initially randomized to placebo for 16 weeks, then received secukinumab Q2W for the remainder of trial M2302 per protocol. At Week 52, prior to transitioning to the long term extension trial (CAIN457M2301E1), the subject's TB screening test was reported as "positive". However, confirmatiory TB testing via ELISpot and sputum samples were negative. Treatment for TB was determined to not be necessary, and the subject was permitted to enroll in the extension trial.

As shown in Table 42, with longer exposure, the rate of fungal infections remained higher for the secukinumab Q2W group (14.7/100 PY) compared to the secukinumab Q4W group (10.1/100 PY). Overall, the majority of fungal infection AEs were nonserious, mild or moderate in severity, and recovered without change in dosage regimen. However, in the secukinumab Q2W group, a serious event of inguinal candida intertrigo occurred in a 33-year-old White female (b) (6) with a history of hypothyroidism approximately 12 weeks after

starting secukinumab Q2W and despite cessation of trial drug for mild intertrigo 3 weeks prior. Although the subject recovered after treatment with fluconazole, zinc oxide, betamethasone-clotrimazole, and prednisolone, she withdrew from the trial.

In the secukinumab Q4W group, there were no serious fungal infections reported; however, there was one severe event of candida infection which required withdrawal of trial drug (b) (6)) and one event of esophageal candidiasis (b) (6).
The event of severe vulvovaginal candidiasis was reported in a 38-year-old White female with a history of tobacco use. The infection occurred approximately 20 weeks after staring secukinumab Q4W and resolved after treatment with fluconazole and withdrawal of trial drug. The AE of esophageal candidiasis occurred in a 38 year-old White male with a history of RA (treated with ibuprofen) and remote tobacco use, who also experienced three episodes of COVID-19 infection while receiving secukinumab Q4W. Approximately 30 weeks after starting secukinumab Q4W, the subject was diagnosed with nonserious, mild esophageal candidiasis and also experienced his second episode of COVID-19, described as mild. Trial drug was interrupted reportedly due to "technical problems" and remained interrupted thereafter due to "patient decision". The events of esophageal candidiasis and COVID-19 were reported as resolved.

Upon analyses of HSV TEAEs occurring after Week 16, 11 more events of HSV were reported in 7 subjects in the secukinumab Q2W group and 14 more events occurred in 12 subjects in the secukinumab Q4W group. All of these HSV events were nonserious, mild or moderate in severity, localized, and resolved or were resolving without change in dosage regimen. However, one subject (b) (6) in the secukinumab Q4W group reported right eye herpes viral keratitis 22 weeks after starting secukinumab. Although the event was described as nonserious, nonsevere, and resolved without change in dose, blindness due to corneal neovascularization, thinning, and scarring secondary to herpetic keratitis can occur if an early diagnosis is not made and immediate treatment is not implemented.[22]

Three events of herpes zoster were reported in 3 subjects: 2 in the secukinumab Q2W group (b) (6)) and 1 in the secukinumab Q4W group (M2302-2038-003). Although none of the events of herpes zoster were serious, disseminated, or severe, all 3 subjects were ≤ 40 years of age. Age is the most significant risk factor for developing herpes zoster with a dramatic increase in the incidence of herpes zoster beginning at approximately age 50 years.[23] Notwithstanding the unexplained rising incidence of zoster worldwide, it is still relatively rare in young adults.

[22] Sinha P et al. Epithelial herpes simplex keratitis in a patient on treatment with secukinumab for psoriasis: An effect of interleukin-17 blockade? Indian J Dermatol Venereol Leprol 2022;88:225-7.
[23] Yawn, BP, et al, A Population-based Study of the Incidence and Complication Rates of Herpes Zoster Before Zoster Vaccine Introduction, Mayo Clin Proc, 2007; 82(11):1341-1349.

In the 120-day safety one subject (b) (6) who transitioned to the extension trial was reported to have had 2 events of severe esophageal candidiasis, the first of which occurred while the subject was receiving placebo and resolved following interruption of dosing. The second event occurred 13 weeks after (re)starting secukinumab Q2W and was ongoing at the time of data submission with an unknown action taken with trial drug. There were no other infections of interest or updates pertaining to subjects who had experienced OIs during trials M2301 or M2302.

Worth describing here and as mentioned in Section 8.2.10. Safety in the Postmarket Setting are plans to modify the COSENTYX USPI to include a number of OIs based on probable causal association and biological plausibility. Following review of several postmarketing cases of OIs retrieved from the FDA Adverse Event Reporting System (FAERS) database and literature, a number of safety labeling changes as listed below are being proposed by the Agency and are undergoing internal discussion at the time of this review:

Given their potential life-threatening impact, OIs determined to have a probable causal relationship with secukinumab use including candidiasis (esophageal and tracheobronchial infections), complicated herpes simplex (encephalitis and keratitis), cutaneous aspergillosis, gastrointestinal CMV, and Pneumocystis jiroveci pneumonia, should be included in the Warnings and Precautions section of labeling.
Subsection 5.1 Infections and Section 17 Patient Counseling will be updated to include the occurrence of hepatitis B reactivation.
Modifications to subsection 5.2 to include the postmarketing findings of pulmonary TB is reasonable to communicate the development of active TB in the setting of no TB prophylaxis, as well as previously treated TB.

While the aforementioned infections are serious and should be considered by healthcare providers when assessing the risks and benefits of prescribing secukinumab, none of the reported cases resulted in a fatal outcome and not all necessitated hospital care. A boxed warning for these OIs (like in the labeling of TNF inhibitors) is not currently indicated; their risk can be sufficiently conveyed in Section 5 Warnings and Precautions.

The addition of hepatitis B reactivation, histoplasmosis and toxoplasmosis to a new subsection, 6.3 Postmarketing Experience is reasonable given secukinumab's role in development of these infections cannot be excluded.

The findings from trials M2301, M2302, and M2301E1 not only reinforce the need for several of these proposed labeling changes, but they also support the inclusion of a statement in subsections **5.1 Infections** and **6.1 Clinical Trials Experience** to convey the higher rate of fungal infections observed with increased dose frequency in the HS population.

8.2.5.3. Hypersensitivity

An analysis wherein preferred terms (PT) of hypersensitivity were grouped for Treatment Period 1 demonstrated that the secukinumab Q2W group had the highest rate of events (19, 5.3%) compared to the secukinumab Q4W (12, 3.3%) and placebo (14, 3.9%) groups (Table 44)

Table 44: Treatment-emergent Hypersensitivity – Treatment Period 1 (Safety Set)

Group Term	Secukinumab 300 mg Q2W N = 361		Secukinumab 300 mg Q4W N = 360		Placebo N = 363	
Preferred Term	n	(%)	n	(%)	n	(%)
Hypersensitivity	**19**	**(5.3)**	**12**	**(3.3)**	**14**	**(3.9)**
Angioedema	2	(0.6)	0	(0.0)	0	(0.0)
Injection site erythema	2	(0.6)	1	(0.3)	0	(0.0)
Injection site pruritus	2	(0.6)	0	(0.0)	0	(0.0)
Swelling of eyelid	2	(0.6)	0	(0.0)	0	(0.0)
Urticaria	2	(0.6)	2	(0.6)	5	(1.4)
Application site erythema	1	(0.3)	1	(0.3)	0	(0.0)
Application site induration	1	(0.3)	0	(0.0)	0	(0.0)
Application site vesicles	1	(0.3)	0	(0.0)	0	(0.0)
Drug hypersensitivity	1	(0.3)	0	(0.0)	0	(0.0)
Eosinophil count increased	1	(0.3)	0	(0.0)	3	(0.8)
Eosinophilia	1	(0.3)	2	(0.6)	2	(0.6)
Injection site inflammation	1	(0.3)	0	(0.0)	0	(0.0)
Injection site papule	1	(0.3)	0	(0.0)	0	(0.0)
Injection site rash	1	(0.3)	0	(0.0)	0	(0.0)
Injection site swelling	1	(0.3)	0	(0.0)	1	(0.3)
Mechanical urticaria	1	(0.3)	0	(0.0)	0	(0.0)
Periorbital edema	1	(0.3)	0	(0.0)	0	(0.0)
Urticaria chronic	1	(0.3)	0	(0.0)	0	(0.0)
Urticarial dermatitis	1	(0.3)	0	(0.0)	0	(0.0)
Wheezing	1	(0.3)	0	(0.0)	0	(0.0)
Application site papules	0	(0.0)	1	(0.3)	0	(0.0)
Eosinophil percentage increased	0	(0.0)	0	(0.0)	1	(0.3)
Generalized edema	0	(0.0)	1	(0.3)	0	(0.0)
Hypersensitivity	0	(0.0)	2	(0.6)	1	(0.3)
Injection site reaction	0	(0.0)	3	(0.8)	1	(0.3)
Lip swelling	0	(0.0)	0	(0.0)	1	(0.3)

Source: Clinical Reviewer's Table; OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q2W); TRT01A = "Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

The above table shows angioedema (2), eyelid swelling (2), and periorbital edema (1) occurred in subjects who were receiving secukinumab Q2W whereas these AEs were not reported in any subjects receiving secukinumab Q4W. A single subject (b) (6) in the secukinumab Q4W group, however, reported an AE of "generalized edema" but the event was nonserious, mild, and resolved without change in dosing of trial drug. Narratives for the 5 subjects in the secukinumab Q2W group are provided below.

Subject (b) (6) urticaria and angioedema due to fish ingestion
A 38-year-old White female who was reported to experience nonserious, moderate "giant urticaria on the upper body and angioedema on the face due to the ingestion of mackerel" approximately 23 weeks after starting secukinumab Q2W. The subject was treated with an antihistamine, bilastine, and no action was taken with the trial drug. Two days later, the subject was reported to have recovered from angioedema.
Given ingestion of seafood served as a likely alternative explanation, it is *unlikely* that the event of angioedema was related to secukinumab Q2W use.

Subject (b) (6) angioedema
A 42-year-old White female with a history of active tobacco use who developed angioedema approximately 44 weeks after starting secukinumab Q2W. The event was reported as non-serious and mild without an affected location specified. There were no concomitant medications reported at the time of the event. No action was taken with trial drug. After treatment with desloratadine, the event resolved. The investigator suspected a relationship between the event of angioedema and trial drug.
Despite resolution of angioedema with continued use of trial drug, there was a reasonable time relationship with drug intake and no other plausible explanations, therefore, it is *possible* that the event of angioedema was associated with secukinumab Q2W.

Subject (b) (6): eyelid swelling
A 33-year-old White male with a history of a sleeping disorder treated with trazodone who developed non-serious, mild swelling of his eyelid approximately 23 weeks after starting secukinumab Q2W. No action was taken with the trial drug, and no treatment was reported. Five weeks later, trial drug was discontinued due to "worsening hidradenitis". At the time of withdrawal of secukinumab, the event of eyelid swelling had not resolved.
Based on the limited information provided in the narrative, CRF, and datasets, causality is *unassessable*.

Subject (b) (6): eyelid swelling
A44-year-old Asian female with a history of active tobacco use, migraine, and back pain treated with ketoprofen who developed non-serious, mild eyelid swelling approximately 13 weeks after starting secukinumab Q2W. No action was taken with the trial drug, and no treatment was reported. Four weeks later, the subject recovered from swelling of the eyelid.
Because the event of eyelid swelling improved despite continuation of trial drug and could be explained by the concomitant use of ketoprofen, causality is determined to be *unlikely* due to secukinumab Q2W use.

Subject (b) (6): periorbital edema
A 53-year-old White female with a history of migraine and allergic conjunctivitis plus cat and dog allergies who was taking loratadine and an unspecified herbal supplement. She developed nonserious, mild eye pruritis 35 weeks after starting secukinumab Q2W and required interruption of trial drug. Upon resumption, nonserious, mild periorbital edema was reported

11 weeks later. No action was taken with the trial drug, and no treatment was documented. Two days later, the AE resolved.
The event of periorbital edema improved despite continuation of trial drug and might be explained by the subject's underlying allergies; therefore, causality is determined to be *unlikely* due to secukinumab Q2W use.

Although causality was assessed as possible in only one of the above five cases and there were no cases determined to be of probable causality, the overall imbalance is concerning.
Analysis of hypersensitivity for the Entire Trial Period, demonstrated similar findings to those for Treatment Period 1 in which the rate of hypersensitivity AEs remained highest for the secukinumab Q2W group (Table 45).

Table 45: Treatment-emergent Hypersensitivity – Entire Treatment Period (Safety Set)

Group Term Preferred Term	Any Secukinumab 300 mg Q2W N = 527 n	(%)	Any Secukinumab 300 mg Q4W N = 533 n	(%)
Hypersensitivity Total	**27**	**(5.1)**	**18**	**(3.4)**
Urticaria	6	(1.1)	3	(0.6)
Eosinophil count increased	3	(0.6)	1	(0.2)
Angioedema	2	(0.4)	0	(0.0)
Injection site erythema	2	(0.4)	1	(0.2)
Injection site pruritus	2	(0.4)	0	(0.0)
Swelling of eyelid	2	(0.4)	0	(0.0)
Application site erythema	1	(0.2)	1	(0.2)
Application site induration	1	(0.2)	0	(0.0)
Application site vesicles	1	(0.2)	0	(0.0)
Drug hypersensitivity	1	(0.2)	0	(0.0)
Eosinophilia	1	(0.2)	4	(0.8)
Injection site inflammation	1	(0.2)	0	(0.0)
Injection site papule	1	(0.2)	0	(0.0)
Injection site rash	1	(0.2)	0	(0.0)
Injection site reaction	1	(0.2)	3	(0.6)
Injection site swelling	1	(0.2)	1	(0.2)
Lip swelling	1	(0.2)	0	(0.0)
Mechanical urticaria	1	(0.2)	0	(0.0)
Periorbital oedema	1	(0.2)	0	(0.0)
Urticaria chronic	1	(0.2)	0	(0.0)
Urticarial dermatitis	1	(0.2)	0	(0.0)
Wheezing	1	(0.2)	0	(0.0)
Application site papules	0	(0.0)	1	(0.2)
Eosinophil percentage increased	0	(0.0)	1	(0.2)
Generalized edema	0	(0.0)	1	(0.2)
Hypersensitivity	0	(0.0)	3	(0.6)

An analysis looking more closely at immunologic responses at a local level was also performed for the Entire Trial Period to assess the rates of type 1 hypersensitivity reactions. Table 46

shows that administration site reactions were highest for the Any secukinumab Q2W group (16, 3.0%) compared to the other treatment groups (10, 1.9% for secukinumab Q4W and 9, 2.5% for placebo); however, the difference in crude rate between the secukinumab Q2W group relative to placebo was small (0.5%). Additionally, the development of treatment emergent antidrug antibodies was not associated with any administration site reactions.

Table 46: Treatment-emergent Administration Site Reactions – Entire Trial Period (Safety Set)

Group Term Preferred Term	Any Secukinumab 300 mg Q2W N = 527 n	(%)	Any Secukinumab 300 mg Q2W N = 533 n	(%)	Placebo N = 363 n	(%)
Administration site reactions	**16**	**(3.0)**	**10**	**(1.9)**	**9**	**(2.5)**
Injection site pain	6	(1.1)	2	(0.4)	4	(1.1)
Injection site erythema	2	(0.4)	1	(0.2)	0	(0.0)
Injection site pruritus	2	(0.4)	0	(0.0)	0	(0.0)
Application site erythema	1	(0.2)	1	(0.2)	0	(0.0)
Application site hematoma	1	(0.2)	0	(0.0)	0	(0.0)
Application site induration	1	(0.2)	0	(0.0)	0	(0.0)
Application site vesicles	1	(0.2)	0	(0.0)	0	(0.0)
Injection site abscess	1	(0.2)	0	(0.0)	1	(0.3)
Injection site bruising	1	(0.2)	0	(0.0)	0	(0.0)
Injection site inflammation	1	(0.2)	0	(0.0)	0	(0.0)
Injection site papule	1	(0.2)	0	(0.0)	0	(0.0)
Injection site rash	1	(0.2)	0	(0.0)	0	(0.0)
Injection site reaction	1	(0.2)	3	(0.6)	1	(0.3)
Injection site swelling	1	(0.2)	1	(0.2)	1	(0.3)
Application site folliculitis	0	(0.0)	1	(0.2)	1	(0.3)
Application site papules	0	(0.0)	1	(0.2)	0	(0.0)
Injection site hematoma	0	(0.0)	2	(0.4)	1	(0.3)
Injection site hemorrhage	0	(0.0)	1	(0.2)	0	(0.0)

Source: Clinical Reviewer's Table, OCS Analysis Studio, Safety Explorer.

Filters: TRTSEQA = "Secukinumab 300 mg every 2 weeks" or "Placebo - Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Any Secukinumab 300 mg Q2W); TRTSEQA = "Secukinumab 300 mg every 4 weeks" or "Placebo - Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Any Secukinumab 300 mg Q2W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

In the safety update report, there were no events of administration site reactions or other hypersensitivity AEs reported.

A positive association between the incidence of these hypersensitivity events and more frequent dosing cannot be ruled out and is concerning for potentially more severe immune reactions and/or escalation of an immune response with repeated dosing beyond the recommended 300 mg every 4 weeks. Noteworthy is that similar findings were observed in a registrational phase 3 trial (CAIN457A2324; NCT03504852) which evaluated the safety and efficacy of secukinumab for a flexible dosing regimen (300 mg Q2W) for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

This higher rate of hypersensitivity coupled with marginally better efficacy on the HISCR50 response, generates a less favorable risk-benefit profile for secukinumab 300 mg dosed every 2 weeks in adults with moderate to severe HS. Therefore, the review team determined that labeling should reflect that for some patients who fail to improve with secukiniumab 300 mg every 4 weeks, a dosage of 300 mg every 2 weeks may be acceptable for the treatment of moderate to severe HS.

Hypersensitivity is labeled under Contraindications and Warning and Precautions in the current secukinumab USPI. While no further updates to the labeling regarding hypersensitivity are indicated at this time, ongoing postmarketing surveillance of these events is necessary.

8.2.5.4. Suicidal ideation and behavior (SIB)

Published literature describes an association between HS, depression, and suicidal behavior[24] as patients with HS experience social isolation and depression due to malodorous abscesses and sinus tracts that subsequently scar; however, the reported prevalence of suicidal ideation and behavior varies across studies.[25]
Trials M2301 and M2302 did not specifically exclude subjects with a history of suicidal ideation and behavior. Eligibility criteria excluded subjects with "current severe progressive or uncontrolled diseases which renders the patient unsuitable for the trial or puts the patient at increased risk, including 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."

During the first 16 weeks of treatment, one subject in each of the secukinumab groups reported an AE of SIB. There were no subjects with an AE of SIB in the placebo group. The subject in the Q2W group (b) (6) was a 23-year-old White female with a history of depression treated with fluoxetine and alprazolam, tobacco use, and severe HS with a HS-PGA score of 5, Hurley stage of III, total AN count of 12, and 9 draining fistulae. Approximately 15 weeks after starting secukinumab 300 mg Q2W, she attempted suicide by mixing drugs with alcohol and was subsequently hospitalized. Secukinumab was discontinued, and the subject withdrew from the trial. She was reported to be recovering at the time of database lock. In the secukinumab Q4W, one subject (b) (6) was reported to experience AEs of suicidal ideation (SI) and intentional overdose. The subject was a 33-year-old Black female with a history of hypertension treated with metoprolol, and depression, anxiety, bipolar disorder, as well as insomnia on numerous psychiatric medications, who presented to the hospital after attempting to harm herself. Approximately 15 weeks after starting secukinumab 300 mg Q4W the subject reportedly experienced a "stressful life event" and intentionally overdosed on her psychiatric medications. She underwent group and individualized psychological therapy and was discharged 23 hours later after being deemed stable. Trial drug was withdrawn.

[24] Deckers, I et al. The Handicap of Hidradenitis Suppurativa, Dermatologic Clinics,2016: 34 (1): 17-22.
[25] Thorlacius, L et al Increased Suicide Risk in Patients with Hidradenitis Suppurativa, Journal of Investigative Dermatology, 2018; 138 (1) 52-57.

Based on the reasonable time relationship, it is possible that both events may be related to secukinumab use in these subjects with underlying mood disorders.

With longer exposure through 52 weeks of treatment, one more subject (b) (6)) in the secukinumab Q2W group had a suicide-related AE. The subject was a 49-year-old White female with a history of hypertension, prior stroke, depression, anxiety, and severe HS with a HS-PGA score of 4, Hurley stage of III, total AN count of 17, as well as no draining fistulae, who experienced suicidal ideation. Approximately 39 weeks after starting secukinumab 300 mg Q2W, the subject was hospitalized for SI. Trial drug was interrupted for 2 weeks. The subject was reported as recovering and completed Trial 2301 per protocol then transitioned to the extension trial.

Although there were numerically more subjects who reported SIB events for the secukinumab Q2W group, the overall numbers were small and the difference in EAIR (0.4/100 PY for the secukinumab Q2W group compared to 0.2/100 PY for the secukinumab Q4W group) as shown in Table 47 was not significant.

Table 47: Exposure-adjusted incidence rates of SIB by PT including Placebo switchers – Entire Trial period (pooled data), Safety set

	Any Secukinumab 300 mg Q2W N=527		Any Secukinumab 300 mgQ4W N=533	
	n/EX (IR)	95% CI	n/EX (IR)	95% CI
Total	2/4.51 (0.4)	(0.1, 1.6)	1/4.50 (0.2)	(0.0, 1.2)
Suicidal ideation	1/4.51 (0.2)	(0.0, 1.2)	1/4.50 (0.2)	(0.0, 1.2)
Suicide Attempt	1/4.51 (0.2)	(0.0, 1.2)	0/4.50 (0.0)	(0.0, 0.8)
Intentional overdose	0/4.51 (0.0)	(0.0, 0.8)	1/4.50 (0.2)	(0.0, 1.2)

Source: Modified Applicant's Table 1.1-2.3 from Information Request Response received January 5, 2023

Within the safety update, two new SAEs of depression and obsessive-compulsive disorder, were reported for one subject in the secukinumab Q2W group (b) (6)). The subject was a 23-year-old American Indian female with no reported past medical history, who reported suicidal ideation as part of her symptomology.

There is insufficient evidence of increased risk of suicidal ideation and behavior with more frequent dosing of secukinumab to recommend updating the labeling for secukinumab. While these events of self-harm do not alter the current recommendations for use of secukinumab, SIB should continue to be evaluated especially for this population and this drug class.

8.2.5.5. Inflammatory bowel disease (IBD)

Given the epidemiologic association and shared histological features between hidradenitis suppurativa and IBD[26], specifically Crohn's disease, IBD is a condition of safety interest. Nonspecific eligibility criteria outlined that subjects with underlying conditions such as inflammatory bowel disease which in the opinion of the investigator significantly immunocompromises the subject and/or places the subjects at unacceptable risk for receiving an immunomodulatory therapy were excluded from the trials.

During the placebo-controlled period, one subject in each of the secukinumab groups reported an AE of IBD. Both events were serious and led to withdrawal of trial drug, as well as discontinuation from the trial. There were no subjects with an AE of IBD in the placebo group.

In the secukinumab Q2W group, subject (b) (6), a 43-year-old White male with a history of pyoderma gangrenosum, developed bloody diarrhea approximately 3 weeks after starting secukinumab. He was hospitalized and diagnosed with ulcerative colitis via colonoscopic biopsies. Despite cessation of secukinumab and a trial of mesalazine, the subject's symptoms persisted. Bloody diarrhea eventually slowed following aminosalicylic acid, prednisolone, pantoprazole and metamizole.

One subject in the secukinumab Q4W group (b) (6)), a 48-year-old White female, was diagnosed with inflammatory bowel disease via colonoscopy approximately 10 weeks after starting secukinumab. She required hospitalization, treatment with mesalazine, and cessation of trial drug. The subject also withdrew from the trial and the event of IBD was reported as ongoing at the time of trial discontinuation.

Despite the negative dechallenge in both cases, the reasonable temporal relationship makes causality possible.

After 52 weeks of exposure, one additional subject in the secukinumab Q2W group (b) (6), a 34-year-old White male with a history of active tobacco use, was diagnosed with Crohn's disease approximately 7 weeks after starting secukinumab. The events of Crohn's disease and diarrhea, although not serious, led to cessation of trial drug and eventual withdrawal from the trial; both events were ongoing at the time of trial discontinuation.

Table 48: Exposure-adjusted incidence rates of IBD by PT including Placebo switchers – Entire Trial period (pooled data), Safety set

	Any Secukinumab 300 mg Q2W N=527		Any Secukinumab 300 mgQ4W N=533	
	n/EX (IR)	95% CI	n/EX (IR)	95% CI
Total	2/4.51 (0.4)	(0.1, 1.6)	1/4.50 (0.2)	(0.0, 1.2)

[26] Ingram J. Hidradenitis suppurativa: Pathogenesis, clinical features, and diagnosis. UpToDate. Accessed May 16, 2023

Ulcerative colitis	1/4.51 (0.2)	(0.0, 1.2)	0/4.50 (0.0)	(0.0, 0.8)
Crohn's disease	1/4.51 (0.2)	(0.0, 1.2)	0/4.50 (0.0)	(0.0, 0.8)
Inflammatory bowel disease	0/4.51 (0.0)	(0.0, 0.8)	1/4.50 (0.2)	(0.0, 1.2)

Source: Modified Applicant's Table 1.1-2.3 from Information Request Response received January 5, 2023

Within the safety update, 5 (0.7%) subjects were identified out of 700 total subjects in the ongoing extension trial (M2301E1) to have had AEs of IBD. All of the subjects were receiving secukinumab 300 mg Q2W at the time of their diagnoses. All IBD events were serious and led to withdrawal of trial drug.

Table 49: Lisiting of subjects with TEAEs of IBD during Trial M2301E1

Treatment dosage regimen	Subject ID	Age/sex/race	Preferred Term	Time to Onset	Serious (Y/N)	Severity	Outcome	Action taken with trial drug
Secukinumab 300 mg Q2W	(b) (6)	34/F/W	Inflammatory bowel disease	82 weeks	Y	Severe	Not recovered/not resolved	Withdrawn
Secukinumab 300 mg Q2W		23/M/W	Crohn's disease	39 weeks (open label)	Y	Severe	Recovering/resolving	Withdrawn
Secukinumab 300 mg Q2W		22/M/W	Crohn's disease	26 weeks (open label)	Y	Severe	Not recovered/not resolved	Withdrawn
Secukinumab 300 mg Q2W		31/W/M	Colitis ulcerative	5 weeks (open label)	Y	Severe	Not recovered/not resolved	Withdrawn
Secukinumab 300 mg Q2W		25/F/B	Crohn's disease	26 weeks (open label)	Y	Severe	Recovered/resolved with sequelae	Withdrawn

Source: Clinical Reviewer's Table

Given the findings from all three phase 3 trials, namely the events reported during the extension trial, it is reasonable to update labeling to reflect that the incidence of IBD might be dose-dependent. Inflammatory bowel disease is labeled under Warning and Precautions and Adverse Reactions in the current secukinumab USPI. The Warnings and Precautions seciton will be modified to include the increased rate of new serious IBD events in the HS population who were administered secukinumab every 2 weeks compared to those who received secukinumab every 4 weeks.

8.2.5.6. Neutropenia

Neutropenia is an adverse drug reaction that has been reported with secukinumab use. Current COSENTYX labeling describes events of Grade 3 neutropenia and an association with serious infections during open-label extension trials conducted in subjects with moderate to severe psoriasis. Based on these reports, neutropenia is an area of safety interest.

In the first 16 weeks of treatment, the rates of AEs of neutropenia were similar between the two secukinumab arms (3, 0.8% for the Q2W group and 2, 0.6% for the Q4W group). There were no events of neutropenia in the placebo group.

With longer exposure, the rates between the secukinumab groups remained comparable as shown in Table 50.

Table 50: Treatment-emergent Neutropenia Events – Entire Trial Period (Safety Set)

Group Term Preferred Term	Secukinumab 300 mg Q2W N = 527 n	(%)	Secukinumab 300 mg Q4W N = 533 n	(%)	Placebo N = 363 n	(%)
Neutropenia	**5**	**(0.9)**	**3**	**(0.6)**	**0**	**(0.0)**
Neutropenia	3	(0.6)	1	(0.2)	0	(0.0)
Neutrophil count decreased	2	(0.4)	2	(0.4)	0	(0.0)

Source: Clinical Reviewer's Table; OCS Analysis Studio, Safety Explorer.

Filters: TRTSEQA = "Secukinumab 300 mg every 2 weeks" or "Placebo - Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q2W); TRTSEQA = "Secukinumab 300 mg every 4 weeks" or "Placebo - Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRTSEQA = "Placebo - Secukinumab 300 mg every 4 weeks" or "Placebo - Secukinumab 300 mg every 2 weeks" or "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

Over the Entire Trial Period, in the secukinumab Q2W group, five subjects reported a total of 6 events of neutropenia/decreased neutrophil count all of which were non-serious and mild in severity. Two subjects (b) (6) had dosing interrupted and the events of neutropenia resolved. All other subjects did not require a change in dosing.

In the secukinumab Q4W group, three subjects experienced 4 events of neutropenia/decreased neutrophil count all of which were nonserious, mild to moderate in severity, and did not require change in dosage regimen. A single subject (b) (6) experienced two events of neutropenia, one of which resolved and the other had not at the time of database lock.

In the safety update report, no new AEs of neutropenia were reported for trials M2301, M2302, or M2301E1.

As discussed in the the section, Laboratory Findings, there were limited cases of low neutrophil counts which were mostly grade 1 or 2 and not associated with infections.

Assessment of AEs of neutropenia/decreased neutrophil count demonstrated comparable rates between secukinumab 300 mg Q2W and secukinumab 300 mg Q4W during the phase 3 HS development program. Additionally, evaluation of hematology laboratory parameters did not show any clinically meaningful differences in new or worsening neutropenia across treatment groups. Therefore, updates to the labeling of COSENTYX which currently describes neutropenia in subsection **6.1 Clinical Trials Experience** is not warranted at this time.

8.2.5.7. Cardiovascular (CV) events including Major CV events (MACE)

Based on literature demonstrating that patients with HS may have a higher risk for cardiovascular (CV) disease,[27,28] and due to the potential association between inhibition of the IL-23/IL-17 axis and CV events[29], major adverse cardiovascular events (MACE) is a safety area of interest. The Applicant defined MACE as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.
Baseline cardiovascular risk factors and baseline history of cardiovascular disease were, in general, comparable across treatment groups.

MACE
In the initial 16 weeks of trials M2301 and M2302, there were no MACE reported.
After 52 weeks of exposure, one subject in the secukinumab Q4W (b) (6)) experienced a fatal myocardial infarction and is discussed in detail under the section, Deaths. In the secukinumab Q2W group, Subject (b) (6) a 35-year-old Asian male with a history of hepatic steatosis, hepatic mass, and active tobacco use had transient non-serious, mild angina pectoris that resolved without change in dosing of trial drug.

Overall Cardiovascular Events
Beyond the evaluation of MACE, the review team performed an analysis of overall treatment emergent cardiovascular (CV) events for the Entire Trial Period. As shown in Table 51, the rates for total CV events were generally comparable with a slight imbalance between the secukinumab arms and placebo arm primarily driven by the AE, hypertension.

Table 51: Treatment-emergent Cardiovascular Events – Entire Trial Period (Safety Set)

Group Term	Any Secukinumab 300 mg Q2W N = 527		Any Secukinumab 300 mg Q4W N = 533		Placebo N = 363	
Preferred Term	n	(%)	n	(%)	n	(%)
Cardiovascular Events	**32**	**(6.0)**	**30**	**(5.6)**	**15**	**(4.1)**
Hypertension	21	(4.0)	12	(2.3)	4	(1.1)
Hypotension	3	(0.6)	2	(0.4)	2	(0.6)
Angina pectoris	1	(0.2)	0	(0.0)	0	(0.0)
Arrhythmia	1	(0.2)	1	(0.2)	1	(0.3)
Arteriosclerosis	1	(0.2)	0	(0.0)	0	(0.0)
Bradycardia	1	(0.2)	0	(0.0)	0	(0.0)
Cardiac failure chronic	1	(0.2)	0	(0.0)	0	(0.0)
Hypertensive crisis	1	(0.2)	1	(0.2)	1	(0.3)

[27] Tzellos T et al. Cardiovascular disease risk factors in patients with hidradenitis suppurativa: a systematic review and meta-analysis of observational studies. Br J Dermatol. 2015;173(5):1142-55.
[28] González-López MA, et al. Increased prevalence of subclinical atherosclerosis in patients with hidradenitis suppurativa (HS). J Am Acad Dermatol. 2016;75(2):329-35.
[29] Ait-Oufella H, Libby P, Tedgui A. Anticytokine Immune Therapy and Atherothrombotic Cardiovascular Risk. Arterioscler Thromb Vasc Biol. 2019;39(8):1510-1519.

Group Term Preferred Term	Any Secukinumab 300 mg Q2W N = 527 n	(%)	Any Secukinumab 300 mg Q4W N = 533 n	(%)	Placebo N = 363 n	(%)
Pericardial effusion	1	(0.2)	1	(0.2)	0	(0.0)
Peripheral venous disease	1	(0.2)	2	(0.4)	1	(0.3)
Pulmonary embolism	1	(0.2)	0	(0.0)	0	(0.0)
Tachycardia	1	(0.2)	5	(0.9)	2	(0.6)
Thrombosis	1	(0.2)	0	(0.0)	0	(0.0)
Aortic arteriosclerosis	0	(0.0)	1	(0.2)	1	(0.3)
Carotid artery disease	0	(0.0)	1	(0.2)	0	(0.0)
Hypertensive emergency	0	(0.0)	1	(0.2)	0	(0.0)
Hypertensive urgency	0	(0.0)	1	(0.2)	1	(0.3)
Left ventricular enlargement	0	(0.0)	1	(0.2)	0	(0.0)
Left ventricular hypertrophy	0	(0.0)	1	(0.2)	0	(0.0)
Myocardial infarction	0	(0.0)	1	(0.2)	0	(0.0)
Pericarditis	0	(0.0)	1	(0.2)	0	(0.0)
Peripheral arterial occlusive disease	0	(0.0)	1	(0.2)	0	(0.0)
Superficial vein thrombosis	0	(0.0)	1	(0.2)	0	(0.0)
Thrombophlebitis	0	(0.0)	2	(0.4)	2	(0.6)

Source: Clinical Reviewer's Table, OCS Analysis Studio, Safety Explorer.
Filters: TRTSEQA = "Secukinumab 300 mg every 2 weeks" or "Placebo - Secukinumab 300 mg every 2 weeks" and SAFFL = "Y" (Any Secukinumab 300 mg Q2W); TRTSEQA = "Secukinumab 300 mg every 4 weeks" or "Placebo - Secukinumab 300 mg every 4 weeks" and SAFFL = "Y" (Any Secukinumab 300 mg Q4W); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

Understanding that AE rates may not be constant over time, comparisons of secukinumab to placebo for the Entire Trial Period should be interpreted with caution. Nonetheless, further analyses of the datasets, CRFs, and narratives demonstrated that all of the events of hypertension were mild to moderate in severity, non-serious, and did not require change in dose of trial drug. Additionally, shifts in baseline systolic and diastolic blood pressures from normal to high and low to high were comparable between treatment groups.

While the evaluation of hypertension AEs appeared to be relatively reassuring, events of hypertensive crisis and hypertensive emergency reported in subjects randomized to the secukinumab arms required further assesssment. AEs of hypertensive crisis were reported in two subjects, one in each secukinumab treatment group ((b) (6) in the Q4W arm and (b) (6) in the Q2W arm). Both events were nonserious, moderate in severity, and recovered without need for change in dose of trial drug. A subject in the secukinumab Q4W group (b) (6) had an SAE of hypertensive emergency in the setting of myopericarditis and is discussed in detail under subsection, Dropouts and/or Discontinuations Due to Adverse Effects.

Events of Pulmonary Embolism and Thrombosis

Adverse events of pulmonary embolism and thrombosis were reported in one subject (b) (6) The subject was a 21-year-old White male with a history of active tobacco use who was diagnosed with thrombosis of the femoral and fibular veins, pulmonary embolism, and left upper lobe pneumonia in the setting of suspected Klinefelter's syndrome approximately 26 weeks after starting secukinumab Q2W. The event was reported as serious, moderate, and

recovered following drug interruption. The subject received dalteparin and antibiotics. Seven weeks later the subject resumed trial drug and completed treatment per protocol, ultimately, transitioning to the extension trial.
The subject's tobacco use and Klinefelter's syndrome more likely contributed to the cause of thromboses than the trial drug.

Serious Cardiovascular events
Three serious CV AEs in each secukinumab arm were reported; none were observed in the placebo group.

In the secukinumab Q2W group, SAEs of thrombosis (b) (6) and hypotension ((b) (6) in the setting of sepsis due to an infected sweat gland, were previously described under the sections describing SAEs and Discontinuations Due to Adverse Effects. A third SAE of worsening dysrrhtymia (b) (6)) was reported in a 50-year-old White male with a history of obesity, chronic atrial fibrillation (treated with diltiazem, metoprolol, and prior ablation), systolic congestive heart failure, and anemia. Approximately 15 weeks after starting secukinumab Q2W, the subject was hospitalized due to "worsening arrhythmia" requiring cardioversion and catheter ablation. He was also treated with amiodarone, heparin, diltiazem, hydrochlorothiazide-lisinopril, apixaban, protamine, and adenosine. No action was taken with trial drug. The subject recovered after a 2-day hospital stay and was discharged.

In the secukinumab Q4W group, events of hypertensive emergency in the setting of pericarditis (b) (6)) and fatal MI (b) (6)) were described in prior sections, Discontinuations Due to Adverse Effects and Deaths, respectively. An SAE of tachycardia (b) (6) was reported in a 60-year-old White male with a history of active tobacco use, stroke, hypertension (treated with ramipril), and glucose intolerance (treated with metformin), who was hospitalized four weeks after starting secukinumab Q4W for "palpitations and tachycardia (severe, serious, heart rate: 96 bpm)". Cardiac stress test was negative, chest X-ray was normal, and ECG confirmed sinus tachycardia, normal QRS (QTcF 412 msec) and left anterior fascicular hemi-block. Left ventricular ejection fraction was greater than 60%. Telemetry monitoring showed sporadic ventricular extra systoles. Treatment included oral bisoprolol. No action was taken with the trial drug. The subject recovered with a heart rate of 88 BPM and blood pressure of 140/88 mmHg.

Safety data from the ongoing extension trial, M2301E1, included events of acute myocardial infarction (b) (6), myocardial infarction, acute coronary syndrome, coronary artery disease, atrial fibrillation, and congestive cardiac failure.

Table 52: Lisiting of subjects with Cardiovascular SAEs during Trial M2301E1

Treatment dosage regimen	Subject ID	Age/sex/race PMH	Preferred Term Method of Diagnosis	Time to Onset	Serious (Y/N)	Severity	Outcome	Action taken with trial drug

Secukinumab 300 mg Q2W	(b) (6)	61/F/W Hypertension, active tobacco use, aortic arteriosclerosis	Acute myocardial infarction Not supported by EKG or cardiac biomarkers	36 weeks	Y	Mild	Recovered/ resolved same day	Interrupted
Secukinumab 300 mg Q2W		51/M/W Obesity, Type 2 DM, active tobacco use	Myocardial infarction Single vessel disease confirmed by coronary angiography	78 weeks	Y	Severe	Recovered/ resolved	No action
Secukinumab 300 mg Q2W		52/F/W No PMH	Acute coronary syndrome Cardiac catheterization showed MINOCA (MI with no obstructive coronary arteries syndrome;grade 3)	13 weeks	Y	Severe	Recovered/ resolved	Interrupted
Placebo		60/M/W CAD, Type 2 DM, active tobacco use	Coronary artery disease Required "insertion of 3 stents"	13 weeks	Y	Moderate	Recovered/ resolved	No action
Secukinumab 300 mg Q2W		57/M/B Hypertension, congestive heart failure, hypercholesterolemia	Congestive cardiac failure (2 episodes) and atrial fibrillation	12 weeks (cardiac failure episode 1) 30 weeks (cardiac failure episode 2) 36 weeks Atrial fibrillation	Y	Moderate Mild	Recovered/ resolved Recovered/ resolved Recovered/ resolved	Interrupted No action No action

Source: Clinical Reviewer's Table. DM=Diabetes mellitus; PMH=Past Medical History

As shown in Table 52, all but one of the subjects who experienced a CV SAE in the extension trial had underlying cardiac risk factors that likely contributed more to the adverse events than the trial drug. All of the subjects recovered and none required withdrawal of secukinumab. For Subject (b) (6), the reasonable temporal relationship and no other alternative explanations for the syndrome of MINOCA (MI with no obstructive coronary arteries) makes causality possible.

The overall number of CV SAEs is relatively small and the incidence of MACE was low; therefore, an increased risk of serious CV events including MACE with either dosage regimen of secukinumab cannot be concluded.

Incorporation of CV risk to the current labeling of COSENTYX is not indicated at this time. Characterization of any potential role secukinumab 300 mg Q2W or Q4W might have with regards to CV risk can be assessed through routine postmarketing pharmacovigilance.

8.2.5.8. Malignancy

Clinical trial and postmarketing data have not identified a risk for malignancy to warrant labeling; however, due to secukinumab's immunomodulating mechanism of action, the risk of malignancy associated with secukinumab use, remains a safety area of interest especially in a population with moderate to severe chronic inflammation.

Analysis of the pooled safety data from trials M2301 and M2302 over the Entire Trial Period demonstrated that each treatment group had 2 subjects with reported malignancies.

In the placebo group, subject (b) (6), a 65-year-old White male, was diagnosed with metastatic lung cancer. The event was serious, severe, and ongoing at the time of database lock. Subject (b) (6)9 was a 59-year-old White male diagnosed with a papillary urothelial tumor (benign). The event was documented as nonserious, severe, and resolved without change in dosage regimen.

In the secukinumab Q2W group, subject (b) (6)a 55-year-old White male with a history of chronic, active tobacco use, was diagnosed with metastatic non-small cell carcinoma 48 weeks after starting secukinumab Q2W. Trial drug was permanently discontinued due to the event and the subject withdrew from the trial. The event was ongoing at the time of trial discontinuation.
Lung adenocarcinoma is the second most common cancer in both men and women and this subject's chronic active smoking history placed him at a higher risk for this malignancy. The diagnosis of metastatic disease was made after less than a year of exposure to secukinumab Q2W. Whether secukinumab accelerated the course of cancer growth cannot be determined based on the information provided.

The second subject in the secukinumab Q2W group, (b) (6), was a 50-year-old White female with a history of chronic active tobacco use, who was diagnosed with serious, severe "breast cancer" approximately 45 weeks after starting secukinumab Q2W. Prior HS medications included several antibiotics but no biologic therapy. Trial drug was discontinued and the subject withdrew from the trial. After treatment with docetaxel, pertuzumab, and trastuzumab, she was reported as recovering from breast cancer at the time of the trial discontinuation.
This subject had limited reported risk factors. Based on the information provided, it is possible that secukinumab Q2W played a role in the development of detectable breast cancer.

In the secukinumab Q4W group, subject (b) (6) a 27-year-old White female with a history of vulvar dysplasia, human papillomavirus, and diabetes mellitus, was diagnosed with mild, nonserious squamous cell carcinoma in-situ lesions (3 vulvar and 2 perianal) due to human papillomavirus approximately 7 weeks after starting secukinumab Q4W. The lesions were excised and the subject was reported as having recovered 5 days later. Three weeks later, mild, nonserious Stage 1 vulval cancer with 2 mm invasion was diagnosed and on the same day, trial drug was discontinued. Radiation and chemotherapy were started at Week 25 at which time the subject withdrew from the trial. The event of vulval cancer was ongoing at the time of the trial discontinuation.
The subject's history of vulvar dysplasia and human papillomavirus were more likely to have contributed to the events of malignancy than trial drug.

Subject (b) (6) was a 45-year-old White female with a history of tobacco use and prior exposure to biologic therapies including infliximab and adalimumab, who was diagnosed with a mild, nonserious solitary basal cell carcinoma (BCC) lesion near the right clavicle approximately 15 days after starting secukinumab Q4W. No action was taken with the trial drug. The subject was treated with topical 5-fluorouracil and excision. She completed the trial per protocol and transitioned to the optional extension trial after 54 weeks.
Given the brief time to onset, it is unlikely the the skin neoplasm was related to secukinumab use.

In the safety update report, 4 malignancies were reported in 4 subjects enrolled in the extension trial. One subject receiving placebo was diagnosed with malignant melanoma and three subjects receiving secukinumab Q2W were diagnosed with metastatic breast cancer (b) (6), pancreatic carcinoma ((b) (6)), and squamous cell carcinoma (b) (6). The three subjects receiving secukinumab Q2W are discussed in more detail below.

Subject (b) (6) – Metastatic Breast Cancer
A 37-year-old White female with a history of active tobacco use was diagnosed with metatastatic breast cancer approximately 88 weeks after starting secukinumab Q2W. Four weeks later the trial drug was discontinued and the subject withdrew from the trial. She was hospitalized and received radiotherapy, goserelin, and letrozole. The event, metastatic breast cancer was ongoing, and the event, invasive cancer of the left breast, was resolving at the time of trial discontinuation.
Breast carcinoma is the most common cancer in the United States followed by lung, prostate, and colon cancers. Nonetheless, this subject was young, and based on the provided information, she had no other risk factors other than tobacco use. Considering these factors, it is possible that secukinumab Q2W accelerated the course of cancer growth.

Subject (b) (6) – Pancreatic Carcinoma
A 72-year-old White male with a history of active tobacco use (138 pack -years), diabetes mellitus type 2, hypertension, and chronic obstructive pulmonary disease, was diagnosed with pancreatic carcinoma approximately 59 weeks after starting secukinumab Q2W. The subject

was hospitalized; however, no details regarding diagnostic and therapeutic interventions were reported. Trial drug was permanently discontinued due to the event of pancreatic carcinoma and at the time of trial discontinuation, pancreatic carcinoma was ongoing.
The time of diagnosis relative to drug intake makes it unlikely that the event of pancreatic carcinoma is a result of secukinumab Q2W use in this subject who's age and chronic tobacco use likely played a more consequential role.

Subject (b) (6) – Squamous Cell Carcinoma – two episodes
A 40-year-old Asian male with a history of active tobacco use who was diagnosed with his first episode of squamous cell carcinoma (SCC) located on his left buttock approximately 17 weeks after starting secukinumab Q2W. The subject was hospitalized and underwent excisional biopsy. No action was taken with trial drug. After 84 weeks a second episode of SCC was diagnosed. The lesion was located in the left inguinal region. After 99 weeks, trial drug was permanently discontinued and the subject eventually withdrew from the trial. The event of SCC was ongoing at the time of trial discontinuation.
Given he SCC lesions were in areas usually protected from ultraviolet radiation and occurred in a relatively young subject whose only apparent risk factor was his tobacco use, the role of secukinumab Q2W cannot be excluded. Based on a reasonable temporal relationship and few risk factors for SCC, it is possible that the skin cancers were related to secukinumab use. The role of the increased dosage frequency is unclear.

The number of malignancy events is relatively small and most subjects had underlying risk factors that could possibly explain their cancers, although a synergistic effect by secukinumab cannot be excluded.Therefore, an increase in overall malignancy risk cannot be concluded in the HS population for either dosage regimen. Continued postmarketing evaluation is necessary to assess the risk of malignancy in patients with moderate to severe HS receiving secukinumab 300 mg every 2 or 4 weeks.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable to this supplement review.

8.2.7. Safety Analyses by Demographic Subgroups

Subgroup analyses of six intrinsic and three extrinsic factors were conducted to assess whether these factors impacted the overall safety profile of secukinumab.

The intrinsic factors included age (<40 years, ≥40 years), sex (female, male), race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple), disease duration (<2 years, 2 to <5 years, 5 to <10 years, ≥10 years), weight (<90 kg, ≥90 kg), and Hurley stage (I, II, III).

The extrinsic factors were current systemic antibiotic use (yes, no), previous biologic exposure (yes, no) and smoking status (current, former, never).

The secukinumab HS clinical safety population was predominantly white (78%) and female (56%). At the time of randomization most subjects weighed ≥ 90 kg (53%), were current smokers (54%), and had not been previously exposed to systemic biologic therapy (77%) nor were using concomitant systemic antibiotics (88%). The median age was 34 years. The population appeared to be representative of the US target population based on sex and age, but not by race as the prevalence of HS appears to be higher among African Americans.[30]

Baseline demographic and disease characteristics were generally balanced across treatment groups in the pooled safety population with differences noted in the categories of age and disease severity. The secukinumab Q2W group had slightly more subjects over the age of 40 years (147, 41%) compared to the Q4W (125, 35%) and placebo (120, 33%) groups and also comprised more subjects with Hurley stage III and higher baseline lesion counts.

The difference in age between the secukinumab Q2W group and other treatment groups did not appear to affect safety as the AE profile by age was comparable between the arms. However, the difference in disease severity may have impacted safety as serious AEs of *worsening HS* were reported at a higher rate in the secukinumab Q2W group compared to the Q4W group as shown in Table 32. The imbalance of baseline disease severity, however, did not appear to impact the risk of serious sweat gland infections.

Intrinsic Factors
Analyses based on intrinsic factors of subjects who received at least one dose of Any secukinumab dose during the Entire Trial Period showed that the incidence of AEs and SAEs was *higher in older* subjects (AEs: 335.5/100 PY and SAEs: 12.9/100 PY in subjects ≥40 years compared to AEs: 262.8 /100 PY and SAEs: 7.2 /100 PY in the the <40 years group). Rates of total AEs were also *higher in female* subjects compared to male subjects (346.4/100 PY compared to 230.4/100 PY, respectively) and in those who *weighed more* (≥ 90 kg, 313.7/100 PY) compared to those who were <90 kg subjects (259.2/100 PY).
Results by race were variable as White subjects who received Any secukinumab Q4W had a higher rate of AEs compared to those in the Any Q2W group, while Asian subjects in the Any secukinumab Q2W group had a higher EAIR for total AEs. Nonetheless, the types of AEs were consistent across treatment groups and races.
For subgroups of disease duration, the incidence of AEs and SAEs were comparable.

Extrinsic Factors
For extrinsic factors, similar analyses of subjects who received at least one dose of Any secukinumab dose during the Entire Trial Period were performed and discussed below.

As previously mentioned, the majority (88%) of subjects did not use concomitant systemic antibiotics. Subjects who did use systemic antibiotics concurrently had a higher EAIR of SAEs compared to those who were not using concomitant systemic antibiotics (13.8/100 PY and 8.7/100 PY, respectively). This imbalance was primarily driven by the higher EAIR of SAEs in Any

[30] Garg A et al. Incidence of hidradenitis suppurativa in the United States: A sex- and age-adjusted population analysis. J Am Acad Dermatol. 2017 Jul;77(1):118-122.

secukinumab Q2W which corresponds to the greater proportion of subjects in the Q2W group who had more severe baseline disease severity. However, due to the large difference in the number of subjects who used concomitant systemic antibiotics compared with the those who did not, meaningful conclusions regarding the differences in AEs between these groups could not be made.
Most subjects (77%) had not been previously exposed to systemic biologic therapy. Subjects who had prior exposure to these treatments had an overall higher EAIR of SAEs during Entire Trial Period compared to those who were naïve to biologics therapy (15.5/100 PY vs 7.5/100 PY). The difference in the number of subjects who previously used systemic biologics compared to those who were "bio-naïve" may be too large to make meaningful conclusions regarding the difference in the EAIR of SAEs during the Entire Trial Period.

For AEs within the SOCs Infections and infestations, Gastrointestinal disorders, and Skin and subcutaneous tissue disorders, the overall EAIRs were higher in current smokers (94.2, 36.2 and 46.2 per 100 PY, respectively) and Former smokers (96.5, 45.1, 58.8 per 100 PY, respectively) compared to the those who had never smokerd (80.4, 23.0, 39.5 per 100 PY, respectively).

Overall, the adverse event profile in different subgroups of intrinsic factors (age, sex, race, body weight, disease duration, and disease severity/Hurley stage) and extrinsic factors (concomitant systemic antibiotic use, previous biologic exposure, and smoking status) was generally consistent with that observed for the overall safety population in the pooled data.

8.2.8. Specific Safety Studies/Clinical Trials

Additional specific study(ies) or clinical trials were not conducted as part of this supplement.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a dedicated trial to assess human carcinogenicity. Refer to Section 8.2.5.8 Malignancy for a discussion of the malignancies reported by subjects who received secukinumab in the HS clinical trials.

Human Reproduction and Pregnancy

Pregnant and breastfeeding women were excluded from participating in the trials.
A total of 5 pregnancies, described below, were reported in subjects who received secukinumab during trials M2301, M2302, and M2301E1. Two pregnancies were reported in subjects receiving placebo. All subjects were discontinued from the trials as per protocol.

Subject (b) (6)
A 26-year-old Black female with a history of diabetes mellitus type I, depression, and two prior elective terminations of pregnancy, was diagnosed with a pregnancy 47 weeks after starting secukinumab Q2W. An ultrasound showed a normal intrauterine pregnancy with a gestational

sac and yolk sac (measuring 5 weeks 5 days). Four weeks later, the subject underwent an elective abortion (9 weeks) due to the undesired pregnancy. After 56 weeks in the trial, the subject withdrew from Trial M2301 due to the pregnancy.

Subject (b) (6)
A 26-year-old White female with a history of active tobacco use and gastric banding. At 52 weeks, the subject completed treatment with secukinumab Q4W and transitioned to the follow-up period. At Week 53, the subject had a positive human chorionic gonadotropin. No other details including the outcome of the pregnancy were reported). The subject had been using oral hormonal contraceptives (desogestrel) since prior to the trial and were ongoing at the time of trial completion at Week 60.

Subject (b) (6)
22-year-old Black female with a history of hypercholesterolemia and acne treated with adapalene and isotretinoin was randomized to receive Placebo during Treatment Period 1 followed by secukinumab Q2W after Week 16. On an unknown date, the subject became pregnant. Her last menstrual period was during Week 12. At Week 18, trial drug was discontinued and the subject withdrew from the trial. The estimated delivery was reported to be during Week 53. The outcome of the event (maternal exposure during pregnancy) was not reported. The subject was lost to follow-up.

Subject (b) (6)
A 27-year-old White female with a history of psoriasis and active tobacco use became pregnant on an unspecified date. The subject reported longstanding use of oral hormonal contraceptives (levonorgestrel-ethinylestradiol. The patient's last menstrual period was during Week 40 of Trial M2302 during which trial medication was permanently discontinued. At week 44, the subject withdrew from the trial due to the pregnancy. The outcome of the event (maternal exposure during pregnancy) was not reported at the time of data cut-off.

During the extension trial, one pregnancy was reported in a 38-year-old White female (b) (6) According to the subject listing within the safety update report, the subject's dose had not changed at the time of data cut-off. The outcome of the event was not reported.

The current USPI describes that "limited available human data with COSENTYX use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. In an embryo-fetal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of secukinumab during organogenesis at doses up to 30 times the maximum recommended human dose (MRHD)." Additionally, the labeling does not advise a pregnancy registry that monitors pregnancy outcomes in female patients exposed to secukinumab during pregnancy.

The information on pregnancy provided from the HS trials did not change the risk-benefit assessment for use of secukinumab in the treatment of adult patients with moderate to severe HS; therefore, changes to section 8.1 of the USPI are not indicated at this time.

Pediatrics and Assessment of Effects on Growth

The new indication for secukinumab triggered the Pediatric Research Equity Act (PREA). The Agreed Initial Pediatric Study Plan under IND 100418 was submitted December 19, 2018. After back-and-forth communication, a No Agreement Letter was sent to the sponsor on April 22, 2020 requesting additional data prior to agreement with the pediatric study design:

> *DDD agrees with the need for a PK/safety study. However, it is premature to agree on the specifics. DDD has seen top-line pediatric data from the ongoing pediatric psoriasis trials. The information indicates potentially higher pediatric exposure and potential safety concerns. DDD would like additional information prior to agreements on pediatric HS trial design. The sponsor is exploring an increased dosing frequency (compared to the approved dose) for the HS indication which may necessitate additional pediatric safety information beyond the 32 subjects proposed in this primarily PK study.*

Updated iPSPs were submitted on November 2, 2020, December 17, 2021, and February 8, 2022. The amendment dated February 8, 2022, contained the Applicant's Agreed Initial Pediatric Study Plan (Agreed iPSP) for the treatment of hidradenitis suppurativa, which provided for the following:

- an **extrapolation approach for HS efficacy** data from adults to adolescents with the assumption that the same level of exposure in adolescent patients as in adult patients will lead to the same level of efficacy in both populations.
- a **population PK model** using data from adult and pediatric psoriasis studies, as well as PK data obtained from adult HS subjects to identify pediatric HS regimen(s) that will achieve similar exposure to regimen(s) considered efficacious and safe in adults with HS.
- a **partial waiver** for the treatment of HS in pediatric patients aged < 12 years, because necessary studies are impossible or highly impracticable as HS typically starts after puberty, and there is a rarity of diagnosis in children aged <12 years of age.
- a **deferral** in pediatric individuals 12 years of age to ≤17 years of age until the population PK model is developed to identify pediatric HS regimen(s) that will achieve similar exposure to regimen(s) considered efficacious and safe in adults with HS.
- an **open-labelled study** to address the pharmacokinetics and safety of secukinumab in adolescent subjects 12 years to less than 18 years old with HS which will consist of approximately 80 male and female subjects 12 to less than 18 years of age (at the start of study treatment) with HS who are candidates for systemic treatment. The subjects will be required to have confirmed diagnosis of HS for at least 6 months involving at least two distinct anatomic body areas with 3 or more inflammatory lesions (abscesses and/or inflammatory nodules). Patients weighing less than 50 kg OR with >10 draining fistulae at entry will be excluded from the trial. The Division acknowledged the inclusion

of adolescent subjects with ≥3 inflammatory lesions which differs from the criteria for baseline disease severity in the adult population (i.e. ≥5 inflammatory lesions.). The proposed modification in disease burden is not expected to impact PK or safety assessment and may assist in recruitment of adolescents with HS.

The iPSP was reviewed at PeRC on February 22, 2022. The Committee agreed with the iPSP and the Division's recommendations.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of secukinumab overdose have been reported in HS subjects.

There is no data to support an association of monoclonal antibodies including secukinumab with the potential for drug abuse. Therefore, the Applicant did not evaluate abuse potential.

The safety of secukinuamb in subjects who had treatment withdrawn and restarted is being assessed in the phase 3 extension trial, M2301E1. Based on the available summary of data from this trial, no new or clinically meaningful changes in AEs were observed with subsequent retreatment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

According to the latest Development Safety Update Report (DSUR, data lock point of June 25, 2022), submitted to IND 100418 on August 19, 2022, over 29,609 patients and healthy individuals have cumulatively received secukinumab in Novartis sponsored clinical trials. The Applicant estimated the cumulative postmarketing patient exposure to be over 1,159,260 patient-years.

Within the DSUR, actions taken for safety reasons included an update to the Core Data Sheet (CDS) to include "dyshidrotic eczema" as a new Adverse Drug Reaction (ADR) with the frequency uncommon. The decision was based on plausible mechanism, disproportionality across multiple databases, and noteworthy individual case safety reports (literature and post-marketing). Additionally, in August 2021, Novartis committed to distribute a Dear Investigator Letter to participating sites in France clarifying the management of patients developing Inflammatory Bowel Disease (IBD) following requests from the French government agency for the Safety of Health Products.

Within the most recent Periodic Adverse Experience Report (PAER) for BLA 125504 for the reporting period of December 26, 2021 to December 25, 2022 that was submitted on February 16, 2023, the Applicant summarized safety-related labeling changes and other regulatory actions taken since the last report and planned to include "Pyoderma gangrenosum" as a new ADR with frequency unknown, in addition to adding the ADR of "dyshidrotic eczema" as

mentioned above. There were reportedly no important foreign regulatory actions taken during this reporting period.

In addition to the ADRs of "pyoderma gangrenosum" and "dyshidrotic eczema", which are currently under review by the Agency, safety labeling changes are planned to add language describing various opportunistic infections (OIs) to the COSENTYX USPI. As discussed under section 8.2.5.2 Infections, following review of numerous postmarketing cases of OIs retrieved from the FDA Adverse Event Reporting System (FAERS) database and literature, the addition of OIs is supported by probable causal association and biological plausibility.

Safety considerations that have arisen from prior experience with secukinumab are addressed in the currently approved Risk Management Plan.

Expectations on Safety in the Postmarket Setting

The dosage regimen, secukinumab 300 mg every two weeks, as administered and used in the HS clinical trials is different from the dosing frequency (every 4 weeks) recommended for all currently approved indications. However, the safety profile of secukinumab 300 mg Q2W and secukinumab 300 mg Q4W in subjects with HS were generally consistent with the known safety profile for secukinumab across multiple indications. There were no new or unexpected safety findings. Treatment with secukinumab 300 mg Q2W and Q4W in subjects with HS was not associated with an increased risk of mortality or serious adverse events. Therefore, based on the available safety data, the expectation is that the postmarketing safety experience for patients with HS will likely be similar to the experience of patients with chronic inflammatory conditions for which secukinumab is approved.

8.2.11. Integrated Assessment of Safety

The data provided in this supplement from adult subjects with moderate to severe HS demonstrated a safety profile for both dosage regimens that is similar to what has been established for the psoriasis population.

During the placebo-controlled period, the most common ARs reported in ≥ 1% of subjects in the secukinumab Q4W group and at least 1% more frequently than in the placebo group were headache (16.7%), abdominal pain (6.7%), cough (4.2%), dental caries (3.9%), oropharyngeal pain (3.6%), eczema (3.1%), lipase increased (3.1%), conjunctivitis (2.8%), vulvovaginal candidiasis (2.5%), psoriasis (2.5%), dermatitis contact (2.5%), and hypertriglyceridemia (2.5%). The most frequently reported ARs occurring in ≥ 1% of subjects in the secukinumab Q2W group and at least 1% more frequently than in the placebo group were upper respiratory infections (27.7%), headache (18.0%), eczema (5.0%), dental caries (4.4%), oropharyngeal pain (4.2%), folliculitis (3.6%), intertrigo (3.3%), psoriasis (2.8%), lipase increased (2.8%), conjunctivitis (2.5%), gastroenteritis (2.5%), oral candidiasis (2.2%), fungal skin infection (1.9%), ear infection (1.7%), and dermatitis psoriasiform (1.1%).
With longer exposure through 52 weeks, the types of adverse events were similar to those

observed during the first 16 weeks of treatment, and the frequencies of events between the Any secukinumab Q2W and Q4W groups were comparable.
The common adverse reactions observed in subjects with moderate to severe HS treated with secukinumab Q2W or Q4W were generally consistent with the adverse reactions in patients with psoriasis. Labeling for COSENTYX will reflect this consistency, but Sections 5 and 6 will also be updated to reflect the increased incidence of fungal infections in the secukinumab Q2W group compared to the secukinumab Q4W group.

Treatment with secukinumab 300 mg Q2W and Q4W in subjects with moderate to severe HS was not associated with an increased risk of mortality. There were no deaths among subjects receiving secukinumab Q2W, and 2 deaths among subjects receiving secukinumab Q4W. Neither of the deaths were assessed as probably related to the drug product.

Serious adverse events (SAEs) were reported in 3.0% of subjects treated with secukinumab 300 mg Q2W, secukinumab 300 mg Q4W, and placebo during the first 16 weeks of treatment. No SAE was reported with greater than 1% frequency. The most common SAEs were worsening hidradenitis and sweat gland infection.
The majority of SAEs were consistent with those expected for a population of patients with moderate to severe HS treated with an immunosuppressive biologic. Although the proportion of subjects with SAEs was the same across secukinumab and placebo groups during the placebo-controlled period, and the incidence rates of SAEs were comparable between the Any secukinumab Q2W and Any secukinumab Q4W groups with longer exposure through 52 weeks, the nature of the events differed. In general, more severe clinical courses and unfavorable outcomes were observed with subjects in the secukinumab Q2W who experienced SAEs.

Adverse events leading to discontinuation occurred in 1.7% of subjects treated secukinumab 300 mg Q2W, 1.7% treated with secukinumab 300 mg Q4W, and 1.4% treated with placebo. The higher dosing frequency of secukinumab Q2W did not appear to impact the rate or type of AEs that led to treatment drug discontinuation.

Adverse events of special interest (AESI) included worsening HS requiring rescue therapies, infections, hypersensitivity, suicidal ideation and behavior (SIB), inflammatory bowel disease (IBD), neutropenia, major adverse cardiovascular events (MACE), and malignancy.

During the placebo-controlled period, the rate of worsening hidradenitis was highest for the placebo group (19.6%) and similar between the secukinumab groups (12.2% for the secukinumab Q2W group and 13.1% for the secukinumab Q4W group. With longer exposure through 52 weeks, the incidence of worsening hidradenitis was consistent with the findings through the initial 16 weeks of treatment. In the first 16 weeks of treatment, a greater proportion of subjects in the placebo group (7.1%) required rescue medications (i.e., stable doses of doxycycline and minocycline) compared to 6.1% in the secukinumab Q2W group and 4.5% in the secukinumab Q4W group. Similarly, a larger proportion of subjects in the placebo group (11.0%) required lesion intervention (i.e., incision, drainage, intralesional corticosteroid

injections) compared to the secukinumab groups (4.4% in secukinumab Q2W and 6.1% in secukinumab Q4W).
With longer exposure, a higher proportion of subjects in the Any secukinumab Q2W group (13.7%) required rescue medications compared to the Any secukinumab Q4W group (12.4%); and a greater proportion of subjects in the Any secukinumab Q4W group (15.4%) necessitated rescue interventions compared to the Any secukinumab Q2W group (9.1%). While the findings are not unexpected for the use of rescue medications, it is not clear why, despite a more severe population enrolled in the secukinumab Q2W arm, more subjects receiving secukinumab Q4W required rescue interventions.

Common infections such as upper respiratory infections, conjunctivitis, and gastroenteritis were reported more frequently in both secukinumab groups as compared to placebo.
During the placebo-controlled period, the incidence of infections involving skin structures was highest for subjects in the placebo group (17.6%) and relatively comparable for the secukinumab Q4W (14.2%) and secukinumab Q2W (13.0%) groups. Given a larger proportion of subjects in the secukinumab Q2W group had more severe baseline disease (based on Hurley staging) and PK data demonstrated that drug clearance is increased with more severe disease, the slight numerical difference in the rates of skin infections between the secukinumab groups might be related to a difference in systemic exposure.
Fungal infections were reported more frequently for the secukinumab Q2W group (5.3%) compared to the secukinumab Q4W (3.9%) and placebo (2.8%) groups during the first 16 weeks of treatment. After 52 weeks of exposure, more infections by SOC were reported for the Any secukinumab Q2W group (94.5/100 PY) compared to the Any secukinumab Q4W group (87.9/100 PY), and this difference appeared to be due to a higher rate of fungal infections. These findings support the inclusion of language in Warnings and Precautions and Adverse Reactions, subsections 5.1 Infections and 6.1 Clinical Trials Experience, to convey the higher rate of fungal infections observed with increased dose frequency in the HS population.

Hypersensitivity events were highest for the secukinumab Q2W group (5.3%) compared to the secukinumab Q4W (3.3%) and placebo (3.9%) groups during the first 16 weeks of treatment. Similar findings after 52 weeks of exposure were observed wherein the rate of hypersensitivity AEs remained higher for the Any secukinumab Q2W group (5.1%) compared to the Any secukinumab Q4W group (3.4%). A positive association between the incidence of these hypersensitivity events and more frequent dosing cannot be ruled out and is concerning for potentially more severe immune reactions and/or escalation of an immune response with repeated dosing beyond the recommended 300 mg every 4 weeks. Hypersensitivity is labeled under Contraindications and Warning and Precautions in the current Cosentyx USPI. While no further updates to the labeling regarding hypersensitivity are indicated at this time, ongoing postmarketing surveillance of these events is necessary.

Suicidal ideation and behavior (SIB) was reported in one subject in each of the secukinumab groups and no subject in the placebo group during the first 16 weeks of treatment. With longer exposure through 52 weeks, one more subject in the secukinumab Q2W group experienced a suicide-related AE. Based on the reasonable time relationship, it is possible that these events

may be related to secukinumab use reported in subjects with underlying mood disorders. However, the number of cases were small and the difference in EAIR (0.4/100 PY for the Any secukinumab Q2W group compared to 0.2/100 PY for the Any secukinumab Q4W group) was not significant. There is insufficient evidence of increased risk of suicidal ideation and behavior with more frequent dosing of secukinumab to recommend updating the labeling for secukinumab. While these events of self-harm do not alter the current recommendations for use of secukinumab, continued postmarket monitoring of SIB especially for this population and this drug class are recommended.

Events of inflammatory Bowel Disease (IBD) were reported more frequently in subjects receiving secukinumab Q2W during the three phase 3 trials, in particular during the randomized withdrawal extension trial (M2301E1), which included information from 700 subjects who completed trials M2301 and M2302 and who wished to continue treatment. Five (0.7%) subjects out of 700 total subjects in the ongoing extension trial were documented to have experienced events of new IBD. All of the subjects were receiving secukinumab 300 mg Q2W at the time of their diagnoses. All IBD events were serious and led to withdrawal of trial drug. IBD is labeled under the Warnings and Precautions and Adverse Reactions sections of the current secukinumab USPI. It is reasonable to modify these sections to include the increased rate of new serious IBD events in the HS population who were administered secukinumab every 2 weeks compared to those who received secukinumab every 4 weeks.

Assessment of AEs of neutropenia/decreased neutrophil count demonstrated comparable rates between secukinumab 300 mg Q2W and secukinumab 300 mg Q4W during the phase 3 HS development program. Additionally, evaluation of hematology laboratory parameters did not show any clinically meaningful differences in new or worsening neutropenia across treatment groups. Therefore, updates to the labeling of COSENTYX which currently describes neutropenia in subsection 6.1 Clinical Trials Experience is not warranted at this time.

The overall number of serious cardiovascular AEs was relatively small, and the incidence of MACE was low; therefore, an increased risk of serious CV events including MACE with either dosage regimen of secukinumab cannot be concluded. Incorporation of CV risk to the current labeling of COSENTYX is not indicated at this time. Characterization of any potential role secukinumab 300 mg Q2W or secukinumab Q4W might have with regards to CV risk can be assessed through routine postmarketing pharmacovigilance.

The number of malignancy events is relatively small, and most subjects had underlying risk factors that could possibly explain their cancers, although a synergistic effect by secukinumab cannot be excluded. Therefore, an increase in overall malignancy risk cannot be concluded in the HS population for either dosage regimen. Given the short duration of the trials and the long latency of malignancy, the absence of a clear safety signal is not in itself reassuring. Routine postmarketing monitoring is necessary to assess the risk of malignancy in patients with moderate to severe HS receiving secukinumab 300 mg every 2 or 4 weeks.

Continued evaluation of AESIs will be conducted for all three ongoing clinical trials.

Among subjects receiving secukinumab in the entire HS development program there were 5 maternal exposure pregnancies. An elective abortion at 9 weeks gestation was reported for one of the subjects, and pregnancy outcomes for the other four subjects were not reported. In the review team's opinion, pregnancy exposure can be assessed through evaluation of data from the long-term extension trial and reports of post-marketing events.

The currently available safety data demonstrate that secukinumab 300 mg Q2W and secukinumab 300 mg Q4W are safe for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). The safety database did not allow for assessment of the risks of secukinumab use children as they were excluded from the clinical trials. Evaluation of the benefit-risk in the pediatric population, will be required as a postmarketing assessment.

The risks of COSENTYX across multiple indications includes immunosuppression with serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, hypersensitivity, suicidal ideation and behavior, inflammatory bowel disease, and neutropenia. There were no new or unexpected safety findings. Treatment with secukinumab 300 mg Q2W and secukinumab 300 mg Q4W in subjects with HS was not associated with an increased risk of mortality or serious adverse events. Based on the available safety data, the expectation is that the postmarketing safety experience for patients with HS will likely be similar to the experience of patients with chronic inflammatory conditions for which secukinumab is approved.

Modifications to the labeling will communicate the increased rates of fungal infections and new inflammatory bowel disease events observed in subjects with HS who received secukinumab at the more frequent dosage regimen of every 2 weeks.

8.3. Statistical Issues

There were no major statistical issues that affected the overall study conclusions.

However, the statistical reviewers found that there were only 2 subjects in Study M2301 and no subjects in Study M2302 classified as on rescue medication (ICE #2) and were treated as 'non-responders' in the applicant's submitted efficacy data set ADHiSCR.xpt/ADHSRMI.xpt. However, there were 37 more subjects in Study M2301 and 53 more subjects in Study M2302 who were either on rescue medication or on rescue therapy according to the applicant's submitted data sets ADCM.xpt/ADPR.xpt. The Agency sent two rounds of IR letter to the applicant and requested the applicant to provide clarification on the discrepancy in identifying subjects who used the rescue medication/therapy between the two sets of submitted data sets, adding single lesion intervention to their definition of 'rescue medication' and provide corrected data sets and update analysis for the primary and secondary points with a consistent approach for handling rescue medication/therapy as "non-responders"per SAP. The applicant submitted updated response data sets in which any use of rescue medication or lesion intervention was considered a treatment failure (non-responder) and the updated multiple imputation datasets

were based on the updated response data. The applicant also submitted the FDA-requested analyses for the primary and secondary endpoints and all the related analyses based on the updated datasets.
The resulting difference in the primary endpoint HiSCR Response between the applicant's analysis and FDA-requested analysis are 14 subjects (3 in secukinumab Q2W, 2 in secukinumab Q4W, and 9 in placebo) in Study M2301 and 24 subjects (7 in secukinumab Q2W, 7 in secukinumab Q4W, and 10 in placebo) in Study M2302 whose HiSCR response status were changed from "responder" or missing response to "non-responder". Notably, more subjects in placebo were on rescue medication/intervention and were changed to be "non-responder" especially in Study M2301, which improved the efficacy effect of secukinumab Q2W and secukinumab Q4W in both studies, especially that of secukinumab Q4W in Study M2301. The efficacy of secukinumab Q4W improved from p=0.0835 to p=0.0123, which is only slightly greater than the pre-specified alpha 0.01.

In addition, the reviewers also conducted additional exploratory analysis to explain

a. the observed lower efficacy effect for secukinumab Q4W vs. placebo between the two studies
b. the observed inconsistent trend of efficacy for secukinumab Q2W vs. Q4W between the two studies
c. the observed inconsistent efficacy results across different regions in the two studies.

It turns out that all of these inconsistent results are associated with the imbalanced distribution of baseline severity level (Hurley stage) among the different treatment groups/regions across the studies.

8.4. Conclusions and Recommendations

To establish the effectiveness of secukinumab for the treatment of adult patients with moderate to severe HS, the Applicant submitted data from two identical, adequate and well-controlled clinical trials, M2301 and M2302. The trials evaluated secukinumab 300 mg every 2 weeks and 300 mg every 4 weeks versus placebo in 1084 adult subjects with moderate to severe HS. Primary efficacy was assessed at Week 16 by the proportion of subjects who achieved a Hidradenitis Suppurativa Clinical Response, HiSCR50, defined as at least a 50% reduction in total abscess and inflammatory nodule count (AN count), with no increase in abscess count, and no increase in draining fistula count relative to baseline.

While the effectiveness standard was met, the results on the primary efficacy endpoint were inconsistent across the two trials.

Based on the Applicant's strategies for handling the use of rescue medication, the secukinumab Q2W dosage regimen showed statistically significantly higher response rates with clinically meaningful differences compared to placebo in both trials (45.0% in vs. 33.7% in M2301, two-

sided p=0.0140 < pre-specified alpha 0.04; 42.3% vs. 31.2% in M2302, two-sided p=0.0299 < 0.04). The secukinumab Q4W dose regimen showed a statistically significantly higher rate with clinically meaningful differences compared to placebo in Trial M2302 (46.1% vs. 31.2%, two-sided p=0.0044 < pre-specified alpha 0.01), but not in Trial M2301 (41.8% vs. 33.7%, two-sided p=0.0835). Moreover, the Q4W regimen in Trial M2302 had the highest response rate (46.1%) compared to the Q2W regimen in both trials (45.0% in Trial M2301 and 41.8% in Trial M2302).

Of note, upon conduct of further analyses (different from the Applicant's strategies for handling the use of rescue medication) wherein subjects who received any rescue medication or underwent lesion intervention were considered treatment failures and handled as non-responders, the results were generally similar to that of the Applicant's aforementioned analyses except that all the p-values were smaller (i.e., more statistically significant). Most notably, the statistical significance of the secukinumab Q4W vs. placebo in Study M2301 considerably improved (41.3% vs. 29.4%, p=0.0123 > pre-specified alpha 0.01).

To understand the inconsistent efficacy results, the review team conducted analyses of response rates based on disease severity (measured by Hurley staging) given there was an imbalanced distribution of subjects with baseline Hurley stage III severity among the three treatment arms between the two trials, and baseline Hurley stage appeared to be the only significant variable in the multivariate logistic regression analysis. Additionally, the submitted data demonstrated a positive correlation between disease severity and drug clearance which corresponded to lower systemic exposures in subjects with worse disease severity.

Although both trials were randomized, the placebo group in Trial M2301 had a significantly smaller proportion of subjects with Hurley stage III disease (28.3%) compared to the placebo group in Trial M2302 (38.3%)—this difference significantly impacted treatment effect. In Trial M2301, because more subjects in the placebo group had milder disease, a higher response rate was observed (33.7%) compared to the response rate for the placebo group in Trial M2302 (31.2%) which had 10% more subjects with Hurley stage III severity. These differences between the placebo groups explain the lower treatment effect observed for the Q4W group relative to placebo in Trial M2301 compared to the treatment effect for the Q4W group in Trial M2302.

In attempts to ascertain why the secukinumab Q4W regimen in Trial M2302 had the highest response rate, the impact of the imbalanced distribution of subjects with Hurley stage III was further assessed. The Q2W group was comprised of a larger proportion of subjects with more severe disease at baseline in both Trial 2301 (38.7% with Hurley stage III severity in the secukinumab Q2W group; 35.0% in the secukinumab Q4W group; 28.3% in the placebo group) and Trial 2302 (45.6% in the secukinumab Q2W group; 37.8% in secukinumab Q4W group and 38.3% in the placebo group). This uneven distribution, along with PK data that demonstrated secukinumab clearance increases with increasing HS severity and efficacy (as measured by HiSCR50) plateaued at higher exposures achieved with the Q2W regimen, together provide a reasonable scientific rationale as to why the Q2W groups in both trials had a lower response rate compared to the Q4W group in Trial M2302.

To support the safety of secukinumab in the population with moderate to severe HS, the review team analyzed pooled data from the phase 3 Trials M2301 and M2302 and conducted a comprehensive assessment of safety. The size of the safety database and the safety evaluations were adequate to identify treatment-emergent adverse reactions.

Overall, the safety profile observed in subjects with moderate to severe HS through Week 52 treated with secukinumab 300 mg Q2W and 300 mg Q4W was similar to the safety profile in subjects with psoriasis.

During the HS program, there were two deaths among subjects receiving secukinumab; both were in the secukinumab Q4W group. Neither of the deaths were assessed as probably related to the drug product.

During the placebo-controlled period, the most common ARs reported in at least 1% of subjects treated with secukinumab Q2W or Q4W and at least 1% more frequently than subjects who received placebo included headache, dental caries, oropharyngeal pain, eczema, lipase increased, and conjunctivitis. With longer exposure through 52 weeks, the types of adverse reactions were similar to those observed during the first 16 weeks of treatment, and the frequencies of ARs between the Any secukinumab Q2W and Q4W groups were comparable.

The review team also evaluated the comparative safety of secukinumab 300 mg Q2W and 300 mg Q4W. The proportion of subjects with SAEs or who discontinued due to AEs was similar across secukinumab and placebo groups during the placebo-controlled period and comparable between the Any secukinumab Q2W and Any secukinumab Q4W groups with longer exposure through 52 weeks. However, more severe clinical courses and unfavorable outcomes were generally observed for subjects in the secukinumab Q2W who experienced SAEs. The AESIs, fungal infections, hypersensitivity, and inflammatory bowel disease, were reported more frequently in subjects treated with secukinumab 300 mg Q2W than 300 mg Q4W. The review team considered these findings in the assessment of benefit-risk and determination of the recommended dosing regimen.

Safety and efficacy data submitted by the Applicant support approval of this sBLA.
While the secukinumab Q2W dosage regimen demonstrated statistically significant superiority over placebo for HiSCR50 in both trials, the secukinumab Q4W dosage regimen had the highest response rate across all treatment groups that was statistically significant in Trial M2302 and was explained by the uneven distribution of baseline disease severity among the three treatment arms in both trials. The findings were also supported by PK results that showed subjects with Hurley stage III disease severity had worse exposure-response (E-R) relationships than those with Hurley stages I and II due to increased secukinumab clearance with increasing HS severity.

The results of the subgroup efficacy analyses and findings of the comparative safety assessments between secukinumab Q2W and Q4W dosing support the Applicant's proposed indication, treatment of adult patients with moderate to severe HS. However, the findings do

not support the Applicant's proposed dosage regimen of 300 mg every 2 weeks for all adults with moderate to severe HS. The higher rate of fungal infections, IBD, and hypersensitivity events coupled with modest efficacy on the primary endpoint (HISCR50 response) for the Q2W dosage regimen, generates a risk-benefit profile that favors a recommended dose of secukinumab 300 mg dosed every 4 weeks in adults with moderate to severe HS. The review team therefore determined that labeling reflect a recommended dose of 300 mg every 4 weeks, and for some patients who fail to improve with secukiniumab 300 mg every 4 weeks, a dosage of 300 mg every 2 weeks may be acceptable for the treatment of moderate to severe HS.

HS is a serious condition with limited available treatment modalities. The proposed product answers an unmet medical need.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not convened for this supplement. No novel or complex regulatory issues were identified that required an open forum discussion for this supplement.

10 Pediatrics

The Applicant submitted no data from assessments in the HS pediatric population. Changes made to **Section 8.4** of labeling were for consistency with the approved indications and to add the required pediatric use regulatory statement for HS as presented below:

> Pediatric Plaque Psoriasis
> The safety and effectiveness of COSENTYX have been established for the treatment of moderate to severe plaque psoriasis in pediatric patients aged 6 years and older who are candidates for systemic therapy or phototherapy *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.
> Safety and effectiveness of COSENTYX in pediatric patients with plaque psoriasis below the age of 6 years have not been established.
>
> Juvenile Psoriatic Arthritis
> The safety and effectiveness of COSENTYX have been established for the treatment of active juvenile psoriatic arthritis (JPsA) in pediatric patients aged 2 years and older who weigh 15 kg or more.
> The safety and effectiveness of COSENTYX in pediatric patients less than 2 years of age with JPsA or with a body weight less than 15 kg has not been established *[see Adverse Reactions (6.1), Clinical Studies (14.6)]*.
>
> Enthesitis-Related Arthritis
> The safety and effectiveness of COSENTYX for the treatment of active enthesitis-related arthritis (ERA) in pediatric patients aged 4 years and older who weigh 15 kg or more has been established *[see Adverse Reactions (6.1) and Clinical Studies (14.6)]*.
> The safety and effectiveness of COSENTYX in pediatric patients below the age of 4 years old or with body weight less than 15 kg have not been established.
>
> Hidradenitis Suppurativa and Non-radiographic Axial Spondyloarthritis
> The safety and effectiveness of COSENTYX in pediatric patients with HS or nr-axSPA have not been established.

Refer to Section 8.2.9 under the heading Pediatrics and Assessment of Effects on Growth for a discussion of the Pediatric Study Plan.

Refer to Section 13 of this review for a discussion of the PMR required under PREA.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Table 53: High Level Summary of Significant Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling	Additional Comments
1 INDICATIONS AND USAGE	Sections 1.1, 1.2, 1.3, 8.4	Proposed and recommended indications align: treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).
2 DOSAGE AND ADMINISTRATION	1.1, 1.3, 8.4	(b) (4) [redacted] Recommended: "300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter. If a patient does not adequately respond, consider increasing the dosage to 300 mg every 2 weeks."
4 CONTRAINDICATIONS	8.2.4	(b) (4) [redacted]
5 WARNINGS AND PRECAUTIONS	1.3, 8.2.5.2, 8.2.5.5, 8.2.11	-Recommend specifying that fungal infections appear dose-dependent. -Recommend addition of a higher incidence of IBD with Q2W dosing.
6 ADVERSE REACTIONS	8.2.5.2, 8.2.5.5, 8.2.11	Specific Adverse Reactions of fungal infections and IBD recommended
7 DRUG INTERACTIONS	6.2.1	(b) (4) [redacted]; however, language in section 7 of labeling was modified to include the HS indication.
8 USE IN SPECIFIC POPULATIONS	8.2.7, 10	
14 CLINICAL STUDIES	7.1, 8.1	

Patient Labeling

The Applicant submitted a revised Medication Guide (MG) and Instructions for Use (IFU) for COSENTXY (secukinumab). The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the submitted patient labeling. The final labeling will reflect their recommendations. Refer to the collaborative Patient Labeling Review by Ruth Mayrosh, PharmD and Carrie Newcomer, PharmD (dated June 16, 2023).

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) under the Office of Medication Error Prevention and Risk Management (OMEPRM) evaluated the proposed COSENTYX Prescribing Information (PI), MG, and IFU, and did not identify areas of vulnerability that may lead to medication errors. Refer to the DMEPA review by Corwin D. Howard, PharmD (dated April 15, 2023).

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

Additional data are needed to characterize the safety profile of secukinumab in the pediatric population with HS ages 12 to less than 17 years.

Based on review of the data in this submission, the following postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) will include the following:

In accordance with 21 CFR 314.55(c)(3)(ii), the Applicant, Novartis, requests a partial waiver of pediatric studies with secukinumab for the treatment of HS in patients younger than 12 years of age. We are waiving the pediatric study requirement for ages 0 to less than 12 years because necessary studies are impossible or highly impracticable. While the prevalence of HS in the pediatric population is unknown, published epidemiologic data for children and adolescents in the United States has shown an overall prevalence of 0.028 % in individuals under the age of 18 years, 97% of whom were 10 years old and older.[31] Other data have shown that the mean age of HS onset is 12.5 years.[32]

In accordance with 21 CFR 314.55(b), the Applicant, Novartis, requests deferral of pediatric studies with secukinumab for the proposed HS indication in 12 to < 18-year-old patients. We are deferring submission of pediatric studies for ages 12 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

A planned study in the pediatric population 12 years to less than 17 years of age who are candidates for systemic treatment was included in the Agreed iPSP and will be deferred. The Applicant is proposing to conduct a single open label clinical trial (CAIN457M2304) for the pediatric investigation plan to assess the PK and safety of secukinuamb in pediatric subjects 12 to < 17 years of age with moderate to severe HS. Efficacy will be included among the secondary objectives and will be later extrapolated based on the PK results from this trial as well as the Week 16 primary endpoint efficacy results from the adult trials (M2301 and M2302). The study will consist of approximately 80 male and female subjects 12 to less than 17 years of age (at the start of study treatment) with HS who are candidates for systemic treatment. The subjects will be required to have confirmed diagnosis of HS for at least 6 months involving at least two distinct anatomic body areas with 3 or more inflammatory lesions (abscesses and/or inflammatory nodules). Patients weighing less than 50 kg OR with >10 draining fistulae at entry will be excluded from the trial.

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[31] Garg A et al. Prevalence Estimates for Hidradenitis Suppurativa among Children and Adolescents in the United States: A Gender- and Age-Adjusted Population Analysis. J Invest Dermatol. 2018 Oct;138(10):2152-2156.
[32] Liy-Wong C et al. Hidradenitis Suppurativa in the Pediatric Population: An International, Multicenter, Retrospective, Cross-sectional Study of 481 Pediatric Patients. JAMA Dermatol. 2021 Apr 1;157(4):385-391.

The required study is listed below.

> Conduct an open-label study to evaluate the pharmacokinetics (PK) and safety in the adolescent population (12 to less than 17 years of age) with moderate to severe hidradenitis suppurativa who are candidates for systemic treatment. Evaluate at least 80 subjects exposed to the highest approved dosage of subcutaneous secukinumab (300 mg every 2 weeks) for the treatment of HS for a minimum of 52 weeks.
>
> The Division recommended the Applicant propose new milestone dates as the original dates for trial completion (March 30, 2025) and final report submission (September 30, 2025) listed in the Agreed iPSP were less applicable given the review of this supplement was extended beyond the original PDUFA goal date. Milestone dates for Initial Protocol Submission, Final Protocol Submission, Trial Completion, and Final Report Submission were proposed by the Applicant as follows:
>
> Draft protocol submission: July 2024
> Final protocol submission: Jan 2025
> Study/trial completion: Aug 2029
> Final report submission: Feb 2030

Rationale: Under Section 2 of the Pediatric Research Equity Act (PREA) the Applicant is required to submit adequate safety and efficacy data for pediatric subjects. There is no clinical pharmacology and safety data for subjects with HS age 12 to < 17 years to support labeling**.** The Division determined that 80 adolescent subjects would be sufficient to evaluate PK and safety given the prevalence of HS in the pediatric population is low.[33] Additionally, PK data from secukinumab registrational trials in subjects with psoriasis who were treated with Q2W dosing can be leveraged.

[33] Garg A et al. Prevalence Estimates for Hidradenitis Suppurativa among Children and Adolescents in the United States: A Gender- and Age-Adjusted Population Analysis. J Invest Dermatol. 2018 Oct;138(10):2152-2156.

14 Deputy DivisionDIrector for Safety Comments

I agree with the review team conclusion to approve the use of Cosentyx for the treatment of severe Hydradenitis Suppurativa (HS). The team conducted comprehensive anylyses of submitted data and concluded that both proposed doses of Cosentyx -300 mg every 2 weeks and 300 mg every 4 weesk- provided adequate evidence of effectiveness coupled with acceptable safety profile, comparable to the safety profile observed in development programs for other indicaitons. However, the use of Cosentyx 300 mg every 2 weesk was shown to be associated with some more safety events. Therefore, this regimen is reserved fo patients who will not achieve adequate response with the lower dosage of 300 mg every 2 weeks.
The use of Cosentyx was not yet evaluated in the adolescent population of patients 12 years of age and above, therefore the sponsor will be required to conduct a PREA study in adolescent population.
Given the limited number of approved treatments for HS, Cosentyx will be an important addition to available treatment options.

15 Appendices

15.1. References

References are included in this review as footnotes.

15.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical trials for secukinumab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical trials as defined in 21 CFR 54.2(e) were trials CAIN457M2301 and CAIN457M2302, which provided the primary data to establish effectiveness and safety of this product for the treatment of adults with moderate to severe HS. Refer to Sections 7.1 and 8.1 for the trial designs. The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study (Name and/or Number): CAIN457M2301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 575		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator of covered study: _____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CAIN457M2302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 516		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 54: Summary of Disclosable Financial Arrangements and Interests

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
Dr. James Krell	CAIN457M2301	5010	(b) (4)	

Source: Applicant's Financial Disclosure Table 4-1

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Method for PK Data

The bioanalytical method, DMPK R2000248-pk, was fully validated by CRO, (b) (4) and the report was released on 01/06/2021. This method was subsequently amended by CRO, (b) (4). The main method was amended to integrate:

- Additional long-term stability at FZ (freezer) and DFZ (deep freezer) temperatures for more than 40 days [nominal temperature for FZ AND DFZ are -20^{0}C and -70^{0}C];
- Additional stability of aliquoted reference material for more than 40 days;
- Target interference (IL-17A).

In addition, in this amendment, the LLOQ concentration was increased from 80.0 to 160 ng/mL as per the amended study plan. The LLOQ concentration was increased as a plate effect was observed and investigated at 80.0 ng/mL in bioanalytical study CAIN457M2302-CBA-02. The plate effect was observed in homogeneity runs at 80.0 but not at 160 ng/mL. Hence, the assay range was adjusted to 160 ng/mL – 2500 ng/mL for all runs reported in the Amendment No. 01 of the main method validation report (DMPK R2000248-pk). The amended document number is DMPK R2000248-pk-01 (first amendment) and the amendment was released on 03/07/2022. Note that all runs performed and reported in the main validation report (DMPK R2000248-pk) were not retrospectively re-evaluated. The review team will focus on both the main validation method (DMPK R2000248-pk) and its subsequent amendment 1 (DMPK R2000248-pk-01).

Table 55: Summary of method validation by (b) (4) and subsequent amendment by (b) (4)). All method validation parameters are within acceptable limit.

Summary of bioanalytical method performance	Validation of a method for the determination of AIN457 in human serum samples by competitive ELISA [DMPK R2000248-pk] by (b) (4)	Amendment by (b) (4) [DMPK R2000248-pk-01] in bold letters

Method description	A purified anti-idiotypic antibody against AIN457 was coated on the microtiter plate. Serum samples (Calibration, Quality Control or unknown samples) and biotin-labeled AIN457 were mixed and added to the plate to compete for binding on the coating antibody. Non-bound material was removed by washing. Bound biotinylated- AIN457 was detected by incubating horseradish peroxidase conjugated to streptavidin with O-phenylenediamine dihydrochloride (OPD) as enzyme substrate.	
Materials used for calibration curve & concentration	Calibration curves consisted of 7 standard calibrators and 3 anchor points (AP) as follows: 10, 40, 80 (LLOQ), 160, 320, 640, 1000, 1500, 2500 (ULOQ), 10000 ng/mL. Among these, 10, 40, and 10000 ng/mL were anchor points.	The amended calibration curve has 7 standard calibrators and 4 anchor points as follows: 10, 40, 80, **160 (LLOQ)**, 320, 640, 1000, 1500, 2500 (ULOQ), 10000 ng/mL. Among these, 10, 40, 80, and 10000 ng/mL were anchor points.
Validated assay range	LLOQ = 80 ng/mL ULOQ = 2500 ng/mL	LLOQ = **160 ng/mL** ULOQ = 2500 ng/mL
Materials used for QCs & concentration	Reference material was spiked in pooled blank human serum at 80.0 (LLOQ), 200 (QC low), 500 (QC medium), 2000 (QC high), 2500 (ULOQ), 40000 (diluted 200-fold) and 400000 (diluted 200-fold) ng/mL	
Minimum required dilutions (MRDs)	1:8	
Regression model & weighting	4-Parameter Logistic (4PL) fit with weighting factor 1	
Validation parameters	**Method validation summary**	
Standard calibration curve performance	Number of standard calibrators from LLOQ to ULOQ	7
	Cumulative accuracy (%bias) from LLOQ to ULOQ AIN457	-3.2% to 3.8%
	Cumulative precision (%CV) from LLOQ to ULOQ AIN457	1.5% to 5.8%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs QCs: AIN457	Intra-assay bias: -13.8% to 14.4% Inter-assay bias: -9.4% to 6.8%
	Inter-batch %CV QCs: AIN457	4.3% to 10.8%
Selectivity & matrix effect	In total 15 lots were tested, 80.0% of the matrix sources spiked at 80.0 ng/mL and 100% of the matrix sources spiked at 2000 ng/mL and the spike control sample result had a bias within acceptance criteria and	

	responses for all 15 unspiked samples (100.0%) were below the validated LLOQ. Selectivity in disease populations were determined at (b) (4)
Interference & specificity	**IL-17A interference with AIN457 at 160 ng/mL and 2500 ng/mL was tested. Results showed no interference with AIN457 up to 3000 pg/mL concentration levels of IL-17A.** [See Table 4-6 of DMPK R2000248-pk-01]
Hemolysis effect	The effect of hemolytic serum samples was tested at AIN457 concentrations of 80 ng/mL in three individual serum batches. 100% of the analyzed samples passed the acceptance criteria. No hemolysis effect was observed.
Lipemic effect	The initial selectivity in 3 lipemic samples failed. After investigation of this unexpected result, 10 additional lots were tested and 90.0% of the matrix sources spiked at 80.0 ng/mL had a bias within acceptance criteria. No effect of lipemic matrix was observed in the additional selectivity experiment performed with artificially prepared lipemic samples (human serum samples spiked with 400 mg/dL triglyceride). **The effect of lipemic serum samples was also tested at AIN457 concentrations of 300 ng/mL and 800 ng/mL in five individual serum batches. 100% of the analyzed samples passed the acceptance criteria. No lipemic effect was observed**. See report DMPK R1701288-pk-int2.
Dilution linearity & hook effect	Samples were spiked at 400000 ng/mL and diluted to 40000, 2000, 1000, 500, 250, 125 and 62.5 ng/mL. No hook effect (tested until 400000 ng/mL)
Bench-top stability	Stability of AIN457 was demonstrated at room temperature for at least 24 hours and **up to 96 hours**. Refer to DMPK RS686053-pk-03 (Table 7-51 and 7-52) for stability up to 96 h.
Freeze-thaw stability	Stable after 5 freeze-thaw cycles in the freezer (FZ); Stable after 5 freeze-thaw cycles in the deep freezer (DFZ).
Long-term storage	**Long-term stability of AIN457 in human serum at or below -15°C was demonstrated for at least 12 months. Long-term stability of AIN457 in human serum at or below -70°C was demonstrated for at least 52 months.** Refer to table 7-7 of DMPK RS686053-pk-01 and Table 7-53 of DMPK RS686053-pk-03.
Parallelism	Parallelism has been successfully demonstrated for targeted populations. It will be reported in an amendment to method validation report.

Method Performance:

As described in the Table 55, the amended bioanalytical method was subsequently used to measure the PK concentrations from studies M2301 and M2302. The in-study method performance is described in **Table 56** presented below. The method performance in both studies is adequate.

Table 56: Method performance summary – determination of secukinumab in human serum

	Study M2301	Study M2302
Assay passing rate	138/142 (97.2%) samples met the acceptance criteria	157/156 (99.4%) samples met the acceptance criteria
Standard curve performance	Cumulative bias range: -3.6% to 3.4% Cumulative precision: ≤ 7.9% CV	Cumulative bias range: -2.0% to 2.5% Cumulative precision: ≤ 8.2% CV
QC performance QC levels: 200 (low), 500 (med), 2000 (high) and 40000 ng/mL (overcurve QC)	Cumulative bias range: -2.5% to 1.5% Cumulative precision: ≤ 7.3% CV	Cumulative bias range: -2.3% to 2.5% Cumulative precision: ≤ 8.0% CV
Method reproducibility[@]	Incurred sample re-analysis was performed in 142 (8.1%) study samples, and 138 (7.9%) samples met the pre-specified criteria.	Incurred sample re-analysis was performed in 157 (8.5%) study samples, and 156 (8.4%) samples met the pre-specified criteria.
Study sample analysis/stability	The stability period covers the maximum length of time from specimen collection (27-Feb-2019) to analysis (22-Apr-2022).	The stability period covers the maximum length of time from specimen collection (11-Mar-2020) to analysis (20-Apr-2022).
Standard calibration curve performance during accuracy and precision runs	10000ng/ml (anchor point), 2500ng/ml, 1500ng/ml, 1000ng/ml, 640ng/ml, 320ng/ml, 160ng/ml, 80ng/ml (anchor point), 40ng/ml (anchor point), 10ng/ml (anchor point).	
Source Documents	DMPK RCAIN457M2301-pka-int2	DMPK RCAIN457M2301-pka-int2

[@] For at least 2/3 of the samples, the relative difference had to be within ±30.0%; ISR assessment is still ongoing and in the final Bioanalytical Data Report, the completed ISR results will be reported.

Note that samples had a minimal pre-dilution of 3-fold on top of the MRD for sample analysis of M2301 and M2302. Because the acceptance criteria did not meet for undiluted but met for 3-fold diluted serum from patients with moderate to severe HS. For undiluted serum, in total 15 lots were tested, 73.3% (<80.0%, outside acceptance criteria) of the matrix sources spiked at LLOQ (80.0 ng/mL) had a bias within acceptance criteria and responses for all 15 unspiked samples (100.0%) were below the validated LLOQ. For 3-fold diluted serum, 14 lots were tested,

100.0% of the matrix sources spiked at 240 ng/mL had a bias within acceptance criteria. Therefore, a minimal pre-dilution of 3-fold was used in this bioanalytical study.

The Applicant also referred to two more method validation reports (actually for method transfer and cross-validation by (b) (4) based on original method validation (b) (4) and cross-validation interim reports are DMPK R1701288-pk-int and DMPK R1701288-pk-int-01 released on 01/13/2020 and 03/11/2020, respectively. However, these validation reports were reviewed before for the studies (e.g., supplement-53) where the method (deemed adequate) was used for PK assays, hence will not be reviewed under this supplement.

(b) (4) method (cross-validation report: DMPK R1701288-pk-int-01) was used to analyze some samples (N = 16) in M2301 studies before the transfer of the method to (b) (4) (report name: DMPK RCAIN457M2301-pk). A summary of this method performance in study M2301 is presented in the **Table 57** below:

Table 57: Method performance in Study M2301 (Source: report DMPK RCAIN457M2301-pk)

Assay passing rate	13/16 (81.3%) samples met the acceptance criteria
Standard curve performance	Cumulative bias range: -3% to 3% Cumulative precision: ≤ 6% CV
QC performance	Cumulative bias range: 2% to 3% Cumulative precision: ≤ 13% CV
Method reproducibility	Incurred sample re-analysis was performed in 0.8% of study samples, and 0.7% of the samples met the pre-specified criteria.
Study sample analysis/stability	The stability period covers the maximum length of time from specimen collection (27-Feb-2019) to analysis (01-Jul-2021) i.e., 855 days in study CAIN457M2301
Standard calibration curve performance during accuracy and precision runs	STD.1 (10000ng/ml, anchor point), STD.2 (2500ng/ml), STD.3 (2000ng/ml), STD.4 (1500ng/ml), STD.5 (1250ng/ml), STD.6 (1000ng/ml), STD.7 (750ng/ml), STD.8 (500ng/ml), STD.9 (400ng/ml, anchor point), STD.10(300 ng/ml, anchor point)

19.4.2. Pharmacometrics Assessment

Applicant's Population Pharmacokinetic Analyses:

- Since the HS studies had sparse PK samples, a population PK analysis was first conducted by the Applicant by pooling data from the two HS (e.g., M2301 and M2302)

and 11 PsO studies to characterize the PK of secukinumab in HS patients. The current popPK model was mainly updated based on a previously built popPK model for subcutaneous administration of secukinumab in PsO patients. The model-derived PK parameters in HS patients were compared with those of PsO patients.

- Subsequently, the E-R analyses were conducted by combining PK parameters derived from the updated popPK model and efficacy data from the two HS studies (M2301 and M2302). For binomial efficacy endpoints, a logistic regression model was fitted to the data and a sigmoidal Emax function of Cmin concentrations was used on the logit scale. The exposure metrics derived from the popPK model to perform the E-R analysis include average cumulative exposure from time 0 to time of efficacy assessment (Cavg,cum, calculated as cumulative area under the curve (CAUC)/Time of efficacy measurement, average exposure between Weeks 20 and 24 (Cavg,cum,20-24), average concentrations at steady state (Cavg,ss), and the predicted trough concentration (Cmin) at the time of efficacy measurement.

- In E-R efficacy analyses, efficacy endpoints included: i) Primary endpoint such as HiSCR50 (HS Clinical Response), ii) secondary endpoints such as flare, skin pain numerical rating scale (NRS30), abscesses and inflammatory nodule (AN) 50 response (AN50, defined as at least 50% decrease in AN count compared to baseline), and iii) major exploratory endpoints such as absolute and percentage change from baseline in AN count, Hidradenitis Suppurative-Physician's Global Assessment (HS-PGA), and Dermatology Life Quality Index (DLQI-PRO) etc.
- Exposure-response analysis with respect to two adverse effects (AE) was also evaluated. The AEs included in E-R analyses were Infections and infestations (SOC, system organ class) and Candida infections (HLT, high level term).

Table 58: Summary of popPK analyses

General Information				
Objectives of popPK analysis		• To characterize the PK properties of secukinumab in HS patients, and compare with the PK from patients with moderate to severe plaque psoriasis (PsO) • Assess the relationship between PK and selected efficacy endpoints in HS.		
Study and population included		HS studies: M2301 and M2302 conducted in patients with moderate to severe HS. Previous PsO studies: A2102, A2103, A2211, A2212, A2220, A2302, A2303, A2308, A2310, A2311 and A2324 conducted in patients PsO. See clinical pharmacology **section 6.3.1** for detailed study design.		
Dose(s) included		Intravenous doses: 1 to 30 mg/kg Subcutaneous doses: 25 to 300 mg		
No. of patients, PK samples, and BLQ		Total number of patients with moderate to severe HS: 990 (M2301: 507, M2302: 483) Total number of patients with moderate to severe PsO: 2852 Total patients: 3842; total PK concentrations included in popPK dataset: 20475 Total BLQs: 4249 (pre-dose: 3150, post-dose: 1099, excluded from the PK analysis). In addition, 659 PK concentrations were excluded due to other reasons (protocol violations, observed prior to first dose, unusual PK concentrations, or |CWRES|>20		
Covariates evaluated		Baseline body weight; population (adult vs pediatric), indication (HS vs PsO). For HS population, concomitant use of antibiotics, baseline disease severity defined by hurley stage and baseline inflammation levels (hsCRP).		
Population Characteristics See **Table 59** and **60** for details	General		PsO (N = 2852)	HS (N = 990)
		Age		
		Mean (SD)	42.9 (14.9)	36.3 (11.5)

		Median (Min – Max)	44 (6 – 83)	35 (18 – 71)
		Weight		
		Mean (SD)	88.1 (25.1)	93.5 (23.7)
		Median (Min – Max)	86.6 (17.6 – 219.0)	91.1 (43 – 205)
		Sex		
		Male (%)	2003 (70%)	439 (44.3%)
		Female (%)	849 (30%)	551 (55.7%)
	Pediatrics	Only included in PsO studies: Total Subjects: 194 (Male: 85, Female: 109) **Age:** Mean (SD): 13.1 (3.2) Median (Min – Max): 14 (6 – 17) **Weight:** Mean (SD): 54.5 (19.3) Median (Min – Max): 52.9 (17.6 – 116.0)		

Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and version	NONMEM version 7.5.0 (b) (4)) For dataset creation, data manipulation, data presentation, construction of plots and logistic regression analyses, R version 3.6.2 and/or version 4.1.3 (the R Foundation for Statistical Computing) was used.	**Acceptable**
Model Structure	The starting point for the population PK modeling was the existing model developed in the previous population PK analysis in PsO patients. This model was a two-compartment disposition model with first-order elimination and first-order absorption for the SC administration and constant rate infusion for the IV administration.	**Acceptable**

Base Model Parameters	**Table 61.** (Note: Body weight was included as a covariate on CL, Vc, Vp, and Q in base model consistent with the previous modeling)	**Acceptable**
Final Model Parameters	**Table 62** (On top of body weight on CL, Vc ,Vp, and Q already included, the other covariates include: indication type, concomitant use of antibiotics, baseline disease severity by hurley stage and baseline hsCRP levels.	**Acceptable**
GOF, VPC plots	The goodness-of-fit plots of the final population PK model are shown in **Figure 8**	**Acceptable**
Significant covariates	On top of body weight, indication, baseline disease severity and hsCRP levels were identified as significant covariates to describe secukinumab PK exposures.	**Acceptable**

Table 59: Summary of Subject Demographics having at least one PK observation (All data)

Covariate	Statistic	A2102	A2103	A2211	A2212	A2220	A2302	A2303
Number of Subjects (%)	-	15 (0)	14 (0)	393 (10)	85 (2)	103 (3)	624 (16)	929 (24)
Baseline weight (kg)	Mean (SD)	93.0 (21.0)	92.9 (18.6)	92.9 (23.6)	96.8 (22.7)	89.7 (21.4)	88.5 (23.8)	83.1 (21.1)
Baseline weight (kg)	Median (Min-Max)	92.4 (58.2-133)	87.6 (65.3-129)	89.1 (43.0-176)	91.7 (59.0-157)	88.0 (52.1-159)	84.9 (48.0-188)	80.9 (43.0-219)
Baseline age (Yr)	Mean (SD)	49.6 (8.99)	46.8 (8.76)	44.1 (12.5)	43.8 (10.5)	45.9 (12.4)	44.8 (13.2)	44.7 (12.9)
Baseline age (Yr)	Median (Min-Max)	49.0 (34.0-64.0)	48.5 (29.0-63.0)	44.0 (18.0-77.0)	45.0 (19.0-62.0)	47.0 (23.0-72.0)	44.5 (19.0-83.0)	45.0 (18.0-82.0)
Gender N (%)	Male	10 (67)	9 (64)	298 (76)	69 (81)	77 (75)	435 (70)	664 (71)
	Female	5 (33)	5 (36)	95 (24)	16 (19)	26 (25)	189 (30)	265 (29)
Covariate	**Statistic**	**A2308**	**A2310**	**A2311**	**A2324**	**M2301**	**M2302**	**Overall**
Number of Subjects (%)	-	172 (4)	110 (3)	84 (2)	323 (8)	507 (13)	483 (13)	3842
Baseline weight (kg)	Mean (SD)	91.6 (24.3)	54.1 (19.4)	55.0 (19.4)	111 (17.9)	94.6 (24.5)	92.3 (22.9)	89.5 (24.8)
Baseline weight (kg)	Median (Min-Max)	88.8 (52.0-204)	50.8 (17.6-116)	55.6 (18.0-110)	105 (90.0-171)	92.0 (43.0-205)	90.0 (50.0-182)	88.0 (17.6-219)
Baseline age (Yr)	Mean (SD)	46.2 (13.9)	13.5 (3.06)	12.6 (3.39)	47.1 (13.1)	36.4 (11.6)	36.3 (11.4)	41.2 (14.4)
Baseline age (Yr)	Median (Min-Max)	46.0 (18.0-77.0)	14.0 (6.00-17.0)	13.0 (6.00-17.0)	48.0 (18.0-83.0)	35.0 (18.0-67.0)	35.0 (18.0-71.0)	41.0 (6.00-83.0)
Gender N (%)	Male	112 (65)	46 (42)	39 (46)	244 (76)	226 (45)	213 (44)	2442 (64)
	Female	60 (35)	64 (58)	45 (54)	79 (24)	281 (55)	270 (56)	1400 (36)

Source: m5.3.5.3, seq 0378: AIN457M-Week52-Modeling Report, table 5-2, page 39.

Table 60: Summary of Subject Demographics (HS studies only)

Covariate	Statistic	M2301	M2302	Overall
Number of Subjects (%)	.	507 (51)	483 (49)	990
Baseline weight (kg)	Mean (SD)	94.6 (24.5)	92.3 (22.9)	93.5 (23.7)
Baseline weight (kg)	Median (Min-Max)	92.0 (43.0-205)	90.0 (50.0-182)	91.0 (43.0-205)
Baseline C-reactive protein	Mean (SD)	15.6 (23.3)	17.3 (28.2)	16.4 (25.8)
Baseline C-reactive protein	Median (Min-Max)	6.82 (0.170-153)	7.41 (0.190-214)	7.04 (0.170-214)
Log Baseline C-reactive protein	Mean (SD)	44.5 (3.58)	44.3 (3.83)	44.4 (3.70)
Log Baseline C-reactive protein	Median (Min-Max)	45.0 (24.0-54.0)	45.0 (29.0-54.0)	45.0 (24.0-54.0)
Concomitant use of antibiotics N (%)	No	442 (87)	432 (89)	874 (88)
	Yes	65 (13)	51 (11)	116 (12)
Baseline disease status N (%)	Stage I	21 (4)	12 (2)	33 (3)
	Stage II	313 (62)	275 (57)	588 (60)
	Stage III	173 (34)	196 (41)	369 (37)
Previous use of biologics N (%)	No	385 (76)	375 (78)	760 (77)
	Yes	122 (24)	108 (22)	230 (23)

Source: m5.3.5.3, seq 0378: AIN457M-Week52-Modeling Report, table 5-3, page 40.

Table 61: Parameter Estimates of Base Population PK Model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	**%RSE**	**95% CI**	
CL PsO [L/day]	0.198	1.94	0.19-0.206	
CL HS [L/day]	0.256	2.06	0.246-0.266	
V_c [L]	3.77	1.78	0.708-0.76	
Q [L/day]	0.406	3.17	0.877-0.993	
V_p [L]	2.86	2.05	3.62-3.92	
KA [1/day]	0.191	5.71	0.361-0.451	
F1 adults	0.734	3.07	2.69-3.03	
F1 pediatrics	0.935	3.63	0.177-0.205	
CL~Weight	0.911	2.29	0.87-0.952	
V_c~Weight	0.783	7.05	0.675-0.891	
Q~Weight	0.849	19.9	0.518-1.18	
V_p~Weight	0.772	9.65	0.626-0.918	
Inter-individual				**CV%* or R**
ω^2_{CL}	0.113	2.64	0.107-0.119	33.6
Covar η_{CL}, η_{Vc}	0.0578	8.34	0.0484-0.0672	0.74
ω^2_{Vc}	0.0543	11.9	0.0416-0.067	23.3
Covar η_{CL}, η_{Vp}	-0.00968	52.4	-0.0196-0.000257	-0.1
Covar η_{Vc}, η_{Vp}	0.0281	18.4	0.018-0.0382	0.4
ω^2_{Vp}	0.0919	6.82	0.0796-0.104	30.3
ω^2_{Ka}	0.135	11.4	0.105-0.165	36.7
Residual variability				**CV%**
σ_{prop}	0.0383	0.632	0.0378-0.0388	19.6
σ_{add}	113000	0.399	112000-114000	336

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V_c = volume of central compartment, Q = inter-compartmental exchange flow rate, V_p = volume of peripheral compartment, KA= absorption rate constant, F1=bioavailability, σ_{prop} = proportional component of the residual error model, σ_{add} = additive component of the residual error model, 95% CI= 95% confidence intervals on the parameter; R= correlation coefficient; ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp} and ω^2_{KA} = variance of random effect of CL, V_c, Q, V_p and KA, respectively; Covar η_{CL}, η_{Vc} = covariance of random effect of CL and V_c; Covar η_{CL}, η_{Vp} = covariance of random effect of CL and V_p ; Covar η_{CL}, η_{Vc} = covariance of random effect of V_c and V_p ; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$)
The reference population is an 91 kg patient.

Source: m5.3.5.3, seq 0378: AIN457M-Week52-Modeling Report, table 5-4, page 41. Reviewer's independent analysis provides the similar base model parameters.

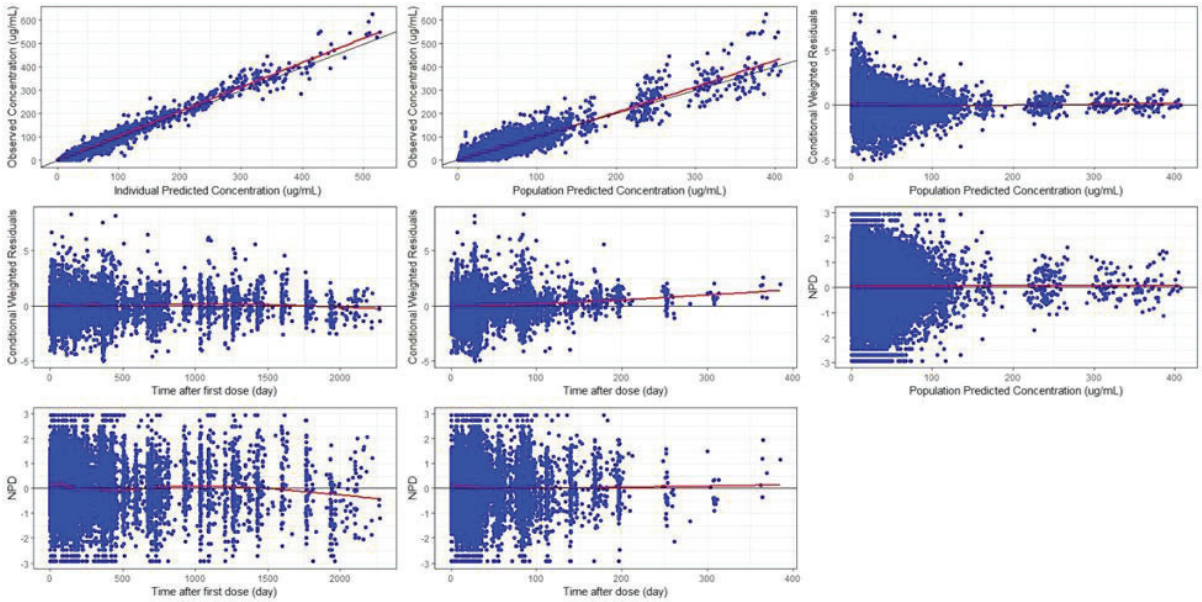
Table 62: Parameter Estimates of Final Population PK Model

	NONMEM Estimates			
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
CL PsO [L/day]	0.198	1.86	0.191-0.205	
V_c [L]	3.79	2.19	3.63-3.95	
Q [L/day]	0.348	4.77	0.315-0.381	
V_p [L]	2.82	3.11	2.65-2.99	
KA [1/day]	0.176	3.04	0.166-0.186	
F1 adults	0.735	1.74	0.71-0.76	
CL~Weight	0.880	2.30	0.84-0.92	
V_c~Weight	0.776	7.15	0.667-0.885	
Q~Weight	0.819	18.7	0.519-1.12	
V_p~Weight	0.751	10.0	0.604-0.898	
F1 pediatrics	0.942	3.08	0.885-0.999	
CL HS (Baseline disease status Stage I&II) [L/day]	0.242	2.21	0.232-0.252	
CL HS (Baseline disease status Stage III) [L/day]	0.283	2.42	0.27-0.296	
CL HS~Baseline hsCRP	0.143	5.12	0.129-0.157	
Inter-individual				**CV%* or R**
ω^2_{CL}	0.101	2.60	0.0958-0.106	31.8
Covar η_{CL}, η_{Vc}	0.0569	7.45	0.0486-0.0652	0.740
ω^2_{Vc}	0.059	11.2	0.046-0.072	24.3
Covar η_{CL}, η_{Vp}	-0.0144	30.9	-0.0231--0.00568	-0.14
Covar η_{Vc}, η_{Vp}	0.0203	25.4	0.0102-0.0304	0.26
ω^2_{Vp}	0.104	6.16	0.0914-0.117	32.2
ω^2_{Ka}	0.123	10.6	0.0975-0.148	35.1
Residual variability				**CV%**
σ_{prop}	0.0402	0.62	0.0397-0.0407	20.0
σ_{add}	1170	18.8	739-1600	34.2

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V_c = volume of central compartment, Q = inter-compartmental exchange flow rate, V_p = volume of peripheral compartment, KA= absorption rate constant, F1=bioavailability, σ_{prop} = proportional component of the residual error model, σ_{add} = additive component of the residual error model, 95% CI= 95% confidence interval on the parameter; R= correlation coefficient; ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp} and ω^2_{KA} = variance of random effect of CL, V_c, Q, V_p and KA, respectively; Covar η_{CL}, η_{Vc} = covariance of random effect of CL and V_c; Covar η_{CL}, η_{Vp} = covariance of random effect of CL and V_p ; Covar η_{CL}, η_{Vc} = covariance of random effect of V_c and V_p ; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$)
The reference population is an 91 kg patient.

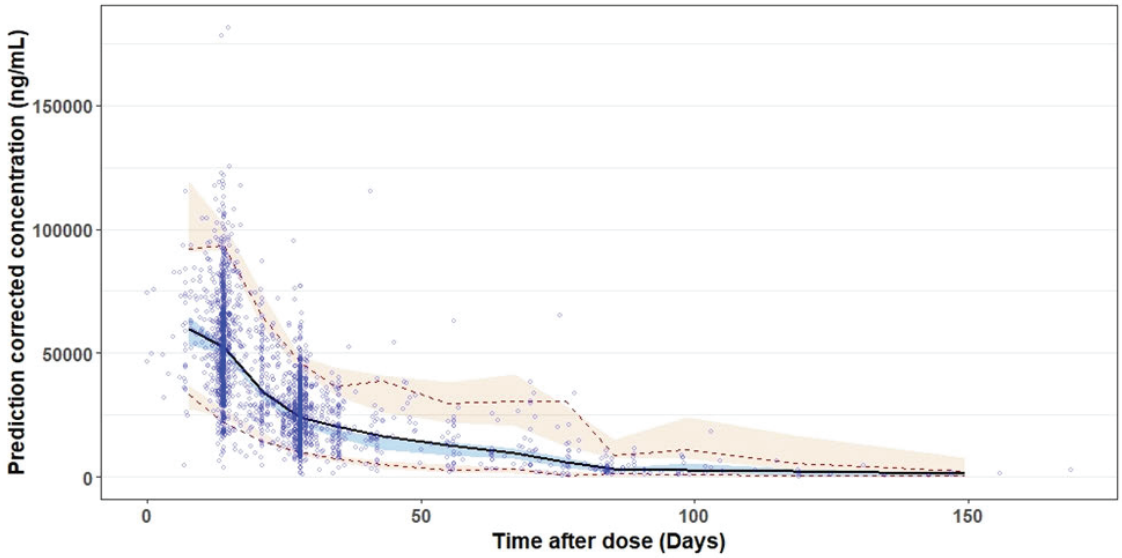
Source: m5.3.5.3, seq 0378: AIN457M-Week52-Modeling Report, table 5-5, page 50. Reviewer's independent analysis provides the same final model parameter estimates.

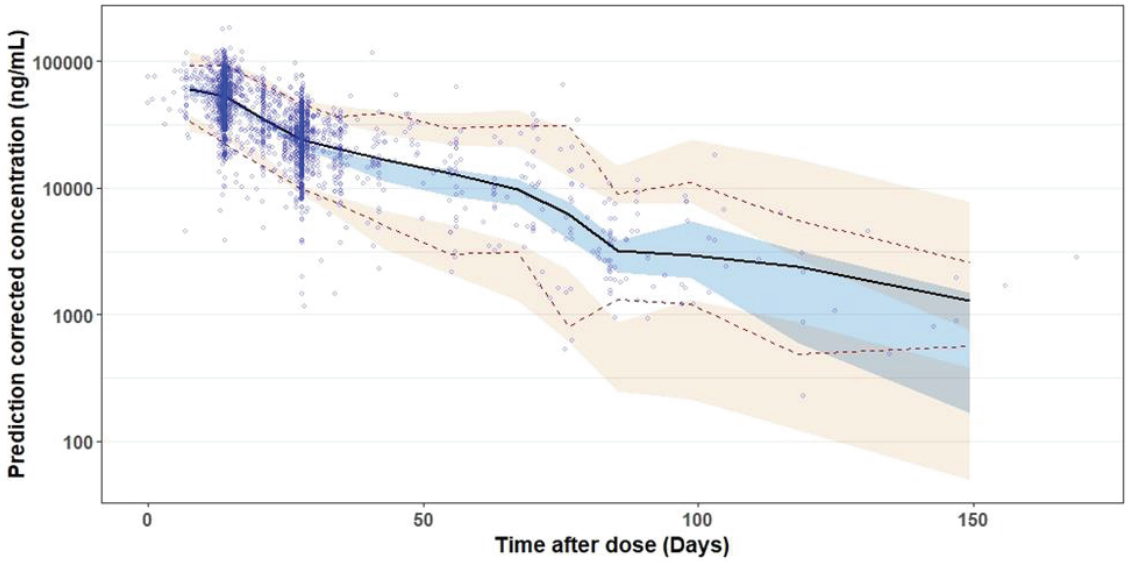
Figure 8: Goodness-of-Fit Plots for the Final Population PK Model



Source: Based on the reviewer's model output from pk035 model run.

Figure 9: Prediction-Corrected Visual Predictive Check for the Final Population PK model of HS studies (Top: Linear Y Scale, Bottom: Logarithmic Y Scale).





Note: The dashed red lines represent the 2.5th percentile and 97.5th percentiles of the observed concentration data. The solid lines represent the median of the prediction data. The colored areas represent the 95% CI for the 5th, 50th, and 95th percentiles of the empirical distribution of the observed concentration data. The CI are obtained by simulations from the final population PK model.
Source: Based on the reviewer's model output from pk035 model run.

Summary of population PK analysis

A two compartment disposition model with first-order elimination and first-order absorption for the SC administration and constant rate infusion for the IV administration adequately described the data from PsO and HS studies. GOF plots (**Figure 8**) indicate that there is a good agreement between the observed and individual predicted or population predicted data. The validity of this model is confirmed by VPC plots (**Figure 9**). The VPC plots for HS studies showed that majority of the data is captured in the prediction interval encompassing 95% of the population as indicated by the 2.5th and 97.5th percentile boundary, indicating that the model was reasonable to adequately describe HS data.

In consistent with previous analysis, body weight is observed as a significant covariate to describe secukinumab serum concentration-time profile. Additionally, indication (PsO vs HS), baseline disease severity (hurley stage I&II vs III), and hsCRP levels were found to have statistically significant covariate effects on the clearance of secukinumab. The concomitant use of antibiotics was not found to have significant effect on the PK of secukinumab.

Present analysis revealed that secukinumab CL was 22% (respectively 43%) higher in HS patients with Stage I&II (respectively Stage III) baseline disease status with hsCRP value of 7 mg/L, compared to PsO patients. Typical secukinumab CL in HS patients was 29% higher than that of PsO patients (0.256 vs 0.198 L/day). The secukinumab CL in HS patient with the available range of baseline hsCRP values (0.17 to 214 mg/L), ranged from 41% lower to 63% higher compared to a HS patient with median baseline hsCRP of 7 mg/L.

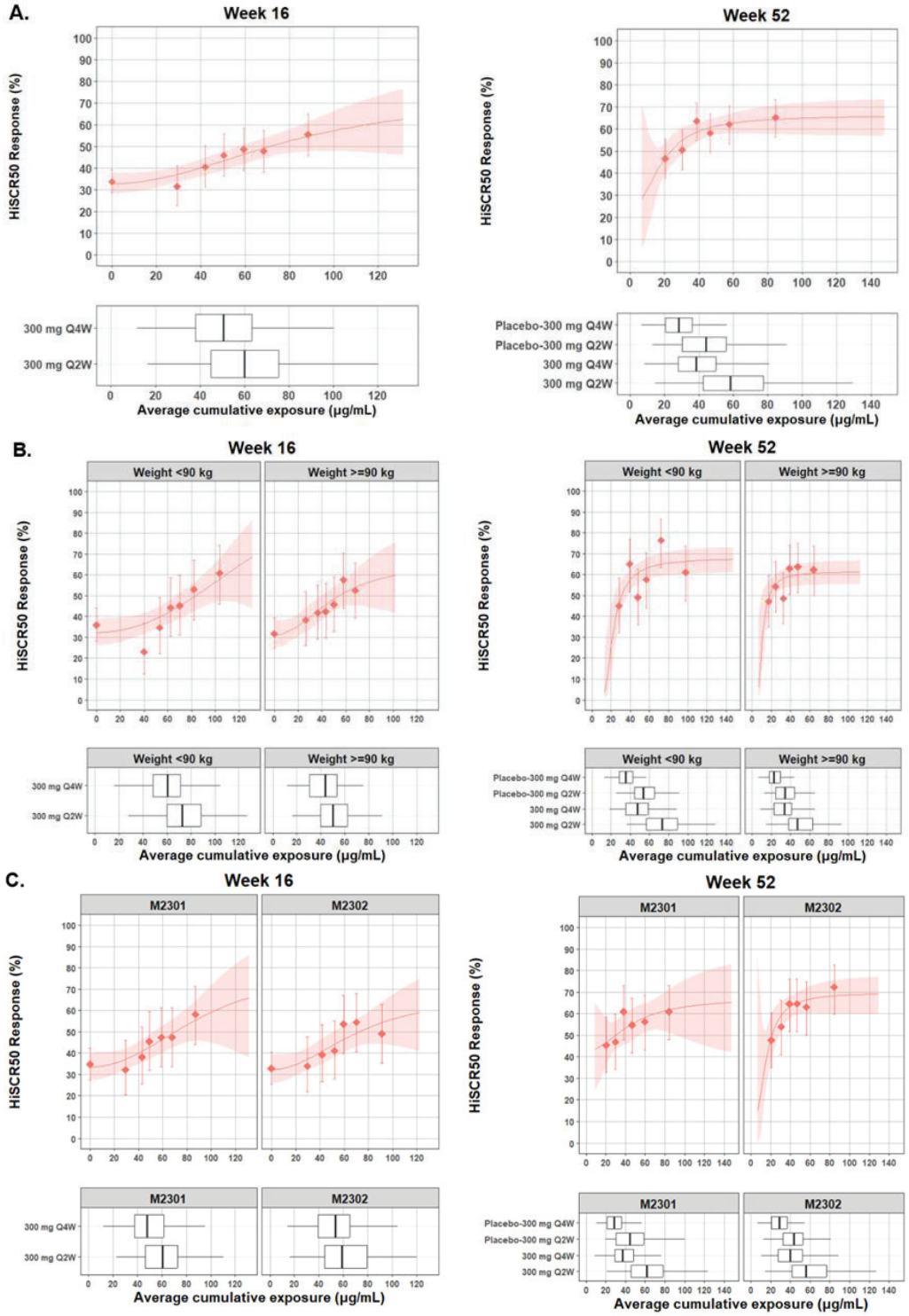
Hence, the popPK analysis indicates that secukinumab exposure is lower in HS patients. The exposure is further decreased if the HS patients have higher baseline disease severity (e.g., hurley stage III) and hsCRP values. For example, the popPK analysis estimated the difference as 9% lower Cavg,ss for subjects with same bodyweight, same disease severity and twice higher hsCRP value at baseline. On the other hand, the exposure (Cavg,ss) was 15% lower in Hurley stage III subjects when compared to Hurley stages I and II subjects with the same bodyweight and same hsCRP value at baseline. However, the difference in exposure in patients with different baseline disease severity, hsCRP levels doesn't seem to be clinically meaningful based on shallow exposure-response relationship described below.

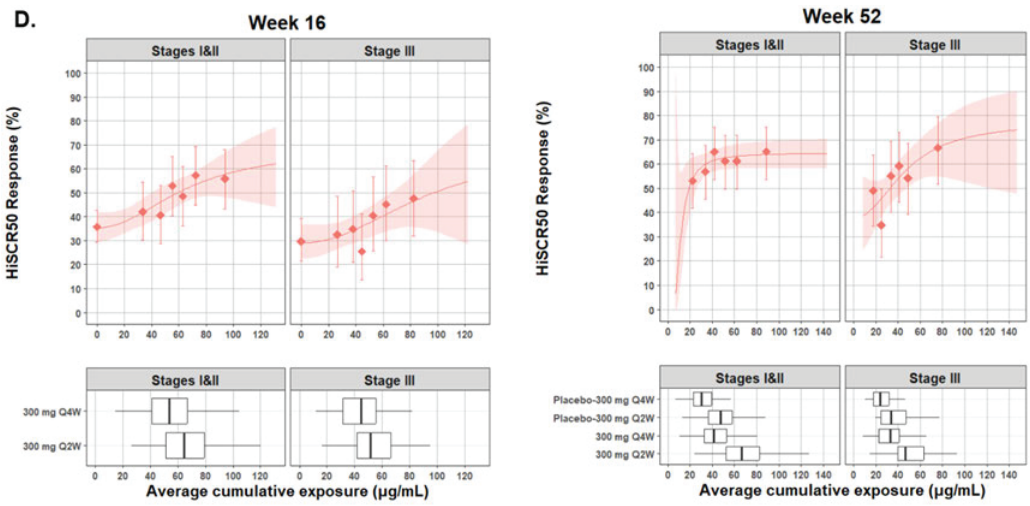
Exposure-Response Analysis

The aim of exposure-response analysis was to characterize the relationship between secukinumab serum exposures and efficacy in patients with hidradenitis suppurativa (HS) using mainly the primary and secondary endpoints. A total of 1042 subjects from two HS studies were included in the E-R analysis. The dose-levels were secukinumab 300 mg at Week 0, 1, 2, 3, 4, then Q2W or Q4W. In addition, those who received placebo up to Week 16, were re-randomized to receive 300 mg at Week 16, 17, 18, 19, 20, then Q2W or Q4W. Hence, two dosing arms (Q2W, and Q4W) up to Week 16 and four dosing arms (Q2W, Q4W, Placebo-Q2W, and Placebo-Q4W) from Week 24 onwards were available for E-R analysis. The pharmacokinetic parameters such as average cumulative exposure (Cavg,cum) and trough concentrations were derived from a separate popPK model described above. The PK parameter, Cavg,cum, was mainly used along with others to describe E-R relationship in HS studies. For the purpose of brevity, exposure-response relationship using Cavg,cum, Cmin with the primary and one of the secondary endpoints (AN50 response) at Week 16 and 52 are reported in this review.

Exposure-response analyses were performed on the two HS studies with respect to the primary and secondary endpoints at relevant timepoints (Weeks 16, 24, 40, and 52) using a logistic regression model for binary endpoints. The E-R relationship was also described with respect to different subgroups such as concomitant use of antibiotics, previous exposure to biologics, baseline disease status (Hurley stages I and II vs. III), body weight (<90 kg versus = 90 kg) and study. Note that all E-R plots were re-generated by the reviewer based on reviewer's independent model analysis.

Figure 10: Exposure-response analysis performed on HiSCR50 response vs average cumulative exposure at Week 16 and Week 52 based on the pooled data from two HS studies (A), body weight strata (B), individual study (C) and hurley stages (D) for different treatment groups.





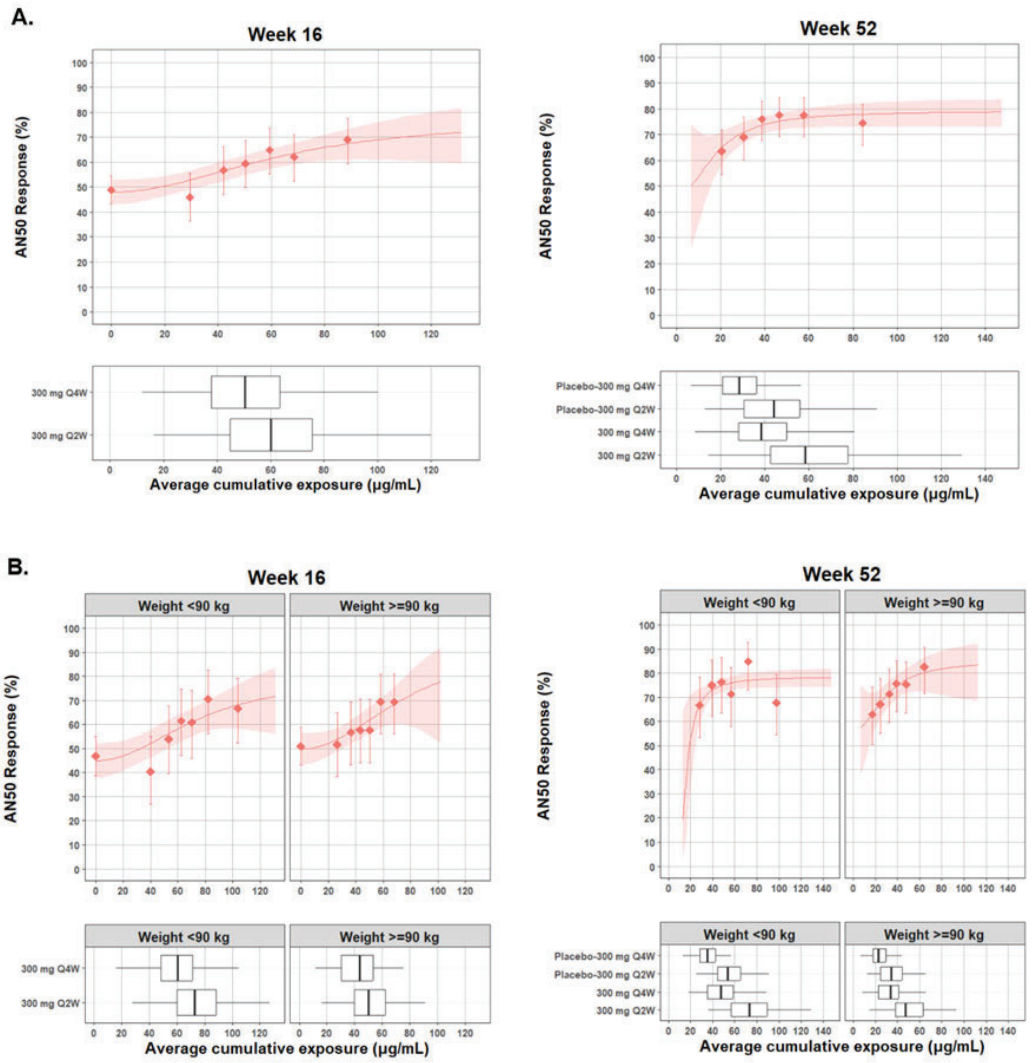
Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies (M2301 and/or M2302). The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range.

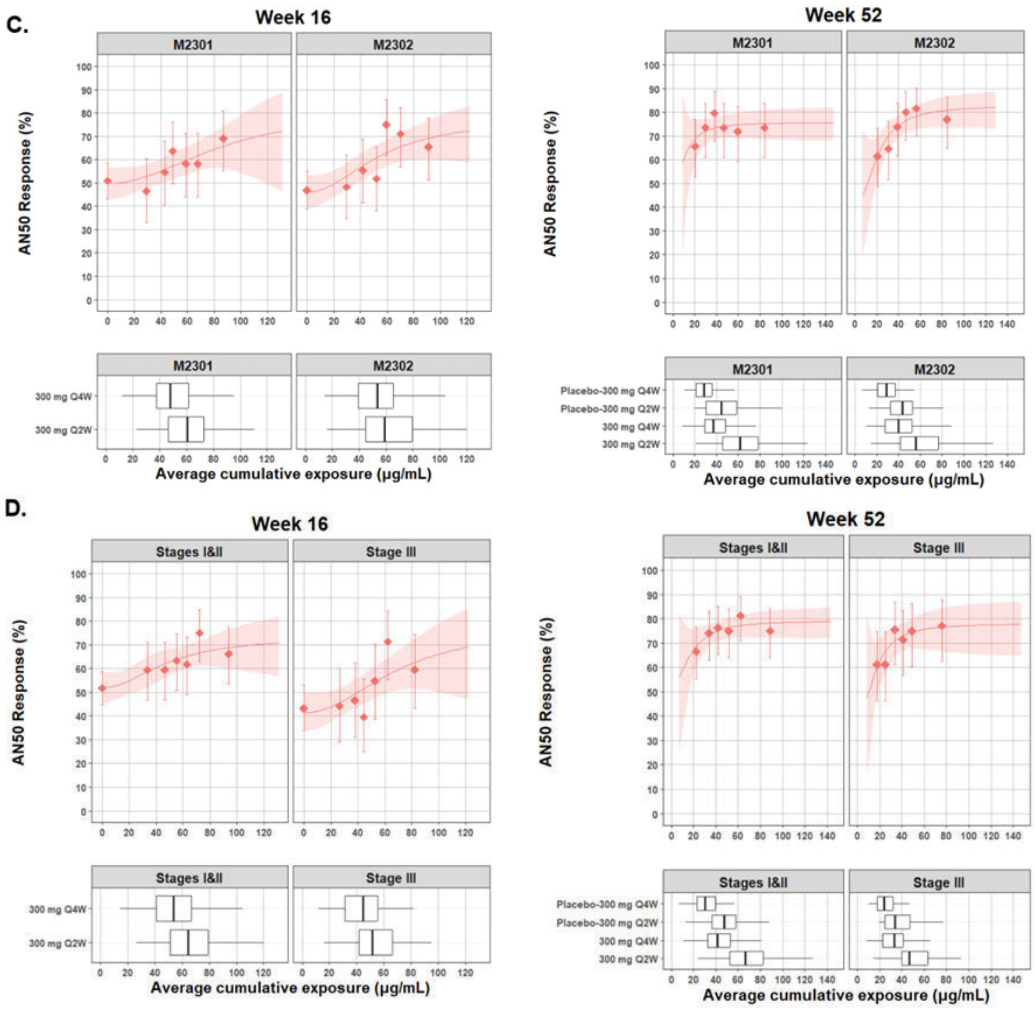
The E-R analysis on HiSCR50 endpoint using pooled HS data showed a numerical increase of ~3% in response rate for Q2W over Q4W regimen at Week 16 beyond which the effect was sustained (~5% increment in response rate at Week 52). Though there is an incremental benefit for subjects achieving higher exposure compared to lower exposure, the exposure-response curve reaches plateau at high exposure expected from Q2W regimen. Therefore, further increase in dose strength or dosing frequency will unlikely provide additional benefit. Moreover, due to a large overlap exposure between Q2W and Q4W regimen and shallow exposure-response relationship, the numerically higher response rate from Q2W regimen is marginal (2 – 5%).

The E-R subgroup analysis did not show different trend. Regardless of subgroups (body weight, study, and baseline disease severity), the response rate is expected to be numerically higher by 2 – 5% for Q2W regimen over Q4W regimen. However, when study was considered, the response was not different between two treatment regimens as observed in study M2302. To note, the Q4W regimen showed higher response rate than that of Q2W regimen in clinical study (see statistical review).

In addition to primary endpoint, HiSCR50 response, E-R analysis performed on other secondary endpoints support the conclusion that overall Q2W treatment can provide a 2 – 5% numerically higher response rate over Q4W regimen. Since there is only a marginally higher benefit for Q2W regimen, totality of evidence can be taken into consideration to approve one regimen over another. E-R analysis usually supports both regimens to treat patients with moderate to severe HS.

Figure 11: Exposure-response analysis performed on AN50 response vs average cumulative exposure at Week 16 and Week 52 based on the pooled data from two HS studies (A), body weight strata (B), individual study (C) and hurley stages (D) for different treatment groups.

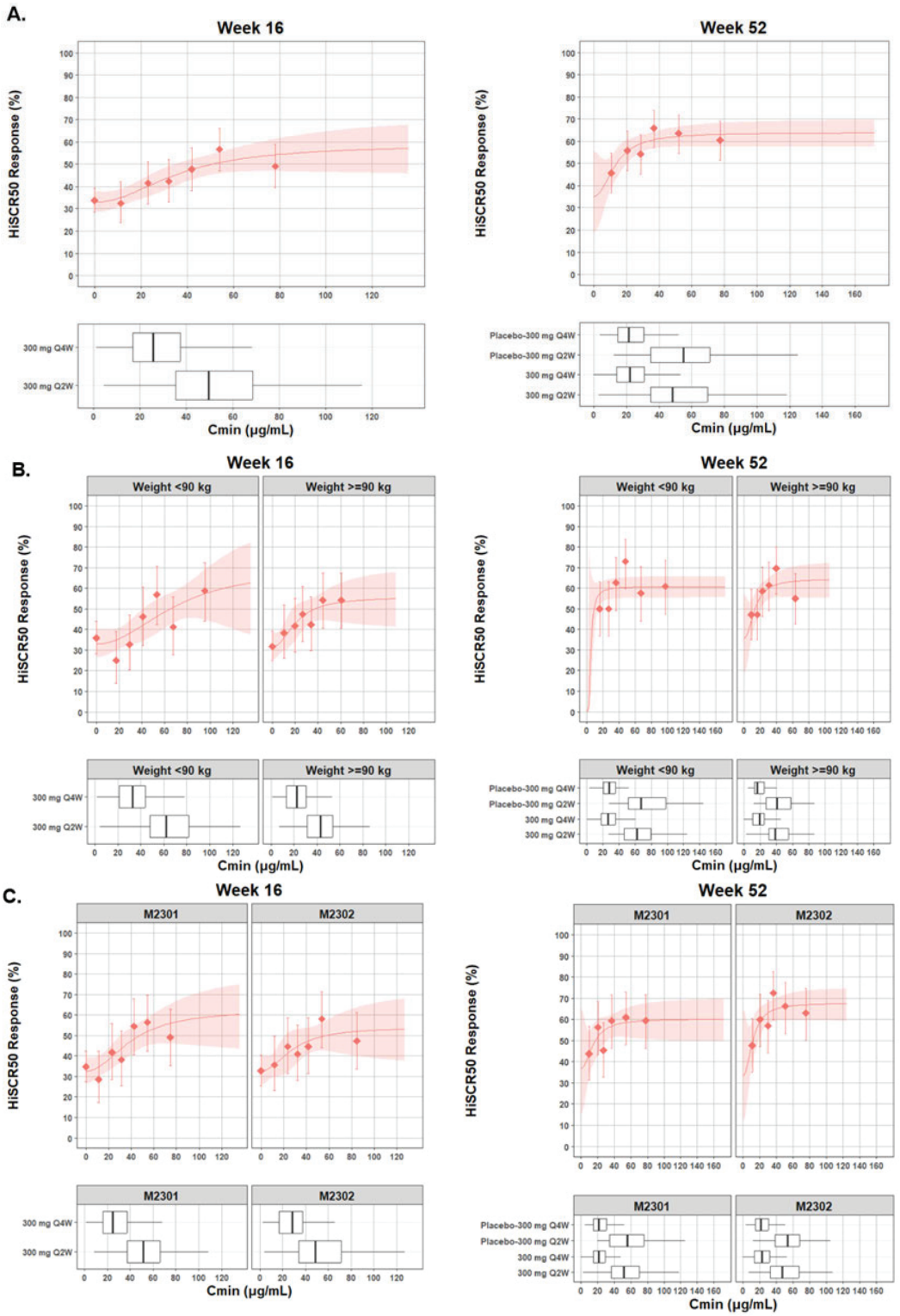


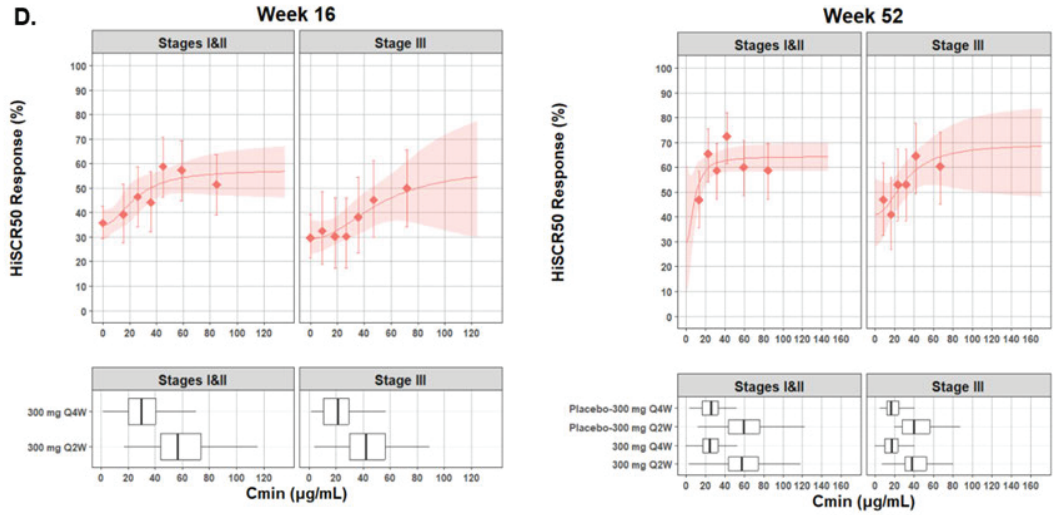


We noted that the exposure (Cmin) was approximately 2-fold higher from Q2W regimen compared to that of Q4W regimen as observed in clinical trial. However, Cavg,cum, which was used in E-R analysis, is only approx. 1.3 to1.5-fold higher following Q2W dose compared to that of Q4W dose. The reason of this discrepancy between Cmin and Cavg,cum is not clear. Hence, the reviewer also conducted E-R analysis using Cmin as an exposure metric and found that the Cmin is consistently 2-fold higher for Q2W than that of Q4W regimen. Since the exposure is 2-fold higher, the E-R curve seems to provide a further incremental benefit up to ~8% for Q2W over Q4W. Moreover, no apparent trend was shown when E-R analysis was performed on different subgroups.

Figure 12: Exposure-response analysis performed on HiSCR50 response vs trough concentration (Cmin) at Week 16 and Week 52 based on the pooled data from two HS studies

(A), body weight strata (B), individual study (C) and hurley stages (D) for different treatment groups



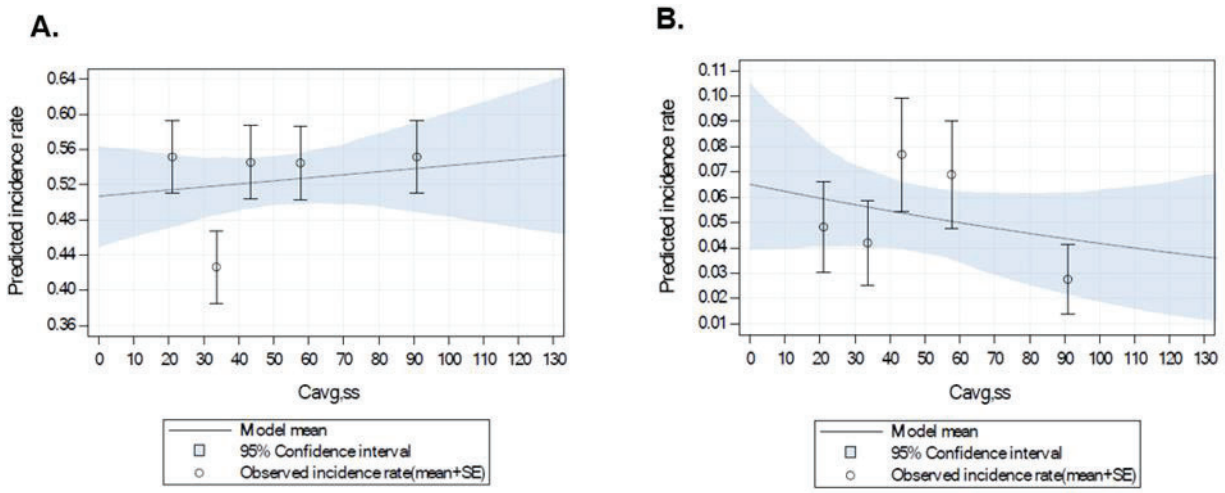


Since Cmin is a measure at single timepoint, the overall exposure such as Cavg,cum will better reflect the response rates in HS studies. Thus, the review team agrees with the Sponsor's conclusion that only 2 – 5% numerically higher benefit can be obtained when Q2W is used over Q4W regimen.

Exposure-safety analyses

To support secukinumab Q2W regimen, the Applicant conducted exposure-response analyses by pooling data from two HS studies (n = 721, randomized to secukinumab 300 mg Q2W or Q4W) and mainly focusing on two types of AEs: Infections and infestations (SOC, system organ class) and Candida infections (HLT, high level term). The relationship between Cavg,ss and the incidence of the selected AEs for one year was further modeled using logistic regression (**Figure 13**). The slight increase of predicted incidence rate of Infections and infections (SOC) and the slight decrease of predicted incidence rate of Candida infections (HLT) at higher Cavg,ss should be interpreted with caution because of the narrow range of predicted incidence rate (y axis).

Figure 13: Estimated relationship between secukinumab average concentration at steady state (Cavg,ss) and incidence of infections and infestations (SOC) [A] or incidence of Candida infections (HLT) [B].



Source: m2.7.4, seq0378: summary of clinical safety – Hidradenitis suppurativa, Figure 2-1 and 2-2, page 71-72
The dots and the vertical bars represent the observed event rate and standard error by range of average secukinumab concentration at steady state (0-28, 28-39, 39-50, 50-68 and >68ug/mL, each includes approximately 20% of the subjects). The regression curve and the grey area represent the event rate and 95% CI as a function of the average secukinumab concentration at steady state, as predicted from the logistic regression models.

The relationships estimated by logistic regression were also used to predict the incidence of the selected AEs for each regimen. Specifically, the predictions were done for Cavg,ss equal to 63.4 µg/mL (average of 300 mg Q2W) and 35.3 µg/mL (average of 300 mg Q4W).

For both Infections and infestations (SOC) and Candida infections (HLT), the predicted incidence rates within one year were comparable between the secukinumab 300 mg Q2W regimen and Q4W regimen. Additionally, the predicted incidence rates of both Infections and infestations (SOC) and Candida infections (HLT) were consistent with the incidence rates observed in the HS studies.

Population PK analysis to estimate DDCP (drug-device combination products) effects

The same popPK model as described above was fitted to the pooled PsO and PsA data (referred as model 1). Afterwards to account for PsA population effect, an effect of PSA on clearance estimate was estimated (referred as Model 2). Lastly, the effect of DDCP was estimated on absolute bioavailability F (referred as Model 3). The hierarchical PK models are described in **Table 63**.

Table 63: List of the population PK models

Data	Model	Description
PK data pool across PsO and PsA studies	Model 1	Same structure as original model in PsO patients
PK data pool across PsO and PsA studies	Model 2	Model 1 + PsA effect on clearance
PK data pool across PsO and PsA studies	Model 3	Model 2 + DDCP effect on absolute bioavailability

Source: m5.3.5.3, seq 0378: AIN457M-Week52-DDCP-Modeling Report, page 14.

In the analysis, the DDCP effect consisted of the multiplication of the effect of the dosage form (1 mL or 2 mL) and the effect of the number of injections (0.5x, 1x, or 2x). Therefore, this analysis made the assumption that potential PK differences resulting from devices are consistent across indications.

The parameters from the original model were re-estimated using pooled datasets of PsO and PsA patients (Model 1, parameter estimate not shown). In model 2, the effect of PsA was assessed as a covariate on clearance to compare the clearance of secukinumab between PsO and PsA. The parameter estimates are presented in **Table 64**.

Table 64: Parameter estimates from model 2 that provides an estimated effect of PsA on clearance

Parameter [units]	Point Estimate	%RSE
CL PsO [L/day]	0.1984	1.11
CL PsA [L/day]	0.1869	1.09
V_c [L]	3.954	0.98
Q [L/day]	0.2793	2.43
V_p [L]	2.768	2.31
ka [1/day]	0.1664	1.75
F	0.7664	0.95
CL ~ Weight	0.891	2.02
V_c ~ Weight	0.6522	3.45
Q ~ Weight	0.7771	9.74
Vp ~ Weight	0.9172	3.18
Inter-individual		
ω^2_{CL}	0.3384	0.92
Covar η_{CL}, η_{Vc}	1	1.45
ω^2_{Vc}	0.2362	2.28
Covar η_{CL}, η_{Vp}	-0.3424	2.88
Covar η_{Vc}, η_{Vp}	-0.3419	5.26
ω^2_{Vp}	0.7374	1.54
ω^2_{Ka}	0.4178	3.46
Residual variability		
σ_{prop}	0.2279	0.27
σ_{add}	29	12.13
Objective Function	645 053	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V_c = volume of central compartment, Q = inter-compartmental exchange flow rate, V_p = volume of peripheral compartment, KA= absorption rate constant, F1=bioavailability, σ_{prop} = proportional component of the residual error model, σ_{add} = additive component of the residual error model; R= correlation coefficient; ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp} and ω^2_{KA} = variance of random effect of CL, V_c, Q, V_p and KA, respectively; Covar η_{CL}, η_{Vc} = covariance of random effect of CL and V_c; Covar η_{CL}, η_{Vp} = covariance of random effect of CL and V_p ; Covar η_{CL}, η_{Vc} = covariance of random effect of V_c and V_p ; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$). The reference population is a 91 kg patient.

In model 3, the effect of DDCP on absolute bioavailability were estimated. The parameter estimates for this model are presented in **Table 65**.

Table 65: Parameter estimates of the population PK model for assessing DDCP effect on absolute bioavailability

Parameter [units]	Point Estimate	%RSE
CL PsO [L/day]	0.1981	1.11
CL PsA [L/day]	0.1901	1.19
V_c [L]	4.095	2.09
Q [L/day]	0.2786	2.56
V_p [L]	2.766	2.42
ka [1/day]	0.1713	1.82
CL ~ Weight	0.9045	2.02
V_c ~ Weight	0.635	3.14
Q ~ Weight	0.8411	9.62
Vp ~ Weight	0.9768	6.07
F ~ LYO	0.7438	0.96
F ~ PFS (1 mL)	0.7887	1.25
F ~ PFS (2 mL)	0.7653	2.72
F ~ AI (1 mL)	0.8363	1.61
F ~ AI (2 mL)	0.8182	4.59
Inter-individual		
ω^2_{CL}	0.3322	0.925
Covar η_{CL}, η_{Vc}	0.9755	1.60
ω^2_{Vc}	0.2364	2.43
Covar η_{CL}, η_{Vp}	-0.329	3
Covar η_{Vc}, η_{Vp}	-0.178	10.46
ω^2_{Vp}	0.7373	1.53
ω^2_{Ka}	0.4163	3.7
Residual variability		
σ_{prop}	0.2273	0.2
σ_{add}	29.44	12.01
Objective Function	644 984	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V_c = volume of central compartment, Q = inter-compartmental exchange flow rate, V_p = volume of peripheral compartment, KA= absorption rate constant, F1=bioavailability, σ_{prop} = proportional component of the residual error model, σ_{add} = additive component of the residual error model; R= correlation coefficient; ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp} and ω^2_{KA} = variance of random effect of CL, V_c, Q, V_p and KA, respectively; Covar η_{CL}, η_{Vc} = covariance of random effect of CL and V_c; Covar η_{CL}, η_{Vp} = covariance of random effect of CL and V_p ; Covar η_{CL}, η_{Vc} = covariance of random effect of V_c and V_p ; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$). The reference population is a 91 kg patient.

Source: m5.3.5.3, seq 0378: AIN457M-Week52-DDCP-Modeling Report, page 27. Reviewer's independent analysis provided similar parameter estimates.

The final model (model 3) was updated with PK data from HS studies M2301 and M2302, which was intended to extrapolate the DDCP effect from PsO and PsA to HS. Hence, the PK parameters of Model 3 were left unchanged with the exception of three new parameters to describe the clearance of HS patients: two parameters related to the severity of the disease (Hurley stages) and one parameter implementing the effect of baseline hsCRP on the exposure. The incorporation of those parameters was suggested by the HS Population PK analysis. The additional parameters estimated to describe the CL of HS patients are presented in **Table 66**.

Table 66: Estimates of additional parameters of the popPK model characterizing DDCP and HS effects (model 3 updated with HS data)

Parameter	Point Estimate	%RSE
CL for HS patient with baseline disease status Stage I&II*	0.249 L/day	1.38
CL for HS patient with baseline disease status Stage III*	0.290 L/day	1.71
Baseline hsCRP effect on CL	0.146	5.15

* CL estimate for a patient with baseline hsCRP of 7mg/L and body weight of 91 kg.

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance.
Baseline hsCRP effect: Doubling baseline CRP results in increasing CL by approximately 11% ($2^{0.146}$).

Diagnostic plots (**Figure 14 and 15**) of model 3 (final, updated with HS data) indicate a reasonable fit of the data across indication and device.

Figure 14: Goodness-of-fit diagnostics per indication - Model 3 (updated with HS data)

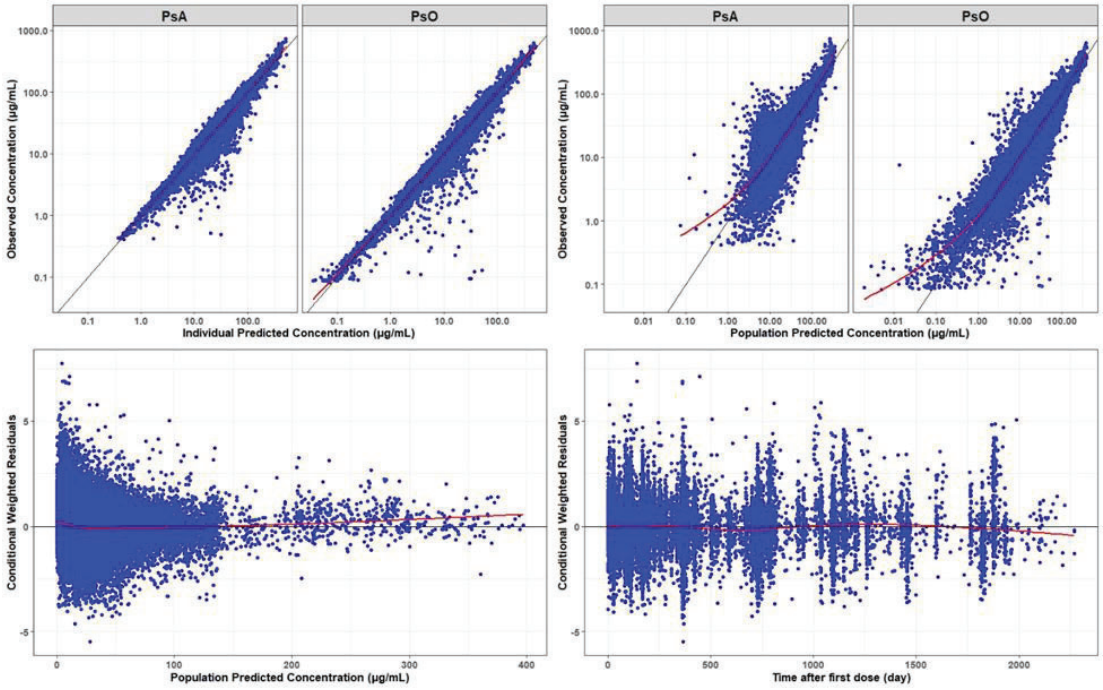
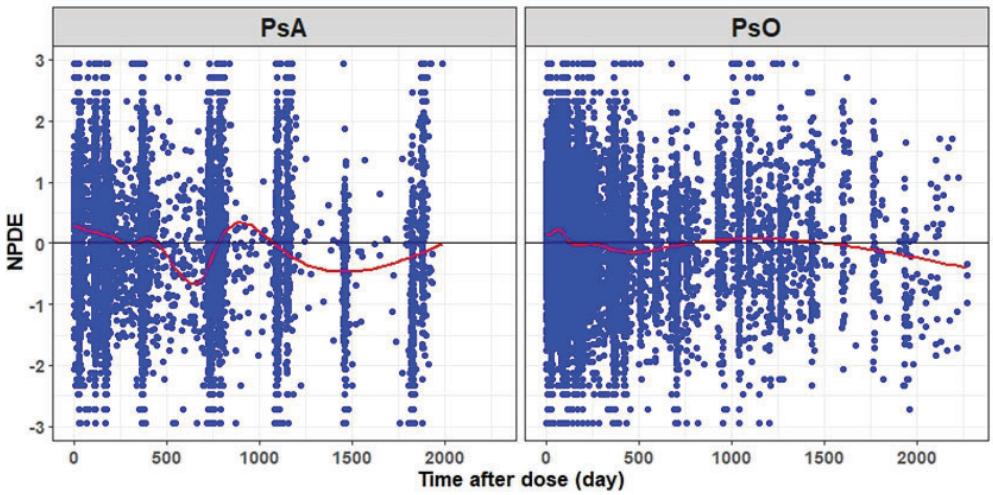


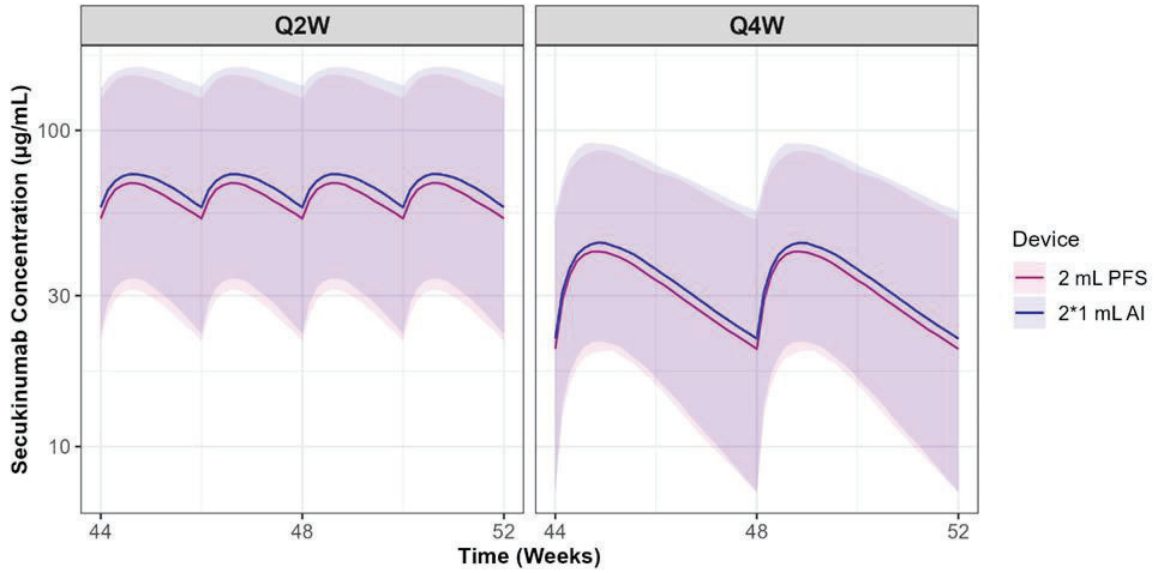
Figure 15: NPDE versus time per indication – Model 3 (updated with HS data)



The resulting final model 3 (built upon PsO, PsA and HS data) was used to simulate the exposure in HS subjects using a 2 x 1 mL AI device and to compare to the exposure of 2 mL PFS device used in M2301 and M2302 studies under the 300mg Q2W or 300mg Q4W (both with weekly induction for the first month of treatment).

Figure 16 exhibits that predicted median serum concentration resulting from 2 × 1 mL AI and 2 mL PFS are comparable for HS patients treated with the 300 mg Q2W and Q4W regimens. The predicted PK exposures (Cmin,ss, Cmax,ss, and Cavg,ss) are mentioned in **Table 67**.

Figure 16: Predicted PK profile at steady state for HS patients treated with 300 mg Q2W and Q4W regimens using 2 x 1 mL AI or 2 mL PFS



The lines – on log scale - represent the median of the secukinumab concentration-time profiles obtained from the updated device population PK model. The colored ribbons correspond to the 90% predictive intervals. Note that

the blue ribbon corresponds to 2 x 1 mL AI and the red ribbon corresponds to 2 mL PFS: the darker ribbon corresponds to the overlap of the two above mentioned ribbons.
The simulations have been obtained using the covariates (body weight, baseline hsCRP, and baseline Hurley stage) of the HS patients from pivotal studies M2301 and M2302 (N=1084).
Source: reviewer's plot.

Table 67: Summary statistics of predicted PK metrics in HS patients treated with 300 mg Q2W and Q4W regimens using 2 x 1 mL AI or 2 mL PFS

	Cmin,ss median [90% PI]		Cmax,ss median [90% PI]		Cavg,ss median [90% PI]	
	Q2W	Q4W	Q2W	Q4W	Q2W	Q4W
2 mL PFS	52.6	20.3	68.4	41.8	62.1	31.9
	[21.5-126.6]	[7.2-52.1]	[31.3-150.7]	[20.2-86.9]	[27.5-143.2]	[14.6-71.8]
2 x 1 mL AI	57.2	21.9	72.8	44.3	67.3	34.1
	[22.7-138.4]	[7.2-56.6]	[34.1-159.1]	[21.7-92.2]	[29.7-152.5]	[15.3-74.7]

The PK metrics were obtained from the updated device population PK model. The simulations have been obtained using the covariates (body weight, baseline hsCRP and baseline Hurley stage) of the HS patients from pivotal studies M2301 and M2302 (N=1084).
Source: m5.3.5.3, seq 0378: AIN457M-Week52-DDCP-Modeling Report, page 32.

Per the popPK predicted results (Table 9), the use of 2 mL AI instead of 2 mL PFS is expected to result in a small, less than 10% serum exposure increase in HS patients. Furthermore, statistical analysis performed on the pooled PsO and PsA data demonstrated comparable PK exposure (only Cmin,ss at pre-dose was considered) across 2-mL PFS, 2×1-mL PFS, 2×1-mL AI, 2-mL AI.

Of note, a PK bridge was established between 2 × 1-mL PFS, 2-mL PFS, and 2-mL AI under supplement 44. Though the exposure from 2-mL PFS fell within no effect boundary of 0.8 – 1.25, it was approximately ~30% higher with 2-mL AI compared to that of reference 2 × 1-mL PFS device. Besides the existing approve USPI of secukinumab indicates that the mean trough concentrations from Sensoready pen (AI device) were 23% to 26% higher than those from the prefilled syringe based on cross-study comparisons. Hence, the review team is recommending this higher exposure from AI be reflected in the label.

15.4. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/s/

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TATIANA OUSSOVA
10/30/2023 07:35:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s063

PRODUCT QUALITY REVIEW (s)

Memorandum of Assessment- Addendum:

Submission Tracking Number (STN):	BLA-125504 Supplement 63/ STN 0378 (4557)
Subject:	This addendum to CMC review memo for S-63 assesses the validation reports for the immunogenicity assays submitted in S-63.
Date Received:	09/30/2022
Assessment Date:	07/21/2023
Primary Assessor:	Qiong Fu, Ph.D., CDER/OPQ/OBP/DBRR II
Secondary Assessor:	Anjali Shukla, Ph.D., CDER/OPQ/OBP/DBRR II
RBPM:	Anika Lalmansingh
Consults:	N/A
Applicant:	Novartis Pharmaceuticals Corporation
Product:	Cosentyx (secukinumab)
Indication:	• moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy. • active psoriatic arthritis (PsA) in patients 2 years of age and older. • adults with active ankylosing spondylitis (AS). • adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. • active enthesitis-related arthritis (ERA) in patients 4 years of age and older.
Filing Action Date:	11/29/2022
Internal Due Date:	06/16/2023
Action Due Date:	07/30/2023

1. Summary Basis of Recommendation:

a. Recommendation:

The CMC assessment team has no objection to the approval of this efficacy supplement.

b. Justification:

The OBP assessment memo finalized in Panorama on June 01, 2023 still applies and is valid. This addendum is to include an assessment of immunogenicity assays submitted in S-63.

2. Background:

In this efficacy supplement (S-63), the Applicant is proposing a new indication for Cosentyx for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). Clinical evidence from two Phase 3 studies CAIN457M2301 (M2301/ SUNSHINE) and CAIN457M2302 (M2302/ SUNRISE) are used to support this efficacy supplement. Studies M2301 and M2302 are identical, randomized, double-blind, multi-center, placebo-controlled, phase 3 studies to demonstrate the short-term (Week 16 and long-term (Week 52) efficacy, safety and tolerability of two subcutaneous secukinumab dosing regimens by using 2 mL PFS device (300 mg Q4W and 300 mg Q2W) compared to placebo in adult subjects with moderate to severe HS.

The product quality review memorandum for Supplement-63 was completed and uploaded into Panorama on June 01, 2021. It can be found at this link BLA-125504 S-63 CMC Review Memo.

In this S-63, the Applicant also submitted immunogenicity results obtained from the two Phase 3 studies. There are the following 3 analytical methods used for the immunogenicity studies in these Phase 3 studies.

1. An enzyme-linked immunosorbent assay (ELISA) method was used for the bioanalytical analysis of AIN457 in serum.
2. An electrochemiluminescence method was used for the detection of potential anti-secukinumab antibody formation.
3. An ELISA method was used for the detection of neutralizing anti-secukinumab antibodies in human serum.

The Applicant stated that bioanalytical methods and the history of manufacturing of drug product used in studies with PsO, AS and PsA patients are presented in [AIN457A SBP 2013] (in original BLA submission) and [AIN457 SBP Addendum 2015] (BLA-125504 S-1 submission), and no new bioanalytical methods have been generated since then. For assessment of the immunogenicity assays for detection of anti-secukinumab antibodies and neutralizing anti-secukinumab antibodies in the original BLA-125504, refer to this 125504 CMC review memo.

Assessor's Comment: *The assessment of the bioanalytical assay to measure AIN457 in serum is deferred to the Office of Clinical Pharmacology. The immunogenicity assays for the detection of anti-secukinumab antibodies and neutralizing anti-secukinumab antibodies will be assessed in the following sections of this memo.*

3. Assessment:

3.1 Immunogenicity assay for the detection of anti-secukinumab antibodies

An electrochemiluminescence method was used for the detection of potential anti-secukinumab antibody formation, based on the ability of anti-drug antibodies (ADA) to form a bridge between biotinylated secukinumab and ruthenylated secukinumab. (b) (4)

(b) (4)

(b) (4)

[redacted]

An overview of anti-secukinumab antibody validation details is provided in Table 5-6 below.

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(b) (4)

[redacted]

Assessor's Comment: *As shown in the table above, the assays for the detection of neutralizing anti-AIN457 antibodies fully validated* (b) (4) *have the same method principle but with some differences. Overall, the methods a* (b) (4) *are both generally suitable for the detection of neutralizing anti-AIN457 antibodies from individuals with hidradenitis suppurativa. The incidence of neutralizing antibodies may be underestimated in the presence of onboard AIN457 drug.*

Assessor's Conclusion:

Overall, these immunogenicity assay validation reports are acceptable, which demonstrated these two immunogenicity assays (for the detection of anti-secukinumab antibodies and neutralizing anti-secukinumab antibodies) are suitable for the intended use.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s063

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

PATIENT LABELING REVIEW

Date:	June 16, 2023
To:	Matthew White Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFUs)
Drug Name (established name), Dosage Form and Route:	COSENTYX (secukinumab) injection, for subcutaneous use • 150 mg/mL solution in a single-dose Sensoready pen • 150 mg/mL solution in a single-dose prefilled syringe • 75 mg/0.5 mL solution in a single-dose prefilled syringe
Application Type/Number:	BLA 125504
Supplement Number:	S-063
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On September 30, 2022, Novartis Pharmaceuticals Corporation submitted for the Agency's review a Prior Approval Supplement – Efficacy to their approved Biologics License Application (BLA) 125504/S-063 for COSENTYX (secukinumab) injection. With this submission, the Applicant proposes a new indication for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on November 16, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for COSENTYX (secukinumab) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 13, 2023.

2 MATERIAL REVIEWED

- Draft COSENTYX (secukinumab) injection MG and 150 mg/mL single-dose Sensoready pen, 150 mg/mL single-dose prefilled syringe, and 75 mg/0.5 mL single-dose prefilled syringe IFUs received on September 30, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 9, 2023.
- Draft COSENTYX (secukinumab) injection Prescribing Information (PI) received on September 30, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 9, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFUs, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

(b) (4)

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Clinical Inspection Summary

Date	June 20, 2023
From	Lee Pai-Scherf, M.D. Michele Fedowitz, M.D., Team Lead Jenn Sellers, M.D. Ph.D., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE/OSI
To	Maryjoy Mejia, M.D., Medical Officer Amy Woitach, M.D., Team Lead Tatiana Oussova, Deputy Director for Safety Division of Dermatology and Dentistry
NDA/BLA #	BLA 125504/S063
Applicant	Novartis Pharmaceuticals Corporation
Drug	Secukinumab (Cosentyx)
NME (Yes/No)	No
Therapeutic Classification	Monoclonal Antibody
Proposed Indication(s)	Treatment of adult patients with moderate to severe hidradenitis suppurativa
Consultation Request Date	October 21, 2022
Summary Goal Date	June 23, 2023
Action Goal Date	July 28, 2023
PDUFA Date	July 30, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two randomized, double-blind, placebo-controlled studies of secukinumab, with similar design (Studies CAIN457M2301 [M2301] and CAIN457M2302 [M2302]) were submitted to the Agency in support of Biological License Application (BLA) 125505/S063 for the above indication. Two clinical investigators, Dr. Maryam Alam (site # 4022), and Dr. Melody Stone (site # 5028) as well as the sponsor were inspected.

Although subjects enrolled at Dr. Stone's site did not have full physical examinations performed at post-treatment follow-up visits as specified in the protocol, this deviation did not appear to have significant impact on the efficacy endpoint or safety evaluation of the investigational product (IP).

Based on the inspections of the Sponsor and the CIs, Drs. Alam and Stone, Studies M2301 and M2302 appear to have been conducted adequately and the data generated by the inspected clinical investigators and submitted by the Sponsor appear acceptable in support of the proposed indication.

Of note, the inspection results of Novartis are based on a summary provided by the FDA field

investigator and are therefore preliminary. If significant new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Novartis seeks approval for secukinumab, a high-affinity recombinant, fully human monoclonal anti-human interleukin (IL)-17A antibody of the IgG1-class for the treatment of adult patients with moderate to severe hidradenitis suppurativa. Secukinumab is approved for the treatment of patients with plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondylarthritis, and two juvenile idiopathic arthritis subtypes.

Data from two phase 3 trials were submitted by Novartis to support the proposed indication of secukinumab for adult patients with moderate to severe hidradenitis suppurativa (HS). Studies M2301 and M2302 are two identical, ongoing, multi-center, randomized, double-blind, placebo-controlled, parallel group, studies conducted to assess the short (16 weeks) and long-term (up to 52 weeks) efficacy and safety of two secukinumab dose regimens compared to placebo in subjects with moderate to severe HS.

Eligible subjects were randomized in a 1:1:0.5:0.5 ratio to:

- Secukinumab 300 mg subcutaneously (s.c.) every 2 weeks (Q2W)
- Secukinumab 300 mg (s.c.) every 4 weeks (Q4W)
- Placebo to secukinumab (s.c.) Q2W, or
- Placebo to secukinumab (s.c.) Q4W

The primary efficacy endpoint was HiSCR50 response at Week 16, defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae from baseline to Week 16. Key secondary endpoint was AN50 response at Week 16, defined as at least a 50% decrease in AN count and flare over 16 weeks: subjects who experienced at least one flare over 16 weeks and NRS30 (skin pain) response at Week 16, among subjects with baseline NRS ≥ 3.

III. RESULTS (by site):

1. **Dr. Maryam Alam (Site # 4022, Study M2302)**
   SimcoMed Health Ltd
   6 Quarry Ridge Rd Suite 105
   Barrie, Ontario, Canada

   Inspection dates: 02/21 – 02/24/2023

   Dr. Alam was inspected as a surveillance inspection for Study M2302. This was the first inspection for Dr. Alam.

The site screened and enrolled 8 subjects with 2 additional subjects transferred from site # 4023 for continue treatment and follow-up. At the time of the inspection, 7 subject had completed the study. One subject discontinued study treatment due to an AE, unrelated to the IP (subject ID (b) (6)).

Source documents for all 10 subjects were reviewed during the inspection. The inspection covered subject's informed consent, demographics, eligibility, adverse event reporting, protocol deviations, laboratory results, concomitant medications, and investigational product/placebo administration records. All subjects met protocol specified inclusion and exclusion criteria and signed informed consent prior to study activities. There was no underreporting of AEs or significant protocol deviations. The primary efficacy measure of Hidradenitis Suppurative Clinical Response (HiSCR) after 16 weeks of treatment (number of abscesses, inflammatory nodules, and draining fistula counts), and secondary measures of skin pain response at Week 16 (skin pain scores), were verifiable with source records and found to be consistent with the data listings provided in the BLA.

Additional records reviewed include delegation of authority log, IRB documents and communication, financial disclosure forms, investigational drug accountability, case report forms, monitoring records, and staff training records. The inspection found no regulatory violations at the site.

2. **Dr. Melody Stone (Site # 5028, Study M2301)**
MediSearch Clinical Trials
1419 Village Drive
St Joseph, MO

Inspection dates: 05/31 – 06/06/2023

Dr. Stone was inspected as a surveillance inspection for Study M2301. This was the first inspection for Dr. Stone.

The site screened 8 and enrolled 5 subjects in Study M2301. Three subjects had completed study treatment, and 2 subjects (# 5028003 and 5028007) were lost to follow-up.

Source documents for all 5 enrolled subjects were reviewed. Records reviewed include but not limited to adverse event reporting, protocol deviations, and study drug administration records. All subjects signed informed consent prior to study activities and met protocol specified inclusion and exclusion criteria. There was no underreporting of AEs, serious AEs, or significant protocol deviations. The primary efficacy measure of HiSCR after 16 weeks of treatment and secondary measure of pain score were verifiable with source data found to be consistent with the listing submitted to the BLA.

Additional documents reviewed during the inspection include, but not limited to investigational drug accountability logs, financial disclosure forms, IRB documents, case report forms, site monitoring and training records.

The inspection observed the following unreported protocol deviations in five subjects:

- Subjects (b) (6) had no full physical exams performed at week 16 and subjects (b) (6) at week 52.

Per protocol, safety assessments with complete physical examinations were to be performed at the end of treatment Period 1 (at week 16) and at End of Treatment Period 2 (at week 52). Physical exam findings were to be captured in the source Physical Examination Form but not need to be entered into the EDC system.

Reviewer's comment: Dr. Stone was unable to provide a reason why the full physical exams were not performed and/or documented in the source documents at the above protocol specified time points. It is noted that subject (b) (6) *was lost to follow-up by week 16 and subject* (b) (6) *lost to follow-up by week 52. Source records indicate that all other protocol specified assessments, including primary and secondary efficacy measures, AE and laboratory tests were assessed as per protocol and were found to be consistent with the data submitted to the BLA. There were no significant AEs or laboratory abnormalities noted at week 16 for subjects* (b) (6) *and week 52 for subjects* (b) (6).

Notwithstanding the above protocol deviation, there is no evidence of subject harm based on the lack of significant AEs and/or laboratory test abnormalities collected at week 16 and 52, thus, data generated by the site appear acceptable in support of the proposed indication.

3. **Novartis Pharmaceuticals Corporation** (Sponsor)
One Health Plaza
East Hanover, NJ 07936

Inspection dates: 06/05 – 06/13/2023

The official establishment inspection report (EIR) is pending. The review below is from the summary close out email and communication with the inspector during the inspection. This report will be updated after review of the official EIR, if relevant additional information is included.

The inspection assessed Novartis' oversight responsibilities for M2301 and M2302 with focus on the Sponsor's selection, training, and oversight of Clinical Research Associate (CRA).

Records reviewed included but were not limited to documents and procedures related to the clinical trial protocols and their amendments, selection and monitoring of clinical investigators and CRAs, monitoring activities safety/adverse event reporting, data collection and handling and financial disclosures related to studies M2301 and M2302**.**

The inspection covered Novartis' hiring/firing, selection, training, misconduct, and potential falsification of visits or visit reports by the study monitors in studies M2301 and M2302. Monitoring files from four clinical sites (sites # 4022 and # 2032 for Study M2032; sites # 5028 and # 2045 for Study M2301) were selected for review. There was no evidence of misconduct or falsification of visit reports or visits to clinical sites for studies M2031 and M2032. In addition, the inspection reviewed Novartis' Quality Management System (QMS) and found it adequate.

The inspection found no regulatory violations and the Novartis' monitoring and oversight of Studies M2301 and M2302 appeared adequate.

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Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Jenn Sellers, MD PhD
Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:
DARRTS: BLA 125504/S063
Review Division /Project Manager/Matthew White
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	April 13, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 125504/S-063
Product Name, Dosage Form, and Strength:	Cosentyx (secukinumab) injection, 75 mg/ 0.5 mL prefilled syringe, 150 mg/vial, 150 mg/mL prefilled syringe, 150 mg/mL SensoReady Pen (150 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	September 30, 2022, and January 3, 2023
TTT ID #:	2022-2090
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Human Factors Team Leader	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 REASON FOR REVIEW

Novartis Pharmaceuticals Corporation submitted a supplement for Cosentyx (dupilumab) injection to provide revised labeling for a new indication of adult Hidradenitis Suppurativa (HS). Subsequently, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Cosentyx Prescribing Information (PI), Medication Guide (MG), and Instruction s for Use (IFU) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Cosentyx Prescribing Information (PI), Medication Guide (MG), and Instruction s for Use (IFU) did not identify areas of vulnerability that may lead to medication errors. Per our Division of Dermatology and Dentistry (DDD) clinical colleagues, they do not expect hand strength or manual dexterity to be affected by moderate to severe hidradenitis suppurativa (HS). We also note that the currently approved dosage form and strengths support the proposed new indication and proposed dose. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cosentyx that Novartis Pharmaceuticals Corporation submitted on January 3, 2023.

Table 2. Relevant Product Information for Cosentyx	
Initial Approval Date	January 21, 2015
Active Ingredient	Secukinumab
Indication	**Plaque Psoriasis** COSENTYX is indicated for the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy. **Psoriatic Arthritis** COSENTYX is indicated for the treatment of active psoriatic arthritis (PsA) in patients 2 years of age and older. **Ankylosing Spondylitis** COSENTYX is indicated for the treatment of adult patients with active ankylosing spondylitis (AS). **Non-Radiographic Axial Spondyloarthritis** COSENTYX is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis (nraxSpA) with objective signs of inflammation. **Enthesitis-Related Arthritis** COSENTYX is indicated for the treatment of active enthesitis-related arthritis (ERA) in patients 4 years of age and older. **Proposed:** **Hidradenitis Suppurativa** COSENTYX is indicated for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	75 mg/ 0.5 mL prefilled syringe, 150 mg/vial, 150 mg/mL prefilled syringe, 150 mg/mL SensoReady Pen
Dose and Frequency	**Plaque Psoriasis:** Adults:

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 dose of 150 mg may be acceptable.

Pediatric Patients 6 Years and Older:
The recommended dosage for pediatric patients 6 years of age and older is based on body weight and administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by dosing every 4 weeks.

Recommended Dose of COSENTYX for Pediatric Patients 6 Years of Age and Older with Plaque Psoriasis

Body weight at time of dosing	Recommended dose
Less than 50 kg	75 mg
Greater than or equal to 50 kg	150 mg

Psoriatic Arthritis:
Adults:
For PsA patients with coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis.

For other PsA 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 PsA, consider a dosage of 300 mg every 4 weeks.
    -

Pediatric Patients:
The recommended dose based on body weight is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.

• For patients weighing ≥ 15 kg and < 50 kg the recommended dose is 75 mg
• For patients weighing ≥ 50 kg the recommended dose is 150 mg

COSENTYX may be administered with or without methotrexate.

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 ○ If a patient continues to have active AS, consider a dosage of 300 mg every 4 weeks. **Non-Radiographic Axial Spondyloarthritis:** 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 **Enthesitis-Related Arthritis:** The recommended dose based on body weight is administered by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. • For patients weighing ≥ 15 kg and < 50 kg the recommended dose is 75 mg • For patients weighing ≥ 50 kg the recommended dose is 150 mg **Proposed:** **Hidradenitis Suppurativa:** Recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4, followed by 300 mg every 2 weeks.
How Supplied	COSENTYX (secukinumab) injection is a clear to opalescent, colorless to slightly yellowish solution available as follows: COSENTYX Sensoready pen: • NDC 0078-0639-41: Carton of two 150 mg/mL (300 mg dose) single-dose Sensoready pens (injection) • NDC 0078-0639-68: Carton of one 150 mg/mL single-dose Sensoready pen (injection) COSENTYX prefilled syringe: • NDC 0078-0639-98: Carton of two 150 mg/mL (300 mg dose) single-dose prefilled syringes (injection) • NDC 0078-0639-97: Carton of one 150 mg/mL single-dose prefilled syringe (injection)

	COSENTYX prefilled syringe (for pediatric patients less than 50 kg): • NDC 0078-1056-97: Carton of one 75 mg/0.5 mL single-dose prefilled syringe (injection) The removable cap of the COSENTYX 150 mg/mL Sensoready pen and prefilled syringe, and 75 mg/0.5 mL prefilled syringe contains natural rubber latex. Each Sensoready pen and prefilled syringe is equipped with a needle safety guard. COSENTYX (secukinumab) for injection is a white lyophilized powder for healthcare professional use only available as follows: • NDC 0078-0657-61: Carton of one 150 mg lyophilized powder in a single-dose vial (for injection)
Storage	Refrigerate COSENTYX Sensoready pens, prefilled syringes, and vials 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. If necessary, COSENTYX Sensoready pens and 150 mg/mL prefilled syringes may be stored for up to 4 days at room temperature not to exceed 30°C (86°F). Write the date COSENTYX was removed from the refrigerator in the space provided on the carton. If unused and not stored above 30°C (86°F), COSENTYX Sensoready pens and 150 mg/mL prefilled syringes may be returned to the refrigerator. Throw away COSENTYX if it has been kept outside of the refrigerator and not been used in over 4 days.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 2, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "Cosentyx". Our search identified 13 previous reviews[a,b,c,d,e,f,g,h,i,j,k,l,m], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Patel, M. Labeling Review for Cosentyx (secukinumab) (BLA 15504/S-055). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUN 03. OSE RCM No.: 2022-473.

(b) (4)

[c] Patel, M. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-046). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 14. RCM No.: 2021-213.

[d] McMillan, T. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-050 & /S-051). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 12. RCM No.: 2021-1432.

[e] McMillan, T. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-035). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 14. RCM No.: 2020-351.

[f] Barlow, M. Human Factors and Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-044). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 NOV 03. RCM No.: 2020-2183.

[g] Whaley, E. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-043). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 05. RCM No.: 2020-1609 and 2020-1608.

[h] McMillan, T. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-031). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 25. RCM No.: 2019-1954.

[i] Patel, M. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/(b) (4) S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 10. RCM No.: 2017-2527 and 2017-2605.

[j] Patel, M. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-013). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 24. RCM No.: 2017-694.

[k] Patel, M. Label and Labeling Review for Cosentyx (secukinumab) (BLA 125504/(b) (4) S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 10. RCM No.: 2017-2527 and 2017-2605.

[l] McMillan, T. Labeling Review for Cosentyx (secukinumab) (BLA 125504/S-001 & S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 15. RCM No.: 2015-1014.

[m] Mena-Grillasca, C. Human Factors, Label, Labeling and Packaging Review for Cosentyx (secukinumab) (BLA 125504). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 27. RCM No.: 2013-2700.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[n] along with postmarket medication error data, we reviewed the following Cosentyx labels and labeling submitted by Novartis Pharmaceuticals Corporation.

- Prescribing Information, Instructions for Use, and Medication Guide (Images not shown) received on January 3, 2023, available from \\CDSESUB1\EVSPROD\bla125504\0403\m1\us\proposed.pdf

[n] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CORWIN D HOWARD
04/14/2023 11:36:33 AM

MADHURI R PATEL
04/14/2023 11:44:48 AM

OLUWAMUREWA OGUNTIMEIN
04/15/2023 04:43:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125504Orig1s063

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BLA 125504/S-063

8- WEEK POSTMARKETING REQUIREMENT (PMR)
COMMUNICATION LETTER

Novartis Pharmaceuticals Corporation
Attention: Gaelle Enderlin
Global Program Regulatory Director
One Health Plaza
East Hanover, New Jersey 07936

Dear Gaelle Enderlin:

Please refer to your supplemental biologics license application (sBLA) dated and received September 30, 2022, submitted under section 351(a) of the Public Health Service Act for Cosentyx (secukinumab) injection.

We also refer to our letter dated December 8, 2022, in which we notified you of our target date of June 30, 2023, for communicating anticipated postmarketing requirements (PMRs) in accordance with the *Biosimilar Biological Product Reauthorization Performance Goals and Procedures - Fiscal Years 2023 Through 2027*. Major safety issues requiring a PMR that were identified based on data submitted after your initial submission may not be included in this letter.

We have made a preliminary evaluation of anticipated PMRs as follows:

REQUIRED PEDIATRIC ASSESSMENTS

If your application is approved, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed-combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration will be required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

1. Conduct an open-label study to evaluate the pharmacokinetics (PK) and safety in the adolescent population 12 to less than 17 years of age with moderate to severe hidradenitis suppurativa who are candidates for systemic treatment. Evaluate at least 80 subjects exposed to the highest approved dosage of subcutaneous secukinumab (300 mg every 2 weeks) for a minimum of 52 weeks.

SUBSEQUENT COMMUNICATIONS ABOUT PMRs and PMCs

During the remainder of the review cycle, subsequent communication about anticipated PMRs and PMCs may occur as needed.

Once FDA communicates that a PMR will be required or PMC will be agreed upon in writing, applicants should propose a schedule of milestones to be reviewed and evaluated by the Agency. Milestones may include: a draft protocol submission, a final protocol submission, a study/trial completion, and a final report submission. Interim report submission milestones may be included as needed. Each PMR and PMC should have at least one milestone in the schedule. These milestones will be used to measure the progress of the study or clinical trial and compliance of requirements.

If you have any questions, contact Sascha Randolph, Regulatory Project Manager, at Sascha.Randolph@fda.hhs.gov or at (301)796-8546.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

TATIANA OUSSOVA
10/24/2023 01:58:42 PM

BLA 125504/S-063

REVIEW EXTENSION –
EFFICACY SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attention: Gaelle Enderlin
Global Program Regulatory Director
One Health Plaza
East Hanover, New Jersey 07936

Dear Gaelle Enderlin:

Please refer to your supplemental biologics license application (sBLA) dated and received September 30, 2022, submitted under section 351(a) of the Public Health Service Act for Cosentyx (secukinumab) injection.

We received your July 10, 2023, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 30, 2023.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2018 THROUGH 2022". If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 2, 2023.

If you have questions, call Matthew White, Senior Regulatory Project Manager, at 301-796-4997.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

TATIANA OUSSOVA
07/19/2023 08:54:11 PM

U.S. FOOD & DRUG ADMINISTRATION

Maryam S. Alam
5 Quarry Ridge Road, Suite 105
Barrie, Ontario L4M 7G1
CANADA

Dear Dr. Alam:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site on February 21, 2023, and February 24, 2023. Investigator Courtney R. Bratina, representing FDA, reviewed your conduct of a clinical investigation (Protocol **CAIN457M2302**, "A Randomized, Double-Blind, Multicenter Study Assessing Short (16 Weeks) and Long-Term Efficacy (Up to 1 Year), Safety, and Tolerability of 2 Subcutaneous Secukinumab Dose Regimens in Adult Patients With Moderate to Severe Hidradenitis Suppurativa (SUNRISE)") of the investigational drug Cosentyx® Unoready® Pen (secukinumab), performed for Novartis Pharmaceuticals Corporation.

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects have been protected.

We have reviewed the FDA Establishment Inspection Report and the documents submitted with that report, and we did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

No response to this letter is necessary. However, if you have any questions or concerns about this letter or the inspection, please write to me at the address given below.

Sincerely,

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5324
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

LORETO CORAZON Y LIM
07/17/2023 03:03:39 PM
Signed for Jenn Sellers, M.D., Ph.D.

U.S. FOOD & DRUG ADMINISTRATION

Melody L. Stone, M.D., F.A.A.D.
MediSearch Clinical Trials
1427 Village Drive
Saint Joseph, MO

Dear Dr. Stone:

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between May 31, 2023, and June 6, 2023. Investigator Carmen Y. Fisher, representing FDA, reviewed your conduct of a clinical investigation (Protocol **CAIN457M2301**, "A Randomized, Double-Blind, Multicenter Study Assessing Short (16 Weeks) and Long-Term Efficacy (Up to 1 Year), Safety, and Tolerability of 2 Subcutaneous Secukinumab Dose Regimens in Adult Patients With Moderate to Severe Hidradenitis Suppurativa (SUNSHINE)") of the investigational drug Cosentyx® Unoready® Pen (secukinumab), performed for Novartis Pharmaceuticals Corporation.

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, our investigator presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the FDA Establishment Inspection Report, and the documents submitted with the report. We acknowledge your June 12, 2023, written response to the inspectional findings and note that you have implemented corrective actions to prevent the recurrence of the inspection findings.

No response to this letter is necessary. However, if you have any questions or concerns about this letter, please write to me at the address given below.

Sincerely,

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5324
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

LORETO CORAZON Y LIM
07/17/2023 02:59:05 PM
Signed for Jenn Sellers, M.D., Ph.D.

U.S. FOOD & DRUG ADMINISTRATION

Vasant (Vas) Narasimhan, M.D., Chief Executive Officer
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Narasimhan:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at Novartis Pharmaceuticals Corporation between June 5, 2023, and June 13, 2023. Investigator Michael Serrano, representing FDA, reviewed your conduct as the sponsor of the following protocols of the investigational drug Cosentyx® Unoready® Pen (secukinumab):

- Protocol **CAIN457M2301**, "A Randomized, Double-Blind, Multicenter Study Assessing Short (16 Weeks) and Long-Term Efficacy (Up to 1 Year), Safety, and Tolerability of 2 Subcutaneous Secukinumab Dose Regimens in Adult Patients With Moderate to Severe Hidradenitis Suppurativa (SUNSHINE)"; and

- Protocol **CAIN457M2302**, "A Randomized, Double-Blind, Multicenter Study Assessing Short (16 Weeks) and Long-Term Efficacy (Up to 1 Year), Safety, and Tolerability of 2 Subcutaneous Secukinumab Dose Regimens in Adult Patients With Moderate to Severe Hidradenitis Suppurativa (SUNRISE)".

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects have been protected.

We have reviewed the FDA Establishment Inspection Report and the documents submitted with that report, and we did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

No response to this letter is necessary. However, if you have any questions or concerns about this letter or the inspection, please write to me at the address given below.

Sincerely,

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5324
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

LORETO CORAZON Y LIM
07/17/2023 03:01:32 PM
Signed for Jenn Sellers, M.D., Ph.D.

BLA 125504/S-063

DEFICIENCIES PRECLUDE DISCUSSION

Novartis Pharmaceuticals Corporation
Attention: Gaelle Enderlin
Global Program Regulatory Director
One Health Plaza
East Hanover, New Jersey 07936

Dear Gaelle Enderlin:

Please refer to your supplemental biologics license application (sBLA) dated and received September 30, 2022, under section 351(a) of the Public Health Service Act for Cosentyx (secukinumab) injection.

We also refer to our December 8, 2022, letter in which we notified you of our target date of June 30, 2023, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the *PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2018 Through 2022*.

As part of our ongoing review of your supplemental application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call me at 301-796-4997.

Sincerely,

{See appended electronic signature page}

Matthew White
Associate Director for Labeling
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

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/s/

MATTHEW E WHITE
06/30/2023 11:30:14 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 21, 2023

To: Matthew White, Associate Director for Labeling
Division of Dermatology and Dentistry (DDD)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for COSENTYX® (secukinumab) injection, for subcutaneous use, COSENTYX® (secukinumab) for injection, for subcutaneous use

BLA: 125504, S-063

Background:
In response to DDD's consult request dated November 16, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU) for Supplement-063 for COSENTYX® (secukinumab) injection, for subcutaneous use and COSENTYX® (secukinumab) for injection, for subcutaneous use. This supplement proposes a new indication for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 8, 2023, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide and IFU, and comments were sent under separate cover on June 16, 2023.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

Following this page, 34 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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/s/

CARRIE A NEWCOMER
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