

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY INDIVIDUAL STUDY SUMMARY

BLA:	STN 125,504
Submission Type:	Original BLA (New Molecular Entity)
Brand Name:	COSENTYX®
Drug Name:	Secukinumab (AIN457)
Submission Date:	10/24/2013
PDUFA Goal Date:	01/23/2015
Priority:	Standard
Proposed Indication:	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Applicant:	Novartis Pharmaceuticals Corporation
Clinical Pharmacology Reviewer:	Jie Wang, Ph.D.
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This document provides the Individual Study Summary for clinical pharmacology and clinical studies listed in Table 2.2.1 of the Clinical Pharmacology Review of the BLA. Refer to the Clinical Pharmacology Review for the regulatory recommendations from a Clinical Pharmacology standpoint.

1. STUDY CAIN457A2106

1.1. Title

- An open-label, randomized, single-dose, parallel-group study in healthy subjects to determine the bioequivalence of a liquid formulation of AIN457 (secukinumab) with respect to the lyophilized form of AIN457 following 300 mg subcutaneous (SC) administration

1.2. Study period

- 27 May 2011 (the first subject enrolled) to 01 November 2011 (the last subject completed)

1.3. Primary objective

- To demonstrate the bioequivalence of a single subcutaneous dose of AIN457 supplied as pre-filled syringe (PFS, test) with respect to the lyophilized formulation (LYO, reference).

1.4. Study design and methods

Study CAIN457A2106 was a multi-center, open-label, randomized, single dose, parallel-group trial in healthy volunteers to determine the bioequivalence of AIN457 in PFS with respect to the lyophilized formulation (LYO).

Subjects

A total of 150 healthy male and female subjects (aged 18 to 45 years, 75% Caucasian) were enrolled. Of the 150, 141 subjects (71 in the PFS group and 70 in the LYO group) completed the study and 9 subjects discontinued due to various reasons. A total of 138 subjects (70 in the PFS group and 68 in the LYO group) had evaluable AIN457 pharmacokinetic parameters and were included in the statistical analysis for the PK comparability evaluation between the two formulations.

Study products

AIN457 300 mg was supplied either in two PFS (AIN457 150 mg PFS, Batch # Y1481210), each with 1 mL (150 mg) solution for SC injection, or in two Vials (AIN457 150 mg Lyophilisate in Vial, Batch #S0007), each containing 150 mg lyophilized powder to be reconstituted with 1 mL of sterile water, for SC injection.

Dose administration

Single dose of AIN457 300 mg was administered by SC injection at baseline (Day 1). The 300 mg dose was given as two injections of 150 mg each.

PK sampling and measurement

Blood samples for PK assessment were collected at pre-dose, 8, 24, 48, 72, 96, 168 hours and 9, 14, 21, 28, 35, 49, 63, 77, 91 and 112 days following SC administration.

A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

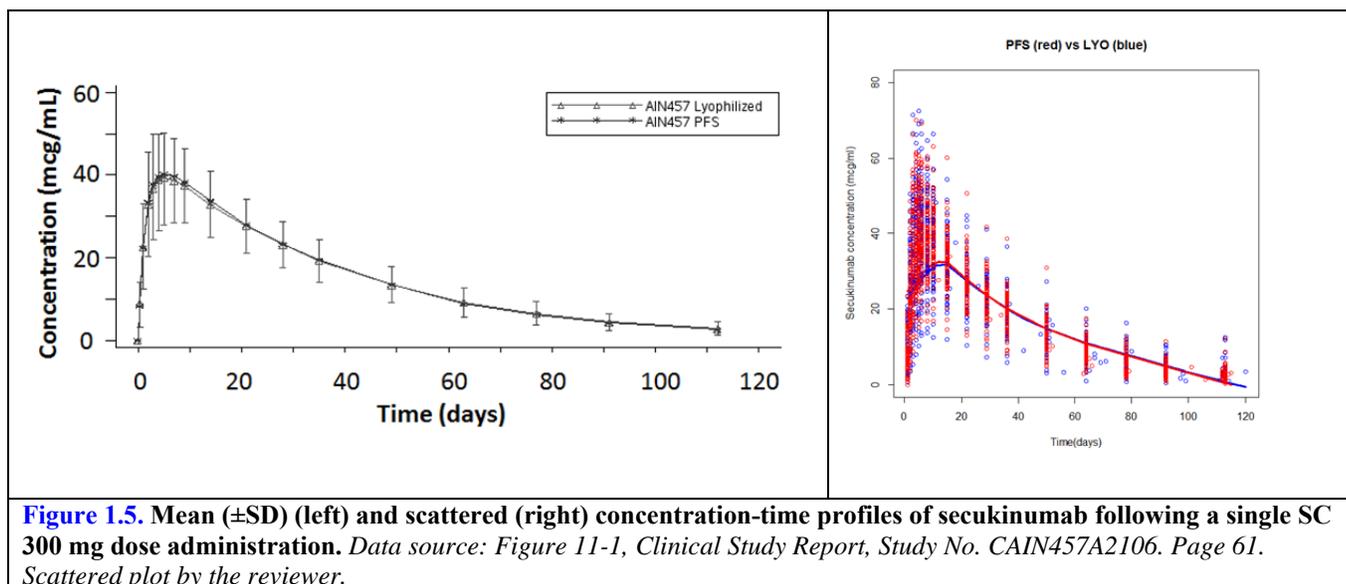
Immunogenicity

Blood samples for immunogenicity testing were collected at Days 1 (predose), 92 and 113.

1.5. Results

PK results

The mean (\pm SD) and scattered serum concentration time profiles of AIN457 by formulation are shown in Figure 1.5. The PK results showed that administration of lyophilized or liquid AIN457 resulted in similar serum concentration-time profiles.



The PK parameters are summarized in Table 1.5. Analysis of the PK parameters of AUC_{last} , AUC_{inf} and C_{max} supported that the two formulations are comparable because the 90% confidence interval for geometric mean ratio of all the three parameters were contained in the interval [0.80, 1.25].

Table 1.5. Descriptive statistics of the PK parameters and the BE analysis for the 90% confidence interval for the geometric mean ratio. N=70 for PFS; N=68 for Lyophilized; test=AIN457 PFS; reference=AIN457 Lyophilized. (Data source: Table 11-2, Table 11-3, Clinical Study Report, Study No. CAIN457A2106. Page 62-63)

PK parameters	formulation	Mean (\pm SD)	Geometric mean ratio(test/reference)	90% CI for geometric mean ratio
AUC_{inf} (day*mcg/mL)	PFS	1785 \pm 461.1	1.00	[0.92, 1.08]
	Lyophilized	1795 \pm 498.0		
AUC_{last} (day*mcg/mL)	PFS	1678 \pm 410.5	1.01	[0.93, 1.08]
	Lyophilized	1675 \pm 432.0		
C_{max} (mcg/mL)	PFS	43.21 \pm 10.39	1.04	[0.96, 1.12]
	Lyophilized	41.96 \pm 11.22		
T_{max} (day, median)	PFS	5	N/A	N/A
	Lyophilized	5		
$T_{1/2}$ (day)	PFS	25.9 \pm 4.59	N/A	N/A
	Lyophilized	26.6 \pm 5.14		
CL/F (L/day)	PFS	0.1808 \pm 0.0549	N/A	N/A
	Lyophilized	0.1815 \pm 0.0564		

Immunogenicity results

One sample from subject 4/5188 (received the LYO formulation) was tested positive for anti-drug antibodies (titer=2) at Day 92 and the sample from the same subject was tested negative at Day 113.

2. STUDY CAIN457A1101

2.1. Title

- A randomized, double-blind, placebo-controlled, single ascending dose study to demonstrate the safety, tolerability, pharmacokinetics and pharmacodynamics of AIN457 administered as intravenous infusion and subcutaneous injection in Japanese healthy male subjects

2.2. Study period

- 16 February 2009 (the first subject enrolled) to 08 September 2009 (the last subject completed)

2.3. Objectives

- To evaluate the safety, tolerability, PK, and PD of AIN457 administered as intravenous infusion and subcutaneous injection to Japanese healthy male subjects

2.4. Study design and methods

Study CAIN457A1101 was a randomized, double-blind, placebo-controlled, 5-cohort, single ascending dose study.

Subjects

Japanese healthy male subjects (20 to 45 years old, mean bodyweight of 63 kg) were enrolled in the study. A total of 42 subjects were randomized to one of 5 cohorts. In Part 1, subjects were randomized to sequential 3 IV cohorts (6 subjects randomized to active treatment and 2 subjects to placebo per cohort). In Part 2, subjects were randomized to sequential 2 SC cohorts (6 subjects randomized to active treatment and 3 subjects to placebo per cohort).

Study products

AIN457 150 mg lyophilized powder for solution (batch #: Y003 0108) was used in the study.

Dose administration

Each subject participated in one of the 5 cohorts. In study Part 1, subjects in Cohorts 1, 2 and 3 received an IV infusion of AIN457 at doses of 1, 3 and 10 mg/kg (or placebo) over approximately 120 minutes, respectively. In study Part 2, subjects in Cohorts 4 and 5 received a SC injection of AIN457 at doses of 150 and 300 mg (or placebo), respectively.

PK measurement

A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

Immunogenicity

Blood samples for immunogenicity testing were collected at Day 29, Day 57 and 113.

Immunogenicity (anti-AIN457 antibody in serum) was assessed by the Biacore method.

2.5. Results

PK results

The PK parameters are summarized in Table 2.5. The estimated absolute bioavailability of AIN 457 in healthy Japanese subjects was 77% by comparing dose-normalized AUC_{inf} after SC injection with those after IV infusion. No apparent deviation from the dose proportionality was observed for C_{max}, AUC_{last} and AUC_{inf} over the entire dose range for both administration route (IV 1, 3, and 10 mg/kg; and SC 150 and 300 mg/kg).

Table 2.5. The mean (±SD) PK parameters following a single IV or SC dose administration in healthy Japanese subjects. (Data source: CSR AIN457A1101, Table 11-2, Page 59).

	Part 1: IV			Part 2: SC	
	1 mg/kg	3 mg/kg	10 mg/kg	150 mg	300 mg
T _{max} (day, median)	0.083	0.167	0.083	8.01	8.01
C _{max} (mcg/mL)	23.97±2.461	70.35±5.892	263.8±43.86	21.07±2.897	46.27±7.634
AUC _{last} (mcg*day/mL)	475±67.7	1499±120.1	5670±580.3	999±132.3	1804±352.6
AUC _{inf} (mcg*day/mL)	520±94.7	1589±153.8	5988±569.0	1074±153.4	1929±408.1
T _{1/2} (day)	31.16±5.115	26.43±5.769	25.89±3.266	30.03±6.933	25.93±5.091
V _Z (L)	5.34±0.981	4.29±0.570	4.23±0.384		
CL (L/day)	0.1212±0.0285	0.1141±0.0103	0.1137±0.0064		

Immunogenicity results

None of the subjects were positive for anti-drug antibodies.

3. STUDY CAIN457A2103

3.1. Title

- A randomized, multiple-dose, open-label study to determine the absolute bioavailability of a subcutaneous administration of AIN457 in patients with chronic plaque-type psoriasis

3.2. Study period

- 27 January 2009 (the first subject enrolled) to 16 May 2009 (the last subject completed)

3.3. Primary objective

- To assess the absolute bioavailability of AIN457 following subcutaneous administration

3.4. Study design and methods

This was an exploratory open label, multiple dose, cross-over study in psoriasis patients to assess the absolute bioavailability of AIN457 following SC administration. All patients received AIN457 on two occasions (SC→IV or IV→SC): one on Day 1 and the next on Day 29. The cross-over trial design did not have a complete washout period following the first dose administration (i.e., the second dose was given when there was still a substantial amount of drug in serum from the first dose).

Subjects

A total 14 male and female psoriasis patients were enrolled and randomized in a 1:1 ratio to receive either (1) IV→SC or (2) SC→IV of AIN457.

Study products

AIN457 150 mg lyophilized powder for solution (batch #: Y003 0108) was used in the study.

Dose administration

All patients received the study medication on two occasions, as the following:

- IV→SC: 1 mg/kg IV at Day 1 followed by 150 mg AIN457 SC at Day 29
- SC→IV: 150 mg AIN457 SC at Day 1 followed by 1 mg/kg AIN457 IV at Day 29

PK sample collection and measurement

Blood samples for PK assessments were collected at pre-dose on Day 1 and Day 29. For IV→SC, post-dose sample were collected on Days 1 (1, 2, 4, and 8 hr), 2, 4, 5, 8, 11, 15, 22, 29 (1, 2, and 8 hr), 30, 32, 33, 36, 39, 43, 50, 57, 71 and 85. For SC→IV, post-dose samples were collected on Days 1 (1 and 8 hr), 2, 4, 5, 8, 11, 15, 22, 29 (1, 2, 4, and 8 hr), 30, 32, 33, 36, 39, 43, 50, 57, 71 and 85.

A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

Immunogenicity

Blood samples for immunogenicity testing were collected on Day 1 (predose), 29 (predose), 57 and 85. Anti-AIN457 antibodies in serum were assessed by the Biacore method.

3.5. Results

PK results

The PK parameters are summarized in [Table 3.5](#). Using non-compartmental analysis the PK results showed an absolute bioavailability estimate of 55% (90% CI; 43% to 70%) of AIN457 in psoriasis patients following SC administration. In the non-compartmental analysis the carry-over corrections following the first dose treatment were based on terminal elimination rate constant (λ -z values) observed in the second treatment period.

Table 3.5. Serum secukinumab PK parameters following a single IV or a SC dose administration in psoriasis patients. (Data source: Table 11-4, Clinical Study Report AIN457A2103, Page 55).

	IV 1 mg/kg (n=14)	SC 150 mg (n=14)
AUC _{inf} (mcg*day/mL)	441.1±102.7	421.3±164.1
AUC _{last} (mcg*day/mL)	375.7±70.5	364.4±134.1
AUC _{0-28 days} (mcg*day/mL)	251.1±36.7	224.4±69.4
C _{max} (mcg/mL)	24.14±3.2	11.83±3.8
T _{max} (day, median)	0.086	8.5
T _{1/2} (day)	27.09±6.30	22.22±7.79
CL (mL/day)	0.22±0.073	
V _z (L)	7.10±2.37	

Reviewer's Comments: The PK results from the current study showed an absolute bioavailability of AIN457 of 55% in psoriasis patients, which is apparently lower than the bioavailability of 77% observed in healthy Japanese subjects in study CAIN457A1101. The differences could have been due to a lack of complete washout period following the first dose administration in the cross-over trial design in the current study.

Immunogenicity results:

None of the subjects were positive for anti-drug antibodies.

4. STUDY CAIN457A2225

4.1. Title

- An exploratory study to investigate the distribution of secukinumab (AIN457) into dermal interstitial fluid (ISF) using open flow microperfusion (OFM) after a single subcutaneous administration of 300 mg in healthy subjects and psoriatic patients

4.2. Study period

- 01 February 2012 (the first subject enrolled) to 28 January 2013 (the last subject completed)

4.3. Primary objectives

- To investigate the distribution of secukinumab into dermal ISF in healthy subjects (Part 1) and in psoriatic patients (Part 2) after single SC administration

4.4. Study design and methods

This was a single center, open label, exploratory study. ISF was collected using OFM in skin areas distant to the site of secukinumab injection. At Day 1, three OFM catheters were placed in the dermis in arm. After completion of the perfusion fluid run-in and up to 12 hr OFM sampling, a single dose of 300 mg secukinumab was administered SC at a body site separate from where OFM was conducted. Blood samples and OFM samples were collected on Day 8 and Day 15.

The study also explored the concentrations of IL-17 and downstream biomarkers such as beta-defensin 2 in dermal ISF and serum. Beta-defensin 2 was quantified using sandwich-based immunoassays validated in human serum with a LLOQ of 32.5 pg/mL.

Sinistrin (an inulin-like compound) was used as external reference to measure secukinumab concentration in the skin tissue fluid by OFM. Sinistrin is a special metabolically inert polysaccharide used to determine the volume of fluid outside the cells. To allow the use of dermal sinistrin recovery for the calculation of secukinumab ISF concentration, two main hypotheses were first verified in Part 1 of this study: (1) equal concentrations of sinistrin in blood and dermal ISF, and (2) comparable relative recovery of sinistrin and secukinumab.

Subjects

There were two study populations: healthy volunteers (Part 1) and psoriasis patients (Part 2). In Part 1, a total of eight healthy volunteers with a mean age of 26 years and mean bodyweight of 78 kg were enrolled and completed the study. In Part 2, a total of eight psoriatic patients with a mean age of 39 years and a mean bodyweight of 94 kg were enrolled and completed the study.

Study products

AIN457 150 mg lyophilized powder for solution (batch #: S0009) was used in the study.

Dose administration

A single dose of 300 mg secukinumab was administered via SC injections.

Sinistrin (Inutest 25% vials of 20 mL contain 5 g sinistrin) for injections were administered via IV bolus with a continuous infusion to achieve steady state serum sinistrin concentration of approximately 250 mg/L.

PK measurement

Blood samples for serum and OFM samples for tissue secukinumab concentrations were collected on Day 8 and Day 15. A competitive ELISA assay was used to assess secukinumab in serum and ISF samples.

Immunogenicity

Immunogenicity samples were collected in Part 2 at Day 1 and Day 22. Anti-secukinumab antibodies were assessed in serum by electrochemiluminescence MSD assay.

4.5. Results

PK results

Serum and dermal ISF secukinumab concentrations following a single SC 300 mg dose administration in healthy subjects and psoriasis patients are summarized in [Table 4.5](#). In healthy subjects the mean secukinumab concentrations in dermal ISF were 21.5%±3.6% and 23.4%±6.5 % of the corresponding serum secukinumab concentrations on Day 8 and Day 15, respectively. In psoriatic patients dermal ISF concentrations in non-lesional and lesional skin were comparable and were in a range between 27% and 40% of the corresponding serum concentrations.

Table 4.5. Serum and ISF secukinumab concentrations following a single SC 300 mg dose administration in healthy subjects and psoriasis patients. ^{a)} Calculated by using the individual recoveries of sinistrin and additional correction factor for difference in recovery between secukinumab and sinistrin; (*Data source: CSR, Table 11-5, page 81; Table 11-6, page 83; Table 11-10, page 86*)

		Day 8	Day15
Healthy Subjects	Serum	36.1±10.5	35.0±10.5
	Dermal ISF (OFM) ^a	7.76±1.30	8.02±3.23
Psoriatic patients	Serum	21.1±4.33	21.2±4.88
	Lesional dermal ISF (OFM) ^a	6.76±2.68	5.65±1.80
	Non-lesional dermal ISF (OFM) ^a	8.34±3.35	6.39±3.35

PD results

- IL-17A

The geometric mean serum baseline free IL-17A levels were 0.53 pg/mL and 0.20 pg/mL in subjects with psoriasis and healthy volunteers, respectively (*Data source: CSR, section 11.4.4.1*).

Pre-dose free IL-17A levels in dermal ISF from psoriatic patients were significantly higher in lesional skin (~ 9.8 pg/mL) compared to non-lesional or healthy skins (<LLOQ in the diluted ISF sample) (*Data source: CSR, Figure 11-7, page 89*).

The free IL-17A ELISA assay could not reliably determine the free IL-17A concentration in the presence of secukinumab; therefore, the free IL-17A levels following secukinumab treatment were not further assessed.

- Beta-defensin 2

Baseline beta-defensin 2 levels in serum were significantly higher in subjects with psoriasis than these in healthy volunteers (geometric mean 5746.2 pg/mL vs. 81.8 pg/mL; p<0.0001) and were significantly decreased in subjects with psoriasis after single 300 mg dose secukinumab administration ([Figure 4.5.1](#)).

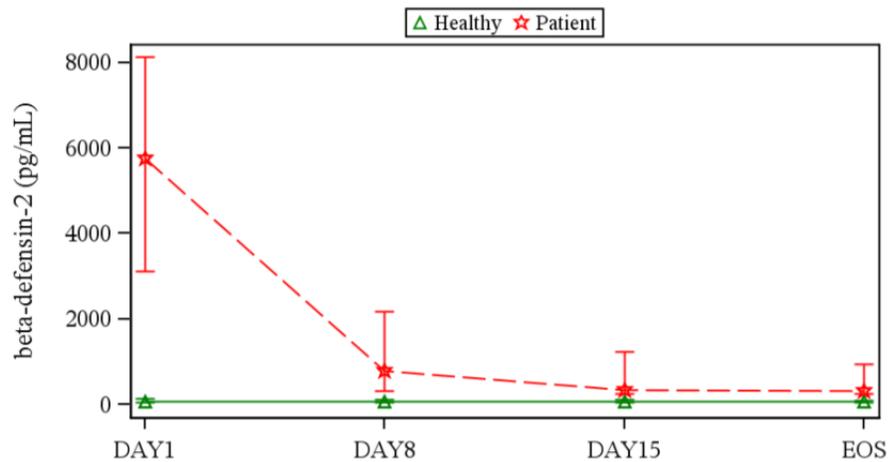


Figure 4.5.1. Serum median (with 25th and 75th percentile) beta-defensin 2 levels in healthy subjects and subjects with psoriasis following a single SC 300 mg secukinumab treatment. (*Data source:* CSR CAIN457A2225, Figure 11-9, Page 91.)

Beta-defensin 2 levels in OFM (diluted dermal ISF) from healthy volunteers are below the LLOQ (32.5 pg/mL) at all the time-points studied. Baseline beta-defensin 2 levels in OFM (diluted dermal ISF) in subjects with psoriasis are significantly higher in lesional than in non-lesional skin or healthy skin. Beta-defensin 2 levels in lesional skin decreased after single 300 mg dose secukinumab at Day 8 and Day 15 (Figure 4.5.2). The absolute beta-defensin 2 levels were estimated to be 2752 pg/mL in lesional skin and 417 pg/mL in non-lesional skin (*Data source:* CSR CAIN457A2225, Page 95).

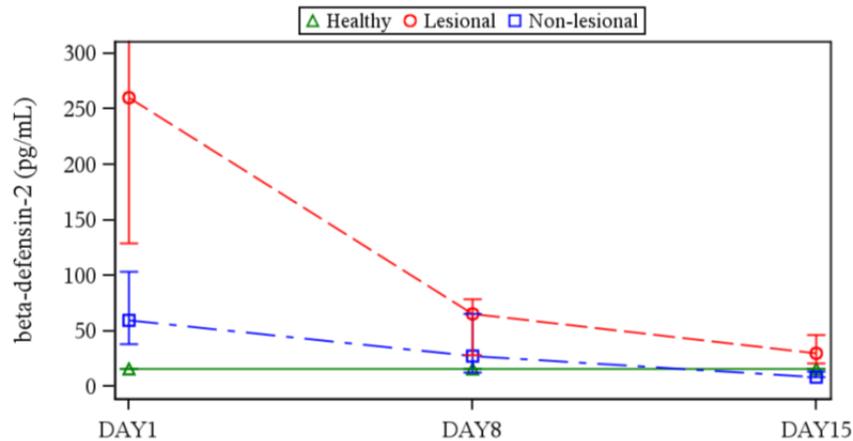


Figure 4.5.2. Dermal ISF median (with 25th and 75th percentile) beta-defensin 2 levels in healthy subjects and subjects with psoriasis following a single SC 300 mg secukinumab treatment. (*Data source:* CSR CAIN457A2225, Figure 11-10, Page 92.)

Immunogenicity results

None of the subjects were positive for anti-drug antibodies.

5. STUDY CAIN457A2228

5.1. Title

- A single-dose safety and tolerability study of 10 mg/kg AIN457 administered in a 30-minute intravenous infusion to healthy subjects

5.2. Study period

- 28 February 2011 (the first subject enrolled) to 04 March 2011 (the last subject completed)

5.3. Objectives

- To determine the safety and tolerability of AIN457 single intravenous infusion of 10 mg/kg administered over a 30-minute period compared to placebo.
- To assess pharmacokinetic parameters following a 30 minute infusion of AIN457 10 mg/kg

5.4. Study design and methods

This was a randomized, placebo-controlled, partially-double blind, single-dose, safety and tolerability study in 12 healthy volunteers. The study consisted of a screening period, baseline period (Day -1), followed by a single dose of AIN457 10 mg/kg or placebo administered on Day 1, followed by an end of study (EOS) visit on Day 8.

Subjects

A total of 12 healthy subjects (mean age of 35 years and mean bodyweight of 77 kg) were enrolled and assigned to receive AIN457 10 mg/kg (n=9) or placebo (n=3).

Study products

AIN457 150 mg lyophilized powder for solution (batch #: Y103-0609) was used in the study.

Dose administration

AIN457 or placebo in 100 mL of 0.9% saline was administered via IV infusion over a period of 30 minutes.

PK measurement

A competitive ELISA method was used for bioanalytical analyses of serum secukinumab with a LLOQ of 80 ng/mL.

5.5. Results

PK results

The mean (\pm SD) C_{max} was of 237 \pm 36.7 mcg/mL and median for the T_{max} value was 0.083 day (Data source: CSR, Table 11-2, Page 42).

Because of the short duration for PK sampling, no other major PK parameters could be derived from this trial.

6. STUDY CAIN457A2211

6.1. Title

- A randomized, double-blind, placebo controlled, multicenter regimen finding study of subcutaneously administered AIN457, assessing Psoriasis Area and Severity Index (PASI) response in patients with moderate to severe chronic plaque-type psoriasis

6.2. Study period

- 28 July 2009 (the first subject enrolled) to 16 December 2010 (the last subject enrolled)

6.3. Primary objectives

- To evaluate the efficacy of three induction regimens of secukinumab (AIN457) administered subcutaneously in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 achievement after 12 weeks of treatment, compared to placebo.

6.4. Study design and methods

Study CAIN4572211 was a parallel-group, randomized, double-blind study. The study consisted of 4 periods: the screening period, the induction period, the maintenance period, and the follow-up period. Eligible patients were randomized (1:2:2:1) ratio at baseline into one of the four induction treatment arms and stratified according to bodyweight (<90 kg or ≥90 kg):

- Induction with single injection arm (“Single”): secukinumab 150 mg SC administered at Week 1
- Induction with monthly injections (“Monthly”): secukinumab 150 mg SC administered at Weeks 1, 5, and 9
- Early loading induction (“Early”): secukinumab 150 mg SC administered at Weeks 1, 2, 3, and 5
- Placebo

At Week 13, patients were classified as responders (achieving at least PASI 75), partial responders (achieving PASI 50, but not PASI 75) or non-responders (not achieving PASI 50). Responders at Week 13 were further randomized to one of the following maintenance treatment arms in a ratio of 1:1:

- Fixed-time interval regimen (“FI”): secukinumab (AIN457) 150 mg SC administered at Week 13 and at Week 25 and placebo at regular scheduled visit at which a start of relapse was observed
- Treatment at start of relapse regimen (“SR”): Placebo administered at Week 13 and at Week 25 (if no start of relapse observed), and secukinumab (AIN457) 150 mg SC administered at regular scheduled visit at which a start of relapse was observed

Responders on placebo regimen remained on the placebo arm and received placebo at Week 13 and at Week 25 and placebo at regular scheduled visit at which a start of relapse was observed.

Non responders and partial responders at Week 13 and patients who experienced 2 consecutive relapses at scheduled visits from Week 13 onwards were eligible to enter the Open Label treatment of secukinumab 150 mg SC administered every 4 weeks.

Study products

AIN457 150 mg lyophilized powder for solution (batch #: Y002 0109) was used in the study.

PK measurement

Blood samples for PK assessments were collected at Days 1, 8, 15, 29, 57, 85, 113, 141, 169, 197 and 225. A competitive ELISA method was used for bioanalytical analyses of serum AIN457.

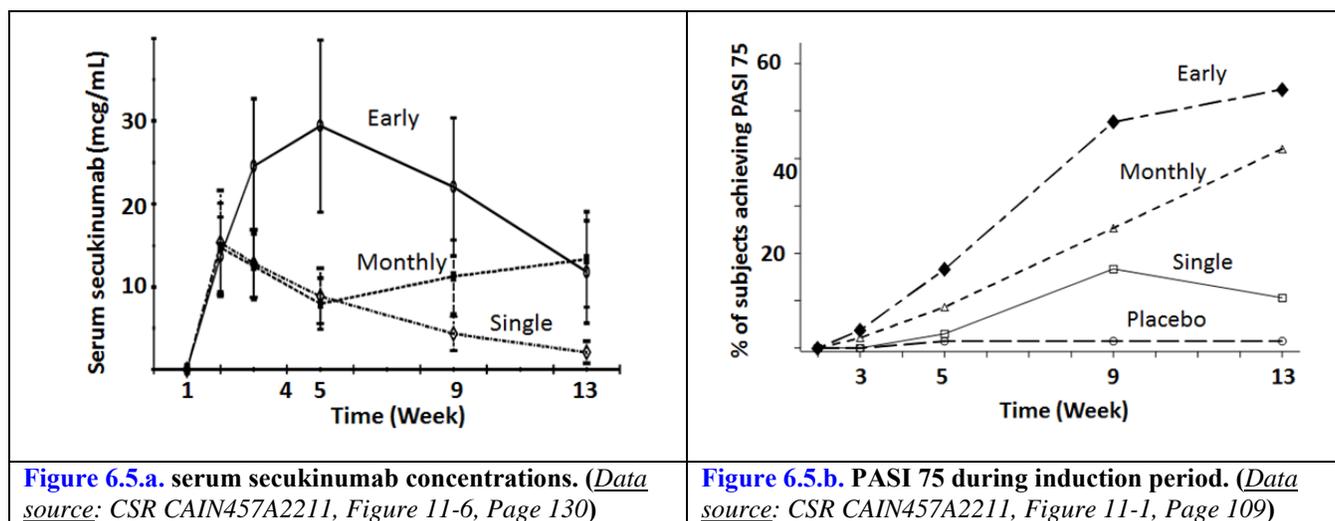
Immunogenicity

Immunogenicity samples were collected at Week 1, 13, 25 during the treatment period and at F4 (4 weeks in follow up period) and F12 (study completion). Anti-drug antibodies were assessed in serum by the electrochemiluminescence MSD assay.

6.5. Results

PK results

Profiles of mean secukinumab serum concentrations during induction treatment period are shown in [Figure 6.5.a](#). The Single induction regimen resulted in mean serum secukinumab concentrations 2.1 mcg/mL at Week 13. Following the Monthly and Early induction regimen, predose trough concentration were 13.3 mcg/mL and 11.8 mcg/mL, respectively, at Week 13.



Induction efficacy results

At Week 13, PASI 75 response rate was 10.6% (n=66) in the Single arm, 42.0% (n=138) in the Monthly arm, 54.5% (n=133) in the Early arm, and 1.5% (n=67) in the Placebo arm ([Figure 6.5.b](#)). (Data source: CSR CAIN457A2211, Table 11-5, Page 108).

Maintenance efficacy results

For the responders who continued into the maintenance period, a higher proportion of patients in the Fixed Interval secukinumab treatment arm (84.6%, n=65) maintained the high PASI 75 achievement at least once from Week 21 to Week 29 compared to 67.2% (n=67) patients in the in the Start of Relapse ([Data source: CSR, Table 11-7, Page 111](#)). See section 2.3 of the QBR for more details of the efficacy results.

Immunogenicity results

No ADA positive subjects were detected in the study.

7. STUDY CAIN457A2220

7.1. Title

- A randomized, double-blind, placebo controlled, multicenter dose ranging study of subcutaneously administered secukinumab (AIN457), assessing Psoriasis Area and Severity Index (PASI) response in patients with moderate to severe chronic plaque-type psoriasis

7.2. Study period

- 01 March 2010 (the first subject enrolled) to 14 February 2011 (the last subject completed)

7.3. Primary objectives

- The primary objective was to assess the efficacy of 3 different doses of secukinumab SC administered monthly (25 mg, 75 mg and 150 mg) or as single administration of 25 mg on PASI 75 achievement 12 weeks after start of treatment, compared to placebo in patients with moderate to severe chronic plaque-type psoriasis.

7.4. Study design and methods

Study CAIN4572220 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients with moderate to severe chronic plaque-type psoriasis. The study consisted of 3 periods: screening, treatment and follow up. Randomization was stratified according to bodyweight (< 90 kg or ≥ 90 kg). Eligible patients were randomized in a ratio of 1:1:1:1:1 to either placebo or one of 4 different regimens of secukinumab (monthly dosing of 25 mg, 75 mg or 150 mg, or a single dose of 25 mg) as below:

- Secukinumab 3×150 mg: 150 mg SC at Weeks 1, 5, and 9 (n=27)
- Secukinumab 3×75 mg: 75 mg SC at Weeks 1, 5, and 9 (n=21)
- Secukinumab 3×25 mg: 25 mg SC at Weeks 1, 5, and 9 (n=26)
- Secukinumab 1×25 mg: 25 mg SC at Week 1 (n=29)
- Placebo (n=22)

The primary efficacy endpoint was PASI 75 response at Week 13 (12 weeks after start of treatment).

Study products

AIN457 150 mg lyophilized powder for solution (batch #: Y127 0609) was used in the study.

PK measurement

Blood samples for PK assessments were collected at Weeks 1, 2, 3, 5, 9, 13, 17, 21, 25, 29, 33, and 37. A competitive ELISA method was used for bioanalytical analyses of secukinumab in serum and the LLOQ was 80 ng/mL.

Immunogenicity

Immunogenicity samples were collected at Week 1, 13, 25, and 37.

Anti-drug antibodies were assessed in serum by BIAcore assay.

7.5. Results

PK results

Mean secukinumab serum concentration time profiles are shown in [Figure 7.5.a](#) by treatment cohorts. Sponsor's analysis showed that the elimination half-life was in the range of 32 to 40 days across the four secukinumab treatment cohorts.

Primary efficacy results

The primary efficacy endpoint is the achievement of PASI 75 response at Week 13 (12 weeks after treatment). A dose-dependent increase in PASI 75 response rate was observed. The proportions of subjects achieving PASI 75 response at Week 13 were 81.5% (n=27), 57.1% (n=21), 19.2% (n=26), 3.4% (n=29), and 9.1% (n=22) for secukinumab 3×150 mg, secukinumab 3×75 mg, secukinumab 3×25 mg, secukinumab 1×25 mg, and placebo, respectively. The time-course of the PASI 75 response rate during the treatment and post the treatment is shown in [Figure 7.5.b](#) by treatment cohorts.

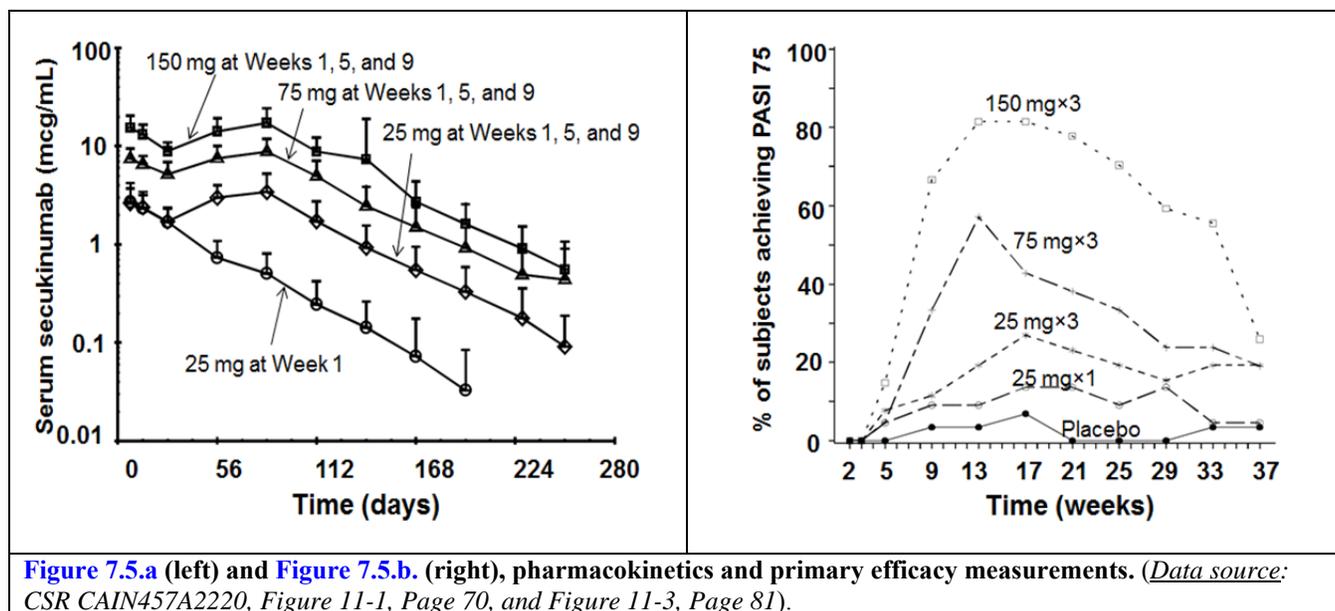


Figure 7.5.a (left) and Figure 7.5.b. (right), pharmacokinetics and primary efficacy measurements. (Data source: CSR CAIN457A2220, Figure 11-1, Page 70, and Figure 11-3, Page 81).

Immunogenicity results

None of the subjects showed positive anti-drug antibodies.

8. STUDY CAIN457A2212

8.1. Title

- Phase II randomized, double-blind, multi-center, parallel-group, placebo-controlled multiple-loading dose regimen study to assess the safety, efficacy and duration of response of AIN457 in patients with chronic plaque-type psoriasis

8.2. Study period

- 10 December 2008 (the first subject enrolled) to 09 September 2010 (the last subjects completed)

8.3. Primary objectives

- To compare the change from baseline in Psoriasis Area and Severity Index (PASI) scores at 12 weeks between the placebo and each of the loading-dose regimens of secukinumab.
- To compare the proportion of patients who have not relapsed at any time up to and including week 56 between each of the loading-dose regimens of secukinumab.

8.4. Study design and methods

Study CAIN457A2212 was a double-blind, parallel-group, placebo-controlled study. The study consisted of 4 periods: a screening period of up to 28 days, a baseline period of 1 to 3 days, a treatment period of up to 29 days, and a follow-up period of up to 56 weeks after the first dose.

Eligible subjects were randomized to 1 of 4 treatment groups:

- Secukinumab 1 × 3 mg/kg: 3mg/kg on Day 1; Placebo on Day 15 and Day 29 (30 patients)
- Secukinumab 1 × 10 mg/kg: 10mg/kg on Day 1; Placebo on Day 15 and Day 29 (30 patients)
- Secukinumab 3 × 10 mg/kg: 10mg/kg on Day 1, Day 15 and Day 29 (30 patients)
- Placebo: Placebo on Day 1, Day 15 and Day 29 (10 patients)

Study products

AIN457 150 mg lyophilized powder for solution (batch #: Y0030108) was used in the study.

PK measurement

Blood samples for PK analyses were collected at baseline, at 2 and 4 hours after the initiation of the intravenous infusions on Day 1, Week 2 (day 15) and Week 4 (day 29), and other scheduled visits till Week 56 or end of study.

A competitive ELISA method was used for bioanalytical analyses of serum secukinumab and the LLOQ was 80 ng/mL.

Peripheral T cell subpopulations

Peripheral T cell subpopulations were assessed by fluorescence-activated cell sorting (FACS). The assays were performed using flow cytometry analysis of cells labeled with fluorescently labeled antibodies. Blood samples were collected at screening, Day 1, Weeks 2, 4, 12, 28 and 56 (end of study).

Immunogenicity

Immunogenicity samples were collected at Week 1, 12, 28, and 56.

Anti-secukinumab antibodies were assessed in serum by BIAcore assay.

8.5. Results

PK results

The mean clearance values were similar across the three dose levels or regimens and were in the range between 0.18 and 0.21 L/day. The mean elimination half-lives ranged between 29.5 and 30.7 days.

The PK parameters and concentration-time profiles of secukinumab are shown in [Figure 8.5.a](#).

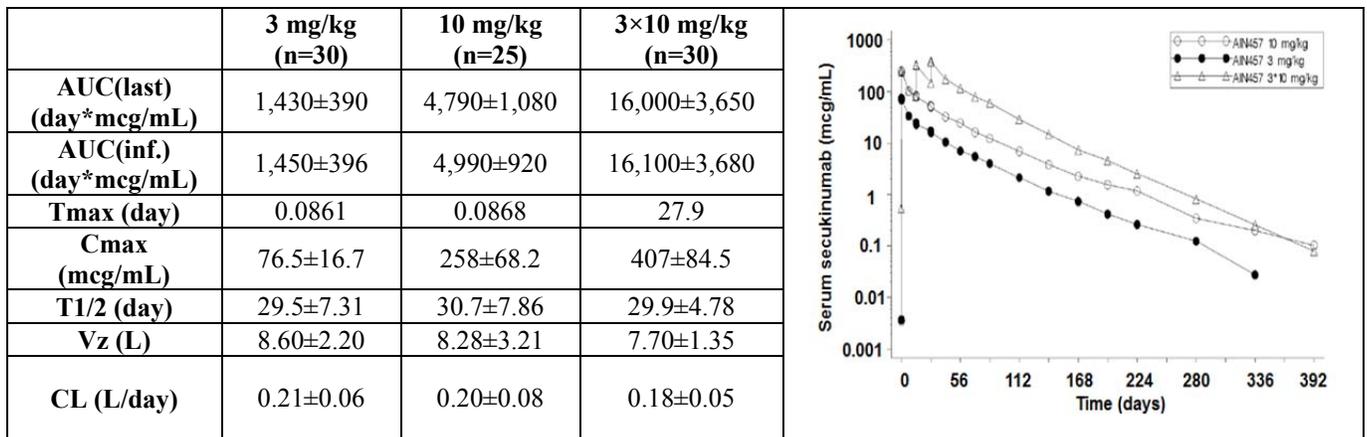


Figure 8.5.a. PK parameters and concentration-time profiles of secukinumab in study CAIN457A2212. (Data source: CSR, Figure 11-4, Page 90 and Table 11-7, Page 91)

Peripheral T cell subpopulations

Overall, secukinumab treatment did not induce major effects on the balance of peripheral cytotoxic T cell and T helper cell populations. Figure 8.5.b and Figure 8.5.c. show the kinetics of the CD3+CD8+ fraction and CD4+ T cell fraction in peripheral blood, following three different dose regimens of secukinumab or placebo in patients with psoriasis, respectively.

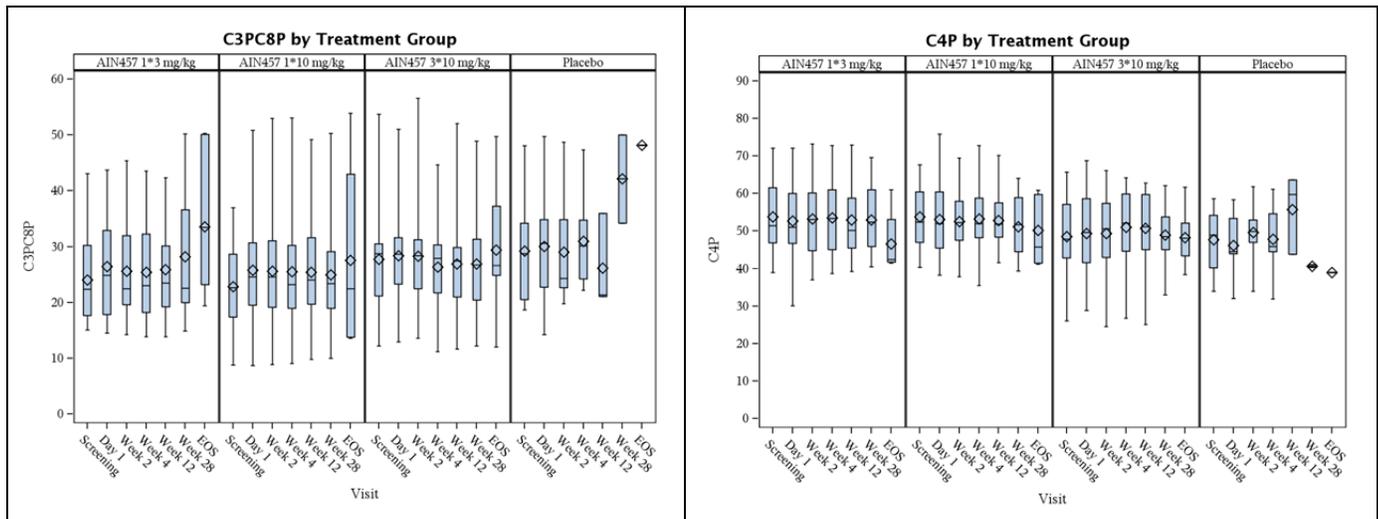


Figure 8.5.b. Kinetics of the CD3+CD8+ T cell fraction in peripheral blood in patients with psoriasis. C3PC8P = CD3+CD8+ T cells; EOS = end of study visit. Y-axis: numbers indicate percent of total peripheral T cell compartment. Bars indicate confidence intervals. Screening and Day 1 are pretreatment time points. (Data source: BMD RAIN457A2212, Figure 9-28, Page 432)

Figure 8.5.c. Kinetics of the CD4+ T cell fraction in peripheral blood in patients with psoriasis. C4P = CD4+ (T helper) cells; EOS = end of study visit. Y-axis: numbers indicate percent of total peripheral T cell compartment. Bars indicate confidence intervals. Screening and Day 1 are pretreatment time points. (Data source: BMD RAIN457A2212, Figure 9-35, Page 439)

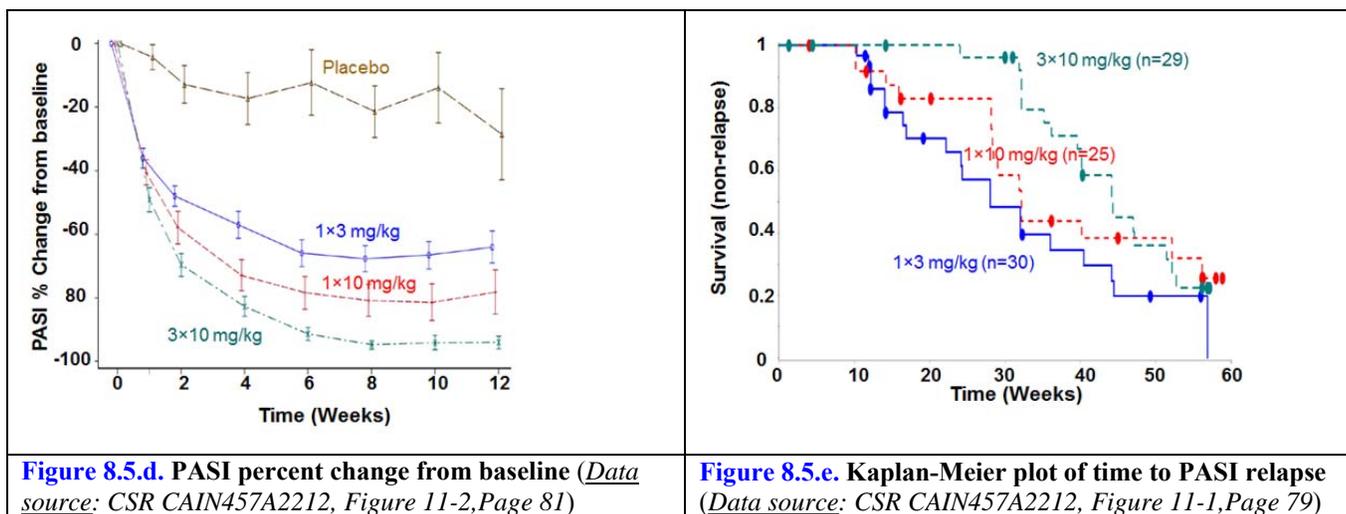
Efficacy results - PASI at Week 12

Mean baseline PASI scores were similar across treatment groups with 20.99, 19.00, 17.65, and 18.93 for the placebo, 1 × 3mg/kg, 1 × 10 mg/kg, 3 × 10 mg/kg treatment groups, respectively. The mean change from baseline at Week 12 was -4.18, -12.46, -13.35, -18.02 for the placebo group (n=5), 1 × 3 mg/kg

(n=27, p=0.02), 1 × 10 mg/kg (n=23, p=0.008), and 3 × 10 mg/kg (n=27, p=0.001) treatment groups, respectively (*Data source: CSR CAIN457A2212, Table 11-3, Page 77*). **Figure 8.5.d** shows the percent change from baseline in PASI scores over time by treatment group. See *section 2.3* of the QBR for more details of the efficacy results.

Efficacy results – relapse

Relapse was defined as an increase in PASI of at least 50% of the maximum PASI improvement. **Figure 8.5.e** shows the Kaplan-Meier analysis for time to PASI relapse. In this analysis, patients who withdrew early were considered to have relapsed, regardless of last PASI score recorded. Between 0 and 10 weeks, the risk of relapse was low in all 3 secukinumab treatment groups. After Week 10, the risk of relapse increased substantially for the 1 × 3 mg/kg and 1 × 10 mg/kg treatments whereas for the 3 × 10 mg/kg group, the risk of relapse remained ≤10% through week 30.



Immunogenicity results:

None of the subjects showed positive anti-drug antibodies.

9. STUDY CAIN457A2102

9.1. Title

- Phase IIa single-dose, randomized, double-blind, multi-center, parallel-group, placebo-controlled proof of concept study to assess the efficacy, safety, tolerability, and population pharmacokinetics of AIN457 in patients with stable plaque-type psoriasis

9.2. Study period

- 20 February 2007 (the first patient enrolled) to 07 November 2007 (the last patient enrolled)

9.3. Objectives

- The primary objective was to evaluate the preliminary efficacy of AIN457 when administered as a single dose infusion to patients with stable plaque psoriasis.
- Exploratory pharmacodynamics and exploratory biomarkers were also assessed.

9.4. Study design and methods

This was a multicenter, double-blind, randomized, two-arm, parallel group, placebo-controlled, proof-of-concept study comparing a single 3 mg/kg IV infusion of secukinumab to placebo in patients with moderate to severe plaque psoriasis.

A total of 36 subjects were enrolled in the study with 18 subjects each assigned to the secukinumab and placebo treatment groups.

Study products

Secukinumab (██████████^{(b) (4)} drug substance) was supplied as a powder for solution for infusion in 6-mL glass vials. Each vial contained 60 mg secukinumab in a lyophilized cake. The batch number was Y145 1204.

PK/PD measurement

Blood samples for measurement of serum secukinumab concentrations and total IL-17 levels were collected at baseline, end of infusion, 1 hr and 2 hr after infusion, and at Weeks 1, 2, 3, 4, 5, 6, 8, 12/End of Study, Follow-up Weeks 16, 20 and 26.

A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL. The limit of quantification (LOQ) for the total IL-17 assay was 15.2 pg/ml.

Immunohistological and biomarker assessments

Histology and biomarkers as measured by mRNA expression in skin biopsies were evaluated at Baseline, Week 4, and Week 12. Change in epidermal thickness was assessed. The mRNA expression analysis was only performed if clinical and/or histological response had been demonstrated.

Immunogenicity

Immunogenicity samples were collected at baseline, Week 12 and Week 26.

Anti-secukinumab antibodies were assessed in serum by the BIAcore assay.

9.5. Results

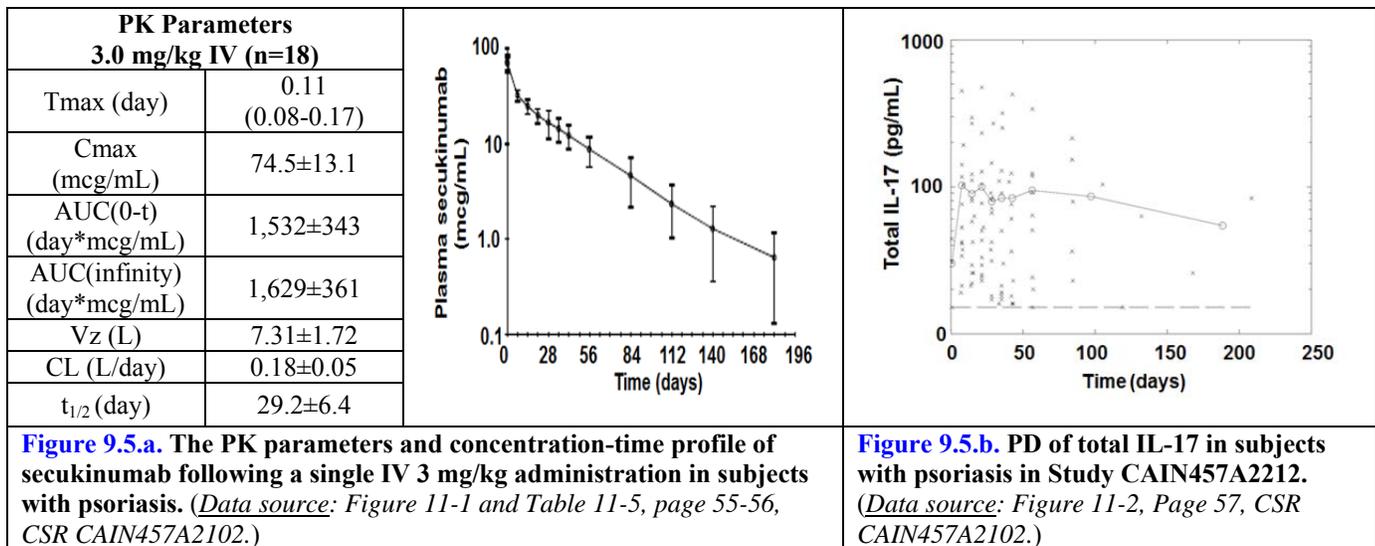
Pharmacokinetics

The PK parameters following a single IV dose (3 mg/kg) administration are summarized in [Figure 9.5.a](#). The PK results showed mean clearance value of 0.18 L/day, apparent volume of distribution of 7.31 L, and elimination half-life of approximately 4 weeks.

Pharmacodynamics

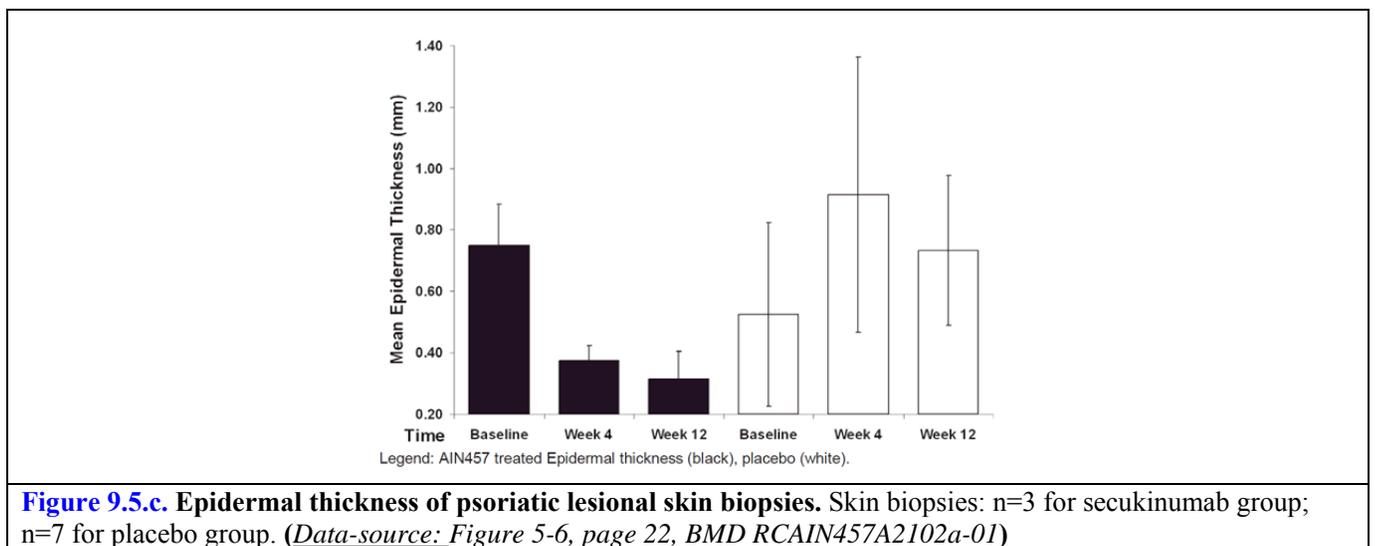
- IL-17A

Baseline IL-17A measurements were below LOQ for all subjects. The total IL-17A level following the secukinumab treatment showed an initial increase then declined slowly after 10-20 days with most measurements below LOQ after Day 50. Following the secukinumab treatment, total IL-17A values were below LOQ for four subjects (5302, 5601, 5704, and 5901) whereas the IL-17A levels in subjects treated with placebo were all below LOQ. The average and individual total IL-17A levels for the secukinumab treatment group are shown in [Figure 9.5.b](#). For the average total IL-17A calculation the LOQ data were not included.



- Histology

The immunohistochemistry results showed that secukinumab significantly decreased the epidermal thickness in psoriatic lesional skin (Figure 9.5.c).



- Biomarkers

Reductions of mRNA levels of IL-17A and other proinflammatory cytokines in lesional skin were observed at Week 4 following a single IV dose of secukinumab at 3 mg/kg (Figure, 9.5.d). The selected molecules were based on their relevance to the IL-17A pathway, as following:

- Molecules derived from IL-17A producing cells: IL-12B, IL-17A, IL-17F, IL-21, IL-22, and IL-26;
- Molecules derived from IL-17A responsive cells: KRT16 and DEFB4;
- Molecules that facilitate Th17 cell generation and recruitment: CCL20;
- Other inflammatory cytokine: IFN γ and TNF.

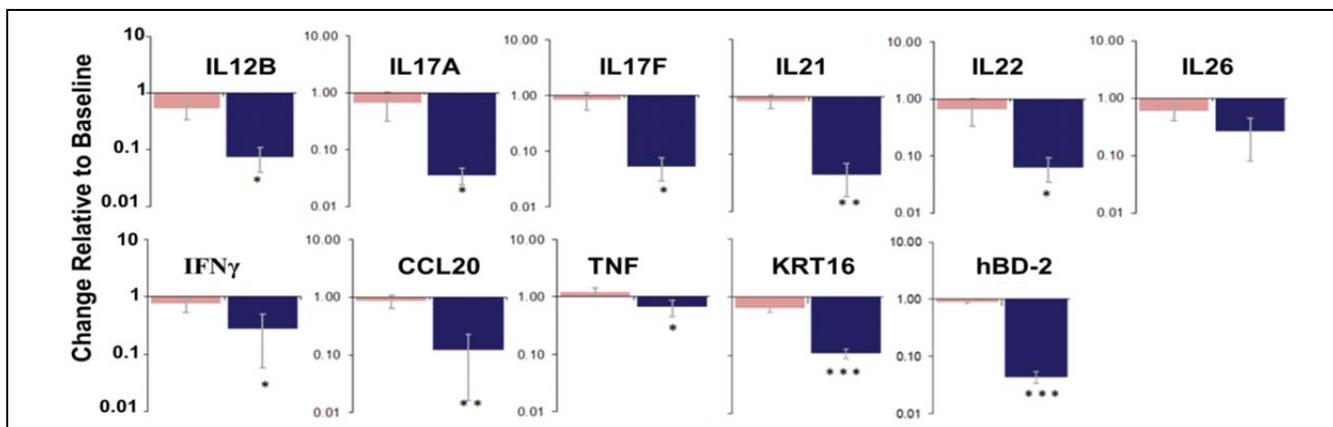


Figure 9.5.d. Pharmacodynamics of mRNA expression at Week 4 relative to baseline following a single IV dose of secukinumab 3 mg/kg. Real-time RT-PCR mRNA analysis showing mean fold of change (\pm SE) relative to baseline. Blue bars, secukinumab (n=3); Pink bars, placebo (n=5); *p<0.05; **p<0.01; ***p<0.001; (Data source: Figure 3-13, Summary of clinical Pharmacology; Figure 5-10, page 25, BMD RAIN457A2102a-01;)

Efficacy

The mean PASI score in the secukinumab treatment group was 49% (Week 2), 58% (Week 4), 64% (Week 8), and 63% (Week 12) lower than the baseline value, comparing to the corresponding reduction of 6%, 4%, 6%, and 9% in the placebo group. In the secukinumab treatment group, 72% of treated patients were PASI 50 responders, 44% PASI 75 responders and 11% PASI 95 responders at Week 12.

Immunogenicity

None of the subjects showed positive anti-drug antibodies.

10. STUDY CAIN457A2204

10.1. Title

- Phase II single dose, randomized, double-blind, multi-center, parallel-group, placebo-controlled study to assess the efficacy of three dose levels of AIN457 in patients with chronic plaque type psoriasis

10.2. Study period

- 10 September 2008 (the first subject enrolled) to 17 September 2009 (the last subject completed)

10.3. Primary objectives

- To evaluate the difference in the change from baseline in PASI at 4 weeks between placebo and each of the three active treatment arms

10.4. Study design and methods

This was a single dose, randomized, double-blind, multi-center, parallel-group, placebo-controlled study to assess the efficacy of IV secukinumab in subjects with chronic plaque-type psoriasis. Eighty patients were assigned to one of the following 4 treatment arms in a ratio of 1:1:1:1:

- Secukinumab IV 0.3 mg/kg

- Secukinumab IV 1.0 mg/kg
- Secukinumab IV 3.0 mg/kg
- Placebo.

Reviewer’s notes: Due to issues identified by the audit of center 0001, 65 subjects enrolled in this center were excluded from the efficacy/safety data analysis. Therefore, the PK and immunogenicity data are summarized below with and without subjects from center 0001.

Study products

Secukinumab was supplied as a powder for solution for infusion in 6-mL glass vials. Each vial contained 50 mg secukinumab in a lyophilized cake. The batch number was Y0170208-7005405.005.

PK measurement

Blood samples for PK analyses were collected at baseline, Day 1 (2 hr, 3 hr, and 4 hr), Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, and 32 after infusion. A competitive ELISA method was used for bioanalytical analyses of serum secukinumab and the LLOQ was 80 ng/mL.

Immunogenicity

Immunogenicity samples were collected at baseline, Weeks 12 and 32 (end of study).

Anti-secukinumab antibodies were assessed in serum by the BIAcore assay.

10.5. Results

Pharmacokinetics

Secukinumab PK parameters derived from subjects enrolled in Center 0001 and the other centers were summarized in [Table 10.5](#). Across dose levels the PK results showed that secukinumab clearance ranged between 0.14 and 0.21 L/day and the mean elimination half-life ranged between 25.7 and 32.3 days.

Table 10.5. Secukinumab PK parameters in Study CAIN457A2204. (Data source: CSR CAIN457A2204, Table 11-3 and Table 11-4, Page 69)

	Center 0001 analysis set			PK analysis set excluding center 0001		
	0.3 mg/kg (n=16-17)	1 mg/kg (n=15-16)	3 mg/kg (n=15)	0.3 mg/kg (n=2)	1 mg/kg (n=4)	3 mg/kg (n=4)
AUC_{inf} (day*mcg/mL)	213.6±86.78	502.9±162.02	1,511±420.39	157.7±95.15	705.6±248.2	1,843±228.53
AUC_{last} (day*mcg/mL)	197.5±52.92	488.8±152.38	1,470±381.07	153.0±92.64	691.6±234.7	1,765±304.86
C_{max} (mcg/mL)	9.51±1.90	26.35±6.19	79.49±18.92	8.23±2.11	39.15±11.01	87.45±17.52
T_{max} (day)	0.083	0.083	0.125	0.11	0.14	0.11
t_{1/2} (day)	30.70±8.41	26.72±5.79	27.11±7.00	25.66±4.21	32.35±12.88	31.55±4.98
CL (L/day)	0.139±0.05	0.215±0.10	0.186±0.05	0.160±0.0045	0.140±0.072	0.184±0.059
V_z (L)	5.78±1.83	7.84±2.84	6.87±1.43	5.94±1.14	5.56±0.92	8.08±1.32

Immunogenicity

None of the subjects showed positive anti-drug antibodies.

11. STUDY CAIN457A2302

11.1. Title

- A randomized, double-blind, placebo-controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis

11.2. Study period

- 09 June 2011 (the first patient first visit) to 07 March 2013 (last patient last visit for Week 52, study ongoing)

11.3. Objectives

- The primary objective was to demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (IGA 0/1) co-primary endpoints) at Week 12, compared to placebo.

The key secondary objectives included the following:

- To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 90 response at Week 12, as compared to placebo.
- To assess the efficacy of secukinumab in maintaining PASI 75 response at Week 52 for patients who were PASI 75 responders at Week 12.
- To assess the efficacy of secukinumab in maintaining IGA 0/1 response at Week 52 for patients who were IGA 0/1 responders at Week 12.
- To demonstrate the superiority of secukinumab in patients with moderate to severe chronic plaque-type psoriasis with respect to psoriasis-related itching, pain and scaling as measured by the Psoriasis Symptom Diary at Week 12 compared to placebo.

11.4. Study design and methods

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in subjects with moderate to severe chronic plaque-type psoriasis. The study consisted of 4 periods:

- Screening (1-4 weeks),
- Induction (12 weeks),
- Maintenance (40 weeks),
- Follow-up (8 weeks).

Randomization was stratified by geographical region and by body weight at Screening (< 90 kg or ≥90 kg). Patients were randomized using a 1:1:1 ratio into one of the treatment groups below:

- **Secukinumab 150 mg:** secukinumab 150 mg (one SC injection of the 150 mg dose + one SC injection of placebo) administered at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo (two SC injections per dose) administered at Weeks 13, 14 and 15.
- **Secukinumab 300 mg group:** secukinumab 300 mg (two SC injections of the 150 mg dose) administered at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and placebo (two SC injections per dose) administered at Weeks 13, 14, and 15.

- **Placebo group:** SC placebo secukinumab (two SC injections per dose) administered at Randomization, Weeks 1, 2, 3, 4, and 8. All patients in the placebo group were assigned to the following treatment groups based on their PASI 75 response status at Week 12. This re-randomization was also stratified by geographical region and by body weight measured at the randomization (< 90 kg or ≥90 kg).
 - **Placebo PASI 75 non-responder** induction period / **secukinumab 150 mg** maintenance period: secukinumab 150 mg (one SC injection of the 150 mg dose + one SC injection of placebo) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
 - **Placebo PASI 75 non-responder** induction period / **secukinumab 300 mg** maintenance period: secukinumab 300 mg (two SC injections of the 150 mg dose) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
 - **Placebo PASI 75 Responder** induction period / **placebo** maintenance period: SC placebo secukinumab (two SC injections per dose) administered at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44 and 48.

Primary efficacy measurement

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA 0/1 response at Week 12.

Study products

AIN457 150 mg lyophilized powder for solution (batch #: S0005, S0011, S0012) was used in the study.

PK measurement

Blood PK samples were collected at baseline, and at Weeks 4, 12, 24, and 52 (4 weeks after the last dose). A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

Demographic and background characteristics:

A total of 738 patients were randomized. The mean age of all patients was 45 years, the mean body weight was 88.6 kg, and the mean BMI was 30.1 kg/m². Approximately 70% subjects were male and Caucasian. All patients had moderate to severe psoriasis, as measured by IGA and PASI criteria. Baseline mean PASI score was 22.1 and 45.3% had a baseline PASI score > 20. The mean total BSA (body surface area) affected was 31.9%.

11.5. Results

Pharmacokinetics

The mean (± SD) serum secukinumab trough concentrations by treatment groups are summarized in [Table 11.5.a](#).

Table 11.5.a. Serum secukinumab trough concentrations by treatment and visits. (Data source: CSR CAIN457A2302, Table 11-18, page 145)

Visits	Secukinumab trough concentrations (mcg/mL)			
	n	Secukinumab 150 mg	n	Secukinumab 300 mg
Baseline	244	0.004±0.021	238	0.246±2.97
Week 4	231	44.9±14.6	226	87.2±30.1
Week 12	216	22.8±10.2	219	44.8±20.6
Week 24	206	17.7±9.43	211	34.4±16.6
Week 52	171	16.7±8.19	177	32.7±14.4

By the end of the induction period at Week 12, the mean (\pm SD) trough secukinumab concentrations were 22.8 \pm 10.2 mcg/mL and 44.8 \pm 20.6 mcg/mL in the 150 mg and 300 mg treatment groups, respectively. During the maintenance treatment period, concentrations reached steady state levels of 16.7-17.7 mcg/mL and 32.7-34.4 mcg/mL in the 150 mg and 300 mg treatment groups, respectively. In general, mean concentrations in the 300 mg group were about 2-fold of these in the 150 mg group, indicating dose-proportional exposure across the two dose levels.

Efficacy

The primary efficacy results are summarized in [Table 11.5.b](#). Secukinumab demonstrated superior efficacy compared to placebo with respect to PASI 75 and IGA 0/1 response rates at Week 12.

Table 11.5.b. Primary efficacy results at Week 12 in Study CAIN457A2302. n=number of patients with response; m=number of patients evaluable. (*Data source: CSR CAIN457A2302, Table 11-7, page 125*)

Endpoint	Treatment comparison (“test” vs “control”)	“test” n/m (%)	“control” n/m (%)	Odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 150 mg vs placebo	125/244 (51.2%)	6/246 (2.4%)	44.18 (18.21, 107.18)	<0.0001
	AIN457 300 mg vs placebo	160/245 (65.3%)	6/246 (2.4%)	70.46 (28.75, 172.70)	<0.0001
PASI 75	AIN457 150 mg vs placebo	174/243 (71.6%)	11/246 (4.5%)	57.64 (28.43, 116.86)	<0.0001
	AIN457 300 mg vs placebo	200/245 (81.6%)	11/246 (4.5%)	82.69 (38.70, 176.71)	<0.0001

At Week 12, PASI 75 response rates were 81.6% in subjects treated with 300 mg secukinumab, 71.6% in subjects treated with 150 mg secukinumab, and 4.5% in subjects treated with placebo. The IGA 0/1 response rate were 65.3%, 51.2% and 2.4% for 300 mg secukinumab, 150 mg secukinumab and placebo treatment groups, respectively.

Comparison of the two secukinumab treatment groups showed that the response rates were approximately 10% higher for PASI 75 and 14% higher for IGA 0/1 in the 300 mg treatment group relative to the 150 mg treatment group. The sponsor’s statistically analysis showed that the p-values for the differences between the 300 mg treatment group and 150 mg treatment group were 0.0080 for PASI 75 and 0.0016 for IGA 0/1, which supported a better efficacy outcome associated with the higher dose.

At Week 12, PASI 90 response was achieved in 59.2% of subjects treated with 300 mg secukinumab, 39.1% of subjects treated with 150 mg secukinumab, and 1.2% of subjects treated with placebo. The PASI 90 response rate at Week 12 was 20% higher in the 300 mg treatment group compared to the 150 mg treatment group (*Data source: CSR CAIN457A2302, Table 11-12, Page 130*).

Subgroup analysis by body weight (<90 kg and \geq 90 kg) showed that the body weight had an effect on the efficacy of secukinumab ([Table 11.5.c](#)). In the same body weight subgroup, the efficacy results for PASI 75, PASI 90 and IGA 0/1 at Week 12 in the secukinumab 300 mg treatment group was associated with numerically higher response rates compared to the secukinumab 150 mg treatment group. At the same dose level, subjects <90 kg showed numerically higher response rates compared to subjects \geq 90 kg. The data also showed that subjects <90 kg received 150 mg dose achieved a similar response rate as subjects \geq 90 kg received 300 mg dose.

Table 11.5.c. Subgroup analysis by bodyweight (<90 kg and ≥90 kg) for PASI 75, PASI 90 and IGA 0/1 at Week 12. n=number of patients with response; m=number of patients evaluable. (*Data source: CSR CAIN457A2302, Table 11-8, Page 127*)

Endpoints	<90 kg			≥90 kg		
	150 mg n/m (%)	300 mg n/m (%)	Placebo n/m (%)	150 mg n/m (%)	300 mg n/m (%)	Placebo n/m (%)
IGA 0/1	75/141 (53.2%)	103/142 (72.5%)	3/142 (2.1%)	50/103 (48.5%)	57/103 (55.3%)	3/104 (2.9%)
PASI 75	104/140 (74.3%)	126/142 (88.7%)	6/142 (4.2%)	70/103 (68.0%)	74/103 (71.8%)	5/104 (4.8%)
PASI 90	63/140 (45.0%)	99/142 (69.7%)	2/142 (1.4%)	32/103 (31.1%)	46/103 (44.7%)	1/104 (1.0%)

Maintenance of PASI 75 and IGA 0/1 responses at Week 52

The Week 52 efficacy results showed that patients treated with 300 mg secukinumab were more likely to sustain PASI 75 and IGA responses than those treated with 150 mg secukinumab.

For subjects who achieved PASI 75 at Week 12, 80.5% (n=200) in the 300 mg maintenance treatment group and 72.4% (n=174) in the 150 mg treatment group maintained the response at Week 52 (*Data source: CSR CAIN457A2302, Table 11-14, Page 133*). The subgroup analysis showed that the cumulative rate of loss of PASI 75 response up to 52 weeks of treatment was higher in patients weighing ≥90 kg (31.0% with 150 mg and 21.2% with 300 mg) than in patients weighing <90 kg (25.3% with 150 mg and 10.1% with 300 mg).

For subjects who achieved IGA 0/1 at Week 12, 74.4% (n=119) in the 300 mg maintenance treatment group and 59.2% (n=74) in the 150 mg treatment group maintained the response at Week 52 (*Data source: CSR CAIN457A2302, Table 11-15, Page 135*). The subgroup analysis showed that the effect of body weight on the cumulative probability of loss of IGA 0/1 response at 52 weeks of treatment was observed only in heavier patients treated with the higher secukinumab dose. Among those treated with 300 mg, patients weighing <90 kg had a 17.4% probability of losing IGA 0/1 response at 52 weeks, whereas patients weighing ≥90 kg had a 48.8% probability of losing this response. The cumulative rate of loss at 52 weeks was similar in the two weight subgroups treated with secukinumab 150 mg (40.7% for <90 kg subgroup vs. 42.4% for ≥90 kg subgroup).

Relapse

Relapse was defined as a 50% reduction of the maximal PASI improvement. The cumulative probability of relapse at >36 to ≤40 weeks of treatment was lower with the higher secukinumab dose: 2.1% with 300 mg in comparison to 6.8% with 150 mg (*Data source: CSR CAIN457A2302, Table 14.2-8.2, Page 1137*).

Rebound

Rebound (defined as increase in PASI to > 125% of baseline PASI within 8 weeks of last dose of study treatment) was more frequently reported in the placebo group (2/15 or 13.3%) than in either secukinumab dose group (4/50 or 8.0% for 150 mg and 2/44 or 4.5% for 300 mg) (*Data source: CSR CAIN457A2302, Table 14.2-8.4, Page 1139*). The rebound data should be interpreted with caution because at time of this CSR not all patient data were available and the assessments of rebound were based on a small, biased sample of discontinued patients.

12. STUDY CAIN457A2303

12.1. Title

- A randomized, double-blind, double-dummy, placebo controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, compared to placebo and etanercept, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis.
 - FIXTURE (Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis)

12.2. Study period

- 14 June 2011 to 07 July 2013 (study ongoing)

12.3. Objectives

- The primary objective of this study was to demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to both Psoriasis area and severity index (PASI) 75 and Investigator's global assessment modified 2011 (IGA mod 2011) 0 or 1 (IGA 0/1) response (co-primary endpoints) at Week 12, compared to placebo.
- The key secondary objectives of this study included the following:
 - The superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 90 response at Week 12, compared to placebo.
 - The non-inferiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 response at Week 12, compared to etanercept.
 - The superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 response and IGA mod 2011 0 or 1 response at Week 12, compared to etanercept.
 - The superiority of secukinumab in maintaining PASI 75 response at Week 52 for subjects who were PASI 75 responders at Week 12, compared to etanercept.
 - The superiority of secukinumab in maintaining IGA mod 2011 0 or 1 response at Week 52 for subjects who were IGA mod 2011 0 or 1 responders at Week 12, compared to etanercept.
 - Superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to psoriasis-related itching, pain and scaling as measured by the Psoriasis Diary at Week 12, compared to placebo.

Reviewer's note: *Clinical results regarding the comparison between secukinumab and etanercept are not assessed in this Clinical Pharmacology review.*

12.4. Study design and methods

This was a multicenter, randomized, double-dummy, double-blind, active and placebo-controlled, parallel-group trial in subjects with moderate to severe chronic plaque-type psoriasis. The study consisted of 4 periods: Screening (1-4 weeks), Induction (12 weeks), Maintenance (40 weeks), and Follow-up (8 weeks).

Randomization was stratified by geographical region and by body weight (< 90 kg or ≥90 kg) at Screening. In the beginning of the induction period, patients were randomized using a 1:1:1:1 ratio into one of the treatment groups below:

- **Active Etanercept comparator group:** SC etanercept 50 mg twice per week from Randomization until Week 12, followed by SC etanercept 50 mg every week from Week 12 through Week 51. Patients self-administered etanercept or etanercept placebo doses at home. To maintain the blind, they also received 2 placebo secukinumab SC injections at Randomization and at Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
- **Secukinumab 150 mg regimen group:** secukinumab 150 mg (1 SC injection of the 150 mg dose + 1 SC injection of secukinumab placebo) administered at Randomization and at Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and secukinumab placebo (2 SC injections per dose) administered at Weeks 13, 14 and 15. In addition, to maintain the blind, placebo etanercept was administered twice per week from randomization through Week 12, and then once per week until Week 51. Patients self-administered placebo etanercept doses at home.
- **Secukinumab 300 mg regimen group:** secukinumab 300 mg (2 SC injections of the 150 mg dose) administered at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and secukinumab placebo (2 SC injections per dose) administered at Weeks 13, 14, and 15. In addition, to maintain the blind, placebo etanercept was administered twice per week from randomization through Week 12, and then once per week until Week 51. Patients self-administered placebo etanercept doses at home.
- **Placebo group:** SC placebo etanercept twice per week until Week 12 and SC placebo secukinumab (2 SC injections per dose) administered at Randomization, Weeks 1, 2, 3, 4, and 8. At Week 12 (prior to receiving the Week 12 dose), patients who had been on placebo for the initial part of the study either remained on placebo or were re-randomized to either secukinumab 150 mg or secukinumab 300 mg based on their PASI 75 response to placebo at Week 12:
 - **Placebo PASI 75 responders** continued to receive placebo secukinumab at Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48 along with placebo etanercept once a week until Week 51.
 - **Placebo PASI 75 non-responders** were re-randomized 1:1 to 150 mg or 300 mg secukinumab (AIN457) and received their treatment on Weeks 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 40, 44, and 48 along with weekly placebo etanercept until Week 51.

Primary efficacy measurement

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA 0/1 response at Week 12.

PK measurement

Blood samples for PK analyses were collected at baseline, and at Weeks 4, 12, 24, and 52 (4 weeks after the last dose). A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

Study products

AIN457 150 mg lyophilized powder in vial for solution (batch #: S0005, S0011, S0014) was used in the study.

Demographic and background characteristics:

Approximately 1264 patients with moderate to severe chronic plaque-type psoriasis were enrolled. At beginning of the induction treatment the mean age was 44.4 years. The mean body mass index (BMI) was 28.34 kg/m². Caucasian was the predominant race (880 patients, 67.4%), and more than two-thirds of patients were male (929 patients, 71.1%). The mean (\pm SD) PASI score was 23.7 (\pm 10.18) with the mean affected BSA of 34.4%

12.5. Results

Pharmacokinetics

Serum trough secukinumab concentrations by treatment and visits are summarized in [Table 12.5.a](#).

Visits	Trough secukinumab concentrations (mcg/mL, Mean \pm SD)			
	n	150 mg	n	300 mg
Week 4	288	46.3 \pm 16.3	296	89.9 \pm 32.6
Week 12	272	23.9 \pm 11.6	284	45.4 \pm 21.2
Week 24	276	18.2 \pm 9.36	276	33.4 \pm 16.7
Week 52	225	18.8 \pm 11.8	236	33.5 \pm 17.7

At Week 12, the mean (\pm SD) serum trough secukinumab concentrations were 23.9 \pm 11.6 mcg/mL and 45.4 \pm 21.2 mcg/mL in the 150 mg and 300 mg treatment groups, respectively. During the maintenance treatment period of Weeks 24 and 52, the trough concentrations reached steady state levels of 18.2-18.8 mcg/mL and 33.4-33.5 mcg/mL in the 150 mg and 300 mg treatment groups, respectively. In general, mean concentrations in the 300 mg group were about 2-fold of those in the 150 mg group, which indicated dose-proportional exposure.

Efficacy

The primary efficacy results at Week 12 are summarized in [Table 12.5.b](#). At Week 12, PASI 75 response rate was 77.1% in subjects treated with 300 mg secukinumab, 67.0% in subjects treated with 150 mg secukinumab, and 4.9% in subjects treated with placebo. The IGA 0/1 response rates were 62.5%, 51.1% and 2.8% for 300 mg secukinumab, 150 mg secukinumab and placebo treatment groups, respectively. Secukinumab demonstrated superior efficacy compared to placebo with respect to PASI 75 and IGA 0/1 response at Week 12.

Endpoint	Treatment comparison ("test" vs "control")	"test" n/m (%)	"control" n/m (%)	Odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 150 mg vs placebo	167/327 (51.1%)	9/324 (2.8%)	40.62 (19.80, 83.35)	<0.0001
	AIN457 300 mg vs placebo	202/323 (62.5%)	9/324 (2.8%)	79.13 (35.97, 174.09)	<0.0001
PASI 75	AIN457 150 mg vs placebo	219/327 (67.0%)	16/324 (4.9%)	42.76 (23.57, 77.60)	<0.0001
	AIN457 300 mg vs placebo	249/323 (77.1%)	16/324 (4.9%)	65.95 (36.07, 20.59)	<0.0001

Comparison of the two secukinumab treatment groups showed that the response rates were 10% higher for PASI 75 and 11% higher for IGA 0/1 in the 300 mg dose group relative to the 150 mg dose group. The sponsor's statistically analysis showed that the p-values for the differences between 300 mg and 150 mg treatment groups were 0.0046 for PASI 75 and 0.0032 for IGA 0/1, which indicated a better efficacy outcome in the treatment group with the higher dose.

At Week 12, PASI 90 response rate was 54.2% in subjects treated with 300 mg secukinumab, 41.9% in subjects treated with 150 mg secukinumab, and 1.5% in subjects treated with placebo (*Data source: CSR CAIN457A2303, Table 14.2-3.1*).

Subgroup analysis by body weight (<90 kg and ≥90 kg) showed that the body weight had an effect on the efficacy of secukinumab ([Table 12.5.c](#)). In the same body weight subgroup, the efficacy results for PASI 75, PASI 90 and IGA 0/1 at Week 12 in the secukinumab 300 mg treatment group was associated with numerically higher response rates compared to the secukinumab 150 mg treatment group. At the same dose level, subjects <90 kg showed numerically higher response rates compared to subjects ≥90 kg. The data also showed that subjects <90 kg received 150 mg dose achieved a similar response rate as subjects ≥90 kg received 300 mg dose.

Table 12.5.c. Subgroup analysis by bodyweight (<90 kg and ≥90 kg) for PASI 75, PASI 90 and IGA 0/1 at Week 12. n=number of patients with response; m=number of patients evaluable. (*Data source: CSR CAIN457A2303, Table 11-7, Page 147*)

Endpoints	<90 kg			≥90 kg		
	150 mg n/m (%)	300 mg n/m (%)	Placebo n/m (%)	150 mg n/m (%)	300 mg n/m (%)	Placebo n/m (%)
IGA 0/1	119/215 (55.3%)	140/217 (64.5%)	8/216 (3.7%)	48/112 (42.9%)	62/106 (58.5%)	1/108 (0.9%)
PASI 75	157/215 (73.0%)	171/217 (78.8%)	15/216 (6.9%)	62/112 (55.4%)	78/106 (73.6%)	1/108 (0.9%)
PASI 90	101/215 (47.0%)	127/217 (58.5%)	5/216 (2.3%)	36/112 (32.1%)	48/106 (45.3%)	0/108 (0%)

Maintenance of PASI 75 and IGA 0/1 responses at 52 weeks

The results indicated that patients treated with 300 mg secukinumab were more likely to sustain PASI 75 and IGA 0/1 response at 52 weeks than those treated with the lower dose of 150 mg. For subjects who achieved PASI 75 at Week 12, 84.3% (n=249) in the 300 mg maintenance treatment group and 82.2% (n=219) in the 150 mg treatment group maintained the response at Week 52 (*Data source: CSR CAIN457A2303, Table 11-15, Page 158*). For subjects who achieved IGA 0/1 at Week 12, 79.7% (n=202) in the 300 mg maintenance treatment group and 67.7% (n=167) in the 150 mg treatment group maintained the response at Week 52 (*Data source: CSR CAIN457A2303, Table 11-16, Page 160*).

Relapse

Relapse was defined as a 50% reduction of the maximal PASI improvement. The cumulative probability of relapse at >36 to <40 weeks of treatment was lower with the higher secukinumab dose: 3.0% with 300 mg treatment in comparison to 6.6% with the 150 mg treatment (*Data source: CSR CAIN457A2303, Table 14.2-9.2, Page 1311*).

Rebound

Rebound (defined as increase in PASI to > 125% of baseline PASI within 8 weeks of last dose of study treatment) was more frequently reported in the placebo group (7/12 or 58.3%) than in either secukinumab dose group (10/43 or 23.3% for the 150 mg treatment group and 6/28 or 21.4% for 300 mg treatment group) (*Data source: CSR CAIN457A2303, Table 14.2-9.4, Page 1315*). These rebound results should be interpreted with caution because at time of this CSR not all patient data were available and the assessments of rebound were based on a small, biased sample of discontinued patients.

13. STUDY CAIN457A2304

13.1. Title

- A randomized, double-blind, multicenter study of subcutaneous secukinumab, assessing Psoriasis Area and Severity Index (PASI) response and maintenance of response in subjects with moderate to severe chronic plaque-type psoriasis on either a fixed dose regimen or on a retreatment at start of relapse regimen. Study Comparing secukinumab Use in Long-term Psoriasis maintenance therapy: fixed regimens vs reTreatment Upon start of Relapse (SCULPTURE).

13.2. Study period

- 04 August 2011 (the first patient enrolled) to 07 March 2013 (the last patient completed the 52-week data cut-off, study ongoing)

13.3. Primary objectives

- The primary objective was to demonstrate the non-inferiority of 150 mg and 300 mg of secukinumab administered at the start of relapse (SoR) versus fixed interval (FI) regimens of 150 mg and 300 mg of secukinumab respectively, in patients with moderate to severe chronic plaque-type psoriasis who were PASI 75 responders at Week 12, with respect to PASI 75 response:
 - at Week 52 for patients in the fixed interval regimen, or
 - at Week 40 for patients in the retreatment at start of relapse regimen who do not require active treatment at Week 40, or
 - at Week 52 for patients in the retreatment at start of relapse regimen who do require active treatment at Week 40.

13.4. Study design and methods

This was a multicenter randomized, double-blind, parallel-group trial in patients with moderate to severe chronic plaque-type psoriasis. The study consisted of four periods: screening, induction (12 weeks), maintenance (40 weeks) and post-treatment follow-up (8 weeks). Eligible patients were randomized using a 1:1 ratio into one of the two induction treatment arms below:

- **Secukinumab 150 mg group:** treated with secukinumab 150 mg at Weeks 1, 2, 3, 4 and 8;
- **Secukinumab 300 mg group:** treated with secukinumab 300 mg Weeks 1, 2, 3, 4 and 8;

At Week 12 (end of induction period), patients were classified and progressed as follows:

- **PASI 75 responders** (patients achieving at least 75% reduction of PASI compared to baseline) were re-randomized into the maintenance period.

- **PASI partial responders** (patients achieving at least 50%, but less than 75% reduction of PASI compared to baseline) could enter protocol CAIN457A2307. Partial responders who did not want to enter protocol CAIN457A2307 entered the treatment-free follow-up period.
- **PASI non responders** (patients achieving less than 50% reduction of PASI compared to baseline) progressed immediately into the treatment-free follow-up period.

Patients who discontinued study treatment prematurely during the induction period entered the treatment-free follow-up period.

Maintenance Period (re-randomization at Week 12 to Week 52):

At Week 12, PASI 75 responders were re-randomized, within their same dose group of either 150 or 300 mg SC secukinumab, in a ratio of 1:1 to one of two treatment schedules: “fixed interval” or “retreatment at start of relapse”, as the following.

- **Fixed interval regimen (FI):** In the maintenance period patients in the FI groups received the same dose they received during the induction period. Thus, secukinumab 150 mg patients continued to receive 150 mg secukinumab every four weeks, and secukinumab 300 mg patients continued to receive 300 mg secukinumab every four weeks, from Week 12 up to and including Week 48.
- **Retreatment at start of relapse regimen (SoR):** In the maintenance period, patients in the SoR group also received the same dose of secukinumab (150 mg or 300 mg) they received during the induction period every 4 weeks; however, after Week 12, a patient was not dosed with active secukinumab until that patient met start of relapse criteria and continued dosing until PASI 75 response was regained. “Start of relapse” was defined as a loss of $\geq 20\%$ of the maximum PASI gain achieved during the study compared to baseline, *and* a loss of PASI 75 response. If a patient did not fulfill the criteria for start of relapse or achieved PASI 75 response after a start of relapse, they received placebo injections (two injections per dose) to maintain the blind. This treatment regimen was applied up to and including Week 48.

Patients who discontinued study treatment prematurely during the maintenance period entered the treatment-free follow-up period.

Study products

AIN457 150 mg lyophilized powder for solution (batch #: S0006, S0007, S0008, S0014) was used in the study.

Primary efficacy measurement

The primary analysis of this trial was to show the non-inferiority of the retreatment at start of relapse regimen to the fixed interval regimen with respect to maintenance of response, separately for the 150 mg and 300 mg dose groups. Maintenance of response is defined as follows:

- for patients in the fixed interval regimens maintenance of response is defined as PASI 75 response (i.e., $\geq 75\%$ improvement from Baseline) at Week 52
- for patients in the start of relapse regimens maintenance of response is defined as
 - PASI 75 response at Week 52 for patients who qualified for active treatment at Week 40 and
 - PASI 75 response at Week 40 for patients who did not qualify for active treatment at Week 40.

PK measurement

Blood samples for PK analyses were collected at baseline, and at Weeks 4, 12, 24, 52 and 60 (Follow-up). A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

13.5. Results

Pharmacokinetics

The mean (\pm SD) serum secukinumab trough concentrations by treatment and visits are summarized in [Table 13.5](#). At Week 12, the mean (\pm SD) serum secukinumab trough concentrations were 23.3 \pm 9.69 mcg/mL and 45.2 \pm 20.5 mcg/mL in the 150 mg and 300 mg treatment groups, respectively. During the maintenance treatment period with FI dosing every four weeks, concentrations reached steady state levels of 16.9-18.9 mcg/mL and 34.4-36.4 mcg/mL in the 150 mg FI and 300 mg FI arms, respectively. The mean trough concentrations in the 300 mg group were about 2-fold of those in the 150 mg treatment group, which indicated dose-proportional exposure.

Table 13.5. Serum secukinumab concentrations by treatment and visits in Study CAIN457A2304. For Week 4 and Week 12, data are from all randomized subjects with available samples. For Week 24 and Week 52, data are only from subjects who received FI treatment with available samples. (*Data source: CSR CAIN457A2304, Table 11-12, Page 155*)

Visits	Secukinumab 150 mg		Secukinumab 300 mg	
	n	Serum secukinumab (mcg/mL, Mean \pm SD)	n	Serum secukinumab (mcg/mL, Mean \pm SD)
Baseline	471	0.262 \pm 2.98	473	0.882 \pm 7.73
Week 4	436	44.1 \pm 14.9	439	85.2 \pm 31.8
Week 12	414	23.2 \pm 9.69	424	45.2 \pm 20.5
Week 24	183	18.9 \pm 9.93	194	36.4 \pm 15.8
Week 52	169	16.9 \pm 7.23	177	34.4 \pm 16.2

Efficacy

The primary endpoint for this study was not met; the re-treatment at SoR maintenance regimen was not non-inferior to the FI regimen. The non-inferiority margin was pre-defined at -15% and the point estimates were approximately -10% different between the SoR and FI groups. However, the lower limit of the adjusted confidence interval (CI) for SoR minus FI was approximately -20% (for both 150 mg and 300 mg) (*Data source: CSR CAIN457A2304, Table 11-9, Table 11-10, Page 137*); therefore, the non-inferiority margin was exceeded and non-inferiority was not achieved.

The PASI75 response rate following the induction treatment period at Week 12 was numerically higher in the 300 mg treatment group than that in 150 mg treatment group. At Week 12, the PASI 75 response rates were 84.4 % (406/481) and 90.1% (435/483) for secukinumab 150 mg and 300 treatment groups, respectively (*Data source, CSR CAIN457A2304, Table 14.2-5.1, Page 1212*).

In the maintenance treatment period subjects treated with FI dosing regimens showed higher response rates compared with SoR dosing regimen at the same dose level (300 mg or 150 mg). At the 150 mg dose, the PASI 75 response rates at Week 52 were 62.1% (126/203) and 52.4% (108/206) for the FI and SoR treatment groups, respectively. At the 300 mg dose, the PASI 75 response rates at Week 52 were 78.2% (169/216) and 67.7% (147/217) for the FI and SoR treatment groups, respectively (*Data source: CSR CAIN457A2304, Table 14.2-1.1, Page 812-813*).

14. STUDY CAIN457A2308

14.1. Title

- A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab in pre-filled syringes to demonstrate efficacy after twelve weeks of treatment, and to assess the safety, tolerability, usability and long-term efficacy in subjects with chronic plaque-type psoriasis: First study of SEcukinumAb in pre-filled syringes in subjecTs with chronic plaqUe-type psoriasis: REsponse at 12 weeks (FEATURE).

14.2. Study period

- 08 May 2012 (the first patient enrolled) to 15 January 2013 (the last patient completed the induction period data cut-off, study ongoing)

14.3. Primary objectives

- The primary objective was to demonstrate the efficacy of secukinumab (150 mg and 300 mg) in patients with moderate to severe chronic plaque-type psoriasis with respect to both Psoriasis Area and Severity Index (PASI) 75 and Investigator's Global Assessment (IGA) mod 2011 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.

14.4. Study design and methods

This is an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderate to severe chronic, plaque-type psoriasis. The study was designed to compare 2 doses of secukinumab (150 mg and 300 mg) and placebo in pre-filled syringes (PFS) administered as SC self-injections. The study consists of 5 periods: Screening (1 to 4 weeks), Induction (12 weeks), Maintenance (40 weeks), Extension (up to 156 additional weeks) and Follow-up (8 weeks).

At randomization, eligible patients were assigned equally to 1 of 3 treatment groups: secukinumab 150 mg, secukinumab 300 mg, or placebo. Doses were administered at randomization and at Weeks 1, 2, 3, 4 and 8 in the induction period and every four weeks in the maintenance period.

Patients randomized to placebo who achieved PASI 75 response at Week 12 were to continue on placebo, while the non-responders were to be re-randomized in a 1:1 ratio to secukinumab 150 mg or 300 mg group.

Study products

Secukinumab 150 mg is provided in 1-mL pre-filled syringe (1 syringe for 150 mg dose, 2 syringes for 300 mg dose). The batch number is U003 0711.

Primary efficacy measurement

The primary evaluation of efficacy was the comparison of secukinumab 150 mg and 300 mg to placebo at Week 12. The two co-primary variables were PASI 75 response and IGA mod 2011 0 or 1 (IGA 0/1) response.

PK measurement

Blood samples for PK analyses were collected at baseline, and at Weeks 4 and 12. A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

14.5. Results

Pharmacokinetics

The Mean (\pm SD) serum secukinumab trough concentrations were 42.9 ± 15.1 mcg/mL and 24.3 ± 10.1 mcg/mL at Weeks 4 and 12, respectively, for the 150 mg secukinumab treatment group, in comparison to 84.8 ± 28.5 mcg/mL and 47.4 ± 21.1 mcg/mL for the 300 mg secukinumab treatment group at the same time points (Table 14.5.a). The PK results in general suggest a dose-proportional increase in exposure across the two dose levels.

Table 14.5.a. Serum secukinumab concentrations by treatment and visits in Study CAIN457A2308. (*Data source: CSR CAIN457A2308, Table 11-12, Page 114*)

Visits	Secukinumab 150 mg		Secukinumab 300 mg	
	n	Serum secukinumab (mcg/mL, Mean \pm SD)	n	Serum secukinumab (mcg/mL, Mean \pm SD)
Week 4	56	42.9 \pm 15.1	55	84.8 \pm 28.5
Week 12	54	24.3 \pm 10.1	49	47.4 \pm 21.1

Efficacy

The response rates for PASI 75, PASI 90 and IGA 0/1 at Week 12 for each treatment group are summarized in Table 14.5.b.

Table 14.5.b. The response rates for PASI 75, PASI 90 and IGA 0/1 at Week 12 in Study CAIN457A2308. n=number of patients with response; m=number of patients evaluable. (*Data source: CSR CAIN457A2308, Table 11-5, page 98*)

Endpoint	Treatment comparison (“test” vs “control”)	“test” n/m (%)	“control” n/m (%)	Odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 150 mg vs placebo	31/59 (52.5%)	0/59 (0%)	52.5 (35.1, 67.2)	<0.0001
	AIN457 300 mg vs placebo	40/58 (69.0%)	0/59 (0%)	69.0 (53.5, 80.5)	<0.0001
PASI 75	AIN457 150 mg vs placebo	41/59 (69.5%)	0/59 (0%)	69.5 (53.9, 81.4)	<0.0001
	AIN457 300 mg vs placebo	44/58 (75.9%)	0/59 (0%)	75.9 (61.5, 86.1)	<0.0001
PASI 90	AIN457 150 mg vs placebo	27/59 (45.8%)	0/59 (0%)	45.8 (27.8, 61.3)	<0.0001
	AIN457 300 mg vs placebo	35/58 (60.3%)	0/59 (0%)	60.3 (43.9, 73.0)	<0.0001

Secukinumab demonstrated superior efficacy compared to placebo with respect to PASI 75 and IGA 0/1 response at Week 12. At Week 12, PASI 75 response rate was 75.9% in subjects treated with 300 mg secukinumab, 69.5% in subjects treated with 150 mg secukinumab, and 0% in subjects treated with placebo. The IGA 0/1 response rates were 69.0%, 52.5% and 0% for 300 mg secukinumab, 150 mg secukinumab and placebo treatment groups, respectively. Comparison of the two secukinumab treatment groups showed that the response rates were 6.4% higher for PASI 75 and 16.5% higher for IGA 0/1 in the 300 mg dose group relative to the 150 mg dose group.

15. STUDY CAIN457A2309

15.1. Title

- A randomized, double-blind, placebo-controlled, multicenter study of subcutaneous secukinumab in autoinjectors to demonstrate efficacy after 12 weeks of treatment, and to assess the safety, tolerability, usability and long-term efficacy in subjects with chronic plaque-type psoriasis: Judging the Efficacy of SecUkinumab in Patients With Psoriasis using Autoinjector: a Clinical Trial EvalUating Treatment REsults (JUNCTURE).

15.2. Study period

- 17 October 2012 (the first patient enrolled) to 10 April 2013 (the last patient completed the induction period cut-off, study ongoing)

15.3. Primary objectives

- The primary objective was to demonstrate the efficacy of secukinumab (150 mg and 300 mg) in subjects with moderate to severe chronic plaque-type psoriasis with respect to both Psoriasis Area and Severity Index (PASI) 75 and Investigator's Global Assessment (IGA) mod 2011 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.

15.4. Study design and methods

This is an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderate to severe chronic, plaque-type psoriasis. The study was designed to compare 2 doses of secukinumab (150 mg and 300 mg) and placebo in autoinjector (AI) administered as SC self-injections. The study consists of 4 periods: Screening (1 to 4 weeks), Induction (12 weeks), Maintenance (40 weeks), and Follow-up (8 weeks).

At randomization, eligible patients were assigned equally to 1 of 3 treatment groups: secukinumab 150 mg, secukinumab 300 mg, or placebo. Doses were administered at randomization and at Weeks 1, 2, 3, 4 and 8 in the induction period and every four weeks in the maintenance period.

Patients randomized to placebo who achieved PASI 75 response at Week 12 were to continue on placebo, while the non-responders were to be re-randomized in a 1:1 ratio to secukinumab 150 mg or 300 mg group.

Study products

Secukinumab 150 mg is provided in 1-mL AI. The batch numbers are S0002 and S0004A.

Primary efficacy measurement

The primary evaluation of efficacy was the comparison of secukinumab 150 mg and 300 mg to placebo at Week 12. The two co-primary variables were PASI 75 response and IGA mod 2011 0 or 1 (IGA 0/1) response.

PK measurement

Blood samples for PK analyses were collected at baseline, and at Weeks 4 and 12. A competitive ELISA method was used for bioanalytical analyses and the LLOQ was 80 ng/mL of serum.

15.5. Results

Pharmacokinetics

The mean (\pm SD) serum secukinumab trough concentrations were 50.7 ± 18.1 mcg/mL and 28.0 ± 11.9 mcg/mL at Weeks 4 and 12, respectively, for the 150 mg secukinumab treatment group, in comparison to 107 ± 34.3 mcg/mL and 58.4 ± 25.9 mcg/mL for the 300 mg secukinumab treatment group at the same time points (Table 15.5.a). The PK results in general suggest a dose-proportional increase in exposure.

Table 15.5.a. Serum secukinumab concentrations by treatment and visits in Study CAIN457A2309. (*Data source: CSR CAIN457A2309, Table 11-12, Page 115*)

Visits	Secukinumab 150 mg		Secukinumab 300 mg	
	n	Serum secukinumab (mcg/mL, Mean \pm SD)	n	Serum secukinumab (mcg/mL, Mean \pm SD)
Week 4	57	50.7 \pm 18.1	56	107 \pm 34.3
Week 12	51	28.0 \pm 11.9	55	58.4 \pm 25.9

Efficacy

The response rates for PASI 75, PASI 90 and IGA 0/1 at Week 12 for each treatment group are summarized in Table 15.5.b. Secukinumab demonstrated superior efficacy compared to placebo with respect to PASI 75 and IGA 0/1 response at Week 12. At Week 12, PASI 75 response rate was 86.7% in subjects treated with 300 mg secukinumab, 71.7% in subjects treated with 150 mg secukinumab, and 3.3% in subjects treated with placebo. The IGA 0/1 response rates were 73.3%, 53.3% and 0% for 300 mg secukinumab, 150 mg secukinumab and placebo treatment groups, respectively. Comparison of the two secukinumab treatment groups showed that the response rates were 15% higher for PASI 75 and 20% higher for IGA 0/1 in the 300 mg dose group relative to the 150 mg dose group.

Table 15.5.b. The response rates for PASI 75, PASI 90 and IGA 0/1 at Week 12 in Study CAIN457A2309. n=number of patients with response; m=number of patients evaluable. (*Data source: CSR CAIN457A2309, Table 11-5, page 99*)

Endpoint	Treatment comparison (“test” vs “control”)	“test” n/m (%)	“control” n/m (%)	Odds ratio estimate (95% CI)	p-value
IGA 0/1	AIN457 150 mg vs placebo	32/60 (53.3%)	0/61 (0%)	53.3 (36.6, 66.7)	<0.0001
	AIN457 300 mg vs placebo	44/60 (73.3%)	0/61 (0%)	73.3 (58.8, 83.9)	<0.0001
PASI 75	AIN457 150 mg vs placebo	43/60 (71.7%)	2/61 (3.3%)	68.4 (53.1, 79.8)	<0.0001
	AIN457 300 mg vs placebo	52/60 (86.7%)	2/61 (3.3%)	83.4 (70.7, 91.7)	<0.0001
PASI 90	AIN457 150 mg vs placebo	24/60 (40.0%)	0/61 (0%)	40.0 (22.5, 55.0)	<0.0001
	AIN457 300 mg vs placebo	33/60 (55.0%)	0/61 (0%)	55.0 (38.4, 68.1)	<0.0001

16. APPENDIX: NEUTROPHIL ANALYSIS REPORT

The Applicant conducted a neutrophil count analysis with pooled data from 18 Phase 1 and Phase 2a trials in healthy volunteers and subjects with a variety of disease conditions. The pooled analysis assessed neutrophil count change at Week 4 compared to the baseline. The treatment effects for longer treatment durations (> 4 weeks) were not assessed.

Treatment groups in pooled analysis

Data pooling adds variability due to differences in dose amount, number of doses, dosing frequency and administration routes (IV versus SC). The following factors were considered to define treatment groups in the pooled analysis:

- Route of administration (IV or SC)
- Amount of dose: The IV group includes the following doses: 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 30 mg/kg, and placebo. The SC group includes 150 mg, 300 mg, and placebo.
- Single or multiple dose administration before the Week 4 time point.

The following assumptions were made in the pooled analysis:

- Secukinumab did not have an immediate effect (within 1 day) on neutrophil count. Therefore, measurements occurring within a window of approximately 24 hours after first dosing were considered as baseline value in case no pre-treatment value was available.
- Likewise, if a second dose was given on the day of or 1 day prior to the Week 4 neutrophil assessment, the treatment group was considered a single dose.

Summary of pooled analysis results

The results are shown in Figure 16.a and Figure 16.b. Secukinumab administrations appeared to be associated with a decrease of peripheral neutrophil counts starting at a threshold dose of multiple 1 mg/kg IV and multiple 300 mg SC. However, the pooled analysis did not show a clear dose-response relationship in the magnitude of change from baseline.

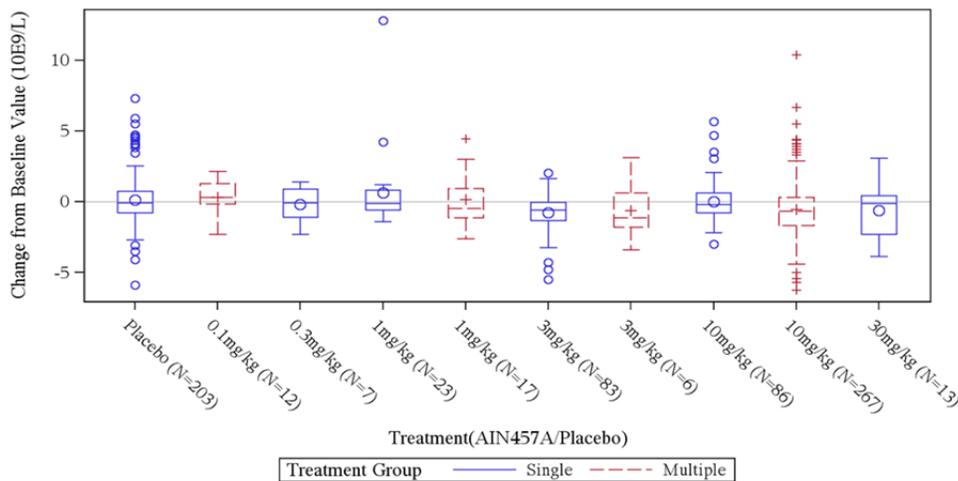


Figure 16.a. Change from baseline to Week 4 in absolute neutrophil counts across a wide range of secukinumab IV doses and placebo. Units on y-axis indicate change in absolute neutrophil counts in 10^9 /liter (or $1000/\mu\text{L}$). For the box-plots, the bottom and top edges of the box indicate the intra-quartile range defined as the range of values between the 25th and 75th percentiles. The horizontal line inside the box indicates the median and the symbol inside the box indicates the mean. (Data Source: NIBR Analysis Report: Figure 4-1, Page 11)

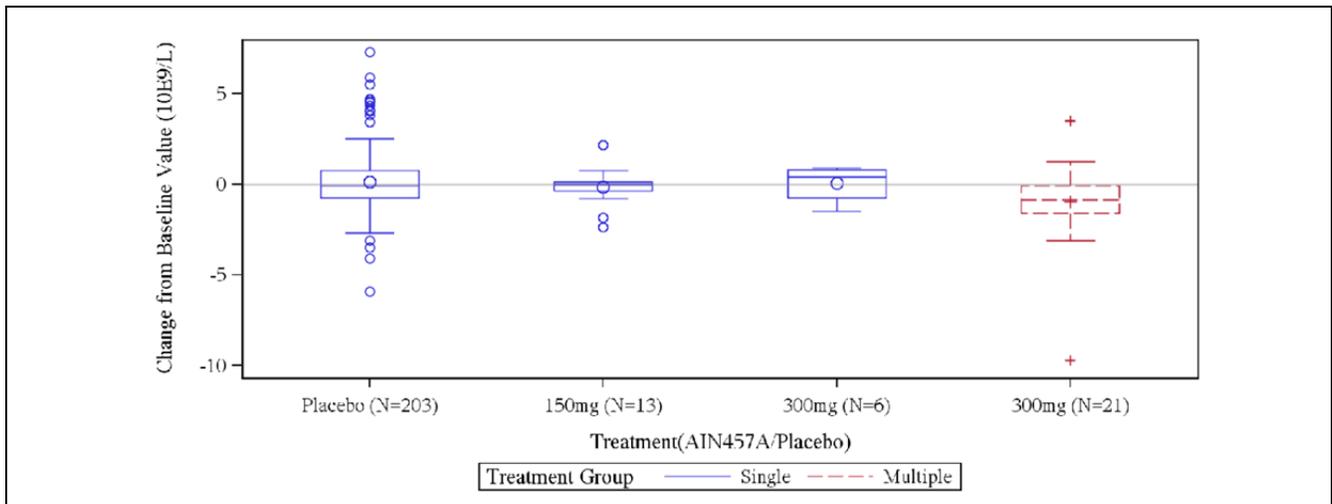


Figure 16.b. Change from baseline to Week 4 in absolute neutrophil counts for 150 mg SC secukinumab, 300mg SC secukinumab and placebo treatment groups. (*Data Source: NIBR Analysis Report: Figure 4-2, Page 12*)

17. APPENDIX: BIOANALYTICAL ASSAY CONSULT

This appendix provides the responses from Division of Applied Regulatory Science (DARS) regarding the bioanalytical methods used for the measurement of serum concentrations of secukinumab (AIN 457) and IL-17A. The responses from DARS are based on limited information provided to consultant and are from a scientific point of view. Refer to the section 2.10 Bioanalytical methods of the Clinical Pharmacology Review for the overall evaluation of the performance and validation of the bioanalytical assays.



Food and Drug Administration
10903 New Hampshire Avenue
White Oak Building 51, Room 3182
Silver Spring, MD 20993

Date: August 26, 2014
From: James Weaver, PhD.; Kristina Howard DVM, PhD; Division of Applied Regulatory Science
Through: Thomas Colatsky, PhD
To: Yow-Ming Wang, DCPIII/OCP
Subject: Evaluation of two ELISA assays used in support of BLA 125504 for secukinumab (AIN 457), an anti-IL17A monoclonal antibody

Background: The assays under discussion are intended to measure two analytes: the cytokine IL-17A and the proposed therapeutic monoclonal anti-IL-17A antibody, secukinumab (AIN 457). IL-17A is one of a family of six related cytokines, IL-17A through F (Gu et al., 2013). All but IL-17B are secreted as disulfide-linked homodimers (Iwakura et al., 2011). IL-17A and IL-17F are the most closely related, sharing 50% amino acid sequence identity. The remaining members share 16% to 30% homology with IL-17A (Iwakura et al., 2011). Both IL-17A and IL-17F are secreted by Th17 cells. In addition, they can form IL-17A/F heterodimers (Chang & Dong, 2009). Both IL-17A/A and IL-17F/F homodimers, as well as IL-17A/F heterodimers, can signal through the same receptor complex (Gu et al., 2013). They share a number of biological functions but can also be distinguished in some areas.

Evaluation

Question 1: *The Applicant stated that the competitive ELISA assay measures the total secukinumab, i.e. free secukinumab plus secukinumab bound to IL-17A (secukinumab - IL-17A complex) in the human serum sample.*

Please evaluate if the assay indeed measures all three entities, secukinumab not bound to any IL-17A, secukinumab bound to one IL-17A, and secukinumab bound to two IL-17A.

Response: The applicants' statement about the performance of the assay to measure AIN 457 in the presence of IL-17 cannot be evaluated from the supplied information. No data have been provided in the supplied documents showing the performance of the assay with IL-17A present, or identifying the site to which the anti-idiotypic antibody is designed to bind. The response of the competitive assay in the presence of IL-17A/F heterodimers or IL-17F/F homodimers is also not reported.

Based on general principles of ELISA design, the competitive assay described in the supplied documents should respond similarly to free AIN 457 and to AIN 457 bound to a single molecule of IL-17A/A. Nearly all anti-idiotypic antibodies block ligand binding, therefore detection AIN 457 with two molecules of IL-17A/A bound is less likely. The actual ability of the assay to detect AIN 457 with two molecules of IL-17A/A bound cannot be excluded or confirmed based on the information supplied.

Question 2: *The Applicant stated that the sandwich assay measures the total IL-17A, i.e., free IL-17A and IL-17A bound to secukinumab. The Applicant further stated that the binding epitope on the IL-17 for the assay reagent differs from the epitope used to bind to secukinumab.*

Please evaluate if the assay indeed measures the total IL-17.

Response: The sandwich assay will measure total IL-17A/A homodimer and the supplied data show that the response is not altered by the presence of AIN 457 up to the maximum projected clinical concentration of 600 µg/ml. The assay does not exhibit classical sigmoidal dose response behavior at the high end of concentrations used, although ULOQ criteria were met at 1000 ng/ml. The determination of a 'hook effect' was not adequate, as only a single point of 10,000 ng/ml was measured. As a practical matter, this may be of little importance since plasma levels of IL-17A/A are reported to be in the pg/ml to single ng/ml range (Maxeiner et al., 2014; Zhao et al., 2014; Forrester et al., 2014). The response of the assay to the homologous IL-17F/F protein or to IL-17A/F heterodimers was not studied in the supplied report.

Item 3: Please describe the evidence that the sponsor provided in support of their description of the two bioanalytical methods. And, when appropriate, please opine on what additional data, if any, would be needed from the Applicant to further substantiate their position about the assays.

Response: There are a number of areas where information could be supplied that would improve the evaluation of the assay.

- At least a brief description of the basic characteristics of the analyte. Where the analyte is a normal human protein, it may be important to know what other proteins may be significantly related to the analyte. In this case, the IL-17F/F protein has potential cross-reactivity to both of the anti-IL-17A/A antibodies. As the IL-17F/F and IL-17-A/F species are biologically active at the IL-17A/A receptor, it may be important to know whether the assay is specific for IL-17A/A or may also be detecting one or both of the other two species.
- For critical assay antibodies, a more detailed description of the antibody, its known specificity and results of any testing for cross-reactivity where appropriate. For example there is no description of the anti-idiotypic anti-AIN457 antibody used as the capture antibody in the competition assay. The performance of this antibody is crucial to the assay yet no data are supplied characterizing the antibody. It is not stated whether the antibody is a monoclonal or polyclonal, which is very important for long term stability of assay performance. The class of the rabbit antibody is not stated, IgM antibodies tend to be lower affinity which increases the relative issue of non-specific binding.
- It is also useful to know the expected clinical and/or normal ranges of the analytes. The LLOQ of the assay measuring AIN-457 is reported to be 80 ng/ml {{(1), page 30}}, but no information is reported in this document about expected therapeutic levels. In the description of the sandwich assay for measuring IL-17A, it is stated that the maximum expected clinical concentration of AIN 457 is 600 µg/ml {{(4), page 9}}. As published reports of plasma levels of IL-17 are in the pg/ml to single ng/ml level, it is entirely possible that therapeutic effect may be occurring at concentrations of AIN 457 below the LLOQ of the competition assay. Therefore it cannot be determined on the basis of this document whether the assay is adequate to measure clinically important levels of AIN 457.

Item 4: In addition, the calibration curve presented in report "BxSD R1180331-pk" (figure 7-1 on page 23) appears to be a truncated curve as compared to those presented in reports "BxSD-RS686053-pk"

and “BMD R0450380”. As the BLA review is ongoing, we are yet to determine if a truncated calibration curve has been utilized to estimate the secukinumab concentration in human serum samples. Please evaluate if the truncated curve is suitable for use to estimate the concentrations in test samples from clinical studies.

Response: The plot in BxSD R1180331-pk” (figure 7-1 on page 23) is plotted on a linear scale for concentration whereas the other two typical calibration curves are plotted on a log scale for concentration. The concentration range of the actual data appears to be about same.

References and Supporting Documents

The competitive ELISA assay was validated in in Report number BMD R0450380 which has an amendment and subsequently cross-validated with upon method transfer. Two cross-validation reports are found in the BLA: BxSD-RS686053-pk and Study 1180331. The links to these files are below. The validation of the sandwich assay for total IL-17A was in the report for Study 1280620.

- (1) BMD R0450380 amendment 1 - <\\cdsesub1\evsprod\bla125504\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\bmd-r0450380\bmd-r0450380-01--pre-clinical-study-report.pdf>
- (2) BxSD-RS686053-pk amendment 1 - <\\cdsesub1\evsprod\bla125504\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\bxsd-rs686053-pk\bxsd-rs686053-pk-01--pre-clinical-study-report.pdf>
- (3) BxSD R1180331-pk - <\\cdsesub1\evsprod\bla125504\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\bxsd-r1180331-pk\bxsd-r1180331-pk--pre-clinical-study-report.pdf>
- (4) report for Study 1280620 - <\\cdsesub1\evsprod\bla125504\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\bxsd-r1280620\bxsd-r1280620--pre-clinical-study-report.pdf>

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Forrester MA, Roberson L, Bayoumi N, Deavney BD, Barker RN, Vickers MA. (2014 ap) Human interleukin-27: wide individual variations in plasma levels and complex interrelationships with interleukin-17A. *Clin Exp Immunol* advanced release, doi: 10.1111/cei.12408.

Gu C, Wu L, Li X. (2013) IL-17 family: Cytokines, receptors and signaling. *Cytokine* **64**, 477-485.

Iwakura Y, Ishigame H, Saijo S, Nakae S. (2011) Functional specialization of Interleukin-17 family members. *Immunity* **34**, 149-162.

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Zhao PW, Jiang WG, Wang L, Jiang ZY, Shan YX, Jiang YF. (2014) Plasma levels of IL-37 and correlation with TNF- α , IL-17A, and disease activity during DMARD treatment of rheumatoid arthritis. *PLOS One*. **9** e95346.

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/s/

JIE WANG
12/11/2014

YOW-MING C WANG
12/11/2014

CLINICAL PHARMACOLOGY REVIEW

BLA:	STN 125,504
Submission Type:	Original BLA (New Molecular Entity)
Brand Name:	COSENTYX®
Drug Name:	Secukinumab (AIN457)
Submission Date:	10/24/2013
PDUFA Goal Date:	01/23/2015
Priority:	Standard
Proposed Indication:	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Proposed Dosing Regimen:	The proposed dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.
Dosage Forms and Strength:	<ul style="list-style-type: none">▪ 150 mg/mL in a single-use prefilled SensoReady® pen for injection;▪ 150 mg/mL in a single-use prefilled syringe for injection;▪ 150 mg powder for solution in a single-use vial for injection
Applicant:	Novartis Pharmaceuticals Corporation
Clinical Pharmacology Reviewer:	Jie Wang, Ph.D.
Pharmacometrics Reviewer:	Jee Eun Lee, Ph.D.
Pharmacometrics Team Leader:	Jeffrey Florian, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	CDER/ODEIII/DDDP

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1. EXECUTIVE SUMMARY

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

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 300 mg by subcutaneous (SC) injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 SC injections of 150 mg. The proposed presentations for secukinumab SC injection include the prefilled SensoReady[®] pen (AI, autoinjector), the prefilled syringe (PFS), and the lyophilized powder in vial (LYO).

A total of 22 clinical trials have been conducted with secukinumab in healthy subjects, subjects with psoriasis, and various other patient populations. Among these 22 clinical trials, this review assesses 16 trials (six Phase 1 trials in healthy subjects and subjects with psoriasis, five Phase 2 trials in subjects with psoriasis, and five Phase 3 trials in subjects with psoriasis) which contain data to support the proposed indication and the clinical pharmacology section of the product labeling.

A required OCP office level briefing was held on September 2, 2014.

1.1. Recommendations

From a Clinical Pharmacology standpoint, the BLA is acceptable for approval of secukinumab for the treatment moderate to severe plaque psoriasis in adult patients provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert. The 300 mg dose regimen as proposed by the Applicant is acceptable. However, the 150 mg dose regimen should be provided as an option for subjects weighing < 90 kg who can achieve the therapeutic goal at 150 mg dose.

Whether or not the AI presentation is acceptable for approval needs to be further assessed from clinical perspectives for the target indication, because the PK comparability between the AI and the LYO has not been established. Additionally, a cross-trial comparison of trough secukinumab concentrations at Week 4 and Week 12 noted higher observed trough secukinumab concentrations after dosing with the AI than those achieved with the LYO, although the cumulative distribution of the trough secukinumab concentration data at 12-weeks showed substantial overlap in exposures between observed exposures from the AI and other presentations. The Clinical Pharmacology review team recommends that the Applicant provides additional clinical experience with the AI presentation in the ongoing clinical study(ies) in lieu of a dedicated study comparing exposures between the AI and LYO presentations.

1.2. Post-Marketing Requirements/Commitments

PMC #1: To conduct psoriasis disease-drug-drug interactions (disease-DDI) studies

We recommend that the Applicant conducts a clinical trial to determine the potential of secukinumab to alter the metabolism of CYP substrates in psoriasis patients (e.g., using a cocktail of relevant CYP probe drugs). This recommendation is based on the current understanding that psoriasis patients have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following the biological treatment.

PMC#2: To explore a higher dosing regimen for the subgroup of subjects with higher body weight

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

1.3. Summary of Clinical Pharmacology Findings

1.3.1. Biopharmaceutics and product comparability

The Applicant proposed to register three presentations (LYO, PFS, and AI) in the BLA. The LYO and the PFS have been shown to have comparable PK in a dedicated PK comparability study (CAIN457A2106). The Applicant did not conduct a dedicated PK study to evaluate the comparability between the AI and the LYO or the PFS.

Results in the PK comparability study (CAIN457A2106) with the LYO and the PFS presentations showed that the 90% confidence intervals for geometric mean ratio (PFS-to-LYO ratio) of AUC_{inf} , AUC_{last} , and C_{max} were [0.92, 1.08], [0.93, 1.08], and [0.96, 1.12], respectively, all within the [0.8, 1.25] BE boundaries. This study evaluated the PK comparability with a single dose of 300 mg secukinumab in healthy subjects.

The AI was shown to achieve higher exposures than the PFS and the LYO based on the comparisons of secukinumab trough concentrations across multiple Phase 3 trials (CAIN457A2302 with the LYO, CAIN457A2303 with the LYO, CAIN457A2308 with the PFS, and CAIN457A2309 with the AI). All four studies evaluated two dose levels (150 mg and 300 mg) and blood samples for PK analysis were collected at multiple time points including Week 4 and Week 12. The results showed that compared to the LYO, the concentrations resulting from the AI were approximately 10%-30% higher across the two doses and two time-points. Similarly, the cross-study comparison also showed that compared to the PFS, the concentrations resulting from the AI were approximately 16%-26% higher.

1.3.2. Dose/Exposure-response relationships and recommended dosing regimen

Overall, the Phase 3 efficacy and safety data as well as the dose/exposure-response relationships support the recommendation of 300 mg dose regimen made by the Applicant. However, because of the significant body weight effect on secukinumab PK exposure and, in turn, efficacy, subjects with lower body weight (< 90 kg) had an approximately 10% higher response rates for PASI 75 or IGA 0/1 when compared to subjects with higher body weight (≥ 90 kg) at the same dose (both 150 mg and 300 mg). The Phase 3 data also showed similar response rates in subjects with lower body weight receiving the 150 mg dose and subjects with higher body weight receiving the 300 mg dose ([Figure 1.3.2.a](#)).

Dose-Response for efficacy in Phase 3 trials

The efficacy and safety of secukinumab were evaluated in four Phase 3 trials (CAIN457A2302, CAIN457A2303, CAIN457A2308, and CAIN457A2309) with similar study designs. Secukinumab

(150 mg or 300 mg) was administered subcutaneously at Weeks 0, 1, 2, and 3, followed by a monthly (q4w) dosing regimen starting at Week 4. The co-primary efficacy endpoints were assessed at Week 12 for PASI 75 ($\geq 75\%$ improvement from Baseline PASI [Psoriasis Area and Severity Index] score) and Investigator's Global Assessment mod 2011 0 or 1 (IGA 0/1: achievement of 0/1 AND improved by at least 2 points on the IGA mod 2011 score which ranges from 0 (clear) to 4 (severe)). As shown in [Figure 1.3.2.a](#), the time course of percentage change from baseline in PASI score for both dose groups was significantly higher than that for the placebo group from Week 1 through Week 12 of treatment.

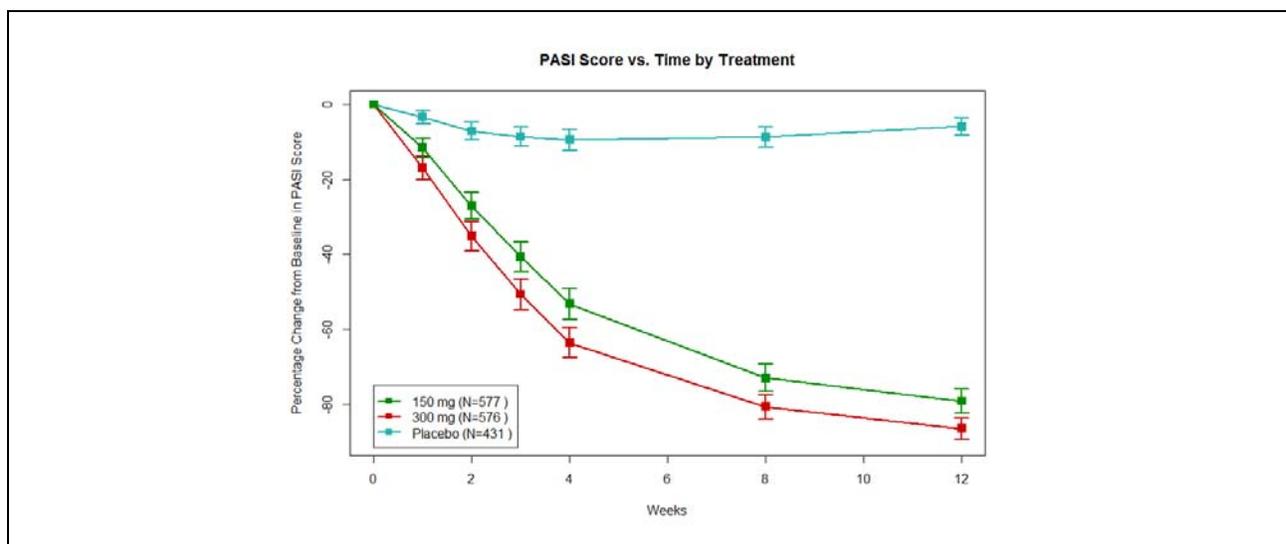


Figure.1.3.2.a. Percentage change from baseline in PASI score over time grouped by treatment arm (Trials CAIN457A2302 and CAIN457A2303). (FDA reviewer's analysis)

The clinical response rates for both primary endpoints are summarized in [Table 1.3.2.a](#). Both doses of secukinumab achieved a significantly higher response rate (p -value <0.0001) compared to the placebo and the 300 mg dose achieved a higher response rate compared to the 150 mg dose.

Table 1.3.2.a. Clinical response rates for PASI 75 and IGA 0/1 in secukinumab psoriasis Phase 3 trials at Week 12. * $p < 0.0001$ compared to the placebo group; (Data source: Summary of Clinical Efficacy)

Phase 3 trial (Product presentation)	PASI 75 response % (number of responders/total)		
	Placebo	150 mg	300 mg
CAIN457A2302 (pivotal, LYO)	4.5% (11/246)	71.6%* (174/243)	81.6%* (200/245)
CAIN457A2303 (pivotal, LYO)	4.9% (16/324)	67.0%* (219/327)	77.1%* (249/323)
CAIN457A2308 (supportive, PFS)	0.0% (0/59)	69.5%* (41/59)	75.9%* (44/58)
CAIN457A2309 (supportive, AI)	3.3% (2/61)	71.7%* (43/60)	86.7%* (52/60)

Phase 3 trial (Product presentation)	IGA 0/1 response % (number of responders/total)		
	Placebo	150 mg	300 mg
CAIN457A2302 (pivotal, LYO)	2.4% (6/246)	51.2%* (125/244)	65.3%* (160/245)
CAIN457A2303 (pivotal, LYO)	2.8% (9/324)	51.1%* (167/327)	62.5%* (202/323)
CAIN457A2308 (supportive, PFS)	0.0% (0/59)	52.5%* (31/59)	69.0%* (40/58)
CAIN457A2309 (supportive, AI)	0.0% (0/61)	53.3%* (32/60)	73.3%* (44/60)

Exposure-Response for efficacy

Both univariate and multivariate logistic regression analyses show that secukinumab concentration at Week 12 was a significant predictor of increasing IGA 0/1 response at Week 12 (p -value $< 2 \times 10^{-16}$). Body weight (a higher body weight resulted in a lower response) and the baseline IGA score (a higher baseline IGA score resulted in a lower response) were identified as significant covariates in addition to secukinumab exposures from multivariate analyses. The regression model predicts an increase in response rate of approximately 12% for a two-fold increase in exposure. The prediction is similar to the observed difference in response between 150 mg and 300 mg (48% and 59% for IGA 0/1 at week 12 with pooled data from Studies A2302 and A2303) (Figure 1.3.2.b).

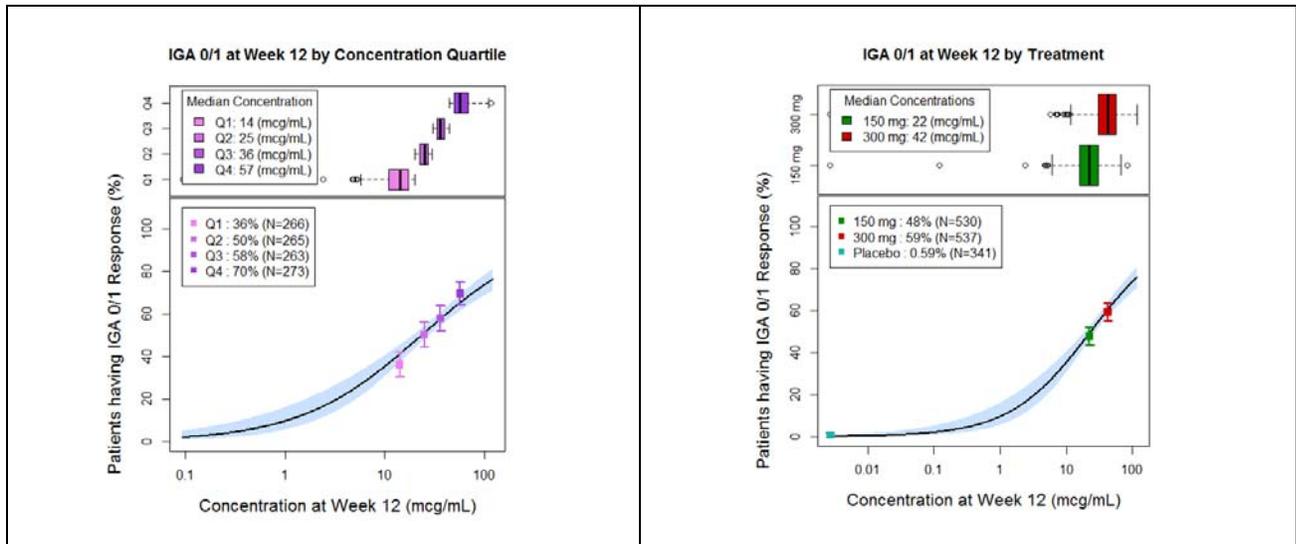


Figure 1.3.2.b. Exposure-response for IGA 0/1 (black line: prediction with a logistic regression, blue shaded area: 95% CI for the prediction). Overlaid points with bars are for the observed response rates by quartiles of observed trough concentrations with 95% CI (left) and observed rates for doses (right) for IGA 0/1 at Week 12 (FDA reviewer’s analysis with data from CAIN457A2302 and CAIN457A2303).

A similar analysis was conducted by the Applicant in response to an information request from the FDA dated July 14, 2014. Similar to the observations from the review team’s analysis, the Applicant’s analysis identified an exposure-response relationship for both co-primary endpoints (PASI 75 and IGA 0/1) for the 150 mg dose (Table 1.3.2.b) and 300 mg dose (Table 1.3.2.c). At both doses, subjects who had trough concentrations in the highest quartile had higher response rates (by ~20% in PASI 75 and by ~30% in IGA 0/1) than subjects who have trough concentrations in the lowest quartile. These observations support the role of higher secukinumab exposure as a significant factor in achieving a higher PASI 75 or IGA 0/1 response.

Table 1.3.2.b. The E-R by serum concentration quartiles at Week 12 for the 150 mg dose. (Data source: Table a65 Q4 1-2.1; Response to FDA IR, July 14, 2014)

Efficacy endpoints	Overall	150 mg dose			
		1 st quartile	2 nd quartile	3 rd quartile	4 th quartile
		≤ 15.3	15.3 to ≤ 22.3	22.3 to ≤ 29.8	>29.8
PASI 75	74.3% (362/487)	61.5% (75/122)	74.6% (91/122)	76.9% (93/121)	84.4% (103/122)
IGA 0/1	55.6% (271/487)	40.2% (49/122)	53.3% (65/122)	59.5% (72/121)	69.7% (85/122)

Table 1.3.2.c. E-R by observed serum concentration quartiles at Week 12 for the 300 mg dose. (*Data source: Table a65 Q4 1-2.2; Response to FDA IR, July 14, 2014*)

Efficacy endpoints	Overall	300 mg dose			
		1 st quartile	2 nd quartile	3 rd quartile	4 th quartile
		≤ 30.1	30.1 to ≤ 42.5	42.5 to ≤ 56.9	>56.9
PASI 75	83.9% (422/503)	73.8% (93/126)	80.2% (101/126)	87.4% (111/127)	94.4% (117/124)
IGA 0/1	67.2% (338/503)	53.2% (67/126)	66.7% (84/126)	68.5% (87/127)	80.6% (100/124)

Effect of body weight on efficacy

Body weight was identified as a significant covariate for the apparent clearance of secukinumab from the population pharmacokinetics analysis. Furthermore, multivariate logistic regression analyses identified both body weight and baseline IGA score as significant covariate on the exposure-response relationship and body weight was also a significant factor with regards to secukinumab exposure. Within each secukinumab dose group (150 mg or 300 mg), the trough concentrations of secukinumab and clinical response rates were generally higher in the lower body weight group (Figure 1.3.2.c).

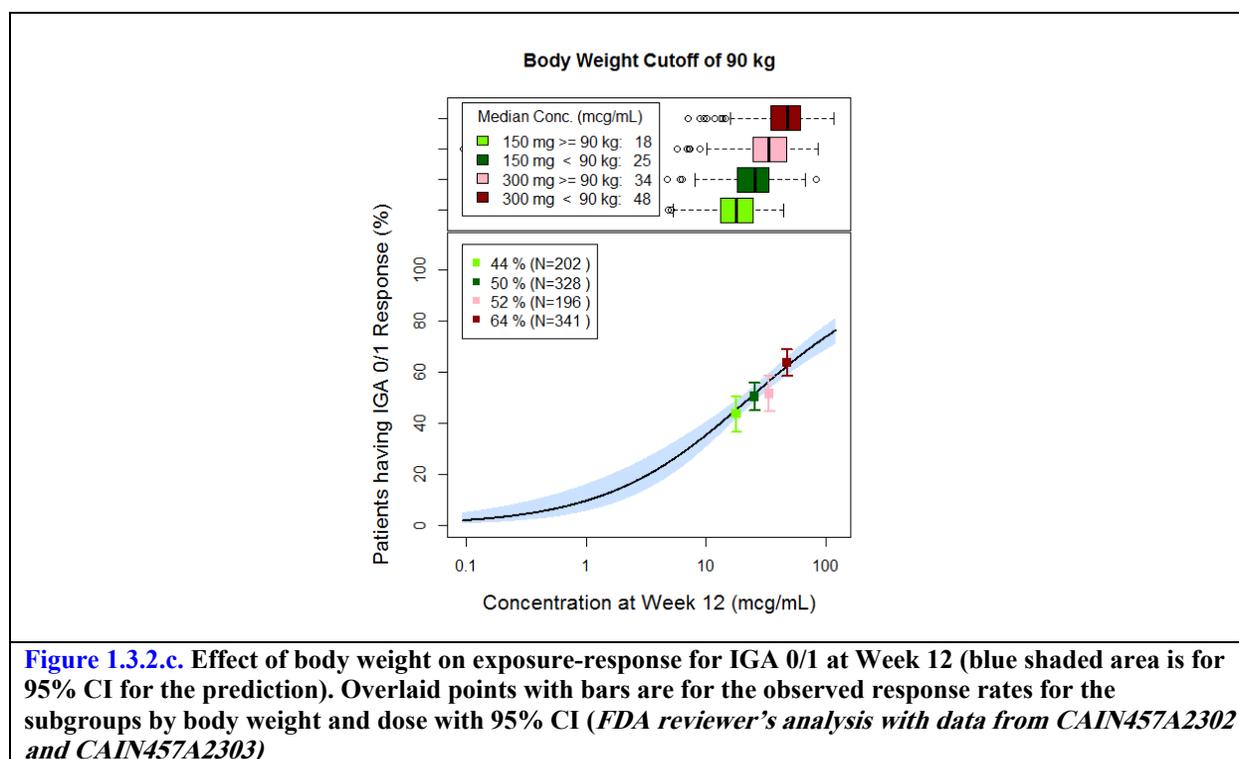


Figure 1.3.2.c. Effect of body weight on exposure-response for IGA 0/1 at Week 12 (blue shaded area is for 95% CI for the prediction). Overlaid points with bars are for the observed response rates for the subgroups by body weight and dose with 95% CI (FDA reviewer’s analysis with data from CAIN457A2302 and CAIN457A2303)

Patients with body weight < 90 kg following 150 mg (N=328, response rate: 50.3%) may expect a similar efficacy to patients with body weight ≥ 90 kg following 300 mg (N=196, response rate: 51.5% (see section 1.3.3 and 2.3.1 for more details). The results also suggest that treatment effect in patients with body weight ≥ 90 kg administered 300 mg may be further increased if the administered dose was increased to 450 mg where a similar exposure to that observed in patients with body weight < 90 kg administered 300 mg is expected.

The Applicant's assessment of the impact of body weight on PASI 75 and IGA 0/1 provided similar results to those identified by the review team (approximately 10% difference in response rate between patients with body weight <90 kg and body weight ≥ 90 kg) (Table 1.3.2.d).

Table 1.3.2.d. Week 12 response rates by body weight randomization strata in combined studies CAIN457A2302 and CAIN457A2303. (Data source: Table a65 Q4 1-1.1; Response to FDA IR, July 14, 2014)

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

Dose- and Exposure-Response for safety

Pooled analysis of 52-week safety data in the two pivotal Phase 3 trials showed an overall AE rate of 80.3% and 81.9%, respectively, for the 150 mg and 300 mg doses, indicating little to no apparent dose-response for safety. An exploratory safety analysis by exposure quartiles showed a trend of increasing AE with increasing exposure only at 300 mg dose. Across the exposure quartiles, the overall AE rates were 75.3%, 88.0%, 84.0% and 73.7% (in an increasing order of the exposure quartile), respectively, for the 150 mg dose, and 72.8%, 80.8%, 83.3% and 87.6%, respectively for the 300 mg dose.

1.3.3. Pharmacokinetics

Secukinumab displayed PK properties typical of a human IgG immunoglobulin.

Healthy subjects

In healthy subjects across several clinical trials, the secukinumab clearance values ranged from 0.11 to 0.12 L/day, the terminal half-life values ranged from 26 to 31 days, and the volume of distribution during the terminal log-linear phase ranged from 4.2 to 5.3 L. Following SC administration, the absolute bioavailability was estimated to be 77%, the Tmax ranged from 5 to 8 days, and the mean±SD values for Cmax were 21.1±2.9 and 46.3±7.6 mcg/mL for 150 mg and 300 mg doses, respectively (Study CAIN457A1101). Secukinumab PK showed approximate dose proportionality for IV doses from 1 mg/kg to 10 mg/kg and for SC doses between 150 mg and 300 mg. The available data did not suggest that PK of secukinumab in Japanese healthy subjects were different from non-Japanese healthy subjects (see Section 2.4.1 for more details).

Subjects with psoriasis

In subjects with psoriasis across several clinical trials, the secukinumab clearance values ranged from 0.14 to 0.22 L/day, the terminal half-life values ranged from 22 to 31 days, and the volume of distribution during the terminal log-linear phase ranged from 7.10 to 8.60 L. Following SC administration, secukinumab showed an absolute bioavailability of 55% in CAIN457A2103 and 73% estimated by population PK analysis. Secukinumab PK was approximately dose proportional for a single dose administration of IV doses from 1 mg/kg to 10 mg/kg and for SC doses from 25 mg to 300 mg. The dermal interstitial fluid secukinumab concentrations in non-lesional and lesional skin were comparable and were in a range between 26% and 40% of the corresponding serum concentrations (Study CAIN457A2225) following a single SC dose of 300 mg.

Following multiple dosing in the Phase 3 trials (CAIN457A2302, CAIN457A2303, and CAIN457A2304), the steady state trough concentrations (mean±SD) for the 150 mg dose ranged from 17.7±9.4 to 18.9±9.9 mcg/mL at Week 24 and from 16.7±8.2 to 18.8±11.8 mcg/mL at Week 52, and ranged from 33.4±16.7 to 36.4±15.8 mcg/mL at Week 24 and from 32.7±14.4 to 33.5±17.7 mcg/mL at Week 52 for the 300 mg dose.

Impact of body weight

At the same dose the secukinumab serum concentrations were higher in subjects with a lower body weight than those in subjects with a higher body weight in the Phase 3 trials. The steady state trough concentration at Week 24 were 22.0±11.5 mcg/mL (body weight <90 kg) and 14.5±6.3 mcg/mL (body weight ≥90 kg) for the 150 mg dose; and 45.1±20.0 mcg/mL (body weight <90 kg) and 27.3±13.7 mcg/mL (body weight ≥90 kg) for the 300 mg dose. These data indicate that the secukinumab clearance was higher in subjects with higher body weight. Based on the post-hoc estimate of the individual clearance data from the population PK analysis, the mean clearance value in subjects with body weight ≥90 kg was approximately 50% higher than that in subjects with body weight <90 kg (0.248±0.098 L/day vs. 0.166±0.058 L/day).

1.3.4. Pharmacodynamics

The serum levels of total IL-17A (free and secukinumab-bound IL-17A) increased following the secukinumab treatment in subjects with psoriasis. In Study CAIN457A2309, the serum total IL-17A concentrations were below the assay quantification limit (20 pg/mL) prior to the secukinumab treatment. At Week 4 and Week 12 post treatment, the median IL-17A concentrations increased to 142 pg/mL and 84.5 pg/mL for the 150 mg secukinumab group and 121 pg/mL and 76.5 pg/mL for the 300 mg secukinumab group, respectively. One hypothesis to explain the increased IL-17A concentrations was that the clearance of IL-17A-secukinumab complex was slower than free IL-17A.

1.3.5. Immunogenicity and its impact on PK, efficacy and safety

In the psoriasis Phase 3 trials, 0.4% (10/2842) of subjects developed secukinumab treatment-emergent anti-drug antibodies (ADA). Of the 10 subjects who developed ADAs, 3 subjects were classified as positive for neutralizing antibodies, 5 subjects were classified as negative for neutralizing antibodies, and the remaining 2 subjects were not characterized for neutralizing antibodies status. Non-treatment emergent ADAs were also observed in the same psoriasis trials in which 1.7% (56/3364) of secukinumab naive subjects had positive ADA at baseline (n=47) or at a post-baseline time point without secukinumab exposure (n=9) in placebo subjects. Among the 56 subjects tested positive for ADA at baseline, 49 subjects did not have any positive ADA samples following the treatment with secukinumab.

Overall, no evidence of altered PK, efficacy or safety has been observed in subjects who developed secukinumab treatment-emergent ADA in psoriasis Phase 3 trials. However, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on the clinical efficacy and/or safety measures because of the small number of subjects with treatment-emergent ADA.

1.3.6. Psoriasis disease-drug-drug-interactions

Drug-drug interaction (DDI) studies have not been conducted for secukinumab.

2. QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What are the highlight of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Secukinumab is a recombinant human IgG1/κ monoclonal anti-IL-17A antibody with a molecular mass of 147,944 Daltons. Secukinumab contains [REDACTED] (b) (4). The drug substance of the to-be-marketed secukinumab products is expressed in a recombinant CHO cell line.

The proposed formulation and presentation for secukinumab SC injection include the following:

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

2.1.2. What are the proposed mechanism of action and therapeutic indication?

Secukinumab selectively binds to the proinflammatory cytokine interleukin-17A (IL-17A) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in the normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis. The proposed indication is the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

2.1.3. What are the proposed dosages and routes of administration?

The proposed dose is 300 mg by SC injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly dosing starting at Week 4. Each 300 mg dose is given as 2 SC injections of 150 mg.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology, biopharmaceutics and clinical studies used to support dosing or claims?

Table 2.2.1 summarizes the clinical trials containing clinical pharmacology assessments relevant to the proposed indication and the proposed product labeling.

There were four placebo-controlled Phase 3 trials (CAIN457A2302, CAIN457A 2303, CAIN457A 2308, and CAIN457A 2309) to support the safety and efficacy of two secukinumab dose levels (150 mg and 300 mg). The two pivotal trials, CAIN457A2302 and CAIN457A 2303, provided safety/efficacy data for a total treatment duration of 52 weeks. In this BLA, the data from the two small Phase 3b trials, CAIN457A2308 and CAIN457A2309, only provide safety/efficacy data for a total treatment duration of 12 weeks. The four Phase 3 trials had almost identical study designs with secukinumab or placebo administered at Weeks 0, 1, 2, 3, followed by a monthly (q4w) dosing regimen starting at Week 4.

One additional Phase 3 trial CAIN457A2304 was conducted to compare two different maintenance regimens: a fixed interval or the initiation of dosing only at “Start of Relapse”.

Table 2.2.1. The clinical trials and their utilities to support clinical pharmacology assessments of secukinumab for the treatment of psoriasis. HS, healthy subjects; NCA, non-compartment analysis; PFS, prefilled syringe; LYO, lyophilized powder; AI, autoinjector

Clinical trial	Subjects	Dose/Treatment (subject#)	Utility of the data and main results to support the clinical pharmacology review
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Phase 1	CAIN4571101	HS (Japanese)	<ul style="list-style-type: none"> - 1 mg/kg IV (n=6) - 3 mg/kg IV (n=6) - 10 mg/kg IV (n=6) - Placebo IV (n=6) - 150 mg SC (n=6) - 300 mg SC (n=6) - Placebo SC (n=6) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA) ▪ Absolute bioavailability (BA) ▪ Dose proportionality
	CAIN457A2228	HS	<ul style="list-style-type: none"> - 10 mg/kg IV (n=9) - Placebo IV (n=3) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA)
	CAIN457A2104	HS	<ul style="list-style-type: none"> - 10 mg/kg IV (n=12) - Placebo (n=6) - Corticosteroid (n=6) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA)
	CAIN457A2225	HS Psoriasis	<ul style="list-style-type: none"> - 300 mg SC (n=8) - 300 mg SC (n=8) 	<ul style="list-style-type: none"> ▪ PK in dermal interstitial fluid (ISF) ▪ PD of IL-17 in dermal ISF
	CAIN457A2103	Psoriasis	<ul style="list-style-type: none"> - 1 mg/kg IV (n=14) - 150 mg SC (n=14) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA) ▪ Absolute BA (cross-over design) ▪ Population PK
Phase 1 (BE)	CAIN457A2106	HS	<ul style="list-style-type: none"> - 300 mg SC PFS (n=75) - 300 mg SC LYO (n=75) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA) ▪ Relative bioavailability (BE assessment)
Phase 2a	CAIN457A2102	Psoriasis	<ul style="list-style-type: none"> - 3 mg/kg IV (n=18) - Placebo IV (n=18) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA) ▪ Population PK ▪ Proof of concept; Biomarker
Phase 2	CAIN457A2204	Psoriasis	<ul style="list-style-type: none"> - 0.3 mg/kg IV (n=20) - 1 mg/kg IV (n=20) - 3 mg/kg IV (n=20) - Placebo IV (n=18) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA) ▪ Dose proportionality <p><i>(Due to issues identified during the audit of center 0001, a majority [65/78] of subjects enrolled were excluded from the efficacy/safety data analysis.)</i></p>
	CAIN457A2212	Psoriasis	<ul style="list-style-type: none"> - 3 mg/kg IV (n=39) - 10 mg/kg IV (n=38) - 10 mg/kg IV ×3 (n=40) - Placebo IV (n=13) 	<ul style="list-style-type: none"> ▪ PK parameters (NCA) ▪ Population PK ▪ Dose proportionality ▪ Dose ranging
	CAIN457A2220	Psoriasis	<ul style="list-style-type: none"> - 25 mg SC (n=29) - 3×25 mg SC (n=26) - 3×75 mg SC (n=21) - 3×150 mg SC (n=27) - Placebo (n=22) 	<ul style="list-style-type: none"> ▪ Dose ranging ▪ Dose proportionality ▪ Population PK
	CAIN457A2211	Psoriasis	<ul style="list-style-type: none"> - 1×150 mg SC (n=66) - 150 mg SC at Weeks 0, 4, 8 (n=138) - 150 mg SC at Weeks 0, 1, 2, 4 (n=133) - Placebo at Weeks 0, 1, 2, 4, 8 (n=67) 	<ul style="list-style-type: none"> ▪ Dose ranging ▪ Dosing interval for maintenance ▪ Population PK
Phase 3	CAIN457A2302	Psoriasis	<ul style="list-style-type: none"> - 150 mg SC (n=245) - 300 mg SC (n=245) - Placebo SC (n=248) 	<ul style="list-style-type: none"> ▪ Confirmatory efficacy/safety ▪ Immunogenicity ▪ Population PK, C_{trough} and steady state PK
	CAIN457A2303	Psoriasis	<ul style="list-style-type: none"> - 150 mg SC (n=327) - 300 mg SC (n=327) - Placebo SC (n=326) 	<ul style="list-style-type: none"> ▪ Confirmatory efficacy/safety ▪ Immunogenicity ▪ Population PK, C_{trough} and steady state PK
	CAIN457A2304	Psoriasis	<ul style="list-style-type: none"> - 150 mg SC (n=482) - 300 mg SC (n=484) 	<ul style="list-style-type: none"> ▪ Fixed dose regimen vs retreatment at start of relapse ▪ Immunogenicity
	CAIN457A2308	Psoriasis	<ul style="list-style-type: none"> - 150 mg SC (n=59) - 300 mg SC (n=59) - Placebo SC (n=59) 	<ul style="list-style-type: none"> ▪ Week 12 efficacy (PFS) ▪ Immunogenicity ▪ C_{trough} and steady state PK
	CAIN457A2309	Psoriasis	<ul style="list-style-type: none"> - 150 mg SC (n=61) - 300 mg SC (n=60) - Placebo SC (n=61) 	<ul style="list-style-type: none"> ▪ Week 12 efficacy (AI) ▪ Immunogenicity ▪ C_{trough} and steady state PK

2.2.2. What are the clinical endpoints for efficacy evaluation and how are they measured?

In the Phase 3 trials, the primary efficacy evaluation was based on two endpoints: the Psoriasis Area and Severity Index (PASI) and the Investigator’s Global Assessment mod 2011 (simplified and referred to as “IGA” in this review). The co-primary efficacy endpoints were PASI 75 response and IGA 0/1 response at Week 12.

PASI

The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling). PASI score is a standard and validated measurement for chronic plaque psoriasis. The PASI 50, PASI 75, PASI 90, and PASI 100 responders are defined as below:

- PASI 50 responders: $\geq 50\%$ improvement (reduction) in PASI score
- PASI 75 responders: $\geq 75\%$ improvement (reduction) in PASI score
- PASI 90 responders: $\geq 90\%$ improvement (reduction) in PASI score
- PASI 100 responders: complete clearance of psoriasis (absolute PASI score of 0)
- Partial responders are defined as $\geq 50\%$ but $< 75\%$ improvement (reduction) in PASI score

IGA

In secukinumab psoriasis Phase 3 trials, a 5-point IGA scale was used for efficacy assessment: “0 = clear”, “1 = almost clear”, “2 = mild”, “3 = moderate”, and “4 = severe”, which represent the physician’s overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Details of the IGA rating scale are provided in [Table 2.2.2](#). A patient was considered an IGA 0/1 responder if they achieved a score of 0 or 1 AND there was an improvement of 2 points or more compared to baseline.

Table 2.2.2. The IGA mod 2011 rating scale used in secukinumab psoriasis Phase 3 trials. (*Data source: Summary of Clinical Efficacy, Table 1-1, page 17*)

Score	Short description	Detailed description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions.

2.2.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, total secukinumab concentrations, i.e., free secukinumab plus secukinumab bound to IL-17A, was determined in human serum using an ELISA method with an LLOQ of 80 ng/mL. The total IL-17 concentrations, i.e., free IL-17A and IL-17A bound to secukinumab, were measured using an ELISA assay with the LLOQ of 20 pg/mL. The observed IL-17A serum concentrations were generally low (a median peak value of approximately 130 pg/mL) in both healthy subjects and subjects with psoriasis

following secukinumab administrations. Assuming 1:1 binding stoichiometry between IL-17A and secukinumab, the serum secukinumab bound to IL-17A represents only approximately 0.16% of the total serum secukinumab at 80 ng/mL (LLOQ) and 0.0006% at 22.2 mcg/mL (the average secukinumab trough concentration for the 150 mg dose at Week 12 in Phase 3 trials). Therefore, the total serum concentrations measured by the ELISA method reasonably represent the free secukinumab concentrations. The ELISA method was also validated to measure the secukinumab concentration in the dermal interstitial fluid with LLOQ of 76 ng/mL. Refer to Section 2.10 for more details.

2.3. Dose/Exposure-Response

2.3.1. What are the characteristics of the dose- or exposure-response relationship for effectiveness? Is the dose and dosing regimen selected consistent with the known E-R relationship?

Yes, the overall efficacy and safety data and dose/exposure-relationship support the recommendation of 300 mg dose proposed by the Applicant.

Overall, a clear dose-response relationship for PASI75 at Week 12 was shown in Phase 2 studies for secukinumab administered via IV route and SC route where secukinumab was administered as a single dose and multiple doses at various dosing frequency and total dose. The dose regimens evaluated ranged from the lowest dose regimen of a single 25 mg SC dose to the highest dose regimen of three IV doses of 10 mg/kg administered every two weeks over the duration of 4 weeks. The dose-response for efficacy observed in Phase 2 studies supported the selection of 150 mg and 300 mg doses for testing in the Phase 3 trials.

In the Phase 3 trials, the efficacy results showed that both 150 mg and 300 mg doses of secukinumab achieved significantly higher response rates for both primary endpoints compared to the placebo and the 300 mg dose achieved a higher response rate compared to the 150 mg dose. An exposure-response relationship was observed for both primary endpoints at Week 12 for both 150 mg dose and 300 mg dose when evaluated by the observed serum concentration quartiles.

Dose-response relationship in Phase 2 trials

The dose-response relationship shown in three Phase 2 trials (CAIN457A2211, CAIN457A2212 and CAIN457A2220) supported the dose selection for the Phase 3 trials.

- In Study CAIN4572212, PASI 75 and IGA 0/1 response rates increased with increasing IV dose of secukinumab from 1×3 mg/kg to 3×10 mg/kg (Table 2.3.1.a). The selection of the 300 mg SC dosing regimen (4 weekly doses followed by monthly dosing) for Phase 3 trials was supported by the model-based PK simulations showing that it achieves a similar exposure as that for the 3×10 mg/kg IV dosing regimen.

Table 2.3.1.a. PASI 75 and IGA 0/1 response rates at Week 12 in CAIN457A2212. (Data source: Summary of Clinical Efficacy, Table 4-2; CSR CAIN457A2212 Table 14.2-3.1)

	Placebo (n=10)	Secukinumab IV		
		1×3 mg/kg (n=30)	1×10 mg/kg (n=25)	3×10 mg/kg at Weeks 0, 2, and 4 (n=29)
PASI 75 (%)	10	40	75	82.8
IGA mod 2007 0/1 (%)	0	26.7	48	75.9

- In Study CAIN457A2220, the PASI 75 and IGA 0/1 response rates increased with increasing dose of SC secukinumab from 1×25 mg to 3×150 mg (Table 2.3.1.b). At 12 weeks after treatment, only the 3×150 mg SC dosing regimen resulted in significant higher response rates for both PASI 75 and IGA 0/1 when compared to the placebo, which supported the selection of the 150 mg dose to be tested in Phase 3.

Table 2.3.1.b. PASI 75 and IGA 0/1 response rates at Week 12 in CAIN457A2220. *Statistically different from placebo. (Data source: Summary of Clinical Efficacy, Table 4-1)

	Placebo (n=22)	Secukinumab SC (single dose or three doses by q4w)			
		1×25 mg (n=29)	3×25 mg (n=26)	3×75 mg (n=21)	3×150 mg (n=27)
PASI 75 (%)	9.1	3.4	19.2	57.1*	81.5*
IGA mod 2009 0/1 (%)	9.1	0	11.5	33.3	48.1*

- In Study CAIN457A2211, PASI 75 and IGA 0/1 response rates increased with increasing dose of SC secukinumab from 1×150 mg to 4×150 mg (Table 2.3.1.c). At 12 weeks after treatment, both the 3×150 mg SC and 4×150 mg SC dosing regimens resulted in significant higher response rates for both PASI 75 and IGA 0/1 when compared to the placebo. The efficacy data overall supported the selection of the 150 mg dose to be tested in Phase 3 and suggested that early induction doses could achieve a higher clinical response rate at Week 12.

Table 2.3.1.c. PASI 75 and IGA 0/1 response rates at Week 12 in CAIN457A2211. *statistically different from placebo. (Data source: Summary of Clinical Efficacy, Table 4-3)

	Placebo (n=67)	Secukinumab SC		
		1×150 mg (n=66)	3×150 mg at Weeks 0, 4, and 8 (n=138)	4×150 mg at Weeks 0, 1, 2, and 4 (n=133)
PASI 75 (%)	1.5	10.6	42.0*	54.5*
IGA mod 2009 0/1 (%)	1.5	4.5	22.6*	37.1*

Dose-response for efficacy in Phase 3 trials

The efficacy and safety of secukinumab were evaluated in four Phase 3 trials (CAIN457A2302, CAIN457A2303, CAIN457A2308, and CAIN457A2309) with similar study designs. Secukinumab (150 mg or 300 mg) was administered subcutaneously at Weeks 0, 1, 2, and 3, followed by a monthly (q4w) dosing regimen starting at Week 4. Two co-primary efficacy endpoints, i.e., PASI 75 and IGA 0/1, were assessed at Week 12. The clinical response rates for both primary endpoints are summarized in Table 1.3.2.a. The results showed that both 150 mg and 300 mg doses of secukinumab achieved a higher response rate (statistically significant) compared to the placebo and the 300 mg dose achieved a higher response rate compared to the 150 mg dose.

Exposure-response for efficacy in Phase 3 trials

An exposure-response relationship was observed for both PASI 75 and IGA 0/1 with the observed serum concentrations at Week 12. The logistic regression analyses show that an increasing secukinumab concentration at Week 12 was a significant predictor of an increasing IGA 0/1 response at Week 12 (p -value $< 2 \times 10^{-16}$). The body weight and the baseline IGA score were identified as significant covariates on the exposure-response relationship; higher body weight and higher baseline

IGA score resulted in lower response rate (Figure 1.3.b.). The consistent results were observed from analysis with trough concentrations within each dose for 150 mg dose (Table 1.3.2.b) and 300 mg dose (Table 1.3.2.c). At both doses, subjects who had trough concentrations in the highest quartile are associated with a higher response rate (by ~20% in PASI 75 and by ~30% in IGA 0/1) than subjects who have trough concentrations in the lowest quartile. Refer to *Pharmacometrics Review* section for more details.

2.3.2. What are the characteristics of the exposure-response relationships for safety?

Overall, no apparent exposure-response relationship for overall treatment emergent adverse events (AEs) was observed based on the pooled safety analysis through Week 52 of Phase 3 trials CAIN457A2302 and CAIN457A2303. Although there are only a limited number of events, a trend for more frequent localized oral mucosal candida infections with higher exposure was observed.

E-R for overall adverse events

Pooled analysis of 52-week safety data in the two pivotal Phase 3 trials showed an overall AE rate of 80.3% and 81.9%, respectively, for the 150 mg and 300 mg doses, indicating little to no apparent dose-response for safety. An exploratory safety analysis by exposure quartiles showed a trend of increasing AE with increasing exposure only at 300 mg dose. Across the exposure quartiles, the overall AE rates were 75.3%, 88.0%, 84.0% and 73.7% (in an increasing order of the exposure quartile), respectively, for the 150 mg dose (Table 2.3.2.a), and 72.8%, 80.8%, 83.3% and 87.6%, respectively for the 300 mg dose (Table 2.3.2.b).

Table 2.3.2.a. Overall treatment emergent adverse events by Week 52 secukinumab trough serum concentration quartiles for the 150 mg dose in pooled analysis for CAIN457A2302 and CAIN457A2303. (Data source: Table 3-1, Table 3-3, Response to FDA information request, July 14, 2014.)

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

Table 2.3.2.b. Overall treatment emergent adverse events by Week 52 secukinumab trough serum concentration quartiles for the 300 mg dose in pooled analysis for CAIN457A2302 and CAIN457A2303. (Data source: Table 3-2, Table 3-4, Response to FDA information request, July 14, 2014.)

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

E-R for Candida infection

The overall number of total events (n=9 for 150 mg and n=19 for 300 mg treatment groups) is small. However, the Phase 3 data showed a trend of association between exposure and candida infection. In the 150 mg treatment group, there is a trend toward more frequent infections in the two higher

exposure quartiles (1.0%, 1.0%, 4.0% and 3.0% in each quartile listed in the order of increasing exposure) (Table 2.3.2.a). In the 300 mg treatment group, a similar trend is observed (1.9%, 3.8%, 6.9% and 5.7% listed in the order of increasing exposure quartile) (Table 2.3.2.b).

2.3.3. What are the efficacy data that explored and supported the maintenance dosing regimen including dosing frequency?

The 300 mg q4w dosing regimen for maintaining the clinical efficacy during the maintenance treatment period is supported by the results from four studies. The Phase 2 trial CAIN457A2211 evaluated 150 mg dose at the dosing frequency of every 12 week for up to 28 weeks as well as a retreatment regimen at the start of relapse, the Phase 3 trial CAIN457A2304 evaluated the doses of 150 and 300 mg at the dosing frequency of every 4 week for up to 48 weeks as well as a retreatment regimen at the start of relapse, and the two pivotal trials (CAIN457A2302 and CAIN457A2303) evaluated the doses of 150 mg and 300 mg at a dosing frequency of every 4 weeks for up to 52 weeks.

Phase 2 Trial CAIN457A2211

In CAIN457A2211, after 12 weeks of treatment, the responders (\geq PASI 75) were re-randomized (1:1) to (1) “Fixed-time interval” regimen with secukinumab injections at Week 12 and at Week 24 (150 mg q12w), and (2) “Start of relapse” regimen with 150 mg secukinumab injections once relapse started (defined as a loss of 1/3 of the PASI gain during the study). The remaining subjects who are partial responders or non-responders (PASI 50-75 or $<$ 50) received “open-label” treatment with 150 mg q4w dose.

The proportion of patients who had PASI 75 on \geq 1 of the 3 visits at Weeks 20, 24, and 28 was greater in the “Fixed-time interval” treatment group than the “Start of relapse” treatment group (Table 2.3.3.a). The results indicated that the PASI 75 response rate decreased over time in initial responders who received dosing every 12 weeks. In contrast, with dosing every 4 weeks in the “open-label” group, 46.2% of partial or non-responders at Week 12 were able to achieve PASI 75 response. The Phase 2 data overall supported the selection of the dosing frequency of q4w for the fixed interval maintenance treatment in the Phase 3 trials. Of note, the study design did not evaluate any dosing intervals longer than 4 weeks and shorter than 12 weeks. At week 16, 23% (15/67) of responders (assessed at Week 12) in the “Start of relapse” treatment group lost the response, compared to 4.6% (3/65) in the fixed interval treatment group, supporting a dosing frequency of q4w.

Table 2.3.3.a. The PASI 75 response rate for 150 mg dose of secukinumab at Weeks 20-28 in CAIN457A2211. (Data source: Summary of Clinical Efficacy, Table 4-4)

Maintenance Regimen	Fixed interval of 12 weeks (n=65)	Start of relapse (n=67)	Open label (n=247)
PASI 75 at Week 20-28	84.6%	67.2%	46.2%

Phase 3 Trials CAIN457A2304

In Study CAIN457A2304, the PASI 75 responders at Week 12 were re-randomized, within their same dose group of either 150 or 300 mg SC secukinumab, in a ratio of 1:1 to one of two treatment schedules: “fixed interval (FI)” or “retreatment at start of relapse (SOR)”. In FI treatment groups, subjects continued to receive secukinumab 150 mg q4w or 300 mg q4w from Week 12 to Week 48. In SOR treatment groups, after week 12, a subject was not dosed with active secukinumab until that subject met start of relapse criteria and continued dosing until PASI 75 response was regained. “Start

of relapse” was defined as a loss of $\geq 20\%$ of the maximum PASI gain achieved during the study compared to baseline, *and* a loss of PASI 75 response.

The results showed that subjects treated with the FI regimen achieved higher response rates compared to subjects treated with the SoR regimen at each of two dose levels (300 mg or 150 mg). The 300 mg dose level achieved a higher response rate than the 150 mg dose level among subjects who were treated with the FI regimen as well as among subjects who were treated with the SOR regimen (Table 2.3.3.b).

Table 2.3.3.b. The PASI75 and IGA 0/1 response rates at Week 52 for responders at Week 12 in Study CAIN457A2304. FI, fix interval regimen; SOR, start of relapse regimen. (*Data source: CSR CAIN457A2304, Table 11-10, Table 11-11*)

Maintenance Regimen	Secukinumab 150 mg		Secukinumab 300 mg	
	FI (4 weeks)	SoR	FI (4 weeks)	SOR
PASI 75 at Week 52	62.1% [126/203]	52.4% [108/206]	78.2% [169/216]	67.7% [147/217]
IGA 0/1 at Week 52	60.3% [88/146]	21.9% [34/155]	68.6% [120/175]	22.6% [42/186]

Phase 3 Trials CAIN457A2302 and CAIN457A2303

The efficacy results at Week 52 in CAIN457A2302 and CAIN457A2303 showed that PASI 75 and IGA 0/1 responses were maintained through Week 52 for both 150 mg q4w and 300 mg q4w with a greater number of responders in the 300 mg dose group compared to that in the 150 mg dose group (Table 2.3.3.c).

Table 2.3.3.c. PASI75 and IGA 0/1 response rate at Week 52 in the pivotal Phase 3 trials CAIN457A2302 and CAIN457A2303.

Phase 3 trial	Treatment	PASI 75	IGA 0/1 (clear or almost clear)
CAIN457A2302	150 mg	60.1% (146/243)	41.4% (101/244)
	300 mg	74.3% (182/245)	60.4% (148/245)
CAIN457A2303	150 mg	65.7% (215/327)	51.4% (168/327)
	300 mg	78.6% (254/323)	67.8% (219/323)

2.3.4. Does this drug prolong QT/QTc Interval?

Thorough QT/QTc studies were not conducted for secukinumab because it is generally not required for a monoclonal antibody biological product.

2.4. Pharmacokinetics

2.4.1. What are the PK characteristics of secukinumab in healthy subjects and in subjects with psoriasis?

Secukinumab PK was evaluated in healthy subjects and in subjects with psoriasis in multiple clinical trials. Secukinumab displayed PK properties typical of a human IgG immunoglobulin. Table 2.4.1.a summarizes the main PK parameters of secukinumab in healthy subjects and in subjects with psoriasis based on the non-compartment analysis. The clearance and the volume of distribution values appear to be higher in subjects with psoriasis than in healthy subjects.

Table 2.4.1.a. Mean PK parameters of secukinumab determined by non-compartment analysis in individual clinical trials. HS, healthy subjects; IV, except for CAIN457A2228 that used 30-min infusion, other studies for IV

administration used 120-min IV infusion. Tmax is the median value. ^a CAIN457A2228 had a short duration (8 days) of the PK sampling and the PK parameters could not be derived. (*Data source: Summary of Clinical Pharmacology, Table 3-1, page 28-29 and individual CSR*)

Clinical trial	Population	Dose	Mean value of PK parameters					
			Cmax (mcg/mL)	Tmax (day)	T1/2 (day)	CL or [CL/F] (L/day)	Vz [Vss] (L)	F
CAIN4571101	HS (Japanese)	1 mg/kg IV	24.0	0.08	31.2	0.121	5.34 [4.77]	-
		3 mg/kg IV	70.3	0.17	26.4	0.114	4.29 [4.23]	-
		10 mg/kg IV	264	0.08	25.9	0.114	4.23 [4.12]	-
		150 mg SC	21.1	8.01	30.0	[0.142]	6.10	0.77
		300 mg SC	46.3	8.00	25.9	[0.162]	5.91	
CAIN457A2106	HS	300 mg SC (PFS)	43.2	5.00	25.9	[0.181]	6.57	-
		300 mg SC(LYO)	42.0	5.00	26.6	[0.181]	6.72	-
CAIN457A2104	HS	10 mg/kg IV	255	0.09	29.8	0.120	5.05 [4.45]	-
CAIN457A2228 ^a	HS	10 mg/kg IV	237	0.08	-	-	-	-
CAIN457A2102	psoriasis	3 mg/kg IV	74.5	0.11	29.2	0.180	7.31	-
CAIN457A2103	psoriasis	1 mg/kg IV	24.1	0.09	27.1	0.222	7.10	-
		150 mg SC	11.8	8.50	22.2	-	-	0.55
CAIN457A2204	psoriasis	0.3 mg/kg IV	9.38	0.09	30.2	0.141	5.80	-
		1 mg/kg IV	28.9	0.11	27.9	0.199	7.36	-
		3 mg/kg IV	81.2	0.13	28.0	0.185	7.12	-
CAIN457A2212	psoriasis	10 mg/kg IV ×3	407	27.9	29.9	0.184	7.70	-
		10 mg/kg IV	258	0.09	30.7	0.197	8.28	-
		3 mg/kg IV	76.5	0.09	29.5	0.210	8.60	-

2.4.2. What are the characteristics of drug absorption following SC administration?

In healthy subjects, secukinumab showed Cmax of 42.0±11.2 mcg/mL and 43.2±10.4 mcg/mL at approximately day 5 following a single SC administration of 300 mg presented in LYO and PFS formulations, respectively (Study CAIN457A2106). In healthy Japanese subjects, secukinumab showed Cmax of 21.1±2.9 and 46.3±7.6 mcg/mL at approximately Day 8 following a single SC administration of 150 mg and 300 mg, respectively.

In subjects with psoriasis, secukinumab showed Cmax of 11.8±3.8 mcg/mL at approximately Day 8 following a single SC administration of 150 mg (Study CAIN457A2103). Based on the population PK simulation, following a single SC dose of either 150 mg or 300 mg in subjects with psoriasis, secukinumab reached peak serum concentrations (C_{max}) of 13.7 ± 4.8 mcg/mL and 27.3 ± 9.5 mcg/mL, respectively, in approximately 6 days post dose.

The data overall suggest lower Cmax values in subjects with psoriasis compared with those observed in healthy subjects when given the same 150 mg or 300 mg dose.

Bioavailability in subjects with psoriasis

Secukinumab showed an estimated absolute bioavailability of 55% in subjects with psoriasis (Study CAIN457A2103). Based on population PK simulation, secukinumab is absorbed with an average bioavailability of 73% in subjects with psoriasis.

In Study CAIN457A2103, a total of 14 subjects were randomized in a 1:1 ratio to receive secukinumab dose administrations of either (1) 1 mg/kg IV at Day 1 followed by 150 mg SC at Day

29, or (2) 150 mg SC at Day 1 followed by 1 mg/kg IV at Day 29. Because the crossover trial design did not have a complete washout period following the first dose administration and the second dose was given while there was still a substantial drug concentration from the first dose, the bioavailability was estimated with the carry-over corrections based on terminal elimination rate constant observed in the second treatment period.

Bioavailability in healthy subjects

The PK results in Study CAIN457A1101 showed an absolute secukinumab bioavailability estimate of 77% in healthy Japanese subjects. In Study CAIN457A1101, a total of 42 Japanese healthy male subjects were randomized to one of 5 cohorts (3 IV cohorts and 2 SC cohorts). Subjects in IV cohorts received an IV infusion of secukinumab at the dose of 1, 3, or 10 mg/kg. Subjects in SC cohorts received a SC injection of secukinumab at the dose of 150 or 300 mg. The absolute bioavailability was calculated by comparing dose-normalized AUC_{inf} after SC injection with those after IV infusion.

2.4.3. What are the characteristics of drug distribution?

Following a single IV administration of 1-10 mg/kg secukinumab, the mean volume of distribution during the terminal phase ranged from 7.10 to 8.60 L in subjects with psoriasis, compared to the range from 4.23 L to 5.34 L in healthy subjects. The volume of distribution values appear to be higher in psoriasis patients than in healthy subjects.

Study CAIN457A2225 investigated the distribution of secukinumab into the dermal interstitial fluid using an open flow microperfusion in healthy subjects and in psoriatic patients. In healthy subjects, the mean secukinumab concentrations in the dermal interstitial fluid was 21.5% and 23.4% of the corresponding serum secukinumab concentrations, respectively, at 1 week and 2 weeks after a single SC dose of secukinumab 300 mg. In subjects with psoriasis, the dermal interstitial fluid concentrations in non-lesional and lesional skin were comparable and were in a range between 26% and 40% of the corresponding serum concentrations.

2.4.4. What are the characteristics of drug metabolism?

The metabolic pathway of secukinumab has not been characterized.

It is assumed that as a human IgG1 κ monoclonal antibody secukinumab is degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

2.4.5. What are the characteristics of drug elimination?

In healthy subjects, the mean half-life values of secukinumab ranged from 26 to 31 days and clearance values of 0.11 to 0.12 L/day across several clinical trials (Table 2.4.1.a).

In subjects with psoriasis, the mean half-life values of secukinumab ranged from 22 to 31 days and the mean apparent clearances values ranged from 0.14 to 0.22 L/day across several clinical trials (Table 2.4.1a). The population PK analysis estimated the average half-life value to be 27 days with 27.2 %CV and the typical apparent clearance value to be 0.19 L/day with 32%CV. The apparent clearance appears to be higher in psoriasis patients than in healthy subjects.

2.4.6. What is the degree of the proportionality of the dose-concentration relationship?

Secukinumab shows dose proportional PK over the dose range from 1 to 10 mg/kg IV and from 25 mg to 300 mg SC.

Dose proportionality following IV administration

In Japanese healthy volunteers (Study CAIN457A1101), the secukinumab PK showed approximate dose proportionality with regard to the PK parameters of C_{max} , AUC_{last} , and AUC_{inf} following IV doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg. In subjects with psoriasis (Study CAIN457A2212), the secukinumab PK showed approximate dose proportionality with regard to PK parameters of C_{max} , AUC_{last} , and AUC_{inf} following IV doses of 3 mg/kg and 10 mg/kg.

Dose proportionality following SC administration

In Japanese healthy volunteers (Study CAIN457A1101), the secukinumab PK showed approximate dose proportionality with regard to the PK parameters of C_{max} , AUC_{last} and AUC_{inf} following SC doses of 150 mg and 300 mg. In subjects with psoriasis (Study CAIN457A2220), dose-proportional increases in the secukinumab trough concentrations were observed over the dose range from 3× 25 mg SC to 3× 150 mg SC administered at Weeks 0, 4, and 8 (Table 2.4.6.a). Dose proportionality in the dose range from 150 mg SC to 300 mg SC was consistently observed in the psoriasis Phase 3 trials by comparing the trough concentrations (see section 2.4.7).

Table 2.4.6.a. Secukinumab trough concentrations in Study CAIN457A2220. SC doses were administered at Weeks 0, 4 and 8 at dose levels of 25, 75 and 150 mg. (*Data source: Summary of Clinical Pharmacology, Table 3-4, Page 33*)

Time	Secukinumab trough concentrations (mcg/mL), mean ± SD (n)		
	25 mg SC	75 mg SC	150 mg SC
Week 4	1.72±0.618 (24)	5.17±1.70 (18)	8.88±2.05 (24)
Week 8	3.00±1.02 (20)	7.50±2.54 (17)	14.1±5.10 (25)
Week 12	3.41±1.87 (23)	8.80±3.06 (18)	17.2±7.18 (23)

2.4.7. What are exposures following chronic dosing?

Across the Phase 3 trials, following chronic dosing of secukinumab 150 mg SC the mean trough concentrations ranged from 17.7 to 18.9 mcg/mL at Week 24 and from 16.7 to 18.8 mcg/mL at Week 52 (Table 2.4.7). Following chronic dosing of secukinumab 300 mg SC the mean trough concentrations ranged from 33.4 to 36.4 mcg/mL at Week 24 and from 32.7 to 33.5 mcg/mL at Week 52 (Table 2.4.7).

Table 2.4.7. Secukinumab trough serum concentrations in Phase 3 trials: Study CAIN457A2302, Study CAIN457A2308, and Study CAIN457A2309.

Dose	Time	Serum secukinumab concentrations (mcg/mL), Mean ± SD (n)		
		CAIN457A2302	CAIN457A2303	CAIN457A2304
150 mg	Week 4	44.9±14.6 (230)	46.3±16.3 (288)	44.1±14.9 (436)
	Week 12	22.8±10.2 (216)	23.9±11.6 (272)	23.2±9.7 (414)
	Week 24	17.7±9.4 (206)	18.2±9.4 (276)	18.9±9.9 (183)
	Week 52	16.7±8.2 (171)	18.8±11.8 (225)	16.9±7.2 (169)
300 mg	Week 4	87.2±30.1 (226)	89.9±32.6 (296)	85.2±31.8 (439)
	Week 12	44.8±20.6 (219)	45.4±21.2 (284)	45.2±20.5 (424)
	Week 24	34.4±16.6 (211)	33.4±16.7 (276)	36.4±15.8 (194)
	Week 52	32.7±14.4 (177)	33.5±17.7 (236)	34.4±16.2 (177)

The population PK model-predicted peak concentrations (C_{max}) at steady state following SC administrations of 150 or 300 mg are 27.6 mcg/mL and 55.2 mcg/mL. The C_{max} at steady-state is approximately 2-fold higher than the C_{max} after the initial dose administration, which is consistent with the half-life of secukinumab and the dosing frequency of every 4 weeks.

2.5. Intrinsic Factors

2.5.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure in psoriasis patients and how much of the variability is explained by the identified covariates?

The inter-subject exposure variability and the intrinsic factors contributing to the variability in subjects with psoriasis were assessed by population PK analysis. The structural model was a linear two-compartmental distribution model with first-order absorption for SC administration and zero-order infusion for IV administration. The base model included the body weight as a covariate. Refer to the *Pharmacometrics Review* section for more detailed information.

Table 2.5.1.a. summarizes the SD, CV% and Range 90% for the values of the simulated PK metrics for the 150 mg regimen and the 300 mg regimen used in the Phase 3 trials.

Table 2.5.1.a. PK parameters of secukinumab determined by population PK simulation in subjects with psoriasis. (Data source: Summary of Clinical Pharmacology, Table 3-6 and Table 3-7, page 38-39)

PK parameters	150 mg regimen			300 mg regimen		
	Mean ± SD	CV%	Range (90%)	Mean ± SD	CV%	Range (90%)
C _{trough} , Week12 (mcg/mL)	22.1 ± 10.3	46.5	[8.7, 41.5]	44.2 ± 20.6	46.5	[17.5, 83.0]
C _{trough} , steady state (mcg/mL)	16 ± 7.7	48	[6.5, 31.5]	32.1 ± 15.4	48	[12.9, 62.9]
C _{max} , single dose (mcg/mL)	13.7 ± 4.8	34.8	[7.1, 22.3]	27.3 ± 9.5	34.8	[14.2, 44.6]
C _{max} , steady state (mcg/mL)	27.6 ± 10.7	38.9	[13.7, 47.4]	55.2 ± 21.5	38.9	[27.5, 94.8]
T _{1/2} terminal (days)	26.9 ± 7.3	27.2	[16.8, 41.0]	26.9 ± 7.3	27.2	[16.8, 41.0]

The typical value for the apparent clearance of secukinumab was estimated to be 0.19 L/day. Potential covariates including body weight, PASI at baseline, age, gender, and race (non-Asian and Asian) were tested in covariate analyses and only the body weight resulted in a change of the reference clearance by more than 20%, which is considered clinically relevant.

Body weight

Body weight was a significant intrinsic factor for the CL, the central volume of distribution, and the peripheral volume of distribution with allometric exponents estimated to be 1.0, 0.81, and 0.56, respectively. The secukinumab clearance increases with increasing body weight (the left panel in Figure 2.5.1.b). The post-hoc estimates of individual CL values are summarized in Table 2.5.1.b for all subjects (N=1233) in the analysis dataset and by two body weight subgroups (≥ 90 kg and < 90 kg). The mean clearance value in subjects with body weight ≥ 90 kg was approximately 50% higher than that in subjects with body weight < 90 kg. The clearance of secukinumab varied with body weight in an allometric relationship with an allometric exponent estimated to be approximately 1.0, indicating a doubling of body weight could result in a nearly 2-fold increase in the clearance. Consequently in the Phase 3 trials, within the same 150 mg or 300 mg dose, the subjects with higher body weight was associated with lower secukinumab trough concentrations when compared to the subjects with lower body weight (Figure 2.5.1.a.).

Baseline PASI

In the population PK database, all 1233 subjects had baseline PASI score available with mean±SD value of 21.1±8.8 [ranging from 8 to 72]. The relationship between the baseline PASI and clearance is shown in Figure 2.5.1.b. Overall, a numeric trend was observed where subjects with higher baseline PASI scores were associated with higher clearance values, but the impact of baseline PASI score on secukinumab exposure was not expected to be of clinical relevance.

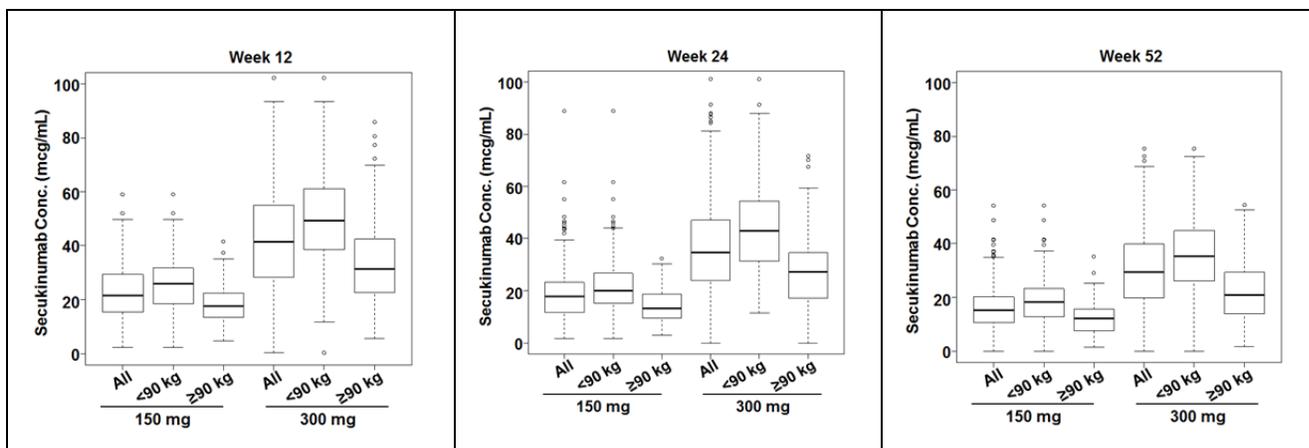


Figure 2.5.1.a. Effect of body weight on secukinumab trough concentration in Phase 3. (Data source: Reviewer's plot using population PK dataset of trial CAIN457A2302)

Table 2.5.1.b. Population PK predicted secukinumab clearance by body weight subgroups. (Data source: Results of population PK analysis on data from studies CAIN457A 2102, CAIN457A2103, CAIN457A2211, CAIN457A2212, CAIN457A2220 and CAIN457A2302. Reviewer's analysis)

	Overall (n=1233)	Body weight ≥90 kg (n=555)	Body weight <90 kg (n=678)
Body weight (kg, mean±SD, [median])	91.6±22.7 [88.8]	110.8±17.4 [105.6]	75.1±10.4 [76.6]
CL (L/day, mean±SD, [median])	0.204±0.089 [0.187]	0.248±0.098 [0.229]	0.166±0.058 [0.156]

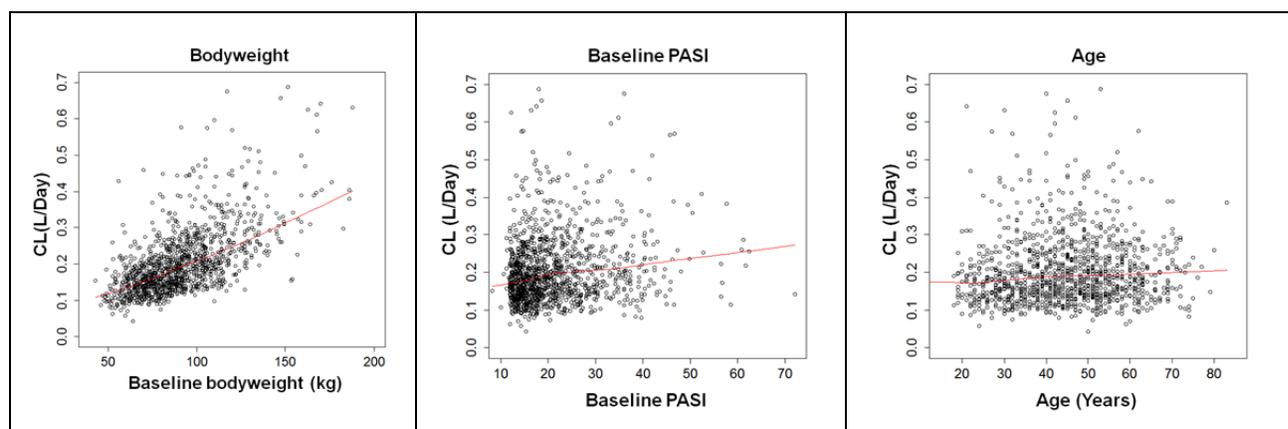


Figure 2.5.1.b. Influences of body weight, baseline PASI score, and age on secukinumab clearance based on population PK analysis. (Data source: reviewer's plot)

Age

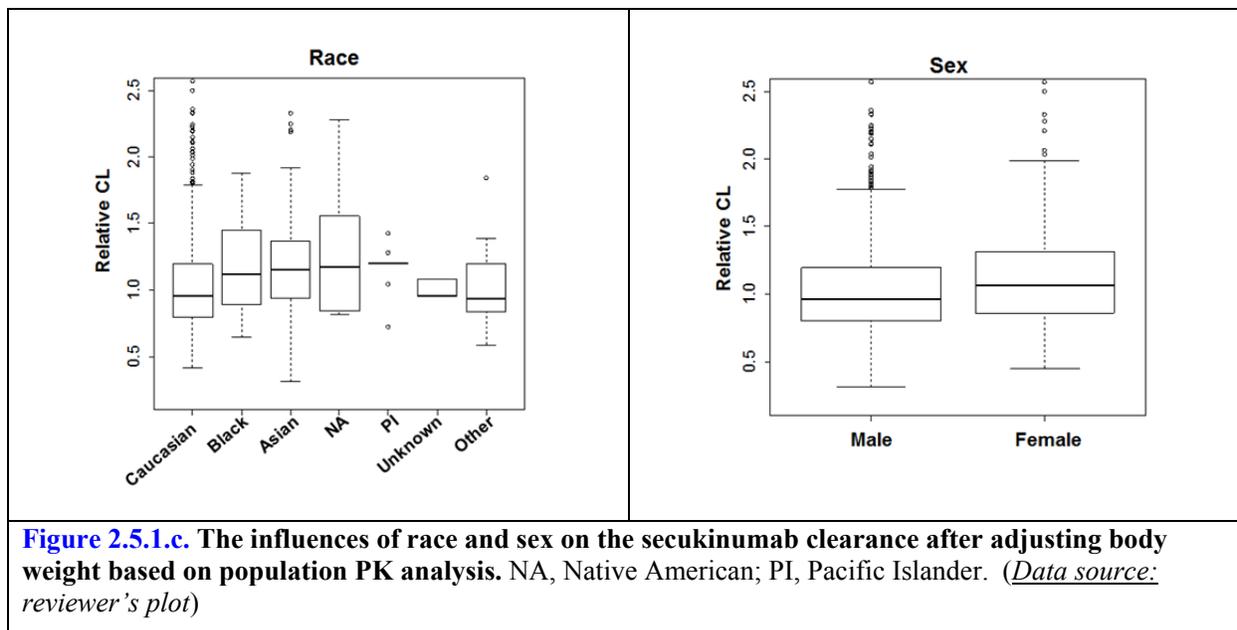
The population PK database had 1195 subjects with age data available, ranging from 18 to 83 years. Of these patients, 71 were of age 65 years and older. The relationship between age and clearance value is shown in Figure 2.5.1.b. Overall, the clearance in patients 65 years and older and patients less than 65 years of age was similar.

Gender

PK data from 897 men and 336 women were included in the population PK analysis. The secukinumab clearance in female patients was estimated to be 10.9% higher than in male patients after adjusting for body weight (Figure 2.5.1.c).

Race

A total of 206 subjects among the 1233 subjects in the population PK database were Asians. After adjustment for body weight, Asian patients showed a 12.4% higher secukinumab clearance compared to non-Asians (Figure 2.5.1.c).



Renal impairment

No formal studies were conducted in subjects with renal impairment. Secukinumab is a human IgG immunoglobulin with large molecular size of approximately 150 kDa; therefore, intact secukinumab are unlikely to be filtered by kidney or excreted in urine.

Hepatic impairment

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

2.5.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended?

The Applicant proposes 300 mg at Week 0, 1, 2, and 3 followed by monthly (q4w) maintenance dosing starting at Week 4, for all patients regardless of body weight. However, due to the significant effect of body weight on the exposure and the response, subjects with lower body weight (<90 kg) had a higher response rate compared to subjects with higher body weight (≥ 90 kg) with the same dosing regimen. Within each dose (150 mg or 300 mg), the clinical response rates were approximately 10% higher in the lower body weight group.

As shown in Figure 2.5.2.a, patients with body weight < 90 kg following 150 mg (N=328, response rate for IGA 0/1: 50.3%) may expect the similar efficacy as patients with body weight ≥ 90 kg following 300 mg (N=196, response rate for IGA 0/1: 51.5%). Patients with body weight ≥ 90 kg attained the lowest IGA 0/1 response rate from 150 mg (N=202, response rate for IGA 0/1: 43.6%) and this treatment regimen is not recommended from the review team. The highest clinical response rates were observed in patients weighing < 90 kg taking 300 mg (N=341, response rate for IGA 0/1:

63.6% (see more details in *Pharmacometrics Review*). As the highest response rate was observed in the patients with the highest exposure (body weight < 90 kg administered 300 mg) with no evidence of a plateau in treatment response, the review team conducted simulations to evaluate the impact of a dose increase in patients with body weight ≥ 90 in order to achieve an exposure matching that in the <90 kg subgroup of patients.

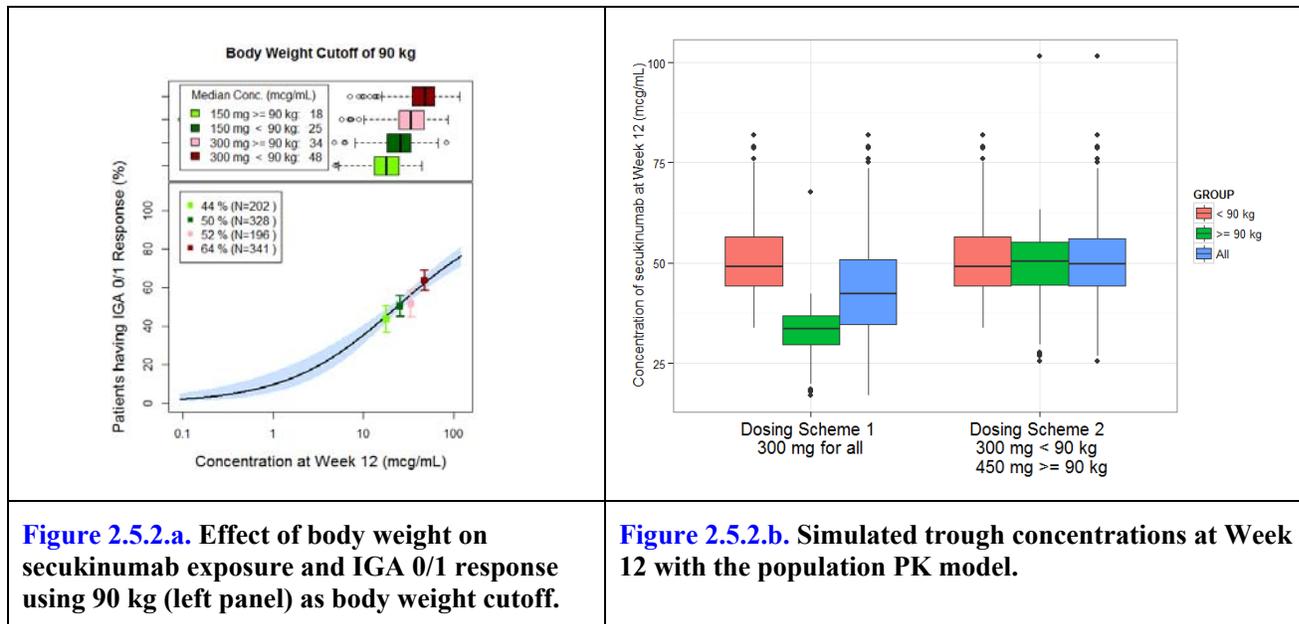


Figure 2.5.2.a. Effect of body weight on secukinumab exposure and IGA 0/1 response using 90 kg (left panel) as body weight cutoff.

Figure 2.5.2.b. Simulated trough concentrations at Week 12 with the population PK model.

Simulations with the Applicant’s population PK model and the demographics from Study CAIN457A2302 indicate that the secukinumab dose of 450 mg administered to subjects with body weight ≥ 90 kg would achieve a similar exposure as the recommended 300 mg dose in subjects with body weight <90 kg (Figure 2.5.2.b). Therefore, it would be reasonable to further explore a higher dose, e.g., 450 mg dose, for the high body weight subgroup of subjects to provide an option to subjects who cannot achieve the therapeutic goal with 300 mg without exceeding secukinumab exposures that were observed for subjects with body weight <90 kg administered 300 mg.

2.5.3. Does genetic variation impact exposure and/or response?

No formal studies were conducted to evaluate the impact of genetic variation on secukinumab exposure or response.

2.6. Extrinsic Factors

2.6.1. What are the extrinsic factors that influence exposure and/or response?

Extrinsic factors that could significantly affect secukinumab exposure and/or response have not been studied or identified.

2.6.2. What are the drug-drug interactions?

Drug-drug interaction (DDI) studies have not been investigated for secukinumab.

2.6.3. Does the label specify co-administration of another drug?

No.

2.6.4. What other co-medications are likely to be administered to the target population(s)?

Secukinumab will be prescribed to patients with moderate to severe plaque psoriasis. Medications co-administered to these patient populations may include low molecular weight immunosuppressants.

2.6.5. Is there a known mechanistic basis for pharmacodynamic- or disease-drug-drug interactions?

Yes, there is a potential for psoriasis disease-drug-drug interaction (disease-DDI) based on the current understanding that psoriasis patients have elevated proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon disease improvement following biological treatment. Therefore, we recommend that the Applicant conducts a clinical trial to determine the potential of secukinumab to alter the metabolism of CYP substrates in psoriasis patients (e.g., using a cocktail of relevant CYP probe drugs).

2.7. Pharmacodynamics

2.7.1. What are the impacts of secukinumab treatment on serum total IL-17A level in subjects with psoriasis?

Serum total IL-17A concentrations (free IL-17A and IL-17A bound with secukinumab) were assessed at baseline, Week 4, and Week 12 in Phase 3 Study CAIN457A2309. Median IL-17A concentrations were below the assay quantification limit (20 pg/mL) at all the three time points in the placebo group and at baseline in the secukinumab treatment groups for both secukinumab treated groups receiving 150 mg and 300 mg doses. At Weeks 4 and 12, the median IL-17A concentrations were 142 pg/mL and 84.5 pg/mL for the 150 mg secukinumab group and 121 pg/mL and 76.5 pg/mL for the 300 mg secukinumab group, respectively (Figure 2.7.1.).

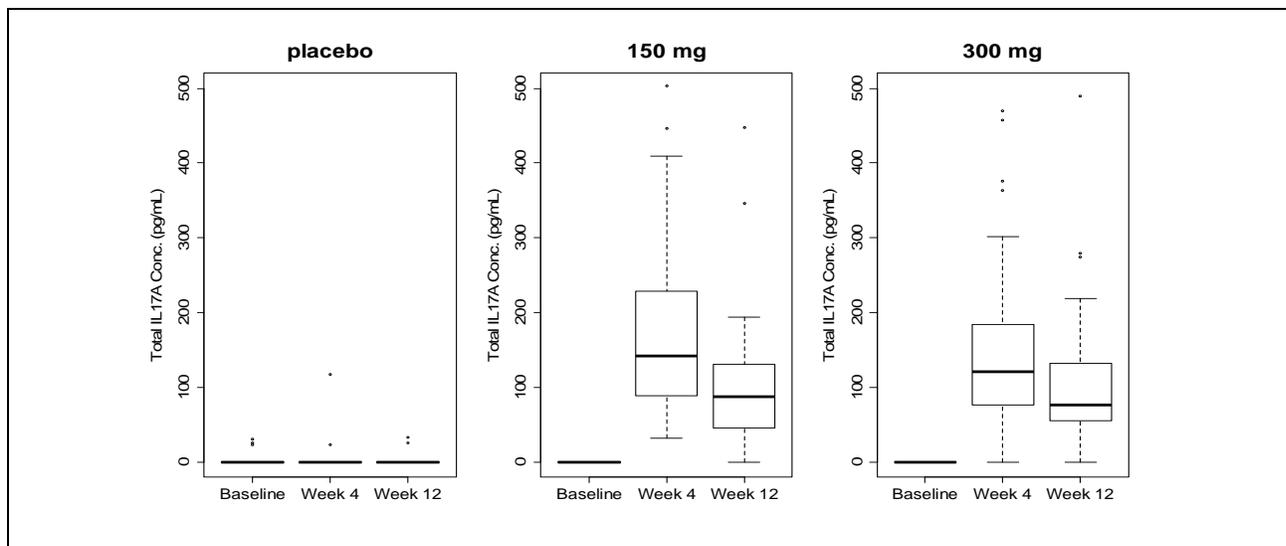


Figure 2.7.1. Serum total IL-17A concentrations in Study CAIN457A2309. (Data source: Reviewer's plot).

The Applicant hypothesized that the increase in total serum IL-17A concentrations following secukinumab treatment compared to those at baseline is due to a slower clearance of IL-17A-secukinumab complex compared to free IL-17A. The increase in IL-17A level in systemic circulation as a result of its binding to secukinumab presumably could reduce the levels of free IL-17A and inhibits its interaction with the IL-17 receptor which is the proposed mechanism of action (*see section 2.1.2*).

2.8. Immunogenicity

2.8.1. What is the incidence (rate) of the formation of the anti-drug/secukinumab antibodies (ADA)? Do the ADA have neutralizing activity?

In psoriasis Phase 3 trials, 0.4% (10/2842) of subjects developed secukinumab treatment-emergent ADA. Of the 10 subjects who developed ADA, 3 subjects were classified as positive for neutralizing antibodies, 5 subjects were classified as negative for neutralizing antibodies, and the remaining 2 subjects were not characterized for neutralizing antibodies status (Table 2.8.1). Secukinumab treatment-emergent ADA are defined as ADA that were developed post-secukinumab treatment in subjects with negative ADA prior to secukinumab treatment. In psoriasis Phase 3 trials, immunogenicity samples were collected and evaluated for ADA status using the MSD assay at baseline, Week 12 (pre-dose), Week 24 (pre-dose), and Week 52 (4 weeks after the last dose).

Non-treatment emergent ADA incidence rate was 1.7% (56/3364) of secukinumab naive subjects had positive ADA at baseline (n=47) or at a post-baseline time point without secukinumab exposure (n=9) in the psoriasis trials. Among the 56 subjects tested positive for ADA at baseline, 49 did not have any positive ADA sample following treatment with secukinumab, which indicate transient ADA responses for the majority of the non-treatment emergent ADA positive subjects.

Table 2.8.1. Secukinumab treatment-emergent ADA and their impacts on PK and efficacy in psoriasis Phase 3 trials.¹ Loss of efficacy is defined as increase in PASI score by 6 points from minimum PASI score achieved on treatment; Nab, neutralizing antibodies; n/a, data not available or not applicable; The numbers in *italic text* represent the time-point when ADA was detected.

Study-Subject ID	Treatment	ADA+ detected			Loss of efficacy ₁	PK (serum secukinumab, mcg/mL)				
		Time	titer	Nab		Week 0	Week 4	Week 12	Week 24	Week 52
2302-5006010	150 mg	W12	none	Yes	No	0	33.9	<i>19.7</i>	11.7	12.5
2302-3081015	P→150 mg	W24	none	No	No	n/a	n/a	n/a	<i>n/a</i>	n/a
2303-3524003	150 mg	W24	6.41	No	No	0	53.1	30.1	<i>25.7</i>	23.4
2303-5108002	150 mg	W12	none	No	No	0	43.0	<i>12.0</i>	15.3	12.3
2303-2129002	300 mg	W12	1.5	No	No	0	63.2	<i>43.5</i>	29.7	<i>57.9</i>
2303-2253014	300 mg	W24	none	No	No	0	92.5	68.0	<i>46.8</i>	56.6
2304-3069017	150 mg	W24	2.84	No	No	0	80.8	33.3	<i>25.2</i>	<i>30.5</i>
		W52	2.69	Yes	No					
2304-4036003	150 mg SoR	W52	1.05	Yes	n/a	n/a	n/a	n/a	n/a	<i>n/a</i>
2304-5030005	150 mg	W12	none	n/a	n/a	0	23.5	<i>11.2</i>	n/a	n/a
2304-3066004	300 mg	W24	none	n/a	No	0	95.4	34.9	<i>26.4</i>	19.8
PK reference: Mean±SD steady state trough concentrations in Study CAIN457A2302						150 mg		22.8±10.2	17.7±9.4	16.7±8.2
						300 mg		44.8±20.6	34.4±16.6	32.7±14.4

2.8.2. What are the impacts of ADA on secukinumab PK, efficacy and safety?

Overall, no evidence of altered PK, efficacy or safety has been observed in subjects who developed secukinumab treatment-emergent ADA in psoriasis Phase 3 trials. However, the small number of subjects with treatment-emergent antibodies to secukinumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to secukinumab and clinical efficacy or safety measures.

In psoriasis Phase 3 trials, the steady state trough concentrations in treatment-emergent ADA positive subjects were in the range of 11.7 mcg/mL to 25.7 mcg/mL for the 150 mg treatment groups and 26.4 mcg/mL to 46.8 mcg/mL for the 300 mg treatment groups at Week 24; and from 12.3 mcg/mL to 30.5 mcg/mL for the 150 mg treatment groups and 19.8 mcg/mL to 57.9 mcg/mL for the 300 mg treatment

groups at Week 52 (Table 2.8.1). The individual steady state trough concentrations in treatment-emergent ADA positive subjects were generally in the observed range for subjects without ADA formation.

In psoriasis Phase 3 trials, subjects with secukinumab treatment-emergent ADA were not associated with a loss of therapeutic efficacy which is defined as increase in PASI score by 6 points from minimum PASI score achieved on treatment. The development of treatment-emergent ADA was not associated with injection site reactions or other severe administration reactions including hypersensitivity events.

2.9. Biopharmaceutics

2.9.1. Was the manufacturing process changed during the development program? What were the drug substance and drug product used in secukinumab clinical trials?

Yes, several drug substance (DS) and drug product (DP) manufacturing changes were introduced during the clinical development of secukinumab for the psoriasis indication. Table 2.9.1.a summarizes the drug substance and drug product used in the development program by clinical trials.

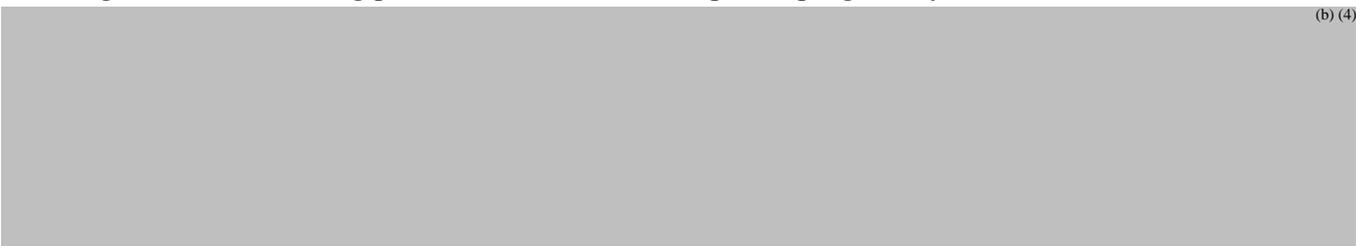


Table 2.9.1.a. Drug substance (DS) and drug product (DP) used in secukinumab clinical trials. LYO, lyophilisate in vial; PFS, pre-filled syringe; AI, pre-filled autoinjector/pen.

DS Cell line	(b) (4) (Process A)	CHO (Process B, C, and D)			
		LYO		PFS 150 mg/mL (Batch #)	AI 150 mg/mL (Batch #)
DP (Formulation/ Presentation)	LYO (Batch #)	LYO 150 mg (Batch #)	LYO 50 mg (Batch #)		
Phase 1	<ul style="list-style-type: none"> ▪ CAIN457A2101 (U018 0806, Y052 0505, Y099 0806, Y182 1206) 	<ul style="list-style-type: none"> ▪ CAIN457A1101 (Y003 0108) ▪ CAIN457A2103 (Y003 0108) ▪ CAIN457A2225 (S0009) ▪ CAIN457A2228 (Y103-0609) 			
Phase 2a	<ul style="list-style-type: none"> ▪ CAIN457A2102 (Y145 1204) 				
Phase 2		<ul style="list-style-type: none"> ▪ CAIN457A2211 (Y002-0109) ▪ CAIN457A2220 (Y127 0609) ▪ CAIN457A2212 (Y003 0108) 	<ul style="list-style-type: none"> ▪ CAIN457A2204 (Y0170208-7005405.005) 		
Phase 3		<ul style="list-style-type: none"> ▪ CAIN457A2302 (S0005, S0011, S0012) ▪ CAIN457A2303 (S0005, S0011, S0014) 		<ul style="list-style-type: none"> ▪ CAIN457A2308 (U003 0711) 	<ul style="list-style-type: none"> ▪ CAIN457A2309 (S0002, S0004A)

		<ul style="list-style-type: none"> ▪ CAIN457A2304 (S0006, S0007, S0008, S0014) 			
BE		<ul style="list-style-type: none"> ▪ CAIN457A2106 (S0007) 		<ul style="list-style-type: none"> ▪ CAIN457A2106 (Y1481210) 	

Secukinumab is proposed to be marketed as 150 mg lyophilisate in vial (LYO), 150 mg/mL solution for injection in pre-filled syringe (PFS), and 150 mg/mL solution for injection in a pre-filled autoinjector/pen (AI). The PFS and AI presentations contain the same liquid formulation with an identical secukinumab concentration, and the same primary syringe; they only differ in the device assembly.

The LYO formulation was used in the two pivotal Phase 3 trials, i.e., Study CAIN457A2302 and Study CAIN457A2303. In addition to the two pivotal trials, the BLA has two small Phase 3b studies evaluated the short-term (12 weeks) safety and efficacy using a liquid formulation presented in either PFS (Study CAIN457A2308) or AI (Study CAIN457A2309).

2.9.2. Was the proposed to-be-marketed formulation/presentation comparable to the formulation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?

No, PK comparability was only demonstrated for one of the two proposed to-be-marketed formulation/presentations that were not tested in the pivotal trials, although each of the two formulation/presentations was evaluated in a small 12-week Phase 3b trial.

The comparability between the PFS and the LYO was demonstrated by the PK results from the bioequivalence (BE) Study CAIN457A2106.

The Applicant did not conduct a dedicated PK study to evaluate the comparability between the AI and the LYO. Results from the cross-study comparison of secukinumab trough concentrations in Phase 3 trials cannot support the PK comparability between the AI and the LYO. Secukinumab trough concentrations resulting from the AI administration appeared to be approximately 10%-30% higher across the two doses (150 mg and 300 mg) and two time-points (Week 4 and Week 12) in comparison to those resulting from the LYO administration.

PK Comparability: PFS vs. LYO

The comparability between the PFS and the LYO was demonstrated by the PK results from the BE Study CAIN457A2106. Study CAIN457A2106 was an open-label, randomized, single-dose, parallel-group study in healthy subjects to determine the BE of the PFS with respect to the LYO. Secukinumab was administered by two SC injections for the single study dose of 300 mg for both the LYO and the PFS. The PK results showed that the point estimate [90% confidence interval] for geometric mean ratio of AUC_{inf}, AUC_{last}, and C_{max} were 1.00 [0.92, 1.08], 1.01 [0.93, 1.08], and 1.04 [0.96, 1.12], respectively, which were all within the [0.8, 1.25] acceptance limit of the BE criteria.

PK Comparability: AI vs. LYO (or PFS)

In the absence of a dedicated PK comparability study for the AI to the LYO, the trough secukinumab concentrations collected across different Phase 3 trials were compared to gain insight on the PK comparability. Table 2.9.2.a summarizes the serum secukinumab trough concentrations resulting from the LYO, the PFS or the AI at Week 4 and Week 12 across the four Phase 3 trials: Study CAIN457A2302 (LYO), Study CAIN457A2303 (LYO), Study CAIN457A2308 (PFS), and Study CAIN457A2309 (AI). Across these four Phase 3 studies, we found no significant differences in

demographic and other background characteristics (e.g., body weight) of the randomized subjects; therefore, the results based on the cross-study comparison are considered informative. The results showed that compared to the LYO, the concentrations resulting from the AI were approximately 10%-30% higher across the two doses and two time-points. Similarly, the cross-study comparison also showed that compared to the PFS, the concentrations resulting from the AI were approximately 16%-26% higher. In contrast, the trough concentrations were similar between the LYO and the PFS, consistent with the findings in the dedicated BE Study CAIN457A2106.

Table 2.9.2.a. Secukinumab trough serum concentrations by formulation/presentation in Phase 3 trials: Study CAIN457A2302, Study CAIN457A2308, and Study CAIN457A2309.

Clinical Trial		Serum secukinumab concentrations (mcg/mL), Mean ± SD (n)				% difference between AI and PFS or LYO		
		CAINA2302	CAINA2303	CAINA2308	CAINA2309	PFS	LYO (2302)	LYO (2303)
Formulation		LYO	LYO	PFS	AI			
Time	Dose							
Week 4	150 mg	44.9±14.6 (230)	46.3±16.3 (288)	42.9±15.1 (56)	50.7±18.0 (57)	18.2%	12.9%	9.5%
Week 4	300 mg	87.2±30.1 (226)	89.9±32.6 (296)	84.8±28.5 (55)	107±34.3 (56)	26.2%	22.7%	19.0%
Week 12	150 mg	22.8±10.2 (216)	23.9±11.6 (272)	24.1±10.1 (55)	28.0±11.9 (51)	16.2%	22.8%	17.2%
Week 12	300 mg	44.8±20.6 (219)	45.4±21.2 (284)	47.4±21.1 (49)	58.4±25.8 (55)	23.2%	30.4%	28.6%

An exploratory analysis was conducted to compare the trough concentrations following the methodology for BE assessment using the LYO as “reference” and the AI as “test”. The results of the exploratory cross-study analysis showed that PK was not comparable because the geometric means of the AI trough concentrations are consistently greater than 1 (ranging between 1.13 and 1.38), and the upper limit of the 90% confidence interval ranged from 1.22 to 1.57 in all four sets of comparisons across both the 150 mg and the 300 mg doses at Week 4 and Week 12 (Table 2.9.2.b). If the classical BE acceptance limit of [0.80-1.25] for 90% confidence interval were applied, the trough concentrations from AI and LYO cannot be considered comparable.

Table 2.9.2.b. Bioequivalence assessment of the secukinumab trough concentrations: AI versus LYO with subjects in Studies CAIN457A2302, CAIN457A2303, and CAIN457A2309. (Data source: Table 3-2, Page 10, Response to FDA information request, June 9, 2014).

Time point	Dose	Presentation	Geometric mean		90 Confidence Interval	
			Conc. (mcg/mL)	Ratio	Lower	Upper
Week 4	150 mg	AI (n=57)	47.2	1.13	1.052	1.220
		LYO (n=518)	41.6			
	300 mg	AI (n=56)	99.6	1.25	1.16	1.349
		LYO (n=522)	79.6			
Week 12	150 mg	AI (n=51)	25.0	1.23	1.101	1.382
		LYO (n=489)	20.3			
	300 mg	AI (n=565)	52.1	1.38	1.218	1.568
		LYO (n=503)	37.7			

Efficacy/safety considerations regarding the comparability between AI and LYO

Table 2.9.2.c summarizes the co-primary efficacy (IGA 0/1 and PASI 75 response rates at Week 12) resulting from the LYO, the PFS and the AI across the Phase 3 trials. At the 150 mg dose, both PFS and AI showed similar efficacy results as LYO based on the IGA 0/1 and PASI 75 response rates at Week 12. However, at the 300 mg dose, AI appeared to have numerically higher response rates than LYO for both IGA 0/1 and PASI 75. However, there was no clear trend showing the impact of AI

compared to LYO or PFS for other endpoints (PASI 90, PASI 100, IGA 0) at Week 12 (data not shown).

Table 2.9.2.c. Cross-study comparisons of IGA 0/1 and PASI 75 response rates at Week 12 in secukinumab psoriasis Phase 3 trials.

Primary efficacy endpoints at Week 12	Phase 3 trials	Product	Secukinumab doses	
			150 mg	300 mg
IGA 0/1 response rate % (n)	CAIN457A2302	LYO	51.2% (244)	65.3% (245)
	CAIN457A2303	LYO	51.1% (327)	62.5% (323)
	CAIN457A2308	PFS	52.5% (59)	69.0% (58)
	CAIN457A2309	AI	53.3% (60)	73.3% (60)
PASI 75 response rate % (n)	CAIN457A2302	LYO	71.6% (243)	81.6% (245)
	CAIN457A2303	LYO	67.0% (327)	77.1% (323)
	CAIN457A2308	PFS	69.5% (59)	75.9% (58)
	CAIN457A2309	AI	71.7% (60)	86.7% (60)

Reviewer’s comments: *Whether or not the AI presentation is acceptable for approval needs to be further assessed from clinical perspectives for the target indication, because the PK comparability between the AI and the LYO has not been established. Additionally, a cross-trial comparison of trough secukinumab concentrations at Week 4 and Week 12 noted higher observed trough secukinumab concentrations after dosing with the AI than those achieved with the LYO, although the cumulative distribution of the trough secukinumab concentration data at 12-weeks showed substantial overlap in exposures between observed exposures from the AI and other presentations. The Clinical Pharmacology review team recommends that the Applicant provides additional clinical experience with the AI presentation in the ongoing clinical study(ies) in lieu of a dedicated study comparing exposures between the AI and LYO presentations.*

2.10. Bioanalytical methods

2.10.1. What bioanalytical methods are used to determine secukinumab concentrations in human serum or dermal interstitial fluid? Briefly describe the performance of the assay.

Competitive ELISA for measurement of secukinumab in human serum

Total secukinumab concentrations, i.e., free secukinumab plus secukinumab bound to IL-17A, was analyzed in human serum using a competitive ELISA method. Because of the low level of IL-17A in serum, the total serum secukinumab concentrations measured by the ELISA method could reasonably represent the free secukinumab concentrations (*see Section 2.2. for more details*).

The competitive ELISA method used a purified, non-neutralizing, anti-idiotypic anti-secukinumab antibody coated on microtiterplates. Serum samples (calibration samples, quality controls or unknown samples) and biotin-labeled secukinumab were simultaneously incubated and competed for binding on the anti-idiotypic anti-secukinumab antibody. Unbound material was removed by washing. Bound biotinylated secukinumab is detected by incubating horseradish peroxidase (HRP)-conjugated to streptavidin with o-phenylenediamine dihydrochloride (OPD) as enzymatic substrate. The ELISA was also validated with “half-area” microplates to reduce the required sample volume (Amendment no. 1). With cross-validation, the ELISA was transferred to (b) (4) during the development program. The validation parameters of the ELISA for measurement of human serum secukinumab concentrations, the amendment no.1, cross-validation reports, and related clinical trials are summarized in [Table 2.10.1.a](#).

Table 2.10.1.a. Assay validations of the ELISA used for measurement of human serum secukinumab concentrations. ELISA: enzyme linked immuno-sorbent assay; LLOQ, lower limit of quantification; ULOQ, upper

limit of quantification; QC, quality control. (*Referenced validation reports and data source: BMD R0450380; BMD R0450380-01; BxSD R1180331-pk; BxSD-RS686053-pk; BxSD-RS686053-pk-1*)

Assay description and validation parameters	Original Report BMD R0450380 (July 20, 2006)
<i>Method</i>	Competitive ELISA
<i>Plate</i>	Normal microtiterplate
<i>Compound analyzed</i>	AIN457 (secukinumab)
<i>Matrix</i>	Human serum
<i>LLOQ</i>	80 ng/mL
<i>ULOQ</i>	2,500 ng/mL
<i>QC samples</i>	Six QC samples: 80 ng/mL, 100 ng/mL, 200 ng/mL, 800 ng/mL, 2000 ng/mL, and 2500 ng/mL.
<i>Intra-day/run accuracy (bias range)</i>	- 23.6% to 18.3%
<i>Intra-day/run precision (range)</i>	1.4% to 17.8%
<i>Inter-matrix accuracy (bias range)</i>	-6.7% to -2.0%
<i>Inter-matrix precision (range)</i>	7.6% to 17.4%
<i>Inter-day accuracy (bias range)</i>	-10.4% to 9.0%
<i>Inter-day precision</i>	7.2% to 15.6%
<i>Stability</i>	Stable in spiked human serum for 24 hours at room temperature (<i>BxSD-RS686053-pk-01</i>); Stable in spiked human serum after 3 freeze-thaw cycles (accuracy range: 71.2% to 91.0%); Stable in spiked human serum for 4 months at or below -18°C (accuracy range: 79.9% to 91.1%); Stable for storage at -65°C to -90°C for up to 39 months (<i>BMD R0450380-01</i>).
<i>Dilution Effect</i>	No effect was observed at dilution tested up to 1:2000 (accuracy range: 87.1% to 101.6%).
<i>Calibration curve</i>	7 calibration samples (13.7 ng/mL to 10,000 ng/mL) with 4-Parameter Logistic fit. Mean accuracy of calibration samples within the working range (80-2500 ng/mL): 96% to 102.2%.
<i>Matrix effect</i>	In subjects with psoriasis, no matrix effect was observed when human serum samples underwent one additional freeze/thaw cycle (14 out of 15 spiked naive disease individual samples were within the acceptance criteria of \pm 25% bias) or underwent five additional freeze/thaw cycles (13 out of 15 spiked naive disease individual samples were within the acceptance criteria of \pm 25% bias) (<i>BxSD-RS686053-pk-1</i>).
<i>Method Amendment no.1</i>	<u>Report: Amendment no.1 BMD R0450380-01</u> (July 18, 2013) <u>Major Change:</u> From using normal microtiter plate to “half-area” plate in order to work with less sample volume Accuracy and precision assessment at five QC samples: 80 ng/mL, 240 ng/mL, 640 ng/mL, 1920 ng/mL, and 2500 ng/mL:

	<p><i>Intra-day/run accuracy (bias range): -13% to 12%</i> <i>Intra-day/run precision (range): 0% to 20%</i> <i>Inter-day accuracy (bias range): -9% to 6%</i> <i>Inter-day precision (range): 7% to 9%</i></p> <p>Accuracy and precision assessment of calibration samples (8 calibration samples of 20 ng/mL to 10000 ng/mL) within the working range (80-2500 ng/mL):</p> <p><i>Mean precision: 2 to 5 %</i> <i>Mean bias: -1% to 2%</i></p> <p>Reanalysis of 80 specimens showed that concentrations of 75 specimens were within 30% of the original analysis.</p>
<p><i>Method transfer and cross-validation:</i> Method transfer to CRO (b) (4)</p>	<p><u>Report to support cross-validation:</u> BxSD R1180331-pk (March 16, 2012); <u>Referenced validation report:</u> BMD R0450380</p> <p><u>Cross-validation study description:</u> Study samples previously analyzed at Novartis were reanalyzed at (b) (4)</p> <p><u>Results:</u> The first cross-validation run with 30 samples failed and the results were all much higher at (b) (4) (up to 311.9%) than concentrations determined at Novartis. The second run with 10 samples was conducted to investigate and confirm identified technical errors that might occur during the first run. The third cross-validation run was conducted using a new set of 30 study samples, in which the normalized difference of results between (b) (4) and Novartis was within $\pm 30\%$ (range: -20.4% to 13.7%) for 30 out of 30 samples.</p> <p><u>Reviewer's notes:</u> In Table 7-4 of the validation report for assessment of accuracy and precision of QCs, the bias% showed high variability at low QC levels with a range from -32.9% to 68.8% at 80 ng/mL and from -31.5% to 18% at 200 ng/mL, although the accuracy and precision assessment met the sponsor-defined acceptance criteria of 50%, per QC level should have bias% $\leq 25\%$.</p> <p><u>Related clinical trials with secukinumab PK measurements:</u> CAIN457A2104; CAIN457A2204; CAIN457A2211; CAIN457A2212; CAIN457A2220</p>
<p><i>Method transfer and cross-validation</i> (b) (4)</p>	<p><u>Report:</u> BxSD-RS686053-pk (August 26, 2011); BsSD-RS686053-pk-1 (Amendment no.1, August 21, 2013).</p> <p><u>Referenced validation report:</u> BMD R0450380</p> <p><u>Cross-validation results:</u> Cross-validation was conducted with 30 incurred study samples. The normalized differences of results between (b) (4) and Novartis were within $\pm 30\%$ for 27 out of the 30 cross-validation samples. The remaining 3 samples showed normalized difference (%) ranging from 32.3% to 42%.</p> <p><u>Related clinical trials with secukinumab PK measurements:</u> CAIN457A2228; CAIN457A2106; CAIN457A2302; CAIN457A2303; CAIN457A2304; CAIN457A2308; CAIN457A2309</p>
<p><u>Other clinical trials with secukinumab PK measurements at Novartis:</u> CAIN457A1101; CAIN457A2225; CAIN457A2103; CAIN457A2102</p>	

Competitive ELISA for measurement of secukinumab in human dermal interstitial fluid

The ELISA assay was further validated to quantify total secukinumab in dermal interstitial fluid (ISF) and blister fluid with LLOQ of 76 ng/mL. The validation parameters of the ELISA for measurement

of human dermal interstitial fluid secukinumab concentrations and related clinical trials are summarized in [Table 2.10.1.b](#).

Reviewer’s comments: *Some validation parameters were generated using perfusate solution because the limited resource of dermal interstitial fluid. Therefore, the assay may not be considered fully validated.*

Table 2.10.1.b. Assay validation of the ELISA method for measurement of human dermal interstitial fluid secukinumab concentrations. ELISA: enzyme linked immuno-sorbent assay; LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; OFM, open flow microperfusion; QC, quality control; AIN457, secukinumab. (Report number and data source: BxSD R1180399)

Assay description and validation parameters	Original Report: BxSD R1180399 (July 17, 2013)
<i>Method</i>	Competitive ELISA
<i>Plate</i>	Normal microtiter plate
<i>Compound analyzed</i>	AIN457 (secukinumab)
<i>Matrix</i>	<ul style="list-style-type: none"> ▪ <i>OFM solution:</i> human dermal interstitial fluid containing perfusate solution <i>Human blister fluid</i> ▪ <i>Perfusate solution:</i> Mostly used in precision and accuracy assessment and in calibration validations. The Applicant described that OFM and blister fluids are very rare to obtain and these matrices are expected to be less complex compared to human serum in which the ELISA method has been validated.
<i>LLOQ</i>	76 ng/mL
<i>ULOQ</i>	2373 ng/mL
<i>QC samples</i>	Five QC samples: 76 ng/mL, 228 ng/mL, 607 ng/mL, 1822 ng/mL, and 2373 ng/mL.
<i>Intra-day accuracy (bias range)</i>	-14% to 20%
<i>Intra-day precision (range)</i>	2% to 20%
<i>Inter-day accuracy (bias range)</i>	2% to 5%
<i>Inter-day precision (range)</i>	10% to 16%
<i>Stability</i>	<p>Spiked AIN457 in OFM solution:</p> <ul style="list-style-type: none"> ▪ stable at RT for up to 24 hr ▪ stable at ≤ -65°C for up to 3 months ▪ unstable after 1 month at ≤ -15°C ▪ stable after three freeze/thaw cycles (≤ -15°C) <p>Spiked AIN457 in perfusate solution:</p> <ul style="list-style-type: none"> ▪ stable at RT for up to 24hr ▪ stable at ≤ -15°C and ≤ -65°C for up to 3 months ▪ stable after three freeze/thaw cycles (≤ -15°C and ≤ -65°C) <p>Spiked AIN457 in blister fluid:</p> <ul style="list-style-type: none"> ▪ stable at RT for up to 24hr ▪ stable at ≤ -65°C for up to 8 months ▪ stable after three freeze/thaw cycles (≤ -65°C)
<i>Dilution Effect</i>	No dilution effect was observed at dilution tested up to 1:5000. Bias ranged from -6% to 5% for OFM solution diluted by perfusate solution and from -8% to -13% for blister fluid diluted by perfusate solution.
<i>Calibration curve</i>	8 calibration samples in perfusate solution (19 ng/mL to 9490 ng/mL) with 4-parameter logistic fit. Within the working range (76-2373 ng/mL), mean

	precision ranging from 2 to 5 % and mean bias ranging from -1% to 1%
<i>Specificity</i>	No interference of up to 500 mg/L inulin in perfusate solution (reference molecule in the clinical study)
<i>Related clinical trials with secukinumab PK measurements:</i> CAIN457A2225	

2.10.2. What bioanalytical methods are used for pharmacodynamic/biomarker studies? Briefly describe the performance of the assays.

MSD ELISA for measurement of IL-17A in human serum

Total IL-17A, i.e., free IL-17A and IL-17A bound to secukinumab, in calibrator samples, quality control samples and incurred samples was captured by an anti-human IL-17 antibody (CBI459), which was biotinylated and immobilized on a MSD Streptavidin multi-array 96 well plate. CBI459 has a different epitope to secukinumab and was able to recognize IL-17A in the presence of secukinumab. IL-17A is a homodimer, so CBI459 could be utilized as both capture and detection reagent. A saturating concentration of secukinumab was added to the prepared calibrator samples, quality control samples and to unknown samples to form IL-17A -secukinumab complexes. Then, these mixtures were added to the plate and IL-17A binds to the immobilized capture antibody. Detection of the bound complex was performed via a CBI459 Fab fragment which was labeled with Ruthenium(II) tris-bipyridine 4-methylsulfonate NHS ester, the ordinary MSD sulfoTAG™ label. Detection was based on electrochemiluminescence (ECL) and the read out was performed on an ECL MSD reader. The LLOQ was 20 pg/mL.

The validation results of the MSD ELISA assay for measurement of total IL-17A in human serum are summarized in [Table 2.10.2.a](#). The assay validation is acceptable.

Table 2.10.2.a. Summary of assay validation results of the MSD ELISA assay for measurement of total IL-17A in human serum. LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; QC, quality control; AIN457, secukinumab. (*Data source: Quantitative determination of total IL-17A in human serum by a sandwich MSD assay: Method description and validation. Report number: BxSD R1280620*)

Assay description and validation parameters	Report BxSD R1280620 (July 17, 2013)
<i>Method</i>	MSD ELISA assay
<i>Plate</i>	MSD streptavidin multi-array 96-well plate
<i>Compound analyzed</i>	AIN457 (secukinumab)
<i>Matrix</i>	Human serum
<i>LLOQ</i>	20 pg/mL in 100% human serum
<i>ULOQ</i>	1000 pg/mL in 100% human serum
<i>QC samples</i>	Five QC samples: 20 pg/mL, 60 pg/mL, 400 pg/mL, 750 pg/mL, and 1000 pg/mL. Working range: 20 pg/mL to 1000 pg/mL)
<i>Intra-day/run accuracy (bias range)</i>	-13% to 24%
<i>Intra-day/run precision (range)</i>	1% to 9%
<i>Inter-day accuracy (bias range)</i>	-5% to 8%
<i>Inter-day precision (range)</i>	8% to 11%
<i>Stability</i>	IL-17A spiked into human serum is:

	<ul style="list-style-type: none"> ▪ stable at RT for up to 4 hours (bias range: -14% to -6%) ▪ stable at 2 to 8°C for up to 1 week (bias range: -17% to 20%) ▪ stable at -15 to -35°C for up to 10 months (bias range: -12% to 7%) ▪ stable at -65 to -90°C for up to 10 months (bias range: -11% to 1%) ▪ stable after three freeze/thaw cycles when stored in between either from -15 to -35°C or from -65 to -90°C.
<i>Dilution Effect</i>	Samples can be pre-diluted up to 1:20 in buffer or human serum (Bias range: -9% to 9%; precision range: 1% to 5%). Samples are not pre-diluted before analysis
<i>Calibration curve</i>	9 calibration samples in 10% human serum (15 pg/mL to 1000 pg/mL) with 5-Parameter Logistic fit. Mean precision range: 2 to 4 % Mean bias: -3% to 3%
<i>Selectivity</i>	No matrix effect was observed in 14 out of 15 individual batches (bias range: -16% to 0%). 1 of the 15 samples resulted in bias of 58.9%.
<i>Specificity</i>	No drug interference was observed up to 600 µg/mL AIN457. At 3 QC levels (20, 400, and 100 pg/mL of IL-17A), the % interference ranged from -10% to 1%.
<i>Incurring sample reanalysis (ISR)</i>	58 clinical samples from Study CAIN4575A2103 54/58 samples passed the ISR criteria (normalized difference within ±30%), with the normalized difference between the measured concentration of analysis and reanalysis varying between -26% and 25%. 19 thereof were in both data sets BLQ. 1/58 ISR sample was just in one data set BLQ and in the other one slightly above. 3/58 didn't meet the ISR criteria with a normalized difference of -31%, 40% and 41%, respectively.
Related clinical studies: CAIN457A2309, CAIN457A1101	

MSD ELISA for measurement of IL-17A in human dermal interstitial fluid

The validation results of the MSD ELISA assay for measurement of total IL-17A in human dermal interstitial fluid are summarized in [Table 2.10.2.b](#). The assay has not been fully validated; therefore, the IL-17A concentrations in human dermal interstitial fluid measure by this method should be interpreted with caution.

Table 2.10.2.b. Summary of assay qualification (not a full validation) results of the MSD ELISA assay for measurement of total IL-17A in human dermal interstitial fluid. LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; QC, quality control; AIN457, secukinumab. (*Data source: Quantitative determination of total IL-17A in human dermal interstitial fluid containing perfusate solution (open flow microperfusion solution) by a sandwich MSD assay: Method description and qualification as fit-for-purpose assay. Report number: BxSD R1381096*)

<i>Assay description and validation parameters</i>	Report BxSD R1381096 (August 16, 2013)
<i>Method</i>	MSD ELISA assay
<i>Plate</i>	MSD streptavidin multi-array 96-well plate
<i>Compound analyzed</i>	AIN457 (secukinumab)
<i>Matrix</i>	OFM solution: human dermal interstitial fluid containing perfusate solution
<i>LLOQ</i>	20 pg/mL
<i>ULOQ</i>	1000 pg/mL
<i>QC samples</i>	Five QC samples: 20 pg/mL, 60 pg/mL, 400 pg/mL, 750 pg/mL, and 1000 pg/mL. (Run 1 used OFM solution and Run 2 used perfusate solution due to limited supplies of OFM solution) Working range: 20 pg/mL to 1000 pg/mL)

Intra-day/run accuracy (bias range)	-10% to 50% (not acceptable)
Intra-day/run precision (range)	0% to 34% (not acceptable)
Inter-day accuracy (bias range)	7% to 19%
Inter-day precision (range)	6% to 27%
Stability	stable at RT for up to 4 hours (Bias: 9% -11%) stable at 2 to 8°C for up to 1 week (Bias: 2% to 9%) stable after three freeze/thaw cycles when stored from -65 to -90°C (bias: 2 to 38%). (not acceptable)
Dilution Effect	Samples can be pre-diluted up to 1:100 in perfusate solution (Bias range: -8% to 0%; precision range: 3% to 7%). Samples are not pre-diluted before analysis
Calibration curve	9 calibration samples in 95% perfusate solution (15 pg/mL to 1000 pg/mL) with 5-Parameter Logistic fit. Mean precision range: 1 to 3 % Mean bias: -1% to 2%
Selectivity	Not assessed
Specificity	No drug interference was observed up to 600 µg/mL AIN457. At 2 QC levels (20 and 100 pg/mL of IL-17A), the % interference ranged from -7% to 16%.
Incurred sample reanalysis (ISR)	Not assessed.

Magnetic Microparticle Immunoassay (MMI) using Erenna® System for IL-17A measurement

The MMI method uses a biotinylated monoclonal anti-human IL-17A capture antibody coated onto streptavidin paramagnetic microparticles. IL-17A binds to the immobilized antibody and unbound IL-17A is removed by washing. An AlexaFluor®647-labeled polyclonal anti-human IL-17A is then added and unbound material is removed by washing. Detection is detected by the Erenna® system after dissociation of the bound IL-17A from the microparticle and transfer to reading plates. The validation results of the MMI for measurement of total IL-17A in human serum are summarized in [Table 2.10.2.c](#).

Reviewer's comment: *Presence of secukinumab in the matrix could significantly interfere with the assay and reduce the detection sensitivity; therefore, only baseline IL-17A levels measured by this assay are reliable. The Applicant stated that AIN457 at concentrations ranging from 1 to 300 mcg/mL could result in > 90 % inhibition of readout signal.*

In study CAIN457A2225, the human dermal interstitial fluid IL-17A concentrations were also assessed in addition to human serum samples. However, the MMI method has not been validated separately in the matrix with human dermal interstitial fluid; therefore, these dermal IL-17A results should be considered exploratory.

Table 2.10.2.c. Summary of assay validation results of MMI for measurement of total IL-17A in human serum. LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; QC, quality control; AIN457, secukinumab. (*Data source: Quantitative determination of IL-17A in human serum using the Erenna System from Singulex: Method description and validation. Report number: BxSD R0950290a*)

Assay description and validation parameters	Report BxSD R0950290a (November 01, 2010)
Method	Magnetic Microparticle Immunoassay using Erenna® system

<i>Capture antibody and reagent</i>	Mouse monoclonal anti-IL17A: biotinylated capture antibody bound to streptavidin-coated super paramagnetic microparticles.
<i>Detection antibody and reagent</i>	Goat polyclonal anti-IL17A: AlexaFluor-647 labeled detection antibody in assay buffer
<i>Compound analyzed</i>	AIN457 (secukinumab)
<i>Matrix</i>	Human serum
<i>LLOQ</i>	0.096 pg/mL in human serum
<i>ULOQ</i>	5.305 pg/mL in human serum
<i>Intra-day/run accuracy (bias range)</i>	-20% to 6%
<i>Intra-day/run precision (range)</i>	2.6% to 24.7%
<i>Inter-day accuracy (bias range)</i>	-6.7% to 0%
<i>Inter-day precision (range)</i>	8% to 18.2%
<i>Stability</i>	IL-17A in fresh human serum is stable at RT and +4°C for 2 weeks, at -80 °C for 1 month. (In study CAIN457A2225, the Applicant reported that IL-17A was stable at -80°C for 1 year.) IL-17A in fresh human serum is stable after 3 freeze-thaw cycles (at -20°C and at -80°C).
<i>Dilution Effect</i>	Samples are not pre-diluted before analysis
<i>Calibration curve</i>	7 calibration samples in 10% human serum (0.098 pg/mL to 6.25 pg/mL) and 4 anchor points (25, 12.5, 0.049, and 0.024 pg/mL) with 5-Parameter Logistic fit. Mean precision range: 6.2 to 16.8 % at the working range (0.098 pg/mL to 6.25 pg/mL); Mean bias: -1.3% to 8.2%
<i>Selectivity</i>	AIN457 at concentrations ranging from 1 to 300 mcg/mL resulted in > 90 % inhibition of readout signal. (<i>Detailed data were not provided in the validation report</i>)
<i>Incurred sample reanalysis (ISR)</i>	Not assessed
Related clinical studies: CAIN457A2225	

2.10.3. What bioanalytical methods are used for immunogenicity assessment? Briefly describe the performance of the assays.

Binding ADA assay

Immunogenicity samples were evaluated for ADA in Phase 3 trials using a Meso Scale Discovery (MSD) bridging assay with a stepwise approach for screening, confirmation, and titration. In brief, ADA are captured in solution by a combination of biotinylated and ruthenium-labeled forms of secukinumab, the formed complex are subsequently captured on an electro-active surface of the MSD streptavidin plates and detected by electrochemluminescence (ECL). An acid dissociation step was built into the assay to improve drug tolerance. The MSD assay has a sensitivity of 4 ng/mL.

Reviewer's assessment on the drug tolerance of the binding assay: Overall, the drug tolerance of the assay appeared to be appropriate to measure the ADA responses in psoriasis Phase 3 trials. The assay drug tolerance level was 53.8 mcg/mL secukinumab when 250 ng/mL of rabbit polyclonal positive control antibody was used and 6.7 mcg/mL secukinumab when a mouse monoclonal positive control was used.

The polyclonal antibody would be considered more relevant to immune response in humans because the human ADA response is polyclonal in nature. The drug tolerance of 53.8 mcg/mL secukinumab for rabbit polyclonal positive control was determined by averaging results from three separate runs (Table 2.10.3.a). The lowest observed drug tolerance level of 29.7 mcg/mL is still generally higher than the mean steady state trough secukinumab concentrations (16.7 to 18.8 mcg/mL) observed for the 150 mg dose, but slightly lower than the mean steady state trough secukinumab concentrations (32.7 to 33.5 mcg/mL) for the 300 mg dose across the Phase 3 trials. Therefore, the possibility of drug interference for Phase 3 ADA assessment could not be entirely excluded.

In the response to FDA IR dated July 22, 2014, the Applicant submitted supporting information of the immunogenicity results at Week 60 (i.e., 12 weeks after the last dose at Week 48). The Applicant stated that among the subjects who stopped treatment in Phase 3 trials and went into the follow-up period, 4 out of 909 patients (~ 0.44%) had a positive ADA sample at Week 60. The Applicant calculated that the majority (~99.6%) of the immunogenicity samples at Week 60 would have secukinumab concentration lower than 29.7 mcg/mL. The low number of positive ADA samples from week 60 supported a low likelihood that the immunogenicity assay used in Phase 3 has missed significant portion of ADA positive samples.

When using the mean assay tolerance level of 53.8 mcg/mL, the drug interference issues is less concerning as it is higher than the steady state trough concentrations for both 150 mg and 300 mg doses.

Among the ten ADA positive subjects in the Phase 3 trials (Table 2.8.1), three subjects (ID 2303-2129002, 2303-2253014, 2304-3069017) had ADA positive samples with secukinumab concentrations higher than 29.7 mcg/mL, the lowest drug tolerance level observed in assay validation.

See Product Quality Review (immunogenicity section) by Tura Camilli, Ph.D., for more detailed information regarding the immunogenicity assay validation.

Table 2.10.3.a. Drug tolerance level of the immunogenicity assays. ADA, anti-drug antibodies; Nab, neutralizing antibodies; PC, positive control.

Method	Report#	ADA PC	Sensitivity	Drug Tolerance Level	
				Secukinumab (mcg/mL)	ADA PC (ng/mL)
Binding ADA	BxSD R1180393-ig	Mouse Monoclonal ADA	4 ng/mL	6.7 mcg/mL	500 ng/mL
				Run 1: 29.7 mcg/mL	250 ng/mL
	BxSD R1180393-ig-01	Rabbit polyclonal ADA	4 ng/mL	Run 2: 43.0 mcg/mL	250 ng/mL
				Run 3: 88.8 mcg/mL	250 ng/mL
				Mean=53.8 mcg/mL	250 ng/mL
Nab ADA	BxSD R1180094-ig	rabbit anti- sera Igor-2	1.48 mcg/mL	25 mcg/mL	10 mcg/mL
				15 mcg/mL	2.5 mcg/mL

Neutralizing ADA assay

For characterization of the neutralizing ADA (Nab), the biotinylated secukinumab is captured on streptavidin-coated plates. After the sample is added, NABs will bind to the IL-17 binding site of secukinumab. After the excess sample is removed, free secukinumab binding sites are detected via a short incubation with excess IL-17, which is then detected by a non-competing anti-IL-17 antibody. In

immunogenicity samples, Nab are expected to bind to the IL-17 binding site of secukinumab and as a consequence, the assay signal decreases in the presence of Nab.

The Nab assay has a sensitivity of 1.48 mcg/mL in human serum. In the presence of 25 mcg/mL of secukinumab, the assay can detect at least 10 mcg/mL of rabbit anti-AIN457 antibody. In the presence of 15 mcg/mL of AIN457, the assay can detect at least 2.5 mcg/mL of rabbit anti-AIN457 antibody.

Reviewer’s assessment on the drug tolerance of the binding assay: *The neutralizing ADA assay appears to be insensitive and could be interfered with the presence of secukinumab. According to the response to FDA IR dated July 22, 2014, the Applicant had developed a new polyclonal antibody with improved affinity against the variable region of secukinumab and used as a positive control in the neutralizing ADA assay. The drug tolerance results obtained from this new positive control antibody showed that the neutralizing antibody assay can detect 250 ng/mL of ADA in the presence of up to 2.37 µg/mL of drug, 1 µg/mL ADA in the presence of up to 17.8 µg/mL of drug, and 5µg/mL ADA in the presence of up to 29.5 µg/mL of drug. The drug tolerance using this new positive control appears to be reasonable; however, the possibility of drug interference for Phase 3 neutralizing ADA assessment could not be excluded.*

As the overall immunogenicity incidence is low for secukinumab in the psoriasis Phase 3 trials and there was no evidence of altered PK, efficacy or safety in the ADA positive subjects, the need to develop an improved neutralizing ADA assay may not be essential at this time from Clinical Pharmacology perspectives.

See Product Quality Review (immunogenicity section) by Tura Camilli, Ph.D., for more detailed information regarding the immunogenicity assay validation.

3. LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The ~~strikethrough in red~~ text indicates recommended deletion by the reviewer. The **texts in blue** are recommended labeling changes by the reviewer.

Proposed labeling by the Applicant	Labeling recommendations
<p>6.2 Immunogenicity</p> <p>Less than 1% of patients treated with secukinumab developed antibodies to secukinumab in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately one-half had antibodies that were classified as neutralizing. Neutralizing antibodies were not associated with loss of efficacy.</p>	<p><i>We concur with the product quality reviewer to include the following into the immunogenicity section of the labeling.</i></p> <p>The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to COSENTYX with the incidences of antibodies to other products may be misleading.</p>
<p>7. DRUG INTERACTIONS</p> <p>Drug interaction studies have not been conducted with COSENTYX.</p>	<p>Section 7.3 is recommended to be included in the labeling as below.</p> <p>7.3 CYP450 Substrates</p> <p>The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN)</p>

	<p>during chronic inflammation. Thus, COSENTYX, an antagonist of IL-17A, could normalize the formation of CYP450 enzymes. A role for IL-17A in the regulation of CYP450 enzymes has not been reported. Upon initiation or discontinuation of COSENTYX in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate as needed.</p>
<p>12 CLINICAL PHARMACOLOGY</p> <p>(b) (4)</p>	<p>12.2 Pharmacodynamics</p> <p>The serum levels of total IL-17A (free and secukinumab-bound IL-17A) is low at baseline and increased following secukinumab treatment (at Week 4 and Week 12) in subjects with plaque psoriasis.</p> <p>12.3 Pharmacokinetics</p> <p><u>Absorption</u></p> <p>Following a single subcutaneous dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak 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. Steady-state concentrations of secukinumab were achieved by Week 24 following the monthly dosing regimens. The mean steady-state trough concentrations ranged from 16.7 ± 8.2 mcg/mL (150 mg) to 34.4 ± 16.6 mcg/mL (300 mg).</p> <p>In healthy subjects and subjects with plaque psoriasis, secukinumab bioavailability ranged from 55% to 77%.</p> <p><u>Distribution</u></p> <p>The mean volume of distribution during the terminal phase (V_z) ranged from 7.10 to 8.60 L following a single intravenous administration in plaque psoriasis patients.</p> <p>Secukinumab concentrations in the interstitial fluid in lesional and non-lesional skin of plaque psoriasis patients ranged from 26% to 40% of those in serum at 1 and 2 weeks after a single subcutaneous dose of secukinumab 300 mg.</p> <p><u>Metabolism</u></p> <p>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.</p> <p><u>Elimination</u></p> <p>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 subjects with plaque psoriasis following intravenous and</p>

(b) (4) subcutaneous administration across different psoriasis trials.

Dose Linearity

Secukinumab exhibited dose-proportional pharmacokinetics in subjects with psoriasis over a dose range from 25 mg to 300 mg following subcutaneous administrations.

Specific Populations

Weight

When given the same 150 mg or 300 mg dose, subjects with plaque psoriasis weighing ≥ 90 kg had lower median serum concentrations compared with those subjects weighing < 90 kg.

Hepatic or Renal Impairment

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

Age:

Subjects with age ≥ 65 years and subjects with age < 65 years had similar apparent clearance values.

4. PHARMACOMETRICS REVIEW

4.1 Summary of Findings

4.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

4.1.1.1 Is there evidence of an exposure-response relationship between week 12 response (IGA 0/1) and secukinumab concentrations at week 12 for the treatment of severe plaque psoriasis?

Yes, an exposure-response relationship was identified that provides supportive evidence of effectiveness of secukinumab for the proposed indication (Figure 1). The dataset for the exposure-response analysis included data from a total of 1408 patients from Study A2302 (N=584) and Study A2303 (N=824). Observed trough concentration at Week 12 was used as the exposure variable while IGA 0/1, the primary efficacy endpoint was utilized as the response variable. Both univariate and multivariate logistic regression analyses show that increasing secukinumab concentration at Week 12 was a significant predictor of increasing IGA 0/1 response at Week 12 (p-value < 2×10^{-16}). Among covariates such as sex, body weight, race, study, age, and baseline disease condition (baseline IGA score) in univariate and multivariate logistic regression analyses, body weight and baseline IGA score were identified as significant covariates on the exposure-response relationship; higher body weight and higher baseline IGA score resulted in a lower response. Body weight was also a significant as a categorical variable with cutoff of 100 kg (N= 322 \geq 100 kg and N=1086 for patients < 100 kg, see Section 1.1.3).

The exposure-response analysis predicts an increase in response of approximately 12% for a two-fold increase in exposure. These predictions are similar to the observed differences in response between 150 mg (51.2% [Study A2302] and 51.1% [Study A2302]) and 300 mg (65.3% [Study A2302] and 62.5% [Study A2303]) for IGA 0/1 at week 12. In addition, due to the relationship between body weight and exposure, there was 32 and 40% differences in exposure between subjects above and below the median body weight (83 kg) within 150 mg and 300 mg dose groups, respectively. This difference in exposure within a treatment arm translated to an observed difference in response of 6-8%, which is similar to the difference in response predicted by the exposure-response relationship. Similar trends between treatment arms were also observed for other secondary endpoints of PASI 75, PASI 100, and IGA 0 (see Section 3 for additional details).

IGA 0/1 at Week 12 by Concentration Quartile

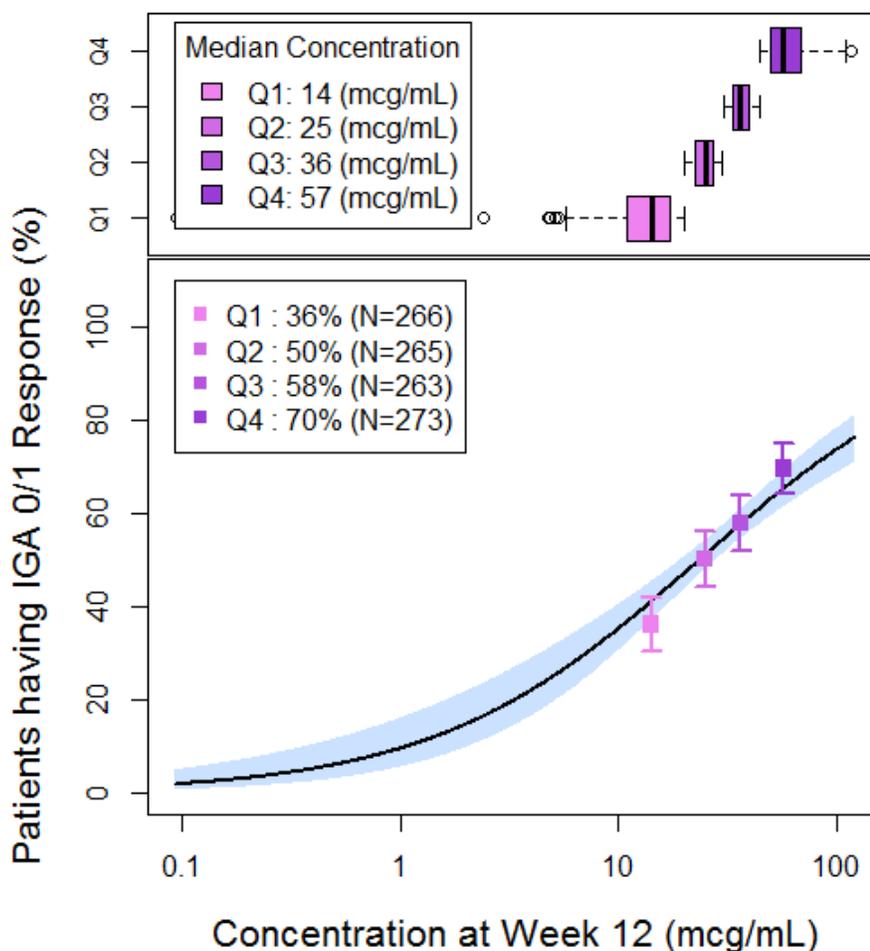


Figure 1. Logistic regression for IGA 0/1 at Week 12 by quartile of secukinumab trough concentration at Week 12. Secukinumab concentrations following both 150 and 300 mg from Study A2302 and Study A2303 were included in the analysis. On top of the regression line with 95% CI, median (95% CI) values for observed response rates for each quartile are overlaid

As an additional comparison between the treatment arms, time course profiles of PASI percentage change from baseline was evaluated for placebo and the 150 mg and 300 mg treatment arms. As shown in Figure 2, the efficacy of secukinumab compared to placebo is distinctive over the first 12-weeks of treatment for both 150 mg and 300 mg doses. Also of note, the 300 mg dose consistently had a larger overall percentage change from baseline from week 3 of treatment through week 12. These observations lend additional supportive information regarding the improved efficacy of the 300 mg regimen, suggesting that the benefits of the higher dose are observed earlier in treatment and maintained up to the week 12 time point when the primary efficacy assessment occurred.

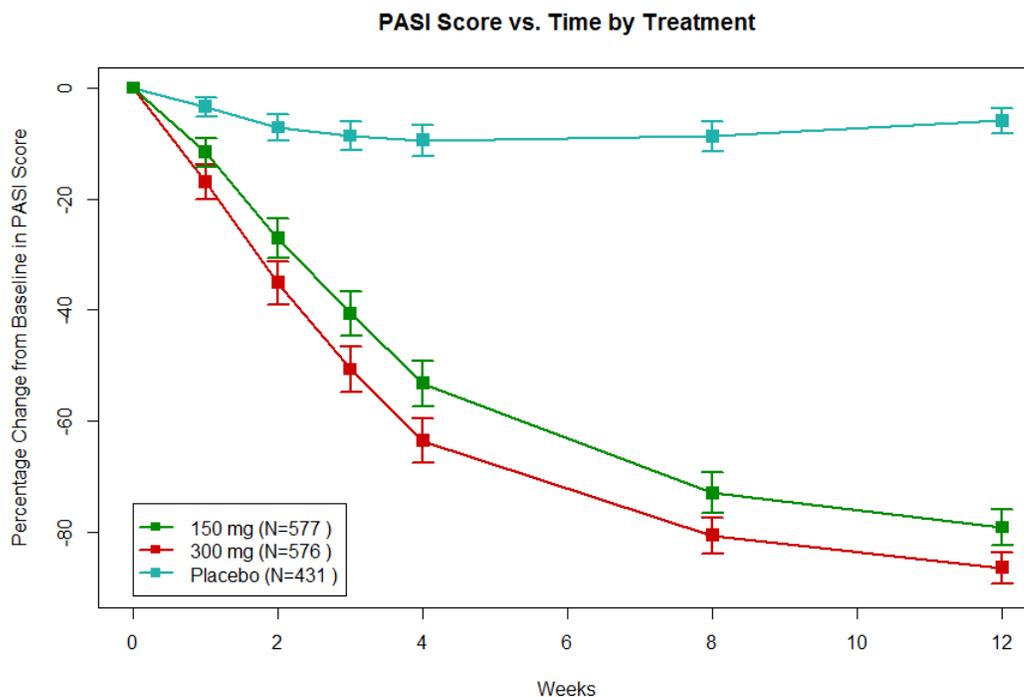


Figure 2. Change from Baseline PASI over time

4.1.1.2 Is there evidence of exposure-safety relationships for secukinumab?

No. The overall AEs were 75.3%, 88.0%, 84.0% and 73.7%, respectively, across the quartiles of serum concentration in order of increasing exposure at Week 52 for the 150 mg dose, and the overall AEs were 72.8%, 80.8%, 83.3% and 87.6%, respectively, across the quartiles of serum concentration in order of increasing exposure at Week 52 for the 300 mg dose. As shown in Table 1, although Candida infection showed a slight increase with higher dose (2.3% in 150 mg dose arm, 4.6% in 300 mg dose arm) and higher exposure, the effect if not significant and the the Candida infection is not considered serious.

Table 1. Adverse Events by Quartiles following 150 mg and 300 mg of Secukinumab

Dose		Secukinumab concentration range by quartiles				
		Q1	Q2	Q3	Q4	
150 mg	Secukinumab Concentration	<11.6 mcg/mL (n=97)	≥11.6 <15.9 mcg/mL (n=100)	≥15.9 <22.1 mcg/mL (n=100)	≥22.1 <94.9 mcg/mL (n=99)	Any concentration (n=396)
	Any AEs	73 (75.3%)	88 (88.0%)	84 (84.0%)	73 (73.7%)	318 (80.3%)

	Candida infection	1 (1.0%)	1 (1.0%)	4 (4.0%)	3 (3.0%)	9 (2.3%)
300 mg	Secukinumab Concentration	<21.5 mcg/mL (n=103)	≥21.5 mcg/mL <31.4 mcg/mL (n=104)	≥31.4 mcg/mL <43.1 mcg/mL (n=102)	≥43.1 mcg/mL <105 mcg/mL (n=105)	Any concentration (n=414)
	Any AEs	75 (72.8%)	84 (80.8%)	88 (86.3%)	92 (87.6%)	339 (81.9%)
	Candida infection	2 (1.9)	4 (3.8%)	7 (6.9%)	6 (5.7%)	19 (4.6%)

(Source: Table 3-1, Tables 3-3 and 3-4, Response to FDA information request, July 14, 2014.)

4.1.1.3 Is proposed dosing regimen appropriate? Can dose be optimized in subgroup of patients with lower efficacy?

The sponsor proposes 300 mg at Week 0, 1, 2, and 3 followed by monthly (q4w) maintenance dosing starting at Week 4, for all patients regardless of body weight or baseline disease condition. However, multivariate logistic regression analyses identified both body weight and baseline IGA score as significant covariate on the exposure-response relationship. From the multivariate logistic regression, the effect of body weight was statistically significant (p-value < 0.0003) indicating that per/kg dosing regimen might be an appropriate dosing regimen. As such, the effect of body weight with two different cutoffs of 90 kg and 100 kg are compared (Figure 3) to better understand the role of body weight on treatment response and whether there is a need for dose adjustments based on body weight.

- Patients with body weight < 90 kg following 150 mg (N=328, response rate for IGA 0/1: 50.3%) may expect the similar efficacy with patients with patients with body weight ≥ 90 kg following 300 mg (N=196, response rate for IGA 0/1: 51.5%).
- Patients with body weight ≥ 90 kg may not get benefit with 150 mg (N=202, response rate for IGA 0/1: 43.6%) as much as those weighing < 90 kg taking 300 kg (N=341, response rate for IGA 0/1: 63.6%)
- Patients with body weight ≥ 100 kg may expect lower efficacy with 300 mg (N=122, response rate for IGA 0/1: 47.5%) than those weight < 100 kg with 150 mg dose (N=412, response rate for IGA 0/1: 51.2%)
- Patients with body weight ≥ 100 kg may not get benefit with 150 mg (N=118, response rate for IGA 0/1: 35.6%) as much as those weighing < 100 kg taking 300 mg (N=415, response rate for IGA 0/1: 62.7%)

Although the effect of body weight is statistically significant with a cutoff of 100 kg, 90 kg would be more clinical relevant cutoff considering the median body weight observed in Phase 3 trials was 82 kg.

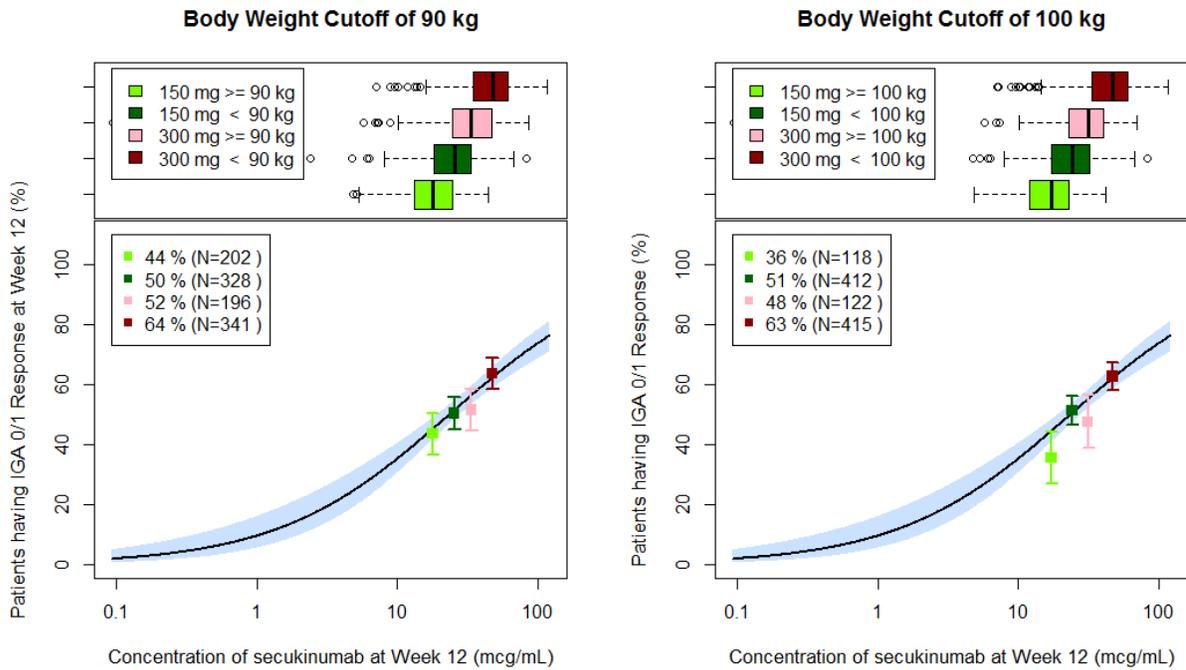


Figure 3. IGA 0/1 at Week 12 by dose and body weight and baseline IGA score

The reviewer further conducted simulations with the population PK model to evaluate the effect of body weight following different dosing schemes. Simulated concentrations of secukinumab at Week 12 were compared among patients following the proposed dosing regimen of 300 mg to overall population and patients weighing \geq 90 kg following 450 mg. As shown in figure, the predicted concentrations in patients weighing \geq 90 kg were lower than those in patients weighing $<$ 90 kg following the same dose of 300 mg. By increasing dose to 450 mg, the concentrations in patients weighing \geq 90 kg became comparable to those in patients $<$ 90 kg.

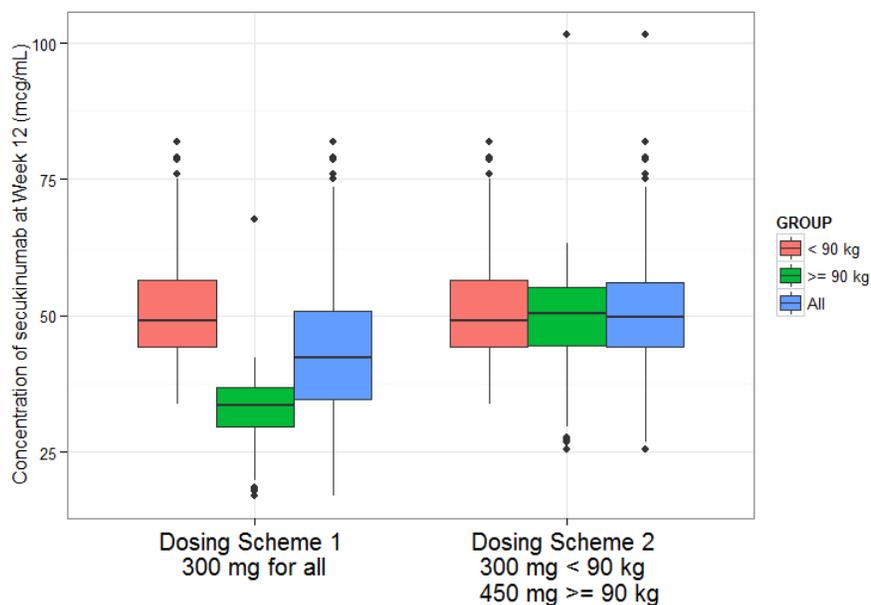


Figure 4. Predicted concentrations of secukinumab following 300 mg for all patients or 300 mg for patients weighing < 90 kg and 450 mg for patients weighing \geq 90 kg using a population PK model

Based on the observations below, the reviewer concludes:

- Patients with higher body weight with cutoff of 90 kg or 100 kg may start with 300 mg dose and patients with lower body weight start with 150 mg dose
- Since there is no exposure-related safety concern, patients with body weight \geq 90 kg may start with 300 mg and patients with body weight < 90 kg may start with 150 mg with additional option of using 300 mg for higher efficacy. To explore an additional option for patients with higher body weight, a clinical trial with 450 mg for patients with body weight \geq 90 kg is recommended as a PMC.

4.1.2 Recommendations

The Office of Clinical Pharmacology Divisions of Pharmacometrics and Clinical Pharmacology 3 have reviewed the information provided in the submission and consider the data are acceptable for supporting the approval of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients. Based on the identified covariates the impact secukinumab exposure and the identified exposure-response efficacy relationships, weight-based dosing appears to be desirable for administration of secukinumab in the target population.

4.1.3 Label Statements

Detailed labeling recommendations are included in *Section 3*.

4.2 Pertinent regulatory background

Secukinumab is a human IgG1 monoclonal antibody that is believed to selectively bind to proinflammatory cytokine interleukin-17A (IL-17A) and inhibit its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a role in the pathogenesis of plaque psoriasis.

The proposed indication is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 300 mg by subcutaneous (SC) injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly (Q4W) maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg. The proposed formulation and presentation for secukinumab SC injection include prefilled SensoReady[®] pen (AI, auto-injector), prefilled syringe (PFS), and lyophilized powder in vial (LYO).

A total of 22 clinical trials have been conducted with secukinumab in healthy subjects, subjects with psoriasis and other various patient populations. Among the 22 clinical trials, 16 trials (six Phase 1 trials in healthy subjects and subjects with psoriasis, 5 Phase 2 trials in subjects with psoriasis, and 5 Phase 3 trials in subjects with psoriasis) are to support the proposed indication and clinical pharmacology section of the product labeling.

Four randomized, double-blind, parallel-group, Phase II studies were used to define the initial dosing regimen [Study A2102, Study A2211, Study A2212, Study A2220] and maintenance regimens [Study A2211] for Phase III studies. These four Phase II studies explored doses ranging from 25 mg SC to 10 mg/kg IV. In the dose ranging study [Study A2220] with Q4W 25 mg, 75 mg and 150 mg, only 150 mg dose showed consistent efficacy after 12 weeks. Dose ranging study [Study A2212] assessed 3-times repeated 10 mg/kg IV, which modeling suggested could be achieved with 300 mg SC. The study compared the effectiveness of three IV loading doses to placebo: singles doses of 3 or 10 mg/kg IV or multiple doses of 10 mg/kg IV (at Randomization, Week 2, and Week 4). The response rates to PASI 75, PASI 90, and IGA mod 2007 0/1 showed dose-related efficacy, with a higher proportion of responders in the 10 mg/kg IV. The PK exposure for these IV doses supported the SC doses chosen for the Phase III studies, with the exposure ranges for the 150 mg and 300 mg SC dose regimens lying within the exposure range achieved with these IV doses. Regimen finding study [Study A2211] examined the effectiveness of 150 mg SC administered initially as one of 4 initial dosing regimens and then administered to responders as one of 2 maintenance treatments (fixed-time interval regimen with doses at Weeks 12 and 24 vs. Start of relapse regimen with dosing resumed once relapse started), with non-PASI 75 responders and those with 2 consecutive relapses at scheduled visits, treated open-label once every four weeks i.e., a third regimen. Start of relapse occurred if the patient lost a third of the maximum PASI response (compared to baseline) achieved at any time before the visit at which the assessment was made. Overall, the study showed that early weekly loading was the most efficacious initial dosing regimen and that a fixed interval maintenance regimen every

four weeks may be appropriate. Thus, two dosing regimens (either 150 mg SC or 300 mg SC with initial dosing once weekly for 4 weeks) and then ever 4 weeks thereafter were chosen for further study in the Phase III.

Four pivotal placebo-controlled Phase III studies [Study A2302, Study A2303, Study A2308, Study A2309], one of which included an active comparator (etanercept), used identical weekly initial dosing regimens and subsequent maintenance regimens with the selected doses of 150 mg and 300 mg SC. Among these 4 Phase III clinical trials, 2 studies [Study A2302, Study A2303] utilized lyophilisate in vial (LYO) formulation, 1 study [Study A2308] utilized new liquid formulation in pre-filled syringe (PFS), and 1 study [Study A2309] utilized new liquid formulation in an auto-injector/pen (AI).

The efficacy variables evaluated were PASI 75 (Psoriasis Area and Severity Index; PASI 75 responder if 75% reduction from baseline), PASI 90 (90% reduction), PASI 100 (100% clearance) and IGA 0/1 mod 2011 (IGA scale used in part of the Phase III program, 5-point scale; IGA 0 or 1 responder if following conditions were met: score of 0 or 1 was achieved, AND if there was an improvement of 2 points or more compared to baseline). The results from the Phase 3 trials are summarized in table.

Table 2. Summary of Efficacy in Phase Studies

Study	PASI 75			IGA 0/1		
	150 mg	300 mg	Placebo	150 mg	300 mg	Placebo
A2302(N=737)	71.6%	81.6%	4.5%	51.2%	65.3%	2.4%
A2303 (N=1305)	67.0%	77.1%	4.9%	51.1%	62.5%	2.8%
A2308 (N=177)	69.5%	75.9%	0%	52.5%	69.0%	0%
A2309 (N=182)	71.7%	86.7%	3.3%	53.3%	73.3%	0%

(Source: Summary of Clinical Efficacy, Table 3-11)

Two additional Phase III studies explored alternative dose or regimens for maintenance therapy (primarily Study A2304) to evaluate up-titration of patients without response at Week 12. In Study A2304, PASI 75 responders were randomized to fixed interval maintenance dosing arm (150 mg: N=203, 300 mg: N=216) or retreatment upon start of relapse arm (150 mg: N=206, 300 mg: N=217). This 48-week study showed better efficacy of fixed interval maintenance dosing compared to retreatment upon start of relapse. A smaller Phase III trial [Study A2307] was conducted in those patients achieving only a partial response in the induction period of Study A2304 and attempted to achieve an enhanced response in these patients by up-titrating the dose. This study was designed to evaluate the superiority of 10 mg/kg intravenous dosing regimen by administering 10 mg/kg IV dose or 300 mg SC dose to Week 8 or Week 12 partial responder from both 150 mg and 300 mg arms. Since too small number of patients (N=21 for 300 mg SC escalation arm [15 from 150 mg SC arm. and 6 from 300 mg SC arm] and N=21 for 10 mg/kg IV escalation arm [14 from 150 mg SC and 8 from 300 mg SC. arm])

to make a definitive conclusion for the superiority of IV dosing regimen. Furthermore, this study was not designed to evaluate potential benefit of dose escalation to non-responders.

4.3 Results of sponsor's analysis

4.3.1 Introduction

First, the sponsor conducted a population PK analysis to characterize the PK of secukinumab and evaluate various covariates to explain inter-patient variability in exposure, such as body weight, age, gender, race, and baseline disease severity (*Source: PK Modeling Report page 8*).

Second, a PK/PD modeling was performed to describe the secukinumab dose-exposure-PASI response relationship in patients with moderate to severe psoriasis, following single and multiple doses of SC or IV administration. This model was used to evaluate alternative dosing options (*Source: Modeling Report, page 7*).

Third, additional analyses for exposure-response for efficacy and safety as well as the effect of body weight on efficacy were performed by the sponsor upon the reviewer's information request as confirmatory analyses for the significant effect of body weight on the exposure-response relationships (*Source Response to FDA IR, July 14, 2014*).

4.3.2 Data sets

The population PK analysis was based on pooled PK data from studies A2102, A2103, A2211, A2212, A2220 and A2302. These studies cover IV regimens from 3 mg/kg up to 3×10 mg/kg and SC regimen from 1×25 mg up to 6×300 mg up to week 12 with various maintenance regimens after week 12. The population PK model was built based on 10193 secukinumab serum concentrations from 1233 patients. The PK/PD modeling linked the population PK model with pooled PASI data from studies A2102, A2103, A2211, A2212, A2220 and A2302. The population PK/PASI model was built based on 26587 PASI observations from 1405 patients. External validation of the dose-exposure-PASI response model was performed with data from study A2303.

Table 3. Summary of Population Pharmacokinetic Analysis Data

Group	N	records	active doses	pbo doses	PK obs
A2102:1x3mg/kg iv	15	192	15	NA	177
A2103:1x150mg	7	172	14	NA	158
A2103:1x1mg/kg iv	7	182	14	NA	168
A2211:1x150mg	66	2615	1370	289	956
A2211:3x150mg	137	4452	2147	409	1896
A2211:4x150mg early	132	4164	2083	286	1795
A2211:placebo	58	2133	1266	292	575
A2212:1x10mg/kg iv	25	494	25	50	419
A2212:1x3mg/kg iv	30	566	30	60	476
A2212:3x10mg/kg iv	30	604	84	NA	520
A2220:1x25mg	29	269	29	53	187
A2220:3x150mg	27	323	77	NA	246
A2220:3x25mg	26	301	75	NA	226
A2220:3x75mg	21	261	62	NA	199
A2302:150mg	242	9398	3562	4888	948
A2302:300mg	243	9674	7344	1378	952
A2302:placebo	138	5427	2609	2523	295
TOTAL	1233	41227	20806	10228	10193

(Source: Population PK Report Table 5-1)

Table 4. Summary of PK-PASI Analysis Data

Group	N	PASI obs
A2102:1x3mg/kg iv	15	155
A2102:placebo	15	156
A2103:1x150mg	7	77
A2103:1x1mg/kg iv	7	77
A2211:1x150mg	66	1859
A2211:3x150mg	138	3329
A2211:4x150mg early	133	3183
A2211:placebo	67	1468
A2212:1x10mg/kg iv	25	349
A2212:1x3mg/kg iv	30	374
A2212:3x10mg/kg iv	30	458
A2212:placebo	10	78
A2220:1x25mg	29	279
A2220:3x150mg	27	282
A2220:3x25mg	26	268

(Source: Pooled population-PK/PASI analysis of secukinumab in psoriasis Modeling Report Table 5-1)

Table 5. Summary of patient demographics and disease characteristics for the population PK model development

	N	missing	mean	sd	median	min	q05	q95	max
Bodyweight [kg]	1233	0	90.7	23.5	88	43	59	133.8	188
Pasi at baseline	1233	0	21.1	8.8	18.2	8.2	12.4	39.2	72
Height [cm]	1233	1	172.7	9.9	173	145	156	188	198
BMI [kg/m ²]	1233	1	30.3	7.2	28.9	16.6	21.2	44.3	70.8
Age [yr]	1233	38	44.6	12.6	45	18	24	66	83

	N	Frequency
Sex	1233	1:897, 2:336
Race	1233	1:967, 2:17, 3:206, 7:13, 8:5, 77:2, 88:23
Ethnicity	1233	1:111, 2:1, 3:1, 4:63, 5:47, 77:31, 88:763, 200:126, 225:1, 250:5, 275:2, 300:22, 800:60
Asian	1233	0:1027, 1:206
Country	1233	ARG:24, CAN:122, COL:15, DEU:108, EST:75, FRA:27, ISL:64, ISR:26, JPN:141, LTU:23, LVA:51, MEX:11, NOR:8, TWN:46, USA:492

(Source: Population PK Report Table 5-3 & 5-4)

Table 10. Summary of patient demographics and disease characteristics for the PK/PASI model development

	N	missing	mean	sd	median	min	q05	q95	max
Bodyweight [kg]	1405	0	90.8	23.8	88	43	58.2	133.6	203.2
PASI at baseline	1405	0	21.3	9	18.2	8.2	12.4	39.6	72
Height [cm]	1405	2	172.7	10	173	145	155.7	188	198
BMI [kg/m ²]	1405	2	30.4	7.3	28.9	16.2	21.2	44.2	70.8
Age [yr]	1405	44	44.8	12.6	45	18	24	66	83

	N	Frequency
Sex	1405	1:1013, 2:392
Race	1405	1:1102, 2:22, 3:226, 7:15, 8:6, 77:2, 88:32
Ethnicity	1405	1:142, 2:1, 3:1, 4:68, 5:64, 77:39, 88:846, 200:141, 225:1, 250:5, 275:2, 300:26, 800:69
Asian	1405	0:1179, 1:226
Country	1405	ARG:33, CAN:138, COL:23, DEU:112, EST:83, FRA:27, ISL:71, ISR:30, JPN:154, LTU:28, LVA:61, MEX:17, NOR:8, TWN:51, USA:569

(Source: Pooled population-PK/PASI analysis of secukinumab in psoriasis (PK-PASI Modeling Report) Table 5-2 & 5-3)

4.3.3 Population PK modeling

The two-compartment with first-order absorption model was chosen as the base model and body weight was included in the final model as a covariate. The final model was qualified by visual predictive check and parameter estimates of the model are presented in Table 6. Shrinkage (%) of random effects (η_{CL} : 4%, η_{V2} : 19.5%, η_{V3} : 32.9%, η_{Ka} : 55.6%, $\epsilon_{proportional}$: 10.7%, $\epsilon_{additive}$: 9.9%) indicates diagnostic plots should be interpreted with caution, especially with individual

prediction in absorption phase (large shrinkage associated with k_a). Large conditional weighted residuals at lower concentrations and at earlier time points (<10 ng/mL and < 240 hours, Figure 5) were observed.

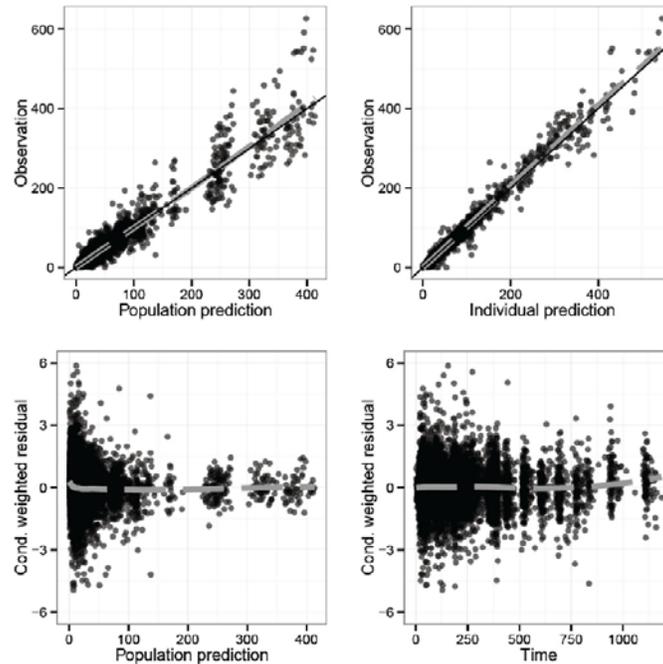


Figure 5. Goodness-of-fit diagnostics for PK model

(Source: Population PK Report Figure 5-7)

Predictive check and external validation with data from study A2303 were also performed and seemed to support the developed population PK model (figures not shown). Moreover, the sponsor performed additional analysis to evaluate time-dependence or dose-dependence of PK and concluded that the PK of secukinumab is linear with no evidence of a time-dependent change in the clearance or a dose-dependence clearance.

The final PK parameters estimated from the population PK modeling are summarized in Table 6. The bioavailability (F) is estimated on a logit scale and can be computed from the estimated parameter TVF1 by an inverse logit transform: $F = \frac{\exp(\text{TVF1})}{1 + \exp(\text{TVF1})}$. Thus F is estimated to be 72% with an approximate RSE of 1.5%. The clearance of secukinumab was 0.19 L/d (18% CV) in a typical psoriasis patient weighing 90 kg. The average terminal half-life is estimated to be 27 days (27% CV). Clearance and volumes both vary with body weight in an allometric relationship. For clearance and central volume of distribution the allometric exponents were estimated to be between 0.8-1.0. Age, gender, race, geographic region and baseline PASI score did not have a clinically relevant influence on clearance (after adjusting for body weight).

Table 6. Parameter estimates of the Final Model

Name	Parameter	Value	%RSE
Objective Function Value	OFV	173520	
CL [L/d]	TH1	0.19	1.9
V2 [L]	TH2	3.61	2.6
Q [L/d]	TH3	0.39	4.6
V3 [L]	TH4	2.87	1.9
KA [1/d]	TH7	0.18	3.6
TVF1	TH8	0.99	5.7
WT on CL	TH10	1	3.6
WT on V2	TH11	0.81	9.4
WT on Q	TH12	0.68	29.5
WT on V3	TH13	0.56	13.6
IIV CL (sd)	OM1:1	0.32	4.2
IIV V2 (sd)	OM2:2	0.3	9.6
IIV CL-V2 (corr)	OM2:1	0.7	8
IIV V3 (sd)	OM3:3	0.18	18
IIV CL-V3 (corr)	OM3:1	0.14	72
IIV V2-V3 (corr)	OM3:2	0.72	14
IIV Q (sd)	OM4:4	0	NA
IIV KA (sd)	OM7:7	0.35	13
IIV TVF1 (sd)	OM8:8	0	NA
Proportional error (sd)	SI1:1	0.17	0.8
Additive Error (sd)	SI2:2	371	0.5

(Source: Population PK Report Table 5-8)

The sponsor further simulated trough concentrations following various dosing strategies including body weight based dosing regimens (Figure 6). Flat dosing with 150 mg is compared to either dosing based on a body weight cutoff (150 mg/300 mg for patients below/above body weight thresholds of 90 kg, 100 kg, 120 kg) or a to a hypothetical mg/kg SC dosing (1.66 mg/kg SC, resulting in 150 mg for a 90 kg patient). Based on simulation, secukinumab average concentrations at steady state following SC administration of 150 mg and 300 mg every 4 weeks are estimated to be 22.2 mcg/mL and 44.5 mcg/mL. From this simulation exercise the sponsor concluded that using two available doses (150 mg and 300 mg) in a dosing strategy based on a body weight threshold would not reduce between-patient PK variability. A theoretical mg/kg-based dosing would only moderately decrease between-patient variability in exposure (from 46.5% CV with 150 mg flat dosing to 37.9%CV with 1.66 mg/kg dosing).

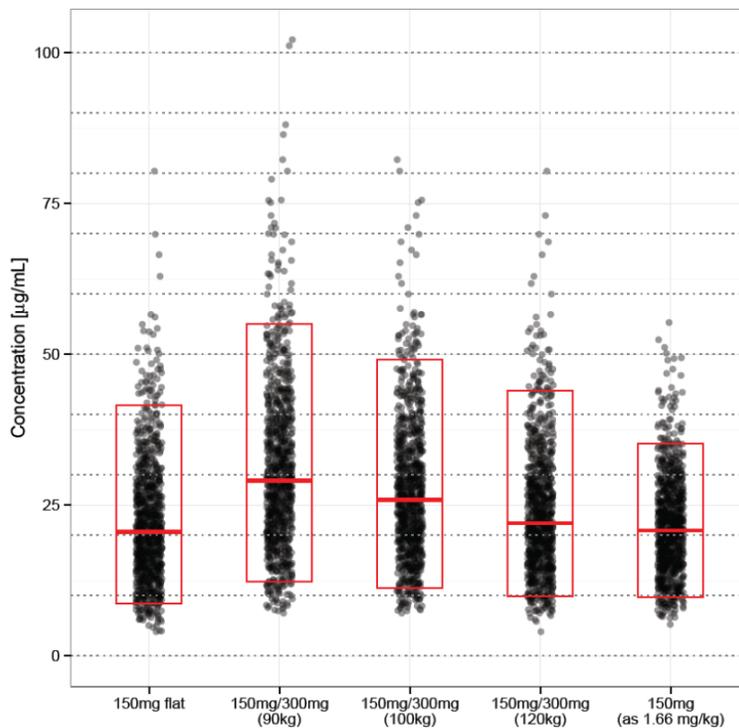


Figure 6. Simulated week 12 trough concentrations for different body weight-based dosing strategies (Source: Population PK Report Figure 5-16)

Reviewer's comments: The comparison between 150 mg flat dose and 150 mg/300mg with 90 kg body weight threshold is not a fair comparison to evaluate the effect of weight-based dosing on variability. For a fair comparison, combined data following 150 mg flat dose and 300 mg flat dose should be compared to 150 mg for patients with body weight < 90 kg and 300 mg for patients with body weight ≥ 90 kg so that median concentrations along with variability could be compared for these dosing regimens. The comparison between 150 mg flat dose and 1.66 mg/kg (150 mg dose was divided by 90 kg) appears to be fair and from that comparison CV was decreased from 46.5% to 37.9%.

4.3.4 PK-PASI Model

A turnover model was chosen for the PASI response model. Response R is described by a differential equation:

$$dR/dt = k_{in} - k_{out} * (1 + DrugEffect) * R$$

$$DrugEffect = E_{max} * C^{\gamma} / (C^{\gamma} + EC50^{\gamma})$$

Disease dynamics model:

In addition to the drug effect the PASI scores might exhibit some disease dynamics/placebo effect, e.g., upwards or downwards trends over time, independent of

the drug effect. The following linear and exponential shapes were explored in addition to the drug-disease model for R outlined above:

Linear decline: $PASI = R - SLOPE * t$

Exponential decline: $PASI = R-FS * PAS0 * (1-\exp(-KS*t))$

The parameters of population PK-PASI model are summarized in Table 7. Shrinkage (%) of random effects (η_{kout} : 20.7%, η_{EC50} : 24.3%, η_{SLOPE} : 18.8%) suggest that slight bias may be introduced and the modeling results should be interpreted with caution. The goodness-of-fit (Figure 7) also suggest some potential distortions in the lower range of PASI scores.

Table 7. Parameters of final PK-PASI model

Name	Parameter	Value	RSE (%)
Objective Function Value	OFV	70048	
kout [1/d]	TH2	0.0012	2.4
EC50 [ng/mL]	TH3	19150.5	3.3
Emax	TH4	56.3879	1.4
Gamma	TH5	2.07	2
SD of additive error	TH10	0.385	0.6
SD of proportional error	TH11	0.3432	0.2
IIV kout (SD)	OM2:2	0.76	5.1
IIV EC50 (SD)	OM3:3	1	6.3
IIV SLOPE (SD)	OM8:8	0.014	2.4

(Source: PK-PASI Modeling Report Table 5-5)

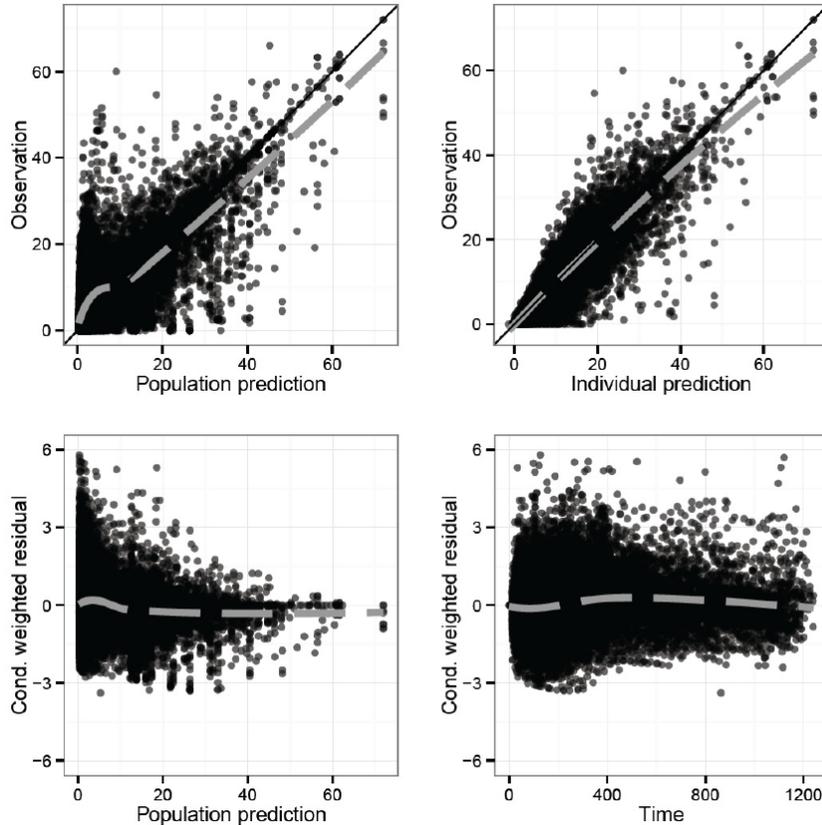


Figure 7. Goodness-of-fit for PASI model

(Source: PK-PASI Modeling Report Table 5-9)

With this PASI model, the sponsor further evaluated effect of covariates by a graphical analysis (Figure 8). With this analysis, the sponsor concluded that there are no clear systemic trends against continuous covariates (body weight, age, PASI at baseline) or categorical covariates (sex, country, non-Asian/Asian).

Reviewer's comments: This covariate assessment could be misleading when the PD parameters are biased. Especially when the prediction can be inaccurate at lower PASI scores, the correlation with baseline PASI with PD model parameters may be of less value.

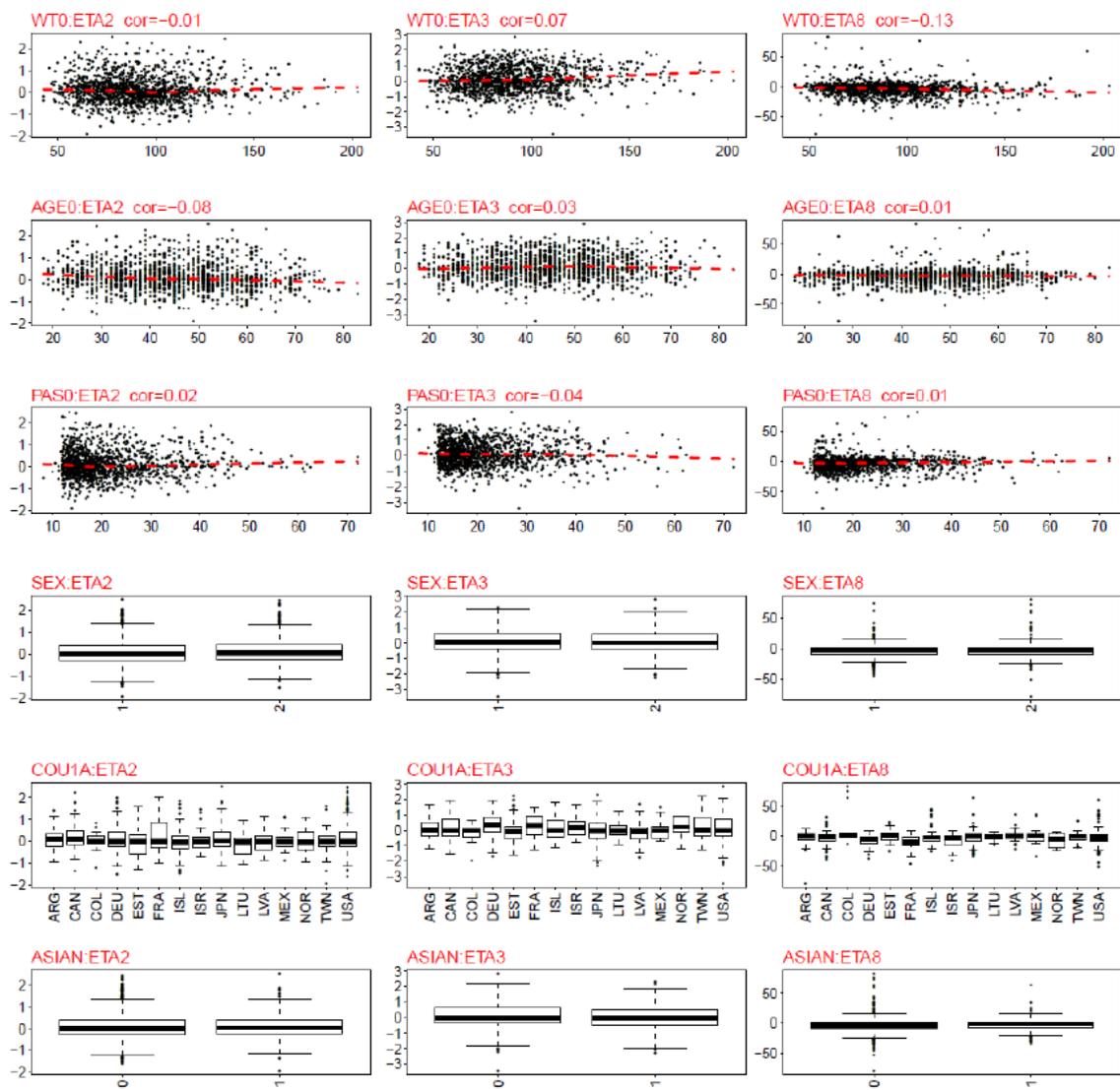


Figure 8. Graphical analysis of selected covariates vs. random effects (ETAs) ETA2 is on kout, ETA3 is on EC50, ETA8 is on SLOPE (Source: PK-PASI Modeling Report Figure 5-12)

4.3.5 Simulation for 150 mg 300 mg dose

The sponsor further simulated PASI 75 response rate with proposed dosing regimen (300 mg) along with other dosing regimens (150 mg and 75 mg for induction and 150 mg for maintenance). As shown in Figure 9 and consistent with observations from the Phase III trials, the 300 mg regimen was predicted to result in higher PASI 75 response compared to 150 mg over the first 12-weeks of treatment. An improvement in response using 300 mg compared to 150 mg was predicted to be continued into the maintenance phase of treatment.

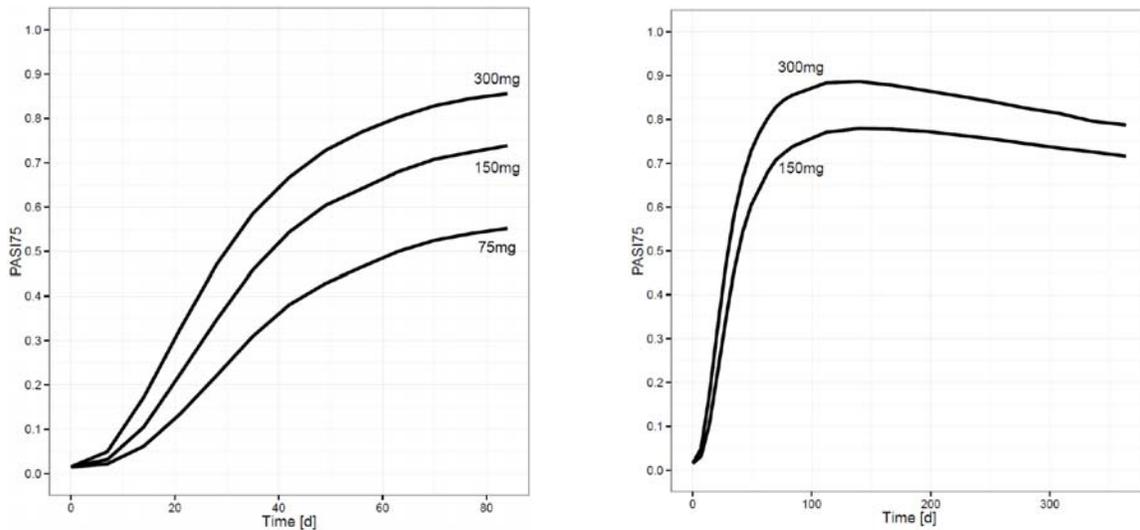


Figure 9. Simulation of PASI 75 responder rate for Phase III regimens (left panel for induction phase, right panel for maintenance phase) (Source: PK-PASI modeling report, Figures 5-14 and 5-15)

4.3.6 Dose-response for efficacy: PASI 75 (Observations)

Percentage of PASI 75 responders at week 12 vs. total bioavailable dose for large Phase II and Phase III studies are presented in Figure 10. The total bioavailable dose is calculated as the sum over doses given during the induction period (up to but excluding week 12) with SC doses being adjusted for the bioavailability of 73%. The sponsor concluded from this analysis that overall a consistent trend of higher exposure was associated with a higher response across the studied regimens and that the 300 mg regimen may not have reached the plateau of the dose-response curve. Response for treatment groups in the Phase II study A2220 is shifted relative to all other studies, but shows a clear dose-response within the study.

Reviewer's comments: The percentage PASI 75 responders for 300 mg in the Phase III study A2309 appears to be higher than those in other Phase studies (Study A2302 and Study A2303) where LYO formulation was utilized. The sample size for Study A2309 is relatively small compared to other two pivotal studies, the definitive conclusion about the exposures and response following this formulation is pending.

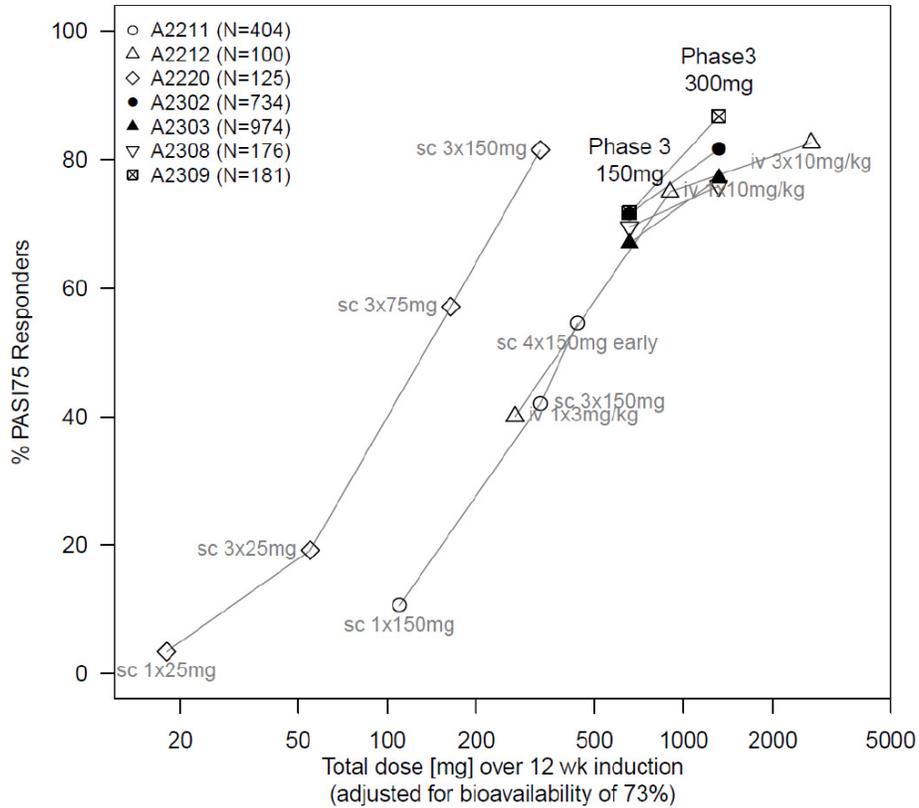


Figure 10. Percentage PASI 75 responders at week 12 vs. total bioavailable dose for Phase II and Phase III regimens (Source: PK-PASI Modeling Report Figure 5-3)

4.3.7 Exposure-response with trough concentrations at Week 12 and co-primary efficacy endpoints

Upon the agency’s information request, the sponsor submitted additional analysis for various efficacy endpoints with observed and model-predicted concentrations. The plots shown in Figure 11 indicate distinctive exposure-response relationships for all efficacy variables.

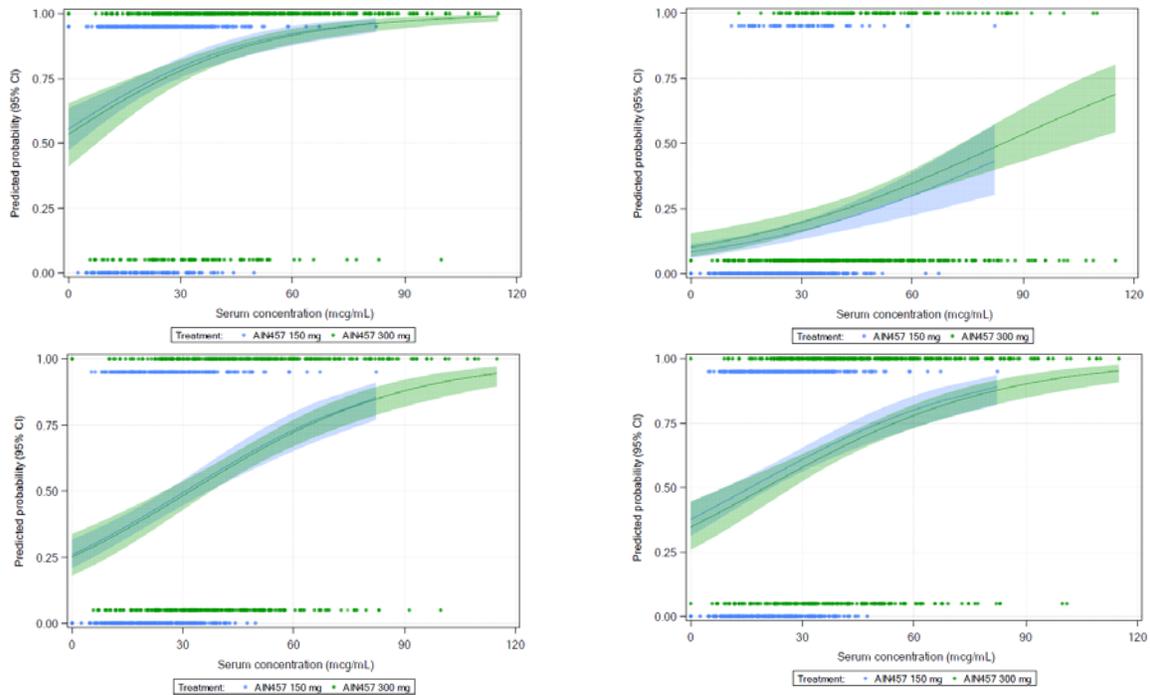


Figure 11. Predicted probabilities for PASI 75 (upper left), PASI 90 (upper right), PASI 100 (lower left), and IGA 0/1 (lower right) at Week 12 vs. observed concentration at Week 12 (Source: Figure a65 Q4-1 Response to FDA IR, July 14, 2014)

Based on the combined data from two pivotal Phase 3 trials (Study A2302 and Study A2303), an exposure-response relationship was observed for both PASI 75 and IGA 0/1 as shown in the response rates summarized by the observed serum concentration quartiles at Week 12 for both 150 mg dose and 300 mg doses (Table 8).

Table 8. The E-R by serum concentration quartiles at Week 12 for the 150 mg dose.

Efficacy endpoints	Overall	150 mg dose			
		1 st quartile	2 nd quartile	3 rd quartile	4 th quartile
		≤ 15.3	15.3 to ≤ 22.3	22.3 to ≤ 29.8	>29.8
PASI 75	74.3% (362/487)	61.5% (75/122)	74.6% (91/122)	76.9% (93/121)	84.4% (103/122)
IGA 0/1	55.6% (271/487)	40.2% (49/122)	53.3% (65/122)	59.5% (72/121)	69.7% (85/122)
		300 mg dose			
		1 st quartile	2 nd quartile	3 rd quartile	4 th quartile
		≤ 30.1	30.1 to ≤ 42.5	42.5 to ≤ 56.9	>56.9
PASI 75	83.9% (422/503)	73.8% (93/126)	80.2% (101/126)	87.4% (111/127)	94.4% (117/124)
IGA 0/1	67.2% (338/503)	53.2% (67/126)	66.7% (84/126)	68.5% (87/127)	80.6% (100/124)

Efficacy endpoints	Overall	300 mg dose			
		1 st quartile	2 nd quartile	3 rd quartile	4 th quartile
		≤ 30.1	30.1 to ≤ 42.5	42.5 to ≤ 56.9	>56.9
PASI 75	83.9% (422/503)	73.8% (93/126)	80.2% (101/126)	87.4% (111/127)	94.4% (117/124)
IGA 0/1	67.2% (338/503)	53.2% (67/126)	66.7% (84/126)	68.5% (87/127)	80.6% (100/124)

(Source: Table a65 Q4_1-2.1 & 2; Response to FDA IR, July 14, 2014)

The exposure-response relationship has been further confirmed with a model-based approach using the serum secukinumab concentration data and the IGA 0/1 clinical response data at Week 12 from the pivotal Phase 3 trials, CAIN457A2302 and CAIN457A2303 (see *Pharmacometrics Review in Appendix*). The logistic regression analyses show that an increasing secukinumab concentration at Week 12 was a significant predictor of an increasing IGA 0/1 response at Week 12 (p -value $< 2 \times 10^{-16}$). The bodyweight (a higher bodyweight resulted in a lower response) and the baseline IGA score (a higher baseline IGA score resulted in a lower response) were identified as significant covariates on the exposure-response relationship.

4.3.8 Exposure-response for efficacy by body weight:

The effect of body weight on exposure-response relationship was also significant. The sponsor emphasizes that the dose of 300 mg is more efficacious in all body weight subgroups compared to the dose of 150 mg.

Table 9. Predicted PASI 75, PASI 90, PASI 100 and IGA 0/1 response rates at Week 12 by weight subgroup (< 90 kg, ≥ 90 kg) based on observed serum concentration at Week 12

Response criterion	AIN457 150 mg		AIN457 300 mg	
	<90 kg (%) (95% CI)	≥90 kg (%) (95% CI)	<90 kg (%) (95% CI)	≥90 kg (%) (95% CI)
PASI 75	80.9 (76.0, 85.0)	65.3 (58.1, 71.9)	89.9 (85.8, 92.9)	78.3 (71.6, 83.8)
PASI 90	49.6 (43.9, 55.3)	34.7 (28.2, 41.9)	68.7 (63.1, 73.8)	47.2 (39.9, 54.6)
PASI 100	17.2 (13.4, 21.9)	9.6 (6.1, 14.8)	32.1 (27.1, 37.5)	17.6 (12.6, 24.0)
IGA 0/1	59.4 (53.7, 64.8)	50.0 (42.8, 57.2)	73.3 (68.0, 78.0)	60.0 (52.5, 67.1)
Mean serum concentration (mcg/mL)	26.08	19.20	50.19	36.14

(Source: Table a65 Q4-1_1-1.1; Response to FDA IR, July 14, 2014)

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

(26.08 mcg/mL); ≥ 90 kg (19.20 mcg/mL). Corresponding predicted PASI 75, PASI 90, PASI 100 and IGA 0/1 response rates in patients with < 90 kg following 300 mg are 90%, 69%, 32%, and 73% respectively, higher than the corresponding efficacy response rates in those patients with body weight ≥ 90 kg (78%, 47%, 18%, and 60%, respectively). As the efficacy measures get stricter (e.g., PASI 100 stricter than PASI 90 stricter than PASI 75), the relative response rates between subjects with body weight ≥ 90 kg and < 90 kg becomes larger.

4.3.9 Exposure-response for safety

Upon the agency's request, the sponsor submitted exposure-response for safety endpoints as well. There are no exposure response relationships that are evident from the data in study A2302 and study A2303 (**Error! Reference source not found.**). In addition, similar analysis with for Candida infection which was identified as an adverse event differed by dose (4.6% for 300 and 2.3% in 150 mg), was conducted and shows a relationship with the exposure (Table 1).

With these analyses, the sponsor emphasized that the observed candida infections were responsive to treatment and limited to non-serious, localized mucosal or cutaneous candidiasis, with no reports of chronic or systemic disease in any treatment group.

Reviewer's comments: The sponsor's exposure-response analysis should have been conducted with pooled data of 150 mg and 300 mg so that the relationship between Candida infection and the serum secukinumab concentration could be better evaluated. By combining concentration quartiles in each dose group, an apparent increasing trend of Candida infection is observed. In all populations, the infection rate in patients whose concentrations are less than approximately 22 mcg/mL was 2% (8/400), while the event rate in patients with concentrations higher than 22 mcg/mL was approximately 5% (20/410). However, Candida infection is not believed to be a serious adverse event that would offset the improvements in efficacy achieved with the high dose. Therefore the reviewer agrees with the applicants' conclusion regarding the exposure-safety relationship and potential clinical impact.

4.4 Reviewer's Analysis

4.4.1 Introduction

The applicant identified an effect of body weight and baseline PASI on secukinumab PK but those were not identified as significant covariates in PK/PD modeling. The reviewer performed an independent analysis to explore the potential effect of body weight and baseline disease states that may limit the efficacy in certain subgroup of patients. Furthermore, the bioavailability of the new formulation in auto-injector (AI) was not formally assessed with a bioequivalence study in comparison with other formulations (LYO or PFS). Thus the adequacy of extrapolation of PK-PASI of AI with given data is evaluated.

4.4.2 Objectives

Analysis objectives are:

1. To analyze exposure-response relationship for efficacy endpoints including IGA 0/1
2. To find risk factors associated with low efficacy and/or high safety for dose optimization

4.4.3 Methods

Logistic regression was utilized for exposure-response analysis between secukinumab concentration at Week 12 and IGA 0/1 response at Week 12.

4.4.4 Data sets

Data sets used in the analysis are summarized in Table 10.

The dataset for the exposure-response analysis were obtained from IGA response data and population PK data that included data from a total of 1566 patients from Study A2302 (N=632) and Study A2303 (N=2303). For the exposure-response for Week 12 response, following data were excluded:

- Ninety nine patients whose concentrations of secukinumab at Week 12 are missing were excluded.
- Placebo data were not included in the analysis, but the results regarding significance of exposure are unchanged whether placebo data were included or excluded from the analysis.
- Among patients in placebo arm during the induction, non-responders were re-randomized (N=397) 1:1 to 150 mg or 300 mg and received their treatment on Weeks 12, 13, 14, 15 and then every 4 weeks starting at Week 16 until Week. Thus, patients in placebo arm prior to Week 12 are supposed to have concentration 0 at Week 12. However, there were 59 patients whose concentrations at Week 12 were above 0, as a result of protocol violation (blood samples taken prior to dosing at Week 12). Therefore, these 59 patients were excluded from the analysis.

The final analysis dataset includes data from a total of 1408 from Study A2302 (N=584) and Study A2303 (N=824).

To evaluate the effect of formulation on concentrations of secukinumab, raw PK data from Studies A2302 (N=633), A2303 (N=935), A2308 (N=147), A2309 (N=182) were utilized.

Table 10. Analysis Data Sets

Study Number	Name	Link to EDR
adres1.xpt adres2.xpt adres3.xpt adiga.xpt	IGA efficacy data for Studies 2302 and 2303	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ise\analysis\adam\datasets
adiga.xpt	IGA efficacy data for Study A2308	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ain457a2308\analysis\adam\datasets
adiga.xpt	IGA efficacy data for Study A2309	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ain457a2309\analysis\adam\datasets
adpc.xpt	PK data for Study A2302	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ain457a2302\analysis\adam\datasets
adpc.xpt	PK data for Study A2303	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ain457a2303\analysis\adam\datasets
adpc.xpt	PK data for Study A2308	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ain457a2308\analysis\adam\datasets
adpc.xpt	PK data for Study A2309	\\cdsesub1\bla\CTD_Submissions\STN125504\0000\m5\datasets\ain457a2309\analysis\adam\datasets
poolnm2.csv		\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\secukinumab_BLA125504_JEL\ER Analyses\Shared Analysis Data

4.4.5 Software

Population pharmacokinetics modeling was performed with NONMEM (version 7.2) and graphical, statistical analysis and simulation were performed with R (version 2.13.1).

4.4.6 Exposure-Response

First, univariate logistic regression analysis was performed for both linear concentration and logarithmic concentration of secukinumab at Week 12 for response variable IGA 0/1 at Week 12. Both linear and logarithmic concentrations were significantly associated with the response with IGA 0/1 (p-value < 4.33×10^{-16}). The observed dose-response relationship was consistent with exposure-response relationship (Figure 1); similar consistent relationships were also observed with respect to other efficacy endpoints such as PASI 75, PASI 90 and PAS100.

Multivariate analysis showed that the baseline IGA score (p-value=0.00172) and body weight (p-value: 0.003) are significant covariates on the exposure-response relationship. After adjustment for both IGA score and body weight, concentration of secukinumab remained a strong predictor of response (p-value < 2×10^{-16}).

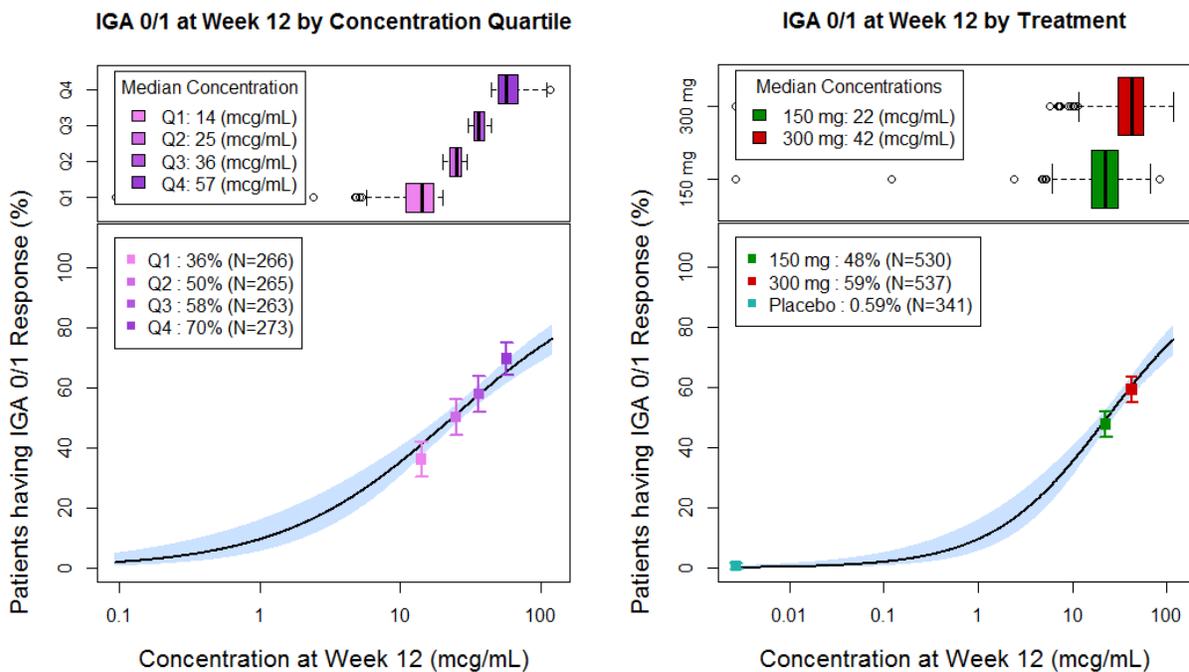


Figure 12. Univariate logistic regression for IGA 0/1 response versus secukinumab trough concentration at Week 12 overlaid by observed values by quartile (left panel) and dose (right panel)

4.4.7 Risk factors in quartiles of secukinumab concentrations

Distribution of patients in each quartile by baseline characteristics including body weight, baseline disease condition, age, sex, race and study, was evaluated. As shown in Figure 13 and Table 11, there are no risk factors other than body weight and baseline disease condition that affect the exposure-response relationship. The effect of baseline disease condition was more significant than that of body weight when body effect was changed into a categorical variable in multivariate logistic regression analyses.

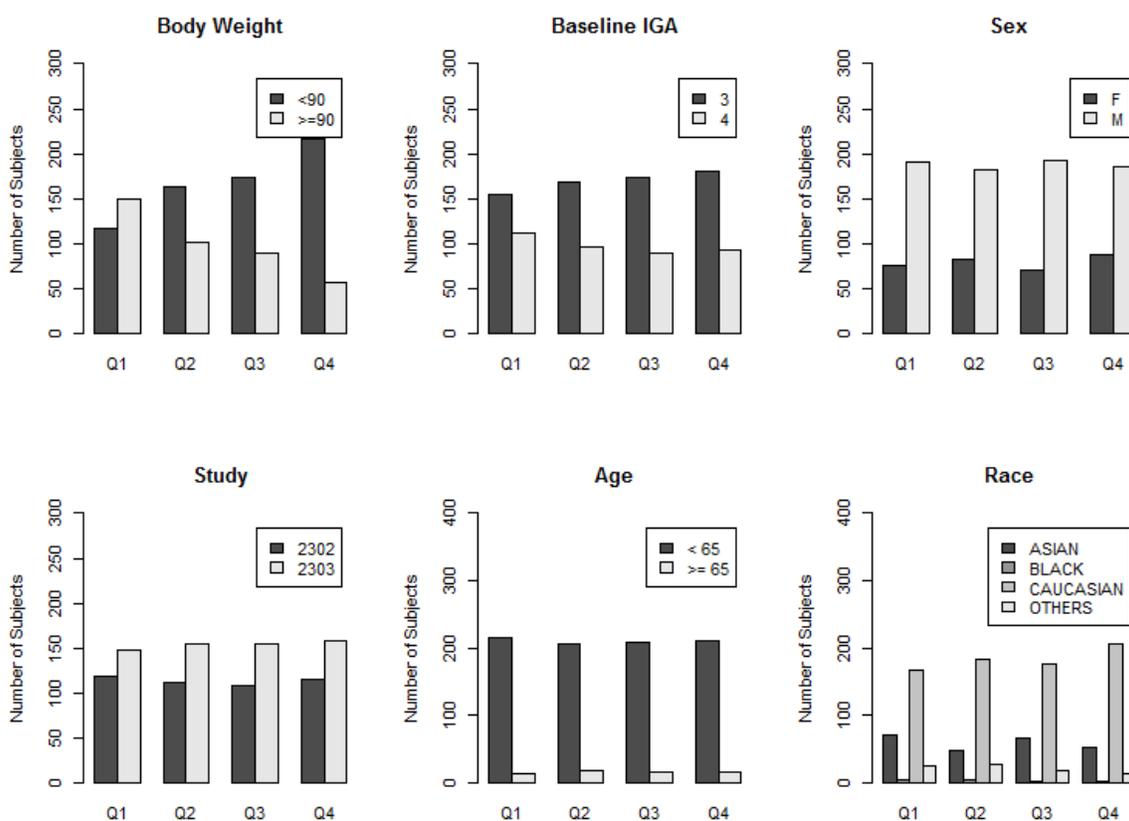


Figure 13. Risk factors in quartile of concentrations of secukinumab

Table 11. Risk factors in each quartile of concentration of secukinumab

	Body Weight < 90 kg	Baseline IGA 3	Female	Study A2302	Age ≥ 65	Race (Caucasian)
Q1 (N=266)	116 (43.6%)	154 (57.9%)	76 (28.6%)	118 (44.4%)	16 (6.0%)	166 (62.4%)
Q2 (N=265)	163 (61.5%)	169 (63.8%)	83 (31.3%)	111 (41.9%)	21 (7.9%)	183 (69.1%)
Q3 (N=263)	173 (65.8%)	174 (66.2%)	71 (27.0%)	108 (41.1%)	22 (8.4%)	177 (67.3%)
Q4 (N=273)	217 (79.5%)	181 (66.3%)	87 (31.9%)	115 (42.1%)	17 (6.2%)	205 (75.1%)

4.4.8 Effect of baseline disease condition and body weight on exposure-response for IGA 0/1

The effect of body weight became insignificant (p-value=0.243) when body weight was changed into a categorical variable with a cutoff of 90 kg (≥ 90 kg or < 90 kg). However, it became significant (p-value= 0.0186) with a body weight cutoff of 100 kg (≥ 100 kg or < 100 kg). In a multivariate logistic regression with baseline IGA score (3 or 4), the effect of baseline IGA score was also significant (p-value=0.00172). There were no other baseline covariates identified as significant during the reviewer's analysis. Multivariate logistic regression analysis adjusted with these significant covariate also showed that secukinumab concentration at Week 12 remained a significant predictor of IGA 0/1 response at Week 12 (p-value $< 2 \times 10^{-16}$).

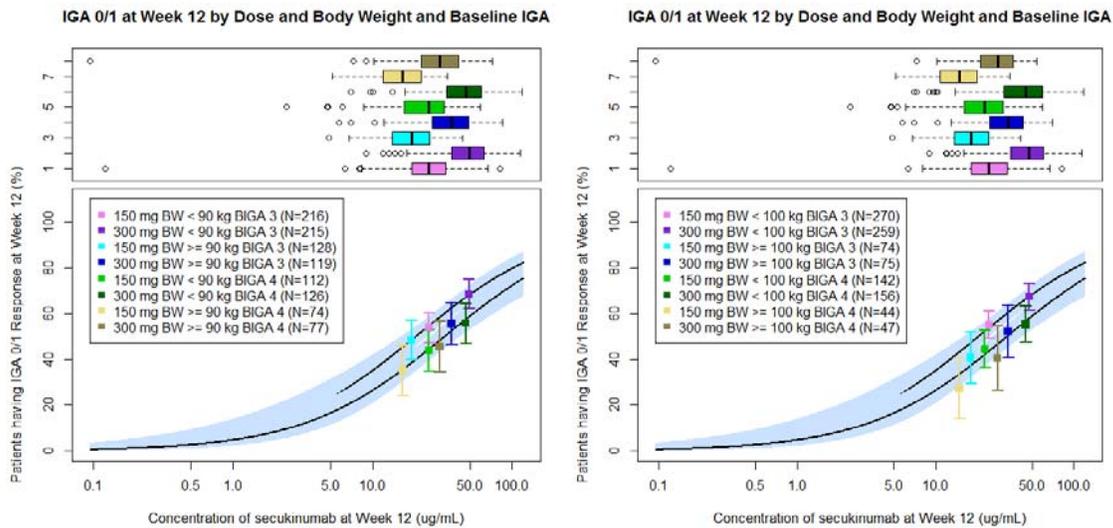


Figure 14. Exposure-response by Body weight and Baseline IGA: Effect of body weight with cutoff of 90 kg (top left); effect of body weight and Baseline IGA score with cutoff of 90 kg (top right); effect of body weight with cutoff of 100 kg (bottom left); effect of body weight and Baseline IGA score with cutoff of 100 kg (bottom right)

The effect of body weight on response was also observed from time course plots of the the percentage change from baseline PASI versus time. Shown below are the time course plots for 150 mg and 300 mg based on body weight cutoffs of 90 kg and 100 kg (Figure 15). In both plots, it was observed that patients weighing greater than 90 kg who received 300 mg have a similar but numerically lower response than that observed in patients weighting less than 90 kg who received 150 mg. The observed trends did not appear to differ whether a body weight cutoff of 90 kg or 100 kg was used in the analysis.

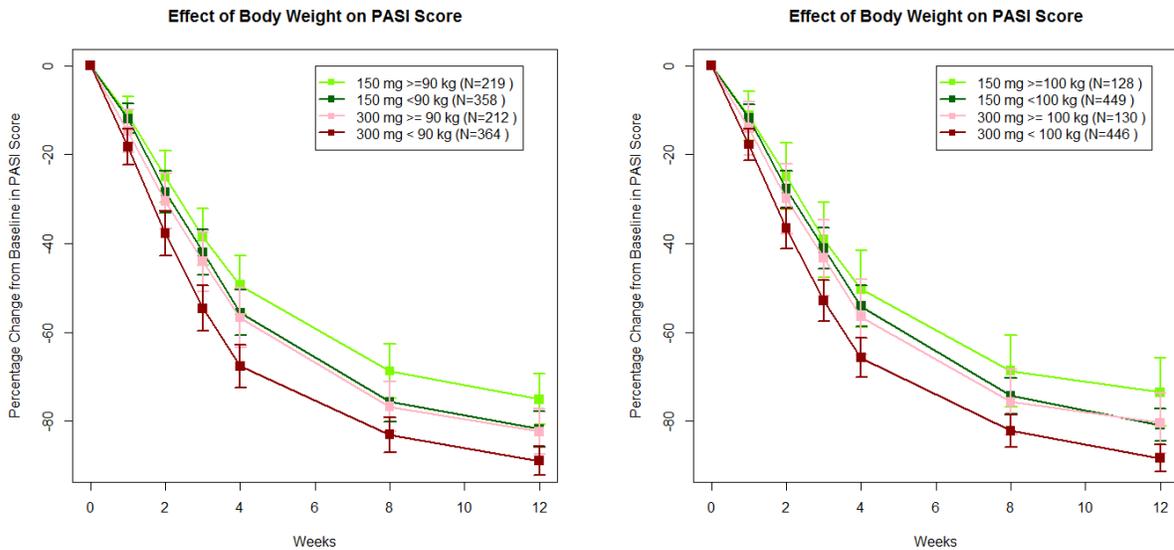


Figure 15. Change from Baseline PASI over time by Body Weight (left: cutoff of 90 kg; right: cutoff of 100 kg)

4.4.9 Exposure-response for auto-injector (AI) formulation

4.4.9.1 Observed concentration and response of auto-injector (AI)

The sponsor proposed to market 150 mg lyophilized powder in vial (LYO), 150 mg/mL solution for injection in pre-filled syringe (PFS), and 150 mg/mL solution for injection in a pre-filled auto-injector/pen (AI). AI was utilized in Study A2309 while LYO in Studies A2302 and A2303 and PFS was utilized in Study A2308. The observed concentrations of secukinumab following AI were higher than those following LYO and PFS (see Section 2.9.2). The concentration and IGA 0/1 response profiles are overlaid on the exposure-response for secukinumab concentration at Week 12 and IGA 0/1 response at Week 12 (Figure 16), and higher concentration and efficacy for AI formulation are envisioned as anticipated. However, the sample size from the Study A2309 was relatively small and the confidence intervals are overlapping with those from other studies. Furthermore, the higher concentrations produced by AI formulation are indeed in range of observed concentrations in Studies A2302 and A2303.

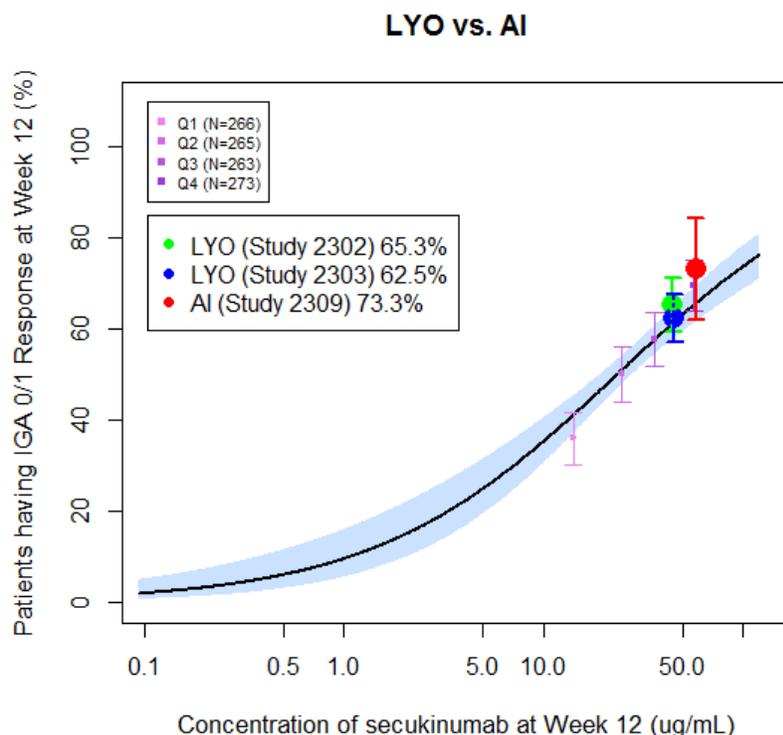


Figure 16. Exposure-response following secukinumab 150 mg/mL solution in auto-injector (AI) compared to lyophilized power (LYO)

4.4.9.2 Cumulative concentrations

To evaluate potential effect of distribution of body weight on secukinumab exposure and response for AI formulation, profiles of cumulative distribution of body weight and trough concentration of secukinumab at Week 12 were generated by studies. There was no significant difference in body weight of patients across the studies, however, the observed concentrations at Week 12 in Study A2309 AI formulation, were distinguished from those in other studies (Figure 17). Upon closer evaluation, it was observed that that the 95th percentile exposure from Studies A2302, A2303, and A2308 corresponds to the 88th percentile from Study A2309. This observation suggests that 7-12% of patients treated with the AI presentation may have exposures exceeding the highest exposures from the LYO and PFS presentations. In addition, there is convergence of the cumulative distribution plots at the upper range of exposures. As such, the higher concentrations in Study A2309 are predominantly within the range of the observed concentrations of the other Phase III studies.

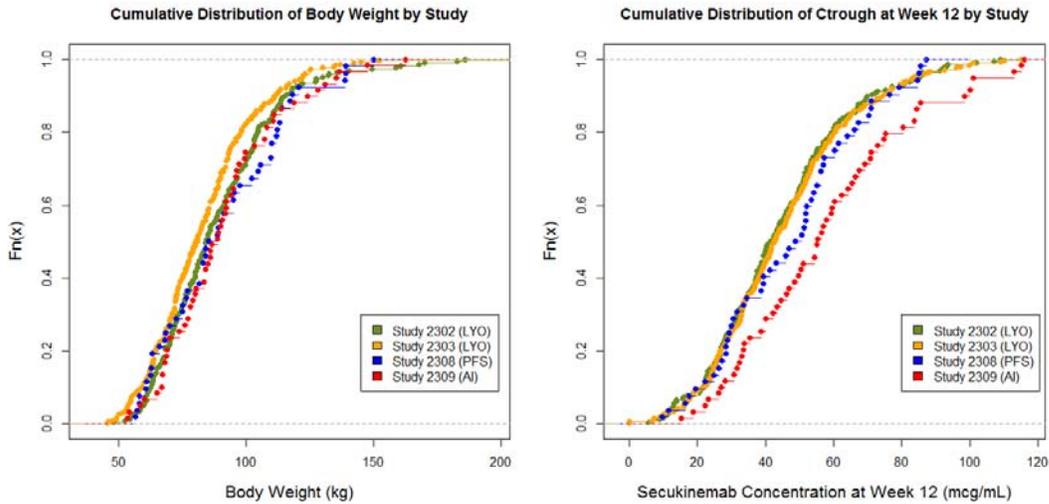


Figure 17. Cumulative distribution of body weight and trough concentration of secukinumab at Week 12 in Studies A2302, A2303, A2308 and A2309.

4.4.10 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Pasi227_mod.txt Pasi325_mod.txt 01_derive_dataset_pk.R 02_derive_dataset_pasi.R	Population PK analysis	Reviews\Ongoing PM Reviews\secukinumab_BLA125504_JEL\PK Analyses
ER Analysis Data Creation.R Efficacy with pooled data IGA.R Efficacy with pooled data PASI.R Comparison of Presentations.R	PKPD analysis Exposure-Response	Reviews\Ongoing PM Reviews\secukinumab_BLA125504_JEL\ER Analyses
Simulation Data Creation 300 and 450 by Body Weight.R Simulation Data Creation 300 for all.R	Simulation data	Reviews\Ongoing PM Reviews\secukinumab_BLA125504_JEL\PK Analyses

1. Filing and review form

CLINICAL PHARMACOLOGY Filing and Review Form for BLA 125,504 (NME)			
<i>General Information about the Submission</i>			
NDA Number	125,504	Brand Name	COSENTYX
OCP Division	DCP-3	Generic Name	Secukinumab (AIN457, NVP-AIN457)
Medical Division	ODEIII/DDDP	Drug Class	Recombinant human IgG1κ monoclonal antibody against interleukin (IL)-17A
OCP Reviewer	Jie Wang, Ph.D.	Indication(s)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Pharmacometrics Reviewer	Jiang Liu, Ph.D.	Dosage Form	<ul style="list-style-type: none"> ▪ 150 mg/mL in a single-use prefilled SensoReady[®] pen (autoinjector) for injection; ▪ 150 mg/mL in a single-use prefilled syringe for injection; ▪ 150 mg powder for solution in a single-use vial for injection
Pharmacometrics Team Leader	Yaning Wang, Ph.D.	Dosing Regimen	<p>The proposed dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4.</p> <p>Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.</p>
OCP Team Leader	Yow-Ming Wang, Ph.D		
Date of Submission	10/24/2013	Route of Administration	Subcutaneous
Estimated Due Date of OCP Review	05/24/2014	Sponsor	Novartis
Estimated Medical Division Due Date	05/30/2014	Priority Classification	Standard
PDUFA Due Date	10/24/2014		

Clinical Pharmacology and Biopharmaceutics Information				
	“×” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	×			
Tabular Listing of All Human Studies	×			
HPK Summary	×			
Labeling	×			
Reference Bioanalytical and Analytical Methods	×			
I. Clinical Pharmacology				
Mass balance:				N/A (not applicable)
Isozyme characterization:				N/A
Blood/plasma ratio:				N/A
Plasma protein binding:				N/A
Pharmacokinetics (Phase I) -				
Healthy Volunteers-				
single dose:	×	7		
multiple dose:				
Patients-				
single dose:	×	2		
multiple dose:	×			
Dose proportionality -				
single dose:	×			
multiple dose:	×			
Drug-drug interaction studies-				<i>See section 3.3.</i> (Potential PMR/PMC)
<i>In-vivo</i> effects on primary drug:				
<i>In-vivo</i> effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	×	1		1 PK study in Japanese healthy subjects; PopPK analysis
gender:				PopPK analysis

pediatrics:				<i>See section 3.7</i>
geriatrics:				PopPK analysis
renal impairment:				N/A
hepatic impairment:				N/A
PD -				<i>See Appendix 1</i>
Phase 2:	×			
Phase 3:	×			
PK/PD -				<i>See Appendix 1</i>
Phase 1 and/or 2, proof of concept:	×	5		
Phase 3 clinical trial:	×	5		
Population Analyses -				
Data rich:				
Data sparse:	×			
II. Biopharmaceutics				
Absolute bioavailability	×	2		In healthy subjects and in psoriasis patients
Relative bioavailability -				N/A
solution as reference:				
alternate formulation as reference:				
PK comparability studies -		4		1 BE for secukinumab PFS vs Lyophilized; 3 BE reports regarding Enbrel (US vs EU).
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				N/A
Bio-waiver request based on BCS				N/A
BCS class				N/A
Dissolution study to evaluate alcohol induced dose-dumping				N/A
III. Other CPB Studies				
Genotype/phenotype studies				N/A
Chronopharmacokinetics				N/A
Pediatric development plan	×			<i>See Section 3.7</i>
Literature References	×			
Total Number of studies	22 Clinical Pharmacology Studies + 5 efficacy/safety Phase 3 trials			

On *initial* review of the NDA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	×			
2	Has the applicant provided metabolism and DDI information?			×	<i>See section 3.3.</i>
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	×			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	×			
5	Has a rationale for dose selection been submitted?	×			
6	Is the clinical pharmacology and biopharmaceutics section of the BLA organized, indexed and paginated in a manner to allow substantive review to begin?	×			
7	Is the clinical pharmacology and biopharmaceutics section of the BLA legible so that a substantive review can begin?	×			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	×			
Criteria for Assessing Quality of a BLA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	×			
10	If applicable, are the pharmacogenomic datasets submitted in the appropriate format?			×	<i>IL-17A PD; see section 3.4</i>
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	×			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	×			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	×			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	×			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			×	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			×	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	×			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	×			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			×	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? [YES]

Clinical Pharmacology Filing Memorandum

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2. Comments to the sponsor

There are no comments to be conveyed to the sponsor at this time.

3. Main clinical pharmacology findings on initial review of the submission

Secukinumab (or AIN457) is a monoclonal anti-human interleukin (IL)-17A IgG1 κ antibody with a molecular weight of 147,944 Daltons. IL-17A is a pro-inflammatory cytokine. In this original BLA application, secukinumab is proposed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Proposed dosing regimens

- The proposed dose is 300 mg by subcutaneous (SC) injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 SC injections of 150 mg.

Proposed dosage forms

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

3.1. Overview of clinical trials and clinical pharmacology program

In addition to 5 Phase 3 clinical trials, the results from a total of 22 clinical pharmacology studies were submitted to support the BLA application (*see Appendix 1*).

3.2. Biopharmaceutics and analytical methods

The to-be-marketed formulation for secukinumab will be presented as LYO, PFS and AI with a strength of 150 mg/mL. The to-be-marketed formulations/presentations were used in all the Phase 3 psoriasis trials, specifically, LYO in Studies CAIN457A2302, CAIN457A2303 and CAINA2304, PFS in Study CAIN457A2308 and AI in Study CAIN4572309. Bioequivalence/comparability of PFS versus LYO was evaluated in Study CAIN457A2106 with a parallel-group design in healthy subjects. Steady state trough

secukinumab concentrations across the Phase 3 studies can be used to further assess the PK comparability among the three different product formulations/presentations.

Reviewer's assessment: Overall, the completed Clinical Pharmacology studies appear sufficient to support the product registration with the final to-be-marketed formulations/presentations.

Analytical methods have been developed for the secukinumab pharmacokinetics and pharmacodynamics studies. The performance and method validations will be reviewed. Brief descriptions are provided below:

Analytical methods for PK measurements

In secukinumab PK studies, total secukinumab, i.e., free secukinumab plus secukinumab bound to IL-17A, was analyzed in human serum using an ELISA method. The sponsor stated that serum secukinumab bound to IL-17A represents only a very small fraction (0.001%) of the total serum secukinumab. The ELISA method was used in all secukinumab clinical PK studies (*Appendix I*).

The ELISA method was further developed to quantify total secukinumab concentration in dermal interstitial fluid and blister fluid.

Analytical method for PD (IL-17A) measurements.

Serum total IL-17A, i.e., free IL-17A and IL-17A bound to secukinumab, was analyzed using a Meso Scale Discovery (MSD) platform for capture and electrochemiluminescence (ECL) for detection.

3.3. Pharmacokinetics

The following PK data were submitted to support the Clinical Pharmacology review of the BLA application:

- General PK characteristics (e.g., CL) in healthy volunteers and psoriasis patients,
- Absolute bioavailability following SC administration in psoriasis patients and healthy subjects
- Dose proportionality following intravenous (IV) and SC administration
- Steady state concentrations in psoriasis patients following SC administrations
- General PK findings from a Population PK analysis (submitted in *module 5.3.3.5*)
- Dermal secukinumab concentrations in non-lesional and lesional skin in psoriasis patients

Drug-dug interactions

The sponsor did not conduct any *in vitro* or *in vivo* studies to evaluate the DDI potential between secukinumab and low molecular weight drugs.

Psoriasis is a disease condition that involves altered expression of a broad-spectrum of pro-inflammatory and anti-inflammatory cytokines. Cytokines or cytokine modulators have been shown to modify the formation and activity of CYP enzymes and consequently affect the metabolism of small molecule drugs that are substrates for P450 enzymes. Because secukinumab is an anticytokine product for the treatment of psoriasis, we may recommend the sponsor to evaluate its potential disease-DDI in a PMR/PMC study. This will be a review issue.

3.4. Pharmacodynamics

Based on the “*summary of clinical pharmacology*”, the results from the following PD studies were submitted to support the BLA application.

- Serum levels of total IL-17A (free plus secukinumab bound forms) were assessed in Study CAIN457A2309 and Study CAIN457A1101. Free IL-17A was not measured due to the limitation of the assay interference.
- Serum levels of beta-defensin-2 (hBD-2) was assessed in Study CAIN457A2225
- Gene expression (mRNA of IL-17A pathway-related molecules) in psoriasis lesional skin were assessed in Study CAIN457A2102 and Study CAIN457A2212
- Protein levels of IL-17A, IL-17F and hBD-2 in psoriasis lesional and/or non-lesional skin were assessed in Study CAIN457A2225
- Histology and immunohistochemistry of psoriasis lesional skin were assessed in Studies CAIN457A2101 and CAIN457A2212.

The review of methodologies and the related analytical assays used in these PD studies will be determined based on the relevance to the product labeling.

3.5. Dose selection and exposure-response relationship

The sponsor submitted an exposure-response (E-R) relationship report in *module 5.3.5.3*. The dose selection rationale and the E-R analysis were summarized in the *Summary of Clinical Efficacy*.

3.6. Immunogenicity

The immunogenicity summary was provided in the *Summary of Clinical Safety (section 4.3, page 173)*. The incidence of anti-drug antibodies (ADA), neutralizing activity of ADA, and the impacts of ADA on safety, efficacy and PK were reported.

Two analytical methods, i.e., a Biacore assay and a MSD assay, were used to detect ADA responses in secukinumab clinical trials. The entire psoriasis Phase 3 program utilized the MSD assay which had a sensitivity of 4 ng/mL and drug tolerance level of 53.8 mcg/mL (at 250 ng/mL of a rabbit polyclonal positive control of anti-secukinumab antibody).

Following SC secukinumab administration of 150 or 300 mg q4w, secukinumab average concentrations at steady state were 22.2 mcg/mL and 44.5 mcg/mL, respectively, and peak concentrations were 27.6 mcg/mL and 55.2 mcg/mL, respectively (*Summary of Clinical Pharmacology, Page 9*). Therefore, the initial assessment of the immunogenicity and PK results indicated that drug interference would not be a major review issue as the steady state drug concentrations were generally below the immunogenicity assay drug tolerance level. The drug tolerance level and other assay performance parameters should be further reviewed and confirmed by OBP reviewers during the BLA review.

3.7. Proposal for a pediatric program

To meet PREA requirements, in a proposal for a pediatric program (*Module 1.9*) the applicant submitted a waiver request for psoriasis studies in pediatric patients who are less than 6 years of age (including neonates) and a deferral request for psoriasis studies in pediatric subjects of 6 to less than 18 years of age.

Appendix 1: clinical trials and clinical pharmacology studies that support the BLA application.

ADA, anti-drug antibodies; AI, auto-injector; DS, drug substances; ELISA, enzyme-linked immunosorbent assay; HS, healthy subjects; MSD, Meso Scale Discovery; n/a, not available or not applicable; PFS, pre-filled syringe; ^{#1}, the immunogenicity testing is not for ADA but for vaccination evaluation; hemagglutination inhibition (HI) for influenza and Serum Bactericidal Assay (SBA) for Neisseria meningitidis Serogroup C. ^{#2}, similar ELISA methods (both validated) were used for both serum and tissue samples;

Clinical studies in healthy subjects (HS)						
Clinical Trials	Design and objectives	Population	Dosing regimen	Formulation/ presentation	PK assay	ADA assay
CAIN457A2101 (Phase 1/2a)	<u>Design:</u> (1) double blind, randomized, placebo controlled, single ascending dose; (2) double-blind, placebo-controlled, multiple ascending dose; <u>Purpose:</u> safety, tolerability, PK, PD and efficacy; <i>FIH</i>	HS and RA	(1) ▪ 0.3 mg/kg i.v. (n=6) ▪ 1 mg/kg i.v. (n=6) ▪ 3 mg/kg i.v. (n=9) ▪ 10 mg/kg i.v. (n=9) ▪ Placebo i.v. (n=10) (2) ▪ 2 x 1mg/kg i.v. (n=6) ▪ 2 x 3mg/kg i.v. (n=6) ▪ 2 x 10mg/kg i.v. (n=26) 2 x placebo i.v. (n=26)	Lyophilized, 50 mg	ELISA	n/a
CAIN457A1101 (Phase 1)	<u>Design:</u> double-blind, randomized, placebo controlled; <u>Purpose:</u> single ascending dose to assess safety, tolerability, PK and PD <i>BA in HS</i> <i>PD of IL-17A</i>	HS, Japanese	Single dose by IV or SC ▪ 1 mg/kg i.v. (n=6) ▪ 3 mg/kg i.v. (n=6) ▪ 10 mg/kg i.v. (n=6) ▪ 150 mg s.c. (n=6) ▪ 300 mg s.c. (n=6) ▪ placebo s.c. (n=6) ▪ placebo i.v. (n=6)	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2106 (Phase 1)	<u>Design:</u> open-label, randomized; <u>Purpose:</u> to determine the BE of liquid formulation (in PFS) and lyophilized form of secukinumab <i>BE: PFS vs Lyophilized</i>	HS	Single SC dose ▪ 300 mg (2 x 150 mg) s.c. PFS (n=75) ▪ 300 mg (2 x 150 mg) s.c lyophilisate (n=75)	PFS, 150 mg; Lyophilized, 150 mg	ELISA	MSD
CAIN457A2228 (Phase 1)	<u>Design:</u> partially double blind, randomized, placebo controlled <u>Purpose:</u> safety, tolerability and PK of 30 minute secukinumab i.v. infusion	HS	Single IV dose ▪ 10mg/kg i.v. (n=9) ▪ placebo i.v. (n=3)	Lyophilized, 150 mg	ELISA	n/a
CAIN457A2224 (Phase 2)	<u>Design:</u> open-label, randomized, parallel group; <u>Purpose:</u> to determine the efficacy of influenza and meningococcal vaccination, safety and tolerability.	HS	Single SC dose ▪ 150 mg s.c. (n=25) ▪ control (n=25)	Lyophilized, 150 mg	N/A	HI and SBA ^{#1}
CAIN457A2104 (Phase 2)	<u>Design:</u> double-blind, randomized, placebo controlled 3-arm; <u>Purpose:</u> assess effects of secukinumab on ozone-induced airway neutrophilia as well as safety and tolerability, PK and PD	HS	Single IV dose ▪ 10 mg/kg i.v. (n=12) ▪ placebo i.v. (n=6) ▪ oral corticosteroid 50mg (n=6)	Lyophilized, 50 mg	ELISA	Biacore

Clinical studies in subjects with psoriasis

Clinical Trials	Design and objectives	Population	Dosing regimen	Formulation/ presentation	PK assay	ADA assay
CAIN457A2225 (Phase 1)	<i>Design:</i> open label, exploratory <i>Purpose:</i> investigate secukinumab concentrations in skin and PD markers <i>Tissue PK</i>	Subjects with psoriasis and HS	<ul style="list-style-type: none"> ▪ 300 mg sc (n=8 HS) ▪ 300 mg s.c. (n=8, Ps) 	Lyophilized, 150 mg	ELISA ^{#2}	MSD
CAIN457A2103 (Phase 1)	<i>Design:</i> open-label, randomized, cross-over; <i>Purpose:</i> To assess absolute bioavailability of sc administration <i>BA in psoriasis patients</i>	Subjects with psoriasis	Multiple dose by IV or SC <ul style="list-style-type: none"> ▪ 1 mg/kg iv → 150 mg sc ▪ 150 mg sc → 1 mg/kg iv 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2102 (Phase 2a, POC)	<i>Design:</i> double-blind, randomized, two-arm, parallel group, placebo controlled; <i>Purpose:</i> evaluate the safety, tolerance, PK and efficacy (See other studies at the bottom of this Table)	Subjects with psoriasis	Single dose by IV <ul style="list-style-type: none"> ▪ 3 mg/kg i.v. (n=18) ▪ placebo i.v. (n=18) 	Lyophilized, 60 mg (b) (4)	ELISA	n/a
CAIN457A2204 (Phase 2a)	<i>Design:</i> double-blind, multi-center, 4 arm, parallel-group, placebo controlled; <i>Purpose:</i> evaluate the difference in the change from baseline in PASI at 4 weeks as well as safety tolerability, PK.	Subjects with psoriasis	Single dose by IV <ul style="list-style-type: none"> ▪ 0.3 mg/kg iv (n=20) ▪ 1.0 mg/kg iv (n=20) ▪ 3.0 mg/kg iv (n=20) ▪ Placebo iv (n=20) 	Lyophilized, 50 mg	ELISA	Biacore
CAIN457A2212 (Phase 2a)	<i>Design:</i> four-arm, double-blind, parallel group, placebo- controlled; <i>Purpose:</i> evaluate safety, tolerability, duration of response and efficacy, dose finding, PK	Subjects with psoriasis	<ul style="list-style-type: none"> ▪ 1 x 3 mg/kg i.v. (n=39) ▪ 1 x 10 mg/kg i.v. (n=38) ▪ 3 x 10.0 mg/kg i.v. (n=40) ▪ 3 x placebo i.v. (n=13) 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2211 (Phase 2)	<i>Design:</i> four-arm, double-blind, parallel group, placebo controlled; <i>Purpose:</i> evaluate safety and efficacy with different induction regimens, dose regimen finding, PK	Subjects with psoriasis	Induction period (12 w): <ul style="list-style-type: none"> ▪ 150 mg s.c.; at wk0 (n=66) ▪ 150 mg s.c.; wks 0, 4, 8; (n=138) ▪ 150 mg s.c. at weeks 0, 1, 2, 4; early (n=133) ▪ placebo at weeks 0, 1, 2, 4, 8 (n=67) 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2220 (Phase 2)	<i>Design:</i> five-arm, double-blind, parallel group, placebo controlled, dose ranging; <i>Purpose:</i> evaluate safety and efficacy with three dose levels administered monthly and with a single dose, dose finding, PK	Subjects with psoriasis	<ul style="list-style-type: none"> ▪ 1 x 25 mg s.c. (n=29) ▪ 3 x 25 mg s.c. (n=26) ▪ 3 x 75 mg s.c. (n=21) ▪ 3 x 150 mg s.c. (n=27) ▪ 3 x placebo s.c. (n=22) 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2302 (Phase 3)	52 Week Placebo Controlled Safety and Efficacy Study: randomized, double-blind, placebo controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.	Subjects with psoriasis	secukinumab 300 mg and 150 mg: s.c. injection once weekly for 4 weeks (at randomization, Weeks 1, 2, and 3), followed by dosing every 4 weeks, starting at Week 4.	Lyophilized, 150 mg	ELISA	MSD

CAIN457A2303 (Phase 3)	52 Week Placebo and Comparator Controlled Safety and Efficacy Study: randomized, double-blind, placebo controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response at Week 12 compared to placebo (co-primary endpoints) and compared to etanercept (key secondary endpoints).	Subjects with psoriasis	Secukinumab 300 mg and 150 mg: same as CAIN457A2302 Etanercept active comparator group: s.c. etanercept 50 mg twice per week until Week 12, followed by s.c. 50 mg every week from Week 12 through Week 51.	Lyophilized, 150 mg EBREL (EU)	ELISA	MSD
CAIN457A2304 (Phase 3)	52 Week Individualized Maintenance Regimen Study: randomized, double blind, multicenter study to assess the efficacy on either a fixed dose regimen or on a retreatment at start of relapse (also termed 'Retreatment as needed') regimen.	Subjects with psoriasis	Secukinumab 300 mg and 150 mg: same as CAIN457A2302 for induction; maintenance period re-randomized to fixed interval regiment or retreatment at start of relapse	Lyophilized, 150 mg	ELISA	MSD
CAIN457A2308 (Phase 3)	Prefilled Syringe – 12 Week Placebo Controlled Safety and Efficacy Study: randomized, double-blind, placebo-controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo and to assess safety, tolerability, and usability of the self administration via PFS of secukinumab.	Subjects with psoriasis	300 mg: n=59 150 mg: n=59 Placebo: n=59	150 mg in 1-mL PFS	ELISA	MSD
CAIN457A2309 (Phase 3)	Autoinjector/SensoReady Pen – 12 Week Placebo Controlled Safety and Efficacy Study: randomized, double-blind, placebo-controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo and to assess safety, tolerability, and usability of the self administration via SensoReady pen of secukinumab. <i>PD of IL-17A</i>	Subjects with psoriasis	300 mg: n=60 150 mg: n=61 Placebo: n=61	150 mg in 1-mL AI	ELISA	MSD
Other studies						
9 Phase 1/2 trials of secukinumab in other disease population	CAIN457A2202 and CAIN457A2202E1 in subjects with Crohn's disease; CAIN457A2206 and CAIN457A2206E1 in subjects with psoriatic arthritis; CAIN457A2208 in subjects with non-infectious uveitis patients; CAIN457A2209 and CAIN457A2209E1 in subjects with ankylosing spondylitis; CAIN457B2201 in subjects with multiple sclerosis; PJMR0092202 in subjects with dry eye syndrome;					
US and EU Enbrel comparability	3 BE clinical study reports in HS: Study CAIN457GP15-101(GP2015 vs EU Enbrel); Study CAIN457GP15-102 (GP2015 vs US Enbrel); Study CAIN457GP15-105 (EU Enbrel vs US Enbrel)					
Across studies PK comparability	PK comparability at 3 mg/kg (IV) across Studies of CAIN457A2102, Study CAIN457A2204, and Study CAIN457A2212 was conducted to compare secukinumab ^{(b) (4)} and from the CHO cell line (used in majority of trials including all Phase 2/3 studies).					

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

/s/

JIE WANG
09/05/2014

JEE E LEE
09/05/2014

JEFFRY FLORIAN
09/05/2014

YOW-MING C WANG
09/05/2014

HAE YOUNG AHN
09/05/2014

1. Filing and review form

CLINICAL PHARMACOLOGY Filing and Review Form for BLA 125,504 (NME)			
<i>General Information about the Submission</i>			
NDA Number	125,504	Brand Name	COSENTYX
OCP Division	DCP-3	Generic Name	Secukinumab (AIN457, NVP-AIN457)
Medical Division	ODEIII/DDDP	Drug Class	Recombinant human IgG1κ monoclonal antibody against interleukin (IL)-17A
OCP Reviewer	Jie Wang, Ph.D.	Indication(s)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Pharmacometrics Reviewer	Jiang Liu, Ph.D.	Dosage Form	<ul style="list-style-type: none"> ▪ 150 mg/mL in a single-use prefilled SensoReady[®] pen (autoinjector) for injection; ▪ 150 mg/mL in a single-use prefilled syringe for injection; ▪ 150 mg powder for solution in a single-use vial for injection
Pharmacometrics Team Leader	Yaning Wang, Ph.D.	Dosing Regimen	<p>The proposed dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4.</p> <p>Each 300 mg dose is given as 2 subcutaneous injections of 150 mg.</p>
OCP Team Leader	Yow-Ming Wang, Ph.D		
Date of Submission	10/24/2013	Route of Administration	Subcutaneous
Estimated Due Date of OCP Review	05/24/2014	Sponsor	Novartis
Estimated Medical Division Due Date	05/30/2014	Priority Classification	Standard
PDUFA Due Date	10/24/2014		

Clinical Pharmacology and Biopharmaceutics Information				
	“×” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	×			
Tabular Listing of All Human Studies	×			
HPK Summary	×			
Labeling	×			
Reference Bioanalytical and Analytical Methods	×			
I. Clinical Pharmacology				
Mass balance:				N/A (not applicable)
Isozyme characterization:				N/A
Blood/plasma ratio:				N/A
Plasma protein binding:				N/A
Pharmacokinetics (Phase I) -				
Healthy Volunteers-				
single dose:	×	7		
multiple dose:				
Patients-				
single dose:	×	2		
multiple dose:	×			
Dose proportionality -				
single dose:	×			
multiple dose:	×			
Drug-drug interaction studies-				<i>See section 3.3.</i> (Potential PMR/PMC)
<i>In-vivo</i> effects on primary drug:				
<i>In-vivo</i> effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	×	1		1 PK study in Japanese healthy subjects; PopPK analysis
gender:				PopPK analysis

pediatrics:				<i>See section 3.7</i>
geriatrics:				PopPK analysis
renal impairment:				N/A
hepatic impairment:				N/A
PD -				<i>See Appendix 1</i>
Phase 2:	×			
Phase 3:	×			
PK/PD -				<i>See Appendix 1</i>
Phase 1 and/or 2, proof of concept:	×	5		
Phase 3 clinical trial:	×	5		
Population Analyses -				
Data rich:				
Data sparse:	×			
II. Biopharmaceutics				
Absolute bioavailability	×	2		In healthy subjects and in psoriasis patients
Relative bioavailability -				N/A
solution as reference:				
alternate formulation as reference:				
PK comparability studies -		4		1 BE for secukinumab PFS vs Lyophilized; 3 BE reports regarding Enbrel (US vs EU).
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				N/A
Bio-waiver request based on BCS				N/A
BCS class				N/A
Dissolution study to evaluate alcohol induced dose-dumping				N/A
III. Other CPB Studies				
Genotype/phenotype studies				N/A
Chronopharmacokinetics				N/A
Pediatric development plan	×			<i>See Section 3.7</i>
Literature References	×			
Total Number of studies	22 Clinical Pharmacology Studies + 5 efficacy/safety Phase 3 trials			

On *initial* review of the NDA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	×			
2	Has the applicant provided metabolism and DDI information?			×	<i>See section 3.3.</i>
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	×			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	×			
5	Has a rationale for dose selection been submitted?	×			
6	Is the clinical pharmacology and biopharmaceutics section of the BLA organized, indexed and paginated in a manner to allow substantive review to begin?	×			
7	Is the clinical pharmacology and biopharmaceutics section of the BLA legible so that a substantive review can begin?	×			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	×			
Criteria for Assessing Quality of a BLA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	×			
10	If applicable, are the pharmacogenomic datasets submitted in the appropriate format?			×	<i>IL-17A PD; see section 3.4</i>
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	×			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	×			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	×			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	×			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			×	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			×	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	×			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	×			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			×	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? [YES]

Clinical Pharmacology Filing Memorandum

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3. MAIN CLINICAL PHARMACOLOGY FINDINGS ON <u>INITIAL</u> REVIEW OF THE SUBMISSION	- 5 -
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2. Comments to the sponsor

There are no comments to be conveyed to the sponsor at this time.

3. Main clinical pharmacology findings on initial review of the submission

Secukinumab (or AIN457) is a monoclonal anti-human interleukin (IL)-17A IgG1 κ antibody with a molecular weight of 147,944 Daltons. IL-17A is a pro-inflammatory cytokine. In this original BLA application, secukinumab is proposed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Proposed dosing regimens

- The proposed dose is 300 mg by subcutaneous (SC) injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 SC injections of 150 mg.

Proposed dosage forms

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

3.1. Overview of clinical trials and clinical pharmacology program

In addition to 5 Phase 3 clinical trials, the results from a total of 22 clinical pharmacology studies were submitted to support the BLA application (*see Appendix 1*).

3.2. Biopharmaceutics and analytical methods

The to-be-marketed formulation for secukinumab will be presented as LYO, PFS and AI with a strength of 150 mg/mL. The to-be-marketed formulations/presentations were used in all the Phase 3 psoriasis trials, specifically, LYO in Studies CAIN457A2302, CAIN457A2303 and CAINA2304, PFS in Study CAIN457A2308 and AI in Study CAIN4572309. Bioequivalence/comparability of PFS versus LYO was evaluated in Study CAIN457A2106 with a parallel-group design in healthy subjects. Steady state trough

secukinumab concentrations across the Phase 3 studies can be used to further assess the PK comparability among the three different product formulations/presentations.

Reviewer's assessment: Overall, the completed Clinical Pharmacology studies appear sufficient to support the product registration with the final to-be-marketed formulations/presentations.

Analytical methods have been developed for the secukinumab pharmacokinetics and pharmacodynamics studies. The performance and method validations will be reviewed. Brief descriptions are provided below:

Analytical methods for PK measurements

In secukinumab PK studies, total secukinumab, i.e., free secukinumab plus secukinumab bound to IL-17A, was analyzed in human serum using an ELISA method. The sponsor stated that serum secukinumab bound to IL-17A represents only a very small fraction (0.001%) of the total serum secukinumab. The ELISA method was used in all secukinumab clinical PK studies (*Appendix I*).

The ELISA method was further developed to quantify total secukinumab concentration in dermal interstitial fluid and blister fluid.

Analytical method for PD (IL-17A) measurements.

Serum total IL-17A, i.e., free IL-17A and IL-17A bound to secukinumab, was analyzed using a Meso Scale Discovery (MSD) platform for capture and electrochemiluminescence (ECL) for detection.

3.3. Pharmacokinetics

The following PK data were submitted to support the Clinical Pharmacology review of the BLA application:

- General PK characteristics (e.g., CL) in healthy volunteers and psoriasis patients,
- Absolute bioavailability following SC administration in psoriasis patients and healthy subjects
- Dose proportionality following intravenous (IV) and SC administration
- Steady state concentrations in psoriasis patients following SC administrations
- General PK findings from a Population PK analysis (submitted in *module 5.3.3.5*)
- Dermal secukinumab concentrations in non-lesional and lesional skin in psoriasis patients

Drug-drug interactions

The sponsor did not conduct any *in vitro* or *in vivo* studies to evaluate the DDI potential between secukinumab and low molecular weight drugs.

Psoriasis is a disease condition that involves altered expression of a broad-spectrum of pro-inflammatory and anti-inflammatory cytokines. Cytokines or cytokine modulators have been shown to modify the formation and activity of CYP enzymes and consequently affect the metabolism of small molecule drugs that are substrates for P450 enzymes. Because secukinumab is an anticytokine product for the treatment of psoriasis, we may recommend the sponsor to evaluate its potential disease-DDI in a PMR/PMC study. This will be a review issue.

3.4. Pharmacodynamics

Based on the “*summary of clinical pharmacology*”, the results from the following PD studies were submitted to support the BLA application.

- Serum levels of total IL-17A (free plus secukinumab bound forms) were assessed in Study CAIN457A2309 and Study CAIN457A1101. Free IL-17A was not measured due to the limitation of the assay interference.
- Serum levels of beta-defensin-2 (hBD-2) was assessed in Study CAIN457A2225
- Gene expression (mRNA of IL-17A pathway-related molecules) in psoriasis lesional skin were assessed in Study CAIN457A2102 and Study CAIN457A2212
- Protein levels of IL-17A, IL-17F and hBD-2 in psoriasis lesional and/or non-lesional skin were assessed in Study CAIN457A2225
- Histology and immunohistochemistry of psoriasis lesional skin were assessed in Studies CAIN457A2101 and CAIN457A2212.

The review of methodologies and the related analytical assays used in these PD studies will be determined based on the relevance to the product labeling.

3.5. Dose selection and exposure-response relationship

The sponsor submitted an exposure-response (E-R) relationship report in *module 5.3.5.3*. The dose selection rationale and the E-R analysis were summarized in the *Summary of Clinical Efficacy*.

3.6. Immunogenicity

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ADA, anti-drug antibodies; AI, auto-injector; DS, drug substances; ELISA, enzyme-linked immunosorbent assay; HS, healthy subjects; MSD, Meso Scale Discovery; n/a, not available or not applicable; PFS, pre-filled syringe; ^{#1}, the immunogenicity testing is not for ADA but for vaccination evaluation; hemagglutination inhibition (HI) for influenza and Serum Bactericidal Assay (SBA) for Neisseria meningitidis Serogroup C. ^{#2}, similar ELISA methods (both validated) were used for both serum and tissue samples;

Clinical studies in healthy subjects (HS)						
Clinical Trials	Design and objectives	Population	Dosing regimen	Formulation/ presentation	PK assay	ADA assay
CAIN457A2101 (Phase 1/2a)	<u>Design:</u> (1) double blind, randomized, placebo controlled, single ascending dose; (2) double-blind, placebo-controlled, multiple ascending dose; <u>Purpose:</u> safety, tolerability, PK, PD and efficacy; <i>FIH</i>	HS and RA	(1) ▪ 0.3 mg/kg i.v. (n=6) ▪ 1 mg/kg i.v. (n=6) ▪ 3 mg/kg i.v. (n=9) ▪ 10 mg/kg i.v. (n=9) ▪ Placebo i.v. (n=10) (2) ▪ 2 x 1mg/kg i.v. (n=6) ▪ 2 x 3mg/kg i.v. (n=6) ▪ 2 x 10mg/kg i.v. (n=26) 2 x placebo i.v. (n=26)	Lyophilized, 50 mg	ELISA	n/a
CAIN457A1101 (Phase 1)	<u>Design:</u> double-blind, randomized, placebo controlled; <u>Purpose:</u> single ascending dose to assess safety, tolerability, PK and PD <i>BA in HS</i> <i>PD of IL-17A</i>	HS, Japanese	Single dose by IV or SC ▪ 1 mg/kg i.v. (n=6) ▪ 3 mg/kg i.v. (n=6) ▪ 10 mg/kg i.v. (n=6) ▪ 150 mg s.c. (n=6) ▪ 300 mg s.c. (n=6) ▪ placebo s.c. (n=6) ▪ placebo i.v. (n=6)	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2106 (Phase 1)	<u>Design:</u> open-label, randomized; <u>Purpose:</u> to determine the BE of liquid formulation (in PFS) and lyophilized form of secukinumab <i>BE: PFS vs Lyophilized</i>	HS	Single SC dose ▪ 300 mg (2 x 150 mg) s.c. PFS (n=75) ▪ 300 mg (2 x 150 mg) s.c lyophilisate (n=75)	PFS, 150 mg; Lyophilized, 150 mg	ELISA	MSD
CAIN457A2228 (Phase 1)	<u>Design:</u> partially double blind, randomized, placebo controlled <u>Purpose:</u> safety, tolerability and PK of 30 minute secukinumab i.v. infusion	HS	Single IV dose ▪ 10mg/kg i.v. (n=9) ▪ placebo i.v. (n=3)	Lyophilized, 150 mg	ELISA	n/a
CAIN457A2224 (Phase 2)	<u>Design:</u> open-label, randomized, parallel group; <u>Purpose:</u> to determine the efficacy of influenza and meningococcal vaccination, safety and tolerability.	HS	Single SC dose ▪ 150 mg s.c. (n=25) ▪ control (n=25)	Lyophilized, 150 mg	N/A	HI and SBA ^{#1}
CAIN457A2104 (Phase 2)	<u>Design:</u> double-blind, randomized, placebo controlled 3-arm; <u>Purpose:</u> assess effects of secukinumab on ozone-induced airway neutrophilia as well as safety and tolerability, PK and PD	HS	Single IV dose ▪ 10 mg/kg i.v. (n=12) ▪ placebo i.v. (n=6) ▪ oral corticosteroid 50mg (n=6)	Lyophilized, 50 mg	ELISA	Biacore

Clinical studies in subjects with psoriasis

Clinical Trials	Design and objectives	Population	Dosing regimen	Formulation/ presentation	PK assay	ADA assay
CAIN457A2225 (Phase 1)	<i>Design:</i> open label, exploratory <i>Purpose:</i> investigate secukinumab concentrations in skin and PD markers <i>Tissue PK</i>	Subjects with psoriasis and HS	<ul style="list-style-type: none"> ▪ 300 mg sc (n=8 HS) ▪ 300 mg s.c. (n=8, Ps) 	Lyophilized, 150 mg	ELISA ^{#2}	MSD
CAIN457A2103 (Phase 1)	<i>Design:</i> open-label, randomized, cross-over; <i>Purpose:</i> To assess absolute bioavailability of sc administration <i>BA in psoriasis patients</i>	Subjects with psoriasis	Multiple dose by IV or SC <ul style="list-style-type: none"> ▪ 1 mg/kg iv → 150 mg sc ▪ 150 mg sc → 1 mg/kg iv 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2102 (Phase 2a, POC)	<i>Design:</i> double-blind, randomized, two-arm, parallel group, placebo controlled; <i>Purpose:</i> evaluate the safety, tolerance, PK and efficacy (See other studies at the bottom of this Table)	Subjects with psoriasis	Single dose by IV <ul style="list-style-type: none"> ▪ 3 mg/kg i.v. (n=18) ▪ placebo i.v. (n=18) 	Lyophilized, 60 mg (b) (4)	ELISA	n/a
CAIN457A2204 (Phase 2a)	<i>Design:</i> double-blind, multi-center, 4 arm, parallel-group, placebo controlled; <i>Purpose:</i> evaluate the difference in the change from baseline in PASI at 4 weeks as well as safety tolerability, PK.	Subjects with psoriasis	Single dose by IV <ul style="list-style-type: none"> ▪ 0.3 mg/kg iv (n=20) ▪ 1.0 mg/kg iv (n=20) ▪ 3.0 mg/kg iv (n=20) ▪ Placebo iv (n=20) 	Lyophilized, 50 mg	ELISA	Biacore
CAIN457A2212 (Phase 2a)	<i>Design:</i> four-arm, double-blind, parallel group, placebo- controlled; <i>Purpose:</i> evaluate safety, tolerability, duration of response and efficacy, dose finding, PK	Subjects with psoriasis	<ul style="list-style-type: none"> ▪ 1 x 3 mg/kg i.v. (n=39) ▪ 1 x 10 mg/kg i.v. (n=38) ▪ 3 x 10.0 mg/kg i.v. (n=40) ▪ 3 x placebo i.v. (n=13) 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2211 (Phase 2)	<i>Design:</i> four-arm, double-blind, parallel group, placebo controlled; <i>Purpose:</i> evaluate safety and efficacy with different induction regimens, dose regimen finding, PK	Subjects with psoriasis	Induction period (12 w): <ul style="list-style-type: none"> ▪ 150 mg s.c.; at wk0 (n=66) ▪ 150 mg s.c.; wks 0, 4, 8; (n=138) ▪ 150 mg s.c. at weeks 0, 1, 2, 4; early (n=133) ▪ placebo at weeks 0, 1, 2, 4, 8 (n=67) 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2220 (Phase 2)	<i>Design:</i> five-arm, double-blind, parallel group, placebo controlled, dose ranging; <i>Purpose:</i> evaluate safety and efficacy with three dose levels administered monthly and with a single dose, dose finding, PK	Subjects with psoriasis	<ul style="list-style-type: none"> ▪ 1 x 25 mg s.c. (n=29) ▪ 3 x 25 mg s.c. (n=26) ▪ 3 x 75 mg s.c. (n=21) ▪ 3 x 150 mg s.c. (n=27) ▪ 3 x placebo s.c. (n=22) 	Lyophilized, 150 mg	ELISA	Biacore
CAIN457A2302 (Phase 3)	52 Week Placebo Controlled Safety and Efficacy Study: randomized, double-blind, placebo controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo.	Subjects with psoriasis	secukinumab 300 mg and 150 mg: s.c. injection once weekly for 4 weeks (at randomization, Weeks 1, 2, and 3), followed by dosing every 4 weeks, starting at Week 4.	Lyophilized, 150 mg	ELISA	MSD

CAIN457A2303 (Phase 3)	52 Week Placebo and Comparator Controlled Safety and Efficacy Study: randomized, double-blind, placebo controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response at Week 12 compared to placebo (co-primary endpoints) and compared to etanercept (key secondary endpoints).	Subjects with psoriasis	Secukinumab 300 mg and 150 mg: same as CAIN457A2302 Etanercept active comparator group: s.c. etanercept 50 mg twice per week until Week 12, followed by s.c. 50 mg every week from Week 12 through Week 51.	Lyophilized, 150 mg EBREL (EU)	ELISA	MSD
CAIN457A2304 (Phase 3)	52 Week Individualized Maintenance Regimen Study: randomized, double blind, multicenter study to assess the efficacy on either a fixed dose regimen or on a retreatment at start of relapse (also termed 'Retreatment as needed') regimen.	Subjects with psoriasis	Secukinumab 300 mg and 150 mg: same as CAIN457A2302 for induction; maintenance period re-randomized to fixed interval regiment or retreatment at start of relapse	Lyophilized, 150 mg	ELISA	MSD
CAIN457A2308 (Phase 3)	Prefilled Syringe – 12 Week Placebo Controlled Safety and Efficacy Study: randomized, double-blind, placebo-controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo and to assess safety, tolerability, and usability of the self administration via PFS of secukinumab.	Subjects with psoriasis	300 mg: n=59 150 mg: n=59 Placebo: n=59	150 mg in 1-mL PFS	ELISA	MSD
CAIN457A2309 (Phase 3)	Autoinjector/SensoReady Pen – 12 Week Placebo Controlled Safety and Efficacy Study: randomized, double-blind, placebo-controlled, multicenter study to demonstrate the efficacy with respect to both PASI 75 and IGA 0 or 1 response (co-primary endpoints) at Week 12 compared to placebo and to assess safety, tolerability, and usability of the self administration via SensoReady pen of secukinumab. <i>PD of IL-17A</i>	Subjects with psoriasis	300 mg: n=60 150 mg: n=61 Placebo: n=61	150 mg in 1-mL AI	ELISA	MSD
Other studies						
9 Phase 1/2 trials of secukinumab in other disease population	CAIN457A2202 and CAIN457A2202E1 in subjects with Crohn's disease; CAIN457A2206 and CAIN457A2206E1 in subjects with psoriatic arthritis; CAIN457A2208 in subjects with non-infectious uveitis patients; CAIN457A2209 and CAIN457A2209E1 in subjects with ankylosing spondylitis; CAIN457B2201 in subjects with multiple sclerosis; PJMR0092202 in subjects with dry eye syndrome;					
US and EU Enbrel comparability	3 BE clinical study reports in HS: Study CAIN457GP15-101(GP2015 vs EU Enbrel); Study CAIN457GP15-102 (GP2015 vs US Enbrel); Study CAIN457GP15-105 (EU Enbrel vs US Enbrel)					
Across studies PK comparability	PK comparability at 3 mg/kg (IV) across Studies of CAIN457A2102, Study CAIN457A2204, and Study CAIN457A2212 was conducted to compare secukinumab ^{(b) (4)} and from the CHO cell line (used in majority of trials including all Phase 2/3 studies).					

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/s/

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