CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125504Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 8, 2014
From	David Kettl, MD
Subject	Cross-Discipline Team Leader Review
BLA # **Supplement#**	BLA 125504 Related IND: 100418 #0
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	October 24, 2013
PDUFA Goal Date	January 23, 2014
Proprietary Name / Established (USAN) names	COSENTYX (secukinumab) subcutaneous injections
Dosage forms / Strength	• 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
Proposed Indication(s)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Recommended:	***Approval***

1. Introduction

This original BLA submission by Novartis Pharmaceuticals Corporation proposes the use of a novel monoclonal antibody, secukinumab, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. This original BLA was reviewed under "the Program" for NME's as authorized in PDUFA V/FDASIA.

The applicant conducted two successful, adequate and well controlled Phase 3 clinical trials in which efficacy was demonstrated at week 12 compared to placebo.

Safety was substantiated on the analysis of the experience of 22 clinical trials to date that have been conducted with secukinumab in healthy subjects, subjects with psoriasis, and various other patient populations for indications under development.

There are no outstanding review issues as of the date of this review beyond conclusion of labeling negotiations with the applicant and final agreement of post marketing requirements and commitments.

A REMS program is neither proposed by the applicant nor recommended by the Agency review team for this application. Labeling is adequate to inform prescribers and patients of the known and expected adverse reactions and clinical risks.

The primary clinical review, by Dr. Amy Woitach, concluded that secukinumab is safe and effective for the treatment of moderate to severe plaque psoriasis. An approval action is recommended by the multidisciplinary review team pending completion of final labeling negotiations with the applicant. This CDTL review concurs with that recommendation to approve this application for secukinumab for the treatment of moderate to severe plaque psoriasis.

2. Background

Secukinumab is a human IgG1κ monoclonal antibody that selectively binds to the pro-inflammatory 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. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Based on the amino acid sequence, the relative molecular mass of secukinumab is 151,000 Da (including glycosylation).

Secukinumab is proposed to be available in three single-use presentations: (a) lyophilisate in vial (150 mg powder for solution for injection) for administration by a health care provider, (b) pre-filled syringe (150 mg/1mL), and (c) pre-filled syringe within a SensoReady® pen device (autoinjector) for self-administration. The planned trade name, Cosentyx, as well as the name of the autoinjector, has been deemed acceptable by the Agency review teams.

If approved, secukinumab would join a group of four other systemically administered antibody products approved for treatment of plaque psoriasis: adalimumab, etanercept, infliximab (all TNF blockers), and ustekinumab, an IL12/23 inhibitor. Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast.

While the applicant had several meetings with the Agency over the course of product development, there was no End of Phase 2 meeting or a Phase 3 Special Protocol Assessment (SPA) on any of the applicant's Phase 3 protocols.

A preBLA meeting was conducted with the applicant on July 24, 2013. Discussion included CMC requirements for the application, and discussion related to the utility of a comparator arm in one of the phase 3 trials which utilized EU approved Enbrel (etanercept) as opposed to US licensed Enbrel. While discussion noted recommendations regarding US vs. EU Enbrel

comparisons, advice was also provided that a superiority demonstration over Enbrel would require demonstration in more than one adequate and well controlled clinical trial to provide confirmation of results. This application contains data from only one trial which compared secukinumab to etanercept, (b) (4) .

The Agency filing communication for this application, dated December 17, 2013, identified several critical review issues that necessitated a substantial response from the applicant. These issues were related to control of the manufacturing process and included: identity testing, cell banks information and (b) (4) during production of the drug product. Their January 15, 2014 response was determined to be a major amendment to the application, and the PDUFA goal date was extended by three months to January 23, 2015. These review issues have been successfully resolved with the submission of the additional information by the applicant. There are no remaining review issues beyond completion of agreed upon labeling with the applicant and final agreements for the post marketing requirements and commitments.

Secukinumab is also under development for other indications under the following IND's:

(b) (4)

3. CMC/Device

The product quality review by Dr. Tura Camilli concludes that:

"The data submitted in this Biologics License Application support the conclusion that the manufacture of Cosentyx (secukinumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA.

The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs."

The key review issue following submission, as described by Dr. Sarah Kennett, the secondary product quality reviewer, was that "This BLA initially included little information regarding control of the manufacturing process. For example, non-critical attributes and key operating parameters were not included, it appeared that in-process limits could be changed without notification, development of the drug substance manufacturing process was not described and no data were provided, insufficient validation data were provided, validation protocols for (b) (4) were not included, and insufficient information (b) (4) was provided, which could affect the acceptability of some aspects of the control strategy. In addition, critical quality attributes (CQAs) were not specifically identified."

Following information requests by the Agency, sufficient information regarding the additional manufacturing process operating ranges and in-process limits was submitted and was adequate to determine that the "the manufacture of Cosentyx is well controlled and leads to a product that is pure and potent."

Agency DMA review determined that the updated specifications are sufficient to ensure adequate quality and safety of secukinumab for the initially marketed product. However, additional manufacturing experience gained post licensure will be requested to facilitate improved specifications.

Therefore, the PMCs listed below in section 13 of this review related to product quality are recommended for this action.

(b) (4)

The product quality microbiology assessments of microbial controls of the drug product manufacturing process and sterility assurance of drug product described in the original BLA and amendments, as well as manufacturing site inspections, were deemed acceptable in the review by Dr. Kalamati Suvarna.

Final reports of facility inspections are were completed on September 17, 2014, as noted in the CDER EES review by Ranjani Prabhakara. The cGMP inspections were found acceptable.

There are no outstanding review issues related to product quality.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical review by Dr. Jill Merrill did not identify any approvability issues from the pharmacology toxicology perspective. Dr. Merrill summarized the following

nonclinical issues in her review, and recommended changes in pertinent areas of product labeling.

The cynomolgus monkey was identified as the most appropriate and relevant nonclinical species. Single-dose and repeat-dose toxicity and embryofetal development studies were conducted with the cynomolgus monkey. A murine surrogate antibody against mouse IL-17A (BZN035) was developed and used for fertility and early embryonic development and peri- and postnatal development studies in mice.

Repeat dose toxicity studies in monkeys (0, 15, 50, 150 mg/kg/week) indicated secukinumab was well tolerated at the injection site with no treatment-related pathology changes during the 26-week treatment and 13-week recovery period. Due to clinical chemistry effects and immunotoxicity (decreases in total lymphocytes, B cells and T cells) observed at the high dose, the NOAEL appears to be 50 mg/kg/week. Clinical dosing at 1/10th the NOAEL (300 mg/60 kg = 5 mg/kg) did not significantly decrease total lymphocytes.

In the pivotal cynomolgus monkey study, AIN457 derived from CHO cells was administered intravenously (15, 50, 150 mg/kg/week; 4/sex/group) for 26 weeks followed by a 13-week recovery period (2/sex for control and high dose group only. Once weekly treatment with secukinumab appeared to cause decreases in CD4+ T lymphocytes and increases in CD16+ lymphocytes at the high dose and decreased NK cell activity at the mid- and high-dose levels.

Immunotoxicity was observed in one high-dose female that developed skin lesions (treated with antibiotics), splenic lymphocytic atrophy, decreased NK cell activity, and decreased T-cell dependent antigen response.

Based on these data, the NOAEL appears to be 50 mg/kg/week.

Weekly subcutaneous administration of secukinumab to pregnant cynomolgus monkeys (gestation day 20 to 90) did not elicit maternal toxicity and no embryo-fetal toxicity or malformations was observed in this study. No treatment related effects on fertility or pre- and post-natal development were noted in mice treated with the mouse analog of secukinumab.

No genetic toxicity or carcinogenicity studies have been conducted with secukinumab. The sponsor has conducted a literature review to assess the carcinogenic risk potential of inhibiting IL-17A which correlates to potential effects after treatment with secukinumab. The literature results were not definitive but the majority of the literature references indicate no increased carcinogenic potential after inhibition of IL-17A. In addition, no preneoplastic lesions were noted during the 26-week repeat-dose toxicity study in monkeys. No nonclinical studies to address the carcinogenic potential of secukinumab are recommended.

Animal studies do not indicate harmful effects for secukinumab with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.

Since this monoclonal antibody product is a new molecular entity, the nonclinical information received tertiary OND review by Dr. Abigail Jacobs, who concurred that there were no

approval issues related to the nonclinical information, and that the pregnancy category is "B". There are no outstanding nonclinical review issues, and no nonclinical PMC/PMR's are recommended.

5. Clinical Pharmacology/Biopharmaceutics

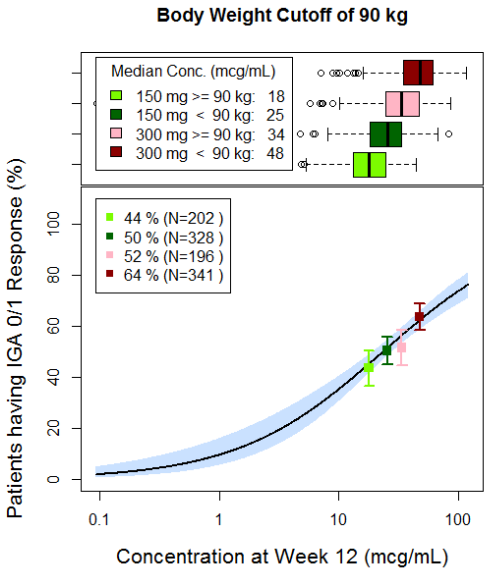
The clinical pharmacology review, by Dr. Jie Wang, supported by the pharmacometrics review by Dr. Jee Eun Lee, concludes that the application can be approved, but offers recommendations on the central review issue of dose and dosing regimens based on analyses of subgroups by weight across the several dosing regimens conducted in the clinical development program.

The central review finding from Dr. Wang's review is "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."

While additional dose ranging explorations were recommended to the applicant during product development, these were not conducted in Phase 2 and the effect of body weight on the treatment effect was evaluated in the population pharmacokinetics analyses as well as modeling scenarios.

The Agency review concluded that 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 and clinical response rates were generally higher in the lower body weight group.

Dr. Wang's table 1.3.2 c is reproduced below, and illustrates the 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:



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). Dr. Wang's Table 1.3.2 d, illustrating 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) is reproduced below:

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)

Analyses of exposure response for efficacy across weight bands supported this assessment on the effects of body weight on treatment effects.

Regarding safety, no 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. Further discussion of safety assessments is found below in the Clinical section of this review.

Briefly, the reviews conclude that 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.

This issue was discussed at length at the October 20, 2014 Advisory Committee meeting. The committee members unanimously agreed that the 300 mg dose appeared safe and effective for the proposed psoriasis indication. They expressed concern that including a 150 mg dose in the prescribing information might adversely impact third party payer considerations for secukinumab upon approval.

It is the recommendation of the review team to approve labeling for the 300 mg dose, although the clinical review by Dr. Amy Woitach proposes to approve both doses to allow flexibility to prescribers. The applicant has concurred with an intermediate statement, "For some patients, a dose of 150 mg may be acceptable" in the Dosage and Administration section of labeling.

For higher weight subjects, modeling scenarios suggest that a higher dose might improve response, though no actual clinical trials were conducted at doses of 450 mg.

The Agency has proposed an additional post marketing trial to explore the possibility of further improving the therapeutic effect in a subpopulation (subjects with body weight ≥90 kg). A post marketing commitment that states…:

> *"Conduct a clinical trial to evaluate the treatment effect and safety profile of a higher dose (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight and to explore the option of dose escalation to 450 mg for those who cannot achieve the therapeutic goal at 300 mg dose."*

…is awaiting concurrence by the applicant as of the date of this review.

The recommended PMC study 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. The lower response rate is in part due to lower exposures in subjects with body weight ≥90 kg compared to that in subjects with body weight <90 kg. 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.

The primary goal of the recommended study is to evaluate whether a higher dose (e.g., 450 mg) of secukinumab would achieve better efficacy (or treatment responses) with acceptable safety profile in psoriasis subjects with higher body weight (e.g., ≥90 kg) compared to the recommended 300 mg dose. A secondary goal for this study can be added to evaluate whether

dose escalation from 300 mg to 450 mg would benefit patients who do not initially respond to the 300 mg dose regimen.

Regarding other issues examined by the clinical pharmacology team, secukinumab was found to exhibit PK properties typical of other human IgG immunoglobulins. 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 in healthy subjects and 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 in psoriasis subjects. 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.

The metabolic pathway of secukinumab was not characterized. Presumably, secukinumab is degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

No formal studies were conducted in subjects with renal impairment. Secukinumab has a large molecular size and is unlikely to be filtered by kidney or excreted in urine. No formal studies were conducted in subjects with hepatic impairment.

PK analyses were conducted to assess the different presentations of secukinumab. The autoinjector was shown to achieve higher exposures than the prefilled syringe and the lyophilized in vial presentations based on the comparisons of secukinumab trough concentrations across multiple Phase 3 trials 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 lyophilized vial presentation, the concentrations resulting from the autoinjector were approximately 10%-30% higher across the two doses and two time-points. Similarly, the cross-study comparison also showed that compared to the prefilled syringe, the concentrations resulting from the autoinjector were approximately 16%-26% higher.

Dr. Wang observed the following results regarding immunogenicity assessments. 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 was observed in subjects who developed secukinumab treatment-emergent ADA in psoriasis Phase 3 trials. No definitive conclusion on the impact of ADA on the clinical efficacy and/or safety measures due to the small number of subjects with treatment-emergent ADA.

Due to the size of the molecule, QT assessments were not recommended by the Agency, as is typical for large monoclonal antibody development programs.

The following PMC is also recommended by the clinical pharmacology team, and concurred with by this CDTL review:

> *Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.*
>
> *Final Protocol Submission: 04/2015*
> *Study/Trial Completion: 11/2015*
> *Final Report Submission: 05/2016*

There are no outstanding review issues remaining from the perspective of the clinical pharmacology team beyond agreement of language in the prescribing information related to the dosing regimen, and final concurrence by the applicant for the post marketing recommendations.

6. Clinical Microbiology

This section is not applicable to this application, as no antimicrobial claims were sought for this indication of moderate to severe psoriasis. Product related microbiology issues were reviewed by the Agency BMAB group and are discussed above in the Product Quality/CMC discussion.

7. Clinical/Statistical- Efficacy

Secukinumab, at doses of 300 mg and 150 mg, was superior to placebo in the treatment of moderate to severe plaque psoriasis in two Phase 3 trials (2302 and 2303), with Trial 2303 including an etanercept comparator arm. The trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with Psoriasis Area and Severity Index (PASI) score ≥12, Investigator's Global Assessment (IGA) score of at least 3, and body surface area (BSA)

involvement ≥10% at baseline. For secukinumab, subjects received a loading dose of weekly injections for the first 4 weeks followed by treatment every 4 weeks.

The co-primary endpoints were the proportion of subjects achieving PASI 75 response (i.e., ≥ 75% reduction in PASI score) at Week 12 and a reduction of scoring to an IGA of 0 or 1 at Week 12, with a key secondary endpoint of PASI 90 response (i.e., ≥ 90% reduction in PASI score) at Week 12.

The Agency Biostatistical review by Dr. Carin Kim summarized the efficacy results in the following table:

	Trial 2302			Trial 2303			
	AIN457 300 mg (N=245)	AIN457 150 mg (N=245)	Placebo (N=248)	AIN457 300 mg (N=327)	AIN457 150 mg (N=327)	Placebo (N=326)	Etanercept (N=326)
Co-primary endpoints							
IGA of clear or almost clear	160 (65%)	125 (51%)	6 (2%)	202 (62%)	167 (51%)	9 (3%)	88 (27%)
PASI 75 Response	200 (82%)	174 (71%)	11 (4%)	249 (76%)	219 (67%)	16 (5%)	142 (44%)
Key secondary endpoint							
PASI 90 response	145 (59%)	95 (39%)	3 (1%)	175 (54%)	137 (42%)	5 (2%)	67 (21%)

Trial 2303 demonstrated noninferiority to etanercept, but also established superiority of secukinumab as well ($p<0.0001$). However, no replication of either finding for the comparisons to etanercept was conducted by the applicant, (b) (4)

Patient reported outcomes (PRO) for itching, pain, and scaling were included as secondary endpoints. However, conclusions for these endpoints are limited by the finding that not all centers had the Psoriasis Diary instrument available and furthermore, subjects could elect not to use the device even if it was available. Approximately 40% of subjects from each trial participated in PRO response assessments for itching, pain, and scaling, and it is not clear whether this subset is a random sample of the total population, so findings from these endpoints may not be generalizable to the overall trial population.

While the review team acknowledged the usefulness of patient reported outcomes in the review of this data, the implementation of the PRO diary instrument somewhat limits the statistical evaluation of the results. The following is recommended for Section 14 of the label related to PRO's:

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

The applicant also conducted a Phase 3 trial to support the safety and efficacy of secukinumab in liquid formulation in prefilled syringes (2308), and autoinjectors (2309). The same co-primary endpoints as those for the pivotal trials were used in Trials 2308 and 2309, and the results of the co-primary efficacy endpoints were statistically significant ($p<0.0001$), but the numbers of subjects in each arm averaged around 60 subjects. These trials were not designed or powered to allow statistical conclusions for the PFS or the AI to compare to those of the original lyophilized in vial formulation of secukinumab which was used in the two pivotal Phase 3 trials. However, the response rates in Trials 2308 and 2309 were generally similar to those of the pivotal trials (2302 and 2303).

Dr. Kim also notes that the applicant also included results from a Phase 3 trial (2304) that compared two maintenance regimens (i.e., retreatment at start of relapse (SoR) regimen versus the retreatment at fixed interval (FI) regimen), as well as results a Phase 3 trial (2307) that investigated up titration in partial responders (i.e., PASI 50 but not PASI 75 responders). However, the primary objective of Trial 2304 was not met as the noninferiority (NI) margin was not met, and the primary objective of Trial 2307 failed to show statistical significance mainly due to the small sample size.

The clinical review by Dr. Woitach concurs with the Agency Biostatistical analyses by Dr. Kim, and this CDTL review concurs that the applicant has demonstrated that secukinumab is effective for the proposed indication of moderate to severe plaque psoriasis.

8. Safety

The safety database was deemed adequate for determining the relevant safety issues related to secukinumab for moderate to severe psoriasis in the clinical review by Dr. Amy Woitach. Novartis reported that 3430 psoriasis subjects were exposed to at least one dose of secukinumab (1395 subjects on 150 mg and 1410 subjects on 300 mg). 2751 subjects treated for at least 6 months and 1641 subjects treated for at least 1 year, adequate for ICH guidelines.

While there were six deaths reported in the development program, with four exposed to secukinumab, no increased mortality risk was seen in subjects exposed to secukinumab, as the Agency review concurs with the applicant assessment that there does not appear to be any treatment-related causes of death in the trials.

In the 12-week pooled analysis of the principal Phase 2 and Phase 3 trials, the incidence of serious adverse events (SAEs) was low and comparable for both doses of secukinumab and

placebo (2.0% for both 300 mg and 150 mg vs. 1.7% for placebo). No SAE was reported in with greater than 1% frequency.

The most common SAE's were overdose and pulmonary edema. Agency cardiology consultation from Dr. Preston Dunnmon (DCRP) concluded that drug induced congestive heart failure was not likely the etiology of these events.

Adverse events of special interest for this immune mediated psoriasis therapy are principally infections, neutropenia, cardiovascular/cerebrovascular safety, and malignancies. While infections were reported more frequently in secukinumab treated subjects, serious infections were infrequently reported.

A higher rate of Candida infections with secukinumab treatment, particularly the higher 300 mg dose, was observed consistently at both 12 weeks and entire treatment periods. Infections related to Candida did appear to show a dose response. Herpes viral infections also occurred in a higher proportion of patients in the 300 mg group than the 150 mg group and both rates were higher than placebo. No cases of disseminated or CNS herpes were reported.

The Agency cardiology review by Dr. Dunnmon identified no cardiovascular safety concerns in the development program, and no labeling for these events is recommended.

While there were rare reports of malignancy in the clinical trials, the clinical review concludes that there is no evidence that secukinumab confers an increased risk for malignancy. Prior confounding psoriasis therapies (phototherapy, chemo-phototherapy, and biologic therapy) which carry a malignancy risk also complicate interpretation of any case reports. This CDTL review concurs that this development program is too short to reliably detect rare events with long latency such as malignancy. The Agency OSE reviews do not recommend a REMS or other mitigation strategy beyond labeling, but enhanced pharmacovigilance reporting requirements similar to that recommended for TNF blockers in the post marketing period will provide additional data to illuminate this issue as post marketing experience is evaluated.

Agency analyses of common adverse events occurred at approximately the same rate in the placebo arm and did not identify any safety issues for labeling. No evidence for important drug induced prolongation of the QT interval or PR interval or other cardiovascular effects were noted.

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

The overall incidence of AEs causing dose interruption over the entire treatment period was slightly higher in the 300 mg dose cohort. Active treatment arms were higher than placebo (5.3%, 4.4% respectively, for any 300 mg, 150 mg dose vs. 1.9% for placebo). AEs contributing to this imbalance were primarily infections which were more frequent for the 300 mg dose than 150 mg dose [45/1410 (3.2%) vs. 32/1395 (2.3%)]. Bronchitis, influenza, and

pneumonia were the infection preferred terms which occurred more frequently (3-4 times) in the 300 mg than 150 mg dose of secukinumab.

Immunogenicity assessments in the Phase 3 trials identified 0.4% (10/2842) of subjects who 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.

Though no definitive conclusions can be made regarding the effect of these antibodies, those subjects with secukinumab treatment-emergent ADA were not associated with a loss of therapeutic efficacy. The development of treatment-emergent ADA was not associated with injection site reactions or other severe administration reactions including hypersensitivity events. The conclusion of the review team is that no evidence of altered PK, efficacy or safety was observed in subjects who developed secukinumab treatment-emergent ADA.

While candida infections, herpes viral infections, staphylococcal skin infections, and all infections that required treatment increased as concentration of secukinumab increased, the numbers of events are relatively low and no safety finding impacts the review team conclusion that the benefits outweigh the risks for secukinumab in the treatment of moderate to severe psoriasis. An acceptable risk-benefit determination has been provided in this application, and an approval action is recommended by the clinical review and concurred with by this CDTL review.

9. Advisory Committee Meeting

A Dermatologic and Ophthalmologic Drugs Advisory Committee meeting was convened on October 20, 2014 to discuss the safety and efficacy results from this application. While there were no critical approvability issues that were left unresolved during the Agency review, the members were asked to comment on the overall safety and efficacy as well as potential dosing regimens based on the data in the application. The following section summarizes the Committee's discussion on the topics and voting questions:

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

Background Information for Consideration (Issue 1): As the question states, we are asking the Committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, does not mean that one must agree with all of the proposed

dosing recommendations or that one must define all labeling recommendations. Questions 2 and 3 that follow the general approval question/vote will give the Committee a chance to provide opinions on more granular issues. If you do not believe the available data support approval, please consider what additional studies should be recommended.

Vote: Yes: 7 No: 0 Abstain: 0

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

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

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

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

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

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

Committee Discussion: *The majority of the committee agreed that the 450 mg dose in patients weighing >90 kg should be considered. Some committee members noted that the 450 mg dose*

may be of benefit for patients who are non-responders to the 300 mg dose, thus a post-market study of the 450 mg dose in slow or non-responders should be conducted.

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

Committee Discussion: *The majority of the committee agreed with the sponsor's suggested post-marketing plan. One committee member noted that the sponsor's post-marketing study is designed to evaluate cardiac events and does not address long term risks such as malignancies or autoimmune diseases. The committee member recommended that additional studies with large databases needs to be evaluated in addition to the sponsor's suggested post-marketing plan to address long term risks. Another committee member noted that if there is an extension study, although this is not a randomized trial, it should be done in a blinded fashion to assess adverse events.*

10. Pediatrics

The requirements needed to address PREA were discussed with the applicant at a guidance meeting on March 2, 2011. Because the development plan meetings for secukinumab predate the requirements under the Food and Drug Administration Safety and Innovation Act (FDASIA), the applicant was not required to submit an initial Pediatric Study Plan (iPSP) within 60 days of an EOP2 meeting. The applicant opted to submit a plan to address PREA with the BLA submission.

The applicant requests a waiver for pediatric patients under 6 years of age based on studies not being feasible to conduct as there are too few children under the age of 6 with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Literature is adequate to concur that the prevalence of moderate to severe psoriasis in pediatric patients is low, and a waiver for this age group is recommended.

For pediatric patients 6 to 17 years of age, the applicant requests a deferral until after 12 months of treatment data in adults from phase 3 trials is available and PK modeling is assessed to guide dosing, proposing to submit the final study report in 2018. Precedent products in the Division have been granted a deferral for study of older children until the post-approval adult experience is better characterized. The TNF blocker post-marketing experience identified adverse events with long latency periods (e.g., malignancies) that raise concerns that long-term adult safety should be better characterized prior to the initiation of pediatric trials. A one year period prior to pediatric trials is likely not adequate to characterize events of special interest, in particular latent malignancies. The Division recommends a deferral until 2022, acknowledging to the applicant that this time frame can be advanced if adequate safety information becomes available in the interim.

The pediatric plan was discussed at the Pediatric Review Committee on July 16, 2014. The committee agreed with the Division to grant a partial waiver in patients ages birth to 6 years because studies are impossible or highly impractical and to the deferral in older children so that post-action safety and effectiveness in adults can be evaluated prior to initiation of pediatric trials.

As noted below in Section 13, the following PREA PMR will be recommended for the action letter:

> *Conduct a study to evaluate the safety and efficacy of secukinumab in pediatric subjects ≥ 6 years of age with plaque psoriasis.*
>
> *Final Protocol Submission: 01/2022*
> *Study/Trial Completion: 12/2025*
> *Final Report Submission: 02/2026*

Should adequate safety information be submitted and reviewed in advance of these dates, the timeframe for pediatric trials can be advanced and does not need to be reviewed by the PeRC.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are complete, and there are no outstanding issues impacting approval from the Office of Compliance. The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA.

The Office of Scientific Investigators (OSI) was consulted to review the conduct of both clinical trials, and included the inspections as noted by Dr. Woitach in her clinical review:

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

The clinical site of Dr. Bardur Sigurgeirsson was selected and inspected independently by the European Medicines Agency (EMA). The findings of the inspection are based on the

Integrated Inspection Report shared by the EMA with FDA. Having reviewed EMA's inspection report on the conduct of Protocol CAIN457A2303 at Dr. Sigurgeirsson's site, OSI is in agreement that the data generated by this site appear acceptable in support of the respective indication."

There are no outstanding regulatory issues that will impact the approval of this application.

12. Labeling

The trade name of "Cosentyx" has been accepted by Office of Medication Error Prevention and Risk Management. While the clinical team expressed reservations regarding the name of the autoinjector, "Sensoready" pen, as it might imply some ability of the device to "sense" the injection site, the Office of Medication Error Prevention and Risk Management in the Office of Surveillance and Epidemiology concluded that the names are acceptable.

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the BLA as well as DMEPA, DRISK, and OPDP consultative reviews.

Labeling is adequate to communicate necessary safety information to prescribers. Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review.

As described above, the central review issue for labeling was whether to accept the applicant's proposal for 300 mg, or consider the data presented for the 150 mg dose and whether a lower dose would be a more preferable or additional alternative balance of safety and efficacy, or some combination related to body weight or other variables. The majority of the review team concurred with the Advisory Committee discussion that the 10-15% improvement in treatment effect observed with 300 mg dosing was clinically significant and lacked significant differences in safety outcomes observed with the 150 mg dosing cohort. The recommended labeling will present the 300 mg dose as the "approved" dose and acknowledge that, "For some patients, a dose of 150 mg may be acceptable". This was discussed by teleconference with the applicant who concurred with this presentation in the Dosage and Administration section. The presentations of the drug product, in 150 mg forms, will allow prescribers some ability to consider the data in labeling to inform the specific dose which is appropriate for an individual patient in clinical practice.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, and concurred by this CDTL review, is that safety and efficacy of secukinumab has been adequately demonstrated by the clinical development program for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. An approval action is recommended pending successful completion of ongoing labeling negotiations.

- Risk Benefit Assessment

Efficacy for moderate to severe plaque psoriasis has been adequately demonstrated by the applicant in two adequate and well controlled clinical trials. The safety findings are not unexpected given the history of other antibiotic products approved for psoriasis.

The benefits of secukinumab outweigh the risks when used as recommended in the prescribing information, and this CDTL review concurs with the review team that this application should be approved. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond final agreement of draft labeling and terminology related to post marketing commitments and requirements.

Varying proposals regarding approval of dosing have been successfully resolved. The applicant agreed to presentation of data in the Section 14 Clinical Studies part of the label for both 150 mg and 300 mg doses, and a statement in Dosage and Administration that states "For some patients, a dose of 150 mg may be acceptable". Since the three presentations of secukinumab allow for dosing in 150 mg increments, dosing flexibility for prescribers is maintained. Treatment effect can be balanced with safety outcomes as additional short and long term experience is acquired for secukinumab.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The review team, in consultation with Agency representatives from OSE, concluded that a REMS is neither required nor recommended for this antibody product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks. Enhanced pharmacovigilance will be conducted by the applicant to monitor for the occurrence of latent adverse reactions, with particular focus on the incidence of malignancies with longer term exposures.

The enhanced pharmacovigilance program will include the following: 1) active query of reporters to obtain additional clinical information related to malignancy diagnoses; 2) expedited reporting to FDA of all initial and follow-up reports of any malignancy. Interim analyses and summaries of new and cumulative safety information will be submitted annually, followed by the final report at the conclusion of the monitoring period.

- Recommendation for other Postmarketing Requirements and Commitments

The majority of the recommended post-marketing studies to be conducted are recommended from the product quality review (#3-#10 below). None of these issues are approvability issues and these can be conducted post-approval.

The PREA PMR #1 is discussed above in Section 10 of this review, and, as noted, the timeframe may be amended as adult safety experience with secukinumab is reviewed and considered. The Clinical Pharmacology recommended study to examine CYP substrates results from recent Agency guidance on this issue. As discussed above, there will also be a requirement for a dose ranging trial at 450 mg dosing.

PMRs

1. Conduct a study to evaluate the safety and efficacy of secukinumab in pediatric subjects ≥ 6 years of age with plaque psoriasis.

Final Protocol Submission: 01/2022
Study/Trial Completion: 12/2025
Final Report Submission: 02/2026

PMCs (506B reportable):

2. Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.

Final Protocol Submission: 04/2015
Study/Trial Completion: 11/2015
Final Report Submission: 05/2016

PMCs (Not 506B reportable):

3. Re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Final Report Submission: 12/2018

4. Re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis

will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Final Report Submission: 12/2019

5. Re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Final Report Submission: 12/2017

6. Conduct routine bioburden testing (b) (4) The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.

Final Report Submission: 12/2015 (method qualification report)
08/2016 (evidence of implementation of test)

7. Conduct routine bioburden testing (b) (4) The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.

Final Report Submission: 12/2015 (method qualification report)
08/2016 (evidence of implementation of test)

8. Conduct routine bioburden and endotoxin testing (b) (4) Routine testing will be implemented for the 2015 manufacturing campaign.

Final Report Submission: 03/2015 (evidence of implementation of test)

9. Conduct additional hold time validation studies on two batches at commercial scale (b) (4) validation will be conducted during the 2015 and 2016 commercial campaigns.

Final Report Submission: 06/2016

10. Evaluate feasibility of (b) (4) secukinumab drug substance and update drug substance specification (b) (4) .

Final Report Submission: 03/2015 (report of the evaluation conducted)

11. "Conduct a clinical trial to evaluate the treatment effect and safety profile of a higher dose (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight and to explore the option of dose escalation to 450 mg for those who cannot achieve the therapeutic goal at 300 mg dose."

Final Report submission not currently determined.

- Recommended Comments to Applicant

There are no comments to be conveyed to the applicant upon agreement of final labeling and agreement on post marketing requirements and commitments. Labeling negotiations are ongoing with the applicant as of the date of this review, but there are only minor differences to be resolved as of the date of this CDTL review.

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

/s/

DAVID L KETTL
12/09/2014