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APPLICATION NUMBER:

125504Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	December 24, 2014
From:	Kendall A. Marcus, M.D. Director, Division of Dermatology and Dental Products
Subject:	Summary and Recommendations
NDA/BLA #:	125-504 Novartis Pharmaceuticals Corporation
Submission Date **PDUFA Goal**	October 22, 2013 January 23, 2015
Proprietary / Generic (USAN) names	COSENTYX (secukinumab) subcutaneous injections
Dosage forms / strength	Powder for solution, solution for injection, 150 mg, 150 mg/mL
Proposed Indication(s)	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

1. Introduction

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 one of the major pro-inflammatory cytokines in immune-mediated inflammatory diseases. It is believed that secukinumab interrupts the inflammatory processes of psoriasis through the inhibition of IL-17A signaling. Studies have shown significantly higher concentrations of IL-17A in the lesional skin as compared to non-lesional skin of psoriasis patients or the skin of healthy volunteers.

The proposed indication for secukinumab is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. If approved, secukinumab would become the first IL-17 blocker indicated for the treatment of plaque psoriasis. Other approved products include TNF blockers (adalimumab, etanercept, infliximab), an IL 12/23 inhibitor (ustekinumab) and the drugs acitretin, methotrexate, cyclosporine and apremilast.

The recommended 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. In addition, it was determined that dosing with a single 150 mg SC injection dose may be appropriate for some patients. 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).

Safety and efficacy of secukinumab in the various presentations are supported by 4 placebo-controlled Phase 3 trials, 4 Phase 2 dose-ranging trials, 2 trials exploring

other dosing schedules, clinical trials for other indications under development and trials in healthy adult volunteers. All psoriasis trials enrolled a similar population, adults with plaque psoriasis who were candidates for systemic therapy or phototherapy.

Currently, secukinumab is also under development for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, uveitis, diabetes mellitus, relapsing forms of multiple sclerosis and asthma.

2. CMC

Please refer to the reviews prepared by Tura Camilli, Ph.D. and Sarah Kennett, Ph.D., of the OPS/OBP/Office of Monoclonal Antibodies and the reviews prepared by Reyes Candau-Chacon, Ph.D and Kalavati Suvarna, Ph.D. of Biotech Manufacturing and Product Quality for full details.

Review of the original BLA submission identified several critical CMC issues that led to an information request and a substantial submission in response from the Applicant. The issues were related to control of the manufacturing process and included: identity testing, cell bank information (b) (4) of the drug product. The Applicants 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 were successfully resolved with the submission of additional information by the Applicant.

In sum, data submitted in the BLA and inspections conducted by FDA staff support the conclusion that the manufacture of 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 set forth by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs.

Postmarketing commitments (PMCs) will be requested in order to ensure that any updated specifications resulting from additional manufacturing experience are sufficient to ensure adequate quality and safety of the initially marketed product.

3. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Jill Merrill, Ph.D., the Pharmacology/Toxicology reviewer for BLA 125504. Dr. Merrill finds this BLA approvable.

No treatment related effects on reproductive function, fertility or early embryo-fetal development were noted in studies conducted in cynomolgus monkeys. No treatment related effects on fertility or pre- and post-natal development were noted in mice

treated with the mouse analog of secukinumab. Based on nonclinical and clinical data submitted with this BLA, assignment of pregnancy category B is considered appropriate.

Repeat dose toxicity studies in monkeys 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.

Although secukinumab cross-reacts with human, marmoset, rhesus and cynomolgus monkey IL-17A, it does not cross-react with rodent IL-17A. Thus a standard 2-year carcinogenicity study is not practical and the sponsor was advised to assess the clinical carcinogenic risk potential of chronic secukinumab-treatment based on the existing scientific literature. There are no concerns relating to the oncogenic potential arising from the molecular structure or metabolites of secukinumab.

4. Clinical Pharmacology

Please refer to the review completed by Jie Wang, Ph.D., the clinical pharmacology reviewer and Jee Eun Lee, Ph.D., the pharmacometrics reviewer. The review team considers this BLA approvable from a clinical pharmacology perspective.

The pharmacokinetics (PK) of secukinumab was evaluated in healthy subjects and in subjects with psoriasis in multiple clinical trials. Secukinumab displayed PK properties typical of a human IgG immunoglobulin, interacting with a soluble target without any sign of target-mediated disposition. The half-life is approximately 27 days. Because significant drug-drug interactions (DDIs) between monoclonal antibodies and low molecular weight drugs are not expected, the DDI potential of secukinumab as a target or culprit was not investigated in vitro or in dedicated interaction clinical studies.

The clearance and the volume of distribution of secukinumab appear to be higher in subjects with psoriasis as compared to healthy subjects. The absolute bioavailability in psoriasis patients was estimated to be 73%. Secukinumab displayed dose-independent PK in psoriasis patients, with dose-normalized exposure unchanged over the dose range studied. Dose-proportionality in the dose range from 150 mg to 300 mg was confirmed in Phase 3 trials.

As previously mentioned, the applicant proposes to register three presentations (LYO, PFS, and AI) in this BLA. The LYO and the PFS were shown to have comparable PK in a dedicated PK comparability study. The AI presentation appeared to achieve higher exposures than the PFS and the LYO presentations based on comparisons of secukinumab trough concentrations across multiple Phase 3 trials. Compared to the

LYO or the PFS, the concentrations resulting from use of the AI appeared to be about 10%-30% higher across the two doses.

The PFS and AI were each evaluated in separate small 52-week trials while the LYO presentation was used in the two pivotal and larger Phase 3 trials. In these and other trials, the cumulative distribution of the trough secukinumab concentration data at Week 12 showed substantial overlap for the three presentations. At the 150 mg dose, both PFS and AI showed similar efficacy results as LYO based on the Investigator's Global Assessment (IGA) 0/1 and Psoriasis Area and Severity Index (PASI) 75 response rates at Week 12. At the 300 mg dose, AI appeared to have numerically higher response rates than LYO for both IGA 0/1 and PASI 75. The observed differences in outcomes for the AI presentation were not considered clinically significant.

From a population PK analysis, body weight was identified as a significant covariate for the apparent clearance of secukinumab. Body weight was also found to be a significant covariate for secukinumab exposure. An analysis of exposure and response was conducted by dividing subjects into two groups, those weighing less than 90 kg and those weighing 90 kg or more. Within each secukinumab dose group (150 mg or 300 mg), the median trough concentrations of secukinumab and clinical response rates were higher in the lower body weight group. Multivariate logistic regression analyses confirmed this observation and identified secukinumab exposure, body weight, and baseline IGA score as independent significant covariates on the exposure-response relationship. Higher secukinumab exposure was associated with an increased treatment response while higher body weight or higher baseline IGA scores were associated with a decreased treatment response.

The co-primary endpoints for the clinical trials were the proportion of subjects achieving PASI 75 response (≥ 75% reduction in PASI score) at Week 12 and a score of IGA 0 or 1 at Week 12. An important secondary endpoint was the PASI 90 response (≥ 90% reduction in PASI score) at Week 12.

Figure 1, reproduced from Jie Wang's review, displays the median trough concentrations of secukinumab in the four weight/dose groups as well as the percentage of IGA 0/1 responders in the same groups at Week 12. Response rates appear similar for subjects weighing less than 90 kg who received 150 mg as compared to subjects weighing 90 kg or more who received the 300 mg dose. The largest difference in response rates amongst the subgroups is observed for subjects weighing less than 90 kg who received 300 mg (64%) as compared to subjects weighing 90 kg or more who received 150 mg (44%).

Figure 1: Response Rates by Dose/Weight Categories

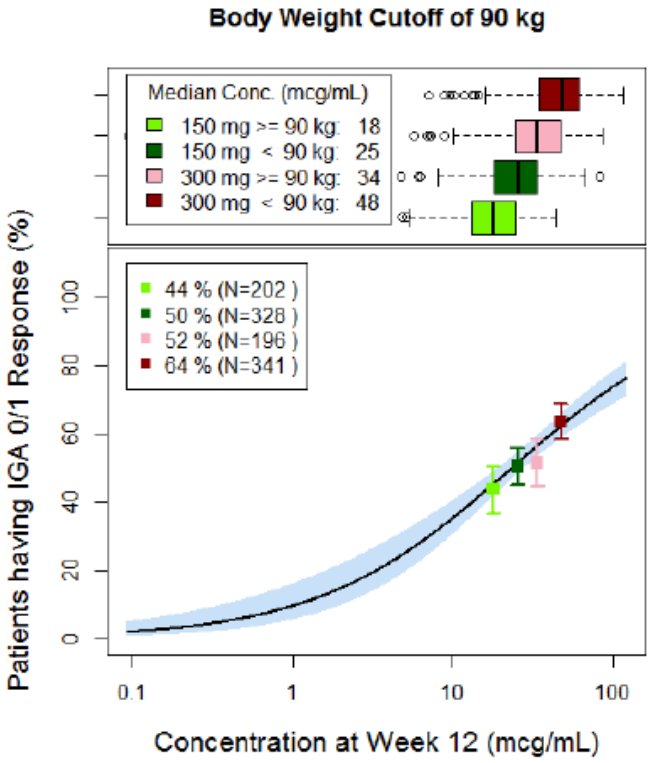

Table 1, reproduced from Jie Wang's review, also shows PASI 75 response rates at Week 12 by weight strata.

Table 1: Outcomes by Weight/Dose Strata

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)

Overall, the clinical pharmacology review team concluded that the dose/exposure-response relationships support the recommendation of 300 mg dose regimen made by the Applicant. Additionally, they observed that many subjects achieved the clinical endpoint at the lowest dose of 150 mg. Because of this observation, as well as the observed body weight effect on secukinumab PK exposure and the impact of baseline IGA score on response, they concluded the 150 mg dose should also be available for patients if the prescriber determines a lower dose may be appropriate.

Similarly, for higher body weight subjects, modeling scenarios suggest that a higher dose might further improve response, though no clinical trials were conducted with a 450 mg

dose. The Agency proposed an additional post marketing trial to explore the possibility of further improving the therapeutic effect in a subpopulation (subjects with higher body weight).

5. Clinical/Statistical

Please refer to the reviews completed by Amy Woitach, D.O., the clinical reviewer and Carin Kim, Ph.D., the biostatistical reviewer. The review team considers this BLA approvable from an efficacy perspective.

Four Phase 2 trials, four placebo-controlled Phase 3 trials that include two pivotal trials and two additional exploratory Phase 3 trials were submitted in support of the proposed indication:

- Four Phase 2 dose-ranging studies explored doses ranging from 25 mg subcutaneous (SC) to 10 mg/kg intravenous (IV).
- Four placebo-controlled Phase 3 trials, one of which included an active comparator (etanercept), evaluated identical 150 mg and 300 mg SC weekly initial dosing regimens followed by monthly maintenance dosing regimens.
- Two Phase 3 studies explored alternative doses or dosing schedules for maintenance therapy.

In the pivotal Phase 3 Trials 2302 and 2303, subjects randomized to secukinumab received either 150 mg or 300 mg by SC injection at Weeks 0, 1, 2, and 3 followed by monthly (maintenance) dosing starting at Week 4 through Week 48. In one of the trials, EU-sourced Enbrel (etanercept) was used as an active comparator product at the request of the European Medicines Agency (EMA). Because it is an unapproved product in the US, this active comparator arm was not used as part of the risk-benefit assessment of secukinumab by the Agency.

These trials enrolled subjects 18 years of age and older who had plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score ≥12, an Investigator's Global Assessment (IGA) score of at least 3 and body surface area (BSA) involvement ≥10% at baseline. Results demonstrated that the overall trial population appeared to be representative of the target patient population of adult patients with moderate to severe plaque psoriasis. The mean PASI score of subjects enrolled in 2302 and 2303 was about 23 and the mean BSA involvement was about 33%. All enrolled subjects had an IGA score of at least 3.

As previously noted, the co-primary endpoints for the clinical trials were the proportion of subjects achieving PASI 75 response (≥ 75% reduction in PASI score) at Week 12 and a score of IGA 0 or 1 at Week 12. An important secondary endpoint was the PASI 90 response (≥ 90% reduction in PASI score) at Week 12.

Table 2 below reproduced from Carin Kim's biostatistical review provides Week 12 outcomes for the primary endpoints of PASI 75 and IGA 0/1 and for the key secondary

endpoint of PASI 90 for Trials 2302 and 2303. Both the 150 mg and 300 mg doses were demonstrated to be superior to placebo for these key endpoints with a p<.0001 for all comparisons. Response rates were numerically higher for the 300 mg dose as compared to the 150 mg dose.

Table 2: Percent Responders at Week 12 in Trials 2302 and 2303

	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%)

In addition to evaluating the pre-specified primary and secondary endpoints, the sponsor created a new 16-item patient-reported outcome (PRO) measure in an electronic Psoriasis Symptom Diary in order to measure itching, pain and scaling in patients with chronic plaque psoriasis in the Phase 3 clinical trials. The 16 items of the diary evaluated signs and symptoms, patient-reported bother and psoriasis-related daily impacts.

In Trials 2302 and 2303, patient-reported outcomes (PRO) on itching, pain, and scaling were included as pre-specified secondary endpoints. Interpretation of trial findings is limited by the fact that data was collected in a minority (40%) of trial subjects due to the lack of availability of the Psoriasis Diary device at all trial sites and because use of the diary was voluntary. Additionally, protocols did not call for minimum baseline itch, pain, or scaling severities as inclusion criteria, which likely contributed to increased inter-subject variability.

From review of the available data, it was observed that improvement in the severity of psoriasis also led to improvement in itching, pain, and scaling. A general statement describing this result was placed in product labeling.

In addition to the two pivotal Phase 3 trials, the applicant also conducted the following clinical trials.

- Two small Phase 3 trials to support the safety and efficacy of secukinumab in the PFS presentation (Trial 2308) and in the AI presentation (Trial 2309)
- Trial 2304 in which two different maintenance dosing strategies were compared
- Trial 2307 that investigated up titration of dose in partial responders

Because of the small trial populations, no conclusions could be reached from these trials.

6. Clinical/Safety

In the secukinumab development program, 3430 psoriasis subjects were exposed to at least one dose of secukinumab (1395 subjects at 150 mg and 1410 subjects at 300 mg). A total of 2751 subjects were treated for at least 6 months and 1641 subjects treated for at least 1 year. Of those treated, 690 subjects received 300 mg as their initial dose and 692 subjects received 150 mg as their initial dose. The majority of the subjects continued to receive the same dose for maintenance every 4 weeks through Week 48. The number of subjects treated with secukinumab was considered adequate to conduct a safety assessment.

Six deaths were reported in the psoriasis clinical trials through initial database lock; none were considered related to secukinumab treatment. In a 12-week pooled analysis of the principal Phase 2 and Phase 3 clinical trial data, the exposure-adjusted incidence of serious adverse events (SAEs) was low and comparable between secukinumab and placebo-treated subjects (2.0% vs. 1.7%). Of note, two SAEs of pulmonary edema were reported in secukinumab-treated subjects. These cases were reviewed by Dr. Preston Dunnmon of the Division of Cardiorenal Products (DCRP) who concluded that these cases were unlikely to represent drug-induced heart failure.

During the induction period of the trials (treatment through Week 12), the incidence of adverse events leading to treatment discontinuation was low and comparable between treatment arms. Only two events were reported as the reason for discontinuation in more than one subject: erythrodermic psoriasis in 2 secukinumab-treated subjects and psoriasis in 5 placebo-treated subjects. The two cases of erythrodermic psoriasis were considered unrelated to treatment.

The small number of subjects receiving placebo after Week 12 makes comparison through the remainder of the clinical trial period difficult. The most frequent adverse events leading to discontinuation ($\geq 0.10\%$) in secukinumab-treated subjects were psoriasis, psoriatic arthropathy and thrombocytopenia. Of four subjects who discontinued secukinumab for thrombocytopenia, three were documented to have low platelets at baseline. No data on platelet counts at baseline was available for the fourth subject.

Potential risks of secukinumab based on its drug class (anti-cytokine) as well as drug substance (foreign protein) were reviewed. Potential risks associated with this type of immunomodulating biologic therapy include infections, neutropenia, cardiovascular/cerebrovascular events, malignancies and autoimmune disorders. Potential risks of a foreign protein include administration or immune reactions, such as hypersensitivity, injection site/infusion reactions and immunogenicity.

Certain types of infections did appear to occur more frequently in secukinumab-treated subjects throughout the treatment period. These included *Candida* infections, herpes infections, staphylococcal skin infections and infections requiring treatment. Additionally, the incidence of these infections appeared to show a dose response with more events observed at 300 mg compared to 150 mg. Infection-related SAEs reported in

secukinumab-treated subjects included pneumonia, cellulitis, bacterial abscess and appendicitis. While infection-related SAEs did not appear to occur at increased frequency relative to placebo, the relatively small incidence of these events makes this comparison difficult.

The incidence of any grade neutropenia on any dose for secukinumab-treated subjects was 9.0% as compared to 2.7% for placebo-treated subjects and appeared to be dose dependent. Neutropenia reported as an adverse event was also higher for secukinumab arms as compared to placebo arms. Two trial subjects receiving secukinumab discontinued for neutropenia; however, most cases of neutropenia associated with secukinumab were transient and reversible. A few AEs of neutropenia were associated with non-serious infections.

Review of Major Adverse Cardiovascular Events (MACE) by Dr. Preston Dunnmon of DCRP did not raise any cardiovascular safety concerns.

While there were a few reports of malignancies in the clinical trials, clinical trial data is insufficient to provide convincing evidence that secukinumab increases the risk for any type of malignancy. Prior psoriasis therapies (phototherapy, chemo-phototherapy, and biologic therapy) which carry a malignancy risk also complicate interpretation of any case reports. The Agency OSE reviews recommend enhanced pharmacovigilance reporting requirements similar to those recommended for TNF blockers in the post-marketing period to provide additional data for evaluation of malignancy risk.

The clinical database was searched for AE terms consistent with hypersensitivity reactions (HSR) and immune/administration reactions. In the pooled 12-week analysis, HSR AEs were reported more frequently with secukinumab as compared to placebo and consisted primarily of cases of urticaria; one case led to treatment discontinuation. Angioedema was reported more frequently in placebo-treated subjects as compared to secukinumab-treated subjects, making any relationship of secukinumab to angioedema unclear. No cases of serious anaphylactic reactions considered related to secukinumab occurred in the psoriasis development program, although one case of a serious immediate hypersensitivity reaction has been reported in the ankylosing spondylitis program.

Immunogenicity assessments in the Phase 3 trials identified 10/2842(0.4%) subjects who developed secukinumab anti-drug antibodies (ADA). Of these 10 subjects, 3 were classified as positive for neutralizing antibodies, 5 were classified as negative for neutralizing antibodies, and the remaining 2 subjects were not characterized for neutralizing antibodies status. No evidence of altered PK, efficacy or safety was observed in subjects who developed secukinumab treatment-emergent ADA.

Reports of autoimmune disorders were also reviewed as part of the safety evaluation. The exposure-adjusted incidence of autoimmune disorders was higher in the placebo arm than any of the treatment arms. However, this imbalance was driven by AE reports of psoriasis and arthropathy in placebo subjects. SAEs of autoimmune disorders not related to psoriasis were reported only in treatment arms. The event rate of autoimmune AEs in the

clinical database was observed to be similar to the rate reported for etanercept. This may indicate that secukinumab is also associated with paradoxical development of autoimmune disease. Currently, the greatest strength of evidence in the clinical database exists for worsening or potential development of Crohn's disease with secukinumab use. Additional evidence should be collected on autoimmune AEs in long term studies and post-marketing to better characterize any potential risk for treatment-related autoimmune disease.

7. Advisory Committee Meeting

A Dermatologic and Ophthalmologic Drugs Advisory Committee meeting was convened on October 20, 2014 to discuss the safety and efficacy results for this application. Committee members were asked to comment as to whether they considered the overall safety and efficacy data presented supported approval of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. They were also asked to comment on potential dosing regimens.

The committee unanimously agreed that based on the potential risks and benefits, the available data support approval of secukinumab for this indication. The committee noted that post-marketing studies will be needed to determine the safety of long term use of secukinumab, but there appears to be a positive risk/benefit with the data that is currently available.

The majority of the committee agreed that the recommended dose should be the 300 mg dose. A few committee members believed the 150 mg should also be available for patients with low body weight, but choice of dose should be at the discretion of the physician. The majority of the committee also agreed that the 450 mg dose in patients weighing >90 kg should be considered, thus a post-market trial of the 450 mg dose in slow or non-responders should be conducted.

The majority of the committee agreed with the Applicants proposed postmarketing pharmacovigilance plan. One committee member stated that the sponsor's proposed post-marketing study is designed to evaluate cardiac events and does not appear to address risks such as malignancies or autoimmune diseases. The committee member recommended that additional studies with large databases should be conducted in addition to the sponsor's suggested post-marketing plan in order to further evaluate long-term risks.

8. Risk Management

Please refer to the memo prepared by Felicia Duffy, RN, BSN from the Division of Risk Management. The Applicant voluntarily submitted a REMS with this application that consisted of a communication plan and labeling, which included a Medication Guide, in order to mitigate the increased risk of infections associated with secukinumab. DDDP and DRISK agree that no Risk Evaluation Mitigation Strategy (REMS) is needed for this application, because the prescriber population that will be responsible for prescribing

secukinumab will be the same that currently prescribes ustekinumab, another biologic product approved for the treatment of moderate to severe plaque psoriasis. Therefore, it is expected that there will be a baseline familiarity with the management of risks associated with this treatment. The primary safety risk identified (increased risk of infection) can be addressed in the professional labeling.

Enhanced pharmacovigilance will be conducted by the applicant to monitor for the occurrence of potential rare, late-occurring adverse reactions, with particular focus on the incidence of malignancies with longer term exposures. The enhanced pharmacovigilance program will include active query of reporters to obtain additional clinical information related to malignancy diagnoses and expedited reporting to FDA of all initial and follow-up reports of malignancies.

In addition to the enhanced pharmacovigilance program, the Applicant has proposed to conduct a patient registry in order to collect data on the occurrence of malignancy with secukinumab treatment. Malignancy and other events of concern will also be assessed through evaluation of data from long-term extension studies.

9. Summary of Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application. The Office of Compliance made an overall "Acceptable" recommendation for the facilities involved in this BLA. The Office of Scientific Investigators (OSI) Inspections are complete and clinical data was found to be acceptable for review.

10. Conclusions and Recommendations

10.1. Regulatory Action

I concur with FDA reviewers and the Advisory Committee that secukinumab should be approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The committee voted unanimously that benefits outweigh the risks and that secukinumab should receive marketing approval. I concur that the treatment effect is robust, substantial, and highly statistically significant. Substantial treatment effects were observed with both the 150 mg and 300 mg SC doses evaluated in Phase 3 clinical trials, although response rates were numerically greater with the 300 mg dose. Because treatment response may be impacted by patient weight and severity of disease (baseline IGA score), I agree that 300 mg SC is the recommended dose, while the 150 mg dose may be acceptable for some patients.

Adverse reactions associated with secukinumab in the psoriasis development program appear to be similar to those reported with other biologic products that inhibit cytokine-mediated inflammatory process. Specifically, secukinumab appears to be associated with an increased risk for certain infections, especially Candida infections, the development of neutropenia, rare but serious HSR and Crohn's disease, an autoimmune disorder. It is

unclear at this time whether use of secukinumab is associated with certain serious risks reported with other biologic products: malignancies; cardiovascular events; more serious fungal infections; reactivation of tuberculosis or hepatitis B; or other autoimmune disorders. I concur the current risks associated with the use of secukinumab can be addressed in professional labeling.

10.2. Postmarketing Trials

In addition to the enhanced pharmacovigilance and the malignancy registry described in Section 8 of this memo, the Applicant will be required to conduct the following postmarketing clinical trials:
1) A clinical trial enrolling pediatric subjects ≥ 6 years of age with plaque psoriasis; and
2) A clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.

The Applicant has also committed to conducting multiple postmarketing evaluations to ensure ongoing product quality.

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/s/

KENDALL A MARCUS
01/02/2015