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APPLICATION NUMBER:

125521Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Summary Review

Date	18 March 2016
From	Jill Lindstrom, MD
Subject	Cross-Discipline Team Leader Review and Summary Review
BLA #	125521
Applicant	Eli Lilly
Date of Submission	23 Mar 2015
PDUFA Goal Date	23 Mar 2016
Proprietary Name / Non-Proprietary Name	TALTZ/ixekizumab
Dosage form(s) / Strength(s)	Injection, 80mg/mL
Applicant Proposed Indication(s)/Population(s)	treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jane Liedtka, MD
Statistical Review	Matthew Guerra, PhD
Pharmacology Toxicology Review	Jill Merrill, PhD
OPQ Review	Xi Di, PhD; Maria Cecilia Tami, PhD; Colleen Thomas, PhD; Bo Chi, PhD; Wayne Seifert
Product labeling Review	Jabril Abdus-Samad, PharmD
Clinical Pharmacology Review	Jie Wang, PhD; Dhananjay Marathe, PhD
Regulatory Review	J. Paul Phillips, MS
DPP	Cara Alfaro, MD; Gregory Dubitsky, MD
DPMH	Leyla Sahin, MD
OPDP	Tara Turner PharmD, MPH
DMPP/PLT	Nathan Caulk, RN
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OSE/DEPI	Gabriella Anic, MD; Andrew Mosholder, MD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
OSE/DRISK	Erin Hachey, PharmD
OSE/Drug Use	Patty Greene, PharmD

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
DPMH=Division of Pediatric and Maternal Health
DMPP=ivision of Medical Policy Programs
PLT=Patient Labeling Team
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a chronic inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life. TALTZ (ixekizumab) injection is a solution proposed for subcutaneous administration via prefilled syringe or autoinjector for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Ixekizumab, the active ingredient in TALTZ, is a humanized immunoglobulin G (IgG) monoclonal antibody that is an antagonist of 17A (IL-17A), a member of the IL-17 family (IL-17A through IL-17F) and a normally occurring pro-inflammatory cytokine that has been implicated in the pathogenesis of psoriasis.

The current therapeutic armamentarium includes topical therapies (corticosteroids, tazarotene, corticosteroid and vitamin D analog combination products), phototherapy and photochemotherapy (methoxsalen), systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and systemic biologic products (adalimumab, etanercept, infliximab, secukinumab, and ustekinumab). Efficacy varies from modest to robust, although no product provides permanent cure or universal success (clear skin for all patients), and loss of response can occur over time. Topical products and phototherapy may be impractical due to administration challenges and time constraints. All of the products have one or more serious adverse reactions, including malignancy and serious infections (methotrexate, cyclosporine, all of the biologic products), malignancy (methoxsalen, phototherapy), teratogenicity (acitretin, methotrexate, tazarotene, possibly apremilast), depression (apremilast), nephrotoxicity, hepatotoxicity, and bone marrow suppression. Because of these short-comings, despite the number of available therapies, there is clear need for additional therapeutic options.

Three pivotal trials, RHAZ, RHBA and RHBC, enrolled 3866 adult subjects with plaque psoriasis with at least 10% BSA involvement, a score of $\geq$3 on sPGA, and a score of $\geq$12 on PASI. The co-primary endpoints were i) the proportion of subjects achieving a sPGA score of 0 or 1, and ii) the proportion of patients achieving a 75% reduction from baseline PASI score, both assessed at week 12. For the proposed dose compared to placebo, the treatment effect for sPGA 0/1 was 79%, 81%, and 74%, and for PASI-75 was 85%, 88% and 80%, in trials RHAZ, RHBA and RHBC, respectively. The treatment effect for the more stringent secondary endpoints of sPGA of 0 and PASI-100 (clear skin) ranged from 35% to 41%. For the proposed dose compared to etanercept (RHBA and RHBC, using the data from US sites only), the treatment effect for sPGA 0/1 and for PASI-75 ranged from 41% to 54%. In trials RHAZ and RHBA, subjects who were responders at week 12 were re-randomized to receive ixekizumab or placebo, for weeks 13 to 60. At week 60, for the proposed dose compared to placebo (drug withdrawal) the treatment effect for sPGA 0/1 of was 67% and 69%. The median time to relapse for subjects randomized to placebo (withdrawal) was 164 days. These results, which are persuasive, demonstrate the robust efficacy of TALTZ for treatment of moderate to severe psoriasis in adults.

The safety database was adequate to characterize the safety profile of TALTZ. In the three pivotal trials, 1167 subjects received the proposed dose of ixekizumab from week 0 to 12, and 332 subjects received the proposed dose from weeks 13 to 60. Infections occurred in 27% of subjects exposed to ixekizumab compared to 23% subjects exposed to placebo, although the rates of serious infection were similar. Serious hypersensitivity ($\leq$0.1%), Crohn's disease (0.1%), and ulcerative colitis (0.2%) and inflammatory bowel disease occurred more frequently in

subjects exposed to ixekizumab than placebo (0%). Common adverse reactions included injection site reactions, upper respiratory infections, nausea and tinea. At this time, the safety profile for TALTZ appears comparable to that for secukinumab, and potentially favorable to alternatives with risks for malignancy and other organ toxicities. However, post-marketing safety studies to assess the risk for malignancy and other serious adverse events, as well as the risk for fetal exposure, are recommended.

Prescription and patient labeling, including a Medication Guide, as well as routine pharmacovigilance are adequate to manage the risks of TALTZ in the post market milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. This is consistent with the approach taken with secukinumab. Recommended post marketing studies include a pediatric safety, activity and PK study, fetal exposure studies, a safety study to assess for malignancy and other serious adverse reactions, and a trial to assess impact of ixekizumab on CYP substrates.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis a chronic inflammatory disease affecting primarily the skin and joints that is characterized by circumscribed erythematous scaly plaques on the skin and substantial impairment of quality of life. Prevalence in the US is approximately 2%, of which an estimated 20% have moderate-to-severe disease. One third of patients have concomitant arthritis. Co-morbidities include depression/suicide, autoimmune disease, cardiovascular disease, metabolic syndrome.	Moderate-to-severe psoriasis is a serious disease because of its chronic nature, impact on quality of life, and co-morbidities.
Current Treatment Options	Treatment options include topical therapies (corticosteroids, vitamin D analogs, tazarotene, combination products), phototherapy and photochemotherapy (methoxsalen), systemic small molecule drugs (acetretin, apremilast, cyclosporine, methotrexate), and systemic biologic products (adalimumab, etanercept, infliximab, secukinumab, and ustekinumab). Based on cross-study comparison of PASI 75 response rates for the systemic agents, secukinumab, ustekinumab, infliximab, adalimumab, and cyclosporine are highly effective, acitretin and apremilast are modestly effective, and the remainder are somewhere in between. For moderate-to-severe disease, topical therapies may be impractical due to the difficulty and time-consuming nature of topical application. Phototherapy and photochemotherapy may be impractical due to the potential need to receive phototherapy in a clinic setting or the need for photoprotection. Acitretin is a potent teratogen; adverse reactions include marked xerosis	There are a number of FDA-approved treatments for moderate-to severe psoriasis in adults. Efficacy of these products ranges from robust to modest, but none provide permanent cure or universal response even for PASI 75 (much less for PASI 100). All of the products have one or more serious risks. Because of the potential for lack of response, loss of response, comorbidities, concomitant illnesses, as well as other individual factors that may impact clinical decision-making, there is need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and hyperlipidemia. Methoxsalen is a photosensitizer and genotoxic; adverse reactions include skin burning, actinic damage, and melanoma. Depression and weight loss are safety concerns with apremilast. The remaining systemic products (the biologic products, methotrexate, cyclosporine) are immunosuppressants; safety concerns include serious infections and malignancy. Cyclosporine is nephrotoxic and may cause hypertension. Methotrexate is teratogenic, hepatotoxic, nephrotoxic, and may cause bone marrow toxicity and pulmonary fibrosis. Loss of effect is seen with the biologic products, and may be associated with anti-drug antibody formation. Serious hypersensitivity may occur with any of the biologic products.	
Benefit	Three pivotal trials, RHAZ, RHBA and RHBC, enrolled 3866 adult subjects with plaque psoriasis with at least 10% BSA involvement, a score of ≥3 on sPGA, and a score of ≥12 on PASI. In each trial, subjects were randomized to receive one of two dosage regimens, 80mg q2wk or 80mg q4wk for 12 weeks (following an initial dose of 160mg), or placebo; in trials RHBA and RHBC subjects were also randomized to receive etanercept during weeks 0 to 12. The co-primary endpoints were i)the proportion of subjects achieving a sPGA score of 0 or 1, and ii) the proportion of patients achieving a 75% reduction from baseline PASI score. For the proposed dose compared to placebo, the treatment effect for sPGA 0/1 was 79%, 81%, and 74%, and for PASI-75 was 85%, 88% and 80%, in trials RHAZ, RHBA and RHBC, respectively; these results were statistically significant. The treatment effect for sPGA of 0 was 37%, 41% and 40%, and the treatment effect for PASI-100 was35%, 39%, and 38%. For the proposed dose compared to etanercept (data from US sites only), the treatment effect for sPGA 0/1 was 48% and 42%, and for PASI-75 was 54% and 41%, in trials RHBA and RHBC, respectively; these results were statistically significant. In trials RHAZ and RHBA, subjects who were responders at week 12 were re-randomized to receive one of two dosages, ixekizumab 80mg q4 wks or 80mg q12 wks, or placebo, for weeks 13 to 60. At week 60, the treatment effect for sPGA 0/1 of the proposed dose compared to placebo (drug withdrawal) was 67% and 69%, in trials RHAZ and RHBA, respectively. The median time to relapse for subjects randomized to	The data submitted by the applicant meet the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive. Achievement of clear or almost-clear skin is intrinsically meaningful for an inflammatory cutaneous disease such as psoriasis. The data suggest that a patient with moderate-to-severe plaque psoriasis treated with ixekizumab at the labeled dose is likely to achieve clear or almost clear skin by 12 weeks, and to maintain this effect with continued treatment to 60 weeks. Patients who develop high titers of anti-drug antibodies, or neutralizing anti-drug antibodies, are less likely to realize these benefits.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo (withdrawal) was 164 days. The efficacy data is very persuasive. The co-primary endpoints are acceptable, clinically relevant, and similar to endpoints for other approved products for this indication. The treatment effect was large and consistent across trials. The secondary endpoints are supportive.	
Risk	• The overall safety database for ixekizumab in psoriasis includes 4204 subjects exposed to ixekizumab at any dose, of whom 2190 were treated for over one year. In the three pivotal trials, 1167 subjects received the proposed dose of ixekizumab from week 0 to 12, and 332 subjects received the proposed dose from weeks 13 to 60. The safety database is adequate and consistent with other products approved for the indication. • Infections occurred more frequently in subjects exposed to ixekizumab compared to subjects exposed to placebo (27 vs 23%), although the rates of serious infection were similar. Upper respiratory infections, noninvasive candidiasis and tinea occurred more frequently in subjects exposed to ixekizumab. • No cases of active tuberculosis occurred in the development program, Subjects were screened for tuberculosis prior to enrollment in the pivotal trials, and screening is recommended in product labeling. • Serious hypersensitivity reactions such as angioedema and urticarial occurred in subjects exposed to ixekizumab. • Inflammatory bowel disease occurred more frequently in subjects exposed to ixekizumab (Crohn's disease 0.1%, ulcerative colitis 0.2%) than placebo. • No drug interaction studies were conducted. The applicant has agreed to a postmarketing commitment to evaluate the impact of the product on metabolism of CYP substrates. • There is no data on the use of ixekizumab in pregnant women. In non-clinical reproductive toxicity study in cynomolgus monkeys, four neonatal deaths occurred following treatment of the pregnant females. Two postmarketing studies are recommended to address the risk of fetal exposure to ixekizumab.	The safety profile of ixekizumab has been adequately characterized. At this time, the safety profile appears similar to secukinumab, the other approved IL 17A antagonist, and favorable compared to other systemic products intended to treat moderate-to-severe psoriasis such as methotrexate, cyclosporine, or the TNF antagonists, which present a risk for malignancy. Methotrexate and cyclosporine also present risk for specific organ toxicities such as hepatotoxicity, pulmonary fibrosis, and nephrotoxicity. The safety profiles for all of the approved therapies are informed by post marketing data, which is not (yet) the case for ixekizumab; however in light of the mechanism of action of ixekizumab and the premarket safety database it is unlikely that postmarketing exposure will identify risks for malignancy or specific organ toxicities of a magnitude that would alter the risk-benefit conclusion. Nonetheless, a postmarketing safety study to assess for risks of malignancy, serious infections, cardiovascular events, autoimmune disease and neurologic or demyelinating disease is recommended, in addition to the postmarketing studies to assess the risk of fetal exposure.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The following PMRs (1-4) and PMC (5) are recommended: 1. PK, safety and activity study in pediatric subjects 6 to <18 years of age with moderate-to-severe psoriasis (with a duration of exposure to ixekizumab of at least one year). 2. An observational study in pregnant women with moderate-to-severe psoriasis using claims or electronic medical record data designed as a retrospective cohort study or as a case-control study to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births in women exposed to TALTZ during pregnancy compared to an unexposed control population. 3. Conduct a prospective registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to TALTZ during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. 4. Conduct a prospective, observational study to assess the long-term safety of ixekizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary	Prescription labeling, patient labeling (including Medication Guide) and routine pharmacovigilance, in conjunction with the post marketing requirements, are adequate to manage the risks of the product. Prescription labeling adequately addresses the potential risks with ixekizumab use, as well as the lack of data for human pregnancy exposure. A Medication Guide is appropriate to help prevent serious adverse reactions and to inform patients of potential risks. In addition, Instructions for Use (IFU) for each presentation are appropriate. PMRs and PMC address remaining data needs, which do not preclude determination of safety and effectiveness in adults with moderate-to-severe plaque psoriasis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and secondary outcomes. For the ixekizumab-exposed and comparator(s), clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment. Provide progress updates on observational study patient accrual and demographic summary data in your Annual Report, and provide observational study safety data in your Periodic Benefit-Risk Evaluation Reports (PBERs), for the reporting period as well as cumulatively, and the complete final study report. 5. Conduct a clinical trial to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab Labeling: Prescription labeling adequately addresses the risks identified during product development, as well as the lack of data from human pregnancy exposure. A Medication Guide was proposed, as well as Instructions for Use for each presentation; these components of patient labeling are appropriate to help prevent serious adverse reactions and inform patients of potential risks. A REMS is not recommended. Secukinumab, the precedent product in the class, has a similar approach to post-marketing risk management (prescription and patient labeling, no REMS).	

2. Background

TALTZ (ixekizumab) injection is a solution, intended for subcutaneous administration via prefilled syringe or autoinjector, for which the applicant seeks licensure under Section 351 of the PHS Act and approval under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the indication of treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Ixekizumab is a humanized immunoglobulin G subclass-4 κ monoclonal antibody that is an antagonist of 17A (IL-17A), a member of the IL-17 family (IL-17A through IL-17F) and a normally occurring pro-inflammatory cytokine that has been implicated in the pathogenesis of psoriasis. Ixekizumab is not currently marketed in the US or other jurisdictions for any indication. Ixekizumab will be the second product in the class of humanized IL-17A antagonists. The proposed dose is 160 mg subcutaneously on day 0 (two 80 mg injections) followed by 80 mg on weeks 2, 4, 6, 8, 10 and 12, and then 80 mg every 4 weeks thereafter.

Psoriasis is chronic inflammatory disease characterized by circumscribed erythematous, scaly plaques on the skin. Sites of predilection include scalp, sacrum, umbilical area, and extensor surfaces of the limbs. Involvement is typically symmetrical. Nail involvement may occur, manifested as onycholysis, subungual hyperkeratosis, nail plate pitting, oil spots or salmon patches. As a result of the isomorphic response (Koebner's phenomenon), lesions may appear at sites of minor trauma, such as the elbows and knees. Associated comorbidities include psoriatic arthritis, other autoimmune inflammatory diseases, coronary artery disease, metabolic syndrome, obesity and depression. For mild to moderate disease, therapeutic options include topical corticosteroids and topical tazarotene. For moderate to severe disease, therapeutic options include phototherapy; small molecule drugs such as apremilast, methotrexate, cyclosporine, and acitretin; and systemic biologic products such as secukinumab, ustekinumab, adalimumab, etanercept and infliximab.

3. Product Quality

The drug substance, ixekizumab, is a humanized IgG4 κ monoclonal antibody that binds IL-17A and is expressed in a recombinant CHOK1SV cell line. Ixekizumab is composed of two identical light chain polypeptides and two identical heavy chain polypeptides with an estimated weight (b) (4). The drug substance is manufactured by Eli Lilly in Dunderrow, Ireland; the site was classified NAI at both the pre-license inspection and three pre-license inspections for other products. Dr. Maria Cecilia Tami found that the manufacture of the drug substance is well-controlled and leads to a product that is pure and potent, free of adventitious infectious agents, and consistent across multiple production runs. The conditions used in manufacturing have been sufficiently validated.

The drug product proposed for marketing is a colorless to yellowish (b) (4) solution for subcutaneous injection, with the following composition:

Ingredient	Function	Quantity (mg) per syringe
Ixekizumab	Active ingredient	80
Sodium citrate dihyddrate	(b) (4)	5.11
Citric acid anyhydrous		0.51
Sodium chloride		11.69
Polysorbate 80		0.30
Water for injection	(b) (4)	

Source: derived from BLA 125521

The primary container closure for the drug product is a 1mL glass syringe barrel with a27G 1/2inch needle with shield and (b) (4) plunger. This (b) (4) syringe is then further assembled to either prefilled syringe or autoinjector. Two year stability data for the (b) (4) syringe support two year expiry fort the prefilled syringe and autoinjector. Dr. Xi Di found that the manufacturing process for the drug product was adequately controlled and produces a product that is well-characterized.

The applicant's request for categorical exclusion from the requirement to prepare an environmental assessment was found acceptable by Dr. Xi Di, the drug product reviewer, as the TALTZ is a protein product that will be broken down in the environment.

Dr. Tami found the assays used to detect antidrug antibodies suitable for use in clinical studies.

Dr. Colleen Thomas found microbial control of the drug product manufacturing process to be adequate for drug product sterility assurance, and recommended two post-marketing commitments for supportive data. Dr. Bo Chi found the drug substance manufacturing to be adequate from a quality microbiology perspective.

Wayne Seifert found all facilities involved in the production and testing of TALTZ to be compliant with FDA cGMP regulations.

The device components for the PFS and AI, neither of which are cleared devices, snap around the semifinished syringe without contact with the drug product. Dr. Raki Dalal found that the device components for the prefilled syringe and autoinjector utilized design control consistent with 21 CFR 80.30, and he recommended approval of the BLA from a device perspective.

Carton and container labels, reviewed by Dr. Jabril Abdus-Sabad, were found acceptable.

4. Nonclinical Pharmacology/Toxicology

Ixekizumab was found to bind specifically to human IL-17A but not with the other members of the IL-17 family (IL-17B through IL-17F). Ixekizumab bound to IL-17A from humans and cynomolgus monkeys with similar affinity (b) (4), but binding affinity was lower ((b) (4) rabbit) or absent (mouse, rat) with IL-17A from other species. The applicant conducted the nonclinical repeat dose toxicity and reproductive toxicity studies in cynomolgus monkeys.

The applicant conducted 8-week (0, 5, 15 and 50 mg/kg)and 9-month (0, 0.5, 5, and 50 mg/kg) repeat-dose toxicity studies in cynomolgus monkeys. Safety pharmacology evaluations of cardiovascular, respiratory and central nervous system functions found no effect at any dose in either study. In the 8-week study, 50 mg/kg was considered the no observed adverse effect level (NOAEL) for this study. In the 9-month study, one monkey in the 5 mg/kg group died after the 20th week injection, but the death was not determined to be product-related. One monkey in the 50mg/kg group developed injection site reactions, which were considered product-related; thus 5 mg/kg was considered the NOAEL for the 9-month study. No remarkable effect was identified on peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, total B cells, natural killer cells, and helper-to-cytotoxic T cell ratio) or natural killer cell assay data.

No genetic toxicology studies were conducted with ixekizumab, consistent with ICH S6 (Guideline for the Safety Evaluation of Biotechnology-Derived Pharmaceuticals) guideline.

The applicant supplied literature to address carcinogenic risk, which identifies that IL-17A appears to have a promoter role based on its expression in various tumor types, pro-inflammatory effect, and promotion of angiogenesis. Dr. Jill Merrill concluded that the literature data overall, while mixed, suggests that IL-17A antagonism by ixekizumab is expected to produce a less favorable environment for tumor growth.

Reproductive toxicity studies conducted in cynomolgus monkeys revealed no impact on fertility or fetal development. In a pre- and post-natal development study, although no effect of ixekizumab was identified on the pregnant females or the developing conceptus, four neonatal deaths occurred. These findings are proposed for inclusion in section 8.1 of labeling.

There are no outstanding nonclinical pharmacology or toxicology issues. Dr. Jill Merrill recommended approval of the application from a nonclinical pharmacology/toxicology perspective.

5. Clinical Pharmacology

TALTZ (ixekizumab) for injection is a recombinant humanized IgG4 monoclonal antibody specific for IL-17A, a pro-inflammatory cytokine involved in immune responses. Ixekizumab binds to IL-17A but not to other members of the IL-17 family. For the treatment of psoriasis, ixekizumab is intended to be administered by subcutaneous injection at a dose of 160 mg for the first dose, 80 mg every two weeks for weeks 2 through 12, inclusive, and then 80 mg every four weeks (week 16 and following). The applicant intends to market two presentations: a pre-filled syringe (PFS) and an auto-injector (AI).

The formulation and strength (80mg/mL solution) used in the three pivotal phase 3 trials (RHAZ, RHBA, RHBC) is the same as the proposed commercial formulation. Two lyophilized formulations (20mg/vial and 48mg/vial) were used in early phase studies. The PFS presentation was used in the three pivotal trials. The PFS and AI were used and

compared in an open-label phase 3 trial, RHBL. The AI incorporates the PFS with no direct interaction with the product.

In Study RHAJ, a phase 2 dose-ranging and efficacy study, the applicant evaluated doses from 10 to 150mg (administered on weeks 0, 2, 4, 8, 12 and 16). In the pivotal trials RHAZ, RHBA and RHBC, the applicant evaluated two initial 12-week regimens (80mg q2wk and 80mg q4wk) following an initial dose of 160mg at week 0, followed by two maintenance regimens (80mg q4wk and 80mg q12wk).

Ixekizumab exposure increased proportionally with doses from 5 to 160mg. Following a single subcutaneous dose of 160mg in subjects with psoriasis (study RHBL), the time to reach peak plasma concentration was approximately 4 days; C_{max} (±SD) was 16.2 ±6.6 mcg/mL. Steady state was achieved by week 8 following the 160 mg starting dose and 80 mg every 2 weeks dosing regimen, with 80% achieved following the initial 160mg dose. The steady state concentration (±SD) was 9.3 ±5.3 mcg/mL. Steady-state concentrations were achieved approximately 10 weeks after switching from the 80 mg every 2 weeks dosing regimen to the 80 mg every 4 weeks dosing regimen at Week 12. The mean ±SD steady-state trough concentration was 3.5 ±2.5 mcg/mL. The average estimated bioavailability after SC injection was 60-81%. Exposure was slightly higher following administration in the thigh compared to the arm or abdomen. Total volume of distribution at steady state was 7.11L.

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

Body weight inversely impacted ixekizumab exposure, with lower serum exposure in subjects weighing more than 100kg compared to those weighing either 80 to 100kg or less than 80kg. Age, sex and race were not identified to have a significant impact on exposure. The impact of renal and hepatic impairment were not formally evaluated, but are expected to have little impact based on knowledge of IgG antibodies.

A thorough QT study was not conducted. Ixekizumab is an IgG antibody, and its size precludes interference with repolarization.

No formal drug-drug interaction studies were conducted. A postmarketing commitment to evaluate the impact of the product on metabolism or pharmacokinetics of CYP substrates is recommended.

The clinical pharmacology reviewers found that the dose-/exposure-response relationships for efficacy and safety supported the proposed dosing regimen. Although higher body weight correlated with lower response on the primary endpoint, body weight was not a significant covariate for explaining differences in the primary endpoint based on exposure-response analysis. Thus no dose adjustment was recommended.

In the pivotal trials, approximately 22% of subjects treated with ixekizumab at the proposed dose developed anti-drug antibodies over the 60-week course of the trials; 9% of subjects

treated with ixekizumab at the proposed dose developed ADA during the initial 12-week dosing period (160mg followed by 80mg q2wk). Of the subjects with ADA, 10% developed neutralizing antibodies. Higher titers of ADA (≥160) and neutralizing antibodies were associated with decreased drug concentration and reduced efficacy.

The Clinical Pharmacology/Biopharmaceutics reviewers, Dr. Jie Wang and Dr. Dhananjay Marathe, found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended Approval from a clinical pharmacology/biopharmaceutics perspective.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical - Efficacy

The applicant submitted data from three pivotal trials, RHAZ, RHBA and RHBC, to establish the effectiveness of their product in the treatment of psoriasis. Though not identical in design, each of these trials were international, multi-center, prospective, randomized, double-blind, placebo-controlled, parallel group studies that investigated two dosage regimens (160 mg at week 0 followed by either 80 mg q2 weeks or 80mg q4 weeks) in the initial 12-week dose period; studies RHBA and RHBC included an active comparator during weeks 0 to 12. In studies RHAZ and RHBA, responders at week 12 were re-randomized to one of two dose regimens (80mg q4wks or 80mg q12wks) or placebo during weeks 13 to 60; study RHBC was open label from week 13 onward.

The studies enrolled similar populations: subjects 18 years and older with plaque psoriasis with ≥10% body surface area (BSA) involvement, a score on the static Physicians Global Assessment (sPGA) of ≥3, and a score on the Psoriasis Area Severity Index (PASI) of ≥12. Per the protocols, subjects were allowed to use low-potency corticosteroids to the face, axillae and groin, in addition to study drug. In study RHAZ, randomization was stratified by geographic region (North America or Other), previous non-biologic systemic therapy (inadequate response to, intolerance to, or contraindication to <3 or ≥3 conventional systemic therapies) and weight (<100 kg or ≥100 kg). In studies RHBA and RHBC randomization was stratified by investigational center.

Primary efficacy measures included sPGA and PASI. Secondary measures included Itch Numeric Rating Scale (NRS), percent BSA involvement, Nail Psoriasis Severity Index (NAPSI), scalp psoriasis severity index, palmoplantar psoriasis severity index, and Dermatology Life Quality Index (DLQI). The primary timepoint was week 12. For all three

studies, the pre-specified co-primary endpoints were the proportion of subjects achieving a sPGA score of 0 or 1 and the proportion of subjects achieving a seventy-five percent reduction from their baseline PASI score (PASI-75), and the pre-specified secondary endpoints included sPGA of 0, PASI-90, and PASI-100. For studies RHAZ and RHAC, additional prespecified secondary endpoints included proportion of subjects who achieved ≥4-point reduction in Itch NRS score from baseline, change from baseline in DLQI and change from baseline in NAPSI.

The results for the primary and key secondary endpoints at twelve weeks are presented below:

Endpoints	**Trial RHAZ**			**Trial RHBA**			**Trial RHBC**		
	TALTZ 80 mg			**TALTZ 80 mg**			**TALTZ 80 mg**		
	Q2W N=433	**Q4W N=432**	**Placebo N=431**	**Q2W N=351**	**Q4W N=347**	**Placebo N=168**	**Q2W N=385**	**Q4W N=386**	**Placebo N=193**
Co-Primary:									
sPGA of 0 or 1	82%	76%	3%	83%	73%	2%	81%	75%	7%
PASI-75	89%	83%	4%	90%	78%	2%	87%	84%	7%
Secondary:									
sPGA of 0	37%	34%	0%	42%	32%	1%	40%	36%	0%
PASI-90	71%	65%	1%	71%	60%	1%	68%	65%	3%
PASI-100	35%	34%	0%	40%	31%	1%	38%	35%	0%
≥ 4-point reduction in Itch NRS from baseline	336/391 (86%)	305/379 (80%)	58/374 (16%)	258/303 (85%)	225/293 (77%)	19/135 (14%)	264/320 (83%)	250/313 (80%)	33/158 (21%)

Source: Statistical Review and Evaluation, BLA 125521, Matthew Guerra, PhD; archived 11/3/2015, p 3.

In all three studies, both ixekizumab dose regimens were statistically superior (p-values < 0.001) to placebo for the co-primary endpoints as well as for the key secondary endpoint presented above.

Studies RHBA and RHBC included an etanercept comparator arm. Subjects randomized to the comparator arm at US sites received US-licensed etanercept, whereas subjects at non-US sites largely received EU-approved etanercept. The applicant did not provide an adequate bridge to allow reliance on the data from the EU-approved product; labeling will include information only from the US sites. Selected results from RHBA and RHBC for the co-primary endpoint at week 12 are presented in the table below:

	RHBA			RHBC		
	TALTZ q2wk	Etanercept	Placebo	TALTZ q2wk	Etanercept	Placebo
sPGA 0/1	73 (70%)	24 (22%)	0 (0%)	105 (74%)	46 (32%)	4 (6%)
PASI-75	89 (86%)	36 (32%)	0 (0%)	124 (88%)	68 (47%)	6 (9%)

Source: derived from Review and Evaluation, BLA 125521, Matthew Guerra, PhD; archived 11/3/2015, pp25-26.

To evaluate maintenance of response, in studies RHAZ and RHBA, two dose regimens were evaluated from weeks 13 to 60. Subjects who were responders (sPGA 0/1) at week 12 were re-randomized to receive either ixekizumab 80mg q4wks, ixekizumab 80mg q12wks, or

placebo. The results for those subjects who were treated with the dose regimen proposed for marketing (80mg q2wks initially followed by 80mg q4wks after week 12) are presented in the table below:

	RHBA		RHBC	
	TALTZ q2wk/q4wk	TALTZ q2wk/Placebo	TALTZ q2wk/q4wk	TALTZ q2wk/Placebo
sPGA 0/1 wk 60	89/117 (75%)	9/117 (8%)	47/62 (76%)	6/86 (7%)

Source: derived from Review and Evaluation, BLA 125521, Matthew Guerra, PhD; archived 11/3/2015, p23.

The reader is referred to the reviews of Dr. Matthew Guerra and Dr. Jane Liedtka for further information and additional analyses, including post hoc explorations of the data and sensitivity analyses. Both Dr. Guerra and Dr. Liedtka concluded that the data support a determination of efficacy.

I conclude that the applicant provided substantial evidence of effectiveness of ixekizumab for the indication of treatment of moderate-to-severe psoriasis. In each of three adequate and well-controlled trials, two of which also include an active comparator arm, a significantly greater proportion of subjects that received ixekizumab demonstrated success on the co-primary endpoint of sPGA of 0 or 1 and PASI-75 compared to placebo, as well as on the more stringent secondary endpoints of sPGA of 0, PASI-90 and PASI-100.

8. Safety

The overall safety database in psoriasis, comprised of subjects with psoriasis who receive any dose of ixekizumab, consisted of 4204 subjects, of which 2190 were treated for over one year. The primary safety database for psoriasis, comprised of pooled data from the placebo-controlled Phase 3 trials (RHAZ, RHBA and RHBC for weeks 0-12, and RHAZ and RHBA for weeks 13-60) for subjects who received the proposed dose for marketing, consisted of 1167 subjects who received TALTZ and 791 subjects who received placebo during weeks 0-12. Three hundred and thirty two subjects received the proposed dose of TALTZ during weeks 13-60. The size of the safety database is adequate to characterize adverse events.

In the psoriasis development program, ten deaths were reported: eight in ixekizumab-exposed subjects, one in an etanercept-exposed subject, and one in a subject prior to randomization. Of the eight ixekizumab exposed-subjects, the causes of death included cardiovascular event (5 subjects), cerebrovascular event (1 subject), accidental (1 subject), and unknown (1 subject). The time-adjusted rates of serious and non-serious adverse events (per subject-year) were similar across both ixekizumab-exposed and placebo-exposed groups. The most frequently reported adverse reactions were injection site reactions, upper respiratory tract infections, nausea and tinea infections. Neutropenia and thrombocytopenia were more common in subjects in the TALTZ group compared to placebo group; were generally low grade and transient, and were not associated with clinical sequelae (infection or bleeding, respectively).

Infections occurred more frequently in TALTZ-exposed subjects compared to placebo-exposed subjects, although the rates of serious infections were low and similar across both groups. Noninvasive candidiasis was seen in approximately 3% of subjects who received ixekizumab; no cases of invasive candida infection were observed. Subjects were screened for active tuberculosis (TB) prior to enrollment; no cases of active TB developed during the development program. Labeling recommends evaluation for TB prior to treatment initiation.

Serious hypersensitivity, including urticaria and angioedema, occurred infrequently in subjects who received in ixekizumab. Hypersensitivity is expected with a protein product, and is addressed in labeling.

New-onset and exacerbation of inflammatory bowel disease occurred more frequently in subjects exposed to ixekizumab (Crohn's disease 0.1%, ulcerative colitis 0.2%) than placebo. This is addressed in labeling.

Suicidality and neuropsychiatric adverse events were carefully evaluated in light of a potential signal for suicide in the development program of a related drug, brodalumab, an IL-17 receptor antagonist. In the ixekizumab psoriasis development program, ten suicide attempts were reported among subjects who received ixekizumab (0.15 per 100 subject-years) and one among subjects who received placebo (0.55 per 100 subject-years); there were no completed suicides in either group. C-CASA analysis was requested but did not identify additional cases of suicidality. Drs. Gabriella Anic and Andrew Mosholder of Division of Epidemiology noted that the exposure-adjusted rate for suicide behavior for ixekizumab was similar to that for brodalumab (0.14 per 100 patient-years) but lower than that for apremilast (0.20 per 100 patient-years) and infliximab (0.24 per 100 patient-years). Dr. Gregory Dubitsky, team leader in the Division of Psychiatry Products, concluded that the clinical trial data did not support a causal link between ixekizumab exposure and suicidality.

Pregnant women were excluded from enrollment in studies during the development program. As a result, there is not human data about the impact of ixekizumab on fetal development. Dr. Leyla Sahin of the Maternal Health Team recommended two post-marketing requirements to address the informational needs regarding pregnancy exposure: a prospective pregnancy registry, and a second study of different design, such as a retrospective cohort study or case-control study.

The reader is referred to the clinical review by Dr. Jane Liedtka for a full review of the safety data.

9. Advisory Committee Meeting

No advisory committee meeting was held, as the application for this second-in-class IL17A antagonist did not present novel issues which merited advisory committee input.

10. Pediatrics

The applicant requested a waiver for study of children 0 through 5 years of age for the reason that studies would be impossible or highly impracticable, and a deferral for study of children 6 to <18 years of age for the reason that the application is ready for approval in adults.

Although additional studies are needed to establish the safety of TALTZ in children prior to extension of the indication to the pediatric age group, the efficacy of TALTZ can be extrapolated from adult data. Psoriasis vulgaris occurs in both children and adults, and although the disease prevalence varies with age, the pathophysiology is understood to be the same across all ages. Additionally, there are not known age-related factors that would make the disease either more or less responsive to treatment in pediatric patients (although there are unique factors in children that may increase their risk for adverse events, or increase the significance of those adverse events should they occur). Therefore it is scientifically appropriate to extrapolate efficacy from the adult population to the pediatric population, but the systemic safety of the product will need to be established for the pediatric age group 6 to <18 years of age.

The applicant initially proposed to conduct two pediatric studies in subjects with psoriasis:

- a PK/ dose-ranging study in subjects ages 6 to <18 years and
- a clinical safety and activity study in subjects ages 6 to <18 years

The applicant subsequently requested to combine the two studies into a single study; this is reasonable.

The application was presented to the Pediatric Review Committee (PeRC) on January 27, 2016. PeRC agreed with the applicant's requests for waiver of studies in children younger than six years of age, and deferral of studies in children 6 to <17 years of age.

The proposed study is recommended as post-marketing requirements under PREA.

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted

12. Labeling

All components of labeling were reviewed.

The proposed proprietary name, TALTZ, was found acceptable from a safety and misbranding perspective.

The carton and container labels were acceptable

The package insert conforms to the Physicians Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Prescription status, product labeling (including a Medication Guide), and routine pharmacovigilance are sufficient to address the post-marketing safety of the product. A REMS was not proposed, and is not recommended.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Postmarketing Requirements under PREA:

1. Conduct a PK, safety and activity study in pediatric subjects 6 to <18 years of age with moderate-to-severe psoriasis (with a duration of exposure to ixekizumab of at least one year).

Final Protocol Submission:	03/2017
Study/Trial Completion:	09/2021
Final Report Submission:	03/2022

Postmarketing Requirements under Section 505(o):

2. Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to ixekizumab and a non-ixekizumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy..

Final Protocol Submission:	09/2016
Study Completion:	12/2021
Final Report Submission:	06/2022

3. Conduct a prospective registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to TALTZ during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Final Protocol Submission: 04/2017
Study Completion: (b) (4)
Final Report Submission:

4. Conduct a prospective, observational study to assess the long-term safety of ixekizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the ixekizumab-exposed and comparator(s), clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment. Provide progress updates on observational study patient accrual and demographic summary data in your Annual Report, and provide observational study safety data in your Periodic Benefit-Risk Evaluation Reports (PBERs), for the reporting period as well as cumulatively, and the complete final study report.

Final Protocol Submission: 04/2017
Study Completion: (b) (4)
Final Report Submission:

Postmarketing Commitments:

Reportable:

5. Conduct a clinical study to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab
Final Protocol Submission: 08/2016
Study/Trial Completion: 01/2018
Final Report Submission: 05/2018

Not reportable:

6. Perform a repeat microbial retention study for the (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation, or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.

Study/Trial Completion: 11/2016
Final Report Submission: 12/2016

7. Provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance. The hold time study should include the maximum hold time at (b) (4) followed by the maximum hold time under ambient conditions. Provide data from two additional commercial drug product batches to support the maximum hold time for drug product prior to (b) (4). The supporting data should include bioburden and endotoxin testing results from samples (b) (4) (b) (4). Data from process simulations performed with media may be provided in lieu of data from drug product batches.

Study/Trial Completion: 11/2016
Final Report Submission: 12/2016

14. Recommended Comments to the Applicant

None.

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

/s/

JILL A LINDSTROM
03/18/2016