CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s000

SUMMARY REVIEW

Acting Division Director Summary Review

Date	(electronic stamp)
From	Jill A Lindstrom, MD
Subject	Acting Division Director Summary Review
BLA #	761055
Applicant	Regeneron Pharmaceuticals, Inc
Date of Submission	29 July 2016
PDUFA Goal Date	29 March 2016
Proprietary Name / Non-Proprietary Name	Dupixent dupilumab
Dosage Form(s) / Strength(s)	Injection / 150mg/mL
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical (b) (4)
Recommended Action for NME:	*Approval*
Recommended Indication/Population(s)	Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Carr, MD
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Renqin Duan, PhD
OPQ Review	Gunther Boekhoudt, PhD (DS, DP); Lakshmi Narasimhan, PhD (DP micro); Maria Jose Lopez-Barragan, PhD (DS micro); Wayne Seifert (facilities); Jibril Abdus-Samad, PhD (labeling); Melinda Bauerlein (RBPM), Truong Quach (RBPM)
Clinical Pharmacology Review	Jie Wang, PhD; Luke Oh, PhD; Luning Zhuang, PhD
Project Management	Matthew White
Labeling	Nancy Xu, MD
OPDP	Silvia Wanis, PharmD, CPH
OSI	Roy Blay, PhD
CDTL Review	Snezana Trajkovic, MD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
OSE/DRISK	Robert Pratt, PharmD
DMPP	Morgan Walker, PharmD, MBA, CPH
CDRH	Sapana Patel, PharmD
CDRH/OC/DMQ	Crystal Lewis

CBER/DVRPA	Madan Kumar, DO
DPMH	Christos Mastroyannis, MD
COA	Ebony Dashiell-Aje, PhD

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
OSE= Office of Surveillance and Epidemiology
DPV= Division of Pharmacovigilance
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP=Division of Medical Policy Programs
COA=Clinical Outcome Assessment Staff

Appears this way on original

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that predominantly affects the children but also occurs in adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, excoriations, and lichenification. The face and flexures are areas of predilection. Pruritus is the primary symptom. AD is associated with multiple comorbidities, and impairs both individual and family quality of life. DUPIXENT (dupilumab) Injection, 150mg/mL, is intended for subcutaneous administration via prefilled syringe for treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, (b) (4) or (b) (4) not advisable. Dupilumab, the active ingredient in DUPIXENT, is human IgG4 κ monoclonal antibody that binds interleukin-4 receptor α chain (IL-4Rα) resulting in inhibition of both IL-4 and IL-13 signaling.

Treatment for AD begins with non-pharmacologic measures such as bathing practices and moisturizers, proceeds to topical drug products such as corticosteroids or calcineurin inhibitors, and, for patients who do not respond to optimized topical therapy, may involve phototherapy or systemic drug treatment. Systemic treatments include corticosteroids, which are FDA-approved for this use, and immunosuppressant drugs such as cyclosporine, azathioprine, methotrexate and mycophenolate mofetil, which are used off-label. These systemic drug products have an array of significant adverse reactions including infections, malignancies, solid organ (liver, kidney, intestine) toxicities, impairment of vaccine responses and reduction in blood counts. Additionally, there is limited information on the effectiveness of these products in the treatment of AD. Because of these limitations, patients with moderate to severe AD not responsive to optimized topical therapy need additional therapeutic options with demonstrated efficacy and a favorable safety profile.

Three pivotal trials (1334, 1416 and 1224), similar in design, enrolled adult subjects with chronic AD with ≥10% body surface area (BSA) involvement, a score of >3 on the Investigator Global Assessment (IGA), and a score on the Eczema Area Severity Index (EASI) of >16, average score for maximum itch intensity ≥3 on the Pruritus Numerical Rating Scale (NRS), and documented history of an inadequate response to (or medically inadvisable to use) topical treatment. The primary efficacy endpoint was the proportion of subjects with both an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16. A significantly greater proportion of subjects in the dupilumab groups achieved success compared to the placebo group; the magnitude of the treatment effect was 27-28% for both dosage regimens across all three studies.

The safety database was adequate to characterize the safety profile of DUPIXENT. Two thousand five hundred and twenty six subjects were exposed to any dose of dupilumab, 739 of whom were treated for more than one year. In the two monotherapy pivotal trials and the relevant arm of a phase 2 trial, 529 subjects received the proposed dose of dupilumab for 16 weeks. Frequently reported adverse reactions included injection site reactions, conjunctivitis and oral herpes. Serious hypersensitivity occurred infrequently, including one case each of serum sickness and

serum sickness-like reaction, both of which were associated with high titers of anti-drug antibodies. These risks are addressed in product labeling.

Prescription and patient labeling and routine pharmacovigilance are adequate to manage the risks of DUPIXENT in the post market milieu; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Recommended post marketing studies include pediatric pharmacokinetic studies and safety and efficacy trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that affects children (predominantly) and adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, and lichenification. The face and flexures are areas of predilection. Pruritus is invariably present and xerosis is common. • In the US, overall prevalence has been reported as 6% and prevalence in children as 11%. Disease onset is typically in childhood: 60% of patients develop skin manifestations by 1 year of age and 85% by five years of age. Of those who develop AD in childhood, in approximately one third the disease will persist into adulthood. Approximately one half of patients report moderate disease and one fifth report severe disease. • Comorbidities include sleep impairment (associated with behavioral deficits and neurocognitive impairment), asthma, allergic rhinitis, food allergies, cutaneous infections, extracutaneous infections, and various psychiatric comorbidities. • Quality of life is impaired for both patients and their families.	Atopic dermatitis is an inflammatory skin disease with significant impact on patients and their families due the cutaneous manifestations, accompanying pruritus, co-morbidities, and impairment of quality of life.
Current Treatment Options	• Available therapy for AD includes i) non-pharmacologic measures such as bathing practices, moisturizers and device creams; ii) topical drugs such as corticosteroids and calcineurin inhibitors, and iii) phototherapy and systemic products such as corticosteroids for	There is a clear need for therapeutic options for patients with moderate to severe atopic dermatitis that is inadequately managed by optimized topical therapy. Although there are

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	injection and various immunosuppressant drugs used off-label. This therapeutic approach is loosely hierarchical in that treatment often begins with non-pharmacologic measures and sequentially adds, depending on response and disease severity, topical corticosteroids, topical calcineurin inhibitors, and either phototherapy or systemic agents. • American Academy of Dermatology (AAD) Guideline recommends systemic therapy for "…patients in whom optimized topical regimens do not adequately control the signs and symptoms of disease…" and for "…patients whose medical, physical, and/or psychological states are greatly affected by their skin disease…." Systemic therapies include corticosteroids, cyclosporine, azathioprine, methotrexate and mycophenolate mofetil, off which all but corticosteroids are used off-label. • Systemic corticosteroids (oral and parenteral) are approved for control of severe or incapacitating AD, but labeling contains no clinical trial data on efficacy. Concomitant use of live vaccines is contraindicated, and vaccine responses may be impaired. Labeled warnings include growth impairment, osteoporosis, hypothalamic-pituitary-adrenal axis suppression, infections, insomnia, depression, psychosis, cataracts, and glaucoma. AAD Guidelines recommend avoidance other than for short-term use as other systemic therapies are being initiated. • Cyclosporine—not approved for AD, but used off-label and included in AAD Guidelines. Risks include decreased vaccine efficacy, malignancies, infections, hypertension, nephrotoxicity and structural renal damage. • Azathioprine—not approved for AD, but used off-label and included in AAD Guidelines. Risks include malignancies, leukopenia, thrombocytopenia, anemia, pancytopenia, serious infections, nausea,	off-label treatments, efficacy data is lacking and they are associated with multiple serious adverse reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	vomiting, gastrointestinal hypersensitivity reaction, and teratogenicity. • Methotrexate—not approved for AD, but used off-label and included in AAD Guidelines. Risks include reduced vaccine efficacy, hepatotoxicity, lymphoma, cytopenias including pancytopenia, interstitial pneumonitis, gastrointestinal distress including hemorrhagic enteritis and perforation, TEN/SJS, nephrotoxicity/acute renal failure, teratogenicity and fetal death. • Mycophenolate mofetil—not approved for AD, but used off-label and included in AAD Guidelines. Risks include reduced vaccine efficacy, malignancy, lymphoma, serious infections, teratogenicity and fetal death, cytopenias, TEN/SJS, diarrhea and ulcerative stomatitis.	
Benefit	• Three pivotal trials (1334, 1416 and 1224), similar in design, enrolled adult subjects with chronic AD with ≥10% body surface area (BSA) involvement, a score of ≥3 on the Investigator Global Assessment (IGA) which rated erythema and induration/papulation, and a score on the Eczema Area Severity Index (EASI) of ≥16, and average score for maximum itch intensity ≥3 on the Pruritus Numerical Rating Scale (NRS), and documented history of an inadequate response to (or medically inadvisable to use) topical treatment. Subjects were randomized to receive placebo or dupilumab injection at one of two dosages (600 mg at Week 0 followed by either 300mg qwk or 300mg q2wk) in the initial 16-week dose period; subjects in Study 1224 used concomitant topical corticosteroids and continued in their respective arms and dose regimens (dupilumab 300mg qwk, dupilumab 300mg q2wk, or placebo) to Week 52. The primary efficacy endpoint was the proportion of subjects with both an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16. A significantly greater proportion of subjects in the dupilumab groups achieved success	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, and demonstrated efficacy for dupilumab injection.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to the placebo group; the magnitude of the treatment effect was 27-28% for both dosage regimens across all three studies.	
Risk	• The overall safety database in AD, based on subjects with AD who received any dose of dupilumab, includes data from 2526 subjects, 739 of whom were treated for more than one year. The pooled data from the monotherapy pivotal studies 1334 and 1416 and the relevant arms from the Phase 2 study 1026, includes data from 1567 subjects, of whom 529 received the proposed dose and 517 received placebo. The size of the safety database is adequate to characterize adverse events. • Frequently reported adverse reactions include injection site reactions, conjunctivitis, and oral herpes. • Serious hypersensitivity occurred, including serum sickness and serum sickness-like reaction in one subject each; the latter two reactions were associated with high levels of anti-drug antibodies (ADA). The risk for hypersensitivity reactions is addressed in labeling.	The safety profile of dupilumab injection has been adequately characterized. The most significant risk is for hypersensitivity; common adverse reactions include injection site reactions, conjunctivitis, and oral herpes.
Risk Management	• Labeling: Prescription labeling adequately addresses the risks identified during product development. Patient labeling, including a Patient Package Insert and Instructions for Use, was proposed; patient labeling is appropriate to inform patients about the risk for hypersensitivity and ocular adverse events, as well as to inform use of the device (PFS or PFS with needle shield). • A REMS is not recommended.	Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the risks of the product. Prescription labeling adequately addresses the potential risks with dupilumab use.

2. Background

DUPIXENT (dupilumab) Injection, 150mg/mL, is a solution, intended for subcutaneous administration via prefilled syringe, 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 atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, (b) (4) or (b) (4) not advisable. Dupilumab is human IgG4 κ monoclonal antibody that binds interleukin-4 receptor α chain (IL-4Rα) resulting in inhibition of both IL-4 and IL-13 signaling. Dupilumab is not currently marketed in the US or other jurisdictions for any indication, although it is in development for the treatment of asthma and nasal polyposis, in addition to atopic dermatitis, for which it was granted Breakthrough Therapy status. Dupilumab will be first in the class of interleukin-4 receptor alpha antagonists. The proposed dose for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

AD is a chronic, pruritic inflammatory skin disease that predominantly affects the pediatric population but also occurs in adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, excoriations, and lichenification. The face and flexures are areas of predilection (distribution varies by age), but involvement can be generalized. Xerosis is common. Pruritus is the primary symptom. Associated comorbidities include sleep impairment (associated with behavioral deficits and neurocognitive impairment), asthma, allergic rhinitis, food allergies, cutaneous infections, extracutaneous infections, and various psychiatric comorbidities. In a population-based survey, the prevalence of AD in the US was found to be 6%, of which 30% reported mild disease, 53% moderate disease and 18% severe disease. Disease onset is typically in early childhood; approximately 45% of patients develop skin manifestations by 6 months of age, 60% by one year of age, and 85% by five years of age. Of those who develop AD in childhood, approximately one third will continue to have the disease into adulthood.

The therapeutic armamentarium for AD includes i) non-pharmacologic measures such as bathing practices, moisturizers and device creams; ii) topical drugs such as corticosteroids and calcineurin inhibitors, and iii) phototherapy and systemic products such as corticosteroids for injection and various immunosuppressant drugs used off-label. This therapeutic approach, outlined in the AAD Guideline of Care for atopic dermatitis, is loosely hierarchical in that treatment often begins with non-pharmacologic measures and sequentially adds, depending on response and disease severity, topical corticosteroids, topical calcineurin inhibitors, and either phototherapy or systemic agents. Compliance with topical pharmacologic agents can be challenging due to the time required for application and the cosmetic awkwardness of some preparations (e.g., stickiness, greasiness, messiness).

3. Product Quality

The drug substance, dupilumab, is a human IgG4 κ monoclonal antibody that binds interleukin-4 receptor α chain (IL-4Rα) and is expressed in a recombinant CHO (b) (4) Dupilumab is composed of two identical light

chain polypeptides and two identical heavy chain polypeptides with an average molecular mass of 147 kD. The drug substance is manufactured by Regeneron in Rensselaer, New York; the site was inspected October 31, 2016 to November 5, 2016 and no 483 items were provided. Dr. Gunther Boekhoudt 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 adequately validated.

The drug product proposed for marketing is a clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection, with the composition as described in Table 1:

Table 1: Drug Product Composition

Ingredient	Function	Quantity (mg) per syringe
Dupilumab	Active ingredient	300
L-histidine	(b) (4)	6.2
L-arginine (b) (4) hydrochloride		(b) (4)
Sodium acetate (b) (4)		(b) (4)
Sucrose		100
Polysorbate 80		4
Water for injection		(b) (4)

Source: derived from BLA 761055, 2.3.P, p9.

The primary container closure for the drug product is a 2.25mL glass syringe barrel with a27G 1/2inch staked needle with rigid shield and (b) (4) plunger with (b) (4) (b) (4) This semi-finished syringe is then further assembled to either prefilled syringe (PFS) or prefilled syringe with needle shield (PFS-S). Stability data for the semi-finished syringe support two year expiry for the PFS and PFS-S, and data from the accelerated stability study of the PFS and PFS-S support the claimed out-of-refrigerator time for (b) (4) days at 25° C. Dr. Xuhong Li 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, as dupilimab is a protein product that will be broken down in the environment.

Dr. Cristina Ausin-Moreno found the assays used to detect antidrug antibodies suitable for use in clinical studies.

Dr. Maria Jose Lopez Barragan found microbial control of the drug product manufacturing process to be adequate for drug product sterility assurance. Dr. Lakshmi Rani Narasimhan found the drug substance manufacturing to be adequate from a quality microbiology perspective.

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

The device components for the PFS-S, which is not a cleared device, snap around the semifinished syringe without contact with the drug product. Dr. Sapna Patel found that the device components for the PFS-S utilized design control consistent with 21 CFR 80.30, and she 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

Dupilumab was found to bind specifically to human interleukin 4 receptor alpha (IL-4Rα), resulting in inhibition of both IL-4 and IL-13 signaling. Dupilumab did not bind to the receptor in rodents or non-human primates, so homologous antibodies were used to study the effect of IL-4Rα blockade in these species. The applicant conducted the nonclinical repeat dose toxicity studies in mice and cynomolgus monkeys, a fertility study in mice, and an enhanced pre/post natal toxicity study in cynomolgus monkeys.

The applicant conducted 5-week (IV), 13-week (SC) and 6-month (IV and SC) repeat dose toxicity studies in cynomolgus monkeys, with a high dose of 100 mg/kg/week. No target organ toxicities were identified in any of the studies, and safety pharmacology evaluations of cardiovascular, respiratory and central nervous system functions found no test-article effect. In the 5-week and 13-week studies as well as the SC arm of the 6-month study, 100 mg/kg/week was considered the no observed adverse effect level (NOAEL); in the IV arm of the 6-month study, 25mg/kg/week was the NOAEL.

No genetic toxicology studies were conducted with dupilumab, consistent with ICH S6 Guidance for Industry-Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

The applicant supplied literature to address carcinogenic risk, which identifies that IL 4 and IL 13 activation of the IL-4Rα pathway is protumorigenic based on proliferative and anti-apoptotic effects on tumor cells and activation of immune regulatory cells that suppress tumor immunity. Hence antagonism of the IL-4Rα pathway is unlikely to cause, and may actually reduce, tumor initiation or promotion. Additionally, nonclinical studies did not identify neoplastic or proliferative lesions in the repeat-dose toxicity studies in cynomolgus monkeys. Finally, because dupilumab does not bind to the rodent IL-4Rα subunit, traditional 2-year rodent carcinogenicity studies would need to conducted with the homologous antibody, which would make study interpretation problematic. Dr. Renqin Duan concluded that the data overall suggests that IL-4Rα antagonism by dupilumab is expected to produce a less favorable environment for tumor growth, and did not recommend additional nonclinical studies to evaluate the carcinogenic potential of dupilumab.

Reproductive toxicity studies conducted in mice revealed no impact on fertility parameters. In an enhanced pre- and post-natal development study, no effect of dupilumab was identified on the pregnant females, fetal development or postnatal growth. (b) (4)

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

5. Clinical Pharmacology

Dupilumab is a recombinant human IgG4 monoclonal antibody specific for IL-4Rα which blocks both IL-4 (Type I and Type II) and IL-13 (Type I) signaling. For the treatment of atopic dermatitis, DUPIXENT (dupilumab) injection is intended to be administered by subcutaneous injection at a dose of 600mg (two 300mg injections in different sites) for the first dose, followed by 300mg every other week. The applicant intends to market two presentations: a prefilled syringe (PFS) and a prefilled syringe with needle shield (PFS-S).

The formulation and strength (150mg/mL solution) used in the three pivotal Phase 3 trials (1334, 1416, and 1224) is the same as the proposed commercial formulation; however the drug substance manufacturing process changed. The manufacturing process for the lots used in Phase 3, (b) (4) Analytic and pharmacokinetic studies demonstrated comparability of product across cell lines (C1 vs C2) and process (P1 or P2). The PFS presentation was used in the pivotal trials. The PFS-S presentation, which is also proposed for marketing, incorporates a needle shield with no direct interaction with the drug product.

In Study AD-1021, a Phase 2 dose-ranging and efficacy study, the applicant evaluated various doses (100 mg q4wk, 300mg q4wk, 200mg q2wk, 300mg q2wk, 300mg qwk). In the pivotal trials 1334, 1416, and 1224, the applicant evaluated two dosing regimens of dupilumab (600mg initial dose followed by 300 mg qwk, 600mg initial dose followed by 300mg q2wk) either with (1224) or without (1334, 1416) adjunctive treatment with topical corticosteroids.

Dupilumab exposure increased in a greater than dose-proportional manner, exhibiting nonlinear pharmacokinetics. Following a single subcutaneous dose of 300mg, the time to reach peak plasma concentration was approximately 7 days (range 3 to 14 days), Cmax (±SD) was 34.8 ±17.5 mcg/mL, and bioavailability was estimated to be 64%. Steady state concentrations were achieved by Week 16 following the initial 600mg dose followed by either the 300mg qwk or the 300mg q2wk dose. In the pivotal trials, the mean ±SD steady-state trough concentrations ranged from 73.3 ±40.0 mcg/mL to 79.9 ±41.4 mcg/mL for the labeled dose (600mg followed by 300mg q2wk). The estimated total volume of distribution was 4.6L.

The metabolic pathway of dupilumab was not characterized. As a monoclonal antibody, dupilumab 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 dupilumab exposure, but subgroup analysis of data from the pivotal trials did not demonstrate significant differences in success rates (IGA 0/1) across body weight subgroups. 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. Dupilumab is an IgG antibody, and its size precludes interference with repolarization.

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

In the three pivotal trials, approximately 14% (studies 1334 and 1416, monotherapy) and 10% (study 1224, with concomitant TCS) of subjects treated with DUPIXENT 300mg q2wk developed antibodies to dupilumab (ADA); of these, 18% (studies 1334 and 1416, monotherapy) and 10% (in study 1224, with concomitant TCS) of subjects with ADA had neutralizing antibodies. The presence of ADA was associated with lower serum concentrations of dupilumab, however no correlation with efficacy outcomes was identified (but numbers were small). Two subjects with high titers of ADA each developed a serious adverse event (SAE): serum sickness-like reaction and serum sickness, respectively.

The clinical pharmacology/biopharmaceutics reviewers, Dr. Jie Wang and Dr. Luke Oh, 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 reviewers 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, 1334, 1416 and 1224, to establish the effectiveness of their product in the treatment of atopic dermatitis. Though not all identical in design (studies 1334 and 1416 were identical), each of these trials was international, multi-center, prospective, randomized, double-blind, placebo-controlled, parallel group studies that investigated two dose regimens (600 mg at Week 0 followed by either 300mg qwk or 300mg q2wk) in the initial 16-week dose period; study 1224 included use of concomitant low and mid-potency topical corticosteroids. After Week 16, subjects in studies 1334 and 1416 either continued in a 12 week follow-up period or enrolled in a maintenance study (if eligible) or an extension study; subjects in study 1224 continued in their respective arms and dose regimens (dupilumab 300mg qwk, dupilumab 300mg q2wk, or placebo) to Week 52.

The studies enrolled similar populations: subjects 18 years and older with chronic atopic dermatitis (present at least 3 years) with $\geq$10% body surface area (BSA) involvement, a score on the Investigator Global Assessment (IGA) of $\geq$3, and a score on the Eczema Area Severity Index (EASI) of $\geq$16, and average score for maximum itch intensity $\geq$3 on the Pruritus Numerical Rating Scale (NRS), and documented history of an inadequate response to (or medically inadvisable to use) topical treatment. Per the protocols, subjects were required to apply emollients (moisturizers) twice daily for 7 days prior to screening and throughout the

study. In Study 1224, subjects applied mid- and low-potency topical corticosteroids according to a standardized regimen.

The primary efficacy measure was the IGA, which rated erythema and induration/papulation on a 5-point scale (0=clear to 4=severe disease); key secondary measures were EASI and Pruritus Numeric Rating Scale (NRS). Other secondary measures included percent BSA involvement, Scoring Atopic Dermatitis (SCORAD), Global Inflammatory Signs Scale (GISS), Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM), and Hospital and Anxiety Depression Scale (HADS). The primary timepoint was Week 16. For all three studies, the pre-specified primary endpoint was the proportion of subjects with both an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16. Key secondary endpoints included the proportion of subjects with an EASI-75 response and the proportion of subjects who achieved >4-point reduction in Itch NRS score from baseline.

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

Table 2: Proportion of Subjects Achieving Treatment Success (IGA 0/1) at Week 16

	Study 1334	Study 1416	Study 1224 (+TCS)
Placebo	10% (23/224)	9% (20/236)	12% (39/315)
Dupilumab 300q2wk	38% (84/224)	36%(83/233)	39% (41/106)
Dupilumab 300qwk	37% (83/223)	36% (86/239)	39% (125/319)

Source: derived from Statistical Review and Evaluation, BLA 761055, Carin Kim, PhD; archived 12/7/16, p.4.

Table 3: Proportion of Subjects Achieving EASI75 at Week 16

	Study 1334	Study 1416	Study 1224 (+TCS)
Placebo	15% (33/224)	12% (28/236)	23% (73/315)
Dupilumab 300q2wk	51% (114/224	44%(102/233)	69% (73/106)
Dupilumab 300qwk	53% (117/223)	47% (113/239)	64% (204/319)

Source: derived from Statistical Review and Evaluation, BLA 761055, Carin Kim, PhD; archived 12/7/16, p.4.

Table 4: Proportion of Subjects Achieving Reduction of ≥4 on NRS from baseline at Week 16

	Study 1334	Study 1416	Study 1224 (+TCS)
Placebo	12% (24/212)	10% (21/221)	20% (59/299)
Dupilumab 300q2wk	40% (86/213)	35%(79/225)	59% (60/102)
Dupilumab 300qwk	40% (81/201)	38% (87/228)	51% (150/295)

Source: derived from Statistical Review and Evaluation, BLA 761055, Carin Kim, PhD; archived 12/7/16, p.4.

The reader is referred to the reviews of Dr. Carin Kim and Dr. Brenda Carr for further information and additional analyses, including post hoc explorations of the data and sensitivity analyses. Both Dr. Kim and Dr. Carr concluded that the data support a determination of efficacy.

I conclude that the applicant provided substantial evidence of effectiveness of dupilumab for the indication of treatment of moderate-to-severe atopic dermatitis. In each of three adequate and well-controlled trials, one of which also included concomitant use of topical corticosteroids, a significantly greater proportion of subjects that received dupilumab demonstrated success on the primary endpoint of IGA of 0 or 1, as well as on selected key secondary endpoints of EASI75 and $\geq$4 point reduction from baseline in the pruritus NRS score.

8. Safety

The overall safety database in atopic dermatitis, comprised of subjects with atopic dermatitis who received any dose of dupilumab, consisted of 2526 subjects, of whom 739 were treated for over one year. The applicant-defined primary safety database for atopic dermatitis, comprised of pooled data from the monotherapy placebo-controlled phase 3 trials (1334 and 1416) as well as the relevant arms from the phase 2 study 1026, consisted of a total of 1567 subjects, of whom 529 received dupilumab 300mg q2wk (proposed dose), 518 received dupilumab 300mg qwk, and 517 received placebo. The size of the safety database is adequate to characterize adverse events.

In the atopic dermatitis development program, three deaths were reported, all of which occurred in dupilumab-exposed subjects: two in the phase 3 monotherapy trial 1416 and one in Phase 3 concomitant topical corticosteroid trial 1224. The causes of death included hypoxic ischemic encephalopathy, asthma and respiratory failure on Day 170, 65 days after last dose of dupilumab, in a 49 year old woman in the 300mg q2wk group; completed suicide on Day 93in a 31 year old man with risk factors for suicide in the 300mg qwk group; and car accident in a 27-year old female in the 300mg q2wk group (plus concomitant topical corticosteroids). The applicant and the clinical reviewer agreed that these deaths were not likely related to study drug. However, because dupilumab is under development for the treatment of asthma, but not yet approved for this use, labeling will advise, “Safety and efficacy of DUPIXENT have not been established in the treatment of asthma. Advise patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.”

The rates of treatment-emergent adverse events were similar across dupilumab-exposed and placebo-exposed groups, for both monotherapy and concomitant topical corticosteroid pools; the rates of treatment-emergent serious adverse events were slightly higher in the placebo groups in both pools. The most frequently reported adverse reactions include injection site reactions, conjunctivitis, and oral herpes. Of note, eczema herpeticum and herpes zoster, which occurred at low incidences in all groups, occurred at similar or higher rates in the placebo group. There was a greater increase in mean eosinophil count, compared to baseline, in dupilumab-exposed subjects as compared to placebo-exposed subjects in the monotherapy pool; the counts returned to near baseline by Week 16 without identified clinical sequelae.

Serious hypersensitivity, including urticaria, serum sickness and serum sickness-like reaction, occurred infrequently in subjects who received dupilumab. One case each of serum sickness and serum sickness-like reaction occurred in the development program, associated in each case with high levels of anti-drug antibody. Hypersensitivity is expected with a protein product, and is addressed in labeling

Pregnant women were excluded from enrollment in studies during the development program; as a result, there is limited human data about the impact of dupilumab on fetal development. Thirty-two pregnancies occurred in subjects exposed to dupilumab, with outcomes of 7 live births (8 healthy infants [1 set of twins]), 2 elective abortions (no fetal malformations reported), 6 spontaneous abortions, and 10 cases ongoing or lost to followup. Dr. Christos Mastroyannis of the Maternal Health Team agreed with the applicant's proposal to conduct a voluntary pregnancy registry, and noted that combining a pregnancy registry with a complementary study with a different design that relies on large databases may address the limitation of limited enrollment in the registry. Two post-marketing requirements are recommended 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. Brenda Carr for a full review of the safety data.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application. Although dupilumab is a new molecular entity and first-in class, the application itself did not present novel issues, not previously discussed, which merited advisory committee input.

A related topic, the timing of pediatric development of systemic products for treatment of patients with moderate to severe atopic dermatitis not adequately controlled with optimized topical therapy, was presented to the Dermatology and Opthalmology Drug Advisory Committee (DODAC) on 9 March, 2015. At that meeting, preliminary safety and efficacy data for dupilumab, gleaned from published literature, was presented to DODAC as an example of a relevant product under development. The committee was not asked to comment on the efficacy and safety of dupilumab per se, but rather to address issues related to pediatric development of products for the specified indication.

10. Pediatrics

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

The pathophysiology of AD in adults and children is presumed to be similar, and the mechanism of action of dupilumab in pediatric patients is presumed to be the same as in adults. However, at this time the applicant proposes to conduct clinical trials to demonstrate the efficacy and safety of their product in the pediatric population. The applicant has an agreed-upon iPSP.

The applicant proposed to conduct the following studies in pediatric subjects with AD:

- PK study in subjects 6 months to <6 years

- (b) (4)
- clinical efficacy and safety trial in subjects 12 to <18 years
- clinical efficacy and safety trial in subjects 6 to <12 years
- clinical efficacy and safety trial in subjects 6 mos to <6 years
- open-label safety study in subjects 6 mos to <18 years of age

The application was presented to the Pediatric Review Committee (PeRC) on November 16, 2016. PeRC agreed with the applicant's requests for waiver of studies in children younger than six months of age, and deferral of studies in children 6 months to <18 years of age.

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, DUPIXENT, 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).

DOSAGE AND ADMINISTRATION: The applicant proposed the following dosage text: "The recommended dose of DUPIXENT for adult patients is an initial dose of 600mg (two 300 mg injections), followed by 300 mg given every other week. (b) (4) was removed from the D&A section of labeling.

CLINICAL STUDIES: The applicant proposed inclusion of the 52-week response rates from Study 1224. Although this was a secondary endpoint, it was assessed for a mixed population (responders at Week 16 and non-responders at Week 16), and the Agency had previously communicated concern that the endpoint would not add significant additional information. To address this, the response rates of each component of the mixed population were also included.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

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

- Other Postmarketing Requirements and Commitments

PMR Description: Conduct a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects 6 years to less than 12 years of age with severe atopic dermatitis. Required under PREA
Final Protocol Submission: March 2018
Trial Completion: June 2019
Final Report Submission: September 2019

PMR Description: Conduct a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects 12 years to less than 18 years of age with moderate-to-severe atopic dermatitis. Required under PREA
Final Protocol Submission: January 2018
Trial Completion: February 2019
Final Report Submission: May 2019

PMR Description: Conduct an open-label trial to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe atopic dermatitis. Required under PREA
Final Protocol Submission: April 2018
Trial Completion: December 2022
Final Report Submission: March 2023

PMR Description: Conduct a safety, pharmacokinetic (PK), and efficacy trial in subjects 6 months to less than 6 years with severe atopic dermatitis. Required under PREA
Reference ID:
Final Protocol Submission: 2018
Trial Completion: 2021
Final Report Submission: 2021

PMR Description: Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab 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: 2018
Study Completion: July 2025
Final Report Submission: July 2026

PMR Description: Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to dupilumab and a non-dupilumab systemic medication or phototherapy 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 atopic dermatitis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.
Final Protocol Submission: March 2019
Study Completion: October 2025
Final Report Submission: October 2026

PMC Description: Complete the ongoing drug-drug interaction clinical study R668-AD-1433 to determine the potential for dupilumab to alter the pharmacokinetics of CYP substrates in subjects with moderate-to-severe atopic dermatitis (AD).
Final Report Submission: June 2017

PMC Description: Revise the (b) (4) CFU/ (b) (4) mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches has been analyzed.
Final Report Submission: December 2017

PMC Description: Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL drug product. Submit the data in the first annual report.
Final Report Submission (may include in first annual report): May 2018

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
03/27/2017