

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761055Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDER Cross Discipline Team Leader Review
Snezana Trajkovic, MD
BLA 761055
DUPIXENT (dupilumab)

Cross-Discipline Team Leader Review

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| Date | March 27, 2017 |
| From | Snezana Trajkovic, M.D. |
| Subject | Cross-Discipline Team Leader Review |
| BLA # | 761055 |
| Applicant | Regeneron Pharmaceuticals, Inc. |
| Date of Submission | July 28, 2016 |
| PDUFA Goal Date | March 29, 2017 |
| Proprietary Name / Non-Proprietary Name | Dupixent/dupilumab |
| Dosage form(s) / Strength(s) | Solution for subcutaneous injection |
| 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 |
| Recommendation on Regulatory Action | <i>Approval</i> |
| Recommended Indication(s)/Population(s) (if applicable) | 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 |

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease that occurs predominantly in children and is characterized by intense pruritus and skin xerosis. An estimated 11-15% of children are affected in the United States. The clinical manifestations vary with age and duration of the disease. In the youngest pediatric age group (less than 2 years of age), typical lesions are red, scaly and crusted papules which are distributed on extensor surfaces, face and scalp. In older children, scaly papules and plaques are distributed on flexor surfaces, neck and back. For 10-30% of patients, AD persists into adulthood. The prevalence of AD in adults is approximately 3%. The intense pruritus and resultant scratching produce secondary changes of lichenification and excoriations which are typical features of chronic AD.

Therapeutic options for the treatment of AD include several approved topical corticosteroid (TCS) products: fluticasone propionate cream, 0.05%; hydrocortisone butyrate cream, 0.1%; mometasone furoate cream, 0.1%; mometasone furoate lotion, 0.1%; halobetasol propionate 0.05%; desonide gel, 0.05%; desonide foam, 0.05%; fluocinonide cream, 0.1%. Two calcineurin products are approved for the treatment of AD: tacrolimus ointment, 0.03% and 0.1%; and pimecrolimus cream, 1%. The newest approved topical treatment for AD is crisaborole ointment, 2%. Crisaborole ointment is the first topical PD-4 inhibitor that provides a non-steroid option for the treatment of mild to moderate AD.

Dupilumab (Dupixent) is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL-4R α) sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is a solution for subcutaneous injection proposed for the 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. The proposed dosing regimen is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

The Applicant provided substantial evidence of effectiveness from 3 adequate and well-controlled clinical trials that evaluated dupilumab in the target population. Two pivotal trials of identical design evaluated dupilumab as a monotherapy, and the third trial evaluated dupilumab with protocol-specified concomitant use of topical corticosteroids (TCS). In all 3 trials, a significantly greater proportion of subjects treated with dupilumab 300mg QW or dupilumab 300mg Q2W achieved success on the primary efficacy endpoint, the proportion of subjects with both Investigator's Global Assessment (IGA) 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥ 2 points, at Week 16, compared to subjects treated with placebo. The proportion of IGA responders, in the 300 mg Q2W regimen recommended for approval, was 38% and 36% in the monotherapy trials and 39% in concomitant TCS trial.

The Applicant adequately characterized the safety profile of dupilumab based on analyses of data from the safety database of 2,526 subjects. The safety profiles were similar whether the dupilumab was administered as monotherapy or with concomitant topical corticosteroids. Three deaths

were reported during the development program for dupilumab. No deaths were considered to be treatment related. The safety profile of dupilumab was similar under both treatment regimens. The most frequently reported adverse reactions in dupilumab treated subjects were: injection site reactions; conjunctivitis; blepharitis, oral herpes; keratitis; eye pruritus; other herpes simplex viral infections; and dry eye.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| <p><u>Analysis of Condition</u></p> | <ul style="list-style-type: none"> • Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease that occurs predominantly in children. An estimated 11-15% of children are affected in the United States. • The clinical manifestations vary with age and duration of the disease. In the youngest pediatric age group (less than 2 years of age), typical lesions are red, scaly and crusted papules which are distributed on extensor surfaces, face and scalp. In older children, scaly papules and plaques are distributed on flexor surfaces, neck and back. The intense pruritus and resultant scratching produce secondary changes of lichenification and excoriations which are typical features of chronic AD. | <p>The AD is a common condition associated with significant discomfort due to inflammatory skin lesions and intense pruritus causing disruption of sleep and difficulties with concentration.</p> |
| <p><u>Current Treatment Options</u></p> | <ul style="list-style-type: none"> • For the Applicant’s target population, the only available FDA-approved systemic treatment is systemic corticosteroids. Because of the potential for serious systemic adverse reactions, systemic corticosteroids are not a first choice of therapy. • Phototherapy is an option for this population. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn like reactions, skin cancer (non-melanoma and melanoma), and cataracts. Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. | <p>There is a need for additional therapeutic options for the population of patients with moderate-to-severe AD</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|-----------------------|--|---|
| <p><u>Benefit</u></p> | <ul style="list-style-type: none"> Two pivotal trials of identical design, R668-AD-1334 and R668-AD-1416, enrolled 1379 adult subjects with moderate-to-severe AD [defined as $\geq 10\%$ of body surface area (BSA) involvement; score of moderate ≥ 3 on Investigator Global Assessment (IGA) scale in which 3 was moderate and 4 was severe and baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity was ≥ 3]. Subjects received injections of 300 mg dupilumab every two weeks (Q2W) SC following a loading dose of 600 mg on Day 1 (subjects received placebo on alternate weeks) or, matching placebo. Subjects were treated for 16 consecutive weeks. The primary endpoint was the proportion of subjects with both IGA score 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥ 2 points at Week 16. A significantly greater proportion of subjects treated with dupilumab 300mg Q2W achieved success on the primary endpoint compared to subjects treated with placebo. Third pivotal trial, R668-AD-1224, enrolled 740 adult subjects. The efficacy of dupilumab administered concomitantly with topical corticosteroids (TCS) was evaluated in adult subjects with moderate-to-severe AD [defined as $\geq 10\%$ of body surface area (BSA) involvement; score of moderate ≥ 3 on Investigator Global Assessment (IGA) scale in which 3 was moderate and 4 was severe and baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity was ≥ 3]. Significantly greater proportion of subjects treated with dupilumab 300mg Q2W plus TCS, achieved success on a primary efficacy endpoint, compared to subjects treated with placebo plus TCS. | <p>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.</p> |
| <p><u>Risk</u></p> | <ul style="list-style-type: none"> The Applicant adequately characterized the safety profile of dupilumab based on analyses of data from the safety database of 2,526 subjects. The safety profiles were similar whether the dupilumab was administered as monotherapy or with concomitant topical | <p>The safety profile of dupilumab has been adequately characterized.</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | <p>corticosteroids.</p> <ul style="list-style-type: none"> • A safety signal for eye disorders (conjunctivitis; blepharitis; keratitis; eye pruritus and; dry eye) was identified during the review of dupilumab clinical trials. Most adverse reactions were mild to moderate in severity, did not lead to discontinuation of treatment, and resolved or were resolving on treatment. • A safety signal for herpes virus infections (oral herpes and “Herpes simplex” not otherwise specified) was identified during the review of dupilumab clinical trials. The incidence rates of eczema herpeticum and herpes zoster were either similar between placebo and dupilumab groups or higher in the placebo group relative to the dupilumab groups. Subjects who developed eczema herpeticum or herpes zoster while receiving dupilumab either had the study treatment temporarily held until resolution of the infection or continued study treatment according to schedule; all ultimately completed dupilumab treatment • The most frequently reported adverse reactions in dupilumab treated subjects were: injection site reactions; conjunctivitis; blepharitis, oral herpes; keratitis; eye pruritus; other herpes simplex viral infections; and dry eye. | |
| <p><u>Risk Management</u></p> | <ul style="list-style-type: none"> • The Applicant has amended the protocol for on ongoing open-label extension trial to formally incorporate ophthalmologic examination at specified time points, at select centers, for certain subjects. These efforts will be helpful in further evaluating the eye disorder signal and, along with routine pharmacovigilance, will allow for further identifying and defining the nature of this risk. • The signal for herpes virus infections can also be assessed during the ongoing open-label study. | <p>Prescription and patient labeling as well as routine pharmacovigilance are adequate to manage the risk of dupilumab in the post market setting. The risks of eye disorders can be further managed by continued assessment in the ongoing open-label study, which includes ophthalmologic study procedures. The signal for herpes virus infections can also continue to be assessed in this trial. A Risk Evaluation and Mitigation Strategy (REMS) is not needed.</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | | Prescription labeling adequately addresses risks identified during product development. |

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2. Background

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease that occurs predominantly in children. An estimated 11-15% of children are affected in the United States. Atopic dermatitis or atopic eczema is characterized by severe pruritus and red, dry, scaly papules and plaques. The disease has a remitting and recurring course. The development of atopic dermatitis is influenced by genetic, immunologic and environmental factors.

The onset of atopic dermatitis commonly occurs between ages 3 and 6 months. Approximately 60% of patients develop AD within the first year of life and 90% by age 5 years. Most patients observe improvement in their skin disease with age; however, 10 to 30% experience symptoms that persist into adulthood. A small proportion of patients develop the disease as adults. Approved drug products indicated for the treatment of atopic dermatitis include topical corticosteroids [fluticasone propionate cream, 0.05%; hydrocortisone butyrate cream, 0.1%; mometasone furoate cream, 0.1%; mometasone furoate lotion, 0.1%; halobetasol propionate 0.05%; desonide gel, 0.05%; desonide foam, 0.05%; fluocinonide cream, 0.1%]; calcineurin inhibitor products (tacrolimus ointment, 0.03% and pimecrolimus cream, 1%) and a topical phosphodiesterase-4 (PDE-4) inhibitor, crisaborole ointment, 2%. For the Applicant's target population, the only available FDA-approved systemic treatment is systemic corticosteroids. Because of the potential for serious systemic adverse reactions, systemic corticosteroids are not a first choice of therapy. Phototherapy is an option for this population. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.

Dupixent is a biologic product for which the Applicant seeks approval under Section 351 (a) of the Federal Food Drug and Cosmetic Act for the 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. The active ingredient is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL-4R α) sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is a new molecular entity which is not marketed as a biologic in the United States.

Dupilumab was developed under the IND 107969 opened on 6/30/2010 by Regeneron Pharmaceuticals, Inc. During their development program, the applicant interacted with the Agency at the following milestone meetings: Pre-IND meeting (05/26/2010); End-of-Phase 2 meeting (05/21/2014); Pre-BLA meeting (scheduled for 12/16/2015 and cancelled by the applicant); Breakthrough Therapy designation (11/18/2014); Breakthrough Therapy designation (10/14/2016).

During the **pre-IND meeting** the Agency provided comments regarding primary efficacy endpoints. The Agency also advised the Applicant that they would need to establish safety and activity of dupilumab in adults (18 and older) before beginning investigations in a pediatric population.

During the **End-of-Phase 2 Meeting** the Agency communicated to the Applicant that they could consider a sequential clinical development program in which they would conduct two adequate and well-controlled Phase 3 trials for one treatment paradigms (either monotherapy or adjunctive therapy); following establishment of an efficacy claim in one paradigm. The Agency stated that a single adequate and well-controlled Phase 3 trial would be sufficient to support an additional claim for the other paradigm.

The FDA reminded the Applicant that the primary efficacy endpoint should be based an Investigator Global Assessment (IGA) where success was defined as “clear” or “almost clear,” with a two-grade improvement from baseline. Change in the eczema area and severity index (EASI) score could be included as a key secondary endpoint. If the Applicant were to include EASI as a co-primary endpoint, subjects should win on both IGA and EASI to be considered a success. The Agency found the Applicant’s proposal for one primary endpoint (IGA 0-1) and EASI75 as a key secondary endpoint to be reasonable.

The Applicant also proposed a numeric rating scale (NRS) for measurement of pruritus as a key secondary endpoint. The Agency agreed that assessment of pruritus was important.

The **pre-BLA meeting** was scheduled for 12/16/2015. However, the Applicant cancelled the meeting following receipt of the preliminary comments from the Agency, which included discussion of the content and format of the marketing application.

Breakthrough Therapy designation (11/18/2014) for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy or when those treatments are not advisable;

(b) (4)

3. Product Quality

Drug Substance

Dupilumab is human IgG4 κ antibody. The heavy chains contain 452 amino acids each, the light chains contain 219 amino acids and, the hinge region has a serine to proline mutation at amino acid 233 to stabilize the interaction between heavy chains. The average molecular mass is 147 kDa. Each heavy chain contains a single N-linked glycosylation site at asparagine 302.

Mechanism of action

Atopic dermatitis is associated with type 2 immune responses. IL-4 and IL-13 are key cytokines required for the initiation and maintenance of the type 2 immune response. Dupilumab binds specifically to the human IL-4/IL-13 receptor (hIL-4R α) and inhibits both IL-4 and IL-13 signal transduction.

Potency Assay

The biological function of dupilumab was characterized for its ability to bind to IL-4R α by surface plasmon resonance-based Biacore and by in vitro cell based bioassays. These bioassays show that dupilumab is able to inhibit IL-4-mediated CD23 up-regulation in primary human B lymphocytes and in human Ramos Burkitt lymphoma cell line and also to inhibit IL-4-induced up-regulation of thymus and activation regulated chemokine in human embryonic kidney (HEK293) cell line. The function of the Fc domain was analyzed for its ability to promote complement-dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). Fc function was not detected.

Dupilumab binds to soluble IL-4R α with high affinity...

The potency release and stability assay uses the HEK293 cell line endogenously expressing IL-4R α and engineered to express luciferase when stimulated with IL-4. Varying doses of dupilumab and a constant dose of hIL-4 are added to plates containing the HEK293 cells and incubated at 37°C to allow for binding prior to addition of luciferase. Dupilumab competes with hIL-4 inhibiting the bioluminescence reaction in a dose-dependent manner.

Dupilumab does not induce Fc mediated cytotoxicity (ADCC or CDC).

Dupilumab does not induce Fc mediated cytotoxicity (ADCC or CDC).

Manufacturing process

The manufacture of dupilumab drug substance

(b) (4)

Drug Product Summary

Potency and Strength

Dupilumab is supplied as a 300 mg/2 mL solution in a single-dose pre-filled syringe (PFS) with or without a safety system.

Summary of Product Design

Dupilumab is a sterile, preservative free, clear to slightly opalescent, colorless to pale yellow solution. Dupilumab is supplied in two presentations: a single-use prefilled syringe assembled with a safety system (PFS-S) and a single-use prefilled syringe without the safety system (PFS). Both syringes contain 2 mL of 150 mg/mL dupilumab.

List of Excipients: L arginine hydrochloride (25 mM), L-histidine (20 mM), polysorbate 80 (0.2% (w/v)), sodium acetate (12.5 mM), sucrose (5% (w/v))

Container Closure System

Dupilumab is supplied in two presentations, prefilled syringe (PFS) and prefilled syringe in safety system (PFS-S).

The PFS is the primary container closure system for dupilumab solution and consists of two components:

- A 2.25 mL clear glass syringe barrel with a 27 gauge (b) (4) needle, protected by a rigid needle shield and
- An (b) (4) plunger stopper (b) (4)

The dupilumab PFS-S presentation is supplied in a ready to use, sterile, single dose, and prefilled and disposable glass syringe assembled with a plunger rod and inserted within a safety system preassembled with a finger flange.

An appropriate compatibility studies were performed for the container closure system.

The CDRH reviewer, Sapana Patel, PharmD., provided the following recommendation regarding device constituent (prefilled syringe with needle safety system):

The reviewer recommends approval of the BLA in the context of device constituent parts for the combination product.

The sponsor has provided within the BLA application data to support the performance requirements of the device constituent of the combination product.

Expiration Date & Storage Conditions: 24 months at 2-8°C.

Facilities

The inspection of the drug product manufacturing and testing facility, Sanofi Winthrop Industrie was conducted February 6-14, 2017 by CDER-DIA and was classified VAI. The facility was approved based on the inspectional assessment.

The inspection of the drug substance manufacture and testing facility, Regeneron Pharmaceuticals Inc. was conducted October 31- November 4, 2017 by CDER/OPQ and was classified NAI.

CDER Cross Discipline Team Leader Review
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The facility review team from the Office of Process and Facility has issued an “Approval” recommendation for the facilities involved in this application.

OPQ Team Conclusion and Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761055 for DUPIXENT manufactured by Regeneron Pharmaceuticals. The data submitted in this application are adequate to support the conclusion that the manufacture of DUPIXENT is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

4. Nonclinical Pharmacology/Toxicology

In support of this application, the Applicant submitted data from an extensive nonclinical program. The following paragraphs contain excerpts from the review of nonclinical pharmacology/toxicology reviewer, Renqin Duan, Ph.D.

General Toxicology

Dupilumab binds specifically to the human IL-4R α and does not bind to IL-4R α in any animal species. The Applicant submitted three pivotal repeat dose toxicity studies and an enhanced pre- and postnatal developmental toxicity study (ePPND) in cynomolgus monkey with REGN646 which is a fully human homologous antibody specific for cynomolgus monkey IL4R α , and a subcutaneous fertility study in mice with REGN1103, a mouse homologous antibody that binds to IL4R α .

The three pivotal repeat dose toxicity studies, including a 5-week intravenous infusion (IV), a 13-week subcutaneous (SC) and a 6-month IV and SC studies, were conducted with REGN646 in peripubertal adolescent cynomolgus monkeys approximately 2.3 to 3.9 years of age, which is comparable to the approximately 8 to 16 year old peripubertal adolescent human based on the development of reproductive and nervous systems. No REGN646-related adverse effects (including effects on the immune system except decreased IgE levels in 13-week study) were observed in these repeat dose toxicology studies in cynomolgus monkeys up to 100 mg/kg/week, the highest dose tested. No target organs of toxicity were identified in these studies. There were no neoplastic or test article-related non-neoplastic proliferative lesions in these studies. The serum concentrations of REGN646 at the NOAEL in the 5-week, 13-week, and 6-month monkey toxicology studies exceeded the concentration required to block IL-4R α signaling in the in vitro and ex vivo assays.

Carcinogenicity

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab or homologous monoclonal antibodies REGN646 and REGN1103.

Literature studies have demonstrated that IL-4/IL-13 activation of the IL-4R α pathway is predominantly protumorigenic in in vitro studies using human and mouse colon tumor cell lines and in colon tumor mouse models. These literature studies indicate that the IL-4/IL-13 activation of the IL-4R α pathway acts via direct action such as proliferative and antiapoptotic effects on tumor cells and/or indirect activation of certain subsets of immune modulatory regulatory cells, such as Th2, TAMs, and MDSCs cells that suppress tumor immunity. The risk of tumor initiation and growth resulting from the blockade of IL-4R α appears very low and there is evidence to suggest that inhibition of IL-4R α pathway is likely to reduce the risk for tumor promotion and proliferation.

Dupilumab does not bind to the rodent IL-4R α receptor. The sponsor has developed two anti-IL-4R α receptor mouse monoclonal antibodies, M2M1869N and REGN1103, which could potentially be tested in a traditional 2-year rodent carcinogenicity study. However, extrapolation of the results from a carcinogenicity study conducted with the mouse homologous antibody REGN1103 instead of the clinical version of the monoclonal antibody that binds to the human IL-4R α receptor would be problematic and not relevant to human carcinogenicity risk assessment.

Reproductive Toxicology

In an ePPND study, weekly subcutaneous administration of REGN646 to pregnant adult female cynomolgus monkeys at doses of 0 (clinical vehicle), 25 and 100 mg/kg/week from approximately GD20 and every week thereafter until parturition was well tolerated. There were no test article related effects on maternal, fetal, or infant parameters during the study.

The postnatal growth and development of the offspring was monitored for a period of 6 months postpartum. Overall, the concentrations of REGN646 in the offspring were comparable to those in the corresponding dams, indicating that the monkey fetuses do have adequate systemic exposure to REGN646 from in utero exposure.

In a subcutaneous fertility study in young sexually mature male and female mice, no REGN1103-related changes in any of the evaluated fertility, early embryonic development and implantation parameters were observed at doses up to 200 mg/kg/week.

The reader is referred to the comprehensive review by Renqin Duan, Ph.D., dated December 5, 2016.

There are no outstanding pharmacology-toxicology issues.

The pharmacology-toxicology reviewer Renqin Duan, Ph.D. recommended *Approval* of this application from nonclinical pharmacology/toxicology perspective (review dated December 5, 2016).

5. Clinical Pharmacology

The information in this section reflects findings and conclusions from the clinical pharmacology and pharmacometrics teams.

Pharmacokinetics (PK)

Absorption

Following a single subcutaneous (SC) dose of 300 mg, dupilumab reached peak mean \pm SD concentrations (C_{max}) of 34.8 \pm 17.5 mcg/mL by approximately 1 week post-dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly or every 2 weeks. Across clinical trials, the mean \pm SD steady-state trough concentrations ranged from 73.3 \pm 40.0 mcg/mL to 79.9 \pm 41.4 mcg/mL for 300 mg administered every 2 weeks and, from 173 \pm 75.9 mcg/mL to 193 \pm 77.0 mcg/mL for 300 mg administered weekly. Dupilumab trough concentrations were lower in subjects with higher body weight.

The bioavailability of dupilumab following an SC dose was estimated to be 64%.

Distribution

The estimated total volume of distribution was approximately 4.6 L.

Metabolism

The metabolic pathway of dupilumab has not been characterized.

Elimination

As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. The mean systemic clearance for the linear elimination pathway was 0.13 L/day. The clearance for the nonlinear elimination pathway is concentration-dependent and plays a role in the studied SC dose range of 75 mg to 300 mg.

Immunogenicity

In the combined Phase 3 monotherapy Studies AD-1334 and AD-1416, approximately 13.6% (61/447) and 7.2% (31/429) of subjects had antidrug antibodies to dupilumab following 16 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the subjects who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimens, approximately 18% (11/61) and 13% (4/31), respectively, had neutralizing antibodies.

In the Phase 3 concomitant treatment with TCS Study R668-AD-1224, approximately 9.5% (10/105) and 10.7% (33/308) of subjects had antidrug antibodies to dupilumab following 52 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the subjects

who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 10% (11/10) and 0% (0/33), respectively, had neutralizing antibodies.

Development of ADA was associated with reduced serum dupilumab concentrations.

Overall, no consistent evidence of reduced efficacy was observed in subjects who developed ADA or NAb in Phase 3 trials. However, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on the clinical efficacy measures because of the small number of subjects with ADA.

Two cases of adverse reactions of serum sickness reaction and serum sickness-like reaction were observed in AD clinical trials. These two adverse reactions were associated with development ADA to dupilumab with high antibodies titer values of 122,880 and 15,360, respectively.

Drug Interactions:

As information on clinical drug interaction for dupilumab in AD patients is not available at this time, we recommend including the following labeling language: “The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-4, IL-6, IL-10, IL-13, TNF α , and IFN) during chronic inflammation. Thus, DUPIXENT, an antagonist of IL-4 receptor alpha, could modulate the formation of CYP450 enzymes. Therefore, upon initiation or discontinuation of DUPIXENT in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.” This recommendation is consistent with the labeling of other biological products that modulate cytokine levels associated with an inflammatory disease condition.

Dosing

The proposed dosing regimen is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week (Q2W). (b) (4)

The dose-response relationship for efficacy in Phase 3 supports the recommended 300mg Q2W dosing regimen (with an initial 600 mg dose). We do not recommend including an option to increase the dose to 300 mg QW based on individual therapeutic response, because the available data do not support such dose adjustment. Specifically, the available data did not show a preferential treatment benefit with 300 mg QW compared to 300 mg Q2W in any particular subset of patients. In addition, a switch from 300 mg Q2W to 300 mg QW based on individual therapeutic response was not evaluated as part of the trial.

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DUPIXENT (dupilumab)

Pharmacodynamics

Results from a small exploratory study showed that serum levels of IL-4 and IL-13 were increased following dupilumab treatment. The relationship between the pharmacodynamic (PD) activity and the mechanism(s) by which dupilumab exerts its clinical effects is unknown.

Post marketing Requirement/Commitment:

The pharmacology team recommended that the Applicant 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).

The clinical pharmacology reviewer, Dr. Jie Wang and pharmacology and pharmacometrics team recommended an approval of this BLA.

The reader is referred to the comprehensive review by, Jie Wang, PhD., for a full discussion of the clinical pharmacology data (dated December 19, 2016).

I concur with the conclusions and recommendations reached by the clinical pharmacology and pharmacometrics review team.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from three pivotal trials, R668-AD-1334; R668-AD-1416 and R668-AD-1224, to establish the effectiveness of their product in the treatment moderate-to-severe AD. All three trials were randomized, double-blind, multicenter, placebo-controlled, parallel-group, Phase 3 trials conducted in 2119 adult subjects. Subjects had moderate-to-severe AD at baseline defined as $\geq 10\%$ of body surface area (BSA) involvement; score of ≥ 3 (moderate) or 4 (severe) on Investigator Global Assessment (IGA) scale; an Eczema Area and Severity Index (EASI) score ≥ 16 and; baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity of ≥ 3 .

Trials R668-AD-1334 and R668-AD-1416 were designed to evaluate the efficacy of dupilumab monotherapy compared to placebo. Pivotal trial R668-AD-1224 was designed to evaluate the efficacy of dupilumab in combination with topical corticosteroids compared to placebo plus topical corticosteroids. In all three trials, subjects in dupilumab group received loading dose of 600mg at Week 0, followed by 300mg QW or Q2W.

Demographic characteristics of study population were similar across the treatment groups. At baseline, the majority of subjects were male (59%) and white (67%). The baseline disease severity was moderate in 52% of subjects and severe in 48% of subjects. The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7.

In all three trials, the primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement, at Week 16.

The key secondary endpoints were: EASI 75 response (i.e., $\geq 75\%$ reduction from baseline in EASI score) and the proportion of subjects with improvement of weekly average of peak daily pruritus NRS score ≥ 4 from baseline to Week 16.

At Week 16, in all three trials, dupilumab was superior to placebo for the primary efficacy endpoint of IGA and secondary endpoint of EASI 75 responses.

Table 1: Proportion of Subjects Achieving Treatment Success at Week 16; Monotherapy Trial 1334 and Trial 1416

| | Study 1334 | | | Study 1416 | | |
|------------------------|---------------------|----------------------|----------|---------------------|----------------------|----------|
| | Dupilumab 300 mg QW | Dupilumab 300 mg Q2W | Placebo | Dupilumab 300 mg QW | Dupilumab 300 mg Q2W | Placebo |
| FAS⁺ | 223 | 224 | 224 | 239 | 233 | 236 |
| IGA 0 or 1 | 83 (37%) | 84 (38%) | 23 (10%) | 86 (36%) | 83 (36%) | 20 (9%) |
| EASI 75 | 117 (53%) | 114 (51%) | 33 (15%) | 113(47%) | 102 (44%) | 28 (12%) |

*Source: Statistical review Table 1

+Full analysis set

Table 2: Proportion of Subjects Achieving Treatment Success at Week 16; Combination Therapy Trial 1224

| | Study 1224 | | |
|------------------------|---------------------------|----------------------------|---------------|
| | Dupilumab 300 mg QW + TCS | Dupilumab 300 mg Q2W + TCS | Placebo + TCS |
| FAS⁺ | 319 | 106 | 315 |
| IGA 0 or 1 | 125 (39%) | 41 (39%) | 39 (12%) |
| EASI 75 | 204 (64%) | 73 (69%) | 73 (23%) |

*Source: Statistical review Table 2

+Full analysis set

Both dupilumab dosing regimens, 300mg QW and 300mg Q2W, were superior to placebo for the primary endpoint of IGA success as well as for the secondary endpoints of EASI 75. However, while the weekly dosing was effective in the target population, there was no clinically meaningful added benefit beyond that of every other week dosing. (b) (4)

Dupilumab was significantly superior to placebo in all three trials for the secondary efficacy endpoint of pruritus response, at Week 16. Treatment responses were similar between the 2 dupilumab dosing regimens in the monotherapy trials R668-AD-1334 and R668-AD-1416. Table 3 presents the results for the secondary efficacy endpoint of pruritus in two monotherapy trials.

Table 3: Proportion of Subjects Achieving Treatment Success at Week 16; Monotherapy Trial 1334 and Trial 1416

| | Trial 1334 | | | Trial 1416 | | |
|--|---------------------|----------------------|---------|---------------------|----------------------|----------|
| | Dupilumab 300 mg QW | Dupilumab 300 mg Q2W | Placebo | Dupilumab 300 mg QW | Dupilumab 300 mg Q2W | Placebo |
| Pruritus FAS (Baseline NRS\geq4) | 201 | 213 | 212 | 228 | 225 | 221 |
| Reduction of at least 4-point change from baseline ⁽¹⁾ | 81 (40%) | 86 (40%) | 24(12%) | 87 (38%) | 79 (35%) | 21 (10%) |

⁽¹⁾ Proportion of subjects with a reduction of weekly average of peak daily pruritus NRS \geq 4. Missing data as well as those that received rescue medication at any time within the 16 weeks was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

*Source: Statistical review Table 1

The treatment responses in all arms i.e., including placebo, were noticeably higher in study R668-AD-1224, which specified concomitant use of TCS. These results may suggest added benefit of concomitant TCS in treatment of pruritus in patients with AD. Table 4 presents the results for the secondary efficacy endpoint of pruritus in the combination therapy trial.

Table 4: Proportion of Subjects Achieving Treatment Success at Week 16; Combination Therapy Trial 1224

| | Study 1224 | | |
|--|---------------------------|----------------------------|---------------|
| | Dupilumab 300 mg QW + TCS | Dupilumab 300 mg Q2W + TCS | Placebo + TCS |
| Pruritus FAS (Baseline NRS\geq4) | 295 | 102 | 299 |
| Reduction of at least 4-point change from baseline ⁽¹⁾ | 150 (51%) | 60 (59%) | 59 (20%) |

⁽¹⁾ Proportion of subjects with a reduction of weekly average of peak daily pruritus NRS \geq 4. Missing data as well as those that received rescue medication at any time within the 16 weeks was imputed as non-responders. The protocol specified using the Cochran Mantel Haenszel (CMH) test stratified by baseline disease severity and region as the primary analysis method.

*Source: Statistical review Table 1

The reader is referred to the reviews of Carin Kim Ph.D. (reviews dated December 7, 2016) and Brenda Carr, M.D. for further information and additional analyses. Both Dr. Kim and Dr. Carr concluded that the data support a determination of efficacy for dupilumab.

I agree with Dr. Kim and Dr. Carr that the applicant provided substantial evidence of effectiveness of dupilumab 300mg Q2W for the indication of 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. In each of three adequate and well-controlled trials, a significantly greater proportion of subjects who were treated with dupilumab 300mg Q2W as a monotherapy or in combination with TCSs, demonstrated success on the primary endpoint of the proportion of subjects achieving score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline on IGA at Week 16, compared to subjects treated with placebo or placebo plus TCS.

8. Safety

The Applicant comprehensively assessed the safety of dupilumab in the target population. The safety database consisted of 2,526 subjects exposed to dupilumab across 11 trials conducted during the clinical development of dupilumab.

The applicant conducted two replicate, randomized, placebo-controlled, Phase 3 trials (R668-AD-1334; R668-AD-1416), in adult subjects with moderate to severe AD. Pooled data from 16-week treatment period of these trials and relevant treatment arms from the Phase 2 dose-ranging trial R668-AD-102, comprised the primary safety database for dupilumab monotherapy. In addition, the applicant conducted a long-term Phase 3 trial R668-AD-1224 that evaluated use of dupilumab with concomitant TCS and provided the data from long-term treatment (52 weeks).

The Applicant is currently conducting an open-label 164-week (148-week treatment with 16 week follow up) clinical trial. This trial is intended to assess the long-term safety (b) (4) with dupilumab administered for up to 3 years. Subjects in this trial have previously participated in controlled trials of dupilumab (trials R668-AD-0914, R668-AD-1026, R668-AD-1117, R668-AD-102, R668-AD-1121, R668-AD-1307) or were screened for a Phase 3 monotherapy trials (either R668-AD-1334 or R668-AD-1416) but could not be randomized because of randomization closure.

The primary safety pool included 1,567 randomized subjects. Three subjects did not receive any study drug and therefore the safety analysis set consists of 1564 subjects. In the primary safety population, the majority of subjects were white and male. The mean age of subjects in the pooled dupilumab group was similar to the mean age of subjects in the placebo group. The majority of subjects in both treatment groups had AD of moderate severity and reported pruritus severity of

7 (scale 0-10). Overall demographic and baseline characteristics for the primary safety population were generally consistent between treatment arms and across trials. In trial R668-AD-1224, 425 subjects were exposed to dupilumab and 315 to placebo. Demographic characteristics of subjects in this trial were similar to subjects in the primary safety pool.

In the primary safety pool and in combination therapy trial R668-AD-1224, the most commonly reported reason for discontinuation was “withdrawal by subject,” and the highest proportion of subjects reporting this reason was in the placebo groups.

Three deaths (asthma, completed suicide and road traffic accident) were reported in the development program for AD. These events were considered not related to the treatment.

During 16-Week treatment period of two pivotal Phase 3 trials, 2.5% (13/529) of subjects in dupilumab Q2W treatment group and, 2.1% (11/518) of subjects in dupilumab QW treatment group reported SAEs, compared to 5% of subjects in the placebo group. Most of reported SAEs occurred in one subject each.

For placebo and dupilumab 300mg Q2W subjects, SAEs most frequently reported were in the “Skin and subcutaneous tissue disorders” System Organ Class (SOC): 9 (1.7%) and 4 (0.8%) subjects, respectively. All SAEs in the Skin and Subcutaneous Tissue Disorders SOC in the placebo group were “dermatitis atopic” while, 3 (0.6%) subjects in dupilumab 300mg Q2W subjects, reported SAEs of “dermatitis atopic”. “Dermatitis atopic” was the only SAE for which there were multiple reports for dupilumab 300mg Q2W subjects.

For dupilumab 300mg QW subjects, SAEs were most frequently reported in the Infections and infestations SOC [4 (0.8%) subjects], and included the following: cellulitis, erysipelas, kidney infection, and viral infection. No SAE was reported in more than one subject in the dupilumab 300mg QW group.

In the TCS concomitant trial R668-AD-1224, a total of 13 SAEs were reported in the initial 16-week period of which, 3 (2.7%) SAEs were in dupilumab 300mg Q2W+ TCS treatment group; 4 (1.3%) in dupilumab 300mg QW+ TCS group; and 6 (1.9%) in the placebo group. There were 2 reports of malignancies: squamous cell carcinoma of the skin and squamous carcinoma of the tongue. Both of these SAEs occurred in subjects in dupilumab 300 mg QW + TCS group. For the 52-week treatment period of this trial, fewer subjects reported SAEs in each dupilumab group compared to placebo. In placebo + TCS group, 5.1% (16/315) SAEs were reported; in dupilumab 300 mg Q2W + TCS group, 3.6% (4/110) SAEs were reported; and in dupilumab 300 mg QW + TCS, 2.9% (9/315) SAEs were reported. No individual SAE was reported in more than one subject.

Evaluation of Adverse Events of Special Interest (AESI) revealed a signal for herpes virus infections, specifically eczema herpeticum and herpes zoster. However, these events were

reported in a higher or similar proportion of subjects on placebo compared to dupilumab. The risks of herpes virus infections can be further evaluated by continued assessment in the ongoing open-label study as well as routine pharmacovigilance. The risk for herpes virus infections is addressed in labeling.

The proportions of subjects reporting an acute allergic reaction requiring treatment in the primary safety pool were: 0.6% in the placebo and 300 mg Q2W groups and 0.2% for the 300 mg QW group. One subject in the trial R668-AD-1224 study experienced an acute allergic reaction. The subject was in the placebo + TCS group. There were no reports of anaphylactic reactions associated with dupilumab. Two subjects had reports of serum sickness and serum-like illness. These two subjects also had high levels of ADAs. The risk for hypersensitivity reactions is addressed in labeling.

A safety signal for eye disorders (conjunctivitis; blepharitis; keratitis; eye pruritus and; dry eye) was identified during the review of dupilumab clinical trials. This signal was not identified in dupilumab development program for asthma or nasal polyposis. Most adverse reactions were mild to moderate in severity, did not lead to discontinuation of treatment, and 65% resolved or were resolving on treatment during 52-week Phase 3 study period. The risks of eye disorders can be further evaluated by continued assessment in the ongoing open-label study, which includes evaluation for ophthalmologic AEs study and, with routine pharmacovigilance. The risk for eye disorders is addressed in labeling.

The most frequently reported adverse reactions in dupilumab treated subjects during 16-week treatment period of the primary safety pool and trial R668-AD-1224 were: injection site reactions; conjunctivitis; blepharitis, oral herpes; keratitis; eye pruritus; other herpes simplex viral infections; and dry eye.

For the concomitant TCS trial R668-AD-1224, TEAEs were similar across treatment arms. The general type and pattern of occurrence of TEAEs did not appear to change with longer term exposure to dupilumab.

9. Advisory Committee Meeting

Not applicable; this application was not presented to the Advisory Committee as the application did not raise novel or controversial issues that would merit outside discussion.

10. Pediatrics

Clinical trials submitted in support of this application were conducted in adult subjects. The Applicant has an Agreed Initial Pediatric Study Plan (iPSP) dated November 11, 2015. The Agreed iPSP includes studies in children ages down to 6 months.

Per the Agreed iPSP, the Applicant will conduct the following clinical trials in children with AD:

1. A randomized, double-blind, placebo-controlled Phase 3 trial to investigate the efficacy and safety of dupilumab in patients, 12 years to less than 18 years of age, with moderate-to-severe atopic dermatitis.
2. A randomized, double-blind, placebo-controlled Phase 3 trial to investigate the efficacy and safety of dupilumab in patients, 6 years to less than 12 years of age, with severe atopic dermatitis.
3. A two-part phase II/III trial to evaluate the safety, pharmacokinetics (PK) and efficacy of dupilumab in patients, 6 months to less than 6 years of age, with severe atopic dermatitis.

(b) (4)

4. An open-label extension trial to assess the long-term safety and efficacy of dupilumab in patients ≥ 6 months to < 18 years of age with atopic dermatitis.

Trials in children younger than 6 months have been waived because trials in this patient population would be impossible or highly impracticable for the following reason:

Since dupilumab is being developed for the treatment of moderate to severe atopic dermatitis (e.g., IGA ≥ 3) in pediatric patients who are not adequately controlled with, or who are intolerant to topical (TCS) medications, it will be impractical to make this determination in patients younger than 6 months of age.

The planned pediatric studies will be listed Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs).

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted. The following is the conclusion reached by OSI reviewer Roy Blay, Ph.D.:

“Based on the results of the clinical investigator and sponsor inspections, the studies of Drs. Sofen, Brüning, and Kolodziej appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.”

12. Labeling

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

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.

13. Postmarketing Recommendations

Pediatric studies delineated in agreed iPSP and discussed in section 10. **Pediatrics** of this review will be listed as Postmarketing Requirements (PMRs).

PREA-PMR-1: A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of dupilumab in patients, 12 years to less than 18 years of age, with moderate-to-severe Atopic Dermatitis

PREA-PMR-2: A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of dupilumab in patients, 6 years to less than 12 years of age, with severe Atopic Dermatitis

PREA-PMR-3: A two-part phase II/III study to evaluate the safety, pharmacokinetics (PK) and efficacy of dupilumab in patients, 6 months to less than 6 years of age, with severe Atopic Dermatitis

(b) (4)

PREA-PMR-4: An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients \geq 6 months to $<$ 18 years of age with Atopic Dermatitis

Product Quality PMCs:

- 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.
- Qualification of the bioburden and sterility test methods was performed with only two batches of drug product. Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL dupilumab drug product. Provide the data in the first annual report.

Clinical Pharmacology PMC:

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).

CDER Cross Discipline Team Leader Review
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14. Recommended Comments to the Applicant

None.

Appears this way on original

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/s/

SNEZANA TRAJKOVIC
03/27/2017