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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

Pharmacology/Toxicology Supervisory Memorandum

BLA number: 761055
SDN/date/type of submission: 4 / July 29, 2016/ New BLA
Applicant: Regeneron Pharmaceuticals, Inc.
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Drug: Dupixent (dupilumab) injection
Pharmacologic class: (b) (4) interleukin 4 receptor alpha antagonist
Indication: Moderate to severe atopic dermatitis

General comments:

- I concur with the overall assessment and conclusions contained in Dr. Renqin Duan's Pharmacology/Toxicology review for this biologic product.
- I concur that there are no nonclinical approval issues for this biologic product and that this BLA is approvable from a Pharmacology/Toxicology perspective.
- I concur that there are no nonclinical Post-Marketing Requirements recommended for this BLA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Duan for Dupixent contained in section 1.3.3 of his review which include:
 - Pharmacologic Class designation of "(b) (4) interleukin 4 receptor alpha antagonist"
 - The revisions proposed for Sections 8.1, 12.1, 13.1 and 13.2 of the label

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/s/

BARBARA A HILL
12/06/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 761055
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Product: Dupixent (dupilumab) Injection
Indication: Moderate-to-severe atopic dermatitis
Applicant: Regeneron Pharmaceuticals, Inc.
Review Division: Dermatology and Dental Products
Reviewer: Renqin Duan, PhD
Supervisor/Team Leader: Barbara Hill, PhD
Division Director: Kendall Marcus, MD
Project Manager: Matthew White

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1 Executive Summary

1.1 Introduction

Dupilumab (dupilumab) is a recombinant human immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) directed against the IL-4 receptor alpha (IL-4R α) subunit, a component of Type I and Type II IL-4 receptors as well as the IL-13 receptor system. The binding of dupilumab to IL-4R α results in inhibition of both IL-4 and IL-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4R α / γ c), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4R α /IL-13R α). Dupilumab is expected to inhibit the Type-2 helper T cell (Th2) pathway selectively, which is responsible for several pathophysiological mechanisms. The sponsor believes that its downregulation may prevent or reverse the development of atopic dermatitis (AD).

The sponsor submitted an original 351a BLA application for Dupixent (dupilumab) Injection (via subcutaneous route), 150 mg/mL indicated 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 sponsor is also developing dupilumab for the treatment of asthma.

1.2 Brief Discussion of Nonclinical Findings

Dupilumab binds specifically to the human IL-4R α and does not bind to IL-4R α in any animal species. The sponsor 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. After 6 months of weekly treatment, the AUC_{0-168h} values are 790,667 μ g.h/mL and 149,246 μ g.h/mL for doses of 100 mg/kg/week, SC and 25 mg/kg/week, IV, respectively.

In an ePPND study, weekly subcutaneous administration of REGN646 to pregnant adult female cynomolgus monkeys at doses of 25 mg/kg/week and 100 mg/kg/week from approximately GD20 and every week thereafter until parturition was well tolerated. There were no neoplastic or test article-related non-neoplastic proliferative lesions. There were no test article related effects on maternal, fetal, or infant parameters during the study. There were no test article related effects on immune system parameters. No test article related macroscopic or microscopic findings were noted for the infants. The postnatal growth and development of the offspring was monitored for a period of 6 months postpartum. Overall, the concentrations of REGN646 in the offsprings were comparable to those in the corresponding dams, indicating that the monkey fetuses do have adequate systemic exposure to REGN646 from in utero exposure. The NOAEL for maternal and developmental toxicity was 100 mg/kg/week based on the results of this study, which is 10 times the maximum recommended human dose (MRHD) on a mg/kg basis.

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.

1.3 Recommendations

1.3.1 Approvability

BLA 761055 is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. With the exception of the Section 8 subheading "Pregnancy Exposure Registry", "Risk Summary" and "Data" which the sponsor underlined per PLLR specifications, it is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the DUPIXENT label text.

Recommended revisions for the nonclinical information contained in Section 8 of the label are made below. Refer to the clinical review for recommended revisions for the clinical information contained in Section 8 of the label. A clean copy of these revised labeling sections is provided in the Appendix as Appendix # 1.

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

DUPIXENT is an ^{(b) (4)} interleukin-4 receptor alpha ^{(b) (4)} antagonist indicated 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. DUPIXENT can be used with or without topical corticosteroids ^{(b) (4)}

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on (b) (4) -DUPIXENT use in pregnant women to inform any drug associated risk. (b) (4)

(b) (4) Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4R α) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) [see Data].



The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In aAn enhanced pre- and post-natal developmental toxicity study, (b) (4) pregnant cynomolgus monkeys were administered weekly subcutaneous doses of (b) (4) homologous antibody against IL-4R α ; (b) (4) up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week); (b) (4) from the beginning of organogenesis to parturition

(b) (4) No treatment-related adverse effects on embryofetal toxicity or malformations or on morphological, functional or immunological development were observed in the infants from birth through 6 months of age.

(b) (4)

Reviewer comment: The subsection "Pregnancy Exposure Registry" in Section 8.1 and Section 8.2 "Lactation" were not included in this review because there were no animal data and all edits were made by other disciplines/Divisions.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dupilumab (b) (4) is a (b) (4) human monoclonal IgG4 (b) (4) antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4R α sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab (b) (4) inhibits IL-4 signaling via the Type I receptor (b) (4), and both IL-4 and IL-13 signaling through the Type II receptor (b) (4).

Blocking IL-4R α inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines and chemokines are (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal (b) (4) studies have not been conducted to evaluate the carcinogenic or mutagenic potential of (b) (4) dupilumab. (b) (4)

(b) (4)

(b) (4)

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature mice that were subcutaneously administered a homologous antibody against IL-4R α at doses up to 200 mg/kg/week.

(b) (4)



(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number:	1190264-60-8
Generic Name:	Dupixent (dupilumab)
Code Name:	REGN668/SAR231893
Molecular Formula/Molecular Weight:	IgG4 monoclonal antibody/147 kDa
Structure or Biochemical Description:	

Dupilumab (IgG4 isotype) is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. Each heavy chain contains a serine-to-proline mutation at amino acid 233, which is located in the hinge region of the Fc domain, to reduce the propensity of the antibody to form half-antibodies in solution. There is a single N-linked glycosylation site (Asn302) in each heavy chain, located within the CH2 domain of the Fc constant region in the molecule. The antibody, based on the primary sequence (in the absence of N-linked glycosylation), has a predicted molecular weight of 146,897.0 Da, taking into account the formation of 16 disulfide bonds and removal of Lys452 from each heavy chain C-terminus. The variable domains of the heavy and light chains combine to form complementarity-determining regions (CDRs) for the binding of dupilumab to its target, interleukin-4 receptor alpha (IL-4R α).

Pharmacologic Class:

IL-4 receptor alpha antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 107969: Atopic dermatitis with DDDP

IND (b) (4)

DMF (b) (4)

DMF (b) (4)

DMF (b) (4)

DMF (b) (4)

2.3 Drug Formulation

The dupilumab drug product is supplied as an (b) (4) sterile solution, pH 5.9 at 150 mg/mL in a 2 mL prefilled syringe (in safety system). The formulation components of the dupilumab solution and nominal composition are provided in the following table.

Appears this way on original

Table 1 - Nominal Composition of Dupilumab Solution for Injection

Component	Function	Reference to Quality Standard	Drug Product Nominal Composition	Nominal Amount per Prefilled Syringe (mg) ^a
Dupilumab	Active pharmaceutical ingredient	Custom specification	150 mg/mL	300
L-Histidine (b) (4)	(b) (4)	USP, Ph. Eur., JP	20 mM	6.2 ^b
(b) (4)		Ph. Eur., JP		
L-Arginine hydrochloride (b) (4)		USP, Ph. Eur., JP	25 mM	(b) (4)
Sodium Acetate (b) (4)		USP, Ph. Eur., JP	12.5 mM	
(b) (4)		USP, Ph. Eur., JP		
Sucrose		NF, Ph. Eur., JP	5% (w/v)	100
Polysorbate 80		NF, Ph. Eur., JP	0.2% (w/v)	4
Water for Injection	USP, Ph. Eur.		(b) (4)	

^a Based on a 2.0 mL injection volume

^b Reported as milligrams histidine base (MW = 155.16 g/mol), calculated assuming a molar concentration of 20 mM histidine

(b) (4)

USP, United States Pharmacopeia; NF, National Formulary; Ph. Eur., European Pharmacopeia; JP, Japanese Pharmacopeia

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

DUPIXENT is an IL-4 receptor alpha antagonist indicated 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. DUPIXENT can be used with or without topical (b) (4).

DUPIXENT is administered by subcutaneous injection.

The recommended dose of DUPIXENT for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week. (b) (4)

(b) (4)

2.7 Regulatory Background

05/26/2010: Pre-IND meeting
06/30/2010: Original IND received
01/23/2013: Guidance meeting
05/21/2014: End-of-Phase 2 meeting
08/04/2014: Guidance meeting
10/02/2015: Guidance meeting
11/04/2015: Guidance meeting

Pre-BLA meeting scheduled for 12-16-2015 was cancelled at the sponsor's request after receiving the Agency's preliminary comments.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

1. In Vitro and In Vivo Characterization of an Anti-mouse IL-4R α Antibody, REGN1103 (Study #: REGN1103-MX-11049-SR-01V2)
2. Characterization of Mice Used to Evaluate the In Vivo Efficacy of REGN668 (Study #: REGN668-MX-15051-SR-01V1)
3. Efficacy of REGN1103 in a Four-Week Mouse Model of Allergen-Induced Lung Inflammation (Study #: REGN1103-MX-15050-SR-01V1)
4. Efficacy of REGN668 in a Four-Week Model of Allergen-Induced Lung Inflammation Using Humanized Mice (Study #: REGN668-MX-15052-SR-01V1)

Pharmacokinetics

1. Dupilumab: Supplemental Pharmacokinetic Analysis in Support of Pharmacokinetic and Toxicokinetic Studies in the Mouse, Rat and Monkey (Study #: REGN668-MX-15079)

Toxicology

1. Amended Carcinogenicity Risk Assessment for Dupilumab (REGN668/SAR231893)

3.2 Studies Not Reviewed

Pharmacokinetics

1. Quantitative Measurement of REGN668 in Monkey Serum (Study #: SOP-PCL2490)
2. Quantitative Measurement of REGN668 in Rat Serum (Study #: SOP-PCL2592)

3. Validation of a Bioanalytical Method for the Quantitative Measurement of REGN1103 in Mouse Serum (Study #: REGN1103-AV-11022-VA-01 V2)
4. Validation of a Bioanalytical Method for the Quantitative Measurement of REGN646 in Monkey Serum (Study #: REGN646-AV-09004-VA-01 V3)
5. Validation of a Bioanalytical Method for Detection of Anti-REGN646 Antibodies in Monkey Serum using Electrochemiluminescence (Study #: REGN 646-A V - 09029-VA -01 V2)

3.3 Previous Reviews Referenced

The following nonclinical studies were reviewed under INDs (b) (4) and 107969.

Pharmacology

1. Characterization of REGN646 – a surrogate IL-4R α blocking monoclonal antibody for toxicology studies in cynomolgus monkeys (Study #: REGN646-MX-09055)
2. Evaluation of Fc Effector Functions for REGN668 (Study #: REGN668-MX-09023)
3. Determination of the Equilibrium Binding Constant for the Interaction of IL-4R α with REGN668 (Study #: REGN668-MX-09024)
4. REGN668 in vitro and in vivo pharmacology (Study#: REGN668-MX-09025)

Pharmacokinetics

1. A Single Dose Pharmacokinetics Study of REGN646 in Cynomolgus Monkeys (Non-GLP) (Study #: (b) (4) 223.34)
2. REGN646: A Pharmacokinetics and Bioavailability Study in Primates (Study #: REGN646-PK-08057/09-3379)
3. A Single Dose Pharmacokinetic Study of REGN668 Administered IV and SC to Cynomolgus Monkeys (non-GLP) (Study #: REGN668-PK-09001/ (b) (4) 223.35)
4. Pharmacokinetic Analysis of REGN668 in Rat Serum Samples (Study #: REGN668-PK-09002/PK09001)

Toxicology

Repeat Dose Toxicity

1. SAR231893 - Exploratory 5-Week Subcutaneous Toxicology Study in Mice with REGN1103 (Study #: REGN1103-TX-10054/ (b) (4) 1347)
2. A 1-Month Exploratory Intravenous Infusion Tolerability and Safety Study of REGN646 in Cynomolgus Monkeys (Study # REGN646-TX-08046/ (b) (4) -460016)

3. A 5-Week (Once-weekly) 30-Minute Intravenous Infusion Toxicity and Toxicokinetic Study of REGN646 with an 8-Week Recovery Period in Cynomolgus Monkeys (Study #: REGN646-TX-08053/ (b) (4) 460017)
4. A 13-Week Subcutaneous Toxicity Study with REGN646 in Cynomolgus Monkeys Followed by a 13-Week Recovery Phase (Study # REGN646-TX-08056/8202348)
5. 6-Month Intravenous Infusion and Subcutaneous Toxicity Study of REGN646 in Cynomolgus Monkeys with a 3-Month Recovery Period (Study # REGN646-TX-10004)

Reproductive and Developmental Toxicology

1. SAR231893 (REGN668): Subcutaneous Fertility Study in Mice with REGN1103 (Study # REGN1103-TX-11097)
2. Enhanced Pre-Postnatal Toxicity Study of REGN646 Administered by Subcutaneous Injection to Pregnant Cynomolgus Monkeys with 6-Months Postnatal Evaluation (Study # REGN646-TX-09099/ (b) (4) 00067)

Other

1. A Carcinogenicity Risk Assessment for Dupilumab (REGN668/ SAR231893)
2. Ex-Vivo Cross-Reactivity Study of REGN668 Monoclonal Antibody with a Panel of Normal Human Tissues and REGN646 Monoclonal Antibody with a Panel of Cynomolgus Monkey Tissues (Study # REGN646-TX-08058/ (b) (4) 00057)

4 Pharmacology

4.1 Primary Pharmacology

Dupilumab is a fully human monoclonal antibody against IL4R α , a component of both Type I and Type II IL4 receptors, as well as the IL 13 receptor system. Dupilumab binds to recombinant soluble monomeric human IL4R α with a KD of ~ 30 pM and to dimeric human IL4R α with a KD of ~ 12 pM.

The ability of dupilumab to antagonize IL-4 (Type I and Type II) and/or IL-13 (Type II) receptor signaling was demonstrated in vitro and in vivo. Dupilumab inhibited IL-4-mediated upregulation of CD23 in human peripheral blood mononuclear cells (PBMC) that express both IL-4 and IL-13 signaling receptors (Type I and II signaling) and in Ramos Burkitt lymphoma cells that express only IL-4 signaling receptors (Type I signaling). Dupilumab also inhibited IL-4 and IL-13 mediated luciferase activity in a HEK293/STAT6 transfected cell line. Finally, dupilumab inhibited IL-4 and IL-13 induced TARC (thymus and activation regulated chemokine, also known as CCL17) in human whole blood. In vivo, dupilumab inhibited lung mucus secretion (produced by IL-25-induced IL-13 signaling) in a mouse model engineered to express IL4R α .

The amino acid sequence homology between murine and human IL-4R α extracellular domains is 52.2%, while the sequence homologies between the IL-4R α extracellular domains from human and various monkey species were 91.8% for cynomolgus monkey, 91.3% for rhesus, and 84% for marmoset. Because dupilumab does not cross-react with species used to evaluate nonclinical safety, the sponsor developed a fully human homologous antibody, REGN646, specific for cynomolgus monkey IL4R α . REGN646 binds to recombinant soluble monomeric monkey IL4R α with a KD of ~ 2.5 nM and to dimeric monkey IL4R α with a KD of ~ 31 pM. The ability of REGN646 to antagonize IL-4 and IL-13 receptor signaling was demonstrated in vitro. REGN646 inhibited IL-4 and IL-13 mediated luciferase activity in a monkey IL-4R α -transfected HEK293/luciferase reporter cell line. REGN646 also inhibited TARC production in cynomolgus monkey whole blood.

The sponsor has also developed two mouse IL-4R α receptor antagonist monoclonal antibodies, M2M1869N and REGN1103. REGN1103 exhibits high affinity binding to monomeric mouse IL-4R α protein (K_D = 86.7pM). The ability of REGN1103 to antagonize IL-4 and IL-13 receptor signaling in mice was demonstrated in vitro and in vivo.

The in vivo efficacy of dupilumab and the mouse homologous antibody, REGN1103, was evaluated using a preventative mouse model of allergen-induced type 2 inflammation. Efficacy of dupilumab was evaluated in *Il4ra*^{hu/hu} *Il4*^{hu/hu} mice and efficacy of REGN1103 was evaluated in wild type Balb/c mice. In both studies, mice were repeatedly exposed intranasally with House Dust Mite (HDM) extract as the source of HDM allergen. The HDM allergen-associated inflammation represents a classic type 2 immune response, causing an increase in eosinophil infiltration into the lung, an increase in goblet cell metaplasia, and increases in serum total IgE and allergen-specific IgG1 levels. Both dupilumab and REGN1103 decrease circulating levels of IgE and allergen-specific IgG1, reduce pulmonary infiltration of eosinophils, and reduce goblet cell metaplasia in this model of type 2-driven inflammation.

4.2 Secondary Pharmacology

None

4.3 Safety Pharmacology

Separate safety pharmacology studies were not required. Evaluation of safety pharmacology parameters were incorporated in repeat dose toxicology studies in cynomolgus monkeys with REGN646. There were no test article-related effects on the central nervous system or respiratory clinical signs noted, and no effects on blood pressure and ECGs were detected in the repeat-dose toxicity studies in monkeys administered REGN646 IV doses up to 100 mg/kg/week for 5 weeks or 25 mg/kg/week for 6 months or weekly SC doses up to 100 mg/kg/week for 6 months.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Dupilumab PK was examined in both rats and cynomolgus monkeys following a single SC or IV injection at multiple dose levels. Although dupilumab does not interact with physiologically relevant affinity to the cynomolgus monkey IL-4 receptor, the single dose non-GLP PK study was performed in this species to provide baseline PK information in the absence of any potential target-mediated elimination mechanisms. Similarly, dupilumab was administered to rat in a single dose non-GLP study to provide baseline PK information to assess the effects of manufacturing process changes during development on the in vivo behavior of dupilumab. In these studies, dupilumab exhibited dose proportionality with respect to C_{max} and AUC_{0-168h} and, as is typical for a monoclonal antibody that does not bind to the host, dupilumab displayed a long circulating half-life (linear kinetics) in both species, indicative of non-target-mediated clearance based elimination. Bioavailability was greater than 90% following SC dosing in monkey and approximately 85% following SC dosing in rat. Dupilumab did not promote substantial immunogenicity following dosing in cynomolgus monkey.

REGN646 PK parameters in cynomolgus monkey were assessed following single dose administration (single IV or SC dose at multiple dose levels) in pilot non-GLP studies. REGN646 exhibited substantial immunogenicity, leading to accelerated drug clearance in most animals. At low dose (1 mg/kg), prior to the onset of the anti-REGN646 antibody response, serum REGN646 was completely cleared from circulation, suggesting that target-mediated clearance based mechanisms dominated the elimination phase of the antibody. At higher REGN646 concentrations (5 mg/kg IV, and 15 mg/kg IV and SC doses), the anti-drug antibody response (ADA) correlated with accelerated clearance in all animals. It is possible that the high rate of ADA arises from expression of IL-4R α on antigen-presenting dendritic cells, which could facilitate internalization and presentation of the bound antibody and give rise to a rapid immune response against the human protein. Consistent with this hypothesis, dupilumab, which does not substantially bind to monkey IL-4R α , was far less immunogenic over a similar time interval.

5.2 Toxicokinetics

Included in toxicity studies

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicology studies were conducted.

6.2 Repeat-Dose Toxicity

Because dupilumab does not cross-react with species used to evaluate nonclinical safety, the toxicology studies were conducted with homologous anti-IL-4R α monoclonal antibodies REGN646 and REGN1103 in cynomolgus monkeys and CD-1 mice, respectively, to identify potential hazards associated with inhibition of IL-4 and IL-13.

The following toxicology studies were reviewed under INDs (b) (4) and 107969. A summary of these studies is provided below.

Study 1 A 1-Month Exploratory Intravenous Infusion Tolerability and Safety Study of REGN646 in Cynomolgus Monkeys (Study # REGN646-TX-08046/ (b) (4) 460016)

In this 1-month non-GLP exploratory toxicity study, REGN646 was administered to cynomolgus monkeys once weekly for 4 weeks (5 doses) via a 30-minute intravenous infusion at doses of 0, 5, 25 or 100 mg/kg/week. One animal per sex per group was included in 5 and 25 mg/kg/week groups and only one male in control and 100 mg/kg/week groups in in this exploratory study. Decreased neutrophils and increased lymphocytes were observed in males versus controls and in females versus pretest values. Dose-related decreases in testes weight correlated with organ development levels were noted; relationship of this finding to the test article is unknown. Both animals in the low dose group developed significant levels of anti-drug antibody (ADA). However, no NOAEL was determined due to inadequate animal numbers and exclusion of females from control and high dose groups. With few animals evaluated, the effects observed in this study are of limited utility.

Study 2 A 5-Week (Once-weekly) 30-Minute Intravenous Infusion Toxicity and Toxicokinetic Study of REGN646 with an 8-Week Recovery Period in Cynomolgus Monkeys (Study #: REGN646-TX-08053/ (b) (4) 460017)

REGN646 was administered to cynomolgus monkeys once weekly for 5 weeks (5 doses) via a 30-minute intravenous infusion at doses of 0, 1, 5, 25 or 100 mg/kg/week. There were 5 monkeys/sex/group with 3 monkeys/sex/group for main study and 2 monkeys/sex/group for recovery period.

No REGN646 related adverse effects on clinical signs, clinical pathology, ophthalmology, food consumption, body weight, body temperature, ECG, blood pressure, or any organ weights were observed in this study. Microscopic findings (i.e. mononuclear infiltrate findings, as well as the microscopic findings in the cecum, colon, duodenum, heart, liver, mesenteric lymph node, and sciatic nerve) were either not observed or did not demonstrate any dose-response in the 13-week SC study, and therefore are not likely test article-related. This conclusion was supported by historical control histopathology data provided by the sponsor. No target organs of toxicity were identified in this study. Therefore, the NOAEL was 100 mg/kg/week in this 5-week monkey IV study, which was associated with an AUC_{all} of 545,832 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and AUC_{all} of 481,904 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in females (male and female average $AUC_{all} = 513,868 \mu\text{g}\cdot\text{hr}/\text{mL}$).

Anti-REGN646 antibodies (ADA) were detected in all dose groups except for the HD group. The incidence of ADA response was inversely related to dose levels. All animals (10/10) and most animals (7/10) had an ADA response in the 1 and 5 mg/kg/week groups, respectively. Monkeys that developed a drug-specific ADA response had a

corresponding reduction in serum REGN646 concentrations relative to ADA-negative animals. The presence of ADA was not associated with adverse effects and did not preclude comprehensive assessment of safety.

Study 3 A 13-Week Subcutaneous Toxicity Study with REGN646 in Cynomolgus Monkeys Followed by a 13-Week Recovery Phase (Study # REGN646-TX-08056/8202348)

REGN646 was administered subcutaneously to cynomolgus monkeys once weekly for 13 weeks (14 doses) at doses of 0, 1, 5, 25 or 100 mg/kg/week. There were 6 monkeys/sex/group with 4 monkeys/sex/group for main study and 2 monkeys/sex/group for recovery period.

No target organs of toxicity were identified in these studies. However, IgE levels were decreased in mid- and high-dose females in the mid- to late dosing phase, as well as in the recovery phase. Decreased IgE levels are a potential pharmacologic effect of this drug class. No REGN646 related adverse effects on clinical signs, clinical and histological pathology, ophthalmology, food consumption, body weight, body temperature, ECG, blood pressure, or any organ weights were observed in this study. Microscopic findings in the 5-week IV study were either not observed or did not demonstrate any dose-response in this study, and therefore are not likely test article-related. This conclusion was supported by historical control histopathology data provided by the sponsor. Therefore, the NOAEL was 100 mg/kg/week in this 13-week monkey SC study, which was associated with an AUC_{all} of 707,900 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and AUC_{all} of 660,700 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in females (male and female average $AUC_{all} = 684,300 \mu\text{g}\cdot\text{hr}/\text{mL}$).

ADA was detected in all dose groups. All animals (12/12) and most animals (11/12) had a positive ADA response in the 1 and 5 mg/kg/week groups, respectively. Although ADA responses were often associated with a corresponding reduction in serum REGN646 concentration, systemic exposure was maintained throughout the dosing period in 23 out of 24 animals that received saturating dosages of REGN646 (i.e., $\geq 25 \text{ mg/kg/week}$). The presence of ADA responses in the REGN646-treated monkeys did not result in any adverse effects and did not preclude comprehensive evaluation of safety.

Study 4 6-Month Intravenous Infusion and Subcutaneous Toxicity Study of REGN646 in Cynomolgus Monkeys with a 3-Month Recovery Period (Study # REGN646-TX-10004)

Repeat weekly administration of REGN646 for 6 months (27 doses) to cynomolgus monkeys at doses of 0 (clinical vehicle), 25 and 100 mg/kg/week by the subcutaneous route (SC) or at 25 mg/kg/week by the intravenous route as a 30-minute infusion (IV) was well tolerated. No test article related effects on clinical signs, body weights, food consumption, ECG and ophthalmology parameters were noted. Clinical pathology (hematology, coagulation, clinical chemistry, and urine analyses) and immunology assessments (total immunoglobulin evaluation, immunophenotyping and TDAR assay)

did not reveal any significant changes attributed to the test article.

Necropsy and histological examination showed that the repeat SC or IV administration of placebo and REGN646 was well tolerated. The microscopic findings noted for the kidney, ovaries, epididymides, seminal vesicle, prostate, skeletal muscle, duodenum, colon, and pancreas are not considered test article related based on the Testing Facility's historical control data provided by the sponsor. No target organs of toxicity were identified in this study.

However, there was REGN646-related and dose-dependent perivascular lymphocytic infiltration (minimal to moderate), with plasma cells, lymphoblasts or lymphoid follicles, in the hypodermis of the SC administration sites from REGN646 treated monkeys, which was partially reversible and suggestive of an immune reaction. Minimal to moderate diffuse or multifocal perivascular inflammation or fibrosis in the hypodermis of the SC administration sites from most control and REGN646 treated monkeys may be attributed to the SC administration procedure or a possible irritant potential of the vehicle. These findings were almost fully reversible by the end of the recovery period.

Sustained exposure to REGN646 was observed throughout each monitored dosing interval for a majority of monkeys that received REGN646 by SC or IV administration. C_{max} and AUC_{0-168h} increased between each dose administration. Drug exposures were essentially at steady-state levels by the middle of the study. The majority of recovery animals had measurable serum REGN646 concentrations at the end of the recovery Week 12.

Anti-REGN646 antibodies were detected in 8 of 32 REGN646-treated monkeys. Four of these monkeys (3 in the 25 mg/kg/week IV group; 1 in the 25 mg/kg/week SC group) had a corresponding decrease in serum REGN646, suggesting that the presence of a positive ADA response may have resulted in the clearance of REGN646. However, the presence of ADA did not preclude most animals from continuous exposure over the course of the treatment period.

Based on the results of this study, the NOAEL following weekly REGN646 administration to cynomolgus monkeys for 6 months was 100 mg/kg/week by the subcutaneous route and 25 mg/kg/week as a 30-minute intravenous infusion. After 6 months of treatment, the AUC_{0-168h} values (males and females combined) are 790,667 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 149,246 $\mu\text{g}\cdot\text{h}/\text{mL}$ for 100 mg/kg/week, SC and 25 mg/kg/week, IV, respectively.

Study 5 SAR231893 - Exploratory 5-Week Subcutaneous Toxicology Study in Mice with REGN1103 (Study #: REGN1103-TX-10054/ (b) (4) 1347)

The toxicity and toxicokinetic profile of mouse homologous antibody REGN1103 was evaluated in a 5 week SC repeat dose exploratory non-GLP study in mice. Following repeated weekly or twice-weekly SC dosing to mice, REGN1103 maximal serum concentrations (C_{max}) increased in a dose-dependent manner and the AUC_{0-168h} values

increased in a greater than dose-proportional manner and showed accumulation of REGN1103 between Weeks 3 and 5. These data indicate that there was substantial exposure to REGN1103 during the dosing period. No REGN1103-related mortality occurred in this study and no REGN1103-related clinical signs were observed. An REGN1103-related decrease in body weight gain of males at 20 mg/kg/week (-16%) and 200 mg/kg/week (-19%), and in females at 10 mg/kg/week (-20%) was observed through the study duration (Day 1-29). There were no test article related effects on food consumption, hematology or clinical chemistry parameters. No REGN1103-related organ weight changes, macroscopic or microscopic findings were observed. The decreased body weight gain did not appear to exhibit a dose related effect. Therefore, the decrease in body weight gain was not considered to be a test article related adverse effect. Therefore, the NOAEL was 200 mg/kg/week (100 mg/kg/dose, 2x/week), under the conditions of this study.

7 Genetic Toxicology

Genetic toxicology studies are not applicable to monoclonal antibodies and were not conducted with dupilumab based on ICH S6 guidance, *Guidance for Industry – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

8 Carcinogenicity

No carcinogenicity studies were conducted with dupilumab or homologous monoclonal antibodies REGN646 and REGN1103 in any species.

The sponsor provided an updated/amended carcinogenicity risk assessment for dupilumab in this BLA submission. The sponsor stated that no changes have been made to the original carcinogenicity risk assessment for dupilumab that was submitted to the Division on April 4, 2014 and reviewed under IND 107969.

This carcinogenicity risk assessment includes a literature evaluation and weight of evidence analysis for the potential role of the IL-4 and IL-13 pathways in tumor development and anti-tumor immunity. This evaluation together with an evaluation of data from tissue-cross reactivity studies and repeat-dose toxicology studies in mice and cynomolgus monkeys, form the basis of this assessment for dupilumab. A brief summary is provided below.

A weight of evidence analysis of published literature regarding the potential biological effects of IL-4R α inhibition does not support a causal mechanistic/target-related link between IL-4R α inhibition and increased cancer risk. Literature studies have demonstrated that IL-4/IL-13 activation of the IL-4R α pathway is predominantly pro-tumorigenic 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 anti-apoptotic 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.

There were no neoplastic or test article-related non-neoplastic proliferative lesions in the completed three pivotal repeat dose toxicity studies conducted in cynomolgus monkeys, including a 5-week intravenous infusion (IV), a 13-week subcutaneous (SC) and a 6-month IV and SC studies, and an enhanced pre- and postnatal developmental toxicity study (ePPND) in cynomolgus monkeys with REGN646. No test article related effects on immune system parameters including serum immunoglobulin concentrations (except IgE levels in 13-week study), hematology, TDAR, lymphocyte phenotyping, microscopic findings in lymphoid tissues were observed in these studies. Similar results were obtained in a 5 week SC repeat dose exploratory study in mice with a mouse homologous antibody REGN1103. Overall, data from toxicology studies do not suggest carcinogenic potential for dupilumab.

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. Adequate labeling based on published literature and animal data from the sponsor as well as post-marketing monitoring of malignancy in patients should be sufficient at this time. Therefore, no additional nonclinical studies are recommended to evaluate the carcinogenic potential of dupilumab from a Pharmacology/Toxicology perspective. The Exec CAC committee members provided their concurrence via email that nonclinical carcinogenicity studies are not needed for dupilumab on May 5, 2014.

9 Reproductive and Developmental Toxicology

A subcutaneous fertility study in young sexually mature male and female mice with REGN1103 and an enhanced pre- and postnatal developmental toxicity study (ePPND) in cynomolgus monkeys with REGN646 were reviewed under IND 107969. A summary of the two studies is provided below.

Study 1 SAR231893 (REGN668): Subcutaneous Fertility Study in Mice with REGN1103 (Study # REGN1103-TX-11097)

In a fertility study, young sexually mature male and female mice (approximately 8 to 9 weeks of age) were administered REGN1103 at 0 (clinical vehicle), 25, 75, or 200 mg/kg by SC injection once weekly. Male mice were administered the vehicle or REGN1103 for 4 weeks prior to cohabitation, through the cohabitation period, and until animal's necropsy (a minimum of 8 doses). Female mice were administered the vehicle or REGN1103 for 2 weeks prior to cohabitation, through the cohabitation period, and into early gestation (Gestation Day (GD) 07) (a minimum of 4 doses).

There was no test article related mortality. No test article related changes in clinical signs, body weights, body weight gains, and food consumption were observed. For males, no test article related changes were observed for any of the mating and fertility parameters, and the weights of the reproductive organs (testes, epididymides, seminal vesicles and prostate). For females, there were no test article related changes in estrous cycling, mating and fertility parameters (male fertility index, pregnancy index, pre/post implantation loss). Pregnancy occurred in 24 (100.0%), 21 (87.5%), 22 (91.7%) and 23 (95.8%) mice in the 0, 25, 75 and 200 mg/kg/week dose groups, respectively. No test article related effects on any ovarian or uterine parameters were noted. There were no test article related microscopic findings.

Therefore, the NOAEL for paternal and maternal toxicity was 200 mg/kg/week under the conditions of this study. The NOAEL for effects on fertility, reproductive performance and embryo viability was 200 mg/kg/week based on the results from this study.

Study 2 Enhanced Pre-Postnatal Toxicity Study of REGN646 Administered by Subcutaneous Injection to Pregnant Cynomolgus Monkeys with 6-Months Postnatal Evaluation (Study # REGN646-TX-09099/ (b) (4) 00067)

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.

For all adult females during gestation through Postpartum Day (PPD) 180, there were no test article related effects on clinical signs or changes in food consumption, body weight, clinical pathology parameters, lymphocyte subsets or serum immunoglobulin concentrations. No test article related effects on fetal development and duration of gestation were observed. During major organogenesis (prior to GD50), embryonic losses in both dose groups were comparable to the vehicle control and were not REGN646 dose-dependent, with the overall losses in REGN646-treated animals comparable to the test facility historical control data. The overall rate of neonatal death was 5 of 20 (25%) in the vehicle group, 10 of 20 (50%) in the 25 mg/kg/week group and 3 of 18 (16.7%) in the 100 mg/kg/week group. There was no dose dependent increase in neonatal death since the high dose group percentage loss was less than the low dose and vehicle groups. Over 85% of the dams were demonstrated to be continuously exposed to REGN646 in the two drug-treated groups during gestation and throughout the first 91 days of the post-partum period.

The postnatal growth and development of the offspring was monitored for a period of 6 months postpartum. REGN646 was detected in serum samples of infants from REGN646-treated dams. Approximately 85% of infants (17 of 20) in both dose groups had measurable REGN646 serum concentrations 28 days post-birth and 11 of 12 infants from the 100 mg/kg/week group had measurable concentrations 91 days post-

birth. Overall, the concentrations of REGN646 in the offsprings were comparable to those in the corresponding dams, indicating that the monkey fetuses do have adequate systemic exposure to REGN646 from in utero exposure. A minority of the REGN646-treated dams (4 in the 25 mg/kg/week group and 1 in the 100 mg/kg/week group) that tested ADA positive had a corresponding decrease in REGN646 serum concentrations relative to similarly treated and ADA negative animals.

No test article related changes in clinical signs, body weight, physical examinations, infant measurements, neurobehavioral assessment, organ weight or skeletal evaluations were noted during the postnatal period. There were no test article related effects on immune system parameters including serum immunoglobulin concentrations, hematology, TDAR, lymphocyte phenotyping, microscopic findings in lymphoid tissues. No test article related macroscopic or microscopic findings were noted for the infants. The growth and development of the infants was within normal limits for infant cynomolgus monkeys.

Under the conditions of this study, the NOAEL for maternal and developmental toxicity was 100 mg/kg/week.

10 Special Toxicology Studies

Study 1 Ex-Vivo Cross-Reactivity Study of REGN668 Monoclonal Antibody with a Panel of Normal Human Tissues and REGN646 Monoclonal Antibody with a Panel of Cynomolgus Monkey Tissues (Study # REGN646-TX-08058/ (b) (4) 00057)

This study was reviewed under both INDs (b) (4) and 107969. A brief summary of the study is provided below.

The potential tissue cross-reactivity of dupilumab and REGN646 was evaluated in a panel of normal human tissues and cynomolgus monkey tissues, respectively (Study No. (b) (4) 00057). Fresh-frozen human and cynomolgus monkey tissues were sectioned, fixed, and incubated with optimal (5.0 µg/mL) or supra-optimal (50.0 µg/mL) concentrations of dupilumab or REGN646, or control article (human IgG4, kappa). Sections of sepharose chromatography beads covalently coupled with recombinant human or cynomolgus monkey IL-4R monomer were used for positive controls. Sections of sepharose chromatography beads coupled with recombinant nerve growth factor were used for negative controls. Immunohistochemistry was validated by staining with anti-CD31. The following tissues from both humans and monkeys were tested (n=3 separate individuals and n=3 separate monkeys for REGN668 and REGN646, respectively): adrenal, bladder, blood, bone marrow, breast, cerebellum cerebral cortex, colon, endothelium (aorta), eye, fallopian tube, gastrointestinal tract, heart, kidney (glomerulus and tubule), liver, lung, lymph node, ovary, pancreas, parathyroid, parotid (salivary) gland, pituitary, placenta, prostate, skin, spinal cord, spleen, striated muscle, testis, thymus, thyroid, tonsil, ureter, and uterus (cervix and endometrium).

Dupilumab binding in human tissues: No dupilumab specific staining was observed in human tissues. Diffuse cytoplasmic staining of individual cells was observed in thymus sections stained with 5.0 µg/mL dupilumab, but not in sections stained with control IgG4, kappa. Similar staining was also observed in sections stained with dupilumab and IgG4, kappa control at 50 µg/mL, thus suggesting that staining in the thymus was nonspecific background. Other nonspecific background staining was noted in scattered, likely inflammatory, cells in blood, colon, GI tract, liver, lung, lymph node, spleen, and tonsil.

Scattered bone marrow cells had dark cytoplasmic staining with both concentrations of dupilumab and IgG, kappa control and were considered uninterpretable.

REGN646 binding in monkey tissues: No REGN646 specific staining was observed in monkey tissues. Nonspecific background staining was noted in the same tissues as in humans (blood, colon, GI tract, liver, lung, lymph node, spleen, tonsil, thymus, and bone marrow).

Juvenile Animal Toxicology Studies:

No juvenile toxicology studies were conducted. A study conducted in cynomolgus monkeys to assess the effects of REGN646 on pre- and post-natal embryo-fetal and infant development revealed no test article-related effects in infant monkeys up to six months of age.

11 Integrated Summary and Safety Evaluation

Dupilumab (dupilumab) is a recombinant human immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) directed against the IL-4 receptor alpha (IL-4Rα) subunit, which is a component of IL-4 receptors Type I and Type II, as well as the IL-13 receptor system. Dupilumab binds to recombinant soluble monomeric human IL-4Rα with a KD of ~ 30 pM and to dimeric human IL-4Rα with a KD of ~ 12 pM. The ability of dupilumab to antagonize IL-4 (Type I and Type II) and/or IL-13 (Type II) receptor signaling was demonstrated in vitro and in vivo. Dupilumab is expected to inhibit the Th2 pathway selectively, which is responsible for several pathophysiological mechanisms. The sponsor believes that its downregulation may prevent or reverse the development of atopic dermatitis.

The sponsor submitted an original 351a BLA application for Dupixent (dupilumab) Injection (via subcutaneous route), 150 mg/mL indicated 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 sponsor is also developing dupilumab for the treatment of asthma.

Because dupilumab does not cross-react with species used to evaluate nonclinical safety, the sponsor developed a fully human homologous antibody, REGN646, specific for cynomolgus monkey IL-4Rα and two anti-mouse IL-4Rα receptor monoclonal antibodies, M2M1869N and REGN1103. REGN646 binds to recombinant soluble monomeric monkey IL-4Rα with a KD of ~ 2.5 nM and to dimeric monkey IL-4Rα with a

KD of ~ 31 pM. The ability of REGN646 to antagonize IL-4 and IL-13 receptor signaling was demonstrated in vitro. Similar results were obtained with M2M1869N and REGN1103 in mice.

The sponsor submitted 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 in cynomolgus monkeys with REGN646.

No REGN646 related adverse effects (including effects on the immune system) 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. However, IgE levels were decreased in mid- and high-dose females in the mid- to late dosing phase, as well as in the recovery phase in the 13-week study in monkeys. Decreased IgE levels are a potential pharmacologic effect of this drug class. No REGN646 related adverse effects on clinical signs, clinical pathology, ophthalmology, food consumption, body weight, body temperature, ECG, blood pressure, or any organ weights were observed in 5- and 13-week studies in the monkey. Microscopic findings in the 5-week IV study in monkeys (i.e. mononuclear infiltrate findings, as well as the microscopic findings in the cecum, colon, duodenum, heart, liver, mesenteric lymph node, and sciatic nerve) were either not observed or did not demonstrate any dose-response in the 13 week SC study in monkeys, and therefore are not likely test article-related. This conclusion was supported by the evaluation of the findings in the 6-month study in monkeys and historical control histopathology data provided by the sponsor. There were no neoplastic or test article-related non-neoplastic proliferative lesions in these studies in monkeys. The NOAEL was 100 mg/kg/week in both the 5-week monkey IV study and the 13-week monkey SC study. The NOAEL following weekly REGN646 administration to cynomolgus monkeys for 6 months was 100 mg/kg/week by the subcutaneous route and 25 mg/kg/week as a 30-minute intravenous infusion, under the conditions of the study.

Anti-REGN646 antibodies (ADA) were detected in 8 of 32 REGN646-treated monkeys in the 6-month study. Four of these monkeys had a corresponding decrease in serum REGN646, suggesting that the presence of a positive ADA response may have resulted in the clearance of REGN646. However, the presence of ADA did not preclude most animals from continuous exposure over the course of the treatment period. TK analyses in these studies revealed adequate exposure of monkeys to REGN646. The serum concentrations of REGN646 at 25 and 100 mg/kg/week in these repeat dose toxicology studies were consistently ≥ 10 -fold above the ex vivo monkey blood bioassay IC_{90} of ~39 $\mu\text{g/mL}$. The serum concentrations of REGN646 at the NOAEL in the 5- and 13-week monkey toxicology studies exceeded the concentration required to block IL 4R α signaling in the in vitro and ex vivo assays. The AUC_{0-168h} values (males and females combined) are 513,868 $\mu\text{g}\cdot\text{hr/mL}$ for 100 mg/kg/week in the 5-week monkey IV study and 684,300 $\mu\text{g}\cdot\text{hr/mL}$ for 100 mg/kg/week in the 13-week monkey SC study. After 6 months of treatment, the AUC_{0-168h} values (males and females combined) are 790,667 $\mu\text{g}\cdot\text{h/mL}$ and 149,246 $\mu\text{g}\cdot\text{h/mL}$ for 100 mg/kg/week, SC and 25 mg/kg/week, IV, respectively.

The toxicity and toxicokinetic profile of mouse homologous antibody REGN1103 was evaluated in a 5 week SC repeat dose exploratory study in mice. Following repeated weekly or twice-weekly SC dosing to mice, REGN1103 maximal serum concentrations (C_{max}) increased in a dose-dependent manner and the AUC_{0-168h} values increased in a greater than dose-proportional manner and showed accumulation of REGN1103 between Weeks 3 and 5. The NOAEL was 200 mg/kg/week (100 mg/kg/dose, 2x/week), under the conditions of this study.

In an ePPND study, weekly subcutaneous administration of REGN646 to pregnant adult female cynomolgus monkeys at doses of 25 mg/kg/week 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. No test article related effects on pregnancy, fetal development and duration of gestation were observed. Over 85% of the dams were demonstrated to be continuously exposed to REGN646 in the two drug-treated groups during gestation and throughout the first 91 days of the postpartum period.

The postnatal growth and development of the offspring was monitored for a period of 6 months postpartum. REGN646 was detected in serum samples of infants from REGN646-treated dams. Approximately 85% of infants (17 of 20) in both dose groups had measurable REGN646 serum concentrations 28 days post-birth and 11 of 12 infants from the 100 mg/kg/week group had measurable concentrations 91 days post-birth. Overall, the concentrations of REGN646 in the offspring were comparable to those in the corresponding dams, indicating that the monkey fetuses do have adequate exposure during the postnatal period. No treatment related effects on clinical signs, body weight, physical examinations, infant measurements, neurobehavioral assessment, organ weight or skeletal evaluations were noted during the postnatal period. There were no test article related effects on immune system parameters including serum immunoglobulin concentrations, hematology, TDAR, lymphocyte phenotyping, microscopic findings in lymphoid tissues during the postnatal period. No test article related macroscopic or microscopic findings were noted for the infants. The growth and development of the infants was within normal limits for infant cynomolgus monkeys. The NOAEL for maternal and developmental toxicity was 100 mg/kg/week based on the results of this study, which is 10 times the maximum recommended human dose (MRHD) on a mg/kg basis.

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.

No genetic toxicology or carcinogenicity studies have been conducted with dupilumab. The sponsor provided an amended carcinogenicity risk assessment for dupilumab. A weight of evidence analysis of published literature regarding the potential biological effects of IL-4R α inhibition does not support a causal mechanistic/target-related link

between IL-4R α inhibition and increased cancer risk. No nonclinical studies to address the carcinogenic potential of dupilumab were recommended.

Dupixent is approvable for the treatment of moderate-to-severe atopic dermatitis from a Pharmacology/Toxicology perspective. There is no nonclinical PMC/PMR for this BLA.

12 Appendix/Attachments

Appendix #1: Recommended Label and Supportive Information

Multiples of human exposure have been derived based on a mg/kg basis.

Maximum recommended human dose:
(2 x 300 mg) \div 60 kg = 10 mg/kg

The NOAEL in monkey ePPND study = 100 mg/kg

Multiple of clinical dose:
100 mg/kg \div 10 mg/kg = 10

Recommended Label

HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated 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. DUPIXENT can be used with or without topical corticosteroids.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on DUPIXENT use in pregnant women to inform any drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4R α) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of a homologous antibody against IL-4R α up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations or on morphological, functional or immunological development were observed in the infants from birth through 6 months of age.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4R α subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor, and both IL-4 and IL-13 signaling through the Type II receptor.

Blocking IL-4R α inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines and chemokines.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab. (b) (4)

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature mice that were subcutaneously administered a homologous antibody against IL-4R α at doses up to 200 mg/kg/week.

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/s/

Renqin DUAN
12/05/2016

BARBARA A HILL
12/05/2016

Comments on BLA 761055 dupilumab

From: A. Jacobs, AD

Date: Nov 1, 2016

1. I concur that there are no nonclinical approval issues
2. The term “homologous” is used in ICHS6R1 and is the preferred term for closely related monoclonal antibodies or other proteins used in toxicology studies of nonhuman species, rather than “analogous” or “surrogate” <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM194490.pdf>
3. I have conveyed some other suggestions to the reviewer and supervisor, and they will be addressed as appropriate.

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

/s/

ABIGAIL C JACOBS
11/02/2016