CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761033Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology/Toxicology Review

Date: March 18, 2016
From: Timothy J. McGovern, PhD, ODE Associate Director for Pharmacology and Toxicology, OND IO
BLA: 761033
Agency receipt date: March 30, 2015
Drug: Cinqair (Reslizumab) Injection
Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Indication: Reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

Reviewing Division: Division of Pulmonary, Allergy, and Rheumatology Products

The primary pharmacology/toxicology reviewer and team leader concluded that the nonclinical data for Cinqair (Reslizumab) Injection support approval for the indication listed above.

Cinqair is an intravenous (IV) injection product containing the active pharmaceutical ingredient reslizumab containing 100 mg reslizumab/10 mL vial. Reslizumab is a humanized monoclonal antibody (IgG4 kappa), specific for interleukin-5 (IL-5). The recommended dose of reslizumab is 3 mg/kg administered once every 4 weeks. The Established Pharmacologic Class (EPC) for reslizumab is "interleukin-5 antagonist (IgG4 kappa)". Currently, the only other approved therapy for asthma that targets IL-5 is NUCALA (mepolizumab), an interleukin-5 antagonist monoclonal antibody (IgG1).

Pivotal nonclinical studies were conducted in CD-1 mice and Cynomolgus monkeys; both were identified as relevant species in a series of pharmacology studies. In toxicology studies up to 6 months duration, no target organs of toxicity were identified in either mice or monkeys at an IV dose up to 25 mg/kg once every 4 weeks. Eosinophil counts were reduced in all treatment groups of mice. The NOAELs of 25 mg/kg provided a safety margin of approximately 3-fold compared to the recommended clinical dose based on systemic exposure comparisons.

Studies in juvenile animals were conducted in CD-1 mice as part of a pre- and post-natal development study and in a stand-alone study in monkeys (1.4-2.3 years of age). In mice, a NOAEL of 10 mg/kg was identified based on clinical signs and death in one animal at the high dose of 25 mg/kg. In monkeys, the NOAEL was the high dose of 15 mg/kg.

Genetic toxicity studies were not applicable for this therapeutic biologic protein though reslizumab was negative in two in vitro assays. A transgenic mouse (Tg.rasH2) carcinogenicity study was conducted with dose concurrence by the Executive Carcinogenicity Assessment Committee (ECAC). No drug-related neoplasms were found after dosing up to 500 mg/kg IV once every two weeks.

Reference ID: 3904991

A complete battery of development and reproductive studies was conducted in CD-1 mice and New Zealand white rabbits; both were identified as relevant species. No effects on fertility or development parameters were identified at doses up to 50 mg/kg IV; exposure margins of approximately 6-fold were available in the mouse studies. A safety margin of 17-fold based on mg/kg comparisons was present in the rabbit study. Reslizumab was observed to cross the placenta of pregnant mice and was found in milk of lactating mice following dosing during pregnancy.

Conclusion: I agree with the Division pharmacology/toxicology conclusion that this BLA can be approved from the pharmacology/toxicology perspective. The EPC for reslizumab is appropriate. I have discussed and am in agreement with labeling revisions proposed by the Division; the labeling follows the Pregnancy and Lactation Labeling Rule (PLLR) format and is consistent with current labeling recommendations.

Reference ID: 3904991

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

/s/

TIMOTHY J MCGOVERN
03/18/2016

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:	BLA 761033
Supporting document/s:	SD44
Applicant's letter date:	1/4/2016
CDER stamp date:	1/4/2016
Product:	CINQAIR (reslizumab) Injection
Indication:	For add-on maintenance treatment of patients with severe asthma 18 years and older, and with an eosinophilic phenotype.
Applicant:	Teva Respiratory, LLC.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Galvis, PhD
Supervisor:	Marcie L. Wood, PhD
Division Director:	Badrul A. Chowdhury, MD, PhD
Project Manager:	Colette Jackson

Reference ID: 3889500

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 INTRODUCTION 3

1.3 RECOMMENDATIONS 3

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 6

Reference ID: 3889500

1 Executive Summary

1.1 Introduction

This review evaluates the nonclinical sections of the proposed labeling for CINQAIR (reslizumab) Injection submitted by Teva Branded Pharmaceutical Products R&D, Inc. on January 4, 2016, under BLA 761033. The following sections of the prescribing information were reviewed and are discussed herein: sections 8.1 "Pregnancy", 8.2 "Lactation", [redacted] (b) (4) 10 "Overdosage", 11 "Description" (first paragraph only), 12.1 "Mechanism of Action", and 13 "Nonclinical Toxicology". An integrated review of the nonclinical program to support approval of this BLA was completed on December 16, 2015.

1.3 Recommendations

1.3.3 Labeling

The following is the recommended language for the aforementioned sections of the prescribing information.

8.1 Pregnancy

Risk Summary

[redacted] (b) (4) Monoclonal antibodies, such as reslizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. [redacted] (b) (4) In animal reproduction studies, there was no evidence of embryo-fetal adverse developmental effects with IV administration of reslizumab during organogenesis to pregnant mice and rabbits at doses that produced exposures up to approximately 6 times the exposure at the maximum recommended human dose (MRHD) in mice and approximately 17 times the exposure at the MRHD in rabbits *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. 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.

<u>Clinical Considerations</u>

Disease-Associated Maternal and/or Embryo-Fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Reference ID: 3889500

Data

Animal Data

In two separate embryo-fetal development studies, pregnant mice and rabbits received a single reslizumab dose during the period of organogenesis at 2, 10, and 50 mg/kg (0.4, 1.5, and 6 times the exposures achieved at the MRHD in mice on an AUC basis and 0.67, 3.3, and 17 times the exposures achieved at the MRHD in rabbits on a mg/kg basis). Reslizumab was not teratogenic in mice or rabbits. Embryo-fetal development of IL-5 deficient mice has been reported to be generally unaffected relative to wild-type mice.

In a prenatal and postnatal development study, pregnant CD-1 mice received reslizumab during organogenesis on gestation days 6 and 18 and on postnatal day 14 at 10 or 50 mg/kg (1.5 and 6 times the exposures achieved at the MRHD on an AUC basis). Reslizumab did not have any effects on fetal development up to approximately 4 months after birth. Reslizumab crossed the placenta of pregnant mice. Serum concentrations in pups were approximately 6-8% of those in the dams (parental female mice) on postnatal day 14.

8.2 Lactation

Risk Summary

It is not known whether reslizumab is present in human milk, and the effects of reslizumab on the breast fed infant and on milk production are not known. However, human IgG is known to be present in human milk. Reslizumab was present in the milk of lactating mice following dosing during pregnancy *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CINQAIR and any potential adverse effects on the breast-fed child from CINQAIR or the underlying maternal condition.

Data

Reslizumab was excreted in milk of lactating CD-1 mice that received reslizumab at 10 or 50 mg/kg (1.5 and 6 times the exposures achieved at the MRHD on an AUC basis) during pregnancy on gestation days 6 and 18 and on postnatal day 14. Levels of reslizumab in milk were approximately 5-7% of maternal serum concentrations.

10 OVERDOSAGE

Single doses of up to (b) (4) mg have been administered intravenously to subjects (b) (4) without evidence of dose-related toxicities. There is no specific treatment for an overdose with CINQAIR. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Reference ID: 3889500

11 DESCRIPTION

CINQAIR (reslizumab) is a humanized interleukin-5 antagonist monoclonal antibody (IgG4κ). Reslizumab is produced by recombinant DNA technology in murine myeloma non-secreting 0 (NS0) cells. Reslizumab has a molecular weight of approximately 147 kDa.

12.1 Mechanism of Action

Reslizumab is an interleukin-5 antagonist (IgG4, kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Reslizumab binds to IL-5 with a dissociation constant of 81 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil surface. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Reslizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of reslizumab action in asthma has not been definitively established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 6-month bioassay, reslizumab was administered intravenously once every two weeks for 26 consecutive weeks (14 total doses) to Tg.rasH2 mice at doses up to 516 mg/kg/dose. There was no evidence of carcinogenicity.

Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as reslizumab is unknown.

In a fertility study, administration of reslizumab to parental mice at doses up to 50 mg/kg (approximately 6 times the MRHD on an AUC basis) had no effects on male or female mating or fertility.

Reference ID: 3889500

11 Integrated Summary and Safety Evaluation

Teva submitted revised labeling for CINQAIR (reslizumab) Injection on January 4, 2016, per the Division's request during a teleconference held on December 14, 2015. The content of the nonclinical sections in the revised prescribing information [sections 8.1 "Pregnancy", 8.2 "Lactation", [redacted] (b) (4) 10 "Overdosage", 11 "Description" (first paragraph only), 12.1 "Mechanism of Action", and 13 "Nonclinical Toxicology"] was evaluated. The approved label for NUCALA (mepolizumab) was used for reference as this is the first approved drug of the same pharmacologic class (i.e., humanized interleukin-5 antagonist monoclonal antibody).

The prescribing information was submitted using the new Pregnancy and Lactation Labeling Rule (PLLR) format; therefore, a review was also conducted by the Division of Pediatric and Maternal Health (DPMH). Final language for sections 8.1 "Pregnancy" and 8.2 "Lactation" is based on agreement between DPMH and DPARP and is consistent with current thinking.

Below is the proposed labeling text with recommended edits. Deleted text is shown as strikethrough text and inserted text is shown in red. An explanation for the proposed changes is included in *italics* under "Rationale for Changes".

LABELING EDITS

8.1 Pregnancy

Risk Summary

[redacted] (b) (4) Monoclonal antibodies, such as reslizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. [redacted] (b) (4) In animal reproduction studies, there was no evidence of embryo-fetal adverse developmental effects with [redacted] (b) (4) -IV administration of reslizumab during organogenesis to pregnant mice and rabbits at doses that produced exposures up to approximately 6 times [redacted] (b) (4) -the exposure at the maximum recommended human dose [redacted] (b) (4) (MRHD) in mice and approximately 17 times the exposure at the MRHD in rabbits *[see Data].*

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. 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.

Reference ID: 3889500

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk
In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data
In two separate embryo-fetal development studies, pregnant mice and rabbits (b) (4) received a single reslizumab dose during the period of organogenesis at (b) (4) 2, 10, and 50 mg/kg/ (b) (4) (0.4, 1.5, and 6 times the exposures achieved at the MRHD in mice on an AUC basis and 0.67, 3.3, and 17 times the exposures achieved at the MRHD in rabbits on a mg/kg basis). (b) (4) Reslizumab was not teratogenic in mice or rabbits. Embryo-fetal development of IL-5 deficient mice has been reported to be generally unaffected relative to wild-type mice.

(b) (4) In a prenatal and postnatal development study, pregnant CD-1 (b) (4) mice (b) (4) received reslizumab during organogenesis on gestation days 6 and 18 and on postnatal day 14 at 10, or 50 mg/kg/ (b) (4) (1.5 and 6 times the exposures achieved at the MRHD on an AUC basis) (b) (4) Reslizumab did not have any effects on fetal development up to approximately 4 months after birth. Reslizumab crossed the placenta of pregnant mice. Serum concentrations in pups were approximately 6-8% of those in the dams (parental female mice) on postnatal day 14.

Rationale for Changes in section 8.1 "Pregnancy"
The proposed edits under "Risk Summary" include recommendations made by the DPMH and are based on the PLLR and current thinking. For the animal data, the exposure ratios were changed (b) (4) to AUC because there are adequate AUC data in CD-1 mice. In addition, the reproductive and developmental toxicity studies were revised to include specific details on the timing of dosing in these studies. Further, information regarding embryo-fetal development in IL-5 deficient mice was included as this is public information relevant to this label and to be consistent with the approved label for mepolizumab (NUCALA).

8.2 Lactation

Reference ID: 3889500

Risk Summary

It is not known whether reslizumab is (b) (4) present in human milk, and the effects of reslizumab on the breast fed infant and on milk production are not known. H (b) (4) owever, human IgG is known to be (b) (4) present in human milk (b) (4) Reslizumab (b) (4) was present (b) (4) in the milk of lactating mice following dosing during pregnancy *[see Data]*. (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CINQAIR and any potential adverse effects on the breast-fed child from CINQAIR or the underlying maternal condition.

Data

(b) (4) Reslizumab (b) (4) was excreted in milk of lactating CD-1 mice that received reslizumab at 10 (b) (4) or 50 mg/kg (1.5 and 6 times the exposures achieved at the MRHD on an AUC basis) during pregnancy on gestation days 6 and 18 and on postnatal day 14, (b) (4) Levels of reslizumab in milk were approximately 5-7% of maternal serum concentrations. (b) (4)

Rationale for Changes in section 8.2 "Lactation"

The proposed edits under "Risk Summary" include recommendations made by the DPMH and are based on the PLLR and current thinking. For the animal data, the exposure ratios were added based on AUC data from CD-1 mice. In addition, the levels (b) (4) *were changed to reslizumab levels in milk compared to maternal serum concentrations as this is considered to have more relevance for humans and to be consistent with the approved label for mepolizumab (NUCALA).*

(b) (4)

10 OVERDOSAGE

Single doses of up to (b) (4) mg have been administered intravenously to subjects (b) (4) [redacted] without evidence of dose-related toxicities. There is no specific treatment for an overdose with CINQAIR. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. (b) (4) [redacted]

Rationale for Changes in section 10 "Overdosage"

This section was reviewed to ensure that there were no animal data included. There are no changes proposed for this section from the nonclinical perspective. The changes proposed above were recommended by the clinical team.

11 DESCRIPTION

CINQAIR (r(b) (4)eslizumab) is a humanized interleukin-5 antagonist monoclonal antibody (IgG4κ) (b) (4) [redacted] Reslizumab is produced by recombinant DNA technology in (b) (4) [redacted] murine myeloma non-secreting 0 (NS0) cells. Reslizumab has a molecular weight of approximately 147 kDa.

Rationale for Changes in section 11 "Description"

This section was revised to include the established pharmacologic class (EPC) for reslizumab, which was determined during review of mepolizumab (NUCALA).

Reference ID: 3889500

12.1 Mechanism of Action

Reslizumab is an interleukin-5 antagonist (IgG4, kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. [redacted] (b) (4) [redacted] (b) (4) Reslizumab [redacted] binds to [redacted] (b) (4) -IL-5 with a dissociation constant of 81 pM, inhibiting the bioactivity of IL-5 by blocking [redacted] (b) (4) its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil surface. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, [redacted] (b) (4) neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Reslizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of reslizumab action is asthma has not been definitely established.

[redacted] (b) (4)

Rationale for Changes in section 12.1 "Mechanism of Action"

This section was revised [redacted] (b) (4) *to match the mechanism of action used in the approved label for mepolizumab (NUCALA).*

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[redacted] (b) (4)

In a 6-month [redacted] (b) (4) -bioassay, [redacted] (b) (4) reslizumab was administered intravenously once every two weeks for 26 consecutive weeks (14 total doses) to Tg.rasH2 [redacted] (b) (4) mice at doses up to [redacted] (b) (4) (516 mg/kg/dose.) [redacted] here was no evidence of carcinogenicity.

Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as reslizumab is unknown.

Reference ID: 3889500

(b) (4)

In a fertility study, administration of reslizumab to parental mice at doses up to 50 mg/kg (approximately 6 times the MRHD on an AUC basis), (b) (4) had no effects on male or female mating or fertility.

Rationale for Changes in section 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility"

This section was revised (b) (4) *to remove unnecessary language, and to include the exposure ratios for the fertility study in mice based on AUC.*

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

/s/

CAROL M GALVIS
02/19/2016

MARCIE L WOOD
02/19/2016

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
PHARMACOLOGY/TOXICOLOGY CONSULTATION

Date:	February 9, 2016
To:	Ramesh Potla, PhD, Chemist, Division of Biotechnology Review and Research III, Office of Biotechnology Products (OBP)
From:	Carol M. Galvis, PhD, Pharmacologist, Division of Pulmonary, Allergy, and Rheumatology products (DPARP), Office of Drug Evaluation II (ODEII), Office of New Drugs (OND)
Subject:	Nonclinical Safety Evaluation of Potential Extractables in Cinqair (reslizumab) injection (BLA 761033)

General Information

BLA Number:	**761033**
Submission Date:	March 28, 2015
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.
Drug Product:	Cinqair (reslizumab) injection
Request Number:	Not applicable. This request was received via email.
Request From:	Ramesh Potla, PhD, Chemist, OBP
Date of Request:	February 3, 2016

This consult review includes a nonclinical safety evaluation of potential extractables in Cinqair (reslizumab) injection. Dr. Ramesh Potla, OBP reviewer, submitted a request via email on February 3, 2016 (Attachment 1) to seek input on the adequacy of an extractables risk assessment conducted by Teva Branded Pharmaceutical Products R&D, Inc. (BLA applicant) [redacted] (b) (4)

[redacted] (b) (4) submitted a quarterly report to the FDA as part of a response to an FDA Form 483 observation made during the site's inspection in [redacted] (b) (4). According to the report, [redacted] (b) (4) committed to perform leachables/extractables studies [redacted] (b) (4) in the manufacture of various drug substances, including reslizumab. [redacted] (b) (4) provided an "Extractables Validation Report" (report #15-3723-SPTC-KVGLG) along with a risk assessment conducted by Teva for all the extractables identified during testing. The extractables testing [redacted] (b) (4) was conducted using identical to worst-case conditions (time, temperature, and repeated cycles) and [redacted] (b) (4) modeled after the actual pharmaceutical formulation. Table 1 below includes a list of extractable substances identified during testing. Reslizumab drug substance is packaged in [redacted] (b) (4)

Table 1: List of Extractable Substances Identified

(b) (4)

[redacted]

The safety of each of these extractables was determined by calculating their potential maximum daily dose in humans. The estimates are based on a maximum proposed clinical dose of 3 mg/kg reslizumab every 4 weeks (180 mg/dose for a 60 kg individual). Reslizumab drug product is manufactured in a vial at a concentration of 10 mg/mL. Each vial contains 10 mL of drug product. Therefore, the potential maximum dose of each extractable substance is approximately (b) (4) µg/dose ((b) (4) µg every 4 weeks). Table 2 below includes an example for one of the extractable substances that is present at (b) (4) mg (the highest amount detected for a single substance (b) (4)).

Table 2: Potential Maximum Dose of Extractables in Humans.

(b) (4)

[redacted]

Reference ID: 3884787

Teva concluded that the total amount of each extractable ([redacted] (b) (4) µg/dose) is below the Safety Concern Threshold (SCT) of [redacted] (b) (4) µg/day (defined by Teva as the threshold in which a leachable/extractable would have a dose so low as to present negligible safety concern from carcinogenic and non-carcinogenic effects) and therefore, it is unlikely that exposure to the extractables [redacted] (b) (4) will adversely impact patient safety.

After review of all the relevant information, this reviewer considers that Teva's approach to assess the risk of these extractables is adequate and agrees that there are no safety concerns for the potential maximum levels of these extractables in humans.

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

/s/

CAROL M GALVIS
02/09/2016

MARCIE L WOOD
02/09/2016

Secondary Pharmacology and Toxicology Review for BLA 761-033

TO: BLA 761-033 (Teva Branded Pharmaceutical Products R&D, Inc.)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: December 23, 2015

Overview: I concur with the recommendation of Dr. Carol Galvis (detailed in a nonclinical review dated December 16, 2015) that the pharmacology and toxicology of Cinqair (reslizumab) have been adequately studied and the drug product should be approved from a nonclinical perspective.

Background: Reslizumab (Code names: CEP-38072, CTx55700, SCH 55700) is a humanized monoclonal antibody (IgG4 kappa), specific for interleukin-5 (IL-5). The applicant's proposed indication is to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. The recommended dose of reslizumab is 3 mg/kg administered once every 4 weeks by IV injection.

Pharmacology: Reslizumab is a humanized monoclonal antibody (IgG4 kappa) that targets human IL-5. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. The pharmacology of reslizumab was evaluated both *in vitro* and *in vivo*. *In vitro*, reslizumab binds with similar affinity to human, monkey, and mouse IL-5 (K_D = 24, 20, and 31 pM, respectively). Reslizumab also inhibited human IL-5 stimulation of TF-1 cells with an IC_{50} of 45 pM. *In vivo*, reslizumab was evaluated in animal models of eosinophilia, including mouse, monkey, rabbit, and guinea pig. Treatment with reslizumab decreased pulmonary eosinophilia after ovalbumin challenge in mice and guinea pigs, as well as in *Ascaris*-challenged monkeys. Reslizumab also reduced eosinophil influx into the skin of antigen challenged New Zealand rabbits.

Toxicology: The nonclinical general toxicology program with reslizumab was conducted in CD-1 mice and Cynomolgus monkeys, both of which were determined to be pharmacologically relevant test species. In a chronic 6-month toxicology study in CD-1 mice that received reslizumab by the IV route at doses up to 25 mg/kg once every 4 weeks, eosinophil counts were generally lower in reslizumab treated animals versus controls, though the decreases were not statistically significant. There were no other reslizumab-related findings in this study. The NOAEL of 25 mg/kg q4 weeks provides adequate safety margin (3-fold on an AUC basis) for the proposed clinical dose of 3 mg/kg IV q4 weeks.

In a chronic 6-month toxicology study in Cynomolgus monkeys that received reslizumab by the IV route at doses up to 25 mg/kg once every 4 weeks, no reslizumab-related findings were observed, and the NOAEL was identified as 25 mg/kg q4 weeks. This NOAEL also provides adequate safety margin (3-fold on an AUC basis) for the proposed clinical dose of 3 mg/kg IV q4 weeks.

Carcinogenicity: A 6-month carcinogenicity study was conducted in HRAS transgenic mice, a confirmed pharmacologically relevant mouse strain. In this study, mice received 100, 250, or 500 mg/kg reslizumab IV once every two weeks. No statistically significant, drug-related neoplastic findings were observed in males or females.

Reproductive and Developmental Toxicology: Reproductive and developmental toxicology studies were conducted in CD-1 mice (fertility, embryo-fetal development, and pre-natal/post-natal development) and New Zealand rabbits (embryo-fetal development). There were no drug-related effects on female or male fertility, teratogenicity, or pre-natal and post-natal development.

Labeling: Nonclinical recommendations for reslizumab labeling are currently being developed, and Dr. Galvis will address reslizumab labeling in a separate review.

There are no outstanding Pharmacology and Toxicology issues for this product.

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

/s/

MARCIE L WOOD
12/23/2015

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:	BLA 761033
Supporting document/s:	SD 1
Applicant's letter date:	3/28/2015
CDER stamp date:	3/30/2015
Product:	Cinqair (Reslizumab) Injection
Proposed Indication:	To reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Galvis, PhD
Supervisor:	Marcie Wood, PhD
Division Director:	Badrul A. Chowdhury, MD, PhD
Project Manager:	Colette Jackson

Reference ID: 3861540

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 5

1 EXECUTIVE SUMMARY 7

1.1 INTRODUCTION 7
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 7
1.3 RECOMMENDATIONS 8

2 DRUG INFORMATION 8

2.1 DRUG 8
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 9
2.3 DRUG FORMULATION 9
2.4 COMMENTS ON NOVEL EXCIPIENTS 10
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 10
2.6 PROPOSED CLINICAL POPULATION AND DOSING REGIMEN 10
2.7 REGULATORY BACKGROUND 10

3 STUDIES SUBMITTED 11

3.1 STUDIES REVIEWED 11
3.2 STUDIES NOT REVIEWED 13
3.3 PREVIOUS REVIEWS REFERENCED 15

4 PHARMACOLOGY 15

4.1 PRIMARY PHARMACOLOGY 15
4.2 SECONDARY PHARMACOLOGY 21
4.3 SAFETY PHARMACOLOGY 21

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 22

5.1 PK/ADME 22
5.2 TOXICOKINETICS 23

6 GENERAL TOXICOLOGY 23

6.1 SINGLE-DOSE TOXICITY 23
6.2 REPEAT-DOSE TOXICITY 25

7 GENETIC TOXICOLOGY 36

8 CARCINOGENICITY 36

9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY 36

9.1 FERTILITY AND EARLY EMBRYONIC DEVELOPMENT 37
9.2 EMBRYONIC FETAL DEVELOPMENT 41
9.3 PRENATAL AND POSTNATAL DEVELOPMENT 48

10 SPECIAL TOXICOLOGY STUDIES 67

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 68

12 APPENDIX/ATTACHMENTS 80

Reference ID: 3861540

Table of Tables

Table 1: Cinqair Drug Product Composition. 10
Table 2: In Vitro Activity Profile of Reslizumab. 16
Table 3: Kinetic Values for Reslizumab Binding to Human, Monkey, and Mouse IL-5. . 16
Table 4: Effect of Reslizumab (SCH55700) on Eosinophil Accumulation in the BAL Fluid and Lung Tissue of Allergic CD-1 Mice. 18
Table 5: Summary of Safety Pharmacology Studies Conducted in Rats. 21
Table 6: Summary of Serum Pharmacokinetic Parameters after Single Intravenous Doses of Reslizumab. 23
Table 7: Summary of Single-Dose Studies Conducted with Reslizumab. 24
Table 8: Study Res-4-0006 Design. 30
Table 9: Summary of Hematology Changes Relative to Controls (Study Week 4) – All Animals (N=12). 31
Table 10: Summary of Organ Weight Changes Relative to Controls (Study Week 4)... 32
Table 11: Summary of Histological Findings Observed in Juvenile Monkeys (Incidence and Severity). 33
Table 12: Reslizumab PK Parameters in Monkeys Receiving 1 mg/kg SCH55700 or CTx55700 Weekly for 4 Weeks. 35
Table 13: Reslizumab Mean PK Parameters in Cynomolgus Monkeys. 35
Table 14: Fertility Study Design - Mice. 39
Table 15: EFD Study #P-6378 Design - Mice. 42
Table 16: Summary of Reproductive Parameters - Mice. 43
Table 17: Summary of Skeletal Observations in Offspring – CD-1 Mice. 44
Table 18: EFD Study #P-6379 Design - Rabbits. 46
Table 19: Summary of Reproductive Parameters - Rabbits. 47
Table 20: PPND Study #DS-2010-020 Design. 51
Table 21: PPND Study Design – F_1 Juvenile Toxicity Portion. 51
Table 22: Summary of F_0 Generation Mortality. 53
Table 23: Summary of F_0 Generation Reproductive Parameters. 54
Table 24: Summary of F_1 Generation Survival. 56
Table 25: Summary of F_1 Generation Reproductive Parameters. 57
Table 26: Summary of F_1 Generation Survival – Juvenile Toxicity Portion. 60
Table 27: Summary of Reproductive Parameters - F_1 Generation Juvenile Toxicity Portion. 62
Table 28: Summary (Incidence and Severity) of Histological Findings - F_1 Generation Juvenile Toxicity Portion. 64
Table 29: Summary of Reslizumab Serum Concentration by Study Group (All Groups). 66
Table 30: Summary of Tissue Cross-Reactivity Studies Conducted with Reslizumab. . 67
Table 31: Exposure Margins for the Proposed Clinical Dose of 3 mg/kg Reslizumab – General Toxicology Studies. 75
Table 32: Exposure Margins for the Proposed Clinical Dose of 3 mg/kg Reslizumab – Reproductive and Developmental Studies. 78

Reference ID: 3861540

Table of Figures

Figure 1: Structural Representation of Reslizumab Disulfide Bond Linkage. 9
Figure 2: Effect of SCH 55700 on the Eosinophils in the Skin of Ovalbumin-Challenged Allergic Rabbits. 19
Figure 3: Effect of SCH 55700 on the Pulmonary Eosinophilia Induced by *Ascaris* Challenge in Cynomolgus Monkeys – 0.3 mg/kg. 20
Figure 4: Effect of SCH 55700 on the Pulmonary Eosinophilia Induced by *Ascaris* Challenge in Cynomolgus Monkeys – 0.1 mg/kg. 21
Figure 5: IL-5-Mediated Signaling. 69

Reference ID: 3861540

List of Abbreviations

ADA	Anti-drug antibodies
ADME	Absorption, Distribution, Metabolism, Excretion
AUC	Area under the curve
BAL	Broncho-alveolar lavage
BLA	Biologics License Application
BLQ	Below the limit of quantification
BW	Body weight
CDR	Complementary determining region
C_{max}	Maximal drug concentration in plasma
CMC	Chemistry, Manufacturing, and Controls
CSF	Cerebro-spinal fluid
ECAC	Executive Carcinogenicity Assessment Committee (FDA)
ECG	Electrocardiogram
EDR	Electronic Document Room
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
F	Female
FC	Food consumption
FOB	Functional observation battery
GALT	Gut-associated lymphoid tissue
GD	Gestational day
GLP	Good Laboratory Practice
HD	High-dose
hr	Hour
k_a	Association rate
k_d	Dissociation rate
K_D	Dissociation constant
IC_{50}	Half-maximal inhibitory concentration
i.e.	*Id est* (That is)
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
IP	Intraperitoneal
IV	Intravenous
kDA	Kilo-Dalton
kg	Kilogram
L	Liter
LC/MS/MS	Liquid chromatography with tandem mass spectrometry
LD	Low-dose
LLOQ	Lower limit of quantitation
M	Male
MD	Mid-dose
mg	Milligram

Reference ID: 3861540

mL	Milliliter
MNU	N-methyl-N-nitrosourea
N (or no.)	Number
NC	Not calculated
nM	Nanomolar
NOAEL	No observed adverse effect level
OVA	Ovalbumin
PK	Pharmacokinetics
pM	Picomolar
PND	Post-natal day
QA	Quality assurance
s	Second
SD	Standard deviation
SEM	Standard error of the mean
SPA	Special protocol assessment
TK	Toxicokinetics
T_{max}	Time to maximal drug concentration in plasma
vs.	Versus

Reference ID: 3861540

1 Executive Summary

1.1 Introduction

This review evaluates nonclinical pharmacology and toxicology data to support the safety of reslizumab. Teva Branded Pharmaceutical Products R&D, Inc. submitted a Biologics License Application (BLA) on March 29, 2015, for Cinqair (reslizumab) injection. Reslizumab is a humanized monoclonal antibody (IgG4/κ isotype) that targets interleukin-5 (IL-5) and is proposed to be marketed to reduce exacerbations, relieve symptoms and improve lung function in patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. Reslizumab was developed for eosinophilic asthma under IND 101,399.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical program for reslizumab included studies conducted in mice, rabbits, and monkeys, which were all considered pharmacologically relevant species based on data from in vivo eosinophilia models in sensitized animals (reslizumab administration significantly reduced eosinophils in these animals). Reslizumab binds with similar affinity to human, monkey, and mouse IL-5 (K_D = 24, 20, and 31 pM; respectively, as determined by BIAcore biosensor assays).

In a 6-month toxicology study, CD-1 mice were treated with 2, 10, or 25 mg/kg reslizumab IV once every 28 days. There were no drug-related findings observed in this study. Eosinophil counts were generally lower in treated animals compared to the vehicle control. However, the change was not statistically significant. Reslizumab systemic exposure in mice decreased over time, suggesting the presence of neutralizing anti-reslizumab antibodies (ADA). However, the ADA test was affected by the presence of free drug in serum.

In a 6-month toxicology study, cynomolgus monkeys were treated with 1, 5, or 25 mg/kg reslizumab IV once every 28 days. No drug-related toxicity findings were observed in this study. A few animals in this study developed ADA. However, reslizumab exposure was confirmed in an adequate number of animals to assess the toxicity parameters.

Reproductive and developmental toxicology studies were conducted in CD-1 mice (fertility, embryo-fetal development, and pre-natal/post-natal development) and New Zealand rabbits (embryo-fetal development). There were no drug-related effects on female or male fertility, teratogenicity, or pre-natal and post-natal development.

Because the mouse was identified as a relevant species for reslizumab, the sponsor conducted a 6-month carcinogenicity study using HRAS transgenic mice (which was confirmed to be a pharmacologically relevant mouse strain). In the 26-week study, mice received 100, 250, or 500 mg/kg reslizumab IV once every two weeks. No statistically significant neoplastic findings were observed in males or females.

Reference ID: 3861540

1.3 Recommendations

1.3.1 Approvability

The nonclinical safety program for reslizumab is considered complete and adequate to support safety of the proposed clinical dose of 3 mg/kg every 4 weeks. BLA 761033 is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

A labeling review will be conducted separately.

2 Drug Information

2.1 Drug

CAS Registry Number: 241473-69-8

Generic Name: Reslizumab

Code Names: CEP-38072, CTx55700, SCH 55700

Chemical Name: Anti-human interleukin-5 (IL-5) monoclonal antibody

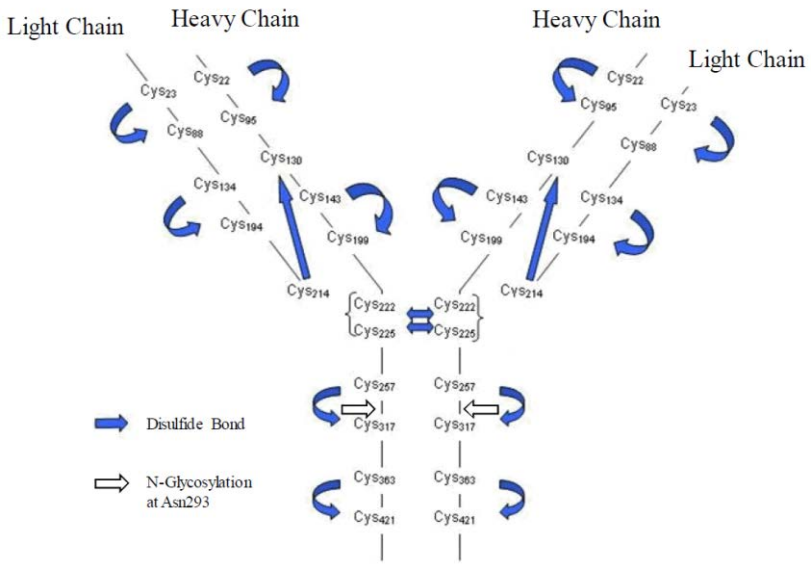
Molecular Weight: 147 kDa

Biochemical Description: Humanized anti-human IL-5 monoclonal antibody of the IgG4 kappa isotype, which contains the CDRs of the rat anti-human antibody (39D10) grafted onto human frameworks.

Structure (figure excerpted from the sponsor's submission):

Reference ID: 3861540

Figure 1: Structural Representation of Reslizumab Disulfide Bond Linkage.



Pharmacologic Class: Humanized interleukin-5 (IL-5) antagonist (IgG_4 kappa)

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application #	*Sponsor*	*CDER OND Division*
BB-IND 009,227	Schering Corporation	DPARP
IND 101,399	Teva Pharmaceuticals[1]	DPARP
IND (b) (4)	Teva Pharmaceuticals	(b) (4)

2.3 Drug Formulation

Cinqair (reslizumab) is supplied as a refrigerated, sterile, single-use, preservative-free solution for intravenous infusion. Cinqair is a clear to slightly hazy/opalescent, colorless to slightly yellow liquid. Since reslizumab is a protein, proteinaceous particles may be present in the solution that appear as translucent to white, amorphous particulates, some of which may have a fibrous nature. Cinqair is supplied as 100 mg in a 10 mL glass vial. Each single vial is formulated as 10 mg/mL reslizumab in an aqueous solution containing 2.45 mg/mL sodium acetate trihydrate, 0.12 mg/mL glacial acetic acid, and 70 mg/mL sucrose, with a pH = 5.5. Cinqair is diluted with saline prior to infusion.

Cinqair solution for infusion is packaged in a Type I clear, borosilicate glass vial, stoppered with a (b) (4) rubber serum stopper and sealed with an aluminum flip-off seal.

The drug product composition and the function of each of the components are listed in Table 1 below (excerpted from the sponsor's submission).

[1] Previous sponsors: Ception and Cephalon

Table 1: Cinqair Drug Product Composition.

Component	Amount per mL	Reference to Standard	Function
Reslizumab (CEP-38072) protein	10 mg	In house specifications	Drug substance
Sucrose (b) (4)	70 mg	NF/Ph. Eur./JP	(b) (4)
Sodium Acetate Trihydrate	2.45 mg	USP/Ph. Eur./JP	
Glacial Acetic Acid	0.12 mg	USP/Ph. Eur./JP	
(D) (4)			

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

There were no impurities or degradants issues that impacted the nonclinical safety program. For any additional issues with drug substance or drug product impurities, refer to the Drug Quality review.

2.6 Proposed Clinical Population and Dosing Regimen

Cinqair is proposed to be indicated to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and older) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. Cinqair is not indicated for acute bronchospasm.

Cinqair is for intravenous (IV) infusion only. The recommended dosing regimen is 3 mg/kg administered once every 4 weeks.

2.7 Regulatory Background

Reslizumab was originally developed for asthma under BB-IND 009,227 (Schering Corporation); which was submitted on August 1, 2000, and subsequently withdrawn on November 6, 2003. On January 16, 2008, two INDs were submitted simultaneously: IND 101,399 was submitted to DPARP to develop reslizumab for the treatment of eosinophilic asthma (b) (4) The following table summarizes the regulatory background for IND 101,399:

Date	*Interaction/Communication to Sponsor*
1/16/2008	*Original IND submitted – clinical studies using the IV route of administration allowed to proceed*
12/29/2009	*Sponsor submitted* (b) (4)
2/23/2010	*PharmTox information request to communicate the following to the sponsor:* (b) (4)

	[redacted] (b) (4)
8/18/2010	*End-of-Phase 2 meeting held with the sponsor*
11/11/2010	*Carcinogenicity white paper submitted by the sponsor* [redacted] (b) (4)
2/7/2011	*PharmTox review of carcinogenicity white paper – a 2-year bioassay in CD-1 mouse* was required to support marketing of reslizumab* ** Later the sponsor discussed* [redacted] (b) (4) *the use of transgenic mice to conduct the carcinogenicity study*
5/31/2012	*Special Protocol Assessment (SPA) submitted for a 6-month carcinogenicity study in transgenic mice*
7/11/2012	*SPA agreement sent to the sponsor (the transgenic mouse strain was appropriate as long as the sponsor provided data to support the use of this strain)*
9/26/2012	*PharmTox information request response from the sponsor (rationale to support the use of the transgenic mouse strain in the 6-month carcinogenicity study)*
11/26/2012	*PharmTox information request to request eosinophil historical control range for the transgenic mouse strain*
11/28/2012	*Eosinophil historical control range provided for the transgenic mouse strain*
2/7/2013	*PharmTox information request for more data (bioassay showing inhibition of antigen or IL5-induced pulmonary eosinophilia or chemotaxis) in the transgenic mouse strain*
11/8/2013	*Additional data from a bioassay provided to support the use of the transgenic mouse strain*
2/25/2014	*Communication to sponsor that the data provided were supportive of the transgenic mouse strain*
1/15/2015	*Pre-BLA meeting with Teva*

BLA 761033 was submitted on March 29, 2015.

3 Studies Submitted

3.1 Studies Reviewed

The following studies were reviewed to support safety of reslizumab during development. A detailed review of a selection of studies is included herein. Other studies were reviewed previously. See below under Section 3.3 "Previous Reviews Referenced".

Study Title	Study Number
Pharmacology	
In vitro evaluation of reslizumab	D26740

Reference ID: 3861540

Surface plasmon resonance analysis of human, monkey, and mouse IL-5 binding to reslizumab	BDR-2014-045-BAR-WC
Effects of reslizumab on allergic pulmonary eosinophilia in mice	D26555
Inhibition of allergic pulmonary eosinophilia in mice by intramuscular reslizumab	D26840
Duration of activity of reslizumab on allergen-induced pulmonary eosinophilia in mice	D27785
Effect of reslizumab on the lung pathology of allergic mice	D27203
Inhibition of allergic pulmonary eosinophilia by reslizumab in CD1 mice	D27201
Effect of IV delivered CEP-38072 in OVA-sensitized CByB6F1-Tg(HRAS)2jic mice	DRR-2013-001
Inhibition by reslizumab of allergen-induced pulmonary eosinophilia and bronchial hyper-responsiveness in guinea pigs	D27175
Effect of reslizumab on acute allergic bronchoconstriction in guinea pigs	D27508
Inhibition of acute bronchoconstriction with IgG antibodies	D27630
Effect of reslizumab on rhIL-5-induced inflammatory cell influx into the BALc fluid of guinea pigs	D27174
Effect of reslizumab on circulating leukocytes in the guinea pig	D26956
Bioactivity of reslizumab in rabbits	D27530
Effects of reslizumab in a monkey model of asthma	D26751
Six-month study with reslizumab in allergic monkeys	D26968
Secondary Pharmacology	
Evaluation of the effects of reslizumab/CEP-38072 in a murine CAC model of experimental allergic conjunctivitis	DRR-2013-006
Safety Pharmacology	
Acute behavioral, neurological and autonomic effects in IL-5 knockout mice	D28259
Single dose with in vivo binding, CSF concentration and/or serum concentration measurements; and full toxicity evaluations at 2 sacrifice dates (IV)	P6670
Single dose with in vivo binding, CSF concentration and/or serum concentration measurements; and full toxicity evaluations at 2 sacrifice dates (intrathecal)	SN99222
Pathological evaluation of IL-5 deficient mice	D28658
General safety pharmacology of reslizumab	D27240
Behavioral, neurological and autonomic pharmacology of reslizumab in rodents	P6661
A pharmacological assessment of the effects of CEP-38072 on the central nervous system of Sprague-Dawley rats	DS-2014-080
A pharmacological assessment of the effects of CEP-38072 on the renal system in Sprague-Dawley rats	DS-2014-081
Pharmacokinetics and Validation	
Pharmacokinetic report: A one-month (four once weekly doses) intravenous bridging toxicity study of reslizumab in juvenile cynomolgus monkeys, with a one-month recovery period and pharmacokinetic and anti-reslizumab antibody evaluations	Res-4-0009
SCH 55700: Pharmacokinetics of SCH 55700 (humanized anti-IL-5 monoclonal antibody) after a single intravenous or subcutaneous dose to male mice	SN00150
SCH 55700: A pilot pharmacokinetic study of humanized anti-IL-5 monoclonal antibody after a single intravenous administration to male mice	D27236
Pharmacokinetics and immunogenicity of reslizumab after intravenous administration to male mice	Res-4-0026
Pharmacokinetics and immunogenicity of reslizumab after a single intravenous or subcutaneous dose to male rats	Res-4-0010
SCH 55700: Pharmacokinetic study of humanized anti-IL-5 monoclonal antibody after a single intravenous administration to male and female rabbits	P6613
Pharmacokinetic studies of a humanized antibody to human IL-5 (SCH 55700) in Ascaris challenged cynomolgus monkeys	D27088

Reference ID: 3861540

Pharmacokinetic analysis (SCH 55700)	D28497
General Toxicology	
Single-dose intravenous toxicity study of reslizumab (anti-IL-5) in mice	P6147
Single-dose intravenous toxicity study of reslizumab anti-IL-5 in rats	P6146
Single-dose intravenous toxicity study of reslizumab (anti-IL-5) in cynomolgus monkeys	P6144
One-month (2-dose) intravenous toxicity study of reslizumab in mice	P6190
4-week (three doses total) dose range-finding intravenous toxicity and toxicokinetic study with CEP-38072 in 001178-W (wild type) mice	DS-2011-017
Six-month intravenous toxicity and toxicokinetic study of reslizumab in mice	SN96264
One-month (2-dose) intravenous toxicity study of reslizumab in cynomolgus monkeys	P6188
A one-month (four once-weekly doses) intravenous bridging toxicity study of reslizumab in juvenile cynomolgus monkeys, with a one-month recovery period and pharmacokinetic and anti-reslizumab antibody evaluations	Res-4-0006
A six-month intravenous toxicity study of reslizumab with neurological evaluations in cynomolgus monkeys	P6749
(b) (4)	
Genetic Toxicology	
Bacterial mutagenicity study of reslizumab	P6214
Chromosome aberration study of reslizumab in human peripheral blood lymphocytes	P6269
Carcinogenicity	
26-week intravenous oncogenicity study with CEP-38072 (reslizumab) in 001178-T (hemizygous) mice	DS-2012-005
Reproductive and Developmental Toxicology	
Preliminary intravenous fertility and postnatal study of SCH 55700 in mice	P6370
Pilot intravenous embryo-fetal development study of SCH 55700 (anti-IL-5) in mice	D27256
Pilot intravenous embryo-fetal development study of SCH 55700 in rabbits	D27243
Intravenous fertility study of reslizumab in mice	P6981
Intravenous embryofetal development study of reslizumab in mice	P6378
Intravenous embryofetal development study of reslizumab in rabbits	P6379
Perinatal/postnatal reproduction, developmental, and juvenile toxicity study of intravenous reslizumab in mice, including a postnatal behavioral/functional evaluation	DS-2010-020

3.2 Studies Not Reviewed

Study Title	Study Number
Pharmacology	
Characterization of a Sch55700 binding protein (b) (4)	D28431
Identification of the reslizumab binding proteins as (b) (4)	D38271
Immunopathology report: cross-reactivity of fluoresceinated humanized monoclonal antibody reslizumab with normal human tissues and selected central neural tissues from the cynomolgus monkey and CD-1 mouse	P6330
Immunohistochemical staining of selected human, cynomolgus monkey, guinea pig, and mouse central neural and ocular tissues with various antibodies directed against IL-5	P6669
In vitro immunohistochemical analysis of SCH 55700 in cynomolgus monkey tissue	P6674

Reference ID: 3861540

Topographical localization of humanized monoclonal antibody SCH 55700 in normal human and cynomolgus monkey central nervous system tissues in vitro	SN96408
In vitro cross reactivity of fluoresceinated SCH 55700 with normal human trigeminal nerve	SN99372
Secondary Pharmacology	
[redacted] (b) (4) treatment with anti-IL-5 monoclonal antibodies, including reslizumab	Res-4-0002
Pharmacodynamic Drug Interactions	
Effect of reslizumab and prednisolone on pulmonary eosinophilia in allergic mice	D26940
Pharmacokinetics and Validation	
Single/multiple (two) dose intravenous toxicokinetic study of SCH 55700 (anti-IL-5) in cynomolgus monkeys	P6187
Single dose intrathecal pharmacokinetic study of SCH 55700 in male cynomolgus monkeys	SN99223
In vitro evaluation of IL-5 and anti-IL-5 antibody (reslizumab) on cell viability and cytochrome P450 expression in cultured human hepatocytes	DM-2013-017
SCH 55700 (IL-5 mAB) TF-1 biological assay for quantitating SCH 55700 levels in cynomolgus monkey and CD-1 mouse sera	P6180
SCH 55700 (IL-5 mAB) TF-1 biological assay for quantitating SCH 55700 levels in rabbit serum	P6363
SCH 55700 (IL-5 mAB) TF-1 biological assay for quantitating SCH 55700 levels in cerebral spinal fluid	D31098
Validation report for the biosensor assay for a humanized anti-IL-5 mAB (SCH 55700) levels in mouse serum	P6306
Cross-validation report for the biosensor assay for humanized anti-IL-5 mAB (SCH 55700) levels in rabbit serum	D28021
Determination of reslizumab in mouse serum by ELISA – amended validation report	Res-4-0022
Report on stability of quality control samples in serum	P6317
Validation of an ELISA method for determination of reslizumab in rat serum	Res-4-0015
Qualification of an ELISA measuring SCH 55700 in cerebrospinal fluid	D27711
Validation report for an ELISA measuring SCH 55700 (humanized anti-IL-5 antibody) in monkey serum	P6308
Qualification of a sensitive ELISA measuring SCH 55700 in serum from cynomolgus monkey	D27710
Validation report – Determination of reslizumab in cynomolgus monkey serum by ELISA	Res-4-0007
Validation of an ELISA method for determination of reslizumab in monkey serum	Res-4-0013
SCH 55700 (IL-5 mAB) TF-1 biological assay for detecting SCH 55700 serum neutralizing factors	P6316
Validation report for the biosensor assay for antibodies to a humanized anti-IL-5 mAB (SCH 55700) in mouse serum	P6307
Cross-validation report for the biosensor assay for antibodies to a humanized anti-IL-5 mAB (SCH 55700) in rabbit serum	D28020
Cross-validation report for the biosensor assay for antibodies to a humanized anti-IL-5 mAB (SCH 55700) in monkey serum	P6309
A qualitative ELISA assay for detection of antibodies against reslizumab in mouse serum	Res-4-0023
A qualitative ELISA assay for detection of antibodies against reslizumab in rat serum – amended validation report	Res-4-0016
Determination of anti-reslizumab antibody in cynomolgus monkey serum by	Res-4-0008

ELISA – Validation report	
A qualitative ELISA assay for detection of antibodies against reslizumab in monkey serum	Res-4-0014
Local Tolerance	
Acute subcutaneous irritation study of reslizumab (anti-IL-5) in rats	SN98072
Pain-on-injection study of a formulation of reslizumab (anti-IL-5) in rats	SN98070
Muscle irritation study of reslizumab (anti-IL-5) in rabbits	SN98071
Intra-arterial tolerance study of reslizumab (anti-IL-5) in rabbits	P6223
Intravenous tolerance study of a reslizumab (anti-IL-5) formulation in rabbits	SN98568

3.3 Previous Reviews Referenced

Application #	*Studies Reviewed*	*Reviewer Name*	*Review Date*
IND 101,399	Safety Review and Genetic Toxicology*	Feleke Eshete, PhD	2/19/2008
IND 101,399	Carcinogenicity White Paper Review	Timothy Robison, PhD, DABT	2/7/2011
IND (b) (4)	PharmTox Memo	Tamal Chakraborti, PhD	3/23/2011
IND 101,399	Chronic Toxicity Studies*	Carol M. Galvis, PhD	5/6/2012
IND 101,399	Special Protocol Assessment	Molly E. Shea, PhD	7/11/2012
IND 101,399	ECAC Meeting Minutes (SPA)	Adele S. Seifried	7/11/2012
IND 101,399	PharmTox Memo	Carol M. Galvis, PhD	2/4/2013
IND 101,399	(b) (4)	Carol M. Galvis, PhD	10/7/2013
IND 101,399	PharmTox Memo	Carol M. Galvis, PhD	2/11/2014
BLA 761033	ECAC Meeting Minutes (Carc)	Adele S. Seifried	6/19/2015
BLA 761033	Carcinogenicity Study	Carol M. Galvis, PhD	6/30/2015

* Reviews included as appendices to this document.

4 Pharmacology

4.1 Primary Pharmacology

Brief summary

Reslizumab is a humanized IL-5 antagonist (monoclonal antibody of the IgG4/κ isotype) that contains the complementarity determining regions (CDRs) of the rat anti-human antibody 39D10 grafted onto human frameworks. Reslizumab binds to IL-5 and prevents its binding to the IL-5 receptor, thereby reducing circulating and tissue eosinophils. Reslizumab binds with similar affinity to human, monkey, and mouse IL-5.

Reslizumab has been tested in vivo in a number of species including mouse (multiple strains), monkey, rabbit, and guinea pig. Reslizumab was shown to inhibit eosinophilia in these species after intraperitoneal (IP) administration (mice and guinea pigs), intramuscular (IM) administration (mice), or intravenous (IV) administration (mice, monkeys, and rabbits).

Most pharmacology studies were reviewed under INDs 101,399 (b) (4) to support development of reslizumab and only a summary is included herein. However, some studies were submitted to the INDs later and a more detailed review is included below.

Reference ID: 3861540

In vitro pharmacology

Reslizumab has been tested in vitro using a number of methods, including a solid-phase antigen competition assay, a kinetic biosensor analysis of antigen-antibody interactions, an in vitro cell binding assay, and a cell proliferation assay. Table 2 below (excerpted from the sponsor's submission – "Pharmacology Written Summary") includes a summary of the in vitro activity profile of reslizumab (CEP-38072) compared with the original rat anti-human antibody (39D10).

Table 2: In Vitro Activity Profile of Reslizumab.

	Biotin-39D10 competition[a] (Relative IC_{50})	BIAcore[b] K_d (pM)	Receptor Binding[c] IC_{50}(nM)	TF-1 Proliferation[d] IC_{50} (nM)
CEP-38072	0.9	81	0.5	45
39D10	2	53	0.28	25

SOURCE: Study D26740

[a] Competition for binding to immobilized human IL-5 by ELISA.

[b] BIAcore direct binding to human IL-5 immobilized on a sensor chip at 37°C.

[c] Competitive inhibition of radiolabeled IL-5 binding to BaF3#5-8 cells expressing human IL-5 receptor.

[d] Antagonism of IL-5 induced proliferation of human erythroleukemia TF-1 cells measured by MTT assay after ~44-48 hour incubation.

IC_{50}=half-maximal inhibitory concentration; K_d=dissociation constant.

Study # BDR-2014-045-BAR-WC: Surface Plasmon Resonance Analysis of Human, Monkey, and Mouse IL-5 Binding to Reslizumab.

This study was conducted to measure the affinity of reslizumab (CEP-38072, lot #12-000792) with human, monkey, and mouse IL-5 using a BIAcore T200 method. Briefly, anti-human Fc was immobilized to both the reference and active surfaces of a CM5 sensor chip surface using amine coupling. Reslizumab (1 µg/mL) was captured with a flow rate of 10 µL/min for 15-30 seconds onto the surface of the active flow cell. Binding to captured antibody was tested using 0.02, 0.07, 0.22, 0.67, and 2 nM IL-5 as the analyte.

The results of this assay are summarized below in Table 3. Reslizumab shows a similar K_D across the species tested (24 pM in human, 20 pM in monkey, and 31 pM in mouse).

Table 3: Kinetic Values for Reslizumab Binding to Human, Monkey, and Mouse IL-5.

Species	k_a (1/Ms)	k_d (1/s)	K_D (pM)
Human	4.47×10^6	1.07×10^{-4}	24
Monkey	4.04×10^6	8.14×10^{-5}	20
Mouse	4.45×10^6	1.36×10^{-4}	31

k_a = association rate; k_d = dissociation rate; K_D = dissociation constant

In vivo pharmacology

Reslizumab has been tested in vivo in a number of models using multiple strains of mice, Hartley guinea pigs, New Zealand rabbits, and Cynomolgus monkeys. For the purposes of this review, only the studies in the nonclinical species used for toxicology assessment (CD-1 mouse, CByB6F1-Tg(HRAS)2Jic mouse, New Zealand rabbits, and cynomolgus monkeys) will be described. Similar findings were observed in other species or strains. Results from these studies support the use of the CD-1 mouse, the CByB6F1-Tg(HRAS)2Jic transgenic mouse, the New Zealand rabbit, and the cynomolgus monkey in the nonclinical pharmacology and toxicology studies discussed herein.

CD-1 Mouse

Study #D-27201: Inhibition of Allergic Pulmonary Eosinophilia by SCH55700 in CD-1 Mice.

This study was conducted to support the use of CD-1 mouse strain for toxicology assessment of reslizumab. Briefly, male CD-1 mice (5-6/group) were sensitized with ovalbumin (OVA, IP injections) and then received OVA booster injections 5 days later. Then animals were exposed to aerosolized OVA (0.5%) for 1 hour in the morning and 1 hour in the afternoon. Reslizumab (SCH55700) was administered by IP injection at 1 or 10 mg/kg 2 hours prior to the aerosolized OVA challenge. At selected times after OVA challenge, mice were sacrificed by CO_2 asphyxiation, the trachea was exposed and cannulated, and lungs were lavaged. Bronchioalveolar lavage (BAL) fluid was collected for differential cell count, pulmonary tissue was collected for histological evaluation to evaluate the number of eosinophils surrounding the bronchi and bronchioles, and blood was collected from these animals to measure serum IgE.

Results from this study show that reslizumab inhibited the development of pulmonary eosinophilia after OVA antigen challenge, measured as a statistically significant decrease in eosinophils in BAL fluid, bronchi, and bronchioles (refer to Table 4 below, excerpted from the study report).

Reference ID: 3861540

Table 4: Effect of Reslizumab (SCH55700) on Eosinophil Accumulation in the BAL Fluid and Lung Tissue of Allergic CD-1 Mice.

Sensitization	Sch 55700 (mg/kg, i.p.)	NUMBER OF EOSINOPHILS[a] BAL Fluid (x 10^3/ml)	Bronchi (#/high power field)	Bronchioles (#/high power field)
-	-	0 ± 0*	1 ± 1*	0 ± 0*
+	-	245 ± 72	43 ± 3	19 ± 3
+	1	96 ± 29*	28 ± 3*	11 ± 3*
+	10	53 ± 18*	19 ± 5*	4 ± 1*

[a] Mean ± SEM (n = 10-12 per dose) number of eosinophils measured 48 hr after OVA challenge.

* $P < 0.05$ compared with the sensitized, challenged group that did not receive Sch 55700.

The data are found in Notebook #34190 pages 149-160 and 290-305.

CByB6F1-Tg(HRAS)2Jic Mouse

Study #DRR-2013-001, "Effect of IV Delivered CEP-38072 in OVA-Sensitized CByB6F1-Tg (HRAS)2jic Mice". This study was reviewed previously to support the use of this transgenic mouse strain for the 26-week carcinogenicity study. Refer to PharmTox memo dated February 11, 2014. The purpose of this study was to test reslizumab in an OVA model using CByB6F1-Tg (HRAS)2jic mice to determine if reslizumab had an effect on allergic airway responses. Briefly, mice (10 males/group) were challenged with ovalbumin (OVA, 20 µg IP) to create an allergic response [*i.e.*, increase in inflammatory cells in bronchioalveolar lavage (BAL)]. OVA-sensitized mice were treated with 10 mg/kg or 250 mg/kg reslizumab IV on study days 21 and 23. Three controls were included: an OVA-sensitized comparator group (treated with 3 mg/kg dexamethasone from study day 21 to study day 23), an OVA-sensitized negative control (treated with vehicle), and a non-sensitized negative control. Animals were euthanized 48-56 hours following the last OVA challenge on study day 23. Blood and BAL fluid were collected from all the animals. Results of this study show that reslizumab attenuates the inflammatory response in OVA-sensitized mice, shown as a statistically significant decrease in eosinophil levels in BAL fluid of mice treated with 250 mg/kg reslizumab IV.

New Zealand Rabbits

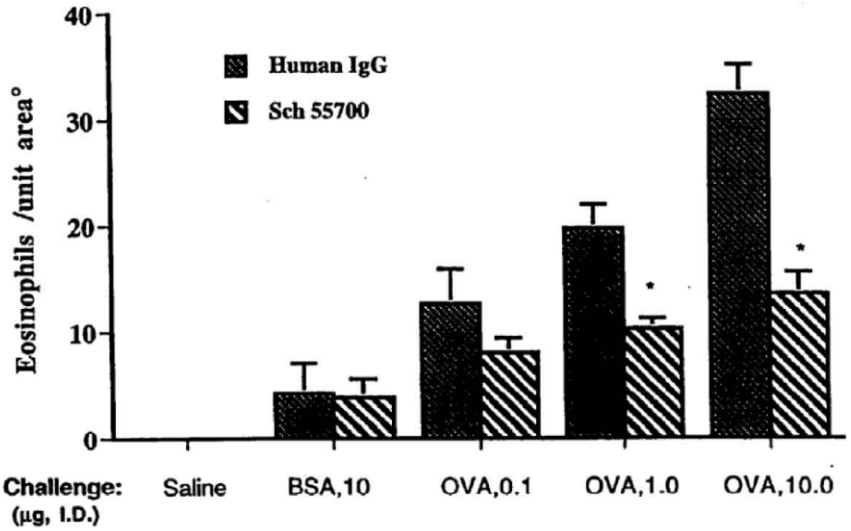
Study #D-27530: Bioactivity of SCH 55700 in Rabbits.
This study was conducted to assess the bioactivity of SCH 55700 (reslizumab) in rabbits to support the use of this nonclinical species in the embryo-fetal development study. A model of passive cutaneous anaphylaxis (PCA) was used to evaluate the effects of reslizumab on the influx of eosinophils into the skin of allergic rabbits in response to antigen challenge (ovalbumin or ragweed extract). Briefly, a group of 20

rabbits was sensitized to ovalbumin (OVA) using 15 mg ovalbumin subcutaneously for a period of approximately 30 days. A separate group of 20 rabbits was sensitized to ragweed extract using 1 mL of 1:100 w/v ragweed extract/rabbit intraperitoneally for a period of approximately 14 days.

After a period of approximately 7 days, IgE antibody titers were measured in the sensitized rabbits by homologous passive cutaneous anaphylaxis (PCA) to determine the animals that had been sensitized to ovalbumin or ragweed extract. Sensitized rabbits received either 5 mg/kg SCH 55700, 5 mg/kg human IgG, or saline intravenously (into an ear vein) two hours prior to antigen challenge. OVA-sensitized rabbits were then challenged with ovalbumin, saline, or bovine serum albumin injected intradermally. Ragweed-sensitized rabbits were challenged with ragweed extract or saline injected intradermally. After 24 hours, animals were sacrificed and skin biopsies were obtained. The total number of inflammatory cells, eosinophils, and neutrophils per unit area was calculated.

Results of this study show that treatment with 5 mg/kg reslizumab 2 hours prior to OVA or ragweed extract challenge significantly reduced the number of eosinophils appearing in the skin of OVA- or ragweed-sensitized rabbits. This data supports the use of this nonclinical species for toxicology studies. Refer to Figure 2 below, excerpted from the sponsor's submission, for the effects of reslizumab treatment in OVA-sensitized rabbits. Results observed in ragweed-sensitized rabbits are not shown.

Figure 2: Effect of SCH 55700 on the Eosinophils in the Skin of Ovalbumin-Challenged Allergic Rabbits.



°Unit area = 0.115 mm ^{2}
*P<0.05 compared to human IgG-treated group.

Cynomolgus Monkeys

Study #D-26751: Effects of a Humanized Monoclonal Antibody to IL-5 (SCH55700) in a Monkey Model of Asthma.

This study evaluated the effect of reslizumab on pulmonary eosinophilia induced by *Ascaris* antigen challenge in wild-caught *Ascaris*-sensitive cynomolgus monkeys. Briefly, *Ascaris*-sensitive male monkeys (6/group) received 0.1 or 0.3 mg/kg reslizumab 1 hour before an aerosol challenge with *Ascaris* antigen. BAL fluid was collected for differential cell count immediately before and 24 hours after the *Ascaris* challenge. In addition, animals were instrumented to measure lung mechanics and an assessment of airway responsiveness to inhaled histamine was conducted.

Results from this study are presented below in Figures 3 and 4, excerpted from the study report. As shown, 0.3 mg/kg reslizumab (SCH55700) treatment resulted in inhibition of pulmonary eosinophilia, measured as a statistically significant decrease in the number of eosinophils in BAL fluid collected from treated animals. No statistically significant effect was observed at 0.1 mg/kg reslizumab (Figure 4). According to the sponsor, the effect of reslizumab on airway hyper-reactivity could not be accurately assessed because there was a shift in baseline airway reactivity in control animals. The study report did not comment on whether or not reslizumab had an effect on lung mechanics.

Figure 3: Effect of SCH 55700 on the Pulmonary Eosinophilia Induced by *Ascaris* Challenge in Cynomolgus Monkeys – 0.3 mg/kg.

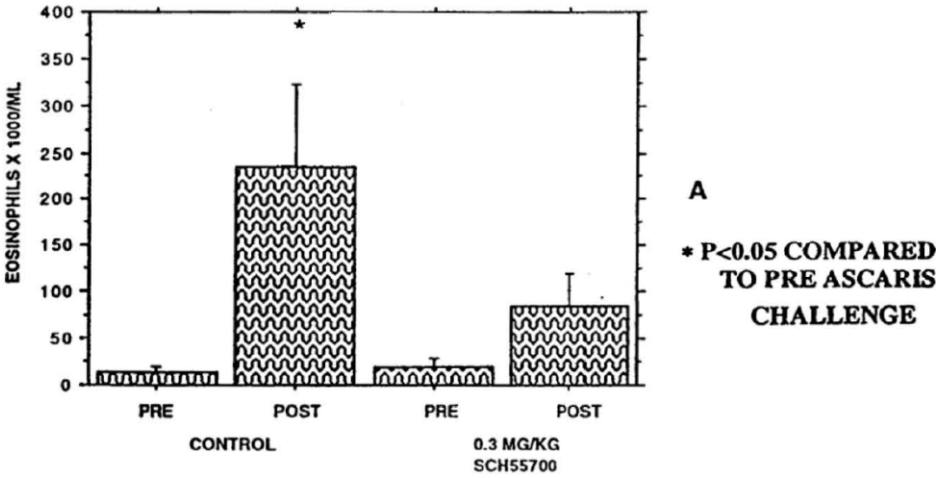
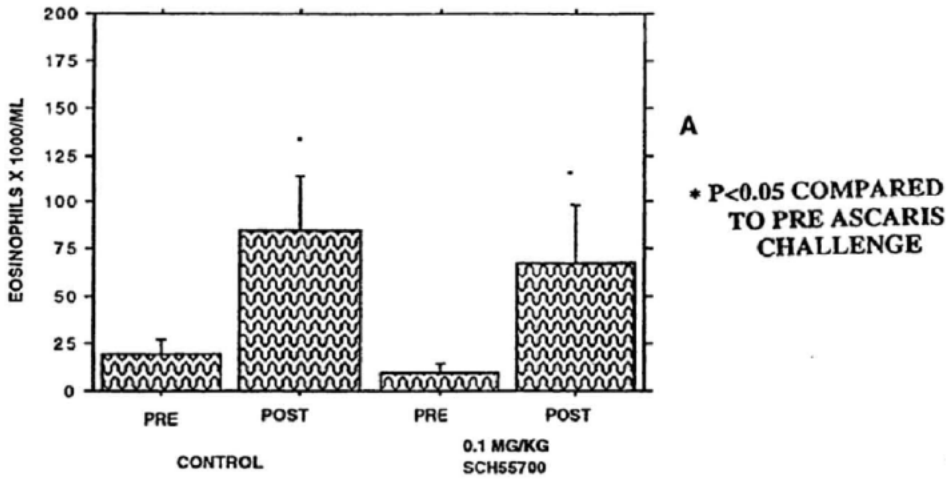


Figure 4: Effect of SCH 55700 on the Pulmonary Eosinophilia Induced by *Ascaris* Challenge in Cynomolgus Monkeys – 0.1 mg/kg.



4.2 Secondary Pharmacology

For secondary pharmacology, the sponsor used a mouse model of allergic conjunctivitis (study #DRR-2013-006). In this model, mice were sensitized with an antigen (ragweed), then challenged again with ragweed 17 days later and randomized to receive vehicle, reslizumab (1 mg/mL eye drops or IV), or prednisolone as a positive control. It is expected that the primary cell types involved in this model are basophils and mast cells. Therefore, the sponsor used this model to test whether reslizumab (which is proposed to specifically affect eosinophils) is effective. Results from this study were variable, but in general reslizumab did not have an effect in decreasing basophils or mast cells in this model.

4.3 Safety Pharmacology

A full battery of safety pharmacology studies was conducted for reslizumab. However, many of these studies were conducted in the rat, which was not evaluated in vitro or in vivo to determine if it is a pharmacologically relevant species to test reslizumab. Only two single-dose studies (one toxicity study in CD rats and one PK study in Sprague-Dawley rats) were conducted in rats (refer to Section 6.1 below). Table 5 below presents a summary of the safety pharmacology studies conducted in rats.

Table 5: Summary of Safety Pharmacology Studies Conducted in Rats.

Study Number	Study Design	Noteworthy Findings
D27240	• 4-11 male CD rats received 10, 30, or 100 mg/kg reslizumab IV – to evaluate CNS, cardiovascular, renal, and gastro-intestinal effects • 10 CD-1 mice received 100 mg/kg reslizumab IV – to evaluate acetic-acid-induced writhing	• No noteworthy findings in the CNS, cardiovascular, or gastro-intestinal systems • There were transient effects in renal function observed at 100 mg/kg (but also observed in some control animals): natriuresis,

	• Ileum tissue from Hartley guinea pigs (6-11 male donors) - to study the effects on agonist-induced contractions	increased urine volume, and hematuria – considered related to the hypotonic vehicle
P6661	5 male Sprague-Dawley rats Reslizumab IV doses: 1, 10, 100 mg/kg Modified Irwin test conducted to assess CNS function	• There were no drug-related effects on behavior, neurological assessments, or autonomic assessments
DS-2014-080	8 male Sprague-Dawley rats Reslizumab IV dose of 100 mg/kg FOB parameters to assess CNS function	• There were no drug-related effects observed
DS-2014-081	8-16 male Sprague-Dawley rats Reslizumab IV dose of 100 mg/kg, vehicle 1, or vehicle 2 (hypotonic vehicle used in study #D27240)	• There were no effects observed with reslizumab or vehicle 1 • Hematuria and proteinuria were observed with the hypotonic vehicle used in study #D27240 within 5 hours post-dosing

In addition to the above studies in rats, the sponsor also conducted study #P6670 in cynomolgus monkeys, a pharmacological relevant species. This study was conducted to assess CNS binding and cerebro-spinal fluid (CSF) levels of reslizumab following a single IV dose of 5 or 25 mg/kg. There were no drug-related effects observed in physical, neurologic, cardiovascular (ECG), or ophthalmic examinations. In addition, immunohistochemical staining did not show reslizumab binding to CNS tissue. Results from CSF analysis showed the presence of low levels of reslizumab (<0.1 µg/mL) in these samples.

An additional study (#SN99222) was conducted in cynomolgus monkeys to further evaluate the potential effects of reslizumab in the CNS. In this study, reslizumab was administered as a single intrathecal injection (0 or 0.07 mg/kg) into the cisterna magna. This route was used in order to achieve CSF concentrations that were higher than the IV concentrations. Organ weight measurements and gross and microscopic examinations were performed on brain, eyes with optic nerve, spinal cord, and trigeminal nerve. In this study, no drug-related effects were observed in any of the aforementioned parameters. Reslizumab concentration in CSF ranged from approximately 82,000-111,000 ng/mL (individual animal values) at the time points assessed.

Further, no findings of concern were observed (behavior, cardiovascular, or respiratory rate) in the pivotal toxicity studies conducted in mice and monkeys and discussed below in Section 6.2

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Brief summary

A number of pharmacokinetic (PK) studies were conducted with reslizumab in CD-1 mouse, Sprague-Dawley rat, New Zealand rabbit, and cynomolgus monkey. A

Reference ID: 3861540

summary of study designs and noteworthy findings is included in Table 7 below under Section 6.1. Table 6 (excerpted from the sponsor's submission) includes a summary of serum PK parameters for intravenous reslizumab across nonclinical species.

Table 6: Summary of Serum Pharmacokinetic Parameters after Single Intravenous Doses of Reslizumab.

Species	Dose mg/kg	Sex	C_{max} µg/mL	AUC_{0-t} µg·h/mL	$t_{½}$ days	t_{last} days	Assay
Mouse	1	M	18.2	2890	ND	28	Biosensor
Mouse	1	M	11.3	1467	ND	21	Biological
Rat	1	M	ND	1100	9.2	47	ELISA
Rabbit	2	M, F	36.9	5893	9.5	27	Biosensor
Rabbit	2	M, F	38.8	3855	11.9	42	Biological
Monkey	1	M, F	25.6	1629	ND	14	ELISA
Monkey[a]	1	M	23.0	ND	5.3	19	ELISA

[a] *Ascaris*-challenged animals (n=2); sample matrix=plasma.
C_{max}=maximum observed serum concentration; AUC_{0-t}=area under the serum concentration-time curve over the dosing interval; $t_{½}$=elimination half-life; t_{last}=time of last measurable serum concentration; ND=not determined; M=male; F=female; ELISA=enzyme-linked immunosorbent assay.

PK parameters were generally dose-proportional for all nonclinical species across a range of doses. There was evidence of anti-drug antibodies (ADAs) development in all nonclinical species tested. Analysis of PK parameters in ADA-positive animals found that the antibodies were neutralizing, as reslizumab was not detected in the blood of these animals.

There were no distribution, metabolism, or excretion studies conducted with reslizumab. As expected for a monoclonal antibody, reslizumab had low systemic clearance, low volume of distribution, and a long terminal half-life across nonclinical species.

Reslizumab was excreted in the milk of lactating mice and there was placental transfer from dams to pups. Refer to Section 9.3 below for additional details.

5.2 Toxicokinetics

The toxicokinetics (TK) parameters of reslizumab are discussed below in Section 6, under each of the studies discussed.

6 General Toxicology

6.1 Single-Dose Toxicity

The sponsor conducted three single-dose IV toxicity studies and a number of pharmacokinetic studies after IV or SC administration of reslizumab to mice, monkeys, rabbits, and rats. No drug-related toxicity findings were reported in any of these studies.

Reference ID: 3861540

A summary of all the single-dose studies with noteworthy findings is presented below in Table 7.

Table 7: Summary of Single-Dose Studies Conducted with Reslizumab.

Study Number	Study Design	Noteworthy Findings
Mouse		
P6147	GLP study CD-1 mice (5/sex) Reslizumab: 500 mg/kg IV into tail vein	• No drug-related clinical signs, BW, FC, gross necropsy observations
SN00150	CD-1 male mice Reslizumab: 25, 50, 100 mg/kg IV or SC	• PK parameters only; SC bioavailability in this study was 76-87%; $t_{½}$ ranged from 9-18 days
D27236	CD-1 male mice Reslizumab: 1, 5, 25 mg/kg IV	• PK parameters only; dose-related increase in PK parameters; $t_{½}$ ranged from 10-14 days
Res-4-0026	CD-1 male mice Reslizumab: 1, 10, 50 mg/kg IV bolus	• PK parameters only; blood collection-related deaths observed across groups; neutralizing antibodies detected in some HD animals
Rat		
P6146	GLP study CD(BR) rats (5/sex) Reslizumab: 500 mg/kg IV into tail vein	• No drug-related clinical signs, BW, FC, gross necropsy observations
Res-4-0010	Male Sprague-Dawley rats (n=8) Reslizumab: 1 mg/kg IV and 1, 5, 25 mg/kg SC	• PK parameters only; similar PK for SC and IV; neutralizing antibodies detected in some animals across dose groups; $t_{½}$ was ~9 days
Rabbit		
P6613	New Zealand rabbits (9/sex) Reslizumab: 2, 10, 50 mg/kg IV	• PK parameters only; dose-related increase in exposure; no gender difference; $t_{½}$ ranged from 10-15 days
Monkey		
P6144	GLP study Cynomolgus monkeys (2/sex) Reslizumab: 100 mg/kg IV into saphenous vein	• No drug-related clinical signs, BW, FC
D27088	*Ascaris*-challenged male Cynomolgus monkeys (n=10) Reslizumab: 0.3, 1, 3 mg/kg Report used data from 2 separate experiments	• PK parameters only and immunogenicity; $t_{½}$ ranged between 1.2-9.3 days; there were no ADAs detectable
D28497	Male Cynomolgus monkeys (n=5) Reslizumab: 3 mg/kg IV	• PK parameters only; $t_{½}$ ranged from 14-23 days; Reslizumab concentration detectable for up to 90 days after single dose

BW = body weights; FC = food consumption

Reference ID: 3861540

6.2 Repeat-Dose Toxicity

Repeat-dose GLP toxicology studies were conducted in CD-1 mice, CByB6F1-Tg(HRAS)2Jic mice, and cynomolgus monkeys using the IV route of administration. These general toxicity studies were reviewed previously to support the use of reslizumab in clinical trials (refer to Appendices 1-3) and only a summary of the study design and noteworthy findings is included below.

In addition, juvenile toxicity studies were conducted in monkeys and mice. These studies were reviewed in detail for the purposes of this review. A summary of the toxicology findings by nonclinical species/strains is included below.

Mouse

CD-1 Mouse

Repeat-dose toxicity studies (4-week and 6-month studies) were conducted in CD-1 mice, a pharmacological relevant species for reslizumab, using the IV route of administration. A summary of these studies follows.

Study #P6190, One-Month (Two-Dose) Intravenous Toxicity of SCH55700 (Anti-IL-5) in Mice. Briefly, male and female CD-1 mice (20/sex/group) received 0, 1, 5, or 25 mg/kg reslizumab IV on study days 1 and 15. At the end of the dosing period, animals were sacrificed and necropsies were performed. Assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, and clinical and anatomic pathology observations. In addition, a satellite group was included for TK and ADA analysis. Necropsies were conducted at study weeks 5 (10 animals/sex/group) and 9 (10 animals/sex/group). No drug-related findings were observed at any dose level in this study and the NOAEL was identified at the 25 mg/kg dose (C_{max} = 354 µg/mL, $AUC_{0\text{-}14days}$ = 83,837 µg.hr/mL in males and females combined).

Study #SN96264, Six-Month Intravenous Toxicity and Toxicokinetic Study of SCH55700 in Mice. Briefly, male and female CD-1 mice (10 mice/sex/group) were treated with 0, 2, 10, or 25 mg/kg SCH 55700 (reslizumab) IV once every 28 days for 6 months (7 doses total). At the end of the dosing period, animals were euthanized and necropsies were performed. Assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology observations. In addition, blood samples were collected for toxicokinetic and antibody analysis. This study did not include a recovery period.

Six animals died during the study: two animals in the LD group (undetermined reason), three animals in the MD group (two undetermined and one sacrificed due to a bronchiolo-alveolar carcinoma), and one animal in the HD group (animal 304, found dead due to urinary tract obstruction). The study report did not mention why the mortalities in the LD and MD groups were undetermined. Animal 304 (HD male) was found dead on the day of necropsy. Histopathology findings in this animal included moderate renal pelvis and ureters dilatation and mild congestion in the urinary bladder.

Reference ID: 3861540

Histopathological findings of concern in this study include renal pelvis and ureters dilatation in two additional HD male animals that correlated with elevated levels of blood urea-nitrogen (BUN), suggesting effects in the urinary tract in treated animals. At the Division's request, the sponsor provided an expert report that included re-examination of kidney tissues from all study animals and a toxicological evaluation of the renal findings. Because a clear dose-response was not observed, the expert report concludes that findings of renal pelvis dilatation are incidental and not related to treatment. This is supported by the fact that it was also observed in one control animal. In addition, literature search found that dilatation is a common incidental finding in CD-1 mice[2]. Therefore, it has been determined that these renal findings in the mouse are not related to treatment.

TK parameters from this study show slightly decreased exposure with time, suggesting the presence of neutralizing antibodies. However, this was not confirmed because the ADA assay was affected by the presence of free reslizumab in serum. Eosinophil levels were measured in all animals and, although eosinophil levels trended lower in the treated groups compared to controls, the change was not statistically significant. The NOAEL for the kidney findings in the mouse is 25 mg/kg/dose (C_{max} = 412 µg/mL, $AUC_{0\text{-}14days}$ = 45,500 µg.hr/mL in males and females combined).

CByB6F1-Tg(HRAS)2Jic Mouse

A 4-week toxicity study was conducted in 001178-W (Wild Type) mice to support the special protocol assessment (SPA) for the 26-week carcinogenicity study in transgenic mice. A brief summary is provided below.

Study #DS-2011-017, 4-Week (Three Doses Total) Dose Range-Finding Intravenous Toxicity and Toxicokinetic Study with CEP-38072 in 001178-W (Wild Type) Mice. Briefly, mice (10/sex/group) were treated with 0 (vehicle), 250, and 500 mg/kg/dose reslizumab IV on study days 1, 15, and 29 (3 doses total). At the end of the dosing period, animals were sacrificed and necropsies were performed. Assessment of toxicity was based on mortality, clinical signs of toxicity, body weights, food consumption, and clinical and anatomic pathology observations. In addition, satellite groups were included for TK and ADA analysis. There were no drug-related toxicities observed in any of the parameters assessed. Therefore, the NOAEL was identified at 500 mg/kg/dose ($AUC_{0\text{-}168\ h}$ of 1326 mg*h/mL for females and 1519 mg.hr/mL for males).

<u>Cynomolgus Monkeys</u>

Repeat-dose toxicity studies (one-month and 6-month IV studies (b) (4) were conducted in cynomolgus monkeys, a pharmacological relevant species for reslizumab. A summary of these studies follows.

[2] Chandra M and Frith CH. *Spontaneous renal lesions in CD-1 and B6C3F1 mice.* (1994) Experimental Toxicology Pathology, Vol. 46, No. 3; pages 189-198.

Study #P6188, Two-Dose/ One-Month Intravenous Toxicity Study of SCH55700 (Anti-IL-5) in Cynomolgus Monkeys. Briefly, male and female monkeys (4/sex/group) received 0, 1, 5, or 25 mg/kg reslizumab IV on study days 1 and 15. At the end of the dosing period, animals were sacrificed and necropsies were performed. Assessment of toxicity was based on mortality, clinical signs of toxicity, body weights, food consumption, physical examinations (including electrocardiograms, body temperature, respiratory rates, heart rates and blood pressure), ophthalmic examinations and clinical and anatomic pathology observations. In addition, blood samples were collected for TK and ADA analysis. There were no drug-related effects observed at any dose level in this study. Therefore, the NOAEL was identified at the 25 mg/kg dose (mean serum reslizumab concentration = 129,716 ng/mL).

Study #P6749, A Six-Month Intravenous Toxicity Study of SCH55700 with Neurological Evaluations in Cynomolgus Monkeys. Briefly, cynomolgus monkeys (4/sex/group) were treated with 0, 1, 5, or 25 mg/kg SCH 55700 IV once every 4 weeks for 6 months (7 doses). At the end of the dosing period, animals were euthanized and necropsies were performed. Two animals in the control and HD groups underwent a 13 week treatment-free phase. Assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, ophthalmic and ECG examinations, and clinical and anatomic pathology observations. In addition, blood samples were collected for toxicokinetic and antibody (ADA) analysis.

No significant SCH 55700-related effects were observed on mortality, clinical signs, body weights, food consumption, ophthalmic examinations, clinical pathology, or neurological and electroneurological examinations. ECG examinations found that one MD male showed a single ventricular extrasystole at week 28, one HD female had two ventricular extrasystoles at week 8 and one HD male showed a single ventricular extrasystole at weeks 16 and 28, and three at week 22.

Histopathology findings include injection site vasculitis observed in 3 HD males but this was not considered dose-limiting. In addition, kidney findings with increased incidence in HD animals include tubular basophilia (4 HD M), and hypoplasia (1 HD F). The sponsor was not able to provide additional information to support that these findings in kidney were not related to treatment. Therefore, they proposed to examine kidney tissues (b) (4)

(b) (4)

(b) (4)

[redacted]

Juvenile Toxicity

The sponsor assessed reslizumab's toxicity in juvenile animals (mice and monkeys). The juvenile toxicity in CD-1 mouse was conducted as part of the peri- and post-natal reproduction and development study (#DS-2010-020) included below under Section 9.3 and, therefore, the review is also included under Section 9.3. The juvenile toxicity in monkeys was assessed in a standalone study (study #Res-4-0006) that is reviewed below.

Study title: A One-Month (Four Once Weekly Doses) Intravenous Bridging Toxicity Study of Reslizumab in Juvenile Monkeys, with a One-Month Recovery Period and Pharmacokinetic and Anti-Reslizumab Antibody Evaluations.

Study no.:	Res-4-0006
Study report location:	EDR
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	September 6, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Reslizumab, lots# 00U-557P-00003 (purity not specified) and #52758 (99.9% pure)

Reference ID: 3861540

Key Study Findings

- Juvenile monkeys (1.4-2.3 years old) were treated with 1 mg/kg (two different reslizumab drug lots, #00U-557P-00003 and #52758) or 15 mg/kg reslizumab intravenously once weekly for 4 consecutive weeks.
- The toxicity profiles and PK parameters were similar for the two drug lots tested from two different manufacturers, supporting bridging for these two drug lots.
- A few histological findings were observed: multifocal hemorrhage in GALT in the rectum of one HD male, bilateral fibrosis in testis of 3/8 LD (37.5%) and 2/4 HD (50%) males, lymphoid depletion in the thymus of 3/16 LD animals and 2/8 HD animals, and menses in 2/4 HD females; but these were not considered related to treatment.
- A few females showed menses during the study, indicating that some of the animals used in the study were sexually mature.
- There was high variability in PK parameters calculated from samples from the 15 mg/kg group. PK parameters in this study increased in a higher than dose-proportional manner from 1 mg/kg to 15 mg/kg. There was no gender difference in exposure. Anti-drug antibodies were not detected in any of the blood samples tested.
- The NOAEL was identified at 15 mg/kg/dose (C_{max} = 774.36 µg/mL; AUC_{ss} = 63,670 µg·hr/mL).

Methods

Doses:	1 or 15 mg/kg reslizumab
Frequency of dosing:	Once weekly for 4 consecutive weeks
Route of administration:	Slow bolus intravenous (IV) infusion
Dose volume:	2.5 mL/kg
Formulation/Vehicle:	Solution containing 2.45 mg sodium acetate trihydrate, 0.12 mg acetic acid glacial, 70 mg sucrose (b) (4)
Species/Strain:	Cynomolgus monkeys from (b) (4)
Number/Sex/Group:	4/sex/group (main) 2/sex/group (recovery)
Age:	1.4-2.3 years
Weight:	Males: 1.6-2.3 kg Females: 1.6-2.6 kg
Satellite groups:	Not applicable
Unique study design:	Four animals/sex/group were euthanized on study day 29 and the remaining 2 animals/sex/group were maintained for a recovery period of 4 weeks (refer to Table 8 below, excerpted from the study report).
Deviation from study protocol:	Protocol deviations were reviewed and judged not to affect the integrity of the study data.

Reference ID: 3861540

The objectives of this study were to evaluate the potential toxicity of reslizumab in juvenile monkeys to support clinical studies in children with eosinophilic disease and to compare the toxicity profile of two manufactured lots of reslizumab [SCH55700 by Schering Corporation (previous sponsor) and CTx55700 by [redacted] (b) (4) on behalf of Ception Therapeutics] to justify the use of toxicity data from previous studies in monkeys using an older lot. The study examined weekly doses of 1 and 15 mg/kg intravenous reslizumab.

Table 8: Study Res-4-0006 Design.

Group No.	Number of M/F	Dose Level (mg/kg)	Reslizumab Identification	Dose Volume (mL/kg)	Dose Solution Conc. (mg/mL)	Terminal Procedures Day 29 (M/F)	Terminal Procedures Day 57 (M/F)
1	6/6	0 (control)	--	2.5	0	4/4	2/2
2	6/6	1	SCH55700	2.5	0.4	4/4	2/2
3	6/6	1	CTx55700	2.5	0.4	4/4	2/2
4	6/6	15	CTx55700	2.5	6	4/4	2/2

M/F = males/females

Observations and Results

Mortality

Animals were observed for signs of mortality and/or morbidity twice daily in the morning and in the afternoon beginning 5 days prior to dosing and continuing through the end of the dosing phase.

No drug-related findings were observed.

Clinical Signs

Cage-side observations were conducted once daily in the morning. Animals were observed for changes in general appearance and behavior.

No drug-related findings were observed. A few females were observed with hemorrhage (menses) and this was confirmed by histopathology. This is not considered related to treatment.

Body Weights

Body weights were measured at least twice prior to the first dose and weekly thereafter. Food was withheld prior to body weight measurements.

No drug-related findings were observed.

Feed Consumption

The number of biscuits remaining from the previous days feeding was observed and recorded every morning. A notation of low food consumption was made when less than approximately half of the rations were consumed.

Reference ID: 3861540

No drug-related findings were observed.

Ophthalmoscopy

Not conducted.

ECG

Not conducted.

Hematology

Blood samples for clinical pathology were collected from all animals prior to initiation of dosing at study week -1, during the week following the final dose (study week 4) and near the end of the recovery period (study week 8). Samples were collected into tubes containing EDTA as anticoagulant. The following hematology parameters were evaluated: red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, reticulocyte count, platelet count, white blood cell count, and blood cell morphology.

Table 9 below presents a summary of hematology changes relative to controls. As presented, eosinophil counts were decreased in all animals in a dose-dependent manner. Lymphocytes and unclassified cells were decreased in animals treated with 15 mg/kg reslizumab. Also, segmented neutrophils were increased in all groups relative to controls.

Table 9: Summary of Hematology Changes Relative to Controls (Study Week 4) – All Animals (N=12).

Reslizumab (mg/kg/dose)	1*	1	15
Parameter			
Lymphocyte count (/µL)	NC	NC	-21%
Eosinophil count (/µL)	-41%	-48%	-82%
Unclassified cell count (/µL)	NC	NC	-37%
Segmented neutrophil count (/µL)	+90%	+97%	+137%

* Reslizumab lot#00U-557P-00003 from Schering Corporation
NC = no drug-related change observed

Clinical Chemistry

Blood samples for clinical pathology were collected from all animals from the femoral vein prior to initiation of dosing at study week -1, during the week following the final dose (study week 4) and near the end of the recovery period (study week 8). The animals were fasted for at least 8 hours prior to blood collection for serum chemistry analysis. A full battery of serum chemistry parameters was evaluated.

No drug-related findings were observed.

Urinalysis

Reference ID: 3861540

Samples for urinalysis were collected at necropsy by cystocentesis. A full battery of urinalysis parameters was evaluated.

No drug-related findings were observed.

Gross Pathology

On study day 29, animals in the main study were sacrificed by exsanguination while under deer anesthesia induced with ketamine and Beuthanasia-D. Animals continuing through the recovery period had blood collected from the vena cava while under Nembutal anesthesia. Following blood collection, animals were sacrificed using Nembutal injection and exsanguination. A terminal body weight was obtained at necropsy.

All animals were subjected to a complete gross necropsy examination that included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

No drug-related findings were observed.

Organ Weights

For all euthanasias, the following organs were weighed before fixation: adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, prostate gland, thyroid with parathyroid, uterus (plus cervix), and salivary glands (mandibular, sublingual, and parotid). Paired organs were weighed together unless gross abnormalities were present, in which case they were weighed separately.

A few changes in organ weights were observed and are summarized below in Table 10. Spleen weight was decreased in HD males but not in females, and thyroid weights were decreased in both groups treated with the new drug product CTx55700 but not with the old product from Schering (SCH55700). It is unclear whether this finding is due to differences in the two products. In addition, pituitary weights were decreased in HD females but not males. In HD females, ovaries and uterus weights were increased and this could be associated with the menses observed upon histopathological examination.

Table 10: Summary of Organ Weight Changes Relative to Controls (Study Week 4).

	Males			Females		
Reslizumab (mg/kg/dose)	**1***	**1**	**15**	**1***	**1**	**15**
Spleen						
Absolute	NC	NC	-34%	NC	NC	NC
Relative to BW	NC	NC	-29%	NC	NC	NC
Relative to brain	NC	NC	-22%	NC	NC	NC
Thyroid						
Absolute	NC	-31%	-31%	NC	-26%	-28%
Relative to BW	NC	-26%	-26%	NC	-27%	-28%

Reference ID: 3861540

Relative to brain	NC	-30%	-19%	NC	-30%	-30%
Pituitary						
Absolute	NC	NC	NC	NC	NC	-23%
Relative to BW	NC	NC	NC	NC	NC	-19%
Relative to brain	NC	NC	NC	NC	NC	-22%
Ovaries						
Absolute				NC	NC	+113%
Relative to BW				NC	NC	+102%
Relative to brain				NC	NC	+105%
Uterus						
Absolute				NC	NC	+95%
Relative to BW				NC	NC	+81%
Relative to brain				NC	NC	+94%

* Reslizumab lot#00U-557P-00003 from Schering Corporation
NC = no drug-related change observed

Histopathology

Adequate Battery
A full battery of tissues was collected at necropsy from all euthanized animals. In addition, a bone marrow smear was collected from the seventh rib of each animal at necropsy, stained, and stored. The smears were not examined microscopically at necropsy as a drug-related alteration in bone marrow sections was not observed.

Peer Review
A peer review was not conducted for this study.

Histological Findings
A summary of histological findings is presented below in Table 11. The following findings were observed in drug-treated animals: multifocal hemorrhage in GALT in the rectum of one HD male, bilateral fibrosis in testis of 3/8 LD (37.5%) and 2/4 HD (50%) males, lymphoid depletion in the thymus of 3/16 LD animals and 2/8 HD animals, and menses in 2/4 HD females. The findings in lymphoid tissues may be considered related to treatment but are not dose-limiting. It is not clear whether the findings in testis are related to treatment. Even though there appears to be a dose-response, one control recovery male had a similar finding with the same severity, which alleviates the concern. In females, menses was observed in 2 HD animals and 1 LD recovery animal, which indicates that some of the females included in the study are sexually mature.

Because none of the aforementioned findings are considered related to treatment, the NOAEL was identified in this study at 15 mg/kg/dose, which is associated with an AUC_{ss} of 63,670 µg·hr/mL (males and females combined at study week 4).

Table 11: Summary of Histological Findings Observed in Juvenile Monkeys (Incidence and Severity).

	Males	Females

Reslizumab (mg/kg/dose) # of animals examined	0 4	1* 4	1$ 4	15 4	0 4	1* 4	1$ 4	15 4
Observations								
Cervix Blood, lumen (menses)	-	-	-	-	0	0	0	1
Rectum Hemorrhage, GALT, multifocal	0	0	0	1	0	0	0	0
Testis Fibrosis, interstitium, bilateral, multifocal	0	2	1	2	-	-	-	-
Thymus Depletion, lymphoid	0	0	1	0	0	1	1	2
Uterus Blood, lumen (menses)	-	-	-	-	0	0	0	2
RECOVERY **# of animals examined = 2/sex/group**								
Cervix Deposition, mucoid, lumen Infiltrate, neutrophil, lumen	- -	- -	- -	- -	0 0	0 0	1 1	1 1
Testis Fibrosis, interstitium, bilateral, multifocal	1	0	0	1	-	-	-	-
Thymus Depletion, lymphoid	0	0	0	0	0	0	1	0
Uterus Blood, lumen (menses)	-	-	-	-	0	0	1	0

(-) = tissue not examined
* = SCH55700 Lot #00U-557P-00003
$ = CTx55700 Lot #52758
GALT = gut-associated lymphoid tissue

Special Evaluation

Blood samples were collected from all available animals for anti-drug antibody (ADA) analysis prior to the first dose on study day 1, prior to the last dose on study day 22, and on study day 29. Samples were also collected from recovery animals on study day 57. A validated ELISA method was used for detection of ADA in the samples.

TK and immunogenicity results were submitted to the BLA in a separate report #Res-4-0009 entitled "Pharmacokinetic Report: A one-month (four once weekly doses) intravenous bridging toxicity study of reslizumab in juvenile cynomolgus monkeys, with a one-month recovery period and pharmacokinetic and anti-reslizumab antibody evaluations". The study report for study #Res-4-0006 has a GLP exception regarding this. None of the samples tested (160 samples from 48 animals across groups) were positive for ADA in this study.

Toxicokinetics

Blood samples were collected from the femoral vein by venipuncture for TK analysis prior to each dose on study days 1, 8, 15, and 22. Additional samples were collected from all animals following the final dose on study day 22 at 15 minutes, 1 hour, 4 hours, 8 hours, and 24 hours post-dose. Samples were evaluated for reslizumab

Reference ID: 3861540

concentrations using a validated enzyme-linked immunosorbent assay (ELISA) method. Analysis of pharmacokinetic parameters was conducted for each animal and dose groups were summarized.

TK and immunogenicity results were submitted to the BLA in study #Res-4-0009. The study report for study #Res-4-0006 has a GLP exception regarding this. Table 12 below, excerpted from the study report, shows that the two drug products from two different manufacturers had similar PK profiles. In addition, there was no gender difference in PK parameters.

Table 12: Reslizumab PK Parameters in Monkeys Receiving 1 mg/kg SCH55700 or CTx55700 Weekly for 4 Weeks.

1 mg/kg SCH 55700 Reslizumab – Treatment Group 2

Animal	C_{maxSS} (µg/mL)	AUC_{SS} (µg.h/mL)	AUC (µg.h/mL)	$t_{1/2}$ (hr)
n	12	12	4	4
Mean	42.01	1259	2758	218.6
SD	10.79	401	700	38.1
CV%	25.7	31.8	25.4	17.4

1 mg/kg CTx55700 Reslizumab - Treatment Group 3

Animal	C_{maxSS} (µg/mL)	AUC_{SS} (µg.h/mL)	AUC (µg.h/mL)	$t_{1/2}$ (hr)
n	12	12	4	4
Mean	35.07	962	2593	220.3
SD	8.17	335	902	31.7
CV%	23.3	34.8	34.8	14.4

AUC = Area under the concentration-time curve through infinity; AUC_{SS} = AUC at steady-state; C_{maxSS} = Maximum serum concentration at steady-state; $t_{½}$ = Terminal half-life.
Note: No statistically significant differences found in any of the parameters ($p \leq 0.05$).

Table 13 below presents a summary of mean PK parameters for reslizumab (CTx55700 drug product). As shown, there was high variability in the samples from the 15 mg/kg group. Reslizumab PK parameters in this study increased in a higher than dose-proportional manner from 1 mg/kg to 15 mg/kg.

Table 13: Reslizumab Mean PK Parameters in Cynomolgus Monkeys.

	1 mg/kg	15 mg/kg
C_{max} (µg/mL)	35.07 ± 8.17	774.36 ± 480.09

AUC_{ss} (µg·hr/mL)	962 ± 335	63,670 ± 65,354

Dosing Solution Analysis

Dosing formulations were analyzed for reslizumab concentration using an ELISA method. In addition, the dosing formulations were analyzed for stability and considered to be stable under the conditions of the study.

Results of dosing formulation analysis were not included in the study report. According to the report, under GLP exceptions, the sponsor was in charge of analyzing the dosing formulations for concentration and homogeneity. The results were provided to the study director but not included in the final report.

7 Genetic Toxicology

Even though reslizumab is a large molecule (a monoclonal antibody) and is not expected to interact with DNA, the sponsor conducted two in vitro genetic toxicology assays, a bacterial reverse mutation (Ames) assay, and an in vitro chromosomal aberration assay. The results of both in vitro assays were negative. Refer to PharmTox review under IND 101,399 dated February 19, 2008 (appendix 1), for additional details.

8 Carcinogenicity

The applicant conducted a 26-week study in Tg.rasH2 mice to assess the carcinogenic potential of reslizumab. The study protocol was discussed with the ECAC in a meeting held on July 10, 2012, and was considered adequate. In addition, the sponsor also provided data from a bioassay (statistically significant decrease in eosinophil levels in BAL fluid of OVA-sensitized mice treated with 250 mg/kg reslizumab) demonstrating that the transgenic mouse strain was pharmacologically relevant (refer to Section 4 “Pharmacology” above).

In the 26-week carcinogenicity study #DS-2012-005, Tg.rasH2 mice (25/sex/group) received 0, 100, 250, or 500 mg/kg reslizumab IV once every two weeks for 26 weeks. A positive control group receiving 75 mg/kg MNU intraperitoneally was also included for comparison. There were no statistically significant neoplastic findings observed in males or females in this study. Refer to PharmTox review under BLA 761033 dated June 30, 2015 for complete details.

9 Reproductive and Developmental Toxicology

A battery of reproductive and developmental toxicology studies was conducted with reslizumab. These studies evaluated the effects of reslizumab on fertility in CD-1 mice (study # P-6981), teratogenicity in CD-1 mice and New Zealand white rabbits (studies # #P-6378 and #P-6379, respectively), and peri- and post-natal development and juvenile toxicity in CD-1 mice (study #DS-2010-020). A detailed review of these studies is included below.

Reference ID: 3861540

The sponsor conducted a number of studies to support the use of the CD-1 mouse and New Zealand rabbit as nonclinical species for assessment of reproductive and developmental toxicity. Refer to Section 4 “Pharmacology” above.

9.1 Fertility and Early Embryonic Development

Study title: Intravenous Fertility Study of SCH 55700 in Mice.

Study no.:	P-6981
Study report location:	EDR
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	February 25, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 55700; Lots #36809-090 (0.4 mg/mL), #36809-091 (2.0 mg/mL), #36809-092 (10 mg/mL); approximately 95% pure (0.4 mg/mL), 93% pure (2.0 mg/mL), and 90% pure (10 mg/mL)

Key Study Findings

- Male and female CD-1 mice were randomized into four groups: 0 (vehicle control), 2, 10, or 50 mg/kg reslizumab intravenously as a bolus injection into the tail vein. Males were given a single dose 28 and 14 days prior to mating and again on the first day of mating and on the 14th day after the start of mating. Females were given single doses 14 days prior to mating and again on the first day of mating and 14 days after.
- No drug-related effects were observed in any of the parameters evaluated: survival, clinical signs of toxicity, body weights and food consumption, gross lesions, male reproductive organ weights, and reproductive parameters.
- Although TK parameters were not calculated for this study, blood concentration in serum was measured and ADA analysis was conducted. A few animals (2 in the LD, 1 in the MD, and 2 in the HD; were positive for ADA and had no or very low reslizumab concentration in serum. In general, serum concentrations were higher on study day 22 compared to study day 30.
- The NOAEL for male and female fertility is the high-dose of 50 mg/kg.

Reference ID: 3861540

Methods

Doses:	0, 2, 10, or 50 mg/kg reslizumab
Frequency of dosing:	Males: dosed twice 28 and 14 days prior to mating and once at the beginning of the mating period and 14 days for those males that were still used for mating. Females: dosed 14 days prior to mating, on the first day of mating, and again 14 days later for those females that did not mate during the first week. Those that mated during the second week were dosed on gestational day 0 (GD0).
Dose volume:	5 mL/kg
Route of administration:	Intravenous (bolus injection into the tail vein). (b) (4) However, no data were provided to confirm this.
Formulation/Vehicle:	Sterile SCH 55700 placebo solution (formulation contained 70 mg/mL sucrose, 2.45 mg/mL sodium acetate trihydrate, and 0.12 mg/mL glacial acetic acid), Batch #35923-135-00.
Species/Strain:	CD-1 mice
Number/Sex/Group:	25/sex/group
Satellite groups:	None
Study design:	Refer to Table 14 below, excerpted from the sponsor's submission.
Deviation from study protocol:	Protocol deviations were not reported. The study report stated that there were no circumstances that may have affected the integrity of the data.

Table 14: Fertility Study Design - Mice.

Intravenous Fertility Study of SCH 55700 in Mice (P-6981): **Study Design**					
Group	Total Daily Dose (mg/kg)	Dose Volume (ml/kg)	Dose Conc. (mg/ml)	Number of Mice	
				Males	Females
Control (SCH 55700 Placebo)	0	5	0	25	25
Low-Dose (SCH 55700)	2	5	0.4	25	25
Mid-Dose (SCH 55700)	10	5	2	25	25
High-Dose (SCH 55700)	50	5	10	25	25

a: Males were dosed twice prior to mating (28 and 14 days) and once at the beginning of the mating period and 14 days for those males that were still used for mating. Females were dosed 14 days prior to mating, on the first day of the mating period and again 14 days later for those females that did not mate during the first week. Those that mated during the second week were dosed on gestation Day 0. The frequency of dosing (at approximately 14-day intervals) was based on the half-life of SCH 55700 in mice which is approximately two weeks.

Rationale for Dose Selection

The doses used in this study were based on a preliminary fertility and post-natal study in CD-1 mice (study #P-6370). In this study, CD-1 mice were randomized to receive 0, 2, 10, or 50 mg/kg reslizumab intravenously (tail vein) on the first day of the pre-mating period and again on the first day of the mating period. Females were re-dosed on gestation day 6 and on post-partum day 2. Results of this study showed a decrease in pregnancy rate in HD females compared to controls (75% in HD *vs.* 90% in controls). No other drug-related effects were observed.

Observations and Results

Mortality

Animals were observed daily for survival. There were five deaths in the study, all in the LD group. Four males (animals #29, #31, #35, and #47) and one female (animal #149) died within 2 hours after receiving the third dose on study week 4. A cause of death was not determined for any of the animals. The study report states that “the deaths appeared to be due to an immunogenic response to a heterologous protein”. Therefore, these were not considered related to treatment.

Clinical Signs

Animals were observed daily for signs of toxicity to reslizumab. There were no drug-related effects observed.

Body Weight

Body weights were recorded once weekly for males and once weekly prior to mating and on days 0 (day of mating), 4, 7, and 14 after mating for females.

There were no drug-related effects observed.

Feed Consumption

Food consumption was measured weekly during the pre-mating period for males and weekly prior to mating and during gestation (GD0-14) for females.

There were no drug-related effects observed.

Toxicokinetics

Blood samples were collected from the abdominal aorta of all males for serum drug concentration and anti-drug antibody analysis days 16, 22, and 30 after the last dose. TK parameters (*e.g.*, C_{max} and AUC) were not calculated in this study.

The following animals were positive for anti-reslizumab antibodies: two in the LD (animals #43 and #48), one in the MD (animal #68), and two in the HD (animals #86 and #95). These animals had no or very low reslizumab concentration in serum, suggesting that the antibodies were neutralizing reslizumab in serum. The serum concentrations were higher on study day 22 compared to study day 30. Serum concentrations on study day 22 ranged from 3.8-14.6 µg/mL in the LD group, from 17-338.7 µg/mL in the MD group, and from 24.3-403.7 µg/mL in the HD group.

Dosing Solution Analysis

Results of dosing solution analyses were not provided in the final study report.

Necropsy

Males were sacrificed after completion of the mating period. Females were sacrificed on gestational day 14.

There were no drug-related effects observed.

Fertility Parameters

<u>Male Fertility</u>
Males were sacrificed approximately three or four weeks after the start of mating. Paired testes weights and epididymal weights were recorded for each animal.

There were no drug-related changes in mating or fertility indices or reproductive organ weights in males.

<u>Female Fertility</u>
The vaginal cytology of all females was checked daily to determine if the estrous cycle was normal from 14 days prior to mating and during the mating period until evidence of mating was observed. Females were sacrificed on gestational day 14 (GD14) and the uteri and ovaries exposed to collect reproduction data (number of implantations, fetuses, resorptions, and corpora lutea). The uteri of apparently non-pregnant mice were also examined for evidence of implantations.

There were no drug-related changes in any of the parameters evaluated in females.

Reference ID: 3861540

9.2 Embryonic Fetal Development

Study title: Intravenous Embryo-Fetal Development Study of SCH 55700 in Mice.

Study no.:	P-6378
Study report location:	EDR
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	February 28, 1996
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #:	SCH 55700, Lots #35923-067-01 (0.4 mg/mL), #35923-068-01 (2.0 mg/mL), and #35923-069-01 (10 mg/mL)

Key Study Findings

- Pregnant CD-1 mice (25/group) received 0, 2, 10, or 50 mg/kg reslizumab intravenously once on gestational day 6 (GD6). Animals were dosed only once because reslizumab's half-life in general is approximately two weeks and this would cover the duration of the study.
- No drug-related effects were observed in any of the parameters evaluated in this study: survival, clinical signs of toxicity, maternal body weights, food consumption (qualitative), gross observations, reproduction parameters, and fetal malformations or developmental variations.
- The NOAEL for both maternal toxicity and teratogenicity is 50 mg/kg.
- Toxicokinetics were not conducted for this study.

Methods

Doses:	0, 2, 10, or 50 mg/kg reslizumab
Frequency of dosing:	Once on gestational day 6
Dose volume:	5 mL/kg
Route of administration:	Intravenous into the tail vein. (b) (4) [redacted] However, no data were provided to confirm this.
Formulation/Vehicle:	Sterile SCH 55700 placebo solution (formulation contained 70 mg/mL sucrose, 2.45 mg/mL sodium acetate trihydrate, and 0.12 mg/mL glacial acetic acid), Batch #35923-009.
Species/Strain:	CD-1 mouse
Number/Sex/Group:	25 mice/group

Reference ID: 3861540

Satellite groups: None
Study design: Refer to Table 15 below, excerpted from the sponsor's submission
Deviation from study protocol: Protocol deviations were not reported for this study.

Table 15: EFD Study #P-6378 Design - Mice.

Intravenous Embryo-Fetal Development Study of SCH 55700 in Mice (P-6378): Study Design				
SCH 55700 Daily Dose				
Group	Total Dose (mg/kg)	Dose Volume (ml/kg)	Dose Conc. (mg/ml)	No. of Females
Control SCH 55700 Placebo	0	5	0	25
Low-Dose	2	5	0.4	25
Mid-Dose	10	5	2.0	25
High-Dose	50	5	10	25

Rationale for Dose Selection

Doses used in this EFD study (2, 10, and 50 mg/kg reslizumab) were selected based on a pilot intravenous embryo-fetal development study of SCH 55700 in CD-1 mice (study #D-27256). In this study, pregnant CD-1 mice (8/group) were treated with 0, 2, 10, or 50 mg/kg reslizumab intravenously (tail vein) once on gestational day 6. Pregnancy rate in the HD group was much lower compared to the vehicle control (37.5% vs. 87.5% in the controls). Therefore, the number of corpora lutea and implantation sites was also lower in the HD group relative to controls. However, the mean number of corpora lutea and implantation sites per pregnant mouse was similar across groups. There were no other drug-related changes observed in this study.

Observations and Results

Mortality

Animals were observed daily for survival status. All animals survived for the duration of the study.

Clinical Signs

Animals were observed daily for any signs of toxicity. There were no drug-related changes observed.

Body Weight

Body weights were recorded on study days 0 (day of mating), and gestational days (GD) 6, 9, 12, 15, and 18 (day of necropsy). There were no drug-related changes observed.

Feed Consumption

Food consumption was measured on days 0 (mating), and GD 6, 10, 15, and 18. There were no drug-related changes observed.

Toxicokinetics

Toxicokinetics were not conducted in this study.

Dosing Solution Analysis

Results of dosing formulation analyses (concentration, homogeneity, stability) were not provided in the final study report.

Necropsy

Animals were sacrificed on GD18 by CO_2 inhalation and the fetuses were removed. The dams were examined for external and visceral changes. The uteri of apparently non-pregnant mice were examined for evidence of implantations.

There were no drug-related effects observed. The number of late resorptions in the MD group was higher than controls (6 in MD vs. 2 in controls), but a dose-response was not observed as the HD group had only 1 late resorption.

Cesarean Section Data

Animals were sacrificed on GD18. The numbers of corpora lutea, implantation sites, and resorptions were counted and distribution of the fetuses in the uterus was determined.

Table 16 below presents a summary of reproduction parameters. There were no drug-related effects observed.

Table 16: Summary of Reproductive Parameters - Mice.

Reslizumab (mg/kg/dose)	0	2	10	50
Parameter				
# of pregnant mice (%)	24/25 (96%)	22/25 (88%)	25/25 (100%)	22/25 (88%)
# of litters evaluated	24	22	25	22
# live fetuses (%)	292 (100%)	252 (99.6%)	282 (99.3%)	274 (99.6%)
# dead fetuses	0	1	2	1
% male fetuses	55.5%	51%	50%	51.6%
% in left horn of uterus	46.9%	46.6%	43%	48.4%
Mean # implantation sites (±SEM)	13.08±0.35	11.91±0.54	12.12±0.31	13.00±0.34
Mean # resorptions (±SEM)	0.92±0.22	0.41±0.16	0.76±0.21	0.50±0.23

Offspring Data

Pups were sacrificed by CO_2 inhalation after removal from the uterus. Approximately 50%of the fetuses from each litter were examined for soft tissue defects by serial slicing. The remaining pups were examined for gross visceral changes and processed for skeletal examination. Late resorptions and dead fetuses were also examined for external changes and, when possible, for skeletal changes. Fetal findings were

Reference ID: 3861540

classified as malformation[3] or developmental variations[4]. All fetal remains were stored in glycerin and alcohol.

There were no drug-related malformations observed in the study. There was a single incidence of testis not fully descended in the HD group (1 fetus in 1 litter) but this was considered probably unrelated to treatment due to the low incidence of the finding. Also, there was a higher incidence (litter and fetuses) of asymmetrical sternebra in treated animals compared to controls (but no dose-response). Because historical controls for CD-1 mice were not provided in the study report, an information request was sent to the sponsor on August 20, 2015 to request that they submit laboratory historical control data from age-matched animals to support their conclusion that this finding of assymetrical sternebra is not related to reslizumab treatment.

The sponsor's response was received on August 28, 2015, and it included historical control data for this finding, which is considered a common skeletal variation in mice. Although the incidence observed in this study is slightly higher than the historical control range, this was the only skeletal variation observed in drug-treated animals and the total incidence of skeletal variations in this study was lower in drug-treated animals compared to controls (60.3%, 39.7%, 41.3%, and 47.9% for control, LD, MD and HD; respectively). This provides sufficient justification for considering this finding as incidental.

Refer to Table 17 below for a summary of skeletal observations.

Table 17: Summary of Skeletal Observations in Offspring – CD-1 Mice.

Reslizumab (mg/kg/dose)	0	2	10	50
Parameter				
# of litters evaluated	24	22	25	22
# fetuses evaluated	151	131	150	144
Asymmetrical Sternebra				
Fetal incidence*	11 (7.3%)	28 (21.4%)	25 (16.7%)	31 (21.5%)
Litter incidence*	8 (33.3%)	16 (72.7%)	14 (56.0%)	18 (81.8%)

* Total # (%)

[3] Malformation = any anomaly which is incompatible with life, grossly impairs normal function or distorts anatomical structure.
[4] Variations = a slight variation in development which may only be temporary (e.g., retarded ossification) or a minor deviation commonly occurring in the species.

Study title: Intravenous Embryo-Fetal Development Study of SCH 55700 in Rabbits.

Study no.:	P-6379
Study report location:	EDR
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	February 5, 1996
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #:	SCH 55700; Lots #35923-113-01 (0.4 mg/mL), #35923-113-01 (2.0 mg/mL), and #35923-114-01 (10 mg/mL)

Key Study Findings

- Pregnant New Zealand rabbits (20/group) were treated with 0, 2, 10, or 50 mg/kg reslizumab intravenously on gestational day 7.
- There was a dose-dependent decrease in the number of corpora lutea and implantation sites in treated dams. This was also observed in the pilot study in rabbits.
- There were no drug-related effects on malformations or developmental variations in treated animals.
- The NOAEL for both maternal toxicity and teratogenicity is 50 mg/kg.
- Toxicokinetics were not conducted for this study.

Methods

Doses:	0, 2, 10, or 50 mg/kg reslizumab
Frequency of dosing:	Once on gestational day 7
Dose volume:	5 mL/kg
Route of administration:	Intravenous using an infusion pump into the marginal ear vein at a rate of approximately 0.24 mL/5 sec. (b) (4) However, no data were provided to confirm this.
Formulation/Vehicle:	Sterile SCH 55700 placebo solution (formulation contained 70 mg/mL sucrose, 2.45 mg/mL sodium acetate trihydrate, and 0.12 mg/mL glacial acetic acid)
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	20 females/group

Reference ID: 3861540

Satellite groups: None.
Study design: Refer to Table 18 below, excerpted from the sponsor's submission and
Deviation from study protocol: None reported.

Table 18: EFD Study #P-6379 Design - Rabbits.

Embryo-Fetal Development Study of SCH 55700 in Rabbits (P-6379): **Study Design**				
Group	Total Daily Dose (mg/kg)	Dose Volume (ml/kg)	Dose Conc. (mg/ml)	Number of Females
Control (SCH 55700 Placebo)	0	5.0	0	20
Low-Dose (SCH 55700)	2	5.0	0.4	20
Mid-Dose (SCH 55700)	10	5.0	2	20
High-Dose (SCH 55700)	50	5.0	10	20

Rationale for Dose Selection

The doses used in this study were selected based on data from a pilot intravenous embryo-fetal development study in rabbits (study #D-27243). Briefly, in study #D-27243, pregnant New Zealand white rabbits (4/group) received 0 (placebo reslizumab), 2, 10, or 50 mg/kg reslizumab intravenously (marginal ear vein) once on gestational day 7 using an infusion pump at a rate of 2.5-2.8 mL/minute. Results of this study show potential reslizumab-related effects in reproduction [*i.e.*, decreased pregnancy rate (50% vs. 100% in the controls), resulting in a decreased number of corpora lutea and implantation sites in the HD group and increase in pre-implantation loss in the MD and HD groups] but no effects on fetal gross observations (malformations or developmental variations) compared to controls. The same doses (2, 10 and 50 mg/kg) were selected for the pivotal study.

Observations and Results

Mortality

All dams were examined daily for survival. There were no drug-related effects in survival.

Clinical Signs

Animals were observed for any signs of toxicity. There were no drug-related effects on clinical signs.

Body Weight

Body weights were recorded on days 0 (day of mating), and GD7, GD10, GD13, GD16, GD19, GD22, GD25, GD28, and GD30.

There were no drug-related effects observed in body weights in dams or offspring.

Feed Consumption

A visual estimate of food consumption was recorded daily for all rabbits.

There were no drug-related effects observed in food consumption (qualitative).

Toxicokinetics

Toxicokinetics were not conducted for this study.

Dosing Solution Analysis

Results of dosing formulation analyses (concentration, homogeneity, stability) were not provided in the final study report.

Necropsy

On GD30, all rabbits were sacrificed, the fetuses removed and the uteri examined.

There were no drug-related necropsy observations observed.

Cesarean Section Data

On GD30, the number of corpora lutea, implantations, and resorptions were counted and distribution of the fetuses in the uterus were determined for all rabbits.

A summary of reproductive parameters is presented below in Table 19. As shown, the number of corpora lutea and implantation sites were decreased in reslizumab-treated groups compared to controls. In addition, there was a slight increase in the number of resorptions in animals at ≥ 10 mg/kg reslizumab.

Table 19: Summary of Reproductive Parameters - Rabbits.

Reslizumab (mg/kg/dose)	0	2	10	50
Parameter				
# of pregnant rabbits (%)	17/20 (85%)	20/20 (100%)	20/20 (100%)	18/20 (90%)
# of litters evaluated	17	20	19	17
# live fetuses (%)	159 (100%)	163 (99.4%)	149 (100%)	129 (100%)
# dead fetuses	0	1	0	0
% male fetuses	41%	55.5%	53.7%	47.3%
% in left horn of uterus	56%	48.2%	44.3%	48.1%
Mean # implantation sites (±SEM)	9.65±0.56	8.40±0.34	7.8±0.62*	7.72±0.50*
Mean # corpora lutea (±SEM)	10.10±0.47	8.65±0.27	8.55±0.56*	8.11±0.46**
Mean # resorptions (±SEM)	0.29±0.11	0.20±0.14	0.35±0.11	0.56±0.29

Offspring Data

Offspring were sacrificed by CO_2 inhalation, dissected, internally sexed, examined for gross visceral changes, tagged and processed for skeletal examination. Dead fetuses and resorptions were also examined grossly for external defects and whenever possible, for visceral and skeletal defects. Fetal findings were classified as

malformation[5] or developmental variations[6]. After examination, fetal remains were stored in glycerine and alcohol.

There were no drug-related malformations. A number of skeletal variations were observed but the numbers were similar across groups, including the vehicle control group. None of these variations were considered related to reslizumab treatment.

9.3 Prenatal and Postnatal Development

Study title: Perinatal/Postnatal Reproduction, Developmental, and Juvenile Toxicity Study of Intravenous Reslizumab in Mice, Including a Postnatal Behavioral/Functional Evaluation.

Study no.:	DS-2010-020 ((b) (4) #UJZ00051)
Study report location:	EDR Module 4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 17, 2008
Date of completion:	April 12, 2010
Study report date:	April 30, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Reslizumab, Lot #0706015, 99.8% pure

Key Study Findings

- Pregnant female CD-1 mice (30/group) received 0, 10, or 50 mg/kg/dose reslizumab intravenously on gestation days 6 and 18, as well as on post-natal day 14. In addition, this study included a juvenile toxicity portion whereby F_1 generation mice were treated with 0, 10, and 25 mg/kg/dose reslizumab on post-natal days 14, 42, and 70.
- There were no reslizumab-related effects on any of the reproductive parameters evaluated for F_0 generation mice.
- Reslizumab was excreted into the milk of F_0 generation mice.
- Reproductive parameters in F_1 generation mice (e.g., mating and fertility index) were not affected by reslizumab treatment.
- Ataxia was observed in all the pups (13 pups) from one litter. However, there were no effects observed in the neurological assessments.

[5] Malformation = any anomaly which is incompatible with life, grossly impairs normal function or distorts anatomical structure.
[6] Variations = a slight variation in development which may only be temporary (e.g., retarded ossification) or a minor deviation commonly occurring in the species.

Reference ID: 3861540

- Reslizumab was detected in pups from treated mice, suggesting that there is placental transfer.
- Animals showed reslizumab exposure. However, a few dams (three in the LD, animals #6433, #6435, and #6454; and three in the HD, animals #6483, #6484, and #6486) were positive for anti-reslizumab antibodies on post-natal day 21. These animals had decreased reslizumab exposure, suggesting that the antibodies were neutralizing. This finding did not affect the outcome of the study since all the parameters were evaluated in a sufficient number of animals with sufficient exposure.
- Anti-reslizumab antibodies were detected in a few pups from treated animals, but this did not affect the outcome of the study because a sufficient number of animals had exposure.
- The following findings were observed in the F_1 juvenile toxicity portion of the study: 1 HD animal presented clinical signs of decreased motor activity, tremors, ataxia, hunched posture, ptosis, and pale body. This animal was found dead during the study on PND23. In addition, treated males showed a transient decrease in motor activity during the treatment period. There were no effects on any of the reproductive parameters evaluated. Kidney was identified as a target organ of toxicity, but it was not possible to determine whether the toxicities observed were due to development of ADA or a direct reslizumab effect.
- The NOAEL for maternal toxicity and F_1 toxicity is 50 mg/kg.
- The NOAEL in the F_1 juvenile toxicity portion is 10 mg/kg due to the clinical signs and one death observed at the HD.

Reference ID: 3861540

Methods

Ninety presumed pregnant female CD-1 mice (F_0 animals) were randomized into one of three groups (30 animals/group): 0 (vehicle: 0.9% USP saline), 10, or 50 mg/kg reslizumab. Study drug was administered on gestation days 6 and 18 (GD6 and GD18) and on post-natal day 14 (PND14) intravenously via the lateral tail vein. Maternal clinical signs of toxicity, behavior, and body weights were recorded. In addition, milk and blood samples were collected from 5 mice/group on PND14 and from all animals on the day of sacrifice (PND21). A necropsy of the thoracic, abdominal and pelvic viscera was performed and the number and distribution of implantations were recorded.

For F_1 generation assessments, 24 pups/sex/group were selected randomly. At least one male and female pup per litter were selected when possible. These animals were not directly treated with reslizumab. All F_1 animals were evaluated for sexual maturation starting on PND21 for females and PND27 (age of preputial separation) for males. Animals were also evaluated for passive avoidance (PND23 – one male and one female per litter), motor activity (PND22 and PND61 – one male and one female per litter), and neurobehavioral assessment [(functional observational battery) on PND77 and PND105 – one male and one female per litter], and reproductive capacity (starting on PND107). Blood samples were collected from these mice for toxicokinetic/ADA analysis.

For the F_1 juvenile toxicity replicate, F_1 generation pups were selected from 16 litters in the maternal (F_0) vehicle group and assigned such that one male and female from each litter was assigned to each of the following groups (at least 8/sex/group): 0 (vehicle), 10, or 25 mg/kg reslizumab intravenously via lateral tail vein. Mice were injected with reslizumab on PND14, PND42, and PND70. All animals in these groups were evaluated for sexual maturation (beginning on PND21 for females and PND27 for males), passive avoidance (PND23 – one male and one female per litter), toxicokinetics and ADA analysis (PNDs 76 and 78), motor activity and functional observational battery (PND77). Also, at necropsy, tissues from these animals were collected for anatomic pathology analysis (gross examinations, organ weights, and histopathological examinations). Additional animals (6-8 animals/group) were maintained for a recovery period to assess reversibility of any drug-related effects.

Doses:	F_0 animals were dosed with 0 (vehicle), 10, or 50 mg/kg reslizumab F_1 animals (juvenile toxicity portion) were dosed with 0 (vehicle), 10, or 25 mg/kg reslizumab
Frequency of dosing:	F_0: Days 6 and 18 of presumed gestation (GD6 and GD18) and day 14 postpartum F_1: PND14, PND42, PND70
Dose volume:	5 mL/kg

Reference ID: 3861540

Route of administration:	IV via lateral tail vein
Formulation/Vehicle:	0.9% sodium chloride for injection, USP
Species/Strain:	Mouse, Crl:CD1 (ICR) from (b) (4)
Number/Sex/Group:	F_0: 30 female mice/group F_1: at least 8 pups/sex/group
Satellite groups:	F_0 generation mice assigned to milk sample collection were also assigned to toxicokinetic and ADA sample collection on lactation day 14.
Study design:	See above under "Methods" and Tables 20 and 21 below (excerpted from the sponsor's submission).
Deviations from study protocol:	Deviations were reviewed and considered to be minor and not to affect the integrity of study data.

Table 20: PPND Study #DS-2010-020 Design.

Dose Group	Dose[a,b] (mg/kg/dose)	Concentration (mg/mL)	Dose Volume (mL/kg)	Injection Rate	Number of Mice	Assigned F0 Generation Mouse Numbers
I	0 (Vehicle)	0	5	Bolus	30	6401 - 6430
II	10	2	5	Bolus	30	6431 - 6460
III	50	10	5	Bolus	30	6461 - 6473, 195[c], 6475 - 6490

a. The test article was considered 100% active/pure for the purpose of dose calculations. The stock test article was provided as a 10 mg/mL solution. Group III mice were administered the test article "neat"; dosing solutions for Group II were diluted with 0.9% sodium chloride injection, USP.

b. The test article and/or vehicle was administered on DGs 6 and 18, and on DL 14. Doses were adjusted for body weights recorded on the day of dose administration, with the exception of the dose administered on DG 18; this dose was based on the body weight recorded on DG 12. Doses were given at approximately the same time each dosing day.

c. Mouse 6474 was found dead on DG 6 due to a probable dosing error and replaced by mouse 195.

Table 21: PPND Study Design – F_1 Juvenile Toxicity Portion.

Dose Group[a]	Dose[b,c] (mg/kg/dose)	Concentration (mg/mL)	Dose Volume (mL/kg)	Injection Rate
IV	0 (Vehicle)	0	5	Bolus
V	10	2	5	Bolus
VI	25	5	5	Bolus

a. F1 generation pups/mice assigned to the juvenile toxicity replicate were test article naïve mice from the vehicle-only maternal dose group (Group I).

b. The test article was considered 100% active/pure for the purpose of dose calculations. The stock test article was provided as a 10 mg/mL solution; dosing solutions were diluted with 0.9% sodium chloride injection, USP.

c. The test article and/or vehicle were administered on PNDs 14, 42, and 70. Doses were adjusted for body weight changes and given at approximately the same time each dosing day.

Rationale for Dose Selection

Doses were selected based on data from a preliminary intravenous fertility and post-natal study conducted with reslizumab (study #P-6370). Briefly, in study P-6370, CD-1 mice (40 males and 80 females) were randomized into 4 groups to receive: 0 (vehicle), 2, 10, or 50 mg/kg reslizumab intravenously (via tail vein) on the first day of the two-week pre-mating period, and again on the first day of the mating period. Females were re-dosed on gestation day 6 (GD6) and post-partum day 2.

On day 18 after mating, 8 females from each group were sacrificed, C-sections were performed, and the following parameters were analyzed: # of corpora lutea, # of implantations, # of resorptions, fetal body weights and gender, and gross examinations of the dams and pups. The remaining of the females were allowed to deliver and rear pups naturally. The length of gestation, litter size, # of live and stillborn pups, and sex distribution were determined for each group. On PND21, dams were sacrificed and the implantation sites were counted. Mating and fertility indices were calculated for all groups. In addition, this study also evaluated the effects of reslizumab on F_1 generation ability to mount an eosinophil response after sensitization and antigen (ovalbumin) challenge.

Results showed a decrease in pregnancy rate [(# of pregnant mice/# of mice allowed to mate) x 100] in HD animals compared to controls (75% in HD *vs.* 90% in controls). No other effects were observed in this preliminary study. Doses of 10 and 50 mg/kg IV reslizumab were selected study #DS-2010-020.

Observations and Results

F_0 Dams

Survival: Animals were observed twice daily for survival.

There were a few deaths during the study (summarized in table 22 below). None of these deaths were considered related to treatment.

Table 22: Summary of F_0 Generation Mortality.

Reslizumab (mg/kg/dose)	0	10	50
Parameter			
# of mice evaluated	30	30	30
# of deaths			
Found dead	2	3	1
Sacrificed	0	1	2

Clinical signs: Animals were observed for clinical observations, abortions, and premature deliveries daily before dosing and between 1-2 hours after dosing; and once daily during non-dosing days. Maternal behavior was recorded on post-partum days 1, 4, 7, 14, and 21.

One HD animal (#6476) had corneal opacity and ptosis. This mouse was found dead on day 17 of lactation.

Body weight: Body weights were recorded weekly during the acclimation period; on gestation days 0, 6, 12, 18, and 23 (mice that did not deliver a litter); on the days of maternal behavior observations (lactation days 1, 4, 7, and 14); and on the day of terminal sacrifice.

There were no drug-related changes in body weights in F_0 generation animals during the gestation (dosing period) or lactation periods.

Feed consumption: Food consumption was not measured in this study.

Uterine content: On post-partum day 21, the number and distribution of implantations were recorded.

Refer to Table 23 below for a summary of the findings.

Necropsy observation: On post-partum day 21, mice were sacrificed. A gross necropsy of the thoracic, abdominal, and pelvic viscera was performed; and the number and distribution of implantations were recorded.

Only one HD animal had a large spleen and iliac lymph nodes. Because of this single incidence, it is not clear whether these findings are related to treatment.

Toxicokinetics/ADA: On PND14, blood samples were collected from the 5

dams/group that were selected for milk sample collection (see below). Samples were collected 6 hours post-dose (the approximate T_{max} in mice). In addition, after completion of the 21-day post-partum period, blood samples were collected from the vena cava as soon as possible after sacrifice from all dams. Serum concentration and ADAs were analyzed using validated ELISA methods.

Treated animals showed reslizumab exposure, measured as serum reslizumab concentration. Animals in the 10 mg/kg group had 84600-121000 ng/mL on PND14 and BLQ-10400 ng/mL on PND21. Animals in the 50 mg/kg group had 343000-563000 ng/mL on PND14 and BLQ-19500 ng/mL on PND21. Of note, three dams in the LD group (animals #6433, #6434, and #6454) and three in the HD group (animals #6483, #6484, and #6486) developed ADA (first detected on PND21) and had no exposure at this time point, suggesting that ADAs were neutralizing. As shown, dams had significantly decreased exposure on PND21 compared to PND14. A summary of reslizumab serum concentrations in this study is presented below in Table 29 (excerpted from the sponsor's submission).

Dosing Solution Analysis: Dosing formulations were tested for concentration. Information for stability of the dosing formulations was provided by the sponsor.

All dosing formulations were within the acceptance criteria for concentration. Dosing formulations were maintained under the conditions tested for stability by the sponsor.

Other: Milk samples were collected (≤0.1-0.2 mL per dam) from 5 mice per dose group on lactation day 14 at 6 hours post-dose.

Reslizumab was detected in milk samples at concentrations of 2790-9000 ng/mL in the LD group and 19000-48300 ng/mL in the HD group (approximately dose-proportional). Reslizumab was not detected in samples from vehicle control animals.

Table 23: Summary of F_0 Generation Reproductive Parameters.

Reslizumab (mg/kg/dose)	0	10	50
Parameter			
# of pregnant mice	27 (90%)	27 (90%)	26 (86.7%)

# of litters delivered	27 (100%)	27 (100%)	26 (100%)
Mean duration of gestation (days)[a]	19.8 ± 0.4	19.6 ± 0.5	19.6 ± 0.5
Gestation Index (%)[b]	100	96.3	96.2
Mean # implantation sites[a]	13.2 ± 2.3	12.0 ± 2.8	12.6 ± 3.2
# mice with stillborn pups	0	2	1
Live litter size on PND1[a]	12.2 ± 2.3	11.5 ± 2.3	11.8 ± 2.9
% male pups on PND1[a]	49.3 ± 11.3	47.2 ± 13.2	48.4 ± 19.0
Viability index[c]	99.1	99.3	98.6
Lactation index[d]	96.0[e,f]	97.8[e,f]	97.7[e,f]

[a] Mean ± S.D.
[b] (# of mice with live offspring/# of pregnant mice) x 100
[c] (# of live pups on PND4/# of liveborn pups on PND1) x 100
[d] (# of live pups on PND21 (weaning)/# of live pups on PND4) x 100
[e] Excludes pups from litters that were sacrificed on PND14 after dam was sacrificed for blood collection
[f] Excludes pups from litters that were sacrificed due to death of dam

F_1 Generation

Survival: Each litter was evaluated for viability at least twice daily.

Table 24 below presents a summary of F_1 generation survival. The number of surviving pups per litter was similar across groups.

Table 24: Summary of F_1 Generation Survival.

Reslizumab (mg/kg/dose)	0	10	50
Parameter			
Delivered litters with one or more liveborn pups	27	26	25
Total # pups delivered	332	304	295
Total # pups liveborn	332	300	295
Pups found dead/presumed cannibalized			
PND1	1/332	0/300	0/295
PND2-4	2/331	2/300	4/295
PND5-7	3/329	0/298	2/291
PND8-14	0/326	3/298	0/289
PND15-21	7/248[a,b]	2/221[a,b]	3/216[a,b]
Surviving pups/litter[c] (mean ± S.D.)			
PND1[d]	12.3 ± 2.3	11.5 ± 2.3	11.8 ± 2.9
PND4	12.2 ± 2.4	11.5 ± 2.3	11.6 ± 3.1
PND7	12.1 ± 2.3	11.5 ± 2.3	11.6 ± 3.0
PND14	12.1 ± 2.3	11.3 ± 2.4	11.6 ± 3.0
PND21	12.0 ± 2.1	11.0 ± 2.7	11.2 ± 3.4

[a] Excludes pups from litters that were sacrificed on PND14 after dam was sacrificed for blood collection
[b] Excludes pups from litters that were sacrificed due to death of dam
[c] Average # of live pups per litter, including litters with no surviving pups
[d] Includes liveborn pups and pups that died before weighing on PND1

Clinical signs: Clinical observations were recorded once daily during the pre-weaning period for all pups, weekly during the post-weaning period, and daily before dose administration (for the juvenile toxicity replicate).

Ataxia was observed in one litter from the HD group (litter #6461) on PND19. It was observed in all 13 pups from that litter. Other clinical signs observed were similar across groups.

Body weight: Body weights were first recorded on PND1 for individual pups after all pups in a litter were delivered and groomed by the dam. In addition; body weights were recorded on PND 4, 7, 14, and 21, and weekly during the post-weaning period.

There were no drug-related effects in body weights compared to controls during the post-natal or post-weaning periods.

Feed consumption: Food consumption was not measured in this study.

Physical Beginning on PND23, one male and one female mouse from each litter

development: were evaluated in a passive avoidance test for learning, short-term retention, and long-term retention (1 week later). In addition, mice were evaluated for motor activity on PNDs 22 and 61. One male and one female mouse from each litter (when possible) were examined throughout the testing period.

Results of the learning and retention tests showed that there were no drug-related effects in learning or long-term retention. Regarding short-term retention, males in the 50 mg/kg reslizumab group showed a shorter retention time (31%) compared to controls.

There were no drug-related changes in motor activity in these mice.

In addition, female mice were evaluated for the age of vaginal patency (average day post-partum that the vagina was observed to be patent) beginning on PND21 and male mice were evaluated for the age of preputial separation (average day post-partum that the prepuce was observed to be separated) beginning on PND27. There were no drug-related changes in preputial separation in males or vaginal patency in females.

Neurological assessment: The functional observational battery (FOB) was conducted unaware of the group assignment of the mouse. One male and one female mouse from each litter (when possible) were evaluated on PND77 and 105.

There was a statistically significant increase in average landing foot splay on PND77 in HD females compared to controls (13%) but this was not observed on PND175. No additional changes were observed.

Reproduction: Reproductive capacity was evaluated starting on approximately PND 107. F_1 generation mice within each dose group were assigned to cohabitation, one male and one female mouse, with the exclusion of sibling matings. The cohabitation period was 14 days maximum. After completion of the cohabitation period, male mice were sacrificed on PND124 through PND128 and examined for gross lesions (thoracic, abdominal, and pelvic viscera). Female mice were C-sectioned on GD13 and examined for number and distribution of corpora lutea, implantation sites and viable/non-viable embryos.

Table 25 below presents a summary of the reproductive parameters for the F_1 generation. LD animals presented a statistically significant decrease in fertility index [(# of pregnancies/# of mice that mated) x 100] relative to controls. However, this was not observed at the HD. In addition, HD animals had a slightly non-significant increase in post-implantation loss {[(# of implantations - # of live embryos) / # of implantations] x 100} compared to controls (approximately 38%).

Table 25: Summary of F_1 Generation Reproductive Parameters.

Reference ID: 3861540

Reslizumab (mg/kg/dose)	0	10	50
Parameter			
F_1 males mating index[a]	95.4%	100%	95.8%
F_1 females mating index[a]	95.4%	100%	96%
F_1 males fertility index[b]	95.2%	75%**	95.6%
F_1 females fertility index[b]	95.2%	75%	91.7%
Mean # corpora lutea[c]	14.4 ± 2.1	13.7 ± 3.1	13.7 ± 2.6
Mean # implantations[c]	14.4 ± 2.0	13.4 ± 3.4	13.6 ± 2.4
Pre-implantation loss (%)[d]	0.3%	3.5%	0.9%
Post-implantation loss (%)[e]	12.0%	9.8%	16.6%

[a] (# of mice that mated/# of mice in cohabitation) x 100
[b] (# of pregnancies/# of mice that mated) x 100
[c] Mean ± S.D.
[d] [(# corpora lutea - # implantations) / # corpora lutea] x 100
[e] [(# implantations - # live embryos) / # implantations] x 100
** $p < 0.01$

In addition to the reproductive parameters above, male mice were evaluated for organ weights and sperm concentration and motility.

LD males had a statistically significant increase in seminal vesicles weight relative to controls (approximately 18%). Also, although the total sperm count was similar across groups, treated males had a dose-dependent (non-significant) decrease in number of motile sperm (22% and 26% for the LD and HD, respectively). An information request was sent to the sponsor on August 20, 2015 to request a justification (*e.g.*, laboratory historical control data from age-matched animals) that this finding of decreased sperm motility is not related to treatment as they claim. The sponsor's response was received on August 28, 2015, and included more detailed information about this finding. Although the values observed are lower than the historical control range, it is noted that the controls are in the lower range for sperm motility and also it is noted that there is a wide variability (large standard deviation). Therefore, it is concluded that this finding is not related to treatment.

Other: Blood samples were collected from all pups of TK F_0 generation animals on PND14 (6 hours post-dose) and PND21. Blood samples were also collected from other F_1 generation animals on the following time points: between PNDs 117 and 121 (males), between GDs 6 and 9-12 (females), and from all mice assigned to the post-weaning development replicate for toxicokinetic and ADA analysis.

Reslizumab was detected in pups on PND14 and PND21. Pups from the LD group had 700-13600 ng/mL reslizumab on PND14 and 3380-23400 ng/mL on PND21. Pups from the HD group had 1530-76400 ng/mL on PND14 and 31900-120000 on PND21. Reslizumab was not detected in any of the animals tested at PND117-121 (males) or GD6-12 (females). A few pups tested for ADA had a positive response in the screening test (including some pups from a few vehicle control dams) but were not re-tested due to limitations in sample volume. As shown, pups had much higher exposure on PND21 compared to PND14. A summary of reslizumab serum concentrations is presented below in Table 29 (excerpted from the sponsor's submission).

F_1 Juvenile Toxicity Portion (Dosed on PND14, PND42, and PND70)

Survival: Animals were evaluated for viability at least twice daily during the dosing period. Table 26 below presents a summary of F_1 generation juvenile study survival.

Table 26: Summary of F_1 Generation Survival – Juvenile Toxicity Portion.

	Males			Females		
Reslizumab (mg/kg/dose)	**0**	**10**	**25**	**0**	**10**	**25**
# of animals examined	**17**	**16**	**16**	**15**	**16**	**16**
Parameter						
# of deaths						
Found dead	0	0	2	1	0	1
Sacrificed	1	1	1	0	0	1
Sac'd (dead dam)	2	2	2	2	2	2

Clinical signs: Clinical observations were recorded daily before dose administration, one to two hours post-dose, and weekly during the post-weaning period.

There was one female at the HD (animal #2106) that presented the following clinical signs of toxicity: decreased motor activity, tremors, hunched posture, ataxia, ptosis, and pale body. This animal was found dead on PND23. No additional drug-related clinical signs were observed.

Body weight: Body weights were recorded on PND1, PND4, PND7, PND14, PND21 (weaning), and weekly during the post-weaning period.

There were no drug-related effects on body weights.

External evaluation: Male and female mice assigned to this portion of the study were sacrificed on PND84 and examined for gross lesions. Gross necropsy included an initial physical examination of external surfaces and all orifices, as well as internal examination of tissues and organs in situ. In addition; the cranial, thoracic, and abdominal cavities were examined.

There were no drug-related effects observed.

Sexual maturation: Female mice were evaluated for the age of vaginal patency beginning on PND21. Male mice were evaluated for the age of preputial separation beginning on PND27.

There were no drug-related effects in the age of vaginal patency in females or the age of preputial separation in males.

Passive avoidance: Starting on PND23, one male and one female from each litter were evaluated in a passive avoidance test for learning, short-term retention and long-term retention.

Results of this test showed a longer retention time (51%) in HD males relative to controls but a shorter retention time (43%) in HD females relative to controls. None of these changes were statistically significant. Because of the opposite findings observed in the two genders, it is not clear whether these are associated with reslizumab treatment.

Reference ID: 3861540

Motor activity: Motor activity was evaluated on PND77 and PND105 (recovery). The movements of each mouse were monitored.

In males, the number of movements and time spent in movement were decreased in both treated groups compared to controls on PND77. For the number of movements, the decrease was 17% in the LD and 6% in the HD, so there is not a clear dose-response. However, the time spent in movement was decreased by 18% in the LD and 27% in the HD, showing a clear dose-response. Both of these parameters were increased on PND105. There were no effects observed in treated females compared to controls.

Neurological assessment: A FOB assessment was conducted in 8 mice/sex/group on PND77 and PND105 (recovery). On days when the FOB occurred on the same day as other evaluations or tests, the FOB was conducted first.

There were no drug-related effects observed.

Reproduction: The reproductive capacity was evaluated starting on approximately PND107. F_1 generation mice within each dose group were assigned to cohabitation, one male mouse per female mouse, with the exclusion of sibling matings. The cohabitation period consisted of a maximum of 14 days. Female mice with a copulatory plug observed were considered to be GD0 and assigned to individual housing. Female mice not mated after completion of the cohabitation period were considered to be GD0 on the last day of cohabitation and assigned to individual housing.

Table 27 below includes a summary of reproductive parameters. There were no drug-related effects observed compared to controls.

Table 27: Summary of Reproductive Parameters - F_1 Generation Juvenile Toxicity Portion.

Reslizumab (mg/kg/dose)	0	10	25
Parameter			
F_1 males mating index[a]	100%	100%	100%
F_1 females mating index[a]	100%	100%	100%
F_1 males fertility index[b]	80%	100%	100%
F_1 females fertility index[b]	80%	85.7%	100%
Mean # corpora lutea[c]	14.2 ± 5.0	14.3 ± 1.5	13.2 ± 4.7
Mean # implantations[c]	14.2 ± 5.0	14.2 ± 1.3	13.2 ± 4.7
Pre-implantation loss (%)[d]	0	1.0 ± 2.6	0
Post-implantation loss (%)[e]	4.8 ± 6.7	9.4 ± 13.2	6.0 ± 8.9

[a] (# of mice that mated/# of mice in cohabitation) x 100
[b] (# of pregnancies/# of mice that mated) x 100
[c] Mean ± S.D.
[d] [(# corpora lutea - # implantations) / # corpora lutea] x 100
[e] [(# implantations - # live embryos) / # implantations] x 100

Histopathology: Mice assigned to this portion of the study were sacrificed on PND84. A battery of tissues was collected from all animals. Only tissues from the control and HD groups, and gross lesions, were examined microscopically. Additionally, kidney tissue was examined for all dose groups.

Refer to Table 28 below for a summary of histological findings. A number of findings (some of them single incidences) were observed in HD animals. However, it is unclear whether these are related to treatment because of the low number of animals. In the kidney, a few HD animals showed findings that correlated with chronic progressive nephropathy, which is a common finding in rodents. It was not possible to determine whether this finding was due to ADA formation and accumulation in the kidneys or a direct drug-related effect.

Femur length and bone density: For mice assigned to this portion, the right hind leg was removed from the carcass by separating the femur from the pelvis. The femur length was measured using a caliper and recorded. In addition, bone densitometry scans and assessments were performed using peripheral quantitative computed tomography (pQCT). The scans were obtained at the diaphysis and the distal metaphysis.

There were no drug-related effects observed in femur length or bone density.

Clinical Pathology: On the day of scheduled sacrifice, blood samples were collected from all available mice for hematological and clinical chemistry evaluations. Samples were collected from the inferior vena cava immediately following sacrifice.

There were no clear drug-related effects in hematology or serum chemistry parameters. Of note, treated females showed a good correlation of decreased eosinophils (PD effect of reslizumab).

Other: Blood samples were collected from the submandibular vein on PNDs 76 and 78 from all available mice assigned to this portion of the study. In addition, blood samples were collected from all mice assigned to the recovery portion of this juvenile toxicity assessment on PND117 and PND123 (males) and GD6, GD10, and GD12 (females). Samples were evaluated for drug concentration in blood and development of ADA.

A summary of reslizumab serum concentrations is presented below in Table 29 (excerpted from the sponsor's submission). Animals in the LD group had 140-122000 ng/mL reslizumab in serum samples. Animals in the HD group had 0-208000 ng/mL reslizumab in serum samples. None of the animals tested from this group had ADA present in serum at any of the time points tested.

Reference ID: 3861540

Table 28: Summary (Incidence and Severity) of Histological Findings - F_1 Generation Juvenile Toxicity Portion.

Reslizumab (mg/kg/dose)	Males			Females		
	0	10	25	0	10	25
# of animals examined*	7	-	7	7	-	7
Observations						
Adrenal gland						
Vacuolation, lipid, zona fasciculata, unilateral, multifocal, minimal	0	-	2	0	-	0
Bone marrow (sternum)						
Myeloid hyperplasia, minimal	0	-	0	0	-	1
Bone (femur)						
Myeloid hyperplasia, minimal	0	-	0	0	-	1
Brain #						
Gliosis, cerebrum, focal, mild	0	-	0	0	-	1
Vacuolation, hippocampus, cerebellum, multifocal, minimal	0	-	0	0	-	1
Hemosiderin deposition, cerebrum, leptomeninges, focal, mild	0	-	0	0	-	1
Atrophy, cerebrum, focal, minimal	0	-	0	0	-	1
Fibrosis, Leptomeninges, focal, mild	0	-	0	0	-	1
Kidney		(1)			(3)	
Hemorrhage, pelvis, bilateral, mild	0	0	0	0	0	1
Inflammation, mixed, capsule, bilateral, moderate	0	0	0	0	0	1
Inflammation, mixed, interstitium, bilateral, multifocal, mild	0	0	1	0	0	0
Pyelonephritis, bilateral, multifocal, marked	0	0	0	0	0	1
Abscess, multifocal, marked	0	0	0	0	0	1
Mesenteric LN	(6)					
Hemorrhage, acute, focal, mild	0	-	0	0	-	1
Histiocytosis, medullary, diffuse, mild	0	-	1	0	-	0
Infiltration, neutrophilic, medullary cords, mutifocal, mild	0	-	0	0	-	1
Plasmacytosis, medullary, minimal	0	-	1	0	-	0
Mandibular LN	(6)		(5)			
Histiocytosis, medullary, diffuse, mild	0	-	1	0	-	0
Plasmacytosis, medullary						
Minimal	0	-	1	0	-	0
Hematopoiesis, megakaryocyte, multifocal, minimal	0	-	0	0	-	1
Pancreas						
Infiltration, mononuclear cell, periductal, focal, minimal	0	-	1	0	-	0
Degranulation, acinar cell, multifocal, mild	0	-	0	0	-	1
Ectopic tissue, spleen	0	-	0	0	-	1
Parathyroid gland						
Adenoma, benign	0	-	0	0	-	1
Spleen						
Leukocytosis, neutrophilic, red pulp, mild	0	-	0	0	-	1
Thymus			(6)			
Cyst, multifocal, minimal	0	-	1	0	-	0
Dilatation, follicle, bilateral, multifocal, mild	0	-	0	0	-	2
Urinary bladder				(6)		
Infiltration, neutrophilic, submucosa, multifocal, minimal	0	-	0	0	-	1
Tail		(2)				(1)
Hemorrhage, acute, dermis, mild	-	0	-	-	-	1
Inflammation, acute, dermis, focal, mild	-	0	-	-	-	1
Necrosis, dermis/epidermis, diffuse, moderate	-	0	-	-	-	1
RECOVERY						
# of animals examined	**7**	**-**	**4**	**5**	**-**	**5**
Brain						

Vacuolation, hippocampus, cerebellum, multifocal, minimal	0	-	0	0	-	1
Kidney						
Infiltration, mononuclear cell, interstitium, right, multifocal, min.	0	-	1	0	-	0
Mesenteric LN						
Infiltration, band neutrophils, medullary cords, focal, minimal	0	-	0	0	-	1
Plasmacytosis, medullary, minimal	0	-	0	0	-	1
Mandibular LN						
Plasmacytosis, medullary, minimal	1	-	0	0	-	0

* = the number in parenthesis is the number of tissues examined for that group
(-) = tissue not examined
= all the brain findings were observed in a single animal

F_2 Generation

Survival: F_2 generation was not evaluated in detail in this study. Only the number of viable F_2 generation embryos was evaluated.

The ratio of viable/non-viable F_2 embryos was not affected by reslizumab treatment.

Table 29: Summary of Reslizumab Serum Concentration by Study Group (All Groups).

Dosage Group	Dosage (mg/kg)	Sample Description[a]	Concentration Range (ng/mL)[b]
F0 Dams and Respective F1 Pups			
I	0	PND14, 6 hours post-dose	All samples BQL (< 100)
I	0	Pups: PND14, 6 hours post-dose	All samples BQL (< 100)
I	0	PND 21	All samples BQL (< 100)
I	0	Pups: PND 21	All samples BQL (< 100)
II	10	PND14, 6 hours post-dose	84,600 – 121,000
II	10	Pups: PND14, 6 hours post-dose	700 – 13,600
II	10	PND 21	BQL (< 100) – 10,400
II	10	Pups: PND 21	3,380 – 23,400
III	50	PND14, 6 hours post-dose	343,000 – 563,000
III	50	Pups: PND14, 6 hours post-dose	1,530 – 76,400
III	50	PND 21	BQL (< 100) – 19,500
III	50	Pups: PND 21	31,900 – 120,000
F1 Postweaning Development Mice			
I	0 (F0)	End of study phase	All samples BQL (< 100)
II	10 (F0)	End of study phase	All samples BQL (< 100)
III	50 (F0)	End of study phase	All samples BQL (< 100)
F1 Juvenile Toxicity Replicate Mice			
IV	0 (F1)	End of study phase	All samples BQL (< 100)
V	10 (F1)	End of study phase	140 – 122,000
VI	25 (F1)	End of study phase	BQL (< 100) – 208,000

[a]: "PND14, 6 hours post-dose" refers to "14-F0" Timepoint/Description/Pup and "PND21" refers to "21-F0" Timepoint/Description/Pup in Tables 6 and 7

[b]: Does not include samples with the comment "ISV for Re-assay"

10 Special Toxicology Studies

The sponsor conducted a few tissue cross-reactivity studies to evaluate the potential binding of reslizumab to human, monkey, and mouse tissues. A summary of the study designs and noteworthy findings is included below in Table 30.

Table 30: Summary of Tissue Cross-Reactivity Studies Conducted with Reslizumab.

Study Number	Study Design	Noteworthy Findings
P-6330 (1996)	• Tissues: cryosections of human tissues and selected neural tissues from monkey and mouse • Fluoresceinated (FITC)-Reslizumab: 2.0 and 20 µg/mL • Positive control: Cryosections of sepharose beads with covalently bound IL-5 • Negative control: no reslizumab or a different fluoresceinated human IgG_4 antibody	• FITC-labeled and unlabeled reslizumab bound to central nervous tissues from human and monkeys [spinal cord, brain (cerebellum) and optic nerve] • There was no binding to mouse tissues
D-28431 (1998)	• Follow-up study to P-6330 conducted to characterize the reslizumab brain binding protein(s) (b) (4) using immunoprecipitation and western blotting	• A protein with an apparent molecular weight (b) (4) was characterized
D-38271 (2001)	• 2nd follow-up study to identify (b) (4) (reslizumab-binding protein in brain)	• (b) (4) was cloned and identified as (b) (4) ((b) (4)
P-6669 (1997)	• Immunohistochemical staining of selected human, monkey, guinea pig, and mouse CNS and ocular tissues with various antibodies against IL-5	• Reslizumab and the parent rat antibody (39D10) stained all sections of CNS tissues of human and monkey in a similar pattern • Mouse or guinea pig tissues were not stained
P-6674 (1997)	• Additional follow-up study to determine whether the methods used in preparing tissues for analysis affected the in vitro binding and stability of reslizumab in selected CNS tissues from monkey	• The methods used are acceptable and do not affect binding or stability of reslizumab
SN96408 (2000)	• Tissues from human and monkey CNS were stained • Reslizumab: 2.0 and 20 µg/mL	• Reslizumab stained monkey tissues predominantly in white matter of the cerebrum, in white matter and granular cell layer of cerebellum, and white and gray matter of spinal cord • Staining of human tissues was affected by intravascular staining
SN99372 (2000)	• Tissue: human trigeminal nerve • Reslizumab: 2.0 and 20 µg/mL	• Reslizumab stained the white matter and granular cell layer of the cerebellum. Reslizumab did not stain either the central or

		peripheral portion of the trigeminal nerves
Res-4-0012 (2008)	• White paper • A review of reslizumab binding to (b) (4) in CNS tissue and possible effects	• It is concluded that reslizumab does not cross the blood-brain barrier to bind to CNS tissues in vivo • There was no evidence of CNS toxicity in the 6-month study in monkeys after IV administration

11 Integrated Summary and Safety Evaluation

Teva Branded Pharmaceutical Products R&D, Inc. submitted a BLA on March 29, 2015, for Cinqair (reslizumab) injection for intravenous use. Reslizumab is a humanized monoclonal antibody that targets IL-5. Teva seeks to market Cinqair to reduce exacerbations, relieve symptoms, and improve lung function in patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids, the standard-of-care for asthma. The proposed dosing regimen is 3 mg/kg every 4 weeks administered intravenously.

Eosinophil-rich inflammation has long been associated with asthma. Both animal and clinical studies have demonstrated a causal role for eosinophils in asthma pathogenesis; including airway hyper-reactivity, elevated mucus production, and airway remodeling. Thus, treatments that target eosinophils are proposed to be effective for the treatment of asthma. IL-5-mediated signal transduction has been associated with differentiation, proliferation, and survival of eosinophils (refer to Figure 5 below). Therefore, therapies that target IL-5 (such as reslizumab) are being developed for the treatment of asthma and other inflammatory diseases. As of the date of this review, only one therapy that targets IL-5 (Nucala, mepolizumab) is approved for the treatment of asthma.

Figure 5: IL-5-Mediated Signaling[7].

COPYRIGHT MATERIAL

Nature Reviews,

A correlation between IL-5 induced eosinophilia and pulmonary hyper-reactivity was also evaluated in IL-5 deficient mice. IL-5-deficient mice were generated by gene targeting in embryonal stem cells. These mice showed 50-80% reduction in CD5+ B cells (B-1) in the peritoneal cavity at 2 weeks old. The number of B-1 cells returned to normal by 6-8 weeks of age[8]. These IL-5-deficient mice were used in a model of allergic pulmonary inflammation to establish the essential role of IL-5 and eosinophils in the initiation of aeroallergen-induced lung damage and the development of airway hyper-reactivity[9]. It is known that sensitization and aerosol challenge of normal mice with ovalbumin results in airways eosinophilia and extensive lung damage analogous to that seen in asthma. When sensitized and challenged with antigen, mice lacking the IL-5 gene failed to develop airway eosinophilia, lung damage, or increased lung responsiveness.

Reslizumab is a humanized anti-human IL-5 monoclonal antibody of the immunoglobulin-G_4 kappa (IgG_4/κ) isotype. It is produced using recombinant DNA technology in the murine myeloma NS0 expression system (b) (4) Reslizumab has a theoretical molecular weight of 147 kDa and is comprised of two heavy chains and two light chains. It works by binding to IL-5 and

[7] Fulkerson PC and Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. (2013) Nature Reviews | Drug Discovery, Vol. 12, pp. 117-129.
[8] Foster PS, Hogan SP, Ramsay AJ, Matthaei KI, and Young IG. Interleukin 5 deficiency abolishes eosinophilia, airways hyper-reactivity, and lung damage in a mouse asthma model. (1996) Journal of Experimental Medicine, Vol. 183, pp. 195-201.
[9] Kopf M, Brombacher F, Hodgkin PD, Ramsay AJ, Milbourne EA, Dai WJ, Ovington KS, Behm CA, Kohler G, Young IG, and Matthaei KI. IL-5-deficient mice have a developmental defect in CD5+ B-1 cells and lack eosinophilia but have normal antibody and cytotoxic T cells responses. (1996) Immunity, Vol. 4, pp. 15-24.

preventing IL-5 binding to the IL-5 receptor, thereby reducing both circulating and tissue eosinophils. Reslizumab contains the CDRs (antigen-binding regions) of the original rat anti-human antibody 39D10 grafted onto a human framework.

The proposed drug product is a preservative-free, sterile aqueous solution presented as 100 mg in a single-use 10 mL glass vial. It is formulated as 10 mg/mL reslizumab in (b) (4) 7% sucrose, pH = 5.5. The drug product is diluted in 0.9% saline prior to infusion. For complete details on the drug product, refer to the drug quality review.

Reslizumab was developed for eosinophilic asthma under IND 101,399. The full clinical program consisted of 14 clinical studies, including 6 Phase 3 studies, 4 Phase 2 studies, and 4 Phase 1 studies. Patient populations across the clinical development program include healthy volunteers and patients with asthma, eosinophilic esophagitis, hyper-eosinophilic syndrome, eosinophilic gastroenteritis, and nasal polyposis. Close to 3,000 subjects have been exposed to reslizumab during development and approximately 400 of these have been treated for greater than 24 months. For complete details on the clinical program for reslizumab, refer to the clinical review by Dr. Kathleen Donohue.

The complete nonclinical safety program for reslizumab included pharmacology (including in vitro and in vivo studies to identify pharmacologically-relevant nonclinical species), pharmacokinetics, general toxicology (in CD-1 mouse and cynomolgus monkeys), genetic toxicology (in vitro Ames and chromosomal aberration assays), carcinogenicity (26-week study in transgenic mouse), and reproductive and developmental toxicology (fertility in CD-1 mouse, embryo-fetal development in CD-1 mouse and New Zealand rabbit, and peri-/post-natal development in CD-1 mouse) studies. The nonclinical program is considered complete and adequate to support the safety of the proposed clinical dose of 3 mg/kg reslizumab intravenously. An integrated summary of the full nonclinical program follows.

Pharmacology

Reslizumab is a humanized IL-5 antagonist. It is a monoclonal antibody of the IgG4/κ isotype containing the CDRs of the rat anti-human antibody 39D10 grafted onto human frameworks. Reslizumab binds to a specific epitope on the IL-5 molecule that appears to be important for the biological activity of IL-5 by preventing its binding to the IL-5 receptor. Reslizumab binds with similar affinity to human, monkey, and mouse IL-5 (K_D = 24, 20, and 31 pM; respectively, as determined by a BIAcore biosensor assay).

To examine the in vitro properties of reslizumab and the parent antibody, 39D10, a cell proliferation assay was conducted using TF-1 (human erythroleukemic) cells after IL-5 stimulation. In this assay, both reslizumab and the parent antibody 39D10 inhibited human IL-5 stimulation of TF-1 cells with an IC_{50} of 45 pM for reslizumab and 25 pM for 39D10.

Reference ID: 3861540

IL-5-mediated signaling plays a role in eosinophil differentiation, proliferation, and survival. Therefore, IL-5 antagonists that prevent binding of IL-5 to the IL-5 receptor (such as reslizumab) have been shown to reduce circulating and tissue eosinophil levels. Reslizumab was tested in models of eosinophilia using a number of species including mouse, monkey, rabbit, and guinea pig.

In sensitized B6D2F1/J mice, ovalbumin challenge produced an increase in total cells and eosinophils in BAL fluid. Treatment with reslizumab (0.01, 0.1, or 1.0 mg/kg intraperitoneally) produced a dose-dependent reduction in the number of total cells and eosinophils in BAL fluid. In a separate study, treatment of sensitized mice with reslizumab (2 mg/kg or 10 mg/kg intraperitoneally) 2 hours prior to ovalbumin challenge resulted in a significant decrease in the number of total cells and eosinophils in BAL fluid. The inhibition was observed for up to 4 weeks at the 2 mg/kg dose and up to 8 weeks at the 10 mg/kg dose. The effects were similar in CD-1 and HRAS transgenic mice strains used for toxicology and carcinogenicity studies, respectively.

In a monkey model of asthma, *Ascaris*-challenged monkeys (who develop pulmonary eosinophilia) received 0.1 or 0.3 mg/kg reslizumab intravenously. A statistically significant inhibition of pulmonary eosinophilia was observed at the 0.3 mg/kg dose level in these monkeys. No effect was observed at 0.1 mg/kg reslizumab. In a separate study, BAL fluid samples were collected from the monkeys treated at the 0.3 mg/kg dose level. These samples were collected 6 months after a single dose of 0.3 mg/kg reslizumab. Results show an inhibition of eosinophilia in these animals, suggesting a prolonged effect after a single dose of reslizumab.

In antigen-challenged allergic New Zealand rabbits, 5 mg/kg reslizumab intravenous resulted in a significant inhibition of eosinophil influx into the skin of these rabbits.

In sensitized Hartley guinea pigs, doses of 0.03 and 30 mg/kg reslizumab intraperitoneally produced a dose-dependent inhibition of antigen-induced airway hyper-reactivity induced by ovalbumin challenge. Complete inhibition was observed at the 30 mg/kg dose level. In a different study, the effects of reslizumab on acute allergic bronchoconstriction in Hartley guinea pigs were evaluated. In this study, 30 mg/kg reslizumab intraperitoneally reduced the bronchoconstrictor response to ovalbumin challenge.

Results from the aforementioned studies support the use of the CD-1 mouse, the CByB6F1-Tg(HRAS)2Jic transgenic mouse, the New Zealand rabbit, and the cynomolgus monkey in the nonclinical studies.

<u>Safety Pharmacology</u>

The potential effects of reslizumab on the CNS, respiratory, cardiovascular, gastrointestinal or renal systems were evaluated in a number of studies conducted in rats (CD or Sprague-Dawley strains). Although no significant drug-related effects were observed, the biological significance of these data is limited as the rat was not tested in

Reference ID: 3861540

vitro or in vivo to determine if it was a pharmacologically relevant species for reslizumab. Of note, no findings of concern were observed in behavior, cardiovascular parameters, or respiratory parameters in the pivotal toxicity studies conducted in CD-1 mice or cynomolgus monkeys (relevant nonclinical species).

Pharmacokinetics (PK)

Reslizumab PK parameters were measured using a validated BIAcore biosensor or ELISA methods. In addition, a biological assay (based on inhibition of proliferation of TF-1 human myeloid cells stimulated with human IL-5, as described above) was used for some studies. Reslizumab PK parameters were generally dose-proportional across a range of doses in a given species. There was no gender difference in exposure identified in any of the species used. Accumulation was observed with repeat dosing.

There were no distribution, metabolism, or excretion studies conducted with reslizumab. As expected for a monoclonal antibody, reslizumab had low systemic clearance (0.247-0.679 mL/hr/kg), low volume of distribution (63.9-81.8 mL/kg), and a long terminal half-life (76.5-253 hr) across nonclinical species for doses of 1-50 mg/kg.

There was evidence of ADA formation in all nonclinical species tested. Analysis of PK parameters in ADA-positive animals found that the antibodies were neutralizing, as reslizumab was not detected in the blood of these animals.

Reslizumab was excreted in the milk of lactating mice and there was placental transfer from dams to pups in CD-1 mice.

General Toxicology

Repeat-dose toxicology studies (6-month duration) were conducted in CD-1 mice and cynomolgus monkeys using the IV route of administration. In the CD-1 mouse, 4-week and 6-month studies were conducted. Because similar findings were observed in both studies, only the 6-month study is discussed in detail for the purposes of this summary. In a 6-month IV toxicity study, CD-1 mice (10/sex/group) received 0 (vehicle control), 1, 5, or 25 mg/kg reslizumab IV once every 28 days for 6 months (7 doses total). This study did not include a recovery period.

No significant drug-related effects were observed on clinical signs, body weights, food consumption and ophthalmic examinations. Six animals died during the study, including 2 LD animals (undetermined reason), 3 MD animals (1 from a bronchiolo-alveolar carcinoma and 2 from undetermined reasons), and 1 HD animal (from urinary tract obstruction).

In addition to the HD animal found dead due to urinary tract obstruction, additional HD animals that survived until the scheduled necropsy also presented similar but less severe urinary tract findings including renal pelvis and urinary tract dilatation that was associated with elevated BUN. At the Division's request, the sponsor provided an

Reference ID: 3861540

expert report that included re-examination of kidney tissues from all the animals in the study and a toxicological evaluation of the findings. The toxicological evaluation concluded that, because a clear dose-response was not observed (one control animal also has renal pelvis dilatation), the renal findings were considered incidental and not related to reslizumab treatment. In addition, the sponsor provided published literature to support that renal dilatation is a common background finding in CD-1 mice[10].

Another hypothesis considered by this reviewer is that the urinary tract findings observed in this study may have been associated with ADA development and complex formation in the kidneys. Although individual TK data were not provided for this study, combined TK data showed that the drug was cleared over time, suggesting development of ADA. However, data from the ADA assay were not useful since the presence of free reslizumab in serum appeared to interfere with antibody detection.

The bronchiolo-alveolar carcinoma observed in a MD animal was not considered related to reslizumab treatment because literature suggest that this type of tumor is a common incidental lesion in mice and no other pre-neoplastic lesions were observed, even at the HD. Further, no neoplastic findings were observed with reslizumab in HRAS transgenic mice (see below under "Carcinogenicity").

TK parameters from this study show slightly decreased exposure with time (study day 168 compared to study day 84), suggesting the presence of neutralizing ADAs. However, this was not confirmed because the ADA assay was affected by the presence of free reslizumab in serum. Eosinophils were generally lower in treated animals compared to controls, but the effect was not statistically significant. Due to lack of drug-related findings, the NOAEL in the mouse was identified at 25 mg/kg/dose (same as the sponsor's NOAEL), which is associated with a C_{max} = 412 µg/mL, $AUC_{0\text{-}14days}$ = 45,500 µg.hr/mL in males and females combined.

In cynomolgus monkeys, 4-week and 6-month studies were conducted using the IV route of administration. (b) (4) Because similar findings were observed in the 4-week and 26-week studies, only the 26-week studies are discussed in detail for the purposes of this summary. In a 26-week IV toxicity study, cynomolgus monkeys (4/sex/group) received 0 (vehicle control), 1, 5, or 25 mg/kg reslizumab IV once every 4 weeks for 6 months (7 doses).

No drug-related effects were observed on mortality, clinical signs, body weights, food consumption, ophthalmic examinations, clinical pathology evaluations, or neurological and electroneurological examinations. Electrocardiographic examinations found that one MD male had a single ventricular extrasystole at week 28, one HD female had two ventricular extrasystoles at week 8 and one HD male had a single ventricular extrasystole on weeks 16 and 28, and three at week 22. These findings were

[10] Chandra M and Frith CH. *Spontaneous renal lesions in CD-1 and B6C3F1 mice.* (1994) Experimental Toxicology Pathology, Vol. 46, No. 3; pages 189-198.

communicated to the medical team by email but because they can be monitored in the clinical study, they were not considered dose-limiting.

Drug-related histological findings in monkeys included injection site vasculitis (3 HD males), and kidney findings of tubular basophilia (4 HD males) and hypoplasia (1 HD female). Injection site findings are not considered dose-limiting because they are judged to be clinically monitorable. Because the sponsor was not able to find the slides from this study for re-examination, they examined kidney tissues (b) (4) (b) (4) (b) (4) to alleviate the concerns of drug-related findings in kidneys.

(b) (4)

Juvenile Toxicity

The sponsor also assessed the effects of reslizumab in juvenile mice or monkeys. The juvenile CD-1 mouse toxicity study was conducted as part of the peri- and post-natal reproduction and development study. The juvenile cynomolgus monkey toxicity study was conducted as a standalone study.

In the juvenile mouse study, neonatal CD-1 mice received 0 (vehicle control), 10, or 25 mg/kg reslizumab IV on post-natal days 14, 42, and 70. The following parameters were evaluated in these animals: survival, clinical signs of toxicity, body weights, external evaluation, sexual maturation, passive avoidance (learning, short-term memory, and long-term memory), motor activity, neurological assessments (FOB), and histological examinations on post-natal day 84 (7/sex/group).

In addition, the reproductive capacity was evaluated in a different group of animals starting on approximately post-natal day 107. F_1 generation mice within each dose group were assigned to cohabitation, one male mouse per female mouse, with the exclusion of sibling matings. The cohabitation period consisted of a maximum of 14 days. Female mice with a copulatory plug observed were considered to be gestation

Reference ID: 3861540

day 0 and assigned to individual housing. Female mice not mated after completion of the cohabitation period were considered to be gestation day 0 on the last day of cohabitation and assigned to individual housing.

In this study, one HD animal had clinical signs of decreased motor activity, tremors, ataxia, hunched posture, ptosis, and pale body. This animal was found dead on post-natal day 23. There were no other findings in any of the parameters evaluated, including reproductive capacity. Therefore, the NOAEL was identified at 10 mg/kg due to the clinical signs and death observed in one HD animal. This differs from the sponsor's NOAEL of 25 mg/kg in this study.

In the juvenile monkey study, cynomolgus monkeys (1.4-2.3 years of age) received 0 (vehicle control), 1, or 15 mg/kg reslizumab IV once weekly for 4 consecutive weeks. There were no drug-related effects observed in this study. Of note, a few females showed menses during the study, indicating that some of the animals used in the study were sexually mature (not considered juvenile). The NOAEL was identified in monkeys at 15 mg/kg (C_{max} = 774.36 µg/mL; AUC_{ss} = 63,670 µg·hr/mL).

In summary, repeat-dose toxicity studies were conducted with reslizumab in two species, mouse and monkey (including juvenile mouse). No target organs of toxicity were identified. A NOAEL was identified both in mice and monkeys and provide adequate exposure margins compared to the exposure at the proposed clinical dose of 3 mg/kg (refer to Table 31 below).

Table 31: Exposure Margins for the Proposed Clinical Dose of 3 mg/kg Reslizumab – General Toxicology Studies.

NOAELs	Safety Margins*
CD-1 mouse 26-week study NOAEL = 25 mg/kg/dose $AUC_{0\text{-}28d}$ = 91000 µg.hr/mL	3
Cynomolgus monkey 26-week study NOAEL = 25 mg/kg/dose $AUC_{0\text{-}28d}$ = 96400 µg.hr/mL	3

* $AUC_{0\text{-}28d,ss}$ = 30362 µg.hr/mL in humans at 3 mg/kg (from sponsor's "Clinical Pharmacology Summary"

Genetic Toxicology

The sponsor conducted two in vitro genetic toxicity studies with reslizumab, a bacterial reverse mutation (Ames) assay and a chromosomal aberration assay. The results of both studies were negative. However, reslizumab is a large molecule and is not expected to interact with DNA. Thus, these findings are not relevant for the safety assessment of reslizumab.

Carcinogenicity

Because the CD-1 mouse was identified as a pharmacologically relevant species for reslizumab, the sponsor was requested to conduct a 2-year bioassay in this species to support a marketing application (refer to the Regulatory Background above). Subsequently, the sponsor proposed to conduct a carcinogenicity study in HRAS transgenic mice to fulfill this requirement. This was considered adequate by the Division, pending data from the sponsor to support the use of this mouse strain. Teva provided data from a bioassay demonstrating that the transgenic mouse strain was pharmacologically relevant (statistically significant decrease in eosinophil levels in BAL fluid of OVA-sensitized mice treated with 250 mg/kg reslizumab).

Based on the above results, Teva conducted a 26-week study in HRAS transgenic mice to assess the carcinogenic potential of reslizumab. The study protocol was discussed with the ECAC in a meeting held on July 10, 2012, and was considered adequate. In the 26-week carcinogenicity study, HRAS transgenic mice (25/sex/group) received 0 (vehicle control), 100, 250, or 500 mg/kg reslizumab IV once every two weeks for 26 weeks. A positive control group receiving 75 mg/kg MNU intraperitoneally was included for comparison. There were no statistically significant neoplastic findings observed in males or females in this study.

Reproductive and Developmental Toxicology

Studies of reproductive and developmental toxicology were conducted in CD-1 mice and New Zealand rabbits using the IV route of administration. These studies evaluated the effects of reslizumab in male and female fertility in mice, teratogenicity in mice and rabbits, and pre- and post-natal development in mice.

Effects on Fertility

The effects of reslizumab on fertility were evaluated in CD-1 mice. Briefly, male and female CD-1 mice received 0 (vehicle control), 2, 10, or 50 mg/kg reslizumab IV as a bolus injection into the tail vein. Males received a single dose 28 and 14 days prior to mating and again on the first day of mating and on the 14th day after the start of mating. Females received a single dose 14 days prior to mating and again on the first day of mating and 14 days after. The dosing regimen was selected based on the half-life of reslizumab, which is approximately 2 weeks. Males were sacrificed after completion of the mating period and females were sacrificed on gestational day 14.

No drug-related effects were observed in any of the parameters evaluated; including survival, clinical signs, body weights, food consumption, gross observations, male reproductive organ weights, and reproductive parameters. TK parameters were not calculated in this study, but blood concentration in serum and ADA analysis were conducted. Two animals in the LD, one in the MD, and two in the HD were positive for ADA and had no or very low reslizumab concentration in serum. However, an adequate number of animals had exposure and were available for evaluation. In general, serum concentrations were higher on study day 22 compared to study day 30 (demonstrating the ADA effect in these animals). The NOAEL for male and female fertility was identified at 50 mg/kg/dose.

Reference ID: 3861540

Teratogenicity
The effects of reslizumab on teratogenicity were evaluated in CD-1 mice and New Zealand rabbits. Pregnant CD-1 mice (25/group) received 0 (vehicle control), 2, 10, or 50 mg/kg reslizumab IV once on gestational day 6. Animals were dosed only once because of reslizumab's half-life of approximately 2 weeks. Animals were sacrificed on gestational day 18 and fetuses were removed for examination of malformations or developmental variations. The dams were examined for external and visceral changes, numbers of corpora lutea, implantation sites, number of resorptions, and distribution of fetuses in uteri. No drug-related effects were observed in any of the parameters evaluated; including survival, clinical signs, maternal body weights, food consumption, gross examinations, reproduction parameters, and fetal malformations or developmental variations. The NOAEL for both maternal toxicity and teratogenicity was identified 50 mg/kg.

Pregnant New Zealand rabbits (20/group) received 0 (vehicle control), 2, 10, or 50 mg/kg reslizumab IV on gestational day 7. Animals were dosed only once based on the half-life of approximately 2 weeks. On gestational day 30, all animals were sacrificed and fetuses were removed for examination of malformations and developmental variations. In addition, the uteri of dams were examined to determine the number of corpora lutea, implantations, number of resorptions, and distribution of fetuses in uteri. There was a dose-dependent decrease in the number of corpora lutea and implantation sites in treated dams compared to the control group. However, it is unclear whether this finding was associated with treatment. There were no drug-related effects on the following parameters evaluated: survival, clinical signs, maternal body weights, food consumption, gross examinations, and fetal malformations or developmental variations. The NOAEL for both maternal toxicity and teratogenicity was identified at 50 mg/kg.

Although no effects were observed in the two embryo-fetal development studies discussed above, it should be noted that the animals were dosed only once during gestation. Because blood samples were not collected for toxicokinetic analyses or measurement of drug concentration in serum, it is not possible to confirm adequate exposure in these animals. Therefore, this reviewer considers that the results of these studies should be judged with caution.

Effects on pre-natal and post-natal development
The effects of reslizumab on pre- and post-natal development were evaluated in CD-1 mice. Pregnant CD-1 mice (30/group) received 0 (vehicle control), 10, or 50 mg/kg reslizumab IV on gestation days 6 and 18 and on post-natal day 14. The dosing regimen was selected based on the half-life of reslizumab, which is approximately two weeks.

Animals were sacrificed on post-natal day 21. Maternal clinical signs of toxicity, behavior, and body weights were recorded. In addition, milk and blood samples were collected from 5 mice/group on post-natal day 14 and from all remaining animals on the day of sacrifice post-natal day 21. A necropsy of the thoracic, abdominal, and pelvic viscera was performed and the number and distribution of implantations were recorded.

Reference ID: 3861540

For F_1 generation assessments, 24 pups/sex/group were selected randomly. At least one male and female pup/litter were selected when possible. All F_1 animals were evaluated for sexual maturation starting on post-natal day 21 (females) or 27 (males, age of preputial separation). Animals were also evaluated for passive avoidance (on post-natal day 23 – one male and one female per litter), motor activity (on post-natal days 22 and 61 – one male and one female per litter), and neurobehavioral assessment [(functional observational battery) on post-natal days 77 and 105 – one male and one female per litter], and reproductive capacity (starting on post-natal day 107). Blood samples were collected for toxicokinetic and ADA analysis.

Ataxia was observed in all pups from one litter (13 pups total). However, there were no effects observed in the neurological assessments. There were no drug-related effects on any of the reproductive parameters evaluated in F_0 generation mice. Reslizumab was excreted into the milk of F_0 generation lactating mice. Reproductive parameters in F_1 generation mice (mating and fertility index) were not affected. Reslizumab was detected in pups from treated mice, suggesting that there is placental transfer of reslizumab. Anti-reslizumab antibodies were detected in a few pups from treated animals, but this did not affect the outcome of the study because a sufficient number of pups had exposure. The NOAEL for maternal toxicity and F_1 generation toxicity was identified at 50 mg/kg.

Although TK parameters were not calculated from the aforementioned studies, the exposure margins were estimated using TK data obtained from other toxicity studies in CD-1 mice. For the rabbit, the safety margins were estimated using mg/kg comparisons between the NOAEL dose and the maximum recommended clinical dose of 3 mg/kg. Table 32 below presents the exposure margins for the proposed clinical dose of 3 mg/kg reslizumab.

Table 32: Exposure Margins for the Proposed Clinical Dose of 3 mg/kg Reslizumab – Reproductive and Developmental Studies.

NOAEL	Safety Margins*
CD-1 mouse fertility study NOAEL = 50 mg/kg/dose $AUC_{0\text{-}28d}$ = 182000 µg.hr/mL	6
CD-1 mouse EFD study NOAEL = 50 mg/kg/dose $AUC_{0\text{-}28d}$ = 182000 µg.hr/mL	6
New Zealand rabbits EFD study NOAEL = 50 mg/kg/dose	17[#]
CD-1 mouse PPND study NOAEL = 50 mg/kg/dose $AUC_{0\text{-}28d}$ = 182000 µg.hr/mL	6

* $AUC_{0\text{-}28d,ss}$ = 30362 µg.hr/mL in humans at 3 mg/kg (from sponsor's "Clinical Pharmacology Summary"
[#] Based on mg/kg comparisons

Special Toxicology Studies

Tissue cross-reactivity studies were conducted using tissues from human, cynomolgus monkeys and mice (the nonclinical species used for the toxicology program). The original study found binding of reslizumab to CNS tissues from human and monkey. No binding was observed in mouse tissues. Therefore, a number of follow-up studies were conducted to determine the specificity of reslizumab binding and to characterize the reslizumab brain binding protein(s). The reslizumab-binding protein was identified (b) (4) [redacted] Reslizumab was shown to stain the white matter tissues in human and monkey.

To evaluate reslizumab's potential to bind CNS tissues in vivo the sponsor conducted two studies in monkeys. In study P6670, monkeys received a single dose of 5 or 25 mg/kg reslizumab IV. In this study, CNS tissues were collected to evaluate reslizumab binding, samples of cerebro-spinal fluid (CSF) were collected to evaluate the levels of reslizumab, and animals were evaluated for physical, neurological, and cardiovascular effects or ophthalmic examinations. There were no drug-related effects observed in any of the parameters evaluated and no binding to CNS tissue. Reslizumab was detected in CSF samples at low levels.

An additional study (#SN99222) was conducted in cynomolgus monkeys to further evaluate the potential effects of reslizumab in the CNS. In this study, reslizumab was administered as a single intrathecal injection (0 or 0.07 mg/kg) into the cisterna magna. This route was used in order to achieve CSF concentrations that were higher than the IV concentrations. Organ weight measurements and gross and microscopic examinations were performed on brain, eyes with optic nerve, spinal cord, and trigeminal nerve. In this study, no drug-related effects were observed in any of the aforementioned parameters.

Therefore, although tissue cross-reactivity studies found reslizumab binding to CNS tissues of human and monkey, in vivo studies in adult monkeys show that reslizumab does not bind to brain tissues after IV administration (probably because it doesn't cross the blood-brain barrier) and there were no drug-related effects in behavior or any of the other CNS parameters evaluated in vivo (including detailed neurological and electro-neurological examinations in the 6-month toxicology study).

Reference ID: 3861540

Recommendation

The nonclinical safety program for reslizumab is considered complete and adequate to support the safety of the proposed clinical dose of 3 mg/kg intravenously every 4 weeks.

From the nonclinical pharmacology/toxicology perspective, the application is recommended for approval with the labeling revisions proposed below.

Labeling Review

A labeling review will be conducted separately.

12 Appendix/Attachments

Appendix 1: PharmTox review under IND 101,399 dated February 19, 2008
Appendix 2: PharmTox review under IND 101,399 dated May 6, 2012
Appendix 3: PharmTox review under IND 101,399 dated October 7, 2013

Reference ID: 3861540

Appendix 1

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND number: 101,399
Sequence number/date/type of submission: N-0000/16-Jan-08/Original submission (Agency receipt date: 18-Jan-08)
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Ception Therapeutics, Inc., 101 Lindenwood Drive, Malvern, PA 19355, USA
Manufacturer for drug substance: (b) (4)

Reviewer name: Feleke Eshete, Ph.D.
Division name: Pulmonary and Allergy Drug Products
Review completion date: February 15, 2008
Drug:

Code name: CTx55700, also SCH 55700[1]
Generic name: Reslizumab
Molecular mass: 146.7 kDa. The product is a humanized monoclonal antibody containing the CDRs of the rat anti-human IL-5 antibody (39D10) grafted onto an IgG4 kappa backbone, (b) (4) into NSO murine myeloma cells.

Structure: The amino acid sequence below was predicted from the cDNA of SCH 55700.

Heavy Chain
(b) (4)
Light Chain
(b) (4)

[1] Resilizumab (SCH 55700) was investigated as BB-IND 9227 by Schering Corporation.

Relevant INDs/NDAs/DMFs:

BB-IND 9227 (Schering, treatment of asthma) (b) (4)

Drug class: Anti-human IL-5 monoclonal antibody. Reslizumab binds to a specific epitope on the IL-5 molecule

Intended clinical population: Poorly controlled asthma with eosinophilic airway inflammation.

Clinical formulation and Route of administration: Reslizumab is sterile solution for infusion supplied as 35 mg (3.5 ml) per vial formulated at 10 mg/ml in (b) (4) pH 5.5.

Component	per mL	Function
Reslizumab drug substance (CTx55700)	10 mg	Active
Sodium Acetate Trihydrate, USP[a] or Ph.Eur.[b]	2.45 mg	Excipient
Acetic Acid Glacial, USP or Ph.Eur.	0.12 mg	Excipient
Sucrose, NF[c] or Ph.Eur.	70 mg	Excipient

(b) (4)

[a] USP = United States Pharmacopeia
[b] Ph.Eur. = European Pharmacopeia
[c] NF = National Formulary

(b) (4)

Route of administration: Intravenous

Proposed clinical protocol: A Single phase II, randomized, double-blind, placebo-controlled study in subjects with poorly controlled asthma with eosinophilic airway inflammation (protocol #. Res-5-0010). The proposed clinical trial will be conducted in about 120 asthmatic subjects aged 18-75 years by administration of 3 mg/kg reslizumab intravenously at intervals of 28 ± 7 days for a total of 4 doses.

Previous clinical experience: **Previous clinical experience**: Three placebo controlled clinical safety, tolerance and pharmacokinetics studies have been conducted with SCH 55700 administered intravenously to patients with eosinophil-associated disorders (Report Nos. 196-350, P00290, and PO1942). None of the studies involved healthy subjects; study 196-350 was a rising, single dose (0.03 to 1.0 mg/kg), randomized, double-blind study in subjects with severe asthma. Study P00290 was a repeat dose, SCH 55700, evaluator-blind, study that examined two doses of SCH 55700 at two dosage levels (0.3 and 1 mg/kg) versus placebo for the treatment of moderate and severe persistent asthma. Study P01942 was a single-dose, randomized, evaluator-blind study that examined two doses of SCH 55700 (1 and 3 mg/kg) versus placebo for the treatment of nasal polyposis. In each of these studies, blood samples were collected at protocol-specified times and assayed for SCH 55700 and antibodies to reslizumab.

Reference ID: 3861540

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

The Schering Corporation conducted nonclinical studies listed below in the development of SCH 55700. Some of the nonclinical studies conducted with SCH 55700 have been reviewed under BB-IND 9227 (see the August, 2000 review by Dr. David M. Essayan appended to this review). In addition to the full study reports of nonclinical studies conducted with SCH 55700, Ception has submitted a bridging study in juvenile monkeys that compared the pharmacokinetic and toxicity profiles, and immunogenicity of reslizumab produced by Schering and (b) (4) for Ception. (b) (4) (b) (4) This summarized review will only present an integrated synopsis of selected studies and the conclusion on the safety of the proposed clinical study for the asthma indication. (b) (4) .

Ception has submitted study reports on the pharmacodynamic profile of reslizumab in addition to nonclinical pharmacokinetic and toxicity studies. The pharmacology studies included in the reports are *in vitro* and *in vivo* pharmacodynamic studies, safety pharmacology studies and pharmacokinetic studies in mice, monkeys and rabbits. The study reports from the toxicology studies are listed below:

P-6147: Single-dose intravenous toxicity study of SCH 55700 (anti-IL-5) in Mice.
P-6146: Single-dose intravenous toxicity study of SCH 55700 anti-IL-5 in rats.
P-6144: Single-dose intravenous toxicity study of SCH 55700 (anti-IL-5) in Cynomolgus monkeys.
SN 99222: Pathologic evaluation of the central nervous system following intrathecal administration of SCH 55700 in Cynomolgus monkeys.
P-6190: One-month (two-dose) intravenous toxicity study of SCH 55700 (anti-IL-5) in mice.
SN 96264: Six-month Intravenous Toxicity and Toxicokinetic Study of SCH55700 in mice.
P-6188/SN 93220: Two dose/one-month intravenous toxicity study of SCH 55700 (anti-IL-5) in Cynomolgus monkeys.
P-6188/SN 93220: Two dose/one-month intravenous toxicity study of SCH 55700 (anti-IL-5) in Cynomolgus monkeys.
P-6749: A six-month intravenous toxicity study of SCH 55700 with neurological evaluations in Cynomolgus monkeys.
Res-4-0006: A one month (four once-weekly doses) intravenous bridging toxicity study of reslizumab in juvenile Cynomolgus monkeys, with one-month recovery period and pharmacokinetic and anti-reslizumab antibody evaluations.
P-6214: Bacterial mutagenicity study of SCH 55700.
P-6269: Chromosome aberration study of SCH 55700 in human peripheral blood lymphocytes.

Reference ID: 3861540

P-6370/SN 95130: Preliminary intravenous fertility and postnatal study of SCH 55700 in mice.
P-6981: Intravenous fertility study of SCH 55700 in mice.
D-27256: Pilot intravenous embryo-fetal development study of SCH 55700 (anti-IL-5) in mice.
P-6378: Intravenous embryo-fetal development study of SCH 55700 in mice.
D-27243: Pilot intravenous embryo-fetal development study of SCH 55700 in rabbits.
P-6379: Intravenous embryo-fetal development study of SCH 55700 in rabbits.
SN-98072: Acute subcutaneous irritation study of SCH 55700 (anti IL-5) in rats.
SN 98071: Muscle irritation study of SCH 55700 (anti IL-5) in rabbits.
SN 98568: Intravenous tolerance study of a SCH 55700 (anti-IL-5) formulation in rabbits.
P-6223: Intra-arterial tolerance study of SCH 55700 (anti-IL-5) in rabbits.
P-6670: Assessment of cerebrospinal fluid levels and *in vivo* central nervous system binding of SCH 55700 in Cynomolgus monkeys.
SN 98070: Pain-on-injection study of a formulation of SCH 55700 (anti-IL-5) in rats.
D-28658: Study 97482: Macroscopic and Light Microscopic Evaluation of IL-5 -/- Mice.

Reference ID: 3861540

TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW 1

2.6.1 INTRODUCTION AND DRUG HISTORY 1

2.6.2 PHARMACOLOGY 6
2.6.2.1 Brief summary 6
2.6.2.2 Primary pharmacodynamics 6
2.6.2.3 Secondary pharmacodynamics 7
2.6.2.4 Safety pharmacology 7
2.6.2.5 Pharmacodynamic drug interactions 8

2.6.4 PHARMACOKINETICS/TOXICOKINETICS 8
2.6.4.1 Brief summary
2.6.4.9 Discussion and Conclusions 8

2.6.5 PHARMACOKINETICS TABULATED SUMMARY 9

2.6.6 TOXICOLOGY 9
2.6.6.1 Overall toxicology summary 9
2.6.6.7 Local tolerance 11
2.6.6.9 Discussion and Conclusions 11

OVERALL CONCLUSIONS AND RECOMMENDATIONS 17

APPENDIX/ATTACHMENTS 21

Reference ID: 3861540

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Reslizumab (CTx55700, also SCH55700) is a humanized anti-human–interlukin-5 (anti-hIL-5) monoclonal antibody of the immunoglobulin G4 (IgG4)/κ isotype. It was constructed by grafting sequences of part of the variable regions of heavy and light chains of a rat monoclonal antibody to human IL-5 (39D10) onto human heavy and light chain variable regions. The grafted sequences [redacted] (b) (4) on the IL-5 that is important for its biological activity. The SCH 55700 cDNAs for the immunoglobulins were [redacted] (b) (4) into NSO murine myeloma cell line. The rationale for development of reslizumab in the treatment of poorly controlled asthma with eosinophilic airway inflammation is based on its blocking of the binding of circulating IL-5 and preventing its binding to the IL-5 receptor expressed on the surface of eosinophils. Eosinophils are thought to play a key role in the pathogenesis of asthma due to their increased presence in asthmatic airways, correlation to disease severity, and owing to their ability to mediate both airway damage and alterations to pulmonary dynamics. IL-5 regulates the production, survival and function of eosinophils.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

Reslizumab blocks the binding of circulating IL-5 and prevents its binding to the IL-5 receptor expressed on the surface of eosinophils.

Drug activity related to proposed indication:

The biological activity of SCH 55700 has been studied *in vitro* using IL-5 receptor binding assay and by examining IL-5 mediated cell-based responses. SCH 55700 exhibited binding to membrane fraction from Ba/F3 cells that stably express human IL-5 receptor α-subunit with a Kd of 81 pM at 37^0C. The affinity of antigen binding was indistinguishable between SCH 5570 and its parental antibody 39D10 as determined by cell-based receptor binding assay, solid phase antigen binding competition assay, and by kinetic analysis of direct antigen-antibody interaction. SCH 55700 also blocked the binding of 500 pM IL-5 to the IL-5 receptor α-subunit expressing BaF3 cells with an IC_{50} = 0.5 nM. Furthermore, it inhibited hIL-5 induced proliferation of human erythroleukemic (TF-1) cells with IC_{50} of45 nM. *In vivo* biological activity of SCH 55700 was measured in monkeys, rabbits, guinea pigs, and mice using antigen-induced bronchoprovocation as methods to induce pulmonary eosinophilia and airway hyper-responsiveness. The monoclonal antibody (mAb) caused dose-dependent inhibition of the accumulation of eosinophils in bronchoalveolar lavage (BAL) fluid and in extravascular lung bronchi and bronchioles, and inhibited pulmonary hyper-reactivity in all the tested species. Reduced pulmonary eosinophilia ensued for up to eight weeks post-dose in mice (10 mg/kg i.p) and for up to six months in monkeys (0.3 mg/kg, i.v.).

Reference ID: 3861540

2.6.2.3 Secondary pharmacodynamics

SCH 55700 has been investigated for the treatment of eosinophilic diseases or diseases with increased eosinophilic effects. There have been no secondary pharmacodynamic animal studies performed with reslizumab.

2.6.2.4 Safety pharmacology

In a series of general safety pharmacology studies, a single dose of 100 mg/kg i.v. SCH 55700 had no effect on hemodynamic and electrocardiographic parameters in the rat. SCH 55700 neither delayed gastric emptying nor intestinal transit in the rat. Similarly, SCH 55700 in doses up to 100 mg/kg i.v. did not induce significant behavioral, neurologic, or autonomic changes, as measured by behavioral observations, and did not modify pentylentetrazole-induced convulsions in rats. In mice, 100 mg/kg i.v. SCH 55700 did not modify acetic acid induced writhing. No effects were observed on agonist-induced isolated guinea pig ileum contractions at a bath concentration of 650 µg/ml.

Safety Pharmacology Studies with Resilzumab

Organ Systems Evaluated	Species (N/sex/dose)	Doses (mg/kg) /Route	Findings
Behavioral, Neurological, Autonomic	Sprague Dawley rats	1, 10, 100 /i.v	- No behavioral, neurological, or autonomic effects specific to reslizumab were noted.
General safety pharmacology	CD rats Mouse/CD-1	10, 30, 100 /i.v 100 /i.v	- No effect cardiovascular function, body temperature, physical activity, behavioral, neurologic and autonomic function in the rat - No delayed gastric emptying or intestinal transit in rats. - No effect on acetic acid-induced writhing in mice.
Guinea pig ileum	Guinea pig/ Hartley	650µg/ml	- Agonist-induced isolated guinea pig ileum contractions were not affected.

Reference ID: 3861540

2.6.2.5 Pharmacodynamic drug interactions

The concomitant effect of SCH 55700 and prednisolone was studied in mice. SCH 55700 had an additive effect with oral prednisolone for suppression of BAL fluid eosinophilia in allergic B6D2F1/J mice.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Pharmacokinetic studies with SCH 55700 were evaluated following single i.v. doses in CD-1 mice (1, 5, and 25 mg/kg), New Zealand white rabbits (2, 10, and 50 mg/kg), and Ascaris-challenged monkeys (0.3, 1, and 3 mg/kg). Limited blood samples were also collected for serum concentration analysis following seven monthly doses of reslizumab in 6-month i.v. toxicity studies at 2, 10, or 15 mg/kg in mice and 1, 10, or 15 mg/kg in C. monkeys. The blood concentration profile and pharmacokinetic parameters of reslizumab were also compared for reslizumab manufactured by Schering (SCH 55700) and by [redacted] (b) (4) (CTx55700) in the juvenile monkey study. Concentrations of reslizumab in animal serum were quantified by one or more of three analytical methods - biological assay, biosensor, and ELISA. Values obtained by the biosensor and ELISA assays were consistently higher than the biological assay values. The sponsor presents that this may possibly be due to the capability of the immunoassays to also detect biologically inactive reslizumab, or due to serum inhibition effects observed with the biological assay.

2.6.4.9 Discussion and Conclusions

Mean serum concentrations increased with dose and were gender-independent in all species. The volume of distribution at steady state ranged from 74.1 to 90.6 ml/kg in mice and 105 to 127 ml/kg in rabbits, approximating the total blood volume of the mouse and twice that of the total blood volume in rabbits. SCH 55700 is a low clearance compound because of its longer half-life. The t½ ranged between 10-14 days in mice, 14-18 days in monkeys and 10-15 in rabbits after administration of ascending single doses. The t½ in humans is reported in the range of 23-30 days.

Reference ID: 3861540

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Single Dose PK Parameters after Reslizumab Administration

Species (N/sex/ dose)	I.V Dose mg/kg	Tmax h	CL ml/min.kg	Vdss ml/kg	t½ (d)
Mice (M/75)	1	1	N.D	ND	ND
	5	1	0.0047	91	10
	25	1	0.0027	74	14
Rabbits [M/F (9/9)]	2	1.2	0.0049	127	9.5
	10	1.25	0.0047	125	12.0
	50	1.5	0.0036	105	14.8
Monkeys (M/5)	3	3	ND	ND	18

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Ception has reported the results of comparability and bridging studies using reslizumab produced by Schering and [redacted] (b) (4) Juvenile monkeys (< 3 years of age) received a 1-month (four once-weekly doses) and recovery groups were observed through 5 weeks post-dose. This study compared the pharmacokinetic, and immunogenicity profiles of reslizumab produced by Schering and [redacted] (b) (4) at 1 mg/kg, and the toxicity profile of CTx55700 at 1 & 15 mg/kg. There were no PK differences between drug substance produced by Schering and [redacted] (b) (4) The juvenile monkey studies were also without reslizumab-related findings.

In the 1-month two-dose (day 1 and 15) studies, SCH 55700 was well tolerated by mice and monkeys at doses of 1, 5, or 25 mg/kg. The NOAEL was the maximum tested dose of 25 mg/kg in monkeys and in female mice based on the lack of SCH 55700-related toxicity. The NOAEL in male mice was 5 mg/kg based on the occurrence of mild decreases in lymphocyte counts, lower mean spleen and thymus weights at the 25 mg/kg dose. The mean systemic exposures in the 1-month studies were $AUC_{(0\text{-}14\ day)}$ of 146, 840 g.h/m in mice and 61,867 μg.h/ml in monkeys. Exposure increased dose-proportionally in both species and there were no gender differences.

In a 6-month study in mice (10/sex/group) 0, 2, 5, 25 mg/kg SCH 55700 was administered once every 28-days for 6-monts (7 doses). There were reductions in eosinophil counts although the sponsor reports these reductions as statistically insignificant. The change in eosinophil fraction was not associated with any histopathological findings, and there were no reports that would suggest blockade of

Reference ID: 3861540

maturation or release of eosinophils from the bone marrow. Therefore this finding was not toxicologically significant. Reduction in lymphocyte count was reported in the 1-month study in mice. This was not however replicated in this 6-month toxicity study. Neutrophil counts were not altered. Minimal cortical thymic atrophy was observed in both control and treated animals. Microscopic examination revealed infiltrations of mononuclear cells in kidneys and liver of both SCH 55700 and control animals. Other postmortem microscopic findings included minimal cellular luminal debris in epididymis and hyperplasia of the interstitial cell in male animals, which were also present in the vehicle treated animals.

All of the above-mentioned histological findings were observed in control and treated animals and are not considered drug-related. Thus, the postmortem evaluations of organs and tissues did not identify any target organs of toxicity in the mouse. The NOAEL was therefore the high dose of 25 mg/kg based on the absence of treatment-related findings. Systemic drug level increased with dose and was gender-independent. Serum concentrations were greater on day 84 (68,500 μg.h/ml) than on day 0 (49,500 μg.h/ml) and day 168 (45,500 μg.h/ml) in the 25 mg/kg dose groups. There was very minimal accumulation of the drug in these animals. Anti-SCH 55700 antibody detection was not conducted; the sponsor reported that measurement was precluded by the presence of free SCH 55770.

Monkeys (7-12/sex/group) in the 6-month study were dosed at 0, 1, 5, 25 mg/kg once every 4-weeks for 6-months (7 doses) with 3-month recovery. Neurological evaluations were conducted in these animals in addition to the standard toxicological examinations because of the binding of reslizumab to CNS tissue as demonstrated in the *in vitro* study. All animals in the 6-month study survived until scheduled termination, and there were no treatment-related effects in monkeys. There was dose-dependent reduction in eosinophil counts, but blood lymphocyte and neutrophil counts were similar to control values. There were no treatment-related histopathological findings at necropsy or in recovery animals. No SCH 55700-related clinical, neurologic, electroneurologic findings were reported. In addition, no SCH 55700 binding was observed to nervous system tissues (brain, spinal cord, optic nerve) that showed binding in the *in vitro* assay. The NOAEL was identified as the highest tested dose of 25 mg/kg based on the absence of treatment-related findings. Mean serum concentrations in the animals used in the 6-month toxicity study increased with dose and were gender-independent. There is no indication of drug accumulation during the study period. Two high and one mid dose animals had no quantifiable SCH 55700 in predose sample obtained in weeks 13 and 25. The inability to detect the mAb may be attributed to the formation of anti-SCH 55700 antibodies, since sample from these same animals had anti-SCH 55700 antibodies.

Genetic toxicology: SCH 55700 did not exhibit genotoxic potential in bacterial reverse mutation (+/- S9) assay with up to 5, 000 ug/plate, and chromosomal aberration test in human lymphocytes (+/- S9) with up to 1, 000 ug/ml.

Carcinogenicity: Not reported

Reference ID: 3861540

Reproductive toxicology: Intravenous fertility studies in mice and embryo-fetal developmental studies in mice and rabbits were conducted at doses of 2, 10, and 50 mg/kg SCH 55700 to assess potential maternal toxicity, embryotoxicity, and teratogenicity. Increased incidence of resorptions were observed at 50 mg/kg in mice, while a reduced pregnancy rate was reported in rabbits dosed with 50 mg/kg on day 7 after mating during a range finding study. Although the mouse finding in the range finding study was treatment-related, it was not seen in the definitive study. The significance of the rabbit finding is not clear since animals were dosed on day 7 after mating. Prenatal and postnatal development (Segment III study) has not been yet conducted.

Special toxicology: FITC-labeled SCH 55700 binding to human, monkey, and mouse tissues was examined to evaluate tissue cross reactivity of SCH 55700. Binding was observed *in vitro* in human tissues of the central nervous system. A very similar pattern of reactivity was seen *in vitro* in CNS tissues of Cynomolgus monkeys. CNS tissues from CD-1 mice did not show reactivity and no specific binding of reslizumab occurred in any of the other human tissues evaluated. Specific binding of SCH 55700 was however observed *in vitro* to CNS tissue in humans and monkeys. Further inquiry on the specific binding to CNS tissue suggested that SCH 55700 was binding (b) (4) [redacted] The pathophysiological consequence of this binding was addressed in the six-month i.v. toxicity study and after intrathecal administration to monkeys. There was no morphological evidence of binding of reslizumab to the CNS after intrathecal administration; no reslizumab-related neurologic, electroneurologic effects; and no histopathological findings in CNS were noted in monkeys during a six-month multiple dose study.

2.6.6.7 Local tolerance

The irritation potential of the parenteral formulation of SCH 55700 was assessed after single subcutaneous injection along with vehicle and mefoxin® in rat. A red-brown discoloration that correlated with histopathologic findings of hemorrhage and/or venous congestion was observed in all groups with the same incidences in control and SCH 55700 group and higher incidence at mefoxin® (injected site. In a local i.v. tolerance study in rabbits, reslizumab produced minimal-to-mild irritation similar to that elicited by the injection of saline or vehicle. There were no macroscopic and microscopic changes associated with the irritation.

2.6.6.9 Discussion and Conclusions

SCH 55700 did not exhibit genotoxic potential in both the Ames test and chromosomal aberration test in human lymphocytes *in vitro*. For characterization of the safety profile of reslizumab, Ception included reports of tissue cross reactivity and tolerance studies; single bolus dose i.v. studies in mice, rats, and monkeys; 1- and 6-month duration i.v. toxicity studies in mice and monkeys; and a single dose intrathecal toxicity study in monkeys with additional endpoints as follow up to the *in vitro* tissue cross reactivity study. In the toxicity studies, changes in body weight, food consumption,

Reference ID: 3861540

clinical signs, ophthalmoscopy, clinical laboratory measurements (hematology, clinical chemistry urinalysis) and postmortem (organ weight, macroscopic and microscopic) evaluation of collected tissues were conducted with parallel estimation of systemic exposures (TK). The sponsor also submitted a report from a range-finding fertility and early embryonic development study with selected postnatal evaluations of offspring in mice, and a study report on fertility in mice and embryo-fetal development studies in mice and rabbits.

In a type-B meeting held on June 28, 2007 (Pre-IND (b) (4)), between representatives of Ception (b) (4) the Division raised the issue of comparability between reslizumab manufactured by Schering (SCH 55700) and used in the nonclinical studies submitted in support of the current proposed clinical trail and the drug substance manufactured by (b) (4) for Ception (CTx55700). The two reslizumab lots were expressed in the same NSO murine myeloma cells, but in addition to the manufacturing site there were manufacturing deviations (b) (4) Ception agreed to address this issue by conducting a bridging toxicology study comparing the old and new drug substance in a 1-month intravenous (IV) infusion bridging toxicity study.

Ception has reported the results of the comparability and bridging studies. The CMC reviewer noted the absence of any significant differences between drug substances produced by Schering and (b) (4) (see the review by Dr. Marjorie Shapiro). Juvenile monkeys (< 3 years of age) received a 1-month (four once-weekly doses); recovery groups were observed through 5 weeks post-dose. This study compared pharmacokinetic, and immunogenicity profiles of reslizumab produced by Schering and (b) (4) at 1 mg/kg, and the toxicity profile at 1 & 15 mg/kg of CTx55700. There were no pharmacokinetic differences between drug substance produced by Schering and (b) (4) The juvenile monkey study was also without reslizumab-related finding with regards to clinical signs, body weights, clinical pathology data (one exception noted below), or macroscopic, organ weight or histopathlogic evaluations. Statistically significant test article-related decrease in eosinophils was noted for all 15 mg/kg CTx55700 treated animals by Week 4. The eosinophil counts had recovered to baseline values by Week 8. Therefore, there are adequate grounds to use the toxicology studies conducted with SCH 55700 in the evaluation of CTx55700.

In the 1-month two-dose (day 1 and 15) studies, SCH 55700 was well tolerated by mice and monkeys at doses of 1, 5, or 25 mg/kg. The NOAEL was the maximum tested dose of 25 mg/kg in monkeys and in female mice based on the lack of reslizumab-related toxicity. The NOAEL in male mice was 5 mg/kg based on the occurrence of mild decreases in lymphocyte counts, lower mean spleen and thymus weights at the 25 mg/kg dose. Mean pharmacokinetic parameters for male and female animals for mice, monkey studies and rabbits are tabulated below. Exposure increased dose-proportionally across species and there were no gender differences.

Reference ID: 3861540

Pharmacokinetic parameters in Mice, Monkeys and Rabbits*

Dose, i.v (mg/kg)		1	5	25
CD-1 Mouse N=225 (Biosensor) Report No. D-27236	Tmax (hr)	1	1	1
	Cmax (µg/ml)	18	109	462
	$AUC_{(0-14d)}$ (µg.h/ml)	2,890	20,421	146,840
	t½ (days)	17.9	17.6	17.3
Dose, i.v (mg/kg)		1	5	25
Monkey n=5 (ELISA) Report No. P-6187	Tmax (hr)	0.083	0.083	1.71
	Cmax (µg/ml)	25.63	165	526.9
	$AUC_{(0-14d)}$ (µg.h/ml)	1,659	8,708.3	66,079
	t½ (days)	ND	ND	ND
Dose, i.v (mg/kg)		2	10	50
Rabbits (n=18) (Biosensor) Report No. P-6613	Tmax	1.2	1.25	1.5
	Cmax (µg/ml)	36.9	191	1,070
	$AUC_{(0-\infty)}$ (µg.h/ml)	6,853	35,780	243,478
	t½ (days)	9.5	12	14.8

* Data are mean values for male and female animals. The mouse and rabbit data are from single ascending i.v. doses, while the monkey data are from two i.v doses administered on day 1 and day 15.

Reference ID: 3861540

Pivotal toxicological data from the 6-month mouse and monkey studies have been used in the evaluation of the potential toxicity of SCH 55700 in the proposed 3-4 month clinical trial. Standard toxicological evaluations were conducted after intravenous administration of 0, 1, 5, 25 mg/kg in monkeys every 4-week for 6-months (total of 7 doses) with 3-month recovery period. A similar dosing schedule of every 28-days for a total of 7 doses was used for administration of 0, 2, 5, 25 mg/kg SCH 55700 in mice.

Five mice were found dead in the 6-month mouse study. The death of these animals was considered incidental and test article unrelated because there were no consistent dose-related gross and microscopic findings. Hematological data with high variability were reported in ≤ five animals/sex/dose. Nonetheless, there were reductions in eosinophil counts, a parameter that is expected to decline that can be monitored clinically. The change in eosinophil fraction was not associated with any histopathological findings, and there were no reports that would suggest blockade of maturation, or release of eosinophils from the bone marrow.

Average for male and females in 6-Month Mouse Toxicity Study (Average values for 3-5 animals are shown)									
		Male				Female			
Parameter (week 29)	Dose (mg/kg)	0	2	10	25	0	2	10	25
Eosinophils (%)		1.02	0.45	0.75	0.79	0.88	1.16	0.71	0.73
Neutrophils (K/μl)		0.76	1.76	0.9	0.5	0.8	0.57	0.53	0.64
Lymphocytes (K/μl)		1.26	2.48	1.03	1.04	1.36	0.53	0.8	2.16

Minimal cortical thymic atrophy was observed in both control and treated animals. Microscopic examination also revealed infiltrations of mononuclear cells in kidneys and liver of both SCH 55700 and control animals. Other postmortem microscopic findings included minimal cellular luminal debris in epididymis and hyperplasia of the interstitial cell in male animals, which were also present in the vehicle treated animals. Thus, the postmortem evaluations of organs and tissues did not identify any target organs of toxicity in the mouse. The NOAEL was therefore the high dose of 25 mg/kg based on the absence of treatment-related findings. Systemic drug level increased with dose and was gender-independent. Serum concentrations were greater on day 84 than on day 0 and day 168 in the 10 and 25 mg/kg dose groups (see the table below). There was minimal accumulation of the drug in these animals. Anti-SCH 55700 antibody detection was not conducted; the sponsor reported that measurement was precluded by the presence of free SCH 55770.

Reference ID: 3861540

Toxicokinetic Parameters in the 6-Month Mouse Study

Parameter	Units	2 mg/kg[a]	10 mg/kg	25 mg/kg
		Day 0		
Cmax	µg/mL	23.9	137	352
Tmax	hr	1.00[b]	1.00[b]	1.00[b]
AUC(tf)[c]	µg·hr/mL	3160	21700	49500
		Day 84		
Cmax	µg/mL	34.2	202	386
Tmax	hr	1.00[b]	1.00[b]	1.00[b]
AUC(tf)[c]	µg·hr/mL	5690	27300	68500
		Day 168		
Cmax	µg/mL	41.6	176	412
Tmax	hr	1.00[b]	1.00[b]	1.00[b]
AUC(tf)[c]	µg·hr/mL	5840	22100	45500
R	---	1.20[d]	1.02	0.921

a: On Day 0, animals received 1.3 mg/kg.
b: The first sampling timepoint
c: tf was 336 hr.
d: The R value was calculated using the dose normalized AUC(tf) values.

In the 6-month toxicological study in monkeys, neurological evaluations were conducted in addition to the standard toxicological examinations because of the binding of SCH 55700 to CNS tissue *in vitro*. All animals in the study survived until scheduled termination, and there were no treatment-related effects in monkeys. As depicted in the table below, there was dose-dependent reduction in eosinophil counts, but blood lymphocyte and neutrophil counts were not different from control values. This is not unexpected finding since this effect was observed in the pharmacodynamic studies. The reduction in eoasiophil counts is not dose limiting since it can be monitored in the clinic.

Reference ID: 3861540

Selected Hematological Findings in a 6-Month monkey Toxicity Study (Values are mean ± SD for males and females combined)

	Dose (mg/kg)			
Parameter (week 28)	0	1	10	25
Eosinophils (K/μl)	0.23±0.37	0.13±0.15	0.06±0.11	0.04±0.08
Segmented Neutrophils (K/μl)	3.83±1.34	4.96±2.46	3.62±1.6	4.48±1.59
Lymphocytes (%)	63±16	57±15	65±16	61±11

There were no treatment-related histopathological findings at necropsy or in recovery animals. One high-dose monkey (N0. F5276F) and another control monkey at recovery group had scattered myofiber atrophy in the skeletal muscles of one pelvic limb. This finding may not however have toxicological significance since it was observed unilaterally in the control (right limb) and on the left pelvic limb of the high dose monkey. Neurological evaluations conducted in the vehicle control and 25 mg/kg groups during the 6-month study before dosing and during week 28 and 29. Assessments of behavior; motor/sensory function and pain sensation; cranial nerve function; and proprioception. Electroneurological evaluations, including electroencephalogram (EEG), electroretinogram (ERG), flash-evoked potential (FEP), brainstem auditory-evoked potential (BAER), and somatosensory-evoked potential (SEP), were conducted on all monkeys. No SCH 55700-related clinical, neurologic, electroneurologic findings were reported. In addition, no reslizumab binding was observed to the nervous system tissues (brain, spinal cord, optic nerve) that showed binding in the *in vitro* assay. The NOAEL was identified as the highest tested dose of 25 mg/kg based on the absence of treatment-related findings. Mean serum concentrations in the animals used in the 6-month toxicity study increased with dose and were gender-independent. There is no indication of drug accumulation during the study period. Two high and one mid dose animals had no quantifiable SCH 55700 in predose sample obtained in weeks 13 and 25. Sample from these same animals also had anti-SCH55700 antibodies.

CNS tissue binding *in vivo* was conducted after administration of single i.v. doses of 5 or 25 mg/kg SCH 55700 to Cynomolgus monkeys. Serum and CSF was also collected from these monkeys on Day 3 and 31 before sacrifice for analysis of reslizumab concentration and for detection of antibodies against SCH 55700. SCH 55700 was detected in CSF (< 0.1 μg/ml) compared to 37.3 μg/ml on day 3 and 199 μg/ml on day 31. The sponsor however concluded that the low level of reslizumab detected in CSF was consistent with low level of blood contamination and concluded that reslizumab did not cross the blood brain barrier. No SCH 55700 binding was observed in tissues (brain,

Reference ID: 3861540

spinal cord, and optic nerve) that exhibited *in vitro* upon immunohistochemical analysis. An additional study was conducted to assess the toxicity of reslizumab in the CNS when administered to Cynomolgus monkeys as a single-intrathecal injection into the cisterna magna. Cynomolgus monkeys received a single intrathecal dose of 0.07 mg/kg SCH 55700 and were subsequently sacrificed on either Day 7 or 29. No reslizumab-related clinical or gross pathology findings were seen in these animals.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The rationale for development of reslizumab in the treatment of poorly controlled asthma with eosinophilic airway inflammation is based on its blocking of the binding of circulating IL-5 and preventing its binding to the IL-5 receptor expressed on the surface of eosinophils. Eosinophils are thought to play a key role in the pathogenesis of asthma due to their increased presence in asthmatic airways and their ability to mediate both airway damage and alterations to pulmonary dynamics. IL-5 regulates the production, survival and function of eosinophils. Reslizumab has previously been used in three placebo controlled clinical studies and was investigated under BB-IND 9227 for the treatment of moderate and severe persistent asthma. The most frequently reported adverse effects in during the human trials were aggravated asthma, headache, pharyngitis, and upper respiratory tract infection. In the current application, Ception has proposed a single phase II, randomized, double-blind, placebo-controlled study in subjects with poorly controlled asthma with eosinophilic airway inflammation. In support of the proposed clinical trial, the sponsor has provided full reports of nonclinical studies conducted with SCH 55700, and a bridging study in juvenile monkeys to compare the pharmacokinetic and immunogenicity and toxicity profiles of reslizumab produced by Schering and by (b) (4) for Ception.

The pivotal toxicological data from the 6-month mouse and monkey studies have been used in the evaluation of the potential toxicity of reslizumab. Standard toxicological evaluations were conducted after intravenous administration of 0, 1, 5, 25 mg/kg in monkeys every 4-weeks for 6-months (total of 7 doses) with 3-month recovery period. A similar dosing schedule of 28-days for a total of 7 doses was used for administration of 0, 2, 5, 25 mg/kg reslizumab in mice. There were no major toxicity findings in both the mouse and monkey studies, except dose-dependent minimal reductions in eosinophils without any suggestion of blockade of maturation or release of eosinophils from the bone marrow. Thus, the NOAEL in mouse was the maximum tested dose of 25 mg/kg with $AUC_{(0\text{-}14\ day)}$ values between 45,000 – 68,000 μg.h/ml. A NOAEL of 25 mg/kg (the highest tested dose) was also proposed in monkeys based on the absence of treatment-related findings. Systemic exposure based on AUC value has not been reported, but mean blood concentrations were reported for monkeys in the 6-month study. An $AUC_{(0\text{-}14\ day)}$ value of 66,079 μg.h/ml was however estimated in a different study (study No. 95355). The t½ in mice ranged between 10-14 days, and 14-18 days in monkeys, and there is no indication of drug accumulation up on repeat dosing in both mice and monkeys.

Reference ID: 3861540

SCH 55700 did not exhibit genotoxic potential in both the Ames test and chromosomal aberration test *in vitro*. Fertility studies in mice and embryo-fetal developmental studies in mice and rabbits conducted at doses of 2, 10, and 50 mg/kg SCH 55700 did not show any test article-related clinical signs of toxicity in parental animals. Nor were there any changes in maternal body weights or fertility parameters, or any necropsy findings compared to controls. There were no effects on embryo-fetal viability and fetal body weights, and no developmental variations, or malformations in offspring were apparent. The irritation potential of the parenteral formulation of SCH 55700 was assessed after single subcutaneous injection along with vehicle and mefoxin® in rat, and by i.v. administration in rabbits. SCH 55700 produced minimal-to-mild irritation similar to that elicited by the injection of saline, vehicle, or sham injection. There were no treatment-related macroscopic and microscopic changes associated with the irritation.

The table below presents the safety margins for the proposed clinical dose of 3 mg/kg compared to the mouse and monkey NOAEL in mg/kg. The safety factor is calculated as a ratio of the proposed human dose and the NOAEL dose from animals. A safety margin of 10 for the mouse and 5 for the monkey would be considered adequate based on this comparison. The dose in humans is supported by the monkey 6-month toxicity study. However, the t½ for reslizumab in humans is about 28 days while the t½ in mice or monkeys ranged between 10 - 18 days. To address the differences in t½, an approach used by the reviewer of BB-IND 9227 (see the appended review) has been used. The reviewer adds an additional factor of 2 based on t½. Using this approach, the safety margin for the 3 mg/kg human dose compared to an extrapolated NOAEL of 12.5 mg/kg would still provide a safety margin close to 5 (4.2).

Safety Margins for the Proposed Clinical Dose of 3 mg/kg Compared to Animal NOAEL

Clinical dose	3 mg/kg (i.v.) at intervals of 28 ± 7 days for a total of 4 doses
6-month mouse study	1, 5, 25 mg/kg (i.v.) at intervals of 28 days for a total 7 doses
NOAEL	25 mg/kg
Safety margins (mg/kg)	8.3
6-month monkey study	1, 5, 25 mg/kg (i.v.) every 4-weeks for total of 7 doses
NOAEL	25 mg/kg
Safety margin	8.3

In addition, drug exposure information from mice (SN#96264), monkeys (report P-6187) and from nasal polyposis patients after 3 mg/kg single dose (study# P01942) are used for further qualification of the safety of the proposed dose. An $AUC_{(0\text{-}29\ day)}$ value of 24,211 µg·hr/ml has been estimated following 3 mg/kg i.v. reslizumab dose in

Reference ID: 3861540

humans. The proposed dose appears to be supported by exposure data assuming a steady sate level of $AUC_{(0\text{-}29\ day)}$ of 48,422 µg·hr/ml, doubling the estimated exposure in humans to account for differences in the t½ between animals and humans (see table below).

Systemic Exposure of Reslizumab in Mice and Monkeys Compared to Humans Single Dose of 3 mg/kg Reslizumab

Species (Gender)[a]	Preclinical Study	Dose (mg/kg)	AUC (t_f) (µg·hr/ml)	t_f (days)	Assay	Animal-to-Human Exposure Ratio[a]
Mouse (M, F)	SN#96264	25	54,500[b]	14	Biosensor	1.1
Monkey (M, F)	Report P-6187	25	61,868[c]	14	ELISA	1.4

[a] Ratio based on assumed steady state $AUC_{(0\text{-}29\ day)}$ of 48,422 µg·hr/ml to reslizumab based on t½ of about 28-days. $AUC_{(0\text{-}29\ day)}$ of 24,211 µg·hr/ml was estimated by Dr. Partha Roy using the software WINNONLIN from mean concentration vs. time points up to 29 days after single 3 mg/kg dose in nasal polyposis patients (study P01942). The sponsor reported an $AUC_{(0\text{-}34\ weeks)}$ of 42,302 µg·hr/ml at the 3 mg/kg dose in the same clinical study.

[b] Average of days 0, 84 & 168 from 6-month toxicokinetic study.

[c] $AUC_{(0\text{-}14)}$ value from a 1-month monkey study is used for comparison because 6-month AUC data was not reported. Accumulation of reslizumab was minimal after two doses administered every 14-day for a month.

Recommendations: The proposed human study is reasonably safe to proceed. The comment below should be sent to the sponsor.

Draft Letter:

(b) (4)

Therefore, we recommend that you submit nonclinical information and annual reports for the asthma indication separately to this Division.

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Reference ID: 3861540

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3861540

APPENDIX/ATTACHMENTS

The following review was forwarded on January 28, 2008 to Dr. Eshete and Dr. Sun by Dr. Anne Pilaro of the Division of Biological Oncology products.

CLINICAL PHARMACOLOGY AND TOXICOLOGY (T REVIEW) WORKSHEET

1. Background

BB IND#: 9227a000
Related INDs: [redacted] (b) (4)
Product: Humanized monoclonal antibody (SCH55700) to IL-5
Clinical indication: Treatment of asthma
Phase of study: 2
Sponsor: Schering Corp.
Investigator(s): N/A
Agency receipt date: 08-01-00
Reviewer receipt date: 08-08-00
 # volumes: 15
Decision date: 08-25-00
Pharm/Tox Reviewer: David M. Essayan, M.D.
Clinical Reviewer: Rieves
Product Reviewer: Miller
CSO: Schneider
Date of review: 08-10-00

2. Key or principle mechanism(s) of action

Asthma is a potentially fatal pulmonary inflammatory disorder with a strong genetic component affecting 4-10% of the general population. Th2-mediated responses to inhaled allergens play a key role in pathogenesis. Histologically, asthma is characterized by edema and desquamation of the airways with late airways remodeling/fibrosis associated with a mononuclear cell infiltrate and influx of eosinophils. Clinically, the disease is characterized by bronchial hyperresponsiveness and an obstructive pulmonary defect that is reversible early on, but may become fixed in chronic, poorly-managed disease.

Eosinophils are felt to play a key role in the pathogenesis of asthma due to their increased presence, correlation to disease activity and allergen exposure, and ability to mediate both airways damage and alterations to pulmonary dynamics. Eosinophil maturation, activation, and survival are intimately linked to the signaling of 3 structurally related cytokines (IL-3, IL-5, and GM-CSF) whose receptors share a common signaling chain. The potential for IL-5 antagonism to affect both eosinophil number and function, as well as the pathogenesis of asthma, has been evaluated in several *in vitro* and *in vivo* model systems, and shows promise.

The product is a humanized monoclonal antibody containing the CDRs of the rat anti-human IL-5 antibody (39D10) grafted onto an IgG4 kappa backbone [redacted] (b) (4) into NSO murine myeloma cells. The product will be developed initially for the treatment of asthma, [redacted] (b) (4)

2.1 Receptor: Human IL-5.
2.2 Species Cross Reactivity: Rodent (mouse, guinea pig, rabbit) and primate.
2.3 Tissue Cross Reactivity: Evaluated at 2 and 20 g/ml with increased stringency. Positive in spinal cord, brain, and optic nerve, occurring in focal irregularly shaped filamentous aggregates several mM in diameter in the neuropil and in and/or around glial cells. No binding to trigeminal nerve. No binding to other tissues. Similar binding in cynomolgus monkey, but not mouse or guinea pig, neural tissue; binding pattern similar for 39D10 but not [redacted] (b) (4) Target is a previously unidentified [redacted] (b) (4) protein.

3. Principle models used for efficacy

Reference ID: 3861540

3.1 In Vitro: Reference to the open literature. IL-3, IL-5, and GM-CSF each regulate eosinophil growth, differentiation, and survival (with the majority of effect mediated by IL-5); these three cytokines signal through heterodimeric receptors with unique chains and a single shared chain. Local or systemic, induced or aberrant baseline elevations in IL-5 may underlie a variety of hypereosinophilic disease states (asthma, Idiopathic Hypereosinophilic Syndrome (IHS), Löffler's Syndrome, response to parasitic infection).

3.2 Preclinical: Reference to the open literature. Several different MAbs to IL-5 have been evaluated in mouse (including SCH 55700 0.01 to 10 mg/kg ip), guinea pig (including SCH 55700 0.03 to 30 mg/kg ip), and cynomolgus monkey (including SCH 55700 0.1 and 0.3 mg/kg iv; only 0.3 effective) models of pulmonary eosinophilia and airway hyperreactivity. In general, these products are associated with dose-dependent inhibition of eosinophil accumulation in BAL following allergen challenge, reduced pulmonary reactivity to antigen and/or chemical challenge (acute phase), and reduced hyperreactivity following antigen challenge.

Of note specific to SCH 55700, PD effects on eosinophil migration occur at 100-1000 fold lower concentration that effects on pulmonary function. The effects of SCH 55700 were additive with steroids in a murine model of allergen-induced BHR. In allergic cynomolgus monkeys subjects to inhaled allergen challenge, a single dose of 0.3 mg/kg inhibited BAL eosinophilia for up to 6 months.

3.3 Clinical: This product has been used in Europe in an initial phase 1 single dose, dose escalation trial for treatment of 32 subjects with severe asthma (I96-350). Doses ranged from 0.03 mg/kg to 1.0 mg/kg. Moderate to severe AEs included headache, allergic reaction to pneumococcal vaccine, hyperglycemia, musculoskeletal pain, respiratory infection, and fatigue. There were no serious infections or tumors. Dose dependent PK was observed with a t ½ of 23-30 days. Clinical findings indicated an appropriate and reversible PD effect (decreases in peripheral blood eosinophil counts) with some indication of clinical benefit (increases in FEV1). A subsequent phase 2 study (P00290) of 0.3 or 1.0 mg/kg vs. placebo in subjects with moderate and severe asthma has recruited approximately 120 subjects without obvious safety concerns in the blinded database.

3.4 Were sufficient and appropriate animal studies performed (Y/N)? Yes.

4. Anticipated risks (adverse effects, organ system or functional endpoints)

Lack of recovery of eosinophils, increased risk of parasitic infections, nonspecific CNS toxicity due to potential tissue binding, hypersensitivity responses.

5. Does this IND contain original toxicology studies not previously reported (Y/N)?

5.1 If yes, indicate the original studies cited in this IND by title and number

In Vitro

1. Kd=81 pM at 37 C.
2. Association rate 4.9 x 10^5 M^{-1} sec^{-1}; dissociation rate 3.9 x 10^5 M^{-1} sec^{-1}.
3. Functional IC_{50} of 45-500 pM, depending on assay.
4. The product blocked the binding of its parent antibody (39D10) in an EIA format.
5. Binding epitope is (b) (4); also critical for IL-5 interaction with IL-5R.

Pharmacology

1. Safety pharmacology in rats (100 mg/kg iv) did not influence electrocardiographic parameters or gastric emptying.
2. Dose dependent PK in CD-1 mice (1, 5, and 25 mg/kg), NZW rabbits (2, 10, and 50 mg/kg) and cynomolgus monkeys (0.3, 1, and 3 mg/kg) following single dose and multiple dose (up to 7 monthly doses in cynomolgus monkeys) administration. Terminal t ½ = 14 days. Immunogenicity (anti-Id) with increased clearance (t ½ = 1 day) seen in one monkey (3 mg/kg). Dose- and gender-independent PK following multiple dose administration (2 doses q 14 d) in mice and cynomolgus monkeys (1, 5, and 25 mg/kg). Accumulation detected at 14 day dosing interval (c/w t ½). Immunogenicity not assessed.

Toxicity

1. Single dose studies with 14 day follow-up in mice (500 mg/kg), rats (500 mg/kg), and cynomolgus monkeys (100 mg/kg). No lethality; no product-related toxicities. PD effect and thresholds as expected from efficacy models.

Reference ID: 3861540

2. Multiple dose studies with 2 and 6 weeks of follow-up in mice and cynomolgus monkeys (1, 5, and 25 mg/kg iv on days 1 and 15). No lethality; no product-related toxicities. PD effect and thresholds as expected from efficacy models.
3. Pivotal six month Cynomolgus monkey trial (N=76; 0, 1, 5, and 25 mg/kg q4 weeks x 6 doses) with 3 month recovery (4/group in placebo and 25 mg/kg groups). Study parameters included in-life observations, physical , neurologic, and ophthalmologic exams, ECG, serum chemistries, hematology, coagulation, U/A, PK, special neurologic studies (EEG, ERG, flash-evoked potentials, BAER, and somatosensory-evoked potentials), necropsy, histopathology, and CNS IHC. No product-related toxicities; dose-dependent PD effect noted. No detection of product in CNS.
4. Immunogenicity noted in 3 animals in the pivotal toxicity study (1 at 5 mg/kg, 2 at 25 mg/kg); 1 of the 25 mg/kg animals had repeated infusion reactions c/w hypersensitivity (salivation, emesis, recumbency within 10 minutes of doses 5-7).
5. Follow-on toxicology studies in cynomolgus monkeys administered the product by the intrathecal route to attains CSF levels in excess (2-4 fold) of the serum Cmax by iv administration of 1 mg/kg (45-80 µg/ml in CSF study samples at 4 weeks) showed no product-related toxicities (clinical or anatomic).

Local tolerance

1. Arterial irritation at 10 mg/ml in rabbits-negative.
2. SQ tolerance similar to placebo in rats.

Genotoxicity

1. Non-mutagenic in the Salmonella/E. Coli mammalian microsomal assay with and without metabolic activation.
2. Induction of chromosomal aberrations in cultured human lymphocytes with and without metabolic activation-negative.

Reproductive/developmental toxicity

1. Maternotoxicity, embryotoxicity, and teratogenicity studies in mice and rabbits at iv doses of 2, 10, and 50 mg/kg-negative.
2. Fertility studies in mice at doses up to 50 mg/kg-negative. No effects on OVA-induced pulmonary eosinophil responses in F1.

***N/B*-5 mice in the 2 mg/kg group died in <2 hours of apparent anaphylaxis following administration of the third dose.**

5.2 Fill in the following and indicate source (by reference to 5.1 or another IND):

Dosage: 0.1 to 100 mg/kg iv in cynomolgus monkeys; 0.01 to 50 mg/kg in mice.
PEL: 0.3 in cynomolgus monkeys; 0.1 in mice.
NOAEL: >100 mg/kg in cynomolgus monkeys; 5 mg/kg in mice.
Max: 500, 500, and 100 mg/kg, respectively in mice, rats, and cynomolgus monkeys.
Equivalency factor: Approximately 1 by binding affinity and *in vitro* assays.
Duration index: 2-2.5 by t ½.

5.3 For the NOAEL, indicate species, dose, toxicity, duration, and dosing regimen:

Mice given 5 mg/kg q14 d x 2 (**males only**) developed decreased spleen and thymus weights, with mild lymphopenia at 25 mg/kg.

6. Indicate:

6.1 Will the study be in normal subjects (Y/N)? No, 180 adult subjects in 40 centers with moderate to severe asthma not adequately controlled on inhaled corticosteroids in a 38 week DBPC, randomized, parallel group study (P00290).

Nb-120 subjects have already been dosed at 35 sites in Europe, Canada, and South Africa since 11-99.

6.2 Initial clinical dose: 0.3 and 1.0 mg/kg iv x 2 doses q 12 weeks vs. placebo.

6.3 Cite previous or ongoing trial(s) with this agent and highest dose used: 1.0 mg/kg in the phase 1 trial.

6.4 Dose escalation scheme and regimen: No dose excalation or modification. Assessment will include PFTs, exacerbations, symptom scores, rescue medication use, peripheral blood eosinophils, induced sputum for eosinophils, PK/PD, and immunogenicity.

Reference ID: 3861540

7. Determine tSF (tentative safety factor and indicate means of computation)
100 mg/kg cynomolgus monkey Max/2.5 duration index/2 for species correction=20 mg/kg
Thus, tSF=20/1=20

8. Are the potential clinical toxicities adequately known (Y/N)?
Yes.

9. Are the toxicities considered extensions of the pharmacological action (Y/N)?
Yes; however, the CNS binding site for this antibody is apparently not IL-5 but a specific structural mimic. The distribution/functional characterization of the alternate target and pharmacology of SCH 55700 as it applies to this target is unknown at this time.

10. Are any additional studies necessary (Y/N)?
No.

11. Recommendations: clinical hold (Y/N):
No.

12. Comments:
CPT-Major
None

CPT-Minor
1. The sponsor should be encouraged to pursue tissue distribution and functional characterization of the (b)(4) kDa CNS protein target as well as the pharmacology of SCH 55700 with this target in order to better characterize and predict potential safety issues with SCH 55700 during clinical development.

Non-CPT (Communicated to the product and/or clinical reviewers for potential inclusion in the product and/or clinical comments at the sole discretion of the product and/or clinical reviewer)
None

Reference ID: 3861540

Linked Applications	Sponsor Name	Drug Name
IND 101399	CEPTION THERAPEUTICS	Reslizumab

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

/s/

FELEKE ESHETE
02/19/2008
Non-Clinical Reviewer

CHING-LONG J J SUN
02/19/2008
Non-Clinical Reviewer
I ocncur.

Appendix 2

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	IND 101,399
Supporting document/s:	42 (eCTD 0011) – General information
	65 (eCTD 0034) – Nonclinical response to IR
Sponsor's letter date:	2/25/2011, 1/4/2012
CDER stamp date:	2/25/2011, 1/4/2012
Product:	Reslizumab (CEP-38072)
Indication:	Poorly controlled asthma with eosinophilic airway inflammation
Sponsor:	Cephalon, Inc.[1]
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Rivera-Lopez, Ph.D.
Supervisor/Team Leader:	Molly E. Topper, Ph.D.
Division Director:	Badrul A. Chowdhury, M.D., Ph.D.
Project Manager:	Colette C. Jackson
	Senior Regulatory Health Project Manager

[1] Previously Ception Therapeutics, Inc. Ception was acquired by Cephalon, Inc. in April of 2010.

Reference ID: 3826750

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 4

1.1 INTRODUCTION 5
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 5

3 STUDIES SUBMITTED 6

3.1 STUDIES REVIEWED 6
3.3 PREVIOUS REVIEWS REFERENCED 7

6 GENERAL TOXICOLOGY 7

6.2 REPEAT-DOSE TOXICITY 7

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 26

Reference ID: 3826750

Tables

Table 1: Study SN 96264 Design 8
Table 2: Summary of SCH 55700-related unscheduled deaths in mice.....9
Table 3: Summary of Histological Observations (Incidence and Severity) - Mouse 12
Table 4: Pharmacokinetic Parameters of SCH 55700 Following IV Administration to CD-1 mice once every 28 days 15
Table 5: Study P6749 Design.....19
Table 6: Summary of Gross Pathology Observations - Monkey.....21
Table 7: Summary of Changes in Organ Weights - Monkey.....22
Table 8: Summary of Histological Observations (Incidence and Severity) - Monkey.....23
Table 9: Mean Concentration of SCH 55700 in Serum (µg/mL) determined by ELISA..26

Reference ID: 3826750

List of Abbreviations

ADA	Anti-drug antibody
AP	Alkaline phosphatase
AST	Aspartate aminotrasferase
AUC	Area under the curve
BAER	Brainstem auditory evoked response
BUN	Blood Urea Nitrogen
BW	Body weight
CDR	Complementarity determining regions
C_{max}	Maximal drug concentration in plasma
CNS	Central Nervous System
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EE	Eosinophilic esophagitis
EEG	Electroencephalogram
EG	Eosinophilic gastroenteritis
ELISA	Enzyme-linked immunosorbent assay
ERG	Electroretinogram
F	Females
FEP	Flash evoked potential
GLP	Good Laboratory Practice
HD	High-dose
HES	Hypereosinophilic syndrome
hr	Hour
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IV	Intravenous
kg	Kilogram
LD	Low-dose
LLOQ	Lower limit of quantitation
M	Males
mAb	monoclonal antibody
MD	Mid-dose
mg	Milligram
mL or ml	Milliliter
No.	Number
NP	Nasal polyposis
ng	Nanogram
NOAEL	No observed adverse effect level
PAI	Pathology Associates International
QA	Quality assurance
SEP	Somatosensory evoked potential
SPU	Schering Plough Units
TK	Toxicokinetics
t_{max}	Time to maximal drug concentration in plasma
vs.	versus
µg	Microgram

Reference ID: 3826750

1 Executive Summary

1.1 Introduction

This review evaluates nonclinical data to support safety of clinical protocols submitted by Cephalon under IND 101,399. The drug product, Reslizumab (Codes[2]: SCH 55700, CTx55700 or CEP-38072), is a humanized anti-human IL-5 monoclonal antibody of the IgG4 kappa isotype, which contains the complementarity determining regions (CDRs) of the original rat anti-human antibody (39D10) grafted onto human frameworks. The proposed indication is moderate to severe eosinophilic asthma in adolescents and adults (12 years of age and older) whose symptoms are not well controlled with inhaled corticosteroids. (b) (4)

Reslizumab has been administered intravenously to approximately 445 human subjects in Phase 1 and Phase 2 studies in patients with asthma, eosinophilic esophagitis (EE), nasal polyposis (NP), hypereosinophilic syndrome (HES), and eosinophilic gastroenteritis (EG). In addition, five Phase 3 clinical studies were proposed by the sponsor as follows: (1) study C38072/3081 is a 16-week study to evaluate safety and efficacy of 0.3 or 3.0 mg/kg Reslizumab in patients 12-75 years of age with eosinophilic asthma, (2) study C38072/3082 is a 12-month study to evaluate safety and efficacy of 3.0 mg/kg Reslizumab in patients 12-75 years of age with eosinophilic asthma, (3) study C38072/3083 is a 12-month study to evaluate safety and efficacy of 3.0 mg/kg Reslizumab in patients 12-75 years of age with eosinophilic asthma, (4) study C38072/3085 is an open-label extension study to evaluate the long-term safety and efficacy of 3.0 mg/kg Reslizumab in patients with eosinophilic asthma, and (5) study C38072/3084 is a 16-week study to evaluate the efficacy and safety of Reslizumab (3.0 mg/kg) treatment in patients with moderate to severe asthma.

A number of nonclinical studies have been submitted by the sponsor to support the aforementioned clinical studies. A preliminary review was completed by Dr. Feleke Eshete on February 19, 2008. This review covers detailed evaluation of two long-term (6-month) studies in mice (study no. SN96264) and monkeys (study no. P6749). Additional reviews will follow to cover detailed evaluation of other nonclinical studies.

1.2 Brief Discussion of Nonclinical Findings

Two long-term GLP toxicity studies (study no. SN96264 in mice and study no. P6749 in monkeys) were submitted in support of the long-term clinical studies and are the subject of this review. Briefly, CD-1 mice (10/sex/group) received 0 (control), 1, 5, or 25 mg/kg SCH 55700 once every 28 days for six months (total of 7 doses). There were six deaths during the study (2 in the LD group, 3 in the MD group, and 1 in the HD group) but the cause of death was determined for only two of these animals; a mid-dose female was sacrificed early because presented poor condition due to a lung carcinoma and a high-dose male was found dead due to urinary tract obstruction. Histopathology

[2] SCH 55700 is the company code used by Schering in the past. CTx55700 is the company code used by Ception in the past. CEP-38072 is the company code currently used by Cephalon.

Reference ID: 3826750

findings of concern in mice include renal pelvis and ureters dilatation in three HD males (including the animal that was found dead), which correlated with increased blood urea-nitrogen (BUN) levels. Tissues from LD and MD groups were not examined for these findings. Therefore, an information request was sent to the sponsor on July of 2011 to request examination of LD and MD tissues or justification for not considering these findings related to treatment. The sponsor provided an expert's report after re-examination of kidney tissues from all animals from all dose groups. After evaluation of all the data, the NOAEL for the kidney findings has been identified as the mid-dose at 10 mg/kg with an associated exposure ($AUC_{0\text{-}336\ hr}$) of 22100 µg·hr/mL. Although the sponsor identified the NOAEL as the high-dose (25 mg/kg), a NOAEL could not be identified for the study because deaths were observed at all dose levels.

Cynomolgus monkeys (4/sex/group) received 0 (control), 1, 5, or 25 mg/kg SCH 55700 once every 28 days for six months (total of 7 doses). The following drug-related ECG findings were observed: one MD male animal had a single ventricular extrasystole at week 28, one HD female had two ventricular extrasystoles at week 8 and one HD male had a single ventricular extrasystole at weeks 16 and 28, and three at week 22. Histopathology findings of concern include vasculitis in heart and cecum in one HD female, injection site vasculitis in three HD males, lymphoid hyperplasia in mandibular lymph nodes in 1 HD female, thymus mineralization in 1 HD male, spleen congestion in 1 HD female, cortical hypertrophy of adrenal gland in 1 HD female, and hemorrhage in skeletal muscle in 1 HD male and in bone (femur) in 1 HD female. In addition, kidney tubular basophilia (4 HD males), tubular casts (1 HD male), tubular vacuolation (1 HD female), and hypoplasia (1 HD female) were observed with higher incidence in HD animals. Tissues from LD and MD groups were not examined for any of these findings.

Although the sponsor identified the NOAEL as the HD (25 mg/kg) for the monkey because they considered all findings as incidental and not drug-related, based on all the aforementioned findings in HD animals, a NOAEL could not be determined by this reviewer. An information request was sent to the sponsor on September 9th, 2011 to request justification for the findings or examination of tissues in the LD and MD groups to support a NOAEL for this study.

Disclaimer: Any tabular information was constructed by this reviewer unless otherwise noted.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Study Number	Submission Date
Toxicology		
Six-Month Intravenous Toxicity and Toxicokinetic Study of SCH 55700 in Mice	SN96264	2/25/2011 (electronic)
A Six-Month Intravenous Toxicity Study of SCH 55700 with Neurological Evaluations in Cynomolgus Monkeys	P6749	2/25/2011 (electronic)

Reference ID: 3826750

3.3 Previous Reviews Referenced

Nonclinical reviews have been completed by Feleke Eshete, Ph.D. (2/19/2008) and Timothy W. Robison, Ph.D., D.A.B.T. (2/3/2010 and 2/7/2011).

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Six-Month Intravenous Toxicity and Toxicokinetic Study of SCH 55700 in Mice

Study no.:	SN 96264
Study report location:	EDR
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	11/16/1999
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 55700; Batch No. 38101-033; >95% pure

Key Study Findings

- Six animals died during the study: 2 in the LD group (undetermined reason), 3 in the MD group (two undetermined, one from a lung carcinoma), and 1 in the HD group (from urinary tract obstruction). Deaths did not follow a dose response.
- Dilatation was observed in the renal pelvis and ureters in two HD males (mild to moderate severity), including animal 304, which was found dead on the day of necropsy. In addition, minimal renal pelvis dilatation was observed in another HD male.
- Increased BUN levels in MD and HD males (21% and 45%, respectively).
- According to the study report, accurate antibody detection was precluded by the presence of free SCH 55700 in the serum. Therefore, results of the ADA assay were not provided.
- The sponsor identified the NOAEL as the high-dose (25 mg/kg) with a justification that all findings observed represented common findings in laboratory mice. However, due to the aforementioned findings in the urinary tract of HD animals, an information request was sent to the sponsor on July 19, 2011 to request examination of tissues in LD and MD males to support a NOAEL or an adequate justification for not considering these findings of concern.
- In their response, the sponsor provided an expert's report with new data after re-examination of kidney tissues from all animals from the control and drug-treated groups.

Reference ID: 3826750

- After evaluation of the new data, the NOAEL for the kidney findings has been identified as the mid-dose at 10 mg/kg with an associated $AUC_{0\text{-}336\ hr}$ of 22100 µg·hr/mL.
- A NOAEL could not be identified for the study due to mortalities observed at all dose levels. However, the deaths did not follow a dose responsive relationship. Deaths may be a result of immunogenic response but it is unknown.

Methods

Doses:	Three dose levels at 0 (control), 2 (LD), 10 (MD), or 25 (HD) mg/kg/dose
Frequency of dosing:	Once every 28 days for six months (7 doses)
Route of administration:	Intravenous
Dose volume:	5 mL/kg
Formulation/Vehicle:	SCH 55700 placebo solution (Batch No. 38101-130). Composition of the placebo solution was not provided in the study report.
Species/Strain:	Crl:CD-1®(ICR)BR VAF/Plus® mice
Number/Sex/Group:	10/sex/group
Age:	6 weeks
Weight:	Males: 22.7 – 32.9 g Females: 18.6 – 26.3 g
Satellite groups:	Forty animals/sex/group were used for toxicokinetic (TK) analysis.
Unique study design:	Forty animals/sex/group were evaluated for serum analysis only (TK).
Deviation from study protocol:	Deviations that could impact study data were not identified.

Table 1: Study SN 96264 Design

Group	Test/Control Article	Number of Mice/Sex		Total Dose (mg/kg) (every 28 days)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Total No. of Doses
		Toxicity Portion	Satellite portion				
C1	Control (SCH 55700 placebo)	10	0	0	5.0	0	7
T1	Low-dose (SCH 55700)	10	40[a]	2[b]	5.0	0.4	7
T2	Mid-dose (SCH 55700)	10	40[a]	10	5.0	2	7
T3	High-dose (SCH 55700)	10	40[a]	25	5.0	5	7

[a] These animals were evaluated for serum analysis only.
[b] On Day 0, animals in Group T1 received 1.3 mg/kg.

Reference ID: 3826750

Observations and Results

Mortality

All animals were observed at least once daily. There were six deaths in the toxicity portion of the study: 2 in the LD group, 3 in the MD group, and 1 in the HD group (see table 2 below). Five mice were found dead and one mouse was sacrificed for humane reasons (bronchiolo-alveolar carcinoma in one MD female, animal no. 252). One HD male animal (animal no. 304) was found dead on the day of necropsy (Day 201) and showed evidence of a chronic urinary tract obstruction (moderate dilatation of the renal pelvis and ureters, and mild congestion in the urinary bladder). Although the study pathologist claims that there were no consistent gross or microscopic findings that would suggest a test article-related death, another HD male animal that survived through necropsy (animal no. 310) showed similar but less severe urinary tract findings (see histopathology table 3 below), suggesting that there is a possibility that this death was related to SCH 55700 treatment. A cause of death was not determined for the rest of the animals (animal numbers 452, 156, 202, and 208).

The findings of increased infections and a carcinoma suggest that the drug has the potential to induce immunosuppression. However, literature suggests that drugs that target eosinophils, like SCH 55700, inhibit tissue damage without inducing systemic immunosuppressive effects[3]. Also, as discussed below, the urinary tract findings associated with obstruction could be due to the formation of anti-drug antibodies. Regarding the bronchiolo-alveolar carcinoma, it was found only in one MD animal and not in any mouse treated with 25 mg/kg SCH 55700 (the HD). In addition, literature suggests this could be a spontaneous lesion in CD-1 mice[4]. This supports the sponsor's conclusion that this finding is not related to treatment.

Table 2: Summary of SCH 55700-related unscheduled deaths in mice

Animal No.	Sex	SCH 55700 dose	Study Day of Death	Cause of death
452	F	2 mg/kg	0	unknown
156	F	2 mg/kg	28	unknown
202	M	10 mg/kg	56	unknown
208	M	10 mg/kg	56	unknown
252	F	10 mg/kg	162	bronchiolo-alveolar carcinoma
304	M	25 mg/kg	201	urinary tract obstruction

[3] Blumchen K, Kallinich T, and Hamelmann E. (2001) Interleukin-5: a novel target for asthma therapy. *Exp. Opin. Biol. Ther.* **1**(3):433-453.
Greenfeder S, Umland SP, Cuss FM, Chapman RW, and Egan RW. (2001) Th2 cytokines and asthma. The role of interleukin-5 in allergic eosinophilic disease. *Respir. Res.* **2**:71-79.
[4] Anon. (2007) The Mouse in Animal Models in Toxicology, 2nd ed., Taylor & Francis Group.
Brayton C. (2007) Spontaneous Diseases in Commonly Used Mouse Strains / Stocks in The Mouse in Biomedical Research, Vol. **2**, 2nd ed., Elsevier, Inc.

Reference ID: 3826750

Clinical Signs

Animals were observed at least once daily for changes in appearance and behavior. All findings observed (e.g., erythema, alopecia, and abnormal hair coat) were considered incidental as they were also observed in control animals or during the pre-dose period.

Body Weights

Body weights were recorded on the day of randomization and weekly, beginning on week 1. In addition, a fasted terminal body weight was measured prior to scheduled necropsy. There was a slight decrease in body weight in females at MD (-17%) and HD (-12%) compared to controls. However, this finding was not statistically significant or dose-dependent. There was no correlation with food consumption. No changes in body weights were observed in males.

Feed Consumption

Food consumption was assessed daily on week 1 and weekly thereafter (toxicity portion mice only). No changes in food consumption were noted in SCH 55700-treated groups.

Ophthalmoscopy

Ophthalmic examinations were performed once pre-test and once on week 27 of the dosing phase. Examinations included focal illumination and indirect ophthalmoscopy in a subdued light setting. No SCH 55700-related effects were observed in males or females. A signed Ophthalmology Report is included in the final study report.

Hematology

Blood was collected via the abdominal aorta from 5 toxicity portion mice during scheduled necropsy on week 29. No pre-dose samples were obtained, therefore only treatment vs. control animals were compared. A complete standard hematological battery was evaluated. A signed Clinical Pathology report is attached to the final study report and includes results of Hematology and Clinical Chemistry.

In general, there was a slight tendency to decreased levels of eosinophils, monocytes, and basophils in some SCH 55700-treated animals compared to controls. However, these changes were sporadic, not statistically significant, and not dose-dependent.

Clinical Chemistry

Blood was collected via the abdominal aorta from 5 toxicity portion mice during scheduled necropsy on week 29. Pre-dose samples were not obtained. Therefore only values from treatment vs. control animals were compared. A complete standard clinical chemistry battery was evaluated.

Blood urea nitrogen (BUN) levels were increased in MD (+21%) and HD (+45%) males (but not females) compared to controls at week 29, which correlate with macroscopic and histopathologic findings in kidneys (table 3 below). In addition, aspartate aminotransferase (AST) levels showed a slight tendency to increase in males at the LD (+28%) and MD (+23%) and females at the HD (+22%) compared to controls at week 29. Also, alkaline phosphatase (AP) levels were decreased in males (but not females)

Reference ID: 3826750

at the HD (-34%) compared to controls at week 29. Because of lack of histopathology findings in liver, these findings were not considered of concern.

Urinalysis

Urinalysis was not conducted for this study.

Gross Pathology

All mice assigned to the toxicity portion of the study were necropsied following an overnight fast (for mice sacrificed at the scheduled necropsy on week 29). Necropsy included complete macroscopic examination. Dilatation of renal pelvis and ureters was observed in two HD males (animal no. 310 and animal no. 304) but not in females. This correlates with histopathology findings of renal pelvis and ureter dilatation in these animals (table 3 below).

Organ Weights

At necropsy, the following organs were weighed for all toxicity portion mice sacrificed as scheduled: brain, epididymides, heart, kidneys, liver, lungs (plus bronchi), ovaries, salivary glands (mandibular), spleen, testes, thymus, uterus (plus cervix). Organ-to-body ratios were calculated.

Results show that mean liver-to-body ratios were slightly increased in SCH 55700-treated males (+11% in LD, +11% in MD, and +9% in HD) compared to controls. This slight increase in weight could be associated to the increased AST observed in LD and MD males. However, no associated histopathology findings in liver were observed in these animals. Mean spleen-to-body ratio was increased in LD males (+86%) compared to controls. These findings were not present in females and are not associated with microscopic findings in spleen. Also, females showed decreased mean ovaries-to-body ratios (-47% in LD, -40% in MD, and -55% in HD). These findings in the ovaries were not statistically significant and are not considered related to SCH 55700 treatment. In addition, there is no correlation of these findings with histopathology findings, therefore, are not considered of concern.

Histopathology

At necropsy, a battery of tissues was collected and examined microscopically for the control and HD animals. Not all tissues were examined in the LD and MD groups for either males or females except for samples where indicated in the table.

<u>Adequate Battery</u>

An adequate battery of tissues from all animals in the control and high dose groups was examined. In addition, all organs and tissues from mice that died or were sacrificed prior to scheduled necropsy were examined. All gross findings were collected.

<u>Peer Review</u>

According to the study report, a pathology peer review was conducted. However, it does not specify the tissues that were peer reviewed. In addition, the name and affiliation of the peer pathologist were not documented in the study report.

Reference ID: 3826750

Histological Findings

Table 3: Summary of Histological Observations (Incidence and Severity) - Mouse

	Males				Females			
SCH 55700 (mg/kg/dose)	**0**	**2**	**10**	**25**	**0**	**2**	**10**	**25**
Number of animals examined	**10**	*****	*****	**10***	**10**	*****	*****	**10**
OBSERVATIONS								
Bone Marrow			(2)			(2)	(1)	
Hyperplasia, myeloid, minimal	0	-	2	1	0	0	0	0
Harderian Glands								
Cellular infiltration, mononuclear cell			(2)			(2)	(1)	
Minimal	0	-	0	2	0	0	0	0
Mild	0	-	0	1	0	0	0	0
Injection Site						(1)		
Cellular infiltration, neutrophilic, mild	0	-	-	2	0	0	-	0
Ulcer, mild	0	-	-	1	0	0	-	0
Fibrosis, dermis, minimal	0	-	-	1	0	0	-	0
Kidneys								
Dilatation, pelvis			(2)			(3)	(1)	
Minimal	0	-	0	1	0	0	0	0
Mild	0	-	0	1	0	0	0	0
Moderate	0	-	0	1	0	0	0	0
Lungs		(1)	(2)			(2)	(1)	
Bronchiolo-alveolar carcinoma	0	0	0	0	0	0	1	0
Bronchiolo-alveolar adenoma	0	0	0	0	1	0	0	1
Ovaries						(7)	(7)	
Hemorrhage, mild	-	-	-	-	0	1	1	0
Dilatation, bursa	-	-	-	-	0	2	2	0
Skin								
Dermatitis		(2)	(3)			(2)	(2)	
Mild	0	0	1	1	0	0	1	1
Moderate	0	2	0	0	0	0	0	0
Testes								
Degeneration			(2)					
Minimal	3	-	1	7	-	-	-	-
Mild	1	-	0	0	-	-	-	-
Ureters								
Dilatation				(2)				
Mild	-	-	-	1	-	-	-	-
Moderate	-	-	-	1	-	-	-	-

* See parenthesis under specific tissue for total number of animals examined
(-) Not evaluated

As shown in Table 3 above, minimal bone marrow hyperplasia was observed in two MD and one HD males. This was not observed in females and was not dose-dependent, so it could be considered incidental. Mononuclear cell infiltration (minimal to mild) was observed in Harderian glands of three HD male animals but not in females. Because this finding is not relevant to humans, it is not considered dose limiting.

Reference ID: 3826750

Injection site histopathology findings include mild neutrophilic cellular infiltration, ulcer and minimal dermis fibrosis in HD male animals but not in females. Lower doses in males were not examined for this finding. These findings are not considered dose-limiting as local injection site irritation is considered clinically monitorable. Also, mild to moderate dermatitis was observed in 2 LD males, 1 MD male, 1 MD female, 1 HD male, and 1 HD female. This was not observed in controls but does not present a dose-dependent relationship. It is not clear whether this finding could be related to SCH 55700 treatment, but is judged to be monitorable in the clinic. Thus, it is not considered dose-limiting.

Hemorrhage and dilatation were observed in ovaries of 3 out of 7 LD and 3 out of 7 MD females. This was not observed in HD females, therefore is considered not related to SCH 55700. In addition, minimal degeneration was observed in testes of 1 MD and 7 HD males. Because this was also observed in controls (4 out of 10 mice), including one animal with increased severity (mild) it is considered incidental and not related to SCH 55700.

A bronchiolo-alveolar carcinoma (malignant tumor) was observed in one MD female (animal no. 252). This animal was sacrificed during the study because presented a poor condition. Bronchio-alveolar adenomas (benign tumors) were observed in one HD (animal no. 360) and one control (animal no. 17) animals. Because literature[5] suggests that bronchio-alveolar adenomas and carcinomas are spontaneous neoplastic lesions in CD-1 mice, these are considered incidental and not related to SCH 55700. Also, at the request of the Division, the sponsor is conducting a carcinogenicity study in mice.

Dilatation was observed in renal pelvis of three HD males (animals 309 - minimal, 310 - mild, and 304 - moderate), but not in the two MD males examined or in females. This correlates with mild to moderate dilatation of ureters observed in the only 2 HD male animals examined (310 - mild and 304 - moderate) for this tissue. Ureters were not examined for lower doses in males or any dose level in females. Because there is correlation of urinary tract findings in these animals (including gross findings), they are considered related to treatment with SCH 55700. Further, this also correlates with increased BUN levels (45%) in HD males.

HD animal 304 (with moderate renal pelvis and ureters dilatation) was found dead on the day of necropsy. The cause of death was determined as an urinary tract obstruction. Although the study pathologist considered this death unrelated to SCH 55700, because similar incidences were found in other HD male animals, this reviewer considers that these urinary tract findings are related to treatment. An information request was sent to the sponsor on 7/19/2011 to request examination of kidney tissues from the LD and MD groups or justification for not considering these urinary tract findings related to SCH 55700 and considering them as incidental. The sponsor submitted a response on January 4th, 2012 and provided an expert's report on renal histopathology of kidney tissues from animals in all dose groups and the vehicle control group. The expert observed renal pelvis dilatation in only three animals from the study. However, his evaluation differs from the original pathologist report in that renal pelvis dilatation was observed in one control male animal (animal no. 9) and two HD male animals (animals 304 and 310). No renal pelvis dilatation was observed in animals from the LD or MD groups. Taking into account all the aforementioned findings from the original study report and the expert

[5] Anon. (2007) The Mouse in Animal Models in Toxicology, 2nd ed., Taylor & Francis Group.
Brayton C. (2007) Spontaneous Diseases in Commonly Used Mouse Strains / Stocks in The Mouse in Biomedical Research, Vol. **2**, 2nd ed., Elsevier, Inc.

Reference ID: 3826750

report, this reviewer has identified the NOAEL for these kidney findings as the MD (10 mg/kg) with an associated systemic exposure ($AUC_{0\text{-}336\ hr}$) of 22100 µg·hr/mL.

Although the increase in urinary tract obstructions and the findings of a carcinoma suggest that the drug could be a potential immunosuppressant, literature suggests that drugs of this class that target primarily eosinophils are not immunosuppressants[6]. Also, urinary tract findings could be due to formation of anti-drug antibodies (ADAs).

Special Evaluation

Antibody analysis

Blood samples for antibody analysis were collected on Day 0 (1, 24, and 336 hours after dosing), Day 84 (1 hour prior to dosing and 1, 24, and 336 hours after dosing), and Day 168 (1 hour prior to dosing and 1, 24, and 336 hours after dosing) from three mice/sex/group/time point assigned to the satellite portion of the study. Blood samples were obtained from the abdominal aorta under isoflurane-induced anesthesia. Necropsy was not performed as all mice bled for serum analysis were sacrificed by exsanguination following blood collection. Serum samples were obtained and stored at -80°C until shipment to the bioanalytical facility for analysis.

A validated biosensor (BIAcore™) immunoassay (P-6306; LLOQ of 1.0 µg/mL) was used to confirm the presence of anti-SCH 55700 antibodies. However, according to the sponsor, accurate antibody detection was precluded by the presence of free SCH 55700 in the serum since it binds to circulating antibodies against SCH 55700. Results of the ADA assay were provided, but only one animal (one LD male, animal number not provided) tested positive at one time point (day 84, 336 hours after drug administration).

Toxicokinetics

A toxicokinetic (TK) analysis was conducted for this study. A signed Toxicokinetic Report is attached to the final study report.

Blood samples were collected on Day 0 (1, 24, and 336 hours after dosing), Day 84 (1 hour prior to dosing and 1, 24, and 336 hours after dosing), and Day 168 (1 hour prior to dosing and 1, 24, and 336 hours after dosing) from three mice/sex/group/time point assigned to the satellite portion. Blood samples were obtained from the abdominal aorta under isoflurane-induced anesthesia. All mice bled for serum analysis were sacrificed by exsanguination following blood collection without necropsy. Serum samples were obtained and stored at -80°C until shipment to the bioanalytical facility for analysis.

SCH 5700 concentrations in serum were measured using a validated Biosensor (BIAcore™) immunoassay (LLOQ of 1.0 µg/mL) and a validated TF-1 biological assay with a LLOQ of 750 SPU/mL. The bioassay measures potency (SPU/mL). Estimates of

---

[6] Blumchen K, Kallinich T, and Hamelmann E. (2001) Interleukin-5: a novel target for asthma therapy. *Exp. Opin. Biol. Ther.* **1**(3):433-453.
Greenfeder S, Umland SP, Cuss FM, Chapman RW, and Egan RW. (2001) Th2 cytokines and asthma. The role of interleukin-5 in allergic eosinophilic disease. *Respir. Res.* **2**:71-79.

Reference ID: 3826750

protein concentration were attained by using the factor of 0.994 SPU = 1 ng of SCH 55700. A separate signed Bioanalytical Report is included in the final study report. The TF-1 biological assay demonstrated a close correlation to the BIAcore immunoassay.

Table 4 below shows a summary of the pharmacokinetic parameters of SCH 55700. In general, SCH 55700 exposure ($AUC_{0\text{-}336\ hr}$) after IV administration once every 28 days in CD-1 mice increased in a dose-related manner.

According to the study report, serum concentrations of SCH 55700 were gender-independent. A review of the data confirms this is true in most cases except for samples of HD animals at Day 168, where males show a systemic exposure ($AUC_{0\text{-}336\ hr}$) of 61300 µg.hr/mL and females 29800 µg.hr/mL, suggesting a 2x increased exposure in males compared to females. Also, drug exposure ($AUC_{0\text{-}336\ hr}$) on Day 168 was lower than exposure at Day 84, which suggests potential ADA formation.

Table 4: Pharmacokinetic Parameters of SCH 55700 Following IV Administration to CD-1 mice once every 28 days[7]

Table 1 Serum SCH 55700 Concentrations and Pharmacokinetic Parameters Following Intravenous Administration of 2[a], 10 and 25 mg SCH 55700/kg to Mice on Days 0, 84 and 168 (Immunoassay)

Serum SCH 55700 (µg/mL)							
		Day 0					
		Males			Females		
Time (hr)	Units	2 mg/kg[a]	10 mg/kg	25 mg/kg	2 mg/kg[a]	10 mg/kg	25 mg/kg
1		26.1	147	353	21.7	127	351
24		12.6	74.7	171	12.3	69.1	178
336		5.1	57.0	121	4.80	45.0	83.0
Cmax	µg/mL	26.1	147	353	21.7	127	351
Tmax	hr	1.00	1.00	1.00	1.00	1.00	1.00
AUC(tf)	µg·hr/mL	3230	23200	51900	3080	20200	47100
tf	hr	336	336	336	336	336	336
Day 84							
1		29.0	235	412	39.4	169	359
24		30.0	112	265	26.3	102	252
336		0.00	42.9	174	7.00	44.6	88.3
Cmax	µg/mL	30.0	235	412	39.4	169	359
Tmax	hr	24.0	1.00	1.00	1.00	1.00	1.00
AUC(tf)	µg·hr/mL	NC	28300	76600	5990	26200	60500
tf	hr	24.0	336	336	336	336	336
Day 168							
1		39.0	190	434	44.1	162	389
24		25.2	111	249	27.0	97.2	178
168		14.8	67.6	150	16.2	43.0	30.6
336		2.40	35.8	139	14.7	26.0	63.3
Cmax	µg/mL	39.0	190	434	44.1	162	389
Tmax	hr	1.00	1.00	1.00	1.00	1.00	1.00
AUC(tf)	µg·hr/mL	5100	25200	61300	6570	19000	29800
tf	hr	336	336	336	336	336	336
R	--	1.03[b]	1.09	1.18	1.39[b]	0.943	0.633

NC = Not calculated as there were only two measurable time-points.
a: On Day 0, animals in Group T1 received 1.3 mg/kg.
b: The R value was calculated using dose normalized AUC(tf) values.

[7] From sponsor's submission – study SN 96264 final report

Reference ID: 3826750

Dosing Solution Analysis

Dosing formulations samples were analyzed for stability and SCH 55700 concentration (duplicate samples from the dosing formulations (including control) prepared on Study Days 0, 28, 56, 84, 112, 140, and 168). The analytical method used was not specified in the study report. Results indicate that the average SCH 55700 concentrations used in the study were within 15% nominal concentration with the exception of the dosing formulation used on day 0 for the low-dose group, which was 65% of nominal (0.261 mg/mL instead of 0.4 mg/mL). SCH 55700 was not present in samples of control article formulations.

Stability results indicate that dosing formulations were stable for up to 24 hours refrigerated. No stability test was conducted for dosing formulation samples at room temperature.

Dosing formulation analyses were also conducted using an immunoassay. No cross-validation report was provided for the two methods. Results were out of the 20% of nominal concentration in most cases using the immunoassay. The immunoassay method used for determination of SCH 55700 levels in the dosing formulations was not specified in the study report, and a separate report was not provided for analysis of dosing formulations. Therefore, it is unknown whether this was the same method used for analysis of serum concentrations, and whether the method was validated.

Study title: A Six-Month Intravenous Toxicity Study of SCH 55700 with Neurological Evaluations in Cynomolgus Monkeys

Study no.:	P6749
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/11/1996
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 55700 Batch No.: 36809-090 (0.4 mg/mL) ~95% pure 36809-091 (2 mg/mL) ~93% pure 36809-092 (10 mg/mL) ~90% pure

Key Study Findings

- One MD male showed a single ventricular extrasystole at week 28. Also, one HD female had two ventricular extrasystoles at week 8 and one HD male showed a single ventricular extrasystole at weeks 16 and 28, and three at week 22
- Heart and cecum vasculitis was observed in one HD female.

Reference ID: 3826750

- Injection site vasculitis was observed in 3 HD males. Although injection site vasculitis was also observed in one control male and one control female, it was observed at a higher incidence in treated animals.
- Kidney findings with increased incidence in HD animals include tubular basophilia (4 HD M), tubular casts (1 HD M), tubular vacuolation (1 HD F), and hypoplasia (1 HD F).
- Mild lymphoid hyperplasia was observed in mandibular lymph nodes in 1 HD F.
- Minimal thymus mineralization was observed in 1 HD M.
- Mild spleen congestion was observed 1 HD F.
- Minimal cortical hypertrophy of adrenal gland was observed in 1 HD F.
- Hemorrhage was observed in skeletal muscle in 1 HD M and in bone (femur) in 1 HD F.
- ADA test was conducted only in samples from two HD and one MD animals (samples obtained prior to dosing in weeks 13 and 25) and in a sample from one HD animal collected during week 41 (post-dose period). Three of the samples tested positive for ADAs. According to the report, presence of the drug interfered with analysis of other samples.
- No NOAEL was identified in the study based on the findings listed above and due to the lack of microscopic examination of the LD or MD groups.
- An information request was sent to the sponsor on September of 2011 to request examination of the aforementioned tissues in LD and MD animals to support a NOAEL or adequate justification for not considering these findings of concern.

Reference ID: 3826750

Methods

Doses:	Three dose levels at 0 (control), 1, 5, or 25 mg/kg/dose
Frequency of dosing:	Every 4 weeks for 6 months (7 doses)
Route of administration:	Intravenous
Dose volume:	2.5 mL/kg
Formulation/Vehicle:	SCH 55700 placebo solution (Batch No. 35923-135-00)
Species/Strain:	Cynomolgus monkey (*Macaca fascicularis*)
Number/Sex/Group:	12/sex for control and high-dose (HD) 7/sex for low-dose (LD) and mid-dose (MD)
Age:	approximately 1½ - 6½ years old
Weight:	Males: 1.9 – 3.9 kg Females: 1.9 – 4.9 kg
Satellite groups:	Two animals/sex in the control and HD groups were used for the treatment-free phase
Unique study design:	After 29 weeks of treatment, 10 animals/sex from control and HD groups and 7 animals/sex from LD and MD groups were euthanized and necropsied to assess toxicity. Prior to necropsy, 3 animals/sex from control and HD groups were perfused with heparin/glutaraldehyde so that selected tissues could be fixed and prepared for possible future examination. In addition, 3 animals/sex/group were perfused with a heparin/saline solution prior to necropsy to allow collection of frozen CNS tissues for immunohistochemical (IHC) evaluation of the presence of SCH 55700 in these tissues (only control and HD groups were evaluated). The other 4 animals/sex/group were euthanized and subjected to a routine necropsy. The remaining 2 animals/sex from control and HD groups were retained for the 3-month post-dose observation period.
Deviation from study protocol:	No deviations that could impact study data were identified.

Reference ID: 3826750

Table 5: Study P6749 Design

Group No.	No. of Monkeys		SCH 55700 Dose level (mg/kg)	Dose Volume (mL/kg)	Dose Solution (mg/mL)	Terminal Procedures (week 29)			Post-Dose Evaluation* (week 42)
	Males	Females				Non-Perfused	Glutaraid-Perfused	Saline-Perfused	
1	12	12	0 (placebo)	2.5	0	4/sex	3/sex	3/sex	2/sex
2	7	7	1	2.5	0.4	4/sex		3/sex	
3	7	7	5	2.5	2	4/sex		3/sex	
4	12	12	25	2.5	10	4/sex	3/sex	3/sex	2/sex

* These animals were not perfused prior to sacrifice

Observations and Results

Mortality

Animals were observed twice daily (morning and afternoon) throughout the study for mortality. All animals survived until scheduled necropsy.

Clinical Signs

Animals were observed twice daily (morning and afternoon) for changes in general appearance and behavior. Findings observed were either also observed in control animals or sporadic. No findings were observed that could be related to treatment.

Body Weights

Body weights were recorded at least within four days prior to dose administration and approximately weekly thereafter through week 29, and approximately every other week from week 29 to week 42 (post-dose evaluation period). No changes in body weights were observed in either males or females treated with SCH 55700 compared to controls.

Feed Consumption

Food consumption was assessed daily for each animal beginning at least five days prior to the first dose and continuing through the end of the post-dose evaluation period. No changes in food consumption were observed in SCH 55700-treated groups compared to controls.

Physical Examinations

All animals were examined by a staff veterinarian pre-dose and during weeks 8, 16, 22, and 28. Physical examinations were also conducted on all remaining animals near the end of the post-dose evaluation period (week 41). The examination included routine abdominal palpation and observations of the condition of integument, respiratory, and cardiovascular systems, as well as recorded measurements of body temperature, blood pressure, heart rate, and respiratory rate. Animals were not sedated for these procedures. No changes were observed that could be attributed to SCH 55700 treatment.

Reference ID: 3826750

Ophthalmoscopy

An ophthalmic direct examination was conducted on all animals within 4 weeks prior to the first day of dosing and during weeks 8, 16, 22, 28, and 41 (recovery period). Animals were lightly sedated with ketamine prior to this procedure. Results were incorporated into the study report with no signed ophthalmology report attached. No abnormalities related to SCH 55700 administration were observed.

ECG

Electrocardiograms (ECGs) were recorded for all animals within 4 weeks prior to the first day of dosing and during weeks 8, 16, 22, and 28. ECGs were also recorded from all remaining animals near the end of the post-dose evaluation period during week 41. Animals were not sedated for this procedure, and were temporarily restrained in primate chairs. A signed Electrocardiography report is attached to the final study report. Only summary of the data was provided. Individual ECG animal data was not provided for review.

One MD male animal showed a single ventricular extrasystole at week 28. In addition, one HD female had two ventricular extrasystoles at week 8 and one HD male showed a single ventricular extrasystole at weeks 16 and 28, and three at week 22. Although the study cardiologist considered these findings as background and not related to treatment, this was only observed at the two highest dose levels and was not observed in control animals. Therefore, this reviewer considers these findings as related to SCH 55700 treatment. No other abnormal findings were observed.

Neurological and Electroneurological Examinations

Neurological and electroneurological examinations were conducted in this study because results of a preliminary tissue crossreactivity study showed staining of CNS tissues (spinal cord, brain, and optic nerve) in humans and cynomolgus monkeys. Each animal was given a full neurological examination 4 weeks and 2 weeks prior to the first day of dosing and during weeks 8, 16, 22, and 28. Neurological examinations were also conducted twice on all remaining animals near the end of the post-dose evaluation period (week 42). Animals were not sedated for this procedure. Two examinations were performed during week 42, one by [redacted] (b) (4) (study site) veterinarian and a second by a veterinary neurologist consultant. A signed neurology report is attached to the study report. Separate electroencephalogram (EEG) and electroretinogram reports are also attached to the study report.

In addition, for all control and HD animals, the following evoked potentials were assessed within one week prior to the first dose and during week 28: electroencephalogram (EEG), electroretinogram (ERG), flash evoked potential (FEP or V[Visual]EP), brainstem auditory evoked response (BAER), and somatosensory evoked potential (SEP). No SCH 55700-related findings were noted in any of the neurological or electroneurological parameters evaluated.

Reference ID: 3826750

Hematology

Blood samples were collected from all animals prior to the first day of dosing and during dosing weeks 8, 16, 22, and 28. Samples were also collected from remaining animals near the end of the post-dose evaluation period (week 41). Animals were fasted overnight prior to blood collections. Samples were collected using EDTA as anticoagulant. A complete standard hematological battery was evaluated. No SCH 55700-related changes were observed.

Clinical Chemistry

Animals were fasted overnight for scheduled blood collections. Blood samples were collected from all animals prior to the first day of dosing and during dosing weeks 8, 16, 22, and 28. Samples were also collected from remaining animals near the end of the post-dose evaluation period (week 41). A complete standard clinical chemistry battery was evaluated. No SCH 55700-related changes were observed.

Urinalysis

Urine was collected on ice over a 24-hour period using specially-designed stainless steel cage pans. Urine was collected prior to the first dose and during weeks 8, 16, 22, and 28, as well as from remaining animals during week 41. A complete standard urinalysis battery was evaluated. No noticeable changes were observed in SCH 55700-treated groups compared to controls.

Gross Pathology

Necropsy included complete macroscopic examination. A summary of findings is provided in Table 6 below. In general, fibrous adhesions in spleen and lungs were observed with higher incidence in SCH 55700-treated animals. However, these findings appear not to be dose-dependent and were not observed after the recovery period evaluation. No associated histopathology findings were observed.

Table 6: Summary of Gross Pathology Observations - Monkey

	Males				Females			
SCH 55700 (mg/kg/dose)	**0**	**1**	**5**	**25**	**0**	**1**	**5**	**25**
Number of animals examined	**6**	**5**	**6**	**4**	**4**	**5**	**6**	**7**
OBSERVATIONS								
Lungs								
Fibrous adhesions to thoracic wall								
Mild	0	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	1	0
Marked	0	1	0	0	0	0	0	0
Fibrous adhesions to diaphragm								
Minimal	0	0	0	0	0	1	0	0
Moderate	0	0	1	0	0	0	1	0
Marked	0	1	0	0	0	0	0	0
Spleen								

Reference ID: 3826750

Fibrous adhesions to peritoneal wall								
Minimal	0	0	0	0	0	0	1	1
Mild	0	2	2	0	0	0	0	0
Moderate	1	0	0	0	0	0	0	0
Marked	0	0	0	0	0	0	1	0

Organ Weights

At necropsy, the following organs from all nonperfused animals were weighed: adrenal glands, brain, epididymides, heart, kidneys, liver, lungs (with bronchi), ovaries, pituitary gland, prostate gland, salivary glands (mandibular), spleen, testes, thymus, thyroid/parathyroid glands, uterus (plus cervix). Organ-to-body and organ-to-brain weight ratios were calculated.

Testes (absolute) weights were decreased in MD but not HD males compared to controls (refer to table 7 below). Testes weights relative to body weights and to brain weights were also decreased in these animals. Prostate gland weights (absolute) were slightly decreased in all treated animals compared to controls. Prostate gland weights relative to body weights and to brain weights were also decreased. None of these findings were dose-dependent. Although testes weights were not decreased in HD males during the dosing period, they were decreased after the recovery period compared to controls. Prostate gland weights were still decreased after the post-dose recovery period (week 42). In the absence of associated histopathology findings these are not considered of concern or related to SCH 55700. These changes in reproductive organ weights could be due to the wide age range of study animals (1 ½ to 6 ½ years old).

Table 7: Summary of Changes in Organ Weights - Monkey

	Males			Females		
SCH 55700 (mg/kg)	**1**	**5**	**25**	**1**	**5**	**25**
Testes						
absolute	NC	-85%	NC	-	-	-
relative to BW	NC	-77%	NC	-	-	-
relative to brain	NC	-86%	NC	-	-	-
Recovery - Testes						
absolute	-	-	-72%	-	-	-
relative to BW	-	-	-62%	-	-	-
relative to brain	-	-	-65%	-	-	-
Prostate gland						
absolute	-61%	-65%	-48%	-	-	-
relative to BW	-47%	-52%	-36%	-	-	-
relative to brain	-59%	-65%	-47%	-	-	-
Recovery - Prostate						
absolute	-	-	-66%	-	-	-
relative to BW	-	-	-61%	-	-	-
relative to brain	-	-	-64%	-	-	-

NC = no treatment-related change
NC = no treatment-related change
(-) = not evaluated

Reference ID: 3826750

Histopathology

At necropsy, a battery of tissues was collected and sent to the sponsor for microscopic examination by a sponsor-appointed pathologist.

Adequate Battery

An adequate battery of tissues from all animals in the control and treatment groups was collected. However, only tissues from the control and HD groups, as well as all gross lesions from animals in LD and MD groups were examined.

Peer Review

A peer review of the slides of nervous system tissue (optic nerve, brain, spinal cord, and sciatic nerve) was performed. In addition, a complete peer review was conducted by the sponsor.

Histological Findings

Table 8: Summary of Histological Observations (Incidence and Severity) - Monkey

	Males				Females			
SCH 55700 (mg/kg/dose)	**0**	**1**	**5**	**25**	**0**	**1**	**5**	**25**
Number of animals examined	**4**	*	*	**4**	**4**	*	*	**4**
OBSERVATIONS								
Mandibular Lymph Nodes								
Hyperplasia, Lymphoid, mild	0	-	-	0	0	-	-	1
Thymus								
Mineralization, minimal	0	-	-	1	0	-	-	0
Heart								
Vasculitis, moderate	0	-	-	0	0	-	-	1
Colon								
Colitis, mild	0	-	-	0	0	-	-	1
Cecum								
Typhlitis, mild	0	-	-	0	0	-	-	1
Vasculitis, mild	0	-	-	0	0	-	-	1
Spleen								
Congestion, mild	0	-	-	0	0	-	-	1
Kidneys								
Tubular basophilia, minimal	1	-	-	4	2	-	-	1
Tubular casts, minimal	0	-	-	1	0	-	-	0
Tubular vac/cortical, minimal	0	-	-	0	0	-	-	1
Hypoplasia,mild	0	-	-	0	0	-	-	1
Adrenal glands								
Cortical hypertrophy, minimal	0	-	-	0	0	-	-	1
Skeletal Muscle								
Atrophy, scattered, minimal	0	-	-	0	0	-	-	1
Hemorrhage, mild	0	-	-	1	0	-	-	0
Bone, femur								
Hemorrhage, periost., minimal	0	-	-	0	0	-	-	1

Reference ID: 3826750

Injection Site								
Vasculitis, minimal - mild	1	-	-	3	1	-	-	0
Fibrosis, minimal	0	-	-	0	0	-	-	1

* See parenthesis under specific tissue for total number of animals examined
(-) Not evaluated

Histopathology (and gross) findings of colitis and typhlitis were observed in one female (animal no. F4811F) in the HD group and correlate with a possible bacterial infection. Therefore, these are considered unrelated to treatment. This animal also presented vasculitis in the heart and cecum. Although the vasculitis observed could be due to ADA formation, it is not possible to confirm this because of the limitation of the ADA assay (see below under "Anti-SCH 55700 antibody analysis"). In addition, injection site vasculitis was observed in 3 HD males and injection site fibrosis was observed in 1 HD female. Although injection site vasculitis was also observed in one control male and one control female, it was observed at a higher incidence in treated animals. Injection site findings could be result of the intravenous route of administration. No injection site findings were observed after the recovery period.

Kidney findings with increased incidence in HD animals include tubular basophilia (4 HD males), tubular casts (1 HD male), tubular vacuolation (1 HD female), and hypoplasia (1 HD female). Because kidneys were identified as a possible target organ of toxicity in mice, these findings are considered possibly related to treatment. These findings in kidneys were not observed after the recovery period, suggesting reversibility.

Other findings that are found only in HD animals (and therefore considered possibly related to treatment) are mild lymphoid hyperplasia of mandibular lymph nodes observed in 1 HD female, minimal thymus mineralization observed in 1 HD male, mild spleen congestion observed 1 HD female, minimal cortical hypertrophy of adrenal gland observed in 1 HD female, and hemorrhage observed in skeletal muscle in 1 HD male and in bone (femur) in 1 HD female. Tissues from LD and MD groups were not examined. None of these findings were observed after the recovery period.

One HD female presented scattered unilateral myofiber atrophy in the skeletal muscle of one pelvic limb. However, this was also observed in one control recovery animal. Therefore is not considered related to SCH 55700 treatment.

A NOAEL could not be identified for this study due to lack of histopathological examination of the LD and MD tissues. An information request was sent to the sponsor on September of 2011 to request examination of the aforementioned LD and MD tissues or justification for considering these findings as incidental and unrelated to SCH 55700. No response has been received from the sponsor as of the date of this review.

Special Evaluations

Immunopathology

At the end of the dosing period (on week 29), 3 animals/sex/group were perfused with a heparin/saline solution prior to necropsy. Frozen sections of central nervous system tissues (cerebrum –frontal cortex, internal capsule, hippocampus, caudal cortex- , mesencephalon/pons, cerebellum, medulla oblongata, and spinal cord) were collected from each animal. In addition, frozen section of cerebrum, cerebellum, and spinal cord were collected from 2 animals/sex in the control and HD groups from the post-dose

Reference ID: 3826750

evaluation (recovery) period. All tissues were sent to Pathology Associates International (PAI) for immunohistochemical determination of the presence of SCH 55700. Only tissues from control and HD groups were examined. No immunohistochemical evidence of SCH 55700-related binding was detected in the CNS tissues examined.

Anti-SCH 55700 antibody analysis

Blood samples were collected from each animal prior to and approximately 5 minutes after the first, fourth (week 13), and last (week 25) doses. Blood samples were also collected approximately monthly from remaining animals during the post-dose evaluation period (during weeks 29, 33, 37, and 41). Serum samples from SCH 55700-treated animals that did not contain any quantifiable SCH 55700 by ELISA were analyzed for the presence of anti-SCH 55700 antibodies.

Specifically, samples from three (two HD and one MD) animals obtained prior to dosing in weeks 13 and 25 and a sample from one HD animal collected during week 41 (post-dose period) were analyzed. Pre-study samples (obtained on Day 1 prior to the first dose) from these animals were also analyzed to provide a baseline reference. The remainder of samples was not analyzed for antibodies because the SCH 55700 present in the samples would interfere with the biosensor assay used. A signed antibody and TK report is attached to the study report.

Anti-SCH 55700 antibodies were detected using a biosensor assay that utilizes the BIAcore 2000. Anti-SCH 55700 antibodies were detected in three of the four animals tested (MD animal F5258F, and HD animals F52007F and F5276F). Although these results suggest that animals developed anti-SCH 55700 antibodies, the results are insufficient to make a determination of gender-specific or dose-specific differences.

Toxicokinetics

A toxicokinetic (TK) analysis was conducted for this study. A signed TK report is attached to the final study report. Blood samples were collected from each animal prior to and approximately 5 minutes after the first, fourth (week 13), and last (week 25) doses. Blood samples were also collected approximately monthly from remaining animals during the post-dose evaluation period (during weeks 29, 33, 37, and 41). Concentrations of SCH 55700 in serum were measured using a sandwich ELISA with a LLOQ of 4.0 ng/mL. In addition, individual samples were also analyzed using a biological assay with a LLOQ of 750 SPU/mL. However, according to the Antibody and TK report, sample stability cannot be guaranteed since samples were received at the test site beyond the time in which sample stability data were available and no further stability tests were conducted.

In general, as shown in table 9 below, the mean SCH 55700 concentration (C_{max}) increased in a dose-dependent manner. However, results suggest drug clearance prior to the next dose (not shown in table 9) and by the end of the dosing period on week 25 compared to week 1. This could be due to the presence of anti-drug antibodies. Although the sponsor reports no significant sex differences in drug concentration, MD and HD males showed slightly higher drug levels compared to females at all weeks. No

Reference ID: 3826750

drug was detected in samples from control animals. Systemic exposure (AUC) data were not provided for this study.

Table 9: Mean Concentration of SCH 55700 in Serum (ng/mL) Determined by ELISA[a]

Group	Dose (mg/kg)	Week 1 (5 minutes post dose)		Week 13 (5 minutes post dose)		Week 25 (5 minutes post dose)	
		Males	Females	Males	Females	Males	Females
2	1	13843	19650	22636	24881	23157	22928
3	5	123393	114588	150000	116390	118500	109551
4	25	698667	615750	780375	674625	681708	569727

[a] Group means for animals with quantifiable SCH 55700 (samples with no SCH 55700 were excluded)

Dosing Solution Analysis

At least one partially used and one unopened vial of the test article were returned to the sponsor after the third dose (week 9), fifth dose (week 17), and last dose (week 25) for analysis of stability under the actual conditions of storage and use in the study. Concentration analysis was not conducted as test and control articles were preformulated by the sponsor and used as received for dose administration. Certificates of analysis were included in the study report. Results show that the drug is stable under the conditions of use (by analysis of open vials compared to unopened vials) and that no SCH 55700 was detected in samples of control article formulation.

11 Integrated Summary and Safety Evaluation

Reslizumab is a humanized anti-IL-5 monoclonal antibody being developed by Cephalon for the treatment of poorly controlled asthma with eosinophilic airway inflammation. Phase 1 and Phase 2 clinical studies have been completed with Reslizumab and five Phase 3 clinical studies (protocols 3081, 3082, 3083, 3085, and 3084) were recently proposed by the sponsor. The proposed dose and dosing regimen is 3.0 mg/kg IV Reslizumab once every four weeks. Data from the completed Phase 2 studies show single doses of 1.0 mg/kg and 3.0 mg/kg (single IV infusion) result in C_{max} of 25.7 and 95.7 µg/mL, respectively, and AUCs of 13714 and 42384 µg·hr/mL, respectively.

The sponsor submitted two long-term (6 months) nonclinical studies in CD-1 mice and cynomolgus monkeys in support of the long-term clinical studies. A preliminary review was completed by Dr.Feleke Eshete on February of 2008. However, a detailed evaluation was not done and is included in this review.

In study SN96264, male and female CD-1 mice (10 mice/sex/group) were treated with 0 (control), 1, 5, or 25 mg/kg SCH 55700 (Reslizumab) intravenously once every 28 days for 6 months (7 doses total). At the end of the dosing period, animals were euthanized and necropsies were performed. Assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology observations. In addition, blood samples were collected for toxicokinetic and antibody analysis. The study did not include a recovery period.

Reference ID: 3826750

No significant SCH 55700-related effects were observed on clinical signs, body weights, food consumption, and ophthalmic examinations. Six animals died during the study, including two animals in the LD group (from an undetermined reason), three animals in the MD group (two were undetermined and one sacrificed due to a bronchiolo-alveolar carcinoma), and one animal in the HD group (animal 304, found dead – urinary tract obstruction). Histopathological findings of concern include renal pelvis and ureters dilatation in three HD male animals. These findings correlate with elevated levels of blood urea-nitrogen (BUN) in MD and HD animals and suggest effects in the urinary tract in treated animals. Animal 304 (HD male) was found dead on the day of necropsy and histopathology findings included moderate renal pelvis and ureters dilatation. In addition, this animal presented mild congestion in the urinary bladder. Although this death was not considered related to treatment, similar but less severe findings were observed in other HD males and suggest that this could have been related to SCH 55700 treatment. One MD female (animal 252) was sacrificed early due to a bronchiolo-alveolar carcinoma. The sponsor did not consider this finding as related to treatment. This reviewer agrees with the sponsor's conclusion as literature suggest that this type of tumor is a common background lesion in mice. Also, no pre-neoplastic lesions were observed. Further, a bronchiolo-alveolar adenoma was observed in one control animal (also in one HD). The role of eosinophils and IL-5 in tumorigenicity is unclear. At the request of the Division, the sponsor is conducting a carcinogenicity study to address this safety concern.

The increase incidence of infections in the urinary tract and the finding of a carcinoma in one treated animal suggest that the drug has the potential to induce immunosuppression. However, a review of available literature found that drugs that target eosinophils are not considered immunosuppressants. The urinary tract findings could also be due to complex formation in the kidneys. However, data from the ADA assay are not useful to identify whether animals affected developed ADAs. Individual animal toxicokinetic data were not provided but combined toxicokinetic data suggest that the drug has been cleared over time, which could be associated with ADA formation.

In study P6749, Cynomolgus monkeys (4/sex/group) were treated with 0 (control), 1, 5, or 25 mg/kg SCH 55700 intravenously once every 4 weeks for 6 months (7 doses). At the end of the dosing period, animals were euthanized and necropsies were performed. Two animals in the control and HD groups underwent a 13 week treatment-free (recovery) phase. Assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, ophthalmic and ECG examinations, and clinical and anatomic pathology observations. In addition, blood samples were collected for toxicokinetic and antibody analysis.

No significant SCH 55700-related effects were observed on mortality, clinical signs, body weights, food consumption, ophthalmic examinations, and clinical pathology. ECG examinations found that one MD male showed a single ventricular extrasystole at week 28, one HD female had two ventricular extrasystoles at week 8 and one HD male

Reference ID: 3826750

showed a single ventricular extrasystole at weeks 16 and 28, and three at week 22. Histopathology findings of concern include heart vasculitis observed in HD female F4811F. Because individual animal ECG data were not provided, it is not possible to determine whether the extrasystoles observed in one HD female are associated with the vasculitis observed in the heart of this HD female. Additional findings in this animal include vasculitis and typhlitis in cecum and colitis. These findings, according to the study pathologist, correlate with a bacterial infection; therefore were not considered related to treatment. Injection site vasculitis was observed in 3 HD males. Although injection site vasculitis was also observed in one control male and one control female, it was observed at a higher incidence in treated animals.

Kidney findings with increased incidence in HD animals include tubular basophilia (4 HD M), tubular casts (1 HD M), tubular vacuolation (1 HD F), and hypoplasia (1 HD F). Because kidneys are a possible target organ in mice, these findings are considered possibly related to treatment. Because the ADA assay was limited by the presence of drug, it was not possible to determine whether the aforementioned findings were due to presence of ADAs. A complete toxicokinetic analysis was not conducted. However, available data suggest that the drug is being cleared prior to the next dose.

Additional findings in monkeys that are considered possibly related to treatment because were only observed in HD animals include lymphoid hyperplasia in mandibular lymph nodes in 1 HD female, thymus mineralization in 1 HD male, spleen congestion in 1 HD female, cortical hypertrophy of adrenal gland in 1 HD female, and skeletal muscle (1 HD male) and bone (1 HD female) hemorrhage. These findings were not observed after the recovery period, suggesting reversibility. None of these findings (or similar findings) were observed in mice.

The sponsor identified the NOAEL in the mouse and monkey studies as the HD (25 mg/kg/dose), because the sponsor considered all findings observed as incidental and not of concern. However, based on the aforementioned findings in mouse, the NOAEL for the renal findings has been identified as the mid-dose (10 mg/kg) with an associated exposure ($AUC_{0\text{-}336\ hr}$) of 22100 µg·hr/mL. A NOAEL could not be identified for the mouse study due to the unexplained deaths observed at the LD and MD.

In the monkey, a NOAEL could not be determined by this reviewer. Examination of LD and MD tissues for the findings listed above is necessary or the sponsor should provide support from historical laboratory histology findings or from literature to support a NOAEL for the monkey study.

Reference ID: 3826750

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

/s/

CAROL M RIVERA-LOPEZ
05/04/2012

MOLLY E SHEA
05/06/2012
I concur.

Appendix 3

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	IND 101,399
Supporting document/s:	SD65 (eCTD 0034) , SD76 (eCTD 0045), SD97 (eCTD 0066)
Sponsor's letter date:	1/4/2012, 5/17/2012, 4/29/2013
CDER stamp date:	1/4/2012, 5/17/2012, 4/29/2013
Product:	Reslizumab
Indication:	Poorly controlled asthma with eosinophilic airway inflammation
Sponsor:	Teva Branded Pharmaceutical Products R&D, Inc.[1]
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Rivera-Lopez, Ph.D.
Supervisor/Team Leader:	Marcie Wood, Ph.D.
Division Director:	Badrul A. Chowdhury, MD, PhD
Project Manager:	Colette C. Jackson

Template Version: September 1, 2010

[1] New sponsor as of March of 2012. Previously Cephalon, Inc.

Reference ID: 3865329

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 4

1 EXECUTIVE SUMMARY 5

1.1 INTRODUCTION 5
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 5
1.3 RECOMMENDATIONS 5

2 DRUG INFORMATION 6

2.1 DRUG 6
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 6
2.3 DRUG FORMULATION 6
2.4 COMMENTS ON NOVEL EXCIPIENTS 7
2.5 COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN 7
2.6 PROPOSED CLINICAL PROTOCOLS 7
2.7 PREVIOUS CLINICAL EXPERIENCE 8
2.8 REGULATORY BACKGROUND (NONCLINICAL) 9

3 STUDIES SUBMITTED 10

3.1 STUDIES REVIEWED 10
3.3 PREVIOUS REVIEWS REFERENCED 10

6 GENERAL TOXICOLOGY 10

6.2 REPEAT-DOSE TOXICITY 10

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 18

Reference ID: 3865520

Table of Tables

Table 1: Drug Product Composition – Solution for Intravenous Infusion. 7
Table 2: (b) (4) 7
Table 3: Previous Clinical Experience in Asthma Patients. 8
(b) (4)

Reference ID: 3865520

List of Abbreviations

ADA	Anti-drug antibody
AUC	Area under the curve
CDR	Complementarity determining regions
C_{max}	Maximal drug concentration in plasma
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
GLP	Good Laboratory Practice
hr	Hour
Ig	Immunoglobulin
IL	Interleukin
IV	Intravenous
kg	Kilogram
LLOQ	Lower limit of quantitation
mg	Milligram
mL	Milliliter
NOAEL	No observed adverse effect level
QA	Quality assurance
SC	Subcutaneous
TK	Toxicokinetics
T_{max}	Time to maximal drug concentration in plasma
µg	Microgram

Reference ID: 3865529

1 Executive Summary

1.1 Introduction

This review evaluates nonclinical pharmacology and toxicology data to support safety of Reslizumab. Reslizumab is a humanized anti-human interleukin-5 (IL-5) monoclonal IgG4 antibody containing the complementary determining regions (CDRs) of the original rat anti-human antibody 39D10 grafted onto human frameworks. The proposed indication under this IND is treatment of moderate to severe eosinophilic asthma in adolescents and adults (*i.e.*, patients 12 years of age and older) whose symptoms are not well controlled with inhaled corticosteroids. (b) (4)

The drug product under development is a single use, unpreserved, sterile solution for infusion (IV) (b) (4) and is presented as 100 mg reslizumab drug substance per vial. (b) (4)

There is extensive clinical experience with reslizumab in patients with asthma (b) (4) A number of clinical studies have been completed or are ongoing using the IV route of administration. (b) (4)

1.2 Brief Discussion of Nonclinical Findings

(b) (4) NOAEL was identified at the 25 mg/kg dose level, which is associated with a systemic exposure ($AUC_{0\text{-}672hr}$) of 96,400 µg·hr/mL on study day 141.

1.3 Recommendations

1.3.1 Clinical Studies Safe to Proceed: Yes

(b) (4)

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

Concerns for findings noted at the high dose of 25 mg/kg IV reslizumab in 6-month monkey toxicity Study No. P6749 have been adequately addressed. We agree that the

Reference ID: 3865529

data from Study No. P6749 [redacted] (b) (4) support a [redacted] (b) (4) NOAEL of 25 mg/kg reslizumab in monkeys.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): Not applicable

Generic Name: Reslizumab

Code Name: SCH 55700, CTx55700, CEP-38072

Chemical Name: Reslizumab

Molecular Weight: 147 kDa

Biochemical Description: Humanized anti-human IL-5 monoclonal antibody of the IgG4 kappa isotype, which contains the CDRs of the rat anti-human antibody (39D10) grafted onto human frameworks.

Pharmacologic Class: Monoclonal antibody against IL-5

2.2 Relevant INDs, NDAs, BLAs and DMFs

[redacted] (b) (4)

2.3 Drug Formulation

[redacted] (b) (4)

Reference ID: 3865529

Table 1: Drug Product Composition – Solution for Intravenous Infusion.

Component	per mL	Function
CEP-38072 drug substance	10 mg	Active
Sodium Acetate Trihydrate, USP[a] or Ph.Eur.[b]	2.45 mg	Excipient
Acetic Acid Glacial, USP or Ph.Eur.	0.12 mg	Excipient
Sucrose, NF[c] or Ph.Eur.	70 mg	Excipient
[redacted] (b) (4)		

[a] USP = United States Pharmacopeia
[b] Ph.Eur. = European Pharmacopeia
[c] NF = National Formulary

[redacted] (b) (4)

[redacted] (b) (4)

2.4 Comments on Novel Excipients

Not applicable.

2.5 Comments on Impurities/Degradants of Concern

Not applicable.

2.6 Proposed Clinical Protocols

[redacted] (b) (4)

[redacted] (b) (4)

Reference ID: 3865529

(b) (4)

[redacted]

2.7 Previous Clinical Experience

There is extensive clinical exposure of reslizumab. Table 3 below includes a summary of clinical studies that have been conducted or are ongoing under this IND. For specific details, refer to Dr. Jennifer R. Pippins clinical review dated June 18th, 2013.

Table 3: Previous Clinical Experience in Asthma Patients.

Study Number	Study Design	Results
I96-350 (completed)	Phase 1, SAD study in severe asthma patients ages 20-65 (n=32) Reslizumab doses: 0.03 and 0.1 mg/kg bolus and 0.3 and 1 mg/kg infusion	- Trend in lung function improvement (FEV_1) at 0.3 and 1 mg/kg - Statistically significant decrease in mean blood eosinophils
P00290 (completed)	Phase 2, multiple-dose study in moderate-severe asthma patients ages 19-77 (n=215) Reslizumab doses: 0.3 and 1 mg/kg infusion on day 1 and day 12 (2 doses)	- No improvement in lung function - Statistically significant decrease in mean blood eosinophils
Res-5-0010 (completed)	Phase 2, multiple-dose study in poorly controlled, eosinophilic inflammation patients with asthma ages 19-69 (n=106) Reslizumab dose: 3 mg/kg infusion every 4 weeks (4 doses)	- Trend in reduction of ACQ - Significant improvement in lung function (FEV_1) - Trend in reduction of exacerbations
C38072/3801 (ongoing)	Phase 3, efficacy and safety study in patients with persistent eosinophilic asthma (inadequately controlled by ICS) ages 12-71 (n=227) Reslizumab doses: 0.3 and 3 mg/kg infusion every 4 weeks x 16 weeks	Results pending; primary endpoint is FEV_1
C38072/3802 (ongoing)	Phase 3, efficacy and safety study in patients with persistent eosinophilic asthma (inadequately controlled by ICS) ages 12-76 (n=438) Reslizumab dose: 3 mg/kg infusion every 4 weeks x 52 weeks	Results pending; primary endpoints are change in FEV_1 and frequency of exacerbations
C38072/3803 (ongoing)	Phase 3, efficacy and safety study in patients with persistent eosinophilic	Results pending; primary endpoint is FEV_1

Reference ID: 3865520

	asthma (inadequately controlled by ICS) ages 12-74 (n=323) Reslizumab dose: 3 mg/kg infusion every 4 weeks x 12 months	
C38072/3804 (ongoing)	Phase 3, efficacy and safety study in patients with moderate to severe asthma ages 18-65 (n=201) Reslizumab dose: 3 mg/kg infusion every 4 weeks x 16 weeks	Results pending; primary endpoint is FEV_1
C38072/3805 (ongoing)	Phase 3, open-label extension long-term safety and efficacy study in patients with moderate to severe asthma ages 12-72 (n=171) Reslizumab dose: 3 mg/kg infusion every 4 weeks x 2 years	Results pending; primary endpoints are adverse events, clinical laboratory tests, physical exams, vital signs, and concomitant medications (safety)

In addition, a number of clinical trials have been conducted in healthy volunteers (b) (4)

2.8 Regulatory Background (Nonclinical)

Reslizumab was originally developed under IND 9,227 (Schering Corporation). Two clinical studies were conducted under this IND, which was subsequently withdrawn in 2003. IND 101,399 was submitted on 1/16/2008 by Ception. A nonclinical safety review was completed on 2/19/2008 by Dr. Feleke Eshete, who considered the proposed clinical studies safe to proceed. A number of clinical studies have been conducted under IND 101,399 and are summarized above under “Previous Clinical Experience”. In addition, a number of interactions have been held with the sponsor to discuss nonclinical support for development of reslizumab under IND 101,399; specifically, assessment of the carcinogenic potential of reslizumab. The sponsor submitted a white paper on 11/12/2010 (b) (4) A discussion with the Executive Carcinogenicity Assessment Committee (ECAC) was held on 12/7/2010 and it was decided that, because the mouse is a relevant species, a 2-year mouse carcinogenicity study should be conducted (refer to PharmTox memo dated 2/7/2011). In the white paper the sponsor also proposed that, if a study was needed, then they would propose a 6-month carcinogenicity study using transgenic mice (*e.g.*, TgRasH2 mouse model). Although this proposal was not accepted originally, it was later accepted by the ECAC. The sponsor submitted the special protocol assessment request to evaluate the 6-month carcinogenicity study protocol on 5/31/2012. A meeting was held on 7/10/2012 with the ECAC to discuss this protocol and comments were sent to the sponsor on 7/11/2012. A PharmTox review of this SPA was completed on 7/11/2012.

Evaluation of the chronic toxicology studies in mouse and monkeys was completed on 5/6/2012 (PharmTox review in DARRTS). Because additional information was needed to identify a NOAEL in both studies, two separate information requests were sent to the sponsor. On 7/19/2011, an information request was sent regarding the mouse study and on 9/9/2011 an information request was sent regarding the monkey study. Responses were received by the sponsor on 1/4/2012 (mouse study) and 5/17/2012 (monkey study).

Reference ID: 3865520

3 Studies Submitted

3.1 Studies Reviewed

(b) (4)

3.3 Previous Reviews Referenced

PharmTox review dated 5/6/2012 (review of mouse and monkey chronic toxicology studies).

6 General Toxicology

(b) (4)

Reference ID: 3865529

7 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

11 Integrated Summary and Safety Evaluation

Reslizumab is a humanized monoclonal antibody that targets IL-5. It is being developed by Teva under this IND for the treatment of poorly controlled asthma with eosinophilic airway inflammation. A number of clinical studies have been conducted (or are ongoing) using IV reslizumab. (b) (4) Currently available clinical PK data using the IV route of administration show systemic exposure ($AUC_{0\text{-}12weeks}$) of 14,049 µg·hr/mL at 1 mg/kg reslizumab.

To support the long-term clinical studies, the sponsor submitted 6-month chronic toxicity studies in mouse and monkey. In these studies, reslizumab doses of 0 (vehicle control) 1, 5, and 25 mg/kg IV were used once every 28 days for six months. A detailed review of these studies was completed on May 6th, 2012. Because of lack of examination of tissues from animals treated at the low- and mid-doses, a NOAEL was not identified for the studies.

A communication was sent to the sponsor on July 19th, 2011 to request additional information for the mouse study. Specifically, findings of renal dilatation and urinary tract obstruction were observed in animals at the highest dose of 25 mg/kg. Because tissues from low- and mid-dose animals were not examined, additional information from the sponsor was necessary to identify a NOAEL in the mouse. The sponsor's response was received on January 4, 2012 and included re-examination of the kidney tissues from all study animals and a toxicological evaluation (an expert report) of the renal findings. In summary, because a clear dose-response was not observed, the expert report concludes that findings of renal pelvis dilatation are incidental and not related to treatment. This is supported by the fact that it was also observed in one control animal. In addition, literature search found that dilatation is a common incidental finding in CD-1 mice[2]. Taking all this together, this reviewer agrees that these renal findings in the mouse are not related to treatment. Therefore, the NOAEL for the kidney findings in the mouse is the high-dose of 25 mg/kg reslizumab.

A separate communication was sent to the sponsor on September 9th, 2011 to request additional information for the monkey study. Specifically, a number of findings were observed in high-dose animals in multiple tissues (refer to the histopathology table in PharmTox review dated May 6th, 2012). Because tissues of low- and mid-dose animals

[2] Chandra M and Frith CH. *Spontaneous renal lesions in CD-1 and B6C3F1 mice.* (1994) Experimental Toxicology Pathology, Vol. 46, No. 3; pages 189-198.

Reference ID: 3865529

were not examined, additional information was requested from the sponsor to allow identification of a NOAEL in the monkey. The sponsor's response was submitted on May 17th, 2012 and included historical control data from the conducting laboratory to support that most findings were considered incidental and not related to treatment. This reviewer agrees with their conclusion. However, the findings of tubular basophilia and hypoplasia in kidneys could not be explained by the data from the historical controls. In the response, the sponsor proposed to examine kidney tissue (b) (4)

(b) (4)

(b) (4) Because renal findings of tubular basophilia and hypoplasia remained outstanding from the May 17th, 2012 IR response; the expert report concluded that (b) (4), it is unlikely that the findings observed in the previous study are considered related to treatment.

A closer look to the histopathology data (b) (4) supports the sponsor's conclusion that this finding is not drug-related. Also, (b) (4) this supports the sponsor's conclusion that this finding is not related to treatment. Then, based on a weigh-of-evidence approach,

Reference ID: 3865529

this reviewer agrees that the findings of tubular basophilia and hypoplasia in kidneys are incidental and not related to reslizumab treatment.

(b) (4)

(b) (4)

In conclusion, due to the lack of toxicity findings, the NOAEL was identified at the 25 mg/kg dose level. This dose is associated with an estimated systemic exposure ($AUC_{0-672hr}$) of 96,400 µg·hr/mL on study day 141.

(b) (4)

Reference ID: 3865529

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

/s/

CAROL M RIVERA-LOPEZ
10/07/2013

MARCIE L WOOD
10/07/2013
I concur

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

/s/

CAROL M GALVIS
12/16/2015

MARCIE L WOOD
12/16/2015

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	BLA 761033
Supporting document/s:	SD 1
Applicant's letter date:	3/29/2015
CDER stamp date:	3/30/2015
Product:	Cinqair (Reslizumab)
Indication:	To reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Galvis, PhD
Supervisor/Team Leader:	Marcie Wood, PhD
Division Director:	Badrul A. Chowdhury, MD, PhD
Project Manager:	Colette Jackson

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA 761033 are owned by Teva Branded Pharmaceutical Products or are data for which Teva Branded Pharmaceutical Products has obtained a written right of reference. Any information or data necessary for approval of BLA 761033 that Teva Branded Pharmaceutical Products does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA

Reference ID: 3785707

finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of BLA 761033.

Reference ID: 3785707

TABLE OF CONTENTS

LIST OF ABBREVIATIONS 6

1 EXECUTIVE SUMMARY 7

1.1 INTRODUCTION 7
1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS 7

2 DRUG INFORMATION 8

2.1 DRUG 8
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS 8
2.7 REGULATORY BACKGROUND 8

3 STUDIES SUBMITTED 9

3.1 STUDIES REVIEWED* 9
3.3 PREVIOUS REVIEWS REFERENCED 9

7 GENETIC TOXICOLOGY 9

8 CARCINOGENICITY 10

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 20

12 APPENDIX/ATTACHMENTS 21

Reference ID: 3785707

Table of Tables

Table 1: Study DS-2012-005 Design. 13
Table 2: Summary of Early Decedents, Number of Animals at Study Termination, and % Survival. 15
Table 3: Day and Cause of Death for Unscheduled Necropsies in Groups 1-4 (Vehicle-treated and Reslizumab-treated). 15
Table 4: Summary of Drug-related Changes in Hematology Parameters Relative to Controls. 17
Table 5: Histological Observations – Neoplastic (All Animals). 18

Reference ID: 3785707

Table of Figures

Figure 1: Kaplan-Meier Survival Function – Males. 14
Figure 2: Kaplan-Meier Survival Function – Females. 14
Figure 3: Mean Body Weights – Males. 16
Figure 4: Mean Body Weights – Females. 17

Reference ID: 3785707

List of Abbreviations

ADA	Anti-drug antibodies
AUC	Area under the curve
B	Benign
BAL	Bronchoalveolar lavage
BLA	Biologics License Application
ECAC	Executive Carcinogenicity Assessment Committee (FDA)
EDR	Electronic Document Room
EDTA	Ethylenediamine tetraacetic acid
F	Female
g	Grams
GLP	Good Laboratory Practice
HD	High-dose
hr	Hour
Ig	Immunoglobulin
IL	Interleukin
IND	Investigational New Drug
IV	Intravenous
kg	Kilogram
LD	Low-dose
M	Male or malignant (neoplastic findings table)
MD	Mid-dose
MFD	Maximum feasible dose
mg	Milligram
mL or ml	Milliliter
MNU	N-methyl-N-nitrosourea
N (or no.)	Number
OVA	Ovalbumin
QA	Quality assurance
SPA	Special protocol assessment
TK	Toxicokinetics

Reference ID: 3785707

1 Executive Summary

1.1 Introduction

This review evaluates the carcinogenic potential of reslizumab. Reslizumab is a monoclonal antibody against human IL-5 and was developed by Teva Branded Pharmaceutical Products for the treatment of eosinophilic asthma.

1.2 Brief Discussion of Nonclinical Findings

Reslizumab was negative in the in vitro bacterial mutagenicity (Ames) and in vitro chromosomal aberration assays.

Teva conducted a 26-week carcinogenicity study in transgenic mice to assess the carcinogenic potential of reslizumab. The study protocol was discussed with the Executive Carcinogenicity Assessment Committee (ECAC) in a meeting held on July 10, 2012, and was found acceptable. Reslizumab did not have a toxicological or pharmacological effect in a 4-week toxicity study in 001178-W (wild type) mice provided in support of the special protocol assessment (SPA). Therefore, the ECAC requested additional data such as inhibition of antigen or IL-5-induced pulmonary eosinophilia or chemotaxis in the proposed mouse strain to confirm that it was a relevant species to assess the carcinogenic potential of reslizumab.

Teva conducted a pharmacology study in OVA-sensitized transgenic mice, whereby reslizumab produced a statistically significant decrease in eosinophils in the bronchoalveolar lavage (BAL) fluid in OVA-sensitized mice treated with 250 mg/kg IV reslizumab.

In the 26-week carcinogenicity study (study #DS-2012-005), Tg(HRAS)2 mice (25/sex/group) received 0 (vehicle control), 100, 250, or 516 mg/kg reslizumab IV once every other week for 26 weeks. The high dose of 516 mg/kg was the maximum feasible dose. A positive control group (75 mg/kg IP MNU) was also included for comparison.

There were no statistically significant tumor findings attributed to reslizumab. Reslizumab induced a statistically significant increase in mortality in the HD female group compared to the vehicle control ($p = 0.038$). Further, the trend test in females showed a statistically significant increase in mortality among all the treatment groups ($p = 0.016$). Survival was not affected in males.

The positive control (75 mg/kg MNU) resulted in increased mortality and induced a strong carcinogenic response, demonstrating the validity of the study. Toxicokinetics were not conducted but reslizumab exposure is assumed based on decreased eosinophils (a pharmacodynamic effect) observed in all reslizumab-treated animals.

The results of this study were discussed with the ECAC during a meeting held on June 16, 2015. The ECAC concluded that the study doses were acceptable, noting prior ECAC concurrence with the doses, and that there were no drug-related neoplasms.

Reference ID: 3785707

2 Drug Information

2.1 Drug

CAS Registry Number: 241473-69-8

Generic Name: Reslizumab

Code Name: CEP-38072, CTx55700, SCH 55700

Chemical Name: Anti-human interleukin-5 (IL-5) monoclonal antibody

Molecular Weight: 147 kDa

Biochemical Description: Humanized anti-human IL-5 monoclonal antibody of the IgG4 kappa isotype, which contains the CDRs of the rat anti-human antibody (39D10) grafted onto human frameworks.

Pharmacologic Class: Monoclonal antibody against IL-5

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application #	*Sponsor*	*CDER OND Division*
009,227	Schering Corporation	DPARP
101,399	Teva Pharmaceuticals	DPARP
(b) (4)	Teva Pharmaceuticals	(b) (4)

2.7 Regulatory Background

Reslizumab was originally developed for asthma under IND 9,227 (Schering Corporation); which was open in 2000 and subsequently withdrawn in 2003. Later, in January of 2008, two IND were submitted simultaneously: IND 101,399 was submitted to DPARP to develop reslizumab for the treatment of eosinophilic asthma (b) (4)

Multiple interactions occurred with the sponsor and (b) (4) DPARP to discuss the need for carcinogenicity studies with reslizumab. A carcinogenicity study in mice (identified as a pharmacologically relevant species) was originally recommended (b) (4) during the pre-IND interactions in June of 2007 (IND (b) (4)) based on the intended chronic use, immunomodulatory effect, and lack of strong evidence of formation of anti-drug-antibodies (ADAs) in rodents.

(b) (4) during an end-of-phase 2 meeting for IND 101,399 on August of 2008. DPARP requested that the sponsor submit a white paper detailing their rationale (b) (4). The sponsor submitted a white paper to IND 101,399 in November of 2010 and the sponsor's rationale was discussed with the ECAC on December 7, 2010. The ECAC concluded that the sponsor's rationale (b) (4) was

Reference ID: 3785707

not acceptable and reiterated that a 2-year study in CD-1 mice was needed. On January of 2011, the sponsor submitted a request to conduct a 26-week transgenic mouse study instead of a 2-year bioassay. This request was found acceptable by the ECAC (refer to Pharm/Tox memo dated March 23, 2011, under IND (b) (4)).

The 26-week transgenic mouse study protocol was discussed with the ECAC on July 10, 2012. The ECAC concurred with the proposed study design, including reslizumab doses. However, it was discussed that, due to the absence of a toxicological or a pharmacological effect in the 4-week toxicity study provided in support of the SPA, it could not be confirmed that the proposed mouse strain was a relevant species and additional data (e.g., inhibition of antigen or IL-5-induced pulmonary eosinophilia or chemotaxis) were needed.

Subsequently, the sponsor submitted a nonclinical pharmacology study report for a study conducted in OVA-sensitized cByB6F1-Tg (HRAS)2jic mice treated with IV CEP-38072 (study #DRR-2013-001). Data from this study showed that reslizumab attenuates the inflammatory response in OVA-sensitized mice (i.e., reslizumab produced a statistically significant decrease in eosinophil levels in BAL fluid of mice treated with reslizumab). This was considered sufficient to support the use of the proposed transgenic mouse strain for the study.

3 Studies Submitted

3.1 Studies Reviewed*

Study Number	*Title*	*Location*
DS-2012-005	*26-Week Intravenous Oncogenicity Study with CEP-38072 (Reslizumab) in 001178-T (hemizygous) Mice*	EDR 4.2.3.4

* This review covers only the carcinogenicity of reslizumab. Other studies submitted under this BLA will be included in an integrated review that will follow.

3.3 Previous Reviews Referenced

Application #	*Studies Reviewed*	*Reviewer Name*	*Review Date*
IND 101,399	Safety Review and Genetic Toxicology	Feleke Eshete, PhD	2/19/2008
IND 101,399	Carcinogenicity White Paper Review	Timothy Robison, PhD, DABT	2/7/2011
IND (b) (4)	PharmTox Memo	Tamal Chakraborti, PhD	3/23/2011
IND 101,399	Special Protocol Assessment	Molly E. Shea, PhD	7/11/2012
IND 101,399	ECAC Meeting Minutes (SPA)	Adele S. Seifried	7/11/2012
IND 101,399	PharmTox Memo	Carol M. Galvis, PhD	2/4/2013
IND 101,399	PharmTox Memo	Carol M. Galvis, PhD	2/11/2014

7 Genetic Toxicology

Reslizumab tested negative in a bacterial mutagenicity (Ames) assay and a chromosomal aberration assay in cultured human lymphocytes.

Reference ID: 3785707

8 Carcinogenicity

Carcinogenicity studies with reslizumab were originally recommended [redacted] (b) (4) in a pre-IND meeting held with the sponsor on June 28, 2007 (IND [redacted] (b) (4)). Later, at an end-of-phase 2 meeting for IND 101,399 held on August 18, 2008; DPARP requested that the sponsor submit a white paper detailing their proposal and rationale [redacted] (b) (4)

The sponsor submitted a white paper to IND 101,399 in November of 2010 and the sponsor's rationale was discussed with the ECAC on December 7, 2010. The ECAC determined that the sponsor's rationale [redacted] (b) (4) was not acceptable and a 2-year study in CD-1 mice (a pharmacologically relevant species) was needed.

On January 24, 2011; the sponsor submitted a request to conduct a 26-week transgenic mouse study in lieu of a 2-year bioassay and it was found acceptable by the ECAC (refer to Pharm/Tox memo dated March 23, 2011, under IND [redacted] (b) (4)). The 26-week transgenic mouse study protocol was discussed with the ECAC on July 10, 2012. The ECAC concurred with the proposed study design. Additional interactions occurred with the sponsor to address the relevance of the proposed transgenic mouse strain (see below under "Appropriateness of Test Models").

Study title: 26-Week Intravenous Oncogenicity Study with CEP-38072 (Reslizumab) in 001178-T (homozygous) Mice

Study no.:	DS-2012-005 ([redacted] (b) (4) #8264527)
Study report location:	EDR
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	May 24, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity[1]:	CEP-38072 (20 mg/mL) Lot #3524-12 CEP-38072 (50 mg/mL) Lot #3524-11 CEP-38072 (103.2 mg/mL) Lot #3524-10
CAC concurrence:	Yes. Refer to ECAC meeting minutes dated July 11, 2012.

Key Study Findings

- Tg(HRAS) mice (25/sex/group) were treated with 0 (vehicle control), 100, 250, or 516 mg/kg reslizumab once every two weeks for 26 weeks. A positive control group was included in the study (75 mg/kg intraperitoneal MNU).

[1] The test article, CEP-38072, was provided pre-formulated by the sponsor at nominal concentrations of 20, 50, and 103.2 mg/mL.

Reference ID: 3785707

- There were no statistically significant reslizumab-related neoplastic findings in males or females. In contrast, MNU induced a strong neoplastic response (including lymphosarcomas, squamous cell carcinomas in the nonglandular stomach, and hemangiosarcomas).
- Reslizumab resulted in a statistically significant increase in mortality in the HD female group compared to the vehicle control ($p = 0.038$). The trend test in females also showed a statistically significant increase in mortality among all the treatment groups ($p = 0.016$). Survival was not affected in males.
- Toxicokinetics were not conducted in this study. A decrease in eosinophil levels was observed in males and females at all dose levels, suggesting that animals had adequate exposure to reslizumab.

Adequacy of Carcinogenicity Study

The study was considered adequate to assess the carcinogenic potential of reslizumab. The doses used were the ones recommended by the ECAC (refer to the ECAC meeting minutes dated July 11, 2012). The duration of exposure was 26 weeks, which is standard and appropriate for this mouse model. None of the groups were terminated early.

Appropriateness of Test Models

The test model is considered appropriate. The study design was evaluated by the ECAC in a meeting held on July 10, 2012. It was discussed that, due to the absence of a toxicological or a pharmacological effect in the 4-week toxicity study provided in support of the special protocol assessment (SPA), it could not be confirmed that the proposed mouse strain was relevant and additional data were needed to demonstrate that the mouse strain is relevant to assess carcinogenicity of reslizumab. This was communicated to the sponsor on July 11, 2012.

Subsequently, the sponsor submitted a nonclinical pharmacology study report for a study conducted in OVA-sensitized cByB6F1-Tg (HRAS)2jic mice treated with IV CEP-38072 (study #DRR-2013-001). Data from this study showed that reslizumab attenuates the inflammatory response in OVA-sensitized mice. Specifically, reslizumab produced a statistically significant decrease in eosinophil levels in BAL fluid of mice treated with 250 mg/kg of the drug. This was considered sufficient to support the use of the proposed transgenic mouse strain for the study.

Evaluation of Tumor Findings

No statistically significant neoplastic findings were observed in reslizumab-treated mice.

Reference ID: 3785707

Methods

Doses:	0 (vehicle control), 100 (low-dose, LD), 250 (mid-dose, MD), or 516 (high-dose, HD) mg/kg. In addition, 75 mg/kg intraperitoneal (IP) N-methyl-N-nitrosourea (MNU, a known carcinogen) was used as positive control to ensure that animals appropriately expressed the oncogene and responded to a carcinogenic insult.
Frequency of dosing:	Once every two weeks
Dose volume:	5 mL/kg
Route of administration:	Intravenous injection (via the tail vein)
Formulation/Vehicle:	CEP-38072 placebo (provided pre-formulated by the sponsor)
Basis of dose selection:	The maximum feasible dose (MFD) based on volume and concentration limitation was used as the highest dose. The LD and MD were selected to evaluate a dose-response.
Species/Strain:	CByB6F1-Tg(HRAS)2jic mice
Number/Sex/Group:	25/sex/group
Age:	8-9 weeks old at initiation of dosing
Weight:	Males: 19.4-27.5 g Females: 14.4-21.1 g
Animal housing:	Male and female mice were housed individually in stainless steel cages (multiple-housed prior to randomization).
Paradigm for dietary restriction:	Not applicable.
Dual control employed:	The study included a negative control (vehicle) and a positive control (75 mg/kg single intraperitoneal MNU).
Interim sacrifice:	Not applicable.
Satellite groups:	Satellite groups were not included in this study.
Deviation from study protocol:	Protocol deviations were reviewed and judged not to affect the integrity of study data.

Reference ID: 3785707

Table 1: Study DS-2012-005 Design.

Group[a,b]	No. of Animals		Dose Level	Dose Concentration
	Male	Female	(mg/kg/day)	(mg/mL)
1 (Control)	25	25	0	0
2 (Low)	25	25	100	20
3 (Mid)	25	25	250	50
4 (High)	25	25	516	103.2
5 (Positive Control)[c]	25	25	75	7.5

a Group 1 received vehicle control article only.
b Groups 1 through 4 were dosed intravenously at a dose volume of 5 mL/kg.
c Group 5 (positive control) was dosed with one intraperitoneal dose of MNU on Day 1 at a dose level of 75 mg/kg/day and a dose volume of 10 mL/kg. These animals were included as a positive control to ensure animals supplied appropriately express oncogene and respond to carcinogenic insult.

Observations and Results

Mortality

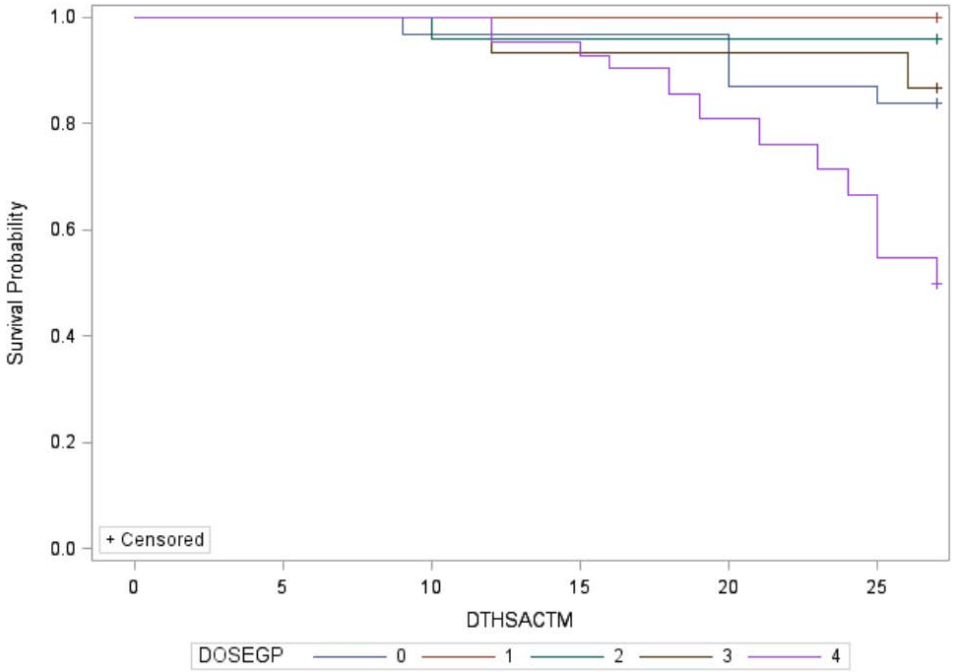
Animals were observed twice daily in the morning and afternoon for mortality.

The percent survival in males at the end of the study was 88%, 100%, 96%, and 92% for vehicle control, LD, MD, and HD; respectively. The percent survival in females at the end of the study was 100%, 100%, 96%, and 88% for vehicle control, LD, MD, and HD; respectively.

A survival analysis conducted by the statistical reviewer, Feng Zhou, showed that the HD female group had a statistically significant increase in mortality compared to the vehicle control group ($p = 0.038$). The trend test in females showed a statistically significant increase in mortality among all the treatment groups (excluding the positive control, $p = 0.016$). Survival was not affected in males.

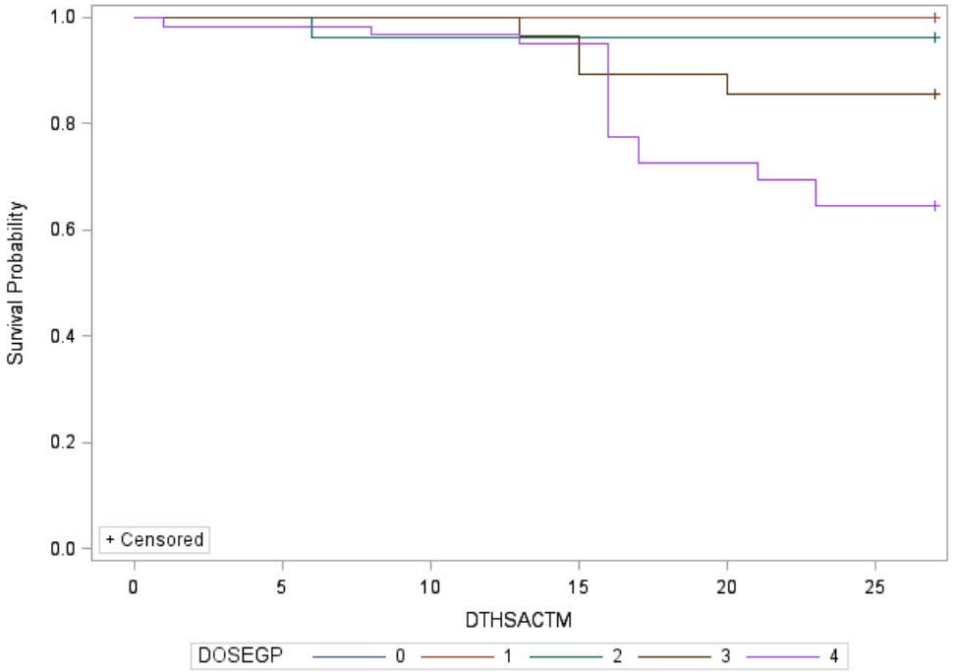
Treatment with 75 mg/kg MNU (positive control) resulted in increased mortality in this group. Refer to figures 1 and 2 below, obtained from the statistical review by Feng Zhou.

Figure 1: Kaplan-Meier Survival Function – Males.



Dose groups: 0 = vehicle control, 1 = LD, 2 = M, 3 = HD, 4 = positive control (75 mg/kg MNU)

Figure 2: Kaplan-Meier Survival Function – Females.



Dose groups: 0 = vehicle control, 1 = LD, 2 = M, 3 = HD, 4 = positive control (75 mg/kg MNU)

Table 2 below presents a summary of early decedents, number of animals at termination, and percent survival for males and females in all groups.

Table 2: Summary of Early Decedents, Number of Animals at Study Termination, and % Survival.

Reslizumab (mg/kg)	Males			Females		
	Early Decedents	Termination	% Survival	Early Decedents	Termination	% Survival
0 (vehicle control)	3	22	88%	0	25	100%
100	0	25	100%	0	25	100%
250	1	24	96%	1	24	96%
516	2	23	92%	3	22	88%
75 MNU	11	14	56%	10	15	60%

Further, table 3 below (excerpted from the pathologist report) presents a summary of the cause of death for early decedents in groups 1-4. As presented in this table, the cause of death for one animal in the control group (animal #A74701) and another animal in the HD group (animal #A74922) were undetermined. These animals did not have neoplastic findings and had very few non-neoplastic histopathology findings that were similar to other surviving animals. Therefore, the cause of death is not considered related to treatment.

Table 3: Day and Cause of Death for Unscheduled Necropsies in Groups 1-4 (Vehicle-treated and Reslizumab-treated).

Group	Sex	Dose mg/kg	Day of Death	Cause of Death
1	Male	0	57	Carcinoma, nonglandular stomach
1	Male	0	139	Hemangiosarcoma
1	Male	0	169	Undetermined
3	Male	250	70	Hemangiosarcoma
4	Male	516	79	Lymphosarcoma
4	Male	516	181	Hemangiosarcoma
3	Female	250	42	Hemangiosarcoma
4	Female	516	91	Inflammation, vessel
4	Female	516	99	Bronchiolo-alveolar carcinoma
4	Female	516	138	Undetermined

Clinical Signs and Palpable Masses

Animals were observed twice daily in the morning and afternoon for any signs of pain or distress and for any abnormalities. Detailed observations were done twice during the pre-dose phase, prior to dosing on study day 1, weekly throughout the dosing phase, and on the day of scheduled necropsy. Daily cage-side observations were conducted the rest of the days.

Animals were also observed for any superficial or palpable masses. The following information was captured weekly for each grossly visible or palpable mass: time of onset, location, size, appearance, and progression.

Reference ID: 3785707

There were no drug-related clinical signs of toxicity or palpable masses.

Body Weights

Body weights were recorded twice during the pre-dose phase, before dosing on study day 1 and weekly thereafter.

Body weights were not affected by reslizumab treatment. Figures 3 and 4 (excerpted from the sponsor's submission) present the mean body weights in males and females, respectively, in grams versus study days.

Figure 3: Mean Body Weights – Males.

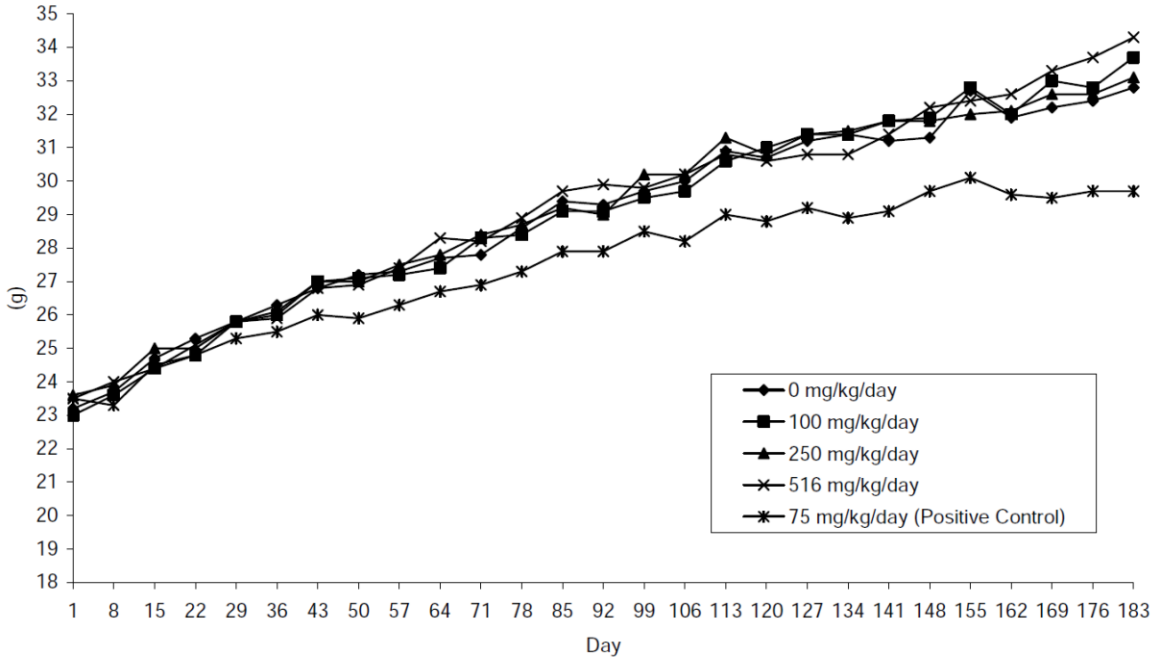
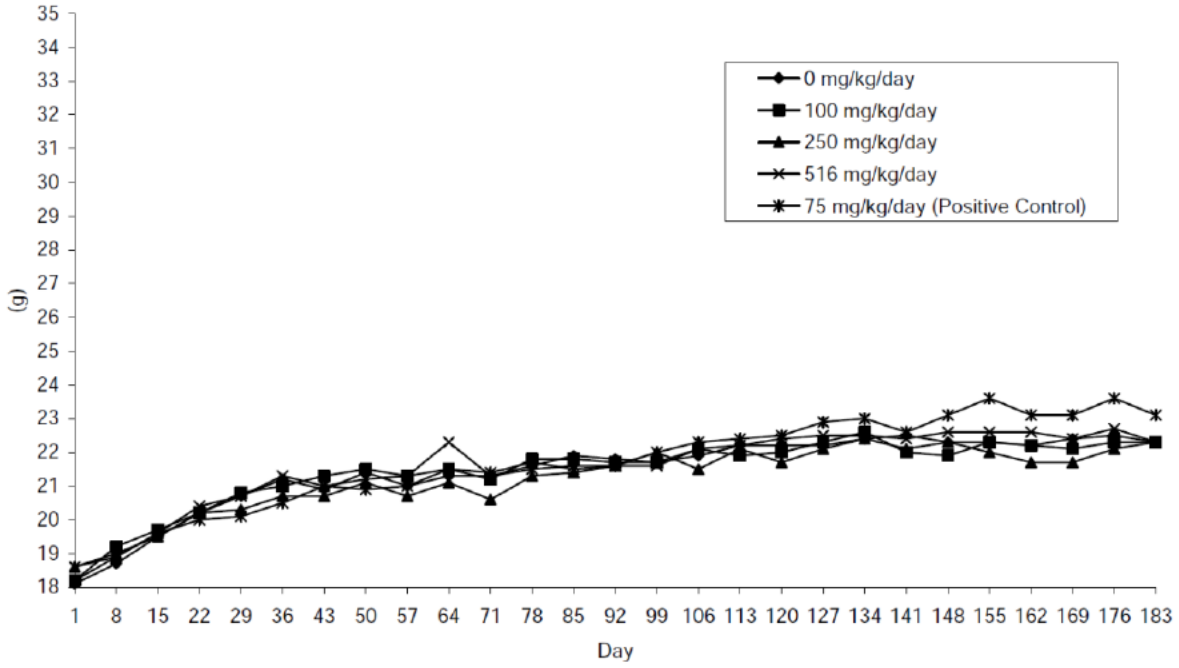


Figure 4: Mean Body Weights – Females.



Feed Consumption

Animals were offered Certified Rodent Diet #2016C (Harlan Laboratories, Inc.). Food consumption was assessed quantitatively weekly during the dosing phase.

Food consumption was not affected by reslizumab treatment.

Hematology

Blood samples were collected from all animals (anesthetized) via cardiac puncture on the day of scheduled necropsy for hematology analysis. Blood was collected into tubes containing potassium EDTA as anticoagulant. In addition, blood smears were also prepared during the necropsy procedure from animals sacrificed at an unscheduled interval but evaluation was not deemed necessary.

A few parameters were affected by reslizumab (refer to Table 4 below). As expected, eosinophils levels were decreased in males and females at all dose levels. In addition; white blood cells, lymphocytes, and large unstained cells were decreased in males at ≥250 mg/kg reslizumab.

Table 4: Summary of Drug-related Changes in Hematology Parameters Relative to Controls.

	Males			Females		
Reslizumab (mg/kg)	**100**	**250**	**516**	**100**	**250**	**516**
White blood cells (10^3/µL)	-	-35%*	-39%*	-	-	-
Lymphocytes (10^3/µL)	-	-37%	-42%*	-	-	-

Eosinophils ($10^3/\mu L$)	-33%*	-50%*	-50%*	-40%*	-40%*	-20%*
LUC	-	-50%	-50%	-	-	-

LUC = large unstained cells
* p<0.05

Gross Pathology

At the end of 184 days (approximately 26 weeks) surviving animals were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. An examination of external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was conducted and terminal body weights were recorded.

There were no drug-related macroscopic lesions observed.

Histopathology

A full battery of tissues from animals in the control and reslizumab-treated groups was collected at necropsy and examined microscopically. In addition, macroscopic lesions and the thymus from animals in the positive control group were collected and examined microscopically. Tissues were preserved in 10% neutral-buffered formalin, with the exception of the eyes, optic nerves, and testes; which were collected in modified Davidson's fixative and stored in 10% neutral-buffered formalin.

Peer Review: A formal pathology peer review was conducted by a second (b) (4) pathologist. Tissues from selected animals were examined microscopically by the reviewing pathologist. The number of animals/sex/group and tissues examined by the peer review were at the discretion of the reviewing pathologist.

Neoplastic Findings

There were no reslizumab-related neoplastic findings in this study. A few neoplastic findings were observed in reslizumab-treated animals but were also observed in the concurrent vehicle controls at similar or slightly higher incidence (refer to Table 5 below). For instance, hemangiomas were observed in one MD male, one LD female, and one HD female. When combined with hemangiosarcomas, as suggested in published literature[2], the number appears to be similar or slightly higher in control animals. Also, in the lung, a few treated animals had bronchioalveolar adenomas or carcinomas (including one HD female who died early on study day 99, see under "Mortality"). A combination of these two tumor types showed that the incidence was similar or slightly higher in the vehicle controls in both males and females.

Table 5: Histological Observations – Neoplastic (All Animals).

	Males	Females

[2] McConnell EE, Solleveld HA, Swenberg JA, and Boorman GA. *Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies.* (1986) Journal of the National Cancer Institute 76(2); pages 283-289.

Reslizumab (mg/kg/dose)	0	100	250	516	0	100	250	516
Number of animals examined	25	25	25	25	25	25	25	25
NEOPLASTIC OBSERVATIONS								
Body, Whole/Cavity								
B-Hemangioma	0	0	1	0	0	1	0	1
M-Hemangiosarcoma	3	2	1	1	2	1	2	2
Body, Whole/Cavity Total (Hemangioma+hemangiosarcoma)	3	2	2	1	2	2	2	3
Harderian gland								
B-Adenoma	0	0	1	1	2	0	3	0
Lung								
B-Bronchioalveolar adenoma	2	2	2	1	1	1	0	1
M-Bronchioalveolar carcinoma	1	0	0	1	1	2	0	1
Lung Total (Adenoma+Carcinoma)	3	2	2	2	2	3	0	2

B = benign
M = malignant

Non-Neoplastic Findings

There were no non-neoplastic findings that were clearly attributed to reslizumab. The following findings were found at slightly higher incidence in reslizumab-treated animals compared to vehicle controls: hyperplasia of the harderian gland, glandular stomach, and lung; mononuclear cell infiltrate in the harderian gland; and cysts in the parathyroid and spinal cord. A clear dose-response was not observed for any of the findings and therefore, it is not clear whether these were related to treatment.

Toxicokinetics

Toxicokinetics were not conducted in this study. However, because a pharmacodynamic effect was observed in reslizumab-treated animals (decrease in eosinophil levels), it is assumed that the animals had sufficient drug exposure.

Toxicokinetics were conducted in the 4-week toxicity study in wild type mice provided in support of the SPA (study #DS-2011-017). The systemic exposure observed at 500 mg/kg/dose reslizumab was $AUC_{0\text{-}168hr}$ = 1326 mg·hr/mL in females and 1519 mg·hr/mL in males.

Dosing Solution Analysis

Dosing formulations (vehicle control and reslizumab) were supplied pre-formulated as ready-to-use solutions and dispensed for dosing using aseptic procedures. MNU formulations were prepared on study day 1 prior to dosing. The positive control article was reconstituted in acidified physiological saline to achieve a target concentration of 7.5 mg/mL [redacted] (b) (4) All dosing formulations were tested by the sponsor for stability and concentration verification from formulations administered on study days 1, 85, and 183 of the dosing phase. Because the test article formulations are solutions, they were not tested for homogeneity.

Reference ID: 3785707

Dosing formulations were within 10% of the nominal concentrations and were stable under the conditions of the study.

11 Integrated Summary and Safety Evaluation

Teva Branded Pharmaceutical Products submitted a 351(a) BLA on March 28, 2015, for reslizumab solution for IV infusion. Reslizumab is a monoclonal antibody against human IL-5 and was developed by Teva for the treatment of eosinophilic asthma (patients with asthma and elevated blood eosinophils) under IND 101,399. The proposed dosing regimen is 3 mg/kg reslizumab every 4 weeks.

Although this is a biologic product and an assessment of genetic toxicity was not necessary, the previous sponsor conducted in vitro genetic toxicity studies. Reslizumab was negative in the in vitro bacterial mutagenicity (Ames) and in vitro chromosomal aberration assays.

Because the mouse was originally identified as a pharmacologically relevant species for reslizumab, Teva conducted a 26-week carcinogenicity study in transgenic mice to assess the carcinogenic potential of reslizumab. The study protocol was discussed with the ECAC in a meeting held on July 10, 2012, and found acceptable. However, it was discussed that additional data (e.g., inhibition of antigen or IL-5-induced pulmonary eosinophilia or chemotaxis) in the proposed transgenic mouse strain were needed to confirm that this strain was relevant to assess carcinogenicity of reslizumab given the absence of a toxicological or a pharmacological effect in the 4-week toxicity study provided in support of the SPA.

Subsequently, the sponsor submitted data from a nonclinical pharmacology study in OVA-sensitized transgenic mice treated with reslizumab (study #DRR-2013-001). In this study, reslizumab (250 mg/kg IV) induced a statistically significant decrease in eosinophil levels in the BAL fluid of treated mice. This finding was considered sufficient to support the use of this mouse strain for the carcinogenicity study.

In the 26-week carcinogenicity study (study #DS-2012-005), Tg(HRAS)2 mice (25/sex/group) were treated with 0 (vehicle control), 100, 250, or 516 mg/kg reslizumab IV once every two weeks for 26 weeks. These doses were selected based on the high dose being the maximum feasible dose and this was considered adequate by the ECAC. In addition, a positive control group (75 mg/kg IP MNU) was included.

There were no statistically significant tumor findings in the study that were attributed to reslizumab. Reslizumab resulted in a statistically significant increase in mortality in the HD female group compared to the vehicle control ($p = 0.038$). The trend test in females also showed a statistically significant increase in mortality among all the treatment groups with a $p = 0.016$. Survival was not affected in males.

Reference ID: 3785707

The positive control (MNU) resulted in decreased survival (56% survival in males and 60% survival in females at the end of the study) and an increased incidence of tumor findings (including lymphosarcoma, squamous cell carcinoma in the nonglandular stomach, and hemangiosarcoma).

Toxicokinetics were not conducted for this study. Exposure is assumed based on a pharmacodynamic effect observed in all reslizumab-treated animals (decrease in eosinophils in serum). Toxicokinetics were conducted in the 4-week toxicity study in wild type mice provided in support of the SPA (study #DS-2011-017). The systemic exposure observed at 500 mg/kg/dose reslizumab (HD in this study) was $AUC_{0\text{-}168hr}$ = 1326 mg·hr/mL in females and 1519 mg·hr/mL in males.

The results from this study were discussed with the ECAC during a meeting held on June 16, 2015. The ECAC concluded that the study was acceptable, noting prior ECAC concurrence with the doses and design, and that there were no drug-related neoplasms.

12 Appendix/Attachments

Appendix 1: ECAC meeting minutes dated July 11, 2012 (ECAC meeting held to discuss the carcinogenicity protocol)

Appendix 2: ECAC meeting minutes dated June 19, 2015 (ECAC meeting held to discuss carcinogenicity conclusions)

7 Pages Have Been Withheld As A Duplicate Copy Of The ECAC Meeting Minutes dated July 11, 2012 and June 19, 2015 Which Are Located In The Administrative Correspondance Section Of This NDA Approval Package.

Reference ID: 3785707

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

/s/

CAROL M GALVIS
06/30/2015

MARCIE L WOOD
06/30/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 761,033 **Applicant: Teva Branded Pharmaceutical Product R&D, Inc.** **Stamp Date: 3/30/2015**

Drug Name: Reslizumab **BLA Type: Original application**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		The formulation is the same as the clinical formulation.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		Yes, the intravenous (IV) route.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		Pivotal studies were conducted in compliance with GLP regulations.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		The proposed labeling is in PLR format. Section 8.1 (Pregnancy) follows the new PLLR. A consult to the Maternal Health staff will be needed.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			There were no impurities issues identified during the IND review or as of the date of this filing review. Impurities issues will be addressed in consult with the reviewing chemist, if needed.
11	Has the applicant addressed any abuse potential issues in the submission?			This section is not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This section is not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

BLA 761,033 is fileable from the Pharmacology/Toxicology perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no comments to the applicant.

Carol M. Galvis, PhD (see electronic signature)
Reviewing Pharmacologist Date

Marcie Wood, PhD (see electronic signature)
Team Leader/Supervisor Date

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

/s/

CAROL M GALVIS
05/19/2015

MARCIE L WOOD
05/19/2015