CLINICAL PHARMACOLOGY REVIEW	
BLA Number:	761033 (related IND 101399 and IND 009227)
Submissions Date:	03/30/2015
Submission Type:	351(a)
Proposed Brand Name:	CINQAIR
Generic Name:	Reslizumab
Sponsor:	Teva Branded Pharmaceutical Products R&D, Inc.
Route of Administration:	Intravenous Infusion
Dosage Form:	Liquid solution
Dosage Strength:	100 mg/10 mL per vial
Proposed Dosing Regimen:	3 mg/kg every 4 weeks
Proposed Indication(s):	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
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader (Acting):	Suresh Doddapaneni Ph.D.
Pharmacometrics Reviewer:	Yunzhao Ren, M.D., Ph.D.
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Note –

In this review, early development name SCH 55700, CTx55700, and CEP-38072 sometimes was used to refer to reslizumab.

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1. EXECUTIVE SUMMARY

Teva Branded Pharmaceutical Products R&D, Inc. has submitted BLA 761033 under 351 (a) pathway seeking the marketing approval for reslizumab (Cinqair®) for the indication of "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 proposed dosing regimen is 3 mg/kg for 20-50 minute intravenous infusion once every 4 weeks. The dosage form is presented as 10 mg/mL reslizumab solution (10 mL per vial).

The clinical development program of this submission includes three Phase 1 studies (Studies 350, 1102, and 1107), two Phase 2 studies (Studies 290 and 10), and five Phase 3 studies (Studies 3081, 3082, 3083, 3084, and 3085).

The following are the major clinical pharmacology findings of the current review:

1. After intravenous dosing, reslizumab peak concentrations occur at the end of infusion and then slowly decline in a biphasic manner. The elimination half-life is about 24 days.

2. The drug product formulation of reslizumab, a solution for intravenous infusion, has remained the same throughout the clinical development program.

3. The FEV1 improvement over 16 week treatment is numerically higher in 3 mg/kg reslizumab treatment group than 0.3 mg/kg treatment group. There is no apparent trend for change in the rate of clinical asthma exacerbations CAE with $C_{av,ss}$. The median baseline creatine phosphokinase, as well as on-treatment median creatine phosphokinase, was higher in the reslizumab-treated groups compared to placebo. There is no significant trend of increase of muscle disorder adverse events (AEs) with $C_{av,ss}$. There is no apparent dose-response trend for serum creatine phosphokinase (CPK) concentration.

4. Body weight is the only significant covariate identified by population PK analysis.

5. The rate of treatment-emergent anti-drug antibody (ADA) following 3 mg/kg reslizumab treatment is 5.4%. Among treatment-emergent ADA positive patients, 43% was transient (only positive in one post-dose sample). The geometric mean titers of ADA was 1:7.6 (CV=121%). There is no apparent impact of ADA on reslizumab PK, efficacy, and safety. The Sponsor did not develop an assay to detect the neutralizing capacity of reslizumab ADA.

1.1 Recommendation

From a clinical pharmacology perspective, the information submitted in this BLA is acceptable to support the approval of CINQAIR for the proposed indication.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Cinqair (reslizumab) is a humanized monoclonal IgG_4 anti-IL5 antibody. IL-5 is a cytokine important in the growth, differentiation, activation and survival of eosinophils. Reslizumab is proposed 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. Reslizumab is supplied as 10 mL 10 mg/mL solution in a single-use vial for IV infusion only. Reslizumab should be diluted with 50 mL saline prior to IV infusion and the infusion time is 20 – 50 minute. The proposed dosing regimen is 3 mg/kg once every 4 weeks.

1.3.2 Biopharmaceutics

Throughout the clinical development program, the drug product formulation of reslizumab (10 mg/mL reslizumab in (b) (4) 7% sucrose, pH 5.5 buffer) has remained the same, and various Type 1 glass vials have been used as the primary container, ranging in size from 2 mL to 10 mL.

1.3.3 Pharmacokinetics

Pharmacokinetics in Healthy Subjects
Reslizumab PK in healthy subjects was evaluated in Study 1102. Four parallel groups of healthy subjects received five Q4week IV doses of 0.3, 1.0, 2.0, or 3.0 mg/kg reslizumab. 100 subjects completed the

study. Following the single dose, peak concentrations were observed in the majority of profiles at the end of infusion (50 minutes). After that, reslizumab serum concentrations declined in a bi-exponential manner. The mean observed accumulation ratio following 5th dose ranged from 1.5 to 1.9. The mean terminal-phase elimination half-life ranged from 25 to 32 days. The exposures were comparable between Japanese and non-Japanese. There was no consistent or notable trend toward a deviation from proportionality following either a single dose or multiple doses.

Pharmacokinetics in Patients
Reslizumab serum concentrations in asthma patients from five studies (350, 290, 10, 3081, and 3082) were pooled with other studies in a population PK analysis. The PK parameters were comparable between healthy subjects and asthma patients.

Reslizumab clearance is approximately 7 mL/hour. The volume of distribution of reslizumab is approximately 5 L. The terminal elimination half-life of reslizumab is approximately 24 days.

Pharmacokinetics in Special Populations
The effect of sex, age, race, and body weight on the PK of reslizumab was assessed using the population approach.

Race, Gender, Age, and Weight
Race, ethnicity, age and gender did not significantly impact the PK of reslizumab. Reslizumab clearance increases with body weight.

Immunogenicity
The same homogenous bridging ELISA assay was applied in all the Phase 3 studies for detecting anti-reslizumab antibody. Following 3 mg/kg reslizumab treatment, the rate of treatment-emergent ADA incidence is 5.4%. Among treatment-emergent ADA positive patients, 43% was transient (only positive in one post-dose sample). The geometric mean titers of ADA was 1:7.6 (CV=121%). There is no apparent impact of ADA on reslizumab PK, efficacy, and safety. The Sponsor did not develop an assay to detect the neutralizing capacity of reslizumab ADA.

1.3.4 Pharmacodynamics and Dose/Exposure-Response Relationship

Study 290 was the only dose-ranging (0.3 mg/kg and 1 mg/kg) Phase 2 study that evaluated clinical efficacy upon two doses administered 12 weeks apart. Total 211 patients enrolled in the study. However, there were no statistical significant differences on FEV1 change from baseline between reslizumab treatment groups and placebo groups.

Study 10 was the only Phase 1/2 study that listed eosinophil count as an inclusion criterion. The enrolled asthma patients were required to have eosinophils in an induced sputum sample of no less than 3%. 106 patients were randomly assigned by a 1:1 ratio to 3.0 mg/kg reslizumab treatment group or placebo group. Approximately half of the patients had baseline blood eosinophil count $\geq$ 500 cells/μL. An exploratory analysis showed that FEV1 improvement from baseline was significantly higher in reslizumab treatment group than the placebo group in the population with blood eosinophil count $\geq$ 500 cells/μL (p=0.04), but not in the population with blood eosinophil count < 500 cells/μL (p=0.07) (Table 4.9). Therefore, blood eosinophil count $\geq$ 400 cells/ μL was selected as an inclusion criteria in all the subsequent Phase 3 trials.

Study 3081 was the only Phase 3 Study investigated more than one dosing levels (0.3 mg/kg and 3 mg/kg). A clear trend of dose-dependent reduction of blood eosinophil count was demonstrated (Figure

4.13). It appeared that the reduction plateau phase was reached at Week 4 and Week 8 for 0.3 mg/kg, and 3 mg/kg treatment group, respectively. The absolute values of blood eosinophil counts reduced maximally to 517, 208, and 48 cells/μL (or reduced by 14%, 68%, and 92%) for placebo, 0.3 mg/kg, and 3 mg/kg treatment group, respectively. In the same study, the FEV1 improvement over 16 week treatment is numerical higher in 3 mg/kg reslizumab treatment group than 0.3 mg/kg treatment group. There is a lack of apparent trend for change in the rate of CAEs with increasing reslizumab exposure.

A pooled data (Studies 350, 290, 10, 3081 and 3082) was used for an exposure-response analysis of blood eosinophil count. The IC_{50} and IC_{90} values of reslizumab concentration that are required for 50% and 90% reduction of blood eosinophils were estimated as 0.77 and 6.96 μg/mL, respectively. For comparison, the estimated $C_{av,ss}$ values following 0.3 mg/kg and 3mg/kg reslizumab treatment was 4.8 and 44.2 μg/mL, respectively.

A pooled data (Studies 290, 10, 3081 and 3082) was used for an exposure-response analysis of FEV1 improvement from baseline. Although there is a statistical significant E-R relationship between reslizumab steady state average concentration $C_{av,ss}$ and FEV1 improvement from baseline, the relationship is generally flat. The model only estimates an approximately 70 mL of more FEV1 improvement at Week 16 from 0.3 mg/kg to 3 mg/kg reslizumab treatment.
There is no apparent trend for change in the rate of CAE with $C_{av,ss}$ (Table 2.4). There is no significant trend of increase of muscle disorder AEs with $C_{av,ss}$ (Table 2.6). There is no apparent dose-response trend for serum creatine phosphokinase (CPK) concentration (Table 8 from Pharmacometrics Review).

1.3.6 Dose Selection

Based on the presence of exposure-response relationship of efficacy endpoint (FEV1 improvement from baseline) and the absence of exposure-response relationship of safety endpoint (muscle disorder AEs), the selection of reslizumab dose 3.0 mg/kg is reasonable.

2. QUESTION BASED REVIEW

2.1 Regulatory history

Reslizumab is a humanized monoclonal antibody (IgG4) targeted against human IL-5. It is the second anti-IL5 antibody submitted as BLA. The first anti-IL5 antibody mepolizumab (BLA 125526) was approved on Nov 4, 2015 for patients with severe asthma. Reslizumab was initiated by Schering Plough with name of SCH 55700 under IND 009227 (IND open date 7/31/2000). Ception, after acquiring reslizumab from Schering, opened a separate IND (IND 101399) on 01/16/2008 and renamed the product under the codename CTx55700. In 2010, Ception was acquired by Cephalon, Inc. Cephalon was then acquired by Teva Pharmaceuticals in 2012. Cephalon and Teva have used the designation CEP-38072 for reslizumab. Therefore, during development reslizumab has been referred to as SCH 55700, CTx55700, and CEP-38072 in various documents.

All the asthma clinical trials of reslizumab were developed under IND 101399. [redacted] (b) (4)

An EOP2 meeting with FDA was held on 08/18/2010. The summary of clinical pharmacology-related question and discussion are listed as following:

Question 12: Sparse samples for pharmacokinetics will be collected in the Phase 3 efficacy trials. These data will be used to characterize the pharmacokinetics of reslizumab and an attempt will be made to correlate systemic exposure with measures of safety and/or response. Does the Agency concur that this approach is adequate to support the clinical development program and BLA filing for the proposed indication?

FDA Response: We generally agree that you may conduct sparse pharmacokinetic sampling in the Phase 3 efficacy trials. However, we noticed the pharmacokinetic information submitted in the background package is limited. Based on the submitted pharmacokinetics summary, you indicated linearity was confirmed in asthma patients in the dose range of 0.03 to 1.0 mg/kg after single dose. You also indicated [redacted] (b) (4) *but it is not mentioned in the package if similar findings were observed for asthma patients. In addition, we note that trial Res-5-0010 evaluated only the 3.0 mg/kg dose and the proposed Phase 3 trials do not include further dose exploration. . Therefore, we recommend that you further characterize the dose response relationship in the population of interest by exploring more dose regimens. We also recommend that you characterize the PK of your product in your target patient population after both single and multiple doses.*

Pre-BLA meeting with FDA was held on 01/15/2015. The summary of clinical pharmacology-related discussions and comments are listed as following:

Question 9.5: In the reslizumab clinical development program, serum samples were analyzed for reslizumab concentration. Detectable values were present in a subset (approximately 25%) of the baseline and placebo samples due to presumed sample matrix effects. As a result, Teva proposes to establish a pre-specified operational cutoff for inclusion of data in the population PK analyses. This cutoff has been selected based on review of the concentration data and represents a small percentage of Cmax. Does the agency concur with the use of a pre-specified cutoff for data handling in the population PK analyses?

FDA Response: We do not agree. You concluded from the bioanalytical investigation report that the baseline and placebo quantifiable values do not have any significant impact on reslizumab PK assessment. Therefore, regardless of pre-specified cutoff, the PK analysis should not be impacted for

either population PK analysis or the PK analysis for individual studies. However, you did not provide a rationale on why the results may be biased if no cut-off is used in the population PK analysis. You should provide justification for the use of the cut-off and conduct the PK analysis, for the popPK study, with and without your specified cut-off.

There were 9 asthmatic adolescents received reslizumab treatment in Phase 3 Study C38072/3081; and Phase 3 Study Res-5-0002 was conducted in 226 children aged 5-18 years with eosinophilic esophagitis. A population PK approach was utilized in Study Res-5-0002.

The Agency agreed Sponsor's initial pediatric study plan (iPSP) on 08/26/2014. The proposed PSP includes the following (b) (4)

(b) (4)

2.2 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the BLA

One *in vitro* and eight *in vivo* clinical pharmacology-related studies have been submitted under BLA 761033. The submission also included two clinical pharmacology reports based on population PK analysis and PK/PD assessment from multiple studies.

In vitro Study XT133130 on effect of reslizumab on expression of CYP enzymes in human hepatocytes was conducted between 11/11/2013 and 12/12/2013. Eight *in vivo* clinical pharmacology-related studies in healthy subjects and asthmatic patients are listed in Table 2.1. Two clinical pharmacology reports are listed in Table 2.2.

Table 2.1 List of Clinical Studies Conducted in Healthy or Asthmatic Subjects Containing PK/PD Evaluation

Study ID	Study Date	Phase	Study Objective(s)	Study Design	Subjects	Treatment Groups
I96-350 (Outside U.S.)	09/18/1997 – 11/11/1999	1	Safety, PK, PD	R, DB, PC, DR, PG, SD	32 patients with severe asthma	0.03 mg/kg, IV[1] 0.1 mg/kg, IV[1] 0.3 mg/kg, IV 1 mg/kg, IV Placebo, IV
P00290	09/14/1999 – 09/06/2001	2	Efficacy, Safety, PK, Immunogenicity	R, SB, PC, DR, PG, RD (2-dose, W1 and 12)	211 patients with moderate and severe persistent asthma	0.3 mg/kg, IV 1 mg/kg, IV Placebo, IV
Res-5-0010	04/16/2008 – 03/05/2010	2	Efficacy, Safety, PK	R, DB, PC, PG, RD (4-dose, Q4W)	106 patients with poorly controlled asthma	3 mg/kg, IV placebo SC
C38072/3081	02/07/2011 – 09/12/2013	3	Efficacy, Safety, PK	R, DB, PC, DR, PG, RD (4-dose, Q4W)	311 patients with inadequately controlled asthma	0.3 mg/kg, IV 3 mg/kg, IV Placebo, IV

C38072/3082	04/12/2011 – 03/03/2014	3	Efficacy, Safety, PK, Immunogenicity	R, DB, PC, PG, RD (48-week, Q4W)	488 patients with inadequately controlled asthma	3 mg/kg, IV Placebo, IV
C38072/3083	03/22/2011 – 04/03/2014	3	Efficacy, Safety, PK	R, DB, PC, PG, RD (48-week, Q4W)	464 patients with inadequately controlled asthma	3 mg/kg, IV Placebo, IV
C38072/3084	02/17/2012 – 08/14/2013	3	Efficacy, Safety	R, DB, PC, PG, RD (16-week, Q4W)	492 patients with moderate to severe asthma	3 mg/kg, IV Placebo, IV
C38072/1102	02/29/2012 – 02/07/2013	1	Safety, PD, PK	R, OL, PG, RD (5-dose, Q4W)	100 Healthy subjects	0.3 mg/kg, IV 1.0 mg/kg, IV 2.0 mg/kg, IV 3.0 mg/kg, IV
C38072/1107	06/04/2013 – 12/03/2013	1	Safety, PD, PK	R, OL, PG, SD	75 Healthy subjects	220 mg, IV 220 mg, SC

[1] IV bolus, all the other doses were given as IV infusion
Source: adapted from section 5.2 Tabular Listing of all Clinical Studies.pdf, Table 1

Table 2.2 List of Clinical Pharmacology Reports of Assessment for Multiple Studies

Report ID	Study Objective(s)		Included Clinical Studies	Included Subjects N
CP-11-006	Population PK		350, 290, 10, 3081, 3082, 1102, 1107, 1942	805
CP-15-001	Exposure-response assessment	for blood eosinophil count	350, 290, 10, 3081, 3082	958
		for FEV1	290, 10, 3081, 3082	955
		for asthma exacerbation	3082	479
		for muscle disorder	290, 10, 3081, 3082	1100

Source: Reviewer's summary

2.3 General Attributes of the Drug

2.3.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Reslizumab is a humanized anti-human interleukin-5 monoclonal antibody (IgG4/kappa). Reslizumab consists of two identical light and two identical heavy chains. The heavy chain contains (b) (4) amino acids and the light chain contains (b) (4) amino acids. The heavy and light chains are covalently linked by a single disulfide bond and the heavy chains are linked to each other by two disulfide bonds resulting in a typical IgG molecule. (b) (4)

(b) (4)
The theoretical molecular mass is 147 KD
Reslizumab drug substance is expressed in a murine myeloma NS0 cell line (b) (4)

There were literature reports identifying certain alpha-gal-specific IgE antibodies generated in human body that might associated with anaphylaxis. For details, refer to primary review by OBP Reviewer Dr. Pedras-Vasconcelos.

Throughout pre-clinical, Phases 1-3 clinical, and the proposed commercial drug product process, the reslizumab Solution for Infusion drug product formulation (10 mg/mL reslizumab in [redacted] 7% sucrose, pH 5.5 buffer) has been essentially unchanged (Table 2.3). There have been two drug substance manufacturing processes in the course of clinical development of reslizumab: the Schering Plough (Schering) SCH 55700 process used for non-clinical and clinical (Phase 1 and 2) development and the Ception CTx55700 process used for clinical (Phase 1 and 2) development. The current reslizumab (Cephalon / Teva) [redacted] manufacturing process, used for Phase 2 and 3 clinical development, is the CTx55700 process. Since the initiation of clinical development by Ception, [redacted], no significant process or formulation changes have been made during development of the CTx55700 process from pilot [redacted] to clinical [redacted] and clinical / commercial scale [redacted] The process used for the pivotal Phase 3 clinical studies is the same as the process which was validated and is proposed as the commercial process.

Reslizumab solution for infusion drug product is a sterile, unpreserved, and colorless to slightly yellow, aqueous solution for infusion supplied in 10 mL single-use Type I clear, borosilicate glass vials containing 100 mg of reslizumab. Reslizumab drug product is diluted with 50 mL saline prior to infusion.
The composition of the reslizumab solution for infusion is listed as following:

Table 2.3 Composition of the Reslizumab Drug Product

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

Source: section 3.2.P.1 Description and Composition of the Drug Product.pdf, page 1, Table 1

2.3.2 What are the proposed mechanism of action and therapeutic indications?

Multiple cell types, including eosinophils, have been shown involved in airway inflammation in asthma. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Reslizumab is a humanized monoclonal antibody (IgG1 kappa) that competitively binds to human IL-5 with a K_d of 81pM as measured by BIAcore. The reslizumab-binding site on IL-5 is mapped to amino acids [redacted] Reslizumab binds to IL-5 receptor with a dissociation constant of 81 pM. The IC_{50} for inhibition of proliferation of human TF1 cells (an IL-5 receptor expressing cell line requires IL-5 for proliferation) by reslizumab is 45 pM. Therefore, the blood eosinophil counts are expected to be reduced upon reslizumab treatment.

The proposed therapeutic indication of reslizumab 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".

2.3.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is 3 mg/kg administered once every 4 weeks. The route of administration is intravenous infusion over a 20–50 minute period.

2.3.4 What drugs (substances, products) indicated for the same indication are approved in the U.S.?

The proposed indication "adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids" is unique for reslizumab. However, this indication description is similar to another biological product, mepolizumab (BLA 125526), whose indication is "severe eosinophilic asthma".

2.4 General Clinical Pharmacology

2.4.1 What is the basis for selecting the response endpoints?

In the pivotal clinical studies 3082 and 3083, the primary efficacy endpoint was the frequency of clinically asthma exacerbations (CAE). An asthma exacerbation event was considered a CAE if the patient met either or both of the criteria listed below and was corroborated by at least 1 other measurement indicating the worsening of clinical signs and symptoms of asthma:

- Use of systemic, or an increase in the use of inhaled, corticosteroid treatment for 3 or more days. For patients already being treated with systemic or inhaled corticosteroids, the dose of corticosteroid would have had to be increased 2 or more fold for at least 3 or more days.
- Asthma-related emergency treatment including at least 1 of the following:
    - an unscheduled visit to the physician's office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms
    - a visit to the emergency room for asthma-related treatment
    - an asthma-related hospitalization

The CAE is a long-term clinical endpoint and was not measured in Phase 1/2 clinical pharmacology studies.

In the Phase 3 clinical studies 3081 and 3084, the primary efficacy endpoint was improvement of lung function as assessed by overall change from baseline in forced expiratory volume in 1 second (FEV1) over 16 weeks of treatment.

2.4.2 Are the active moieties in serum and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Serum concentration of reslizumab was measured to assess its pharmacokinetic parameters and exposure response relationships.

2.5 Dose/Exposure response

2.5.1 What are the characteristics of the dose/exposure-response relationship for effectiveness?

The dose/exposure-response relationship for two efficacy endpoints (FEV1 change from baseline and CAE rate) was evaluated. The FEV1 improvement over 16 week treatment is numerical higher in 3 mg/kg reslizumab treatment group than 0.3 mg/kg treatment group. There is a lack of apparent trend for change in the rate of CAEs with increasing reslizumab exposure.

- Dose-response relationship of FEV1

Study 3081 was the only Phase 3 Study investigated more than one dosing levels (0.3 mg/kg and 3 mg/kg) for efficacy (FEV1 change from baseline over 16 weeks was the primary efficacy endpoint). Reslizumab significantly improved FEV1from baseline over 16 weeks compared to placebo treatment (Figure 2.1). The placebo-adjusted FEV1 improvement over 16 weeks was 0.115 (95% CI=0.016, 0.215) L and 0.160 (95% CI=0.060, 0.259) L following 0.3 mg/kg and 3 mg/kg reslizumab treatment, respectively (Table 2.4). There is only a numerical increase of FEV1 improvement from 0.3 mg/kg group to 3 mg/kg group.

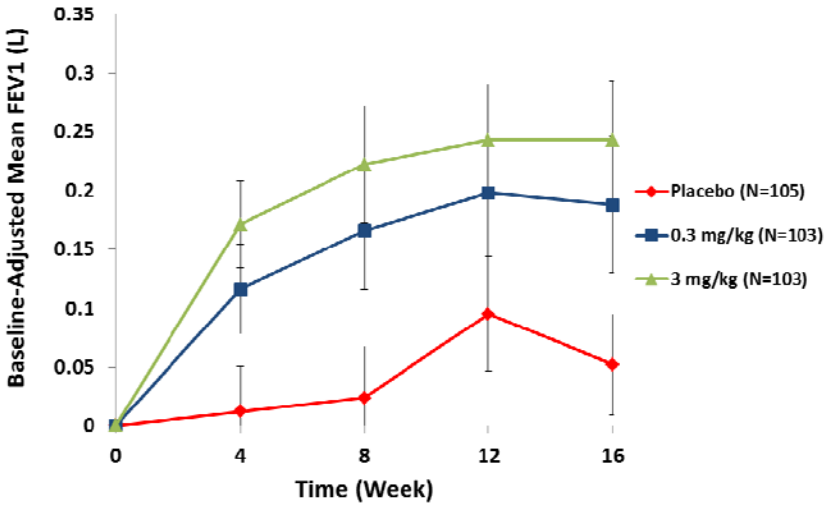

Figure 2.1 Observed baseline-adjusted mean FEV1-time profile following 16-week, Q4 week treatment of placebo (red), 0.3 mg/kg reslizumab (blue), and 3 mg/kg reslizumab (green). Error bars represent standard error. (Source: adapted from CSR3081, page 330-332, Summary 15.20)

Table 2.4 Change from Baseline in FEV1 over 16 Weeks and at Week 16 by Treatment Group (Full analysis Set)

	Parameter	Placebo (N=105)	Reslizumab 0.3 mg/kg (N=103)	Reslizumab 0.3 mg/kg (N=103)
FEV1 (L) Change from Baseline over 16-week	LS mean (SE)	0.126 (0.0549)	0.242 (0.0556)	0.286 (0.0548)
	Difference from Placebo (95% CI)		0.115 (0.016, 0.215)	0.160 (0.060, 0.259)
	p-value		0.0237	0.0018
FEV1 (L) Change from Baseline at 16-week	LS mean (SE)	0.137 (0.0622)	0.266 (0.0624)	0.302 (0.0616)
	Difference from Placebo (95% CI)		0.129 (0.001, 0.257)	0.165 (0.037, 0.293)
	p-value		0.0481	0.0118

Source: adapted from Report CSR3081, Page 104, Table 22

- Expose-Response (E-R) relationship of FEV1

Although there is a statistical significant E-R relationship between reslizumab steady state average concentration $C_{av,ss}$ and FEV1 improvement from baseline, the relationship is generally flat.

The Sponsor proposed a time-dependent E_{max} model for the E-R relationship for FEV1. The model presumes that E_{max} value is linear proportional to the $C_{avg,ss}$ value; and the FEV1 change from baseline follows a time-dependent increase E_{max} model.

Assuming the median reslizumab average concentration at steady state $C_{av,ss}$ as 0, 4.8 µg/mL and 44.2 µg/mL following placebo, 0.3 and 3 mg/kg reslizumab treatment, the model-predicted increases in FEV1 from baseline are 0.088, 0.096 and 0.164 L at Week 16, respectively (Figure 2.2). The observed FEV1 change from baseline from Study 3081 was 0.052, 0.188, and 0.243 at Week 16 following placebo, 0.3 mg/kg and 3 mg/kg treatment, respectively (CSR 3081, page 112, Table 22).

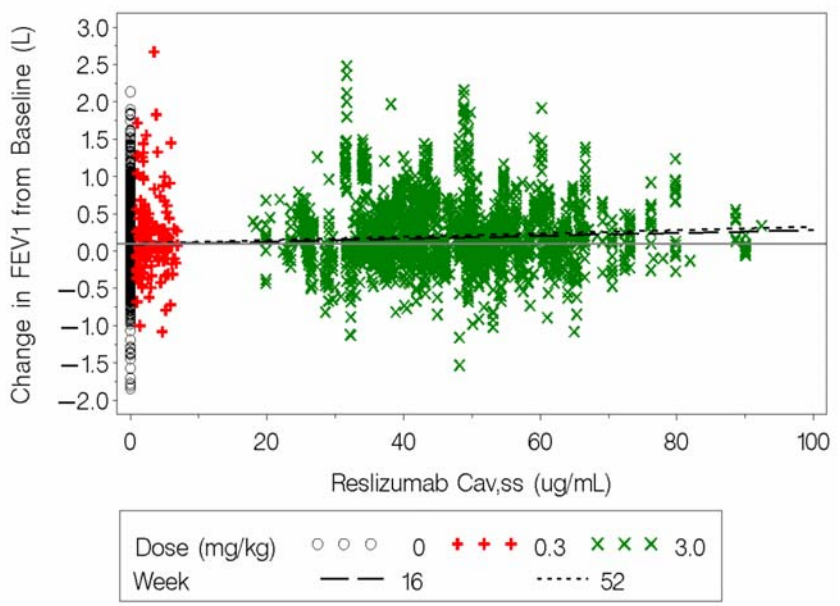

Figure 2.2 Scatterplot of FEV1 change from baseline versus predicted reslizumab concentration $C_{av,ss}$, by dose. The dashed line represent the model-predicted FEV1 for Weeks 16 and 52 assuming the median $C_{av,ss}$ for a Q4W dosing regimen for a White, female patient with median age (47 years) and BWI=27 kg/m^2. (Source: Summary-Clin-Pharm.pdf, page 58, Figure 22)

- E-R relationship of clinical asthma exacerbation (CAE)

There is a lack of apparent trend for change in the rate of CAEs with increasing reslizumab exposure (Table 2.4); therefore no PK/PD modeling was performed for the CAE data.

Table 2.5 Observed Frequency Distributions of CAE Rate, by Reslizumab Exposure Quartile for 3 mg/kg Treatment Arm

Clinical asthma exacerbations per year	First $C_{av,ss}$ quartile [18.3, 37.2] (µg/mL)	Second $C_{av,ss}$ quartile (37.2, 44.4] (µg/mL)	Third $C_{av,ss}$ quartile (44.4, 54.1] (µg/mL)	Fourth $C_{av,ss}$ quartile (54.1, 92.4] (µg/mL)
[0, 0.5]	33	40	40	33
(0.5, 1.5]	12	11	9	11
(1.5, 2.5]	8	5	4	8
(2.5, 3.5]	2	3	3	2
(3.5, 4.5]	3	0	1	1
(4.5, 5.5]	0	0	1	2
(5.5, 6.5]	1	0	0	1
(6.5, 7.5]	0	0	1	0
(7.5, 9.36]	0	0	0	1

Source: Report CP-15-001, Page 13

The dose-response relationship of CAE is unclear as there was only one dose (3 mg/kg) studied in the Phase 3 studies (3082 and 3083) that used CAE as the primary endpoint.

2.5.2 What are the characteristics of the exposure-response relationship for safety?

There is no significant E-R relationship between $C_{av,ss}$ and muscle disorder AE. There is no apparent dose-response trend for serum creatine phosphokinase (CPK) concentration.

- E-R relationship of muscle disorder AE

Among adverse events incidences that were no less than 1% in the reslizumab 3.0 mg/kg treatment group, only myalgia showed approximately 2-fold increase of the incidence compared to placebo group (Table 2.6). The myalgia occurred 0.55% (4/730) of placebo-treated patients and 0.97% (10/1028) in reslizumab 3 mg/kg-treated patients for Cohort 3 (Studies 10, 3081, 3082, 3083 and 3084). In addition, creatine phosphokinase (CPK) elevations beyond the designated potentially clinically significant threshold for the ISS/SCS (CTCAE°grade 3: >5 × ULN) were observed more frequently during reslizumab 3.0 mg/kg treatment compared with placebo (2% and 1%, respectively). These values were generally transient and asymptomatic; there is no evidence of treatment-related myopathy, rhabdomyolysis, or myositis.

Table 2.6 Adverse Events Occurring in at Least 1% of Patients in the Reslizumab 3.0 mg/kg Treatment Group and More Frequently Than in the Placebo Group by Treatment Groups

MedDRA Preferred Term	Number (%) of patients	
	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Patients with at least 1 AE	589 (80.7)	690 (67.1)
Urinary tract infection	24 (3.3)	34 (3.3[a])
Oropharyngeal pain	16 (2.2)	27 (2.6)
Blood creatine phosphokinase increased	12 (1.6)	20 (1.9)
Nasal congestion	7 (1.0)	13 (1.3)
Respiratory tract infection viral	8 (1.1)	12 (1.2)
Myalgia	4 (0.55)	10 (0.97)

Data of Cohort 3 (Studies 10, 3081, 3082, 3083, and 3084) were summarized
Source: Summary of clinical safety.pdf, Page 65, Table 19

Because the myalgia incidence was less than 1% and PK information was unavailable from Studies 3083 and 3084, the E-R analysis was conducted in a separate pooled PK/PD data set. A total of 1100 patients with 59 muscle disorder AE records from Studies 10, 290, 3081, and 3082 were used for development of the population PK/PD model for muscle disorder AE. The occurrence of muscle disorder adverse events used in this analysis was defined by a broadly ranging muscle disorder category based on the standardized Medical Dictionary for Regulatory Activities queries; and this classification was not listed as an independent category in safety summary of Phase 3 clinical studies. For clinical meaning of this muscle disorder classification, refer to primary review by medical reviewer Dr. Donohue.

(b) (4)

(b) (4)

the usage of (b) (4) as

reslizumab exposure in the exposure-response analysis is not appropriate. (b) (4)

No significant exposure-response relationship was established by the Sponsor when reslizumab C_{min} or $C_{av,ss}$ were used as exposure variable. The median exposure measures for the patients who experienced muscle disorders were generally lower as compared to the median for those patients who did not experience muscle disorders (Table 2.7).

Table 2.7 Comparison of Reslizumab Exposure Variables between Patients with or without Muscle Disorder Adverse Events*

	Patient Number	(b) (4)	C_{min} (µg/mL)	$C_{av,ss}$ (µg/mL)
Reslizumab-Treated Patients with Muscle Disorder AE	33		3.47 (111%)	11.46 (45%)
Reslizumab-Treated Patients without Muscle Disorder AE	601		5.02 (104%)	12.08 (47%)

*Geometric means (CV%) of dose normalized exposure variables in patients received reslizumab treatment

(b) (4)

C_{min}: Reslizumab trough concentration.
Cav,ss: Reslizumab average concentration at steady state.
Source: Reviewer's summary from aefirst.xpt

Reviewer conducted an independent exposure-response analysis based on the C_{min} or $C_{av,ss}$ values. No significant relationship was observed (Table 17 and Table 18 from Pharmacometrics Review). This confirmed the Sponsor's analysis.

In addition, dose-response relationship of muscle disorder AE was not clearly demonstrated (Table 2.8). The muscle disorder AE incidence was comparable between placebo and reslizumab 3mg/kg treatment (~ 5%). The incidence was lower (~ 3%) in 0.3 mg/kg treatment group and higher in (~ 10%) 1 mg/kg group. The majority of the muscle disorder AEs (approximately 70%) occurred during the first 90 days of treatment.

Table 2.8 Incidence of Muscle Disorder Adverse Events and Median Age by Reslizumab Dose

	Placebo	Reslizumab		
		0.3 mg/kg	1 mg/kg	3 mg/kg
Muscle Disorder AE*	26/466 (5.6%)	6/174 (3.4%)	7/73 (9.6%)	20/387 (5.2%)
Age (years)#	45.6 (14.3)	44.9 (13.7)	46.5 (14.1)	45.5 (14.0)

* Number of patients who had AE/patients total number (incidence)
# Arithmetic mean (SD)
Source: Reviewer's summary from aefirst.xpt

- E-R relationship of serum CPK

Although the mean increase of CPK values were numerically higher in reslizumab treatment groups than the placebo group, the CPK baseline values were higher in reslizumab treatment groups than the

placebo group (Table 8 of Pharmacometrics Review). In addition, there is no clear dose-response trend observed for CPK in a 10-fold range of reslizumab dose. Therefore no PK/PD modeling was performed for the safety lab CPK since no exposure-response relationship was apparent.

2.5.3 Does this drug prolong the QT or QTc interval?

No thorough QTc study was conducted for reslizumab. The potential for reslizumab to prolong QT or QTc interval is low.

In Study 1102, triplicate ECGs were collected at each PK time point and were compared to baseline. There was no apparent trend toward an increase in QTcF with an increase in the serum concentration of reslizumab (Table 4.17). Overall, values of mean increases of QTcF were minimal and without indication of a relationship to increasing dose, expected time of maximal concentration, or increasing duration of exposure to reslizumab.

2.5.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Yes, the proposed dosing regimen of 3 mg/kg is consistent with the known E-R relationship.

- For E-R relationship for efficacy:
  - There is a lack of apparent trend for change in the rate of CAE with increasing reslizumab exposure (Table 2.4); therefore no dose adjustment is needed for the purpose of reduction of CAE.

  - There is an E-R relationship for FEV1 improvement from baseline. A dose-dependent numerical increase of FEV1 at Week 16 was observed from Phase 3 Study 3081. A time-dependent E_{max} model estimated an approximately 70 mL of more FEV1 improvement at Week 16 from 0.3 mg/kg to 3 mg/kg reslizumab treatment. Therefore a higher dose (3mg/kg) is preferred for the purpose of greater improvement of FEV1 from baseline.

- For E-R relationship for safety:

There is no significant E-R relationship between reslizumab steady state average concentration $C_{av,ss}$ and muscle disorder AE.

For all the adverse events incidences that were no less than 1% in the reslizumab 3.0 mg/kg treatment group, only myalgia showed approximately 2-fold increase of the incidence compared to placebo group (Table 2.5). Although CPK elevations were observed more frequently during reslizumab 3.0 mg/kg treatment compared with placebo group, there was no case of rhabdomyolysis reported.

An E-R analysis was conducted on muscle disorder adverse events, which was defined by a broadly ranging muscle disorder category based on the standardized Medical Dictionary for Regulatory Activities queries. The results showed there was no significant E-R relationship between $C_{av,ss}$ and muscle disorder AE. Therefore no dose adjustment is needed for the purpose of reduction of muscle disorder adverse events.

2.6 PK Characteristics of the Drug

2.6.1 What are the single and multiple dose PK parameters of drug in healthy adults?

Study 1102 compared reslizumab PK profiles following administrations of single IV dose and five IV doses (Q 28 days) in healthy adults. In total 50 Japanese and 50 non-Japanese healthy subjects received reslizumab treatment with dosing levels of 0.3 mg/kg, 1 mg/kg, 2 mg/kg, and 3 mg/kg.

The PK parameters were similar between Japanese and non-Japanese subjects (Table 4.13 and Table 4.14). The PK profiles following the first dose and the fifth dose of 3 mg/kg reslizumab in non-Japanese subjects are shown in Figure 2.3. The summary of PK parameters following the first dose and the fifth dose of 3 mg/kg reslizumab in non-Japanese subjects are shown in Table 2.9. The mean CL and volume of distribution for reslizumab was 0.110 mL/h/kg (or 0.193 L/day for subjects weighing 73 kg) and 94.2 mL/kg (or 6.88 L for subjects weighing 73 kg), respectively. The mean elimination half-life was about 26 days. The observed accumulation ratio following fifth dose was about 1.5.

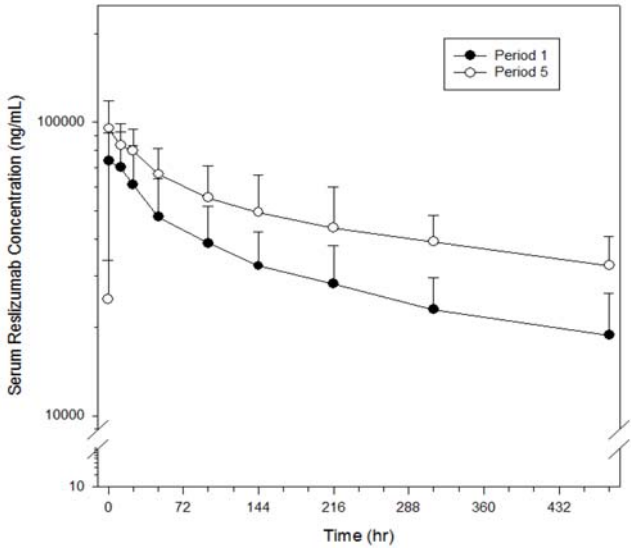

Figure 2.3 Mean (±SD) reslizumab serum concentration-time profiles (semi-log scale) following 3 mg/kg IV single dose (Period 1, N=21) and multiple dose (Period 2, N=17) administration in non-Japanese healthy subjects from Study 1102. (Source: summary-clin-pharm.pdf, page 32, Figure 1)

Table 2.9 Mean (SD) PK Parameters Following the First Dose and the Fifth Dose of 3 mg/kg Reslizumab IV Administration in Non-Japanese Healthy Subjects

	First Dose (N=21)	Fifth Dose (N=17)
C_{max} (µg/mL)	78.0 (20.4)	96.2 (22.1)
T_{max}* (h)	0.85	0.85
AUC_{0-t} (µg·h/mL)	17988 (5606)	47956 (12544)
AUC_{0-D28}[§] (µg·h/mL)	18117 (5485)	28442 (6306)
$t_{1/2}$[#] (Day)	-	25.8 (7.8)
CL (mL/h/kg)	-	0.110 (0.025)
Vz (mL/Kg)	-	94.2 (16.4)
R_{obs}	-	1.53 (0.32)

* Median
[#] Harmonic mean
[§] $AUC_{0-\tau}$ for the fifth dose
Source: summary-clin-pharm.pdf, page 33 Table 6

2.6.2 How does the PK of the drug in healthy adults compare to that in patients with the target disease?

The geometric mean of CL was similar between healthy subjects and asthmatic patients.
According to the popPK analysis, the geometric mean of CL of healthy subjects (from Studies 1102 and 1107) and asthmatic subjects (from Studies 350, 290, 10, 3081, and 3082) was 7.27 and 7.21 mL/hr, respectively (Figure 2.4).

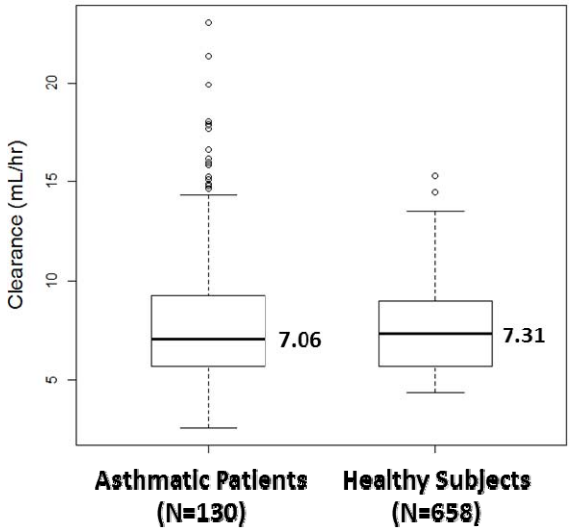

Figure 2.4 Box plot of reslizumab clearance between asthmatic patients (N=658) and healthy subjects (N=130) from popPK analysis. (Source: reviewer's analysis)

2.6.3 What are the characteristics of drug absorption?

Although the IV infusion is the proposed administration route, subcutaneous (SC) route was also investigated in Study 1107. The absolute bioavailability via SC route was approximately 67%.

2.6.4 What are the characteristics of drug distribution?

The estimated typical value of central volume and peripheral volume is 3.13 L (CV=26.0%) and 2.05 L (CV=54.8%), respectively (Table 1 of Pharmacometrics Review). The post-hoc geometric mean of volume of distribution at steady state is 5.27 L (CV=26.3%).

2.6.5 What are the characteristics of drug metabolism?

Reslizumab is a humanized IgG_4 monoclonal antibody that is believed to be degraded by enzymatic proteolysis into small peptides and amino acids. As reslizumab binds to a soluble target, linear non-target-mediated clearance is expected.

2.6.6 What are the characteristics of drug elimination?

The estimated reslizumab CL is 7.16 ml/h or 0.172 L/day (CV=33.3%) in a subject weighing 73 kg following 3 mg/kg IV administration (Table 1 of Pharmacometrics Review). The mean apparent terminal elimination half-life based upon final population mean parameter estimates is estimated at approximately 568 hours or 23.7 days.

2.6.7 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

The exposure of reslizumab was approximately dose proportional.

Although a dose range of 0.3 to 3 mg/kg was investigated in Study 1102, the study was not powered to assess the dose proportionality. Therefore, an exploratory graphic were undertaken to assess whether there was any indication of a consistent deviation from dose proportionality (Figure 2.5).

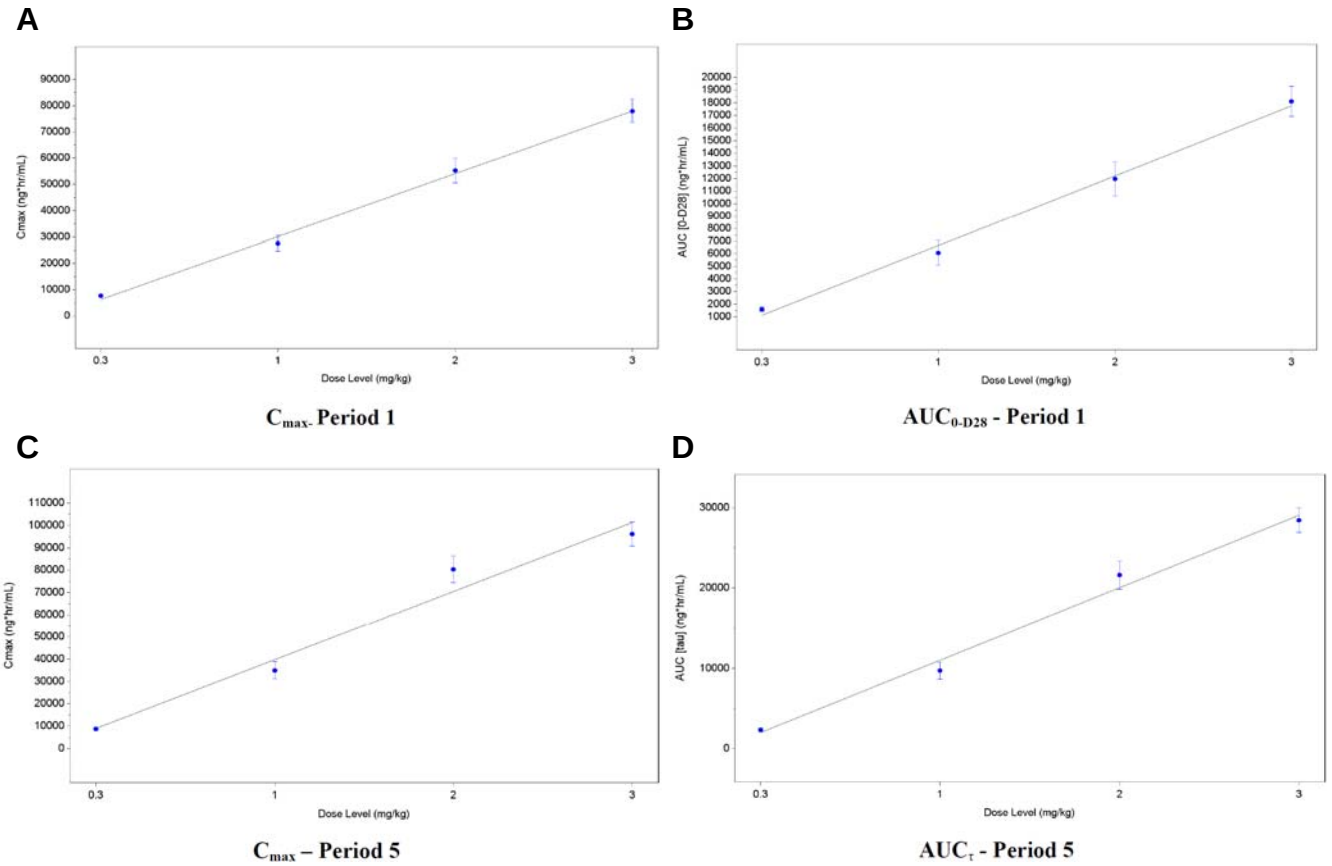

Figure 2.5 Mean C_{max} and AUC following the first dose (A and B) and the fifth dose (C and D) of IV administration of 0.3, 1, 2, and 3 mg/kg reslizumab in non-Japanese healthy subjects from study 1102. (Source: summary-clinical-pharmacology.pdf, page 38, Figure 4)

The results of this analysis showed no consistent or notable trend toward a deviation from proportionality following either a single dose or multiple doses.

2.6.8 How do the PK parameters change with time following chronic dosing?

Reslizumab PK is time-independent. The CL of reslizumab following the first dose and the fifth dose were similar in both Japanese and non-Japanese subjects (Table 2.10).

Table 2.10 Mean (SD) PK Parameters Following the First Dose and the Fifth Dose of Reslizumab IV Administration in Study 1102

Clearance (mL/hr/kg)		First Dose*	Fifth Dose*
0.3 mg/kg	Japanese	0.119 (0.069)	0.130 (0.045)
	Non-Japanese	0.147 (0.05)	0.136 (0.031)
1.0 mg/kg	Japanese	0.140 (0.049)	0.134 (0.035)
	Non-Japanese	0.139 (0.069)	0.114 (0.041)

2.0 mg/kg	**Japanese**	0.108 (0.034)	0.091 (0.017)
	Non-Japanese	0.127 (0.047)	0.098 (0.025)
3.0 mg/kg	**Japanese**	0.140 (0.048)	0.124 (0.028)
	Non-Japanese	0.123 (0.036)	0.110 (0.025)

* Arithmetic mean (SD)
Source: Report DP-2013-035, page 19, Table 2

2.6.9 Is there evidence for a circadian rhythm of the PK?

There was no evidence for a circadian rhythm of reslizumab in healthy subjects or asthma patients.

2.7 Intrinsic Factors

2.7.1 What are the major intrinsic factors responsible for the inter-subject variability exposure in patients with the target disease and how much of the variability is explained by the identified covariates?

Body weight was the only statistically significant covariate for clearance.

The popPK analysis (Report CP-11-006) evaluated the effects of following intrinsic factors on CL: age, race, sex, baseline weight, baseline body mass index, baseline renal function, baseline liver function tests, and ADA status. Body weight was the only statistically significant covariate for clearance. The inter-subject variability (CV%) of CL reduced from 36.1% to 33.3% by introducing the body weight as a covariate.

2.7.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

The effect of body weight on PK is not clinically important given the flatness of E-R relationship for efficacy (reduction of clinical asthma exacerbation), so no dose adjustment is warranted with regard to body weight.

2.7.2.1 Severity of Disease state

The effect of disease severity was not evaluated in the popPK analysis (Report CP-11-006). Reslizumab CL was similar between healthy subjects and asthmatic patients.

2.7.2.2 Body Weight

In popPK analysis (Report CP-11-006), body weight was identified as a statistically significant covariate for CL. The power for body weight on CL is estimated to be 0.561 (SE=0.0457). The effect of body weight on reslizumab CL was summarized in Figure 2.6. 804 subjects from popPK analysis outcome were divided into four quartiles and the post-hoc geometric mean CL of the fourth quartile (median body weight=96.6) is 42% higher than that of the first quartile (median body weight=56.7).

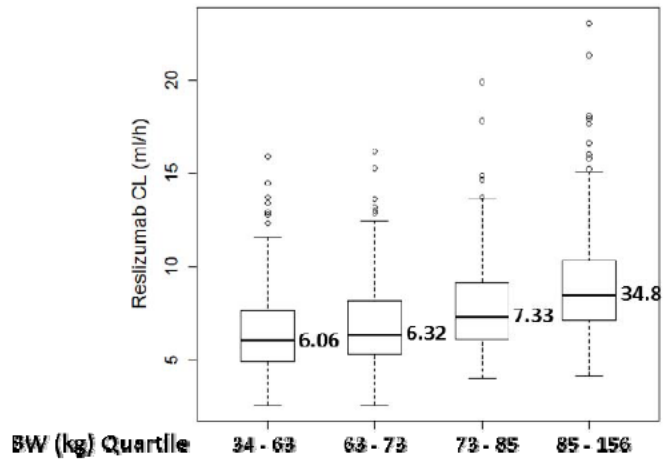

Figure 2.6 Box plot of CL of reslizumab by body weight quartiles (N ~ 200 for each quartile) via popPK analysis (Report CP-11-006). (Source: Model 001, reviewer's analysis).

2.7.2.3 Elderly

In popPK analysis (Report CP-11-006), age was not identified as a statistically significant covariate for CL. Reslizumab CL is similar between elderly (age ≥ 65 years) and younger adults (65 years > age ≥ 18 years). The post-hoc geometric mean of CL in elderly and younger adults was 7.36 and 7.19 mL/h, respectively (Figure 2.7).

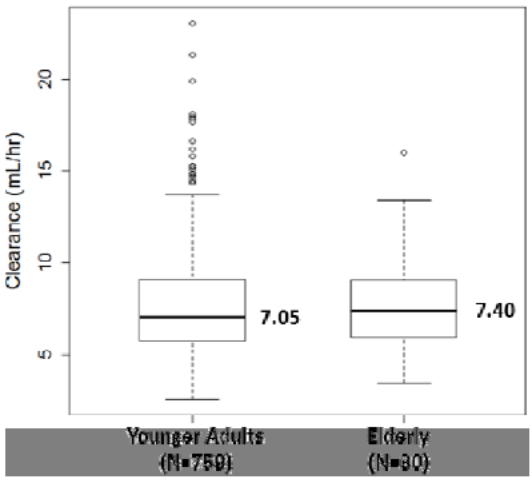

Figure 2.7 Box plot of CL of reslizumab in elderly (age ≥ 65 years, N=30) and younger adults (65 years > age ≥ 18 years, N=759). (Source: Model 001, reviewer's analysis).

2.7.2.4 Pediatric Patients

A total 15 adolescents (9 from Study 3081 and 6 from Study 3082) were included in popPK analysis (Report CP-11-006). Age was not identified as a statistically significant covariate for CL. (b) (4) The post-hoc geometric mean of CL in adolescents and younger adults was (b) (4) mL/h, respectively (Figure 2.8).

Figure 2.8 Box plot of CL of reslizumab in adolescents (age < 18 years, N=15) and younger adults (65 years > age ≥ 18 years, N=759). (Source: Model 001, reviewer's analysis).

Results from Phase 3 studies showed there was a lack of efficacy (reduction of exacerbation and improvement of FEV1) in adolescent population as the point estimate favored placebo treatment. For details, refer to primary review by medical reviewer Dr. Donohue. (b) (4)

2.7.2.5 Race/Ethnicity

In popPK analysis (Report CP-11-006), age was not identified as a statistically significant covariate for CL (Figure 3 of Pharmacometrics Review). The post-hoc geometric mean of CL in Whites, Blacks, and Asians is 7.21, 8.82, and 6.78, respectively.

2.7.2.6 Renal Impairment

No formal study was conducted to assess the effect of renal impairment on the reslizumab PK. In popPK analysis (Report CP-11-006), renal function was not identified as a statistically significant covariate for CL (Figure 7 of Pharmacometrics Review). The post-hoc geometric mean of CL in patients with normal renal function (EGFR ≥ 90 mL/min), mild renal impairment (90 > EGFR ≥ 60 mL/min), and moderate renal impairment (60 > EGFR ≥ 30 mL/min) is 7.36, 7.16, and 6.70, respectively. There was only one patient with severe renal impairment (EGFR < 30 mL/min) in the popPK analyzing dataset. The CL of that subject was 9.41 mL/h.

2.7.2.7 Hepatic Impairment

No formal study was conducted to assess the effect of hepatic impairment on the reslizumab PK. In popPK analysis (Report CP-11-006), hepatic function was not identified as a statistically significant covariate for CL (Figure 8 of Pharmacometrics Review). The post-hoc geometric mean of CL in patients with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (as classified by NCI hepatic dysfunction grouping) is 7.24, 6.28, and 8.19, respectively. There was no patient with severe hepatic impairment included in the popPK analyzing dataset.

2.7.2.8 What pregnancy and lactation use information is available?

There are no adequate and well-controlled studies with reslizumab in pregnant women. IV doses of reslizumab in mice (150 mg/m^2) on gestation day 6 and in rabbits (600 mg/m^2) on gestation day 7, which is equivalent to 1.35- (mice) and 5.4- (rabbits) times an adult human dose of 3 mg/kg (111 mg/m^2) on a mg/m^2 basis, did not result in any maternal toxicity or fetal malformations.

2.7.3 Does genetic variation impact exposure and/or response?

No analysis was conducted on genetic variation impact on exposure and/or response.

2.7.4 Immunogenicity

2.7.4.1 What is the incidence of the formation of the ADA, including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Three generations of ADA detecting methods were developed and SOP1-015162 was used in all the Phase 3 studies. The rate of pre-existing antibodies in 3 mg/kg groups from four Phase 3 studies was 3.0% (Table 2.11). The rate of treatment-emergent ADA response [if 1) the patient was tested pre-dose sample negative and post-dose sample positive; or 2) the ADA titer of post-dose sample increase ≥4 folds comparing to the positive titer of pre-dose sample of the patient] in 3 mg/kg groups from four Phase 3 studies was 5.4%. Among treatment-emergent ADA positive patients, 43% was transient (only positive in one post-dose sample). The geometric mean titers was 1:7.6 (CV=121%). The ADA sampling schedules for Phase 3 studies were adequate (Table 2.11).

Table 2.11 Summary of ADA Results from Four Phase 3 Studies in Asthma Patients

Study	Reslizumab Dose (mg/kg)	Rate of Pre-existing ADA	Rate of treatment-emergent ADA	Transient ADA rate	ADA Titer*	Duration of Study	ADA sampling schedule
3081	0.3	8.0% (8/100)	11.8% (12/102)	25% (3/12)	1:7.3 (80%)	16 weeks	Baseline, Week 8,16
	3	7.9% (8/101)	10.7% (11/103)	55% (6/11)	1:7.9 (86%)		
3082	3	1.6% (4/243)	3.3% (8/245)	63% (5/8)	1:4.6 (47%)	52 weeks	Baseline, Weeks 16, 32, 48, and 52
3083	3	1.9% (4/207)	6.6% (15/226)	13% (2/15)	1:8.7 (125%)	52 weeks	Baseline, Weeks 16, 32, 48, and 52
3084	3	3.2% (13/402)	4.6% (19/409)	53% (10/19)	1:8.2 (160%)	16 weeks	Baseline, Week 8,16
3 mg/kg in Total	3	3.0% (29/953)	5.4% (53/983)	43% (23/52)	1:7.6 (121%)	-	-

*geometric mean (CV%) of treatment-emergent ADA positive samples
Source: adapted from section 5.3.5.3 Integrated Immunogenicity Report, Page 36, Table 15

2.7.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

There is no apparent impact of ADA on reslizumab PK, eosinophil response, and clinical efficacy in terms of FEV1 and CAE measurements.

Only 561 subjects included in the final popPK data set (ph123pk3) had their immunogenicity results available. 41 (7.3%) of them were treatment-emergent ADA positive. The geometric mean of reslizumab CL in ADA-positive subjects was approximately 8% higher than that of ADA-negative subjects.

Blood eosinophil counts at each visit were compared between the ADA-negative and ADA-positive patients in studies 10, 3081, 3082, 3083, and 3084 utilizing the 3 mg/kg dose. The overall pattern of blood eosinophil suppression by reslizumab in treatment-emergent ADA-positive patients, as a group, was not different from ADA-negative patients.

2.7.4.3 Does the ADA have neutralizing activity?

The neutralizing capacity of reslizumab ADA was not evaluated in the asthma program. For details, refer to primary review by OBP Reviewer Dr. Pedras-Vasconcelos.

2.7.4.4 What is the impact of ADA on clinical efficacy?

In studies 3082 and 3083, CAE was evaluated in 477 patients treated with 3 mg/kg reslizumab. Among them, 23 patients were treatment-emergent ADA-positive. The adjusted CAE rate was 0.11 (95% CI=0.02, 0.53) and 0.95 (95% CI=0.68, 1.31) for ADA-positive and ADA-negative patients (Table 3 of Pharmacometrics Review). Therefore, CAE was not increased in ADA-positive patients. In addition, there was no significant difference for FEV1 improvement from baseline between ADA-positive and ADA-negative patients (Table 4 of Pharmacometrics Review)

2.7.4.5 What is the impact of ADA on clinical safety?

Overall, the adverse event profile in patients with positive ADA status during the treatment period was not meaningfully different from the ADA negative population.

Adverse events from studies 10, 3081, 3082, 3083, and 3084 were pooled to analyze the effect of ADA on safety. 7.2% (81/1131) patients were ADA-positive. The incidence of adverse events by system organ class was similar across ADA-positive (64% patients) and negative (66%) patients. The incidence of adverse events by most common adverse events (≥ 5%) was also similar across ADA-positive (64% patients) and negative (66%) patients.

Results from Phase 3 studies demonstrated that there were 4 anaphylaxis cases in reslizumab treatment group whereas 1 case in placebo group. All the anaphylaxis patients were tested ADA negative for all their samples. For potential role of anti-α gal IgE antibody involved in anaphylaxis, refer to primary review by OBP Reviewer Dr. Pedras-Vasconcelos.

2.8 Extrinsic Factors

2.8.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The effects of reslizumab, IL-5 and reslizumab on the mRNA levels of CYP enzymes were evaluated in cultured human hepatocytes in an *in vitro* study XT133130. Following 3-day treatment of 200 µg/mL reslizumab (approximately 2-fold as high as the C_{max} following 3 mg/kg treatment), hepatocyte CYP1A2, 2B6, and 3A4 mRNA level changed -16%, +5%, and -14%, respectively. CYP enzyme mRNA levels changed less than 5% upon 3-day 400 pg/mL IL-5 treatment (Table 4.29).

2.8.2 What are the drug-drug interactions?

There is currently no evidence in the literature discussing drug-drug interactions associated with IL-5 or anti-IL-5 antibodies and there are no data to suggest that IL-5 is involved in the regulation of enzymes or pathways responsible for drug metabolism. No clinical studies to specifically evaluate drug-drug interactions with reslizumab have been conducted.

The popPK analysis did not identify that two classes of concomitant medications, systemic corticosteroid and leukotriene antagonist, had significant effects on reslizumab PK (Figure 10 of Pharmacometrics review).

2.8.3 Does the label specify co-administration of another drug?

Reslizumab is indicated in adults [redacted] (b) (4)

2.8.4 What other co-medications are likely to be administered to the target population?

The baseline asthma therapy regimen for patients in Phase 3 Studies (3081, 3082, and 3083) included, but not limited to: inhaled corticosteroids, oral corticosteroids, leukotriene antagonists, 5-lipoxygenase inhibitors, and leukotriene antagonists.

2.9 General Biopharmaceutics

2.9.1 How is the proposed to-be-marketed formulation/device linked to the clinical development formulation/device?

The proposed to-be marketed formulation is the same as the clinical development formulation.

Throughout the clinical development program, the drug product formulation of reslizumab has remained the same, and various Type 1 glass vials have been used as the primary container, ranging in size from 2 mL to 10 mL.

2.9.2 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The intravenous administration route is unaffected by food and no food-effect studies have been conducted.

2.10 Analytical Section

2.10.1 What bioanalytical methods were used to assess reslizumab serum concentrations?

Serum concentrations of reslizumab were determined by enzyme-linked immunosorbent assay (ELISA) method. The assay utilized a sandwich ELISA format. [redacted] (b) (4)

[redacted] (b) (4)

The assays analyzing reslizumab concentrations from earlier studies (Studies 350, 290) were conducted by Schering-Plough Research Institute (validation Report S-30264). The LLOQ of these earlier assays ranged from 120 ng/mL to 32 ng/mL. The assay analyzing reslizumab concentrations from later studies (Studies 10, 1102, 1107, 3801, 3802, 3083, and 3085) were conducted by [redacted] (b) (4) (validation Report [redacted] (b) (4) 256-0702). The LLOQ of this assay was 20 ng/mL.

2.10.2 For all moieties measured, is free, bound, or total measured?

Free reslizumab was measured.

2.10.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

The bioanalytical assays used in Phase 2/3 studies (Studies 10, 1102, 1107, 3801, 3802, 3083, and 3085) were shown to be sensitive, selective, reproducible and accurate for the determination of free reslizumab in human serum, with an LLOQ of 20 ng/ml and a coefficient of variance (CV) for the inter- and intra-assay precision of less than 20%.

The range of the standard curve was 20 to 420 ng/mL. The lower limit of quantitation is 20 ng/mL. The intra-batch and inter-batch accuracy ranged from -3.8% to +18.1%, and -3.3% to +11.0%, respectively. The intra-batch and inter-batch precision ranged from 0.8% to 7.0%, and 4.4% to 5.9%, respectively. The serum samples were stable in room temperature for 7 hours. The serum samples could sustain 11 cycles of freeze/thaw at -70 ºC and 3 cycles of freeze/thaw at -20 ºC (Table 2.12).

Table 2.12 Summary of Key Validation Parameters of Reslizumab PK Method

Report Title	**Validation of an ELISA Method for Determination of Reslizumab in Human Serum**
Report Number	[redacted] (b) (4) 256-0702
Minimum Required Dilution	1:10 (as of Amendment 4)
Calibration Range:	20 - 420 ng/mL
Matrix QC Concentrations	20, 60, 100, 320 and 420 ng/mL (LLOQ, Low, Mid, High, and ULOQ QC)
QC Intra-batch Precision (%CV)	0.8% - 7.0%
QC Intra-batch Accuracy (%Diff)	-3.8% - 18.1%
QC Inter-batch Precision (%CV)	4.4% - 5.9%
QC Inter-batch Accuracy (%Diff)	-3.3% - 11.0%
Room Temperature Stability Human Serum	7 hours at Room Temperature
Freeze/Thaw Stability in Human Serum	11 cycles at -70°C, and 3 cycle at –20°C
Long-term Frozen Stability in Human Serum	189 days at -20°C, 1008 days at -70°C
Dilution Linearity	25,000 ng/mL diluted 5, 10, 25, 100, 250, and 400 fold; 100,000 ng/mL diluted 400 and 800 fold, 400,000 ng/mL diluted 2,000 and 4,000 fold
Selectivity (10 healthy sera lots, spiked 60 ng/mL)	>90% of tested spiked lots had recovery within 100±30%
Selectivity (15 asthma sera lots, spiked 60 ng/mL)[a]	>90% of tested spiked lots had recovery within 100±30%
Selectivity (15 asthma sera lots, spiked 320 ng/mL) [a]	100% of tested spiked lots had recovery within 100±30%

[a] Method SOP 172-1204
QC = quality control; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; CV = coefficient of variation.

Source: section 2.7.1, summary-biopharm.pdf, page 29, Appendix Table 2

2.10.4 What bioanalytical methods are used to assess IL-5 concentrations?

The IL-5 serum concentration was measured in Study 1102 as an exploratory PD biomarker. The analysis was conducted at [redacted] (b) (4) Serum IL-5 was measured using a quantitative multiplex bead assay using kits (reference range 0 to 5 pg/mL). All the serum IL-5 values were within the normal range, with the exception of period 5 values for Subject 005085 (non-Japanese, 3.0 mg/kg reslizumab). For this subject, IL-5 level prior to period 5 dosing was high, 6.7 pg/mL (normal range 0 to 4.5 pg/mL), and for the postdose values up to day 3 after dosing values remained high, ranging between 5.8 and 8.9 pg/mL for all subsequent time points (from day 7 onwards), values of IL-5 were within normal ranges for the subject.

2.10.5 What bioanalytical methods are used to assess the formation of the anti-drug antibodies?

A total three generations of assay were developed to detect anti-reslizumab antibody (Table 2.13). (b) (4)

[redacted]

Table 2.13 Three Generations of Assays Used to Determine Reslizumab Anti-Drug Antibodies

Sponsor	Binding ADA method			
	Format	Positive Control	Screen cut point	Confirmatory cut point
Schering Plough	(b) (4)			
Cephalon				
Teva				

ADA = anti-drug antibody; RU = response units; ELISA = enzyme-linked immunosorbent assay; OD = optical density

(Source: section 2.7.1, summary-biopharm.pdf, page 6, Table 5)

Figure 2.9 Configuration of homogenous bridging ELISA assay (Reviewer's diagram)

The drug tolerance, selectivity, relative sensitivity, accuracy, precision, and cut point are listed in Table 2.14.

2.10.6 What is the performance of the neutralizing assay?

The neutralizing capacity of reslizumab ADA was not evaluated in the asthma program. For details, refer to primary review by OBP Reviewer Dr. Pedras-Vasconcelos.

Table 2.14 Summary Method Performance Parameters of SOP-015162 Homogenous Bridging ELISA Assay

Validation Parameters	Results
	(b) (4)

(Source: section 5.3.1.4, Validation Report SOP-015162-AVR-01.pdf, page 9-10, Table 2)

3 DETAILED LABELING RECOMMENDATIONS

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

4. Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study I96-350 (Study 001)

Study Type: Phase 1 single dose, dose-ranging PK, PD and safety study in adult patients with severe asthma
Study Dates: 09/18/1997 – 11/11/1999
Sponsor: Schering-Plough Corporation

Title:
Rising single-Dose, safety, tolerance, and pharmacokinetics of SCH 55700 in subjects with severe asthma

Objective:

- To evaluate the safety and tolerability of SCH 55700 when administered intravenously at single doses of 0.03, 0.1, 0.3 and 1 mg/kg to male and female subjects with severe asthma.
- To determine the single dose pharmacokinetics of SCH 55700 in subjects with severe asthma.
- To evaluate the activity of SCH 55700 on the clinical course of severe asthma.

Study Design and Method:
This study was conducted outside the U.S. This investigation was a randomized, multicenter, double-blind, placebo-controlled, five-parallel-group, single IV dose, dose-ranging (0.03, 0.1, 0.3 and 3 mg/kg) study in 32 male patients with severe asthma. The study was conducted in five groups and within each group patients were randomized to receive one of the following treatments:

Group 1: 0.03 mg/kg SCH 55700 (n=2) or matching placebo (n=1)
Group 2: 0.1 mg/kg SCH 55700 (n=4) or matching placebo (n=1)
Group 3: 0.3 mg/kg SCH 55700 (n=6) or matching placebo (n=2)
Group 4: 1 mg/kg SCH 55700 (n=6) or matching placebo (n=2)
Group 5: 1 mg/kg SCH 55700 (n=6) or matching placebo (n=2)

Groups 1 and 2 were to receive their dose as an IV bolus, while Groups 3, 4, and 5 were to receive their dose as an IV infusion over 30 minutes. Group 1 must have demonstrated acceptable safety and tolerability at the Day 15 visit before Group 2 subjects were dosed. Likewise, the next higher dose in the dose progression was to be administered only if the safety and tolerability of the previously administered dose had been demonstrated at the Day 15 visit.

Subjects must have had a diagnosis of asthma for at least 2 years and subject's baseline FEV1must have been ≥40% and ≤80% predicted normal value at the Baseline Visit. Subjects must currently take any of the following:

- 1600 µg/daily budesonide
- 2000 µg/daily beclomethasone
- 1000 µg/daily fluticasone
- Oral corticosteroids

No cutoff of eosinophil counts from any tissues or body fluid was proposed for inclusion criteria.

Pulmonary function (FEV1 and FVC measurement) was measured at baseline, 1h, 6h, 24 h, 48 h, Day 8, 15, 30, 60, 90, 120, 150 and 180 following the single dose treatment for patients in Groups 3, 4 and 5. Pulmonary function was measured only up to 90 days post-dose from patients in Group 1 and 2.

Blood samples for PK evaluation were obtained prior to drug administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24 and 48 hr and on Days 8, 15, 30, 90, 120, 150 and 180 following drug administration for patients in Groups 3, 4 and 5. Blood samples were collected only up to 90 days post-dose from patients in Groups 1 and 2.

Blood/serum samples were analyzed for SCH 55700 using a validated immunoassay (ELISA) with an LOQ of 120 ng/ml and/or a validated Bioassay with an LOQ of 300 Schering-Plough Units (1 SPU = 1.15 ng/ml) by the Department of Biotechnology, Schering-Plough Research Institute. Assay results less than 300 SPU/ml were reported as BQL. Displayed PK parameters were estimated from non-compartment model.

47 blood samples were collected for detecting serum neutralizing factors via either biosensor (BIAcore) assay or bioassay.

Primary Endpoints:
No primary endpoints were pre-defined in this study.

PK Results:
Following IV bolus or infusion administration, serum SCH 55700 concentrations declined in a bi-exponential manner (Figure 4.1). Overall, SCH 55700 exposures (C_{max} and AUC) increased in a dose-proportional manor from 0.03 to 1 mg/kg (Table 4.1). The mean volume of distribution and mean was 55.7 – 81 mL/kg and was similar to plasma volume. The mean terminal half-life ranged 25 to 30 days via non-compartment analysis. The high variability of the observed T_{max} values is likely to be an artifact of the slow SCH 55700 elimination and distribution, the frequent sampling during the first 48 hr post-dose and assay variability.

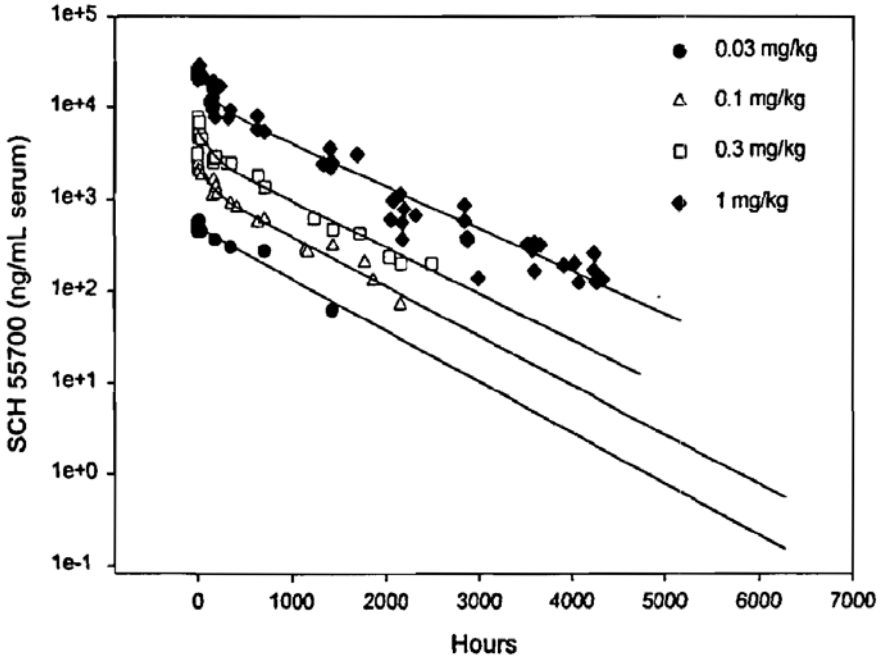

Figure 4.1 Mean serum SCH 55700 serum concentration-time profiles (semi-log scale) following single dose IV administration of 0.03 mg/kg (n=2), 0.1 mg/kg (n=4), 0.3 mg/kg (n=6), and 1.0 mg/kg (n=12) SCH 55700. (Source: CSR 350, page 929, Figure 1)

Table 4.1 Mean (SD) PK Parameters for SCH 55700 Following Single Intravenous Administration

Parameter	Unit	0.03 mg/kg	0.1 mg/kg		0.3 mg/kg		1 mg/kg	
		Mean[b]	Mean[c]	%CV	Mean[e]	%CV	Mean[f]	%CV
Cmax[g]	µg/mL	0.607	2.51	5	7.50	6	30.3	25
Tmax	hr	14	3.02	81	4.85	169	6.88	193
tf	hr	1080	1740	24	1956	32	3482	33
AUC(tf)	µg·hr/mL	314	1119	17	2942	16	12514	32
t½	hr	722[a]	546	17	603[d]	25	588	26
AUC(I)	µg·hr/mL	561[a]	1261	10	3288[d]	12	12885	28
Vd	mL	55.7[a]	63.1	20	81.1[d]	34	68.7	31
CL	mL/hr	0.0500[a]	0.0800	11	0.0922[d]	11	0.0840	32

a: n=1
b: n=2
c: n=4
d: n=5
e: n=6
f: n=12
g: Observed value

(Source: CSR 350, page 919, Table 1)

Immunogenicity Results:

Out of 47 samples, (46 for bioassay} 45 were classified as negative for serum neutralizing factors by both BIAcore and bioassay. The bioassay identified one sample positive for serum neutralizing factors, (patient 3, (b) (4) - visit 8). The BIAcore identified one sample, patient 17 ((b) (6) visit 10) as positive for SNF activity with a borderline value of 107.10 RUs. The sample volume for patient 25 (pre) was only sufficient for analysis by BIAcore and was subsequently not analyzed by bioassay.

Efficacy/PD Results:

- FEV1

Mean changes (unadjusted) in FEV 1 from baseline following placebo and SCH 55700 treatments are presented in Figure 4.2. Subjects in the 0.3 and 1 mg/kg dose groups experienced consistent improvement of FEV1 compared to baseline for at least 90 days.

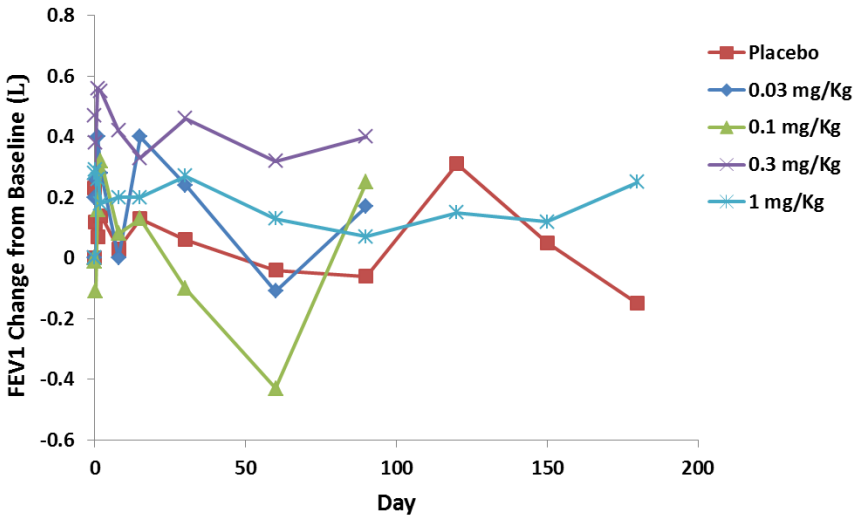

Figure 4.2 FEV1 mean (unadjusted) change from baseline time profile following single dose IV administration of placebo (n=8), 0.03 mg/kg (n=2), 0.1 mg/kg (n=4), 0.3 mg/kg (n=6), and 1.0 mg/kg (n=12) SCH 55700. (Source: adapted from CSR 350, page 60, Table 7)

- Blood Eosinophil Counts

Absolute blood eosinophil counts over time following placebo and SCH 55700 treatments are presented in Figure 4.3. The baseline counts were not balanced as the mean values ranged from 140 cells/μL (0.1 mg/kg group) to 510 cells/μL (0.03 mg/kg group). The blood eosinophil counts reduced from the baseline within 2 days following all the active treatments. The maximal reductions also appeared on Day 2 for all the active treatment groups. The maximal reduction could only be maintained in 1 mg/kg group up to 30 days; whereas the blood eosinophil counts rebound instantly (0.03 mg/kg) or gradually (0.1 mg/kg and 0.3 mg/kg groups).

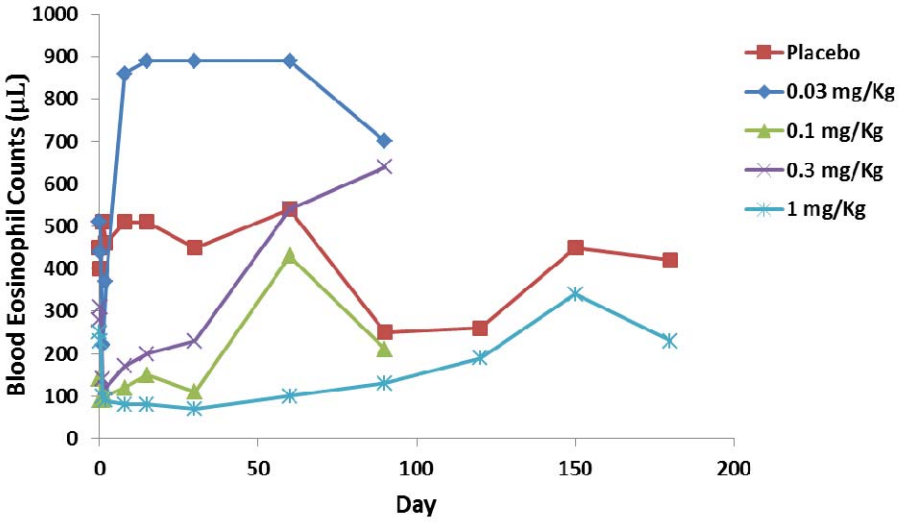

Figure 4.3 Blood eosinophil counts time profile following single dose IV administration of placebo (n=8), 0.03 mg/kg (n=2), 0.1 mg/kg (n=4), 0.3 mg/kg (n=6), and 1.0 mg/kg (n=12) SCH 55700. (Source: adapted from CSR 350, page 63, Table 8)

Conclusions:

- Following single-dose IV administration of SCH 55700, C_{max} and AUC generally increased in a dose-proportional manor from 0.03 to 1 mg/kg. The mean terminal half-life ranged 25 to 30 days.

- A trend toward improved FEV1 was evident through at least Day 90 postdose in the 0.3 and 1 mg/kg treatment groups.

- All the doses of SCH 55700 could reduce blood eosinophil counts and the maximal reduction was achieved on Day 2. Only 1 mg/kg group could maintain the maximal reduction level up to 30 days.

- Among all the groups, there was only one cardiovascular adverse event reported (edema legs) in 1 mg/kg group. No deaths were reported during the study, or within 30 days of the last study visit. Four subjects experienced serious adverse events with two in placebo group and two in 0.1 mg/kg group.

4.1.2 Study P00290 (Study 290)

Study Type: Phase 2, two-dose, dose-ranging, efficacy, immunogenicity and safety study in patients with moderate and severe asthma
Study Dates: 09/14/1999 – 09/06/2001
Sponsor: Schering-Plough Corporation

Title:
Efficacy, safety, and tolerance of two doses of SCH 55700 vs placebo in adults with moderate and severe persistent asthma

Objective:
- To evaluate the activity of SCH 55700 on the clinical course of subjects with asthma maintained, but not adequately controlled on inhaled corticosteroids.
- To evaluate the safety and tolerability of SCH 55700 when administered intravenously at single doses of 0.3 and 1.0 mg/kg to male and female subjects with asthma
- To evaluate the immunogenicity of a repeat dose of SCH 55700

Study Design and Method:
This study was an international trial containing sites located in the U.S. This investigation was a randomized, multicenter, evaluator-blind, placebo-controlled, four-parallel-group, two IV doses (30-minute infusion), dose-ranging (0.3 mg/kg and 1 mg/kg) study in 215 adult patients with inadequately controlled moderate and severe asthma. 38 subjects only received a single dose at Week 1, and 173 subjects received two doses (Week 1 and Week 12). At the baseline visit, subjects meeting the eligibility criteria were randomized to receive one of the following treatments in a 2:2:1:1 ratio:

	First Dose Visit 3 (Baseline)	Second Dose Visit 9 (Week 12)
Group 1	1 mg/kg SCH 55700	1 mg/kg SCH 55700
Group 2	0.3 mg/kg SCH 55700	0.3 mg/kg SCH 55700
Group 3	placebo 0.1 cc/kg	placebo 0.1 cc/kg
Group 4	placebo 0.03 cc/kg	placebo 0.03 cc/kg

Key eligibility criteria included:
- Subjects had moderate to severe, persistent asthma of at least 1 year before enrollment.
- The subject's baseline FEV1 must have been ≥ 50% and ≤ 80% of predicted normal value at screening and baseline visits.
- Subjects must have demonstrated an increase in absolute FEV1 of 12% or greater with an absolute volume increase of at least 200 mL after reversibility testing at screening, or within the previous 12 months.
- An average daily asthma score ≥4 for 7 days prior to Visit 2 and 4 days prior to Visit 3 (randomization visit).
- Mean use of beta-agonists must have been 3-10 inhalations/day measured for 7 days prior to Visit 3.
- Subjects must have been treated with inhaled corticosteroids (≥200 to 500 µg/day) for at least 30 days prior to screening:
    - Fluticasone propionate ≥200µg/day
    - Flunisolide ≥500µg/day
    - Beclomethasone dipropionate ≥400µg/day

- Budesonide DPI ≥200µg/day
- Budesonide MDI ≥400µg/day
- Triamcinolone ≥400µg/day

Pulmonary function (FEV1 and FVC measurement) was measured on Day 1 and during Week 12 prior to dose, and at 1, 4, and 96 h post-dose, and at Week 1, 2, 4, 9, 13, 14, 16, 20, 26, 32, and 38.
Blood samples (4 mL) for PK evaluation were drawn at pre-first-dose, 1h, 4h, 96h, Week 2, 4, 9 following the first dose; and at Week 12 (pre-second-dose, 1h, 4h, 96h), Week 14, 16, 20, 26, 32 and 38 following the second dose.

Serum concentrations of SCH 55700 were determined using a validated immunoassay (ELISA) with an LOQ of 32 ng/ml and/or a validated biological assay with an LOQ of 300 Schering-Plough Units/ml. The ELISA and bioassay methods were calibrated over a range of 32 to 320 ng/mL and 300 to 39760 SPU/mL, respectively. Assay results less than the LLOQ were reported as zero. The PK analysis was performed only on ELISA data.

Blood samples (8 mL) for the determination of anti SCH 55700 antibodies and serum neutralizing factors (SNF) were obtained prior to dosing on Day 1 and during Week 12, and at Week 26, 32, and 38, respectively. Serum samples were analyzed for SNF using a validated biological assay and for anti-SCH 55700 antibodies using a validated biosensor assay

ECG was monitored at screening visit (Day -14) and final visit (Week 38).

Primary Endpoints:
No primary endpoints were pre-defined in this study.

PK Results:
Blood samples of 71/71 and 74/75 treated subjects were collected from 0.3 mg/kg and 1 mg/kg group, respectively. 11 and 16 subjects from 0.3 mg/kg and 1 mg/kg group, respectively, had only Day 1 PK data because these subjects did not receive the second dose.

Following a 30-minute infusion, serum SCH 55700 concentrations declined in a biphasic manner (Figure 4.4). SCH 55700 C_{max} and AUCs increased dose-proportionally from 0.3 mg/kg to 3 mg/kg (Table 4.2). With a dosing interval of 12 weeks, mean C_{trough} of SCH 55700 were less than 5% of the C_{max} obtained on Day 1 (0.3 mg/kg: C_{max} = 9.73 µg/mL vs C_{min} = 0.347 µg/mL; 1 mg/kg: C_{max} = 28.1 µg/mL vs C_{min} = 1.35 µg/mL). Comparison of individual CL values between Day 1 and Week 12 did not reveal any significant changes. The mean volume of distribution was 55.6 to 69.5 mL/kg. The mean terminal half-life was 23 to 26 days.

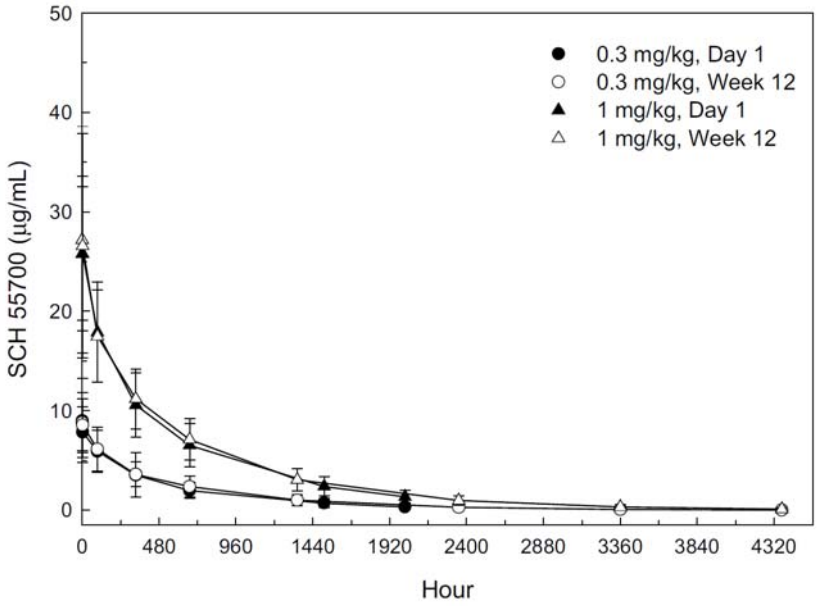

Figure 4.4 Mean (SD) SCH 55700 serum concentration-time profiles following 30-minute IV infusion of 0.3 mg/kg or 1 mg/kg to subjects with moderate to severe asthma. (Source: CSR 290, page 3554, Figure 1)

Table 4.2 Mean PK Parameters for SCH 55700 Following Two-Dose IV Infusion

		0.3 mg/kg						1 mg/kg					
		Day 1			Week 12			Day 1			Week 12		
Parameter	Unit	Mean	CV	n	Mean	CV	n	Mean	CV	n	Mean	CV	n
Cmax	(µg/mL)	9.73	42	68	9.52	32	58	28.1	24	72	29.0	41	53
DN-Cmax	(µg/mL)	32.4[a]	42	68	31.7	32	58	28.1[a]	24	72	29.0	41	53
Tmax[b]	(hr)	15.1	395	68	8.77	261	58	2.55	59	72	2.86	55	53
Cmin	(µg/mL)	0.347	66	58	NA	NA	NA	1.35	47	52	NA	NA	NA
AUC(0-12 wk)	(µg·hr/mL)	4255[c]	31	67	4672[c]	33	57	13367	24	67	14049	22	53
DN-AUC(0-12 wk)	(µg·hr/mL)	14182[c]	31	67	15573[c]	33	57	13367	24	67	14049	22	53
AUC(tf)[d]	(µg·hr/mL)	4283	32	68	5033	36	57	13299	28	72	15446	23	53
AUC(I)	(µg·hr/mL)	4623[c]	33	67	5149[c]	36	56	14656	24	65	15594	23	53
DN-AUC(I)	(µg·hr/mL)	15412[c]	33	67	17163[c]	36	56	14656	24	65	15594	23	53
K	(hr^{-1})	0.00127	24	67	0.00131[a]	27	56	0.00119	22	65	0.00115[a]	21	53
t½[e]	(day)	24.1	25	67	23.4[a]	24	56	25.3	21	65	26.4[a]	25	53
CL	(mL/hr/kg)	0.0727	37	67	0.0703[f]	41	54	0.0730	28	65	0.0752[f]	34	50
Vd	(mL/kg)	58.9	36	67	55.6[a,f]	40	54	63.1	31	65	69.5[a,f]	51	50
C(tf)	(µg/mL)	0.343	81	68	0.134	196	60	1.50	111	73	0.143	87	58
tf	(hr)	2259	27	68	3288	26	60	2366	44	73	4228	10	58

a: Statistically significant ($p<0.05$) difference between 0.3 mg/kg and 1 mg/kg.
b: Median Tmax = 1.58 hr or 2.71 hr for 0.3 mg/kg; and, 1.58 hr or 1.67 hr for 1 mg/kg
c: Statistically significant ($p<0.05$) difference between Day 1 and Week 12.
d: Statistical analysis for potential phase effect was not performed on AUC(tf).
e: t½ = 580 hr (Day 1) or 560 hr (Week 12) for 0.3 mg/kg; and, 607 hr (Day 1) or 635 hr (Week 12) for 1 mg/kg
f: Determined using AUC(I) adjusted for residual AUC from the first dose.
NA = Not applicable

Source: CSR 290, page 3553, Table 4

Immunogenicity Results:

All serum samples tested for the presence of antibodies to SCH 55700 were negative and the majority of the samples testing negative SNF. To be noted, some of these positive samples were obtained from placebo-treated subjects or were pre-dose samples.

Efficacy/PD Results:

- FEV1

There were no statistical significant differences among treatment groups in FEV1 at baseline. There was no statistical significance for FEV1 change from baseline between active treatment group and placebo group at any time point between Day 1 and Week 38. In general, no clear trend was observed in the mean response of all treatment groups (Table 4.3)

Table 4.3 FEV1 Change from Baseline Following Two IV Dose of Treatments

	0.3 mg/kg (A)			1.0 mg/kg (B)			Placebo (C)		
Time Point	N	Mean[a]	(Mean % Change)[b]	N	Mean	(Mean % Change)	N	Mean	(Mean % Change)
Baseline	71	2.22		75	2.24		65	2.31	
Change from Baseline									
1 hour	71	0.02	(1.6%)	75	0.02	(1.4%)	65	0.02	(2.8%)
4 hours	71	0.01	(1.3%)	75	0.02	(1.5%)	65	0.07	(3.3%)
Day 4	60	0.00	(1.7%)	62	-0.02	(-0.3%)	53	0.03	(3.4%)
Week 1	67	0.07	(3.9%)	71	0.01	(1.3%)	64	0.10	(5.2%)
Week 2	68	-0.02	(0.8%)	71	0.03	(1.8%)	63	0.02	(3.2%)
Week 4	70	-0.02	(1.2%)	70	0.06	(3.3%)	61	0.05	(4.3%)
Week 9	55	0.01	(1.9%)	52	0.12	(6.3%)	51	0.05	(4.7%)
Week 12 (Dose 2)	60	0.06	(5.5%)	58	0.04	(4.7%)	55	0.00	(3.1%)
Week 12 (1 hour)	60	0.06	(4.8%)	58	0.03	(3.3%)	55	0.03	(5.3%)
Week 12 (4 hours)	60	0.04	(3.6%)	58	0.05	(3.5%)	55	0.04	(4.8%)
Week 12 (+ 4 days)	42	0.09	(5.0%)	42	0.11	(6.7%)	40	0.07	(5.1%)
Week 13	58	-0.00	(3.4%)	54	0.01	(2.7%)	52	-0.01	(3.2%)
Week 14	59	0.07	(5.4%)	54	0.08	(4.0%)	53	0.03	(2.7%)
Week 16	59	0.03	(2.8%)	56	0.10	(6.5%)	54	0.09	(6.8%)
Week 20	60	0.04	(5.1%)	57	0.08	(6.3%)	54	-0.01	(4.9%)
Week 26	57	0.02	(4.2%)	58	0.06	(4.3%)	49	0.03	(4.1%)
Week 32	58	0.05	(3.8%)	56	0.10	(5.4%)	51	0.05	(4.9%)
Week 38	54	0.02	(4.6%)	54	0.07	(6.5%)	49	0.01	(3.9%)

Source: CSR 290, page 73-74, Table 49 and Table 10

Mean levels of blood eosinophils at predose were similar between groups (340 ~ 390 /μL) except higher for 0.5 mg/kg treatment group (590 /μL). Following drug administration, blood eosinophil count decreased in a time dependent manner with the maximum reduction reached approximately at Day 5 (Fig.4.5). The maximum percentage reduction values for placebo, 0.5 mg/kg, 2.5 mg/kg, and 10 mg/kg groups were approximately 30%, 80%, 85%, and 90% from the baseline, respectively (or maximally reduced to 230, 130, 60, and 30 / μL, respectively). A more than 50% reduction was observed at 24 hours following the active treatment.

- Time to First Asthma Worsening

There were 129 subjects who met one or more of the criteria for worsening of asthma: 47 (65%), 44 (59%), and 38 (56%) subjects from 0.3 mg/kg, 1 mg/kg and placebo group, respectively. The median time to first asthma worsening was 91 days, 65 days, and 107 days in 0.3 mg/kg, 1 mg/kg and placebo group, respectively. There was no statistical significant treatment effect in the Kapan-Meier time to first asthma worsening analysis.

- Clinical asthma exacerbations

A total of 86 subjects (40%) experienced at least one clinical asthma exacerbation: 25, 33, and 28 subjects from 0.3 mg/kg, 1 mg/kg and placebo group, respectively.

- Blood Eosinophil Counts

Mean blood eosinophil counts decreased within 4 days following the first dose and remained below baseline through the Week 4 for both 0.3 mg/kg and 1 mg/kg treatment group (Table 4.4). The reduction extent was greater in 1 mg/kg group than 0.3 mg/kg group. Blood eosinophil count was also evaluated for subjects who received a second dose of SCH 55700 at Week 12. Similarly, the mean eosinophil counts deceased within 4 days post-second-dose and remained below the baseline for up to 4 weeks for both active treatment groups (Table 4.5).

Table 4.4 Least Square Mean Blood Eosinophil Change from Baseline Following the First Dose Treatments

	0.3 mg/kg			1.0 mg/kg			Placebo		
Time Point	N	LS Mean [a]	(Mean % Change)[b]	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Baseline	62	0.23		68	0.23		60	0.26	
Change from Baseline									
1 hour	60	0.04	(24.4%)	64	0.02	(10.2%)	55	0.01	(3.4%)
4 hours	61	0.01	(23.5%)	61	-0.00	(24.2%)	58	-0.01	(10.6%)
Day 4	51	-0.11	(-41.1%)	53	-0.16	(-57.9%)	48	0.02	(23.6%)
Week 1	10	-0.16	(-55.5%)	15	-0.09	(-12.3%)	10	0.00	(9.6%)
Week 2	53	-0.10	(-32.1%)	55	-0.14	(-30.3%)	53	-0.04	(1.4%)
Week 4	56	-0.10	(-38.7%)	59	-0.18	(-57.9%)	56	-0.03	(16.2%)
Wk 4 Endpoint[c]	**62**	**-0.10**	**(-40.2%)**	**68**	**-0.16**	**(-57.0%)**	**60**	**-0.03**	**(12.2%)**

Source: CSR 290, page 78, Table 13

Table 4.5 Least Square Mean Blood Eosinophil Change from Baseline Following the Second Dose Treatments

	0.3 mg/kg			1.0 mg/kg			Placebo		
Time Point	N	LS Mean [a]	(Mean % Change)[b]	N	LS Mean	(Mean % Change)	N	LS Mean	(Mean % Change)
Baseline	54	0.25		51	0.26		50	0.28	
Change from Baseline									
Week 9	47	0.08	(30.6%)	45	-0.10	(-24.1%)	45	0.02	(7.7%)
Week 12 (Dose 2)	48	0.01	(25.3%)	47	-0.11	(-30.7%)	45	-0.01	(19.3%)
Week 12 (1 hour)	49	0.07	(42.4%)	48	-0.08	(-21.6%)	45	0.01	(11.0%)
Week 12 (4 hours)	48	0.12	(64.0%)	49	-0.05	(-20.2%)	44	0.02	(9.5%)
Week 12 (+ 4 days)	36	-0.13	(-25.6%)	35	-0.23	(-68.5%)	37	-0.08	(25.7%)
Week 13	15	-0.04	(-16.0%)	15	-0.20	(-16.2%)	14	-0.10	(-12.2%)
Week 14	47	-0.06	(-7.4%)	48	-0.19	(-47.9%)	44	-0.02	(14.0%)
Week 16	49	-0.10	(-38.0%)	47	-0.17	(-36.3%)	46	-0.03	(9.8%)
Week 20	52	0.02	(11.0%)	47	-0.17	(-45.4%)	46	0.02	(47.5%)

Source: CSR 290, page 79, Table 14

Conclusions:

- Following IV administration of SCH 55700, C_{max} and AUC increased in a dose-proportional manor from 0.3 to 1 mg/kg. There was no significant change of CL following the first dose and the second dose of SCH 55700. C_{trough} of SCH 55700 obtained 12 week post-dose was less than 5% of the C_{max} obtained on Day 1. The mean terminal half-life ranged 23 to 26 days.

- No trends or significant differences were observed for the comparison of two active treatment groups versus placebo group for any of the efficacy parameters evaluated: FEV1, FVC, and $FEF_{25\%-75\%}$ change from baseline, AM and PM PEFR change from baseline, asthma symptoms change from baseline, rescue medicine (albuterol/salbutamol) use, nocturnal awakenings, time to first asthma worsening, and clinical asthma exacerbation.

- Although a dose-dependent decrease in blood eosinophils was observed, there was no corresponding improvement in lung function as determined by FEV1, FVC, and $FEF_{25\%-75\%.}$

- 61 (85%), 70 (93%), and 58 (85%) subjects from 0.3 mg/kg, 1 mg/kg and placebo group experience at least one adverse event. Only hypertension was reported as cardiovascular adverse event which only happened in active treatment groups (4 from 0.3 mg/kg group and 2 from 1 mg/kg group). No clinical-relevant QT elongation was observed from ECG record.

4.1.3 Study Res-5-0010 (Study 10)

Study Type: Phase 2 PK, efficacy and safety, 4-dose (Q4W) study in patients with poorly controlled asthma
Study Dates: 04/16/2008 – 03/05/2010
Sponsor: Ception (although the clinical report was finished by Cephalon)

Title:
An Efficacy and Safety Study of Reslizumab (CTx55700) in the Treatment of Poorly Controlled Asthma in Subjects With Eosinophilic Airway Inflammation

Objective:

- Primary objective:
  To demonstrate the ability of reslizumab treatment to improve asthma control in patients with active asthma and eosinophilic airway inflammation

- Secondary objectives:
  - To study the ability of reslizumab treatment to reduce induced sputum eosinophil counts in patients with asthma
  - To study the ability of reslizumab treatment to reduce the number of clinical asthma exacerbations (CAEs) in patients with asthma. A CAE was defined as a 20% or more decrease in FEV1 from the baseline value, a requirement for emergency treatment of asthma, hospital admission for asthma, or treatment with 3 or more days of oral corticosteroids for asthma worsening
  - To assess the safety and tolerability of reslizumab treatment in patients with asthma

Study Design and Method:
This investigation was a randomized, multicenter, double-blind, placebo-controlled, two-parallel-group, fixed-dosage (3.0 mg/kg), four IV doses (Q4W) study in 106 patients with poorly controlled, active eosinophilic asthma. Patients who fulfilled all entry criteria were randomly assigned by a 1:1 ratio to reslizumab (3.0 mg/kg) treatment group or placebo group, with stratification on the basis of the baseline ACQ score (≤2 versus >2). Each dose was administered by IV infusion at a rate no faster than 2 mL per minute.

Key eligibility criteria included:

- Male and female patients between 18 and 75 years of age with FEV1 between ≥ 50% and ≤ 70% or confirmed airway reversibility (≥ 20% in FEV1 decline following methacholine challenge).
- The patient must have an ACQ score of 1.5 or more at the end of screening.
- The patient required treatment with a fluticasone dose of 440 μg or more twice daily (or equivalent) and 1 or more other agents for the treatment of asthma.
- The patient had eosinophils in an induced sputum sample of 3% or more at the end of screening.

Patients completed the ACQ evaluation during screening, at weeks 4, 8, and 12, and at the end of therapy (Week 15 or early withdrawal). Pulmonary function tests were performed before treatment at baseline, at week 4, and at the end of therapy.

Induced sputum samples were obtained at baseline and at the end of therapy to measure the eosinophil counts in the sputum. Eosinophil counts in the blood were also evaluated at baseline, at weeks 4, 8, 12, and at week 15 or early withdrawal.

Blood samples obtained for exploratory analyses at baseline, end of therapy, and 90 days after the last dose of study drug. Serum concentration data from study 10 were included in a pooled population PK analysis which was reported separately (population PK report CP-11-006). Serum concentrations of reslizumab were determined using a validated immunoassay (ELISA) with an LOQ of 20 ng/ml. The ELISA and bioassay methods were calibrated over a range of 20 to 420 ng/mL (validation report 256-0702).

Blood samples obtained at baseline, end of therapy, and at the final visit were tested for the presence of anti-drug-antibodies, and positive samples in the screening ELISA were re-assayed in a confirmatory ELISA.

Efficacy Endpoints:

- The primary efficacy variable for this study was the change from baseline to end of therapy in ACQ score.
- The secondary efficacy variables:
  - the proportion of ACQ score responders at the end of therapy
  - the change in FEV1 from baseline to the end of therapy
  - the change in percent predicted FEV1 from baseline to the end of therapy
  - the change in eosinophil counts in induced sputum samples from baseline to the end of therapy
  - the proportion of patients experiencing a CAE during the study
  - the time to the first occurrence of a CAE

Efficacy Results:

- Change in ACQ score from baseline to the end of therapy

There was a trend toward greater reduction (improvement) in ACQ score with reslizumab treatment compared with placebo treatment, although the difference between treatment groups was not statistically significant. At the end of therapy, mean ACQ score was reduced (improved) by 0.7 (SD=1.02) in the reslizumab treatment group and by 0.3 (SD=1.01) in the placebo treatment group (p=0.0541).

Table 4.6 Change from Baseline to End-of-Therapy in ACQ Score (ITT Analysis Set)

Variable Statistic	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=53)
Baseline ACQ score		
Mean	2.8	2.5
SD	0.79	0.73
SE	0.11	0.10
Median	2.6	2.4
Min, max	1.6, 5.0	1.6, 5.1
EOT ACQ score		
Mean	2.0	2.3
SD	1.05	1.14
SE	0.14	0.16
Median	2.0	2.1
Min, max	0.3, 4.3	0.3, 5.6
Change in ACQ score from baseline to EOT		
Mean	–0.7	–0.3
SD	1.02	1.01
SE	0.14	0.14
Median	–0.6	–0.1
Min, max	–4.3, 2.0	–2.7, 2.0
Comparison to placebo		
Adjusted mean difference (SE)	–0.38 (0.194)	—
95% confidence interval	–0.76, 0.01	—
p-value[a]	0.0541	—

EOT=end of therapy ((Week 15 or early withdrawal))
The p-value for the treatment comparison is based on the ANCOVA with adjustment for stratification factor and for variable at baseline.
Source: CSR 0010, page 77, Table 15

- Secondary Efficacy Variable
  - ACQ responders at the end of therapy

An ACQ responder was defined as a patient achieving a 0.5 or more reduction in ACQ score from baseline to the end of therapy. Although not significantly different compared with placebo, there was a numerically higher proportion of ACQ responders among patients treated with reslizumab (Table 4.7). At the end of therapy, 29 (55%) patients in the reslizumab treatment group and 19 (36%) patients in the placebo treatment group were ACQ responders (p=0.0848).

Table 4.7 Proportion of ACQ Responders at End-of-Therapy (ITT Analysis Set)

Variable Statistic	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=53)
Responder, n (%)[a]		
Yes	29 (55)	19 (36)
No	24 (45)	34 (64)
Comparison to placebo		
Odds ratio	2.01	—
95% confidence interval	0.91, 4.46	—
p-value[b]	0.0848	—

The p-value for the treatment comparison was based on logistic regression with adjustment for stratification factor.
Source: CSR 0010, page 80, Table 17

  - Change from baseline to the end of therapy in FEV1

Patients treated with reslizumab had a significantly greater increase in FEV1 at the end of therapy compared with those treated with placebo: the FEV1 increased from baseline by a mean of 0.18 liters (SD=0.372) in the reslizumab treatment group and decreased by a mean of 0.08 liters (SD=0.413) in the placebo treatment group (p=0.0023) (Table 4.8).

As an exploratory subgroup analysis, the change from baseline in FEV1 was evaluated on the basis of baseline blood eosinophil counts (<500 cells/μL vs. ≥500 cells/μL). At the end of therapy, the adjusted mean difference from placebo for FEV1 was 0.19 L (SE=0.102, p=0.0737) in patients with a lower baseline eosinophil counts and 0.25 L (SE=0.121, p=0.0419) in patients with a higher baseline eosinophil counts (Table 4.9).

Table 4.8 Change from Baseline to the End-of-Therapy in FEV1 (ITT Analysis Set)

Timepoint Statistic	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=53)
Baseline FEV_1, L		
n	52	52
Mean	2.08	2.26
SD	0.609	0.746
SE	0.084	0.103
Median	2.01	2.09
Min, max	1.02, 3.95	0.95, 4.69
EOT FEV_1, L		
n	52	52
Mean	2.26	2.17
SD	0.656	0.769
SE	0.091	0.107
Median	2.14	1.97
Min, max	1.13, 4.19	0.91, 4.12
Change in FEV_1 from baseline to EOT, L		
n	52	52
Mean	0.18	-0.08
SD	0.372	0.413
SE	0.052	0.057
Median	0.20	-0.10
Min, max	–0.71, 1.08	–1.40, 1.12
Comparison to placebo		
Adjusted mean difference (SE), L	0.240 (0.077)	—
95% confidence interval, L	0.088, 0.392	—
p-value[a]	0.0023	—

The p-value for the treatment comparison was based on the ANCOVA with adjustment for stratification factor and for variable at baseline.
Source: CSR 0010, page 81, Table 18

Table 4.9 Change from Baseline to the End-of-Therapy in FEV1 by Baseline Blood Eosinophil Counts (ITT Analysis Set)

	Baseline Eosinophil Counts <500/µL		**Baseline Eosinophil Counts ≥500/µL**	
	Placebo (N=25)	Reslizumab (N=24)	Placebo (N=27)	Reslizumab (N=28)
FEV1 Change from Baseline (L)*	-0.12 (0.067)	0.08 (0.073)	-0.05 (0.092)	0.27 (0.069)
Difference from Placebo (L)#		0.19 (-0.02, 0.39)		0.25 (0.01, 0.50)
p value		0.0737		0.0419

* Mean (SE)
# Adjusted mean difference (95% CI)
Source: adapted from CSR 0010, page 83, Table 19

o Change from baseline to the end of therapy in percent predicted FEV1

Patients treated with reslizumab had a statistically significant greater increase in percent predicted FEV1 at the end of therapy compared with those treated with placebo (Table 4.10). At the end of therapy, the percent predicted FEV1 increased by a mean of 6.2% (SD=11.8%) from baseline in the reslizumab treatment group and decreased by a mean of 2.4% (SD=12.9) in the placebo treatment group (p=0.0010).

Table 4.10 Change from Baseline to End-of-Therapy in Percent Predicted FEV1 (ITT Analysis Set)

Timepoint Statistic	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=53)
Baseline percent predicted FEV_1, %		
n	52	52
Mean	66.31	68.90
SD	15.13	16.33
SE	2.10	2.26
Median	64.5	66.1
Min, max	41.0, 110.0	43.0, 116.0
EOT percent predicted FEV_1, %		
n	52	52
Mean	72.50	66.45
SD	16.60	17.54
SE	2.30	2.43
Median	71.1	67.0
Min, max	41.0, 115.8	36.0, 118.0
Change in percent predicted FEV_1 from baseline to EOT, %		
n	52	52
Mean	6.2	–2.4
SD	11.76	12.93
SE	1.63	1.79
Median	5.5	-4.0
Min, max	–25.0, 33.0	–44.0, 31.0
Comparison to placebo		
Adjusted mean difference (SE), %	7.98 (2.36)	—
95% confidence interval, %	3.30, 12.65	—
p-value[a]	0.0010	—

The p-value for the treatment comparison was based on the ANCOVA with adjustment for stratification factor and for variable at baseline.

Source: CSR 0010, page 84, Table 20

o Change from baseline to the end of therapy in induced sputum eosinophil counts

The arithmetic mean of sputum eosinophil counts at baseline was higher in reslizumab group [19.4% (SE=2.8%, 54 records)] than placebo group [16.5% (SE=2.9%, 53 records)] (Figure 4.5). The arithmetic mean of sputum eosinophil counts reduced to 2-3% at Week 4 following the first dose reslizumab 3 mg/kg treatment and was maintained at that level till the end of therapy. The arithmetic mean of sputum eosinophil counts from placebo group kept fluctuating around the baseline value throughout the study.

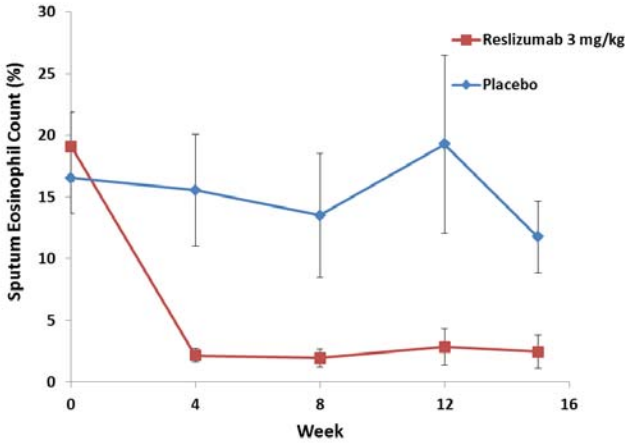

Figure 4.5 Arithmetic mean (SE) of sputum eosinophil counts (%) time profile following placebo (N=52) and 3 mg/kg reslizumab (N=53) treatment. Some subjects had more than one sputum eosinophil record per scheduled visit. (Source: reviewer's analysis)

The change in sputum eosinophil counts from baseline to the end of therapy was statistically different in the reslizumab treatment group compared with the placebo treatment group (Table 4.11). The percentage of sputum eosinophils was reduced from baseline to the end of therapy by 82.0% for the reslizumab treatment group and increased by 45.9% for the placebo treatment group (p=0.0068).

Table 4.11 Change from Baseline to End-of-Therapy in Induced Sputum Eosinophil Counts (ITT Analysis Set)

Timepoint Statistic	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=53)
Baseline sputum eosinophil level, %		
n	38	36
Mean	17.4	15.5
SD	15.94	18.69
SE	2.59	3.12
Median	10.7	8.5
Min, max	1.7, 67.6	3.0, 77.0
EOT sputum eosinophil level, %		
n	38	36
Mean	2.5	14.7
SD	8.46	21.39
SE	1.37	3.57
Median	0.3	6.7
Min, max	0.0, 47.0	0.3, 79.0
Change in sputum eosinophil level from baseline to EOT, %		
n	38	36
Mean	–82.0	45.9
SD	66.88	265.79
SE	10.85	44.30
Median	–95.4	–38.7
Min, max	–100.0, 315.9	–96.0, 1480.0
Difference from placebo		
Adjusted mean (SE), %	–125.29 (44.885)	—
95% confidence interval, %	–214.81, –35.77	—
p-value[a]	0.0068	—

Geometric means are listed.
The p-value for the treatment comparison was based on the ANCOVA with adjustment for stratification factor and for variable at baseline.
Source: CSR 0010, page 92, Table 25

o The proportion of patients experiencing a clinical asthma exacerbation

Although not significantly different, a smaller number of reslizumab-treated patients experienced clinical asthma exacerbations than placebo-treated patients during the study (Table 4.12). Exacerbations occurred in 4 (8%) patients in the reslizumab treatment group and in 10 (19%) patients in the placebo treatment group (p=0.0833). Most of the CAEs in either group were considered exacerbations because of treatment with 3 or more days with oral corticosteroids for asthma worsening.

Table 4.12 Occurrence of Clinical Asthma Exacerbations (ITT Analysis Set)

Variable Statistic	Reslizumab 3.0 mg/kg (N=53)	Placebo (N=53)
Proportion of patients experiencing a CAE, n (%)	4 (8)	10 (19)
Comparison to placebo		
Odds ratio	0.33	—
95% confidence interval	0.10, 1.15	—
p-value[a]	0.0833	—
Criteria for CAE[b], n (%)		
20% decrease in FEV_1 (absolute value) from the baseline value	1 (2)	5 (9)
Requirement for emergency treatment of asthma	3 (6)	4 (8)
Hospital admission for asthma	1 (2)	0
Treatment with 3 or more days of oral corticosteroids for asthma worsening	4 (8)	9 (17)

The p-value for the treatment comparison was based on logistic regression with adjustment for stratification factor.
Source: CSR 0010, page 89, Table 23

o The time to the first occurrence of a CAE

There was no statistically significant difference (p=0.0809) in Kaplan-Meier estimates of time to first CAE between treatment groups (Figure 4.6).

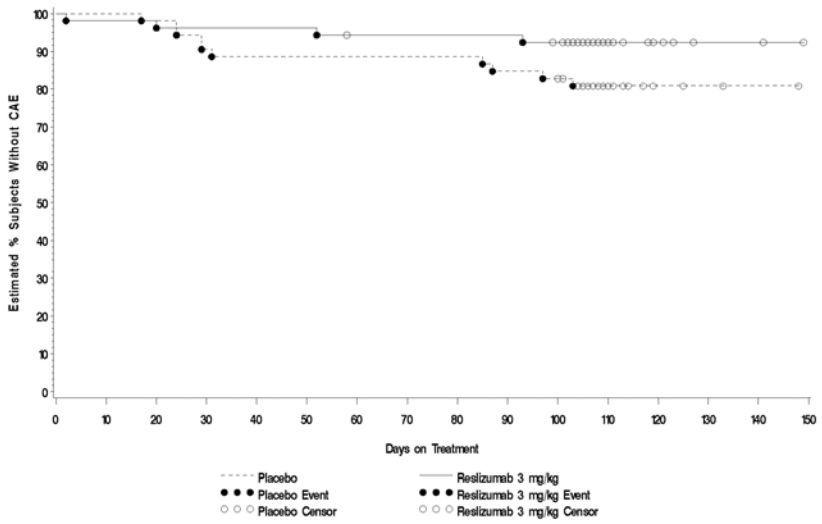

Figure 4.6 Kaplan-Meier plot of time to clinical asthma exacerbation from study 0010. (Source: CSR0010, page 90, Figure 5).

Immunogenicity Results:
The immunogenicity assay was not optimal as the anti-reslizumab antibody was reported positive (or borderline) in 9 patients (8.6%) at the baseline from a confirmatory antibody assay. A total of 11 patients who tested negative for anti-drug antibodies at baseline had positive (or borderline) results at a post-baseline assessment. Of these, 5 patients were from placebo group.

Conclusions:

- A numerically greater improvement in asthma control, as measured by ACQ score, with reslizumab treatment compared with placebo treatment was observed, although the difference between treatment groups was not significant.

- Consistent significant improvements in other parameters of asthma control and pulmonary function were observed in reslizumab treatment group compared to placebo group.

- Treatment-emergent adverse events considered by the investigator to be treatment related were reported in 12 (23%) patients in the reslizumab treatment group and 8 (15%) patients in the placebo treatment group. There were no deaths during the study. Three patients had treatment-emergent serious adverse events, 2 (4%) patients in the reslizumab treatment group and 1 (2%) patient in the placebo treatment group. None of the serious adverse events was considered by the investigator to be treatment related.

Reviewer's comments:
Although reduction of blood eosinophil counts was not listed as an endpoint of study 10, it is worth to compare the blood eosinophil time profile between reslizumab treatment group and the placebo group in addition to the sputum eosinophil time profile comparison (Figure 4.7).

The arithmetic mean of blood eosinophil counts at baseline was higher in reslizumab group [525 cells/μL (SE=46, N=53)] than placebo group [487 cells/μL (SE=44, N=52]. The arithmetic mean of sputum eosinophil counts reduced to 57 cells/μL (or 89% reduction) at Week 4 following the first dose reslizumab 3 mg/kg treatment and the maximum reduction of 33 cells/μL (or 94% reduction) was reached at the end of the therapy (Week 15). The arithmetic mean of sputum eosinophil counts from placebo group kept fluctuating around the baseline value throughout the study.

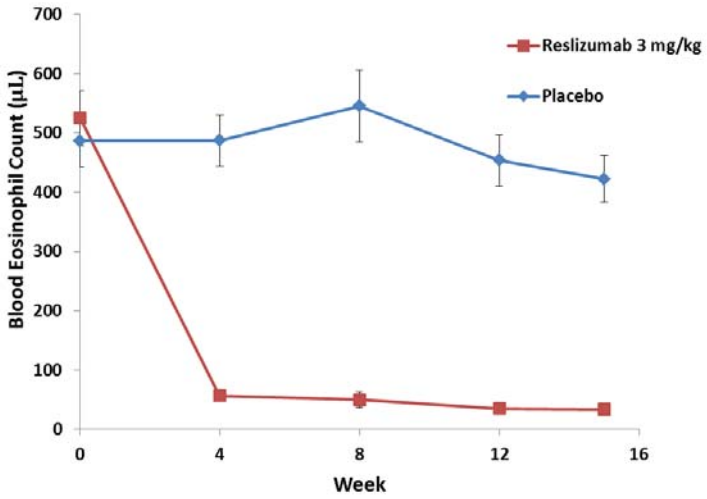

Figure 4.7 Arithmetic mean (SE) of blood eosinophil counts (cells/µL) time profile following placebo (N=52) and 3 mg/kg reslizumab (N=53) treatment. (Source: reviewer's analysis)

4.1.4 Study C38072/1102 (Study 1102)

Study Type: Phase 1, five-dose, PK, PD and safety study in healthy subjects
Study Dates: 02/29/2012 – 02/07/2013
Sponsor: Teva

Title:
A Randomized, Open-Label Study to Characterize the Pharmacokinetics, Pharmacodynamics, and Safety of Multiple Doses of Reslizumab in Healthy Japanese and Non-Japanese Subjects

Objective:

- Primary

  To characterize the pharmacokinetic profile of reslizumab following administration of 0.3, 1, 2, or 3 mg/kg to healthy Japanese and non-Japanese subjects by assessing serum drug concentrations over time.

- Secondary
  - To characterize the safety profile, including ECG findings of reslizumab following multiple dose administration of 0.3, 1, 2, or 3 mg/kg to healthy Japanese and non-Japanese subjects.
  - To assess the immunogenicity of reslizumab

Study Design and Method:
This study was conducted in the US. This investigation was a randomized, open-label, four-parallel-group, five IV infusion dose study in 100 healthy subjects (50 Japanese and 50 non-Japanese). Reslizumab was administered at a dose of 0.3, 1.0, 2.0, or 3.0 mg/kg as an IV infusion over 50 minutes. The dosing interval was 28 (±2) days.

The Japanese subjects were required to be born in Japan, have a passport issued from Japan and have Japanese parents and grandparents.

Blood samples (5 mL) for PK were collected immediately (within approximately 5 minutes) before the start of each infusion, upon completion of the infusion, and at 12 and 24 hours after each study drug administration. In study drug administration periods 1, 3, and 5, blood samples were also collected on day 3. In study drug dosing periods 1 and 5, blood samples for pharmacokinetics were collected on days 5, 7, 10, 14 (±1 day), and 21 (±1 day).

The PK bioanalytical assay utilized a validated sandwich ELISA in which microtiter plates were coated with recombinant human IL-5 to capture reslizumab. The amount of bound reslizumab was detected by an HRP-conjugated mouse anti-human IgG4. The assay has a validated quantifiable range of 20.0 to 420 ng/mL for reslizumab in human serum. Details of the method description and the validation results are presented in the validation report (Teva Report 256-0702. Samples with unquantifiable concentrations of reslizumab (<20.0 ng/mL) were designated as "BLQ".

Blood samples for measurement of serum IL-5 and blood eosinophils were collected at the same time points as the pharmacokinetic samples.

Blood samples for measurement of anti-drug antibodies were obtained pre-dose at dosing periods 1 and 3 and at days 28, 56 and 84 following the last dose. ADAs were detected by incubating samples with a mixture of biotinylated reslizumab and digoxigenin-conjugated reslizumab in solution. The antibody complex was captured by streptavidin coated plate and detected by HRP labeled anti-digoxigenin

antibody. The strategy for immunogenicity assessment of reslizumab included 3 tiers of analysis of anti-reslizumab antibodies: screening, confirmatory, and characterization including antibody titer analysis. A subject was classified as having a treatment-emergent ADA response if sample was tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample.

PK Endpoints:

- For all periods, the observed C_{max} and T_{max}.
- For dosing periods 1 and 5, the terminal rate constant for elimination from serum (λz) and terminal elimination half-life ($t_{½}$)
- $AUC_{0\text{-}D28}$ /AUC_{τ} or $AUC_{0\text{-}t}$
- AUC0-∞ for dosing period 1 only
- The percentage of $AUC_{0\text{-}\infty}$ extrapolated.
- The serum clearance (CL) after IV infusion.
- The apparent volume of distribution (Vz).
- The steady-state volume of distribution (V_{ss}).
- The accumulation factors were as follows:
    - predicted accumulation ratio (R_{pred}): $AUC_{0–\infty}/AUC_{0–D28}$
    - observed accumulation ratio (R_{obs}): AUC_{τ} to $AUC_{0\text{-}D28}$
    - steady-state accumulation ratio (R_{ss}): $AUC_{\tau}/AUC_{0\text{-}\infty}$

PD Endpoints:
Blood samples for measurement of serum IL-5 and blood eosinophils

Immunogenicity Endpoints:
Immunogenicity assessment of reslizumab included 3 tiers of analysis of anti-reslizumab antibodies: screening, confirmatory, and characterization including antibody titer analysis.

PK Results:
In total 50 Japanese and 50 non-Japanese healthy subjects received reslizumab treatment (1 Japanese subject was randomized, but not treated). All non-Japanese subjects are Caucasians. 10 (20%) Japanese subjects (including the subject mentioned above) and 9 (18%) non-Japanese subjects discontinued from the study. The mean body weight was similar between Japanese subjects and non-Japanese subjects in all treatment groups (Table 4.13).

Table 4.13 Demographic Characteristics by Dose Level and Group of Randomized Subjects

	0.3 mg/kg		1.0 mg/kg		2.0 mg/kg		3.0 mg/kg	
	J (N=10)	NJ (N=9)	J (N=10)	NJ (N=10)	J (N=10)	NJ (N=10)	J (N=21)	NJ (N=21)
Age (year)	29.1 (6.4)	34.7 (6.4)	33.8 (9.7)	29.5 (7.7)	31.2 (7.4)	31.7 (7.7)	30.1 (7.0)	31.1 (7.6)
Body Weight (kg)	65.0 (6.6)	68.9 (5.9)	64.1 (6.9)	68.2 (9.2)	64.3 (9.4)	69.3 (8.6)	62.8 (6.6)	69.8 (7.4)
BMI (kg/m^2)	22.9 (1.8)	22.5 (1.9)	22.5 (2.2)	23.5 (2.9)	22.9 (2.0)	23.0 (2.4)	21.9 (1.7)	23.1 (2.2)

Mean (SD)
J = Japanese, NJ = non-Japanese
Source: CSR 1102, page 341, Summary 15.2

Non-BLQ concentrations of reslizumab were measured in 13 of 100 pre-first-dose samples. The presence of low concentrations of reslizumab in these samples is likely due to a presumed matrix effect in the bioanalytical assay.

- PK results following the first dose

Reslizumab concentration-time profiles following the first IV dose from Japanese and non-Japanese subjects are shown in Figure 4.8. A side-by-side comparison of PK parameters following the first IV dose from Japanese and non-Japanese subjects are listed in Table 4.14. Generally C_{max} and AUCs increased dose proportionally from 0.3 mg/Kg to 3 mg/kg. The values of C_{max} and AUCs following the first dose were comparable between Japanese and non-Japanese with difference of mean less than 15% except $AUC_{0\text{-}D28}$ of 0.3 mg/kg. Although peak concentrations were observed in the majority of profiles at the end of infusion (0.83 hours), C_{max} was not observed until the next time points, 12.0 or 24.0 hours, for some subjects.

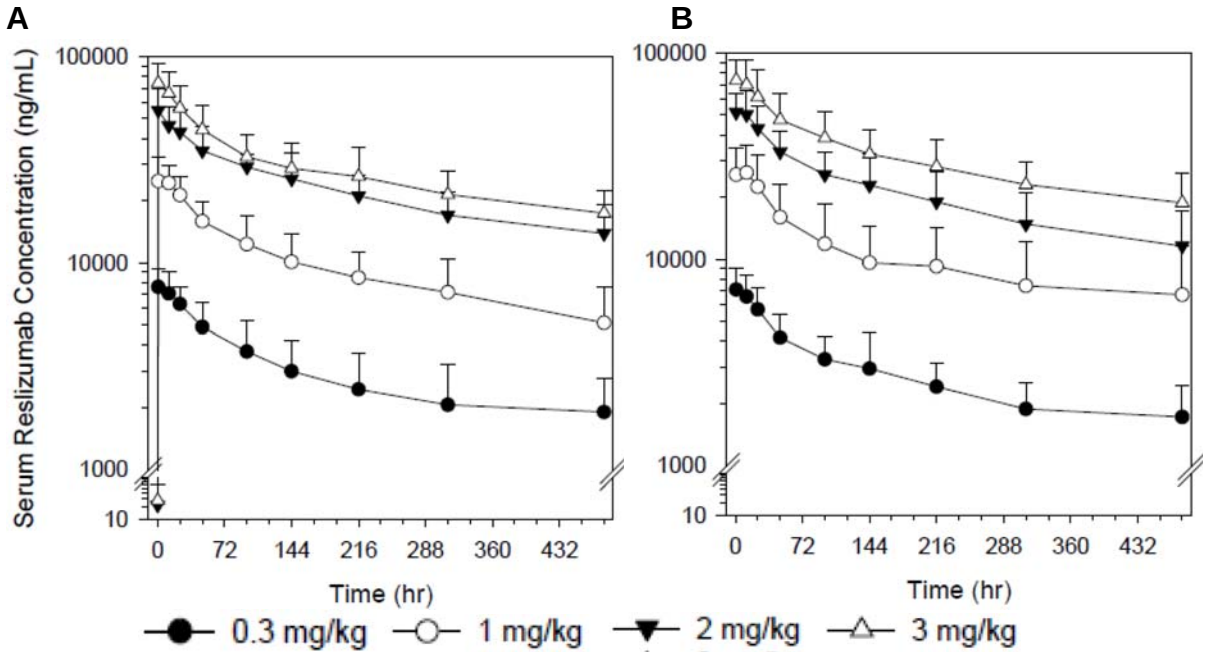

Figure 4.8 Mean (+SD) serum reslizumab concentration-time profiles of Japanese (A) and non-Japanese (B) healthy subjects following the first dose IV infusion of reslizumab (0.3, 1.0, 2.0, or 3.0 mg/kg). (Source: CSR 1102, page 78, Figure 3 and Page 80 Figure 4)

Table 4.14 Mean (SD) PK Parameters following the First Dose Reslizumab IV Infusion in Japanese and Non-Japanese Subjects

	0.3 mg/kg		1.0 mg/kg		2.0 mg/kg		3.0 mg/kg	
	J (N=9)	NJ (N=9)	J (N=10)	NJ (N=10)	J (N=10)	NJ (N=10)	J (N=21)	NJ (N=21)
C_{max} (µg/mL)	8.12 (1.37)	7.63 (1.73)	27.1 (6.61)	27.6 (9.32)	55.5 (15.5)	55.2 (14.7)	76.4 (18.9)	78.0 (20.4)
T_{max}* (h)	12.00	0.85	6.43	12.00	0.85	0.88	0.85	0.85
$AUC_{0\text{-}t}$ (µg·h/mL)	1704 (708)	1586 (502)	5484 (1895)	5997 (3225)	13472 (3533)	11988 (4305)	16074 (4458)	17988 (5606)
$AUC_{0\text{-}D28}$ (µg·h/mL)	1948 (766)	1536 (510)	5728 (1706)	5407 (2310)	13390 (3614)	11970 (4303)	16312 (4211)	18117 (5485)

* Median
J = Japanese, NJ = non-Japanese
Source: CSR 1102, page 79, Table 9 and page 81, Table 10

- PK results following multiple dose

Reslizumab concentration-time profiles following the five-dose (20 weeks) IV infusion from Japanese and non-Japanese subjects are shown in Figure 4.9. A side-by side comparison of PK parameters following the first IV dose from Japanese and non-Japanese subjects are listed in Table 4.15.

Generally C_{max} and AUCs increased dose proportionally from 0.3 mg/Kg to 3 mg/kg. All the values of C_{max} and AUCs following five-dose infusion were comparable between Japanese and non-Japanese with difference of mean less than 20%. Although peak concentrations were observed in the majority of profiles at the end of infusion (0.83 hours), C_{max} was not observed until the next time points, 12.0 or 24.0 hours, for some subjects. The mean observed accumulation ratio following 5th dose ranged from 1.5 to 1.9. The mean half-life ranged from 25 to 32 days. Apparent clearance ranged from 0.098 to 0.136 mL/h/kg. Apparent volume of distribution ranged from 80.2 to 151.3 mL/kg.

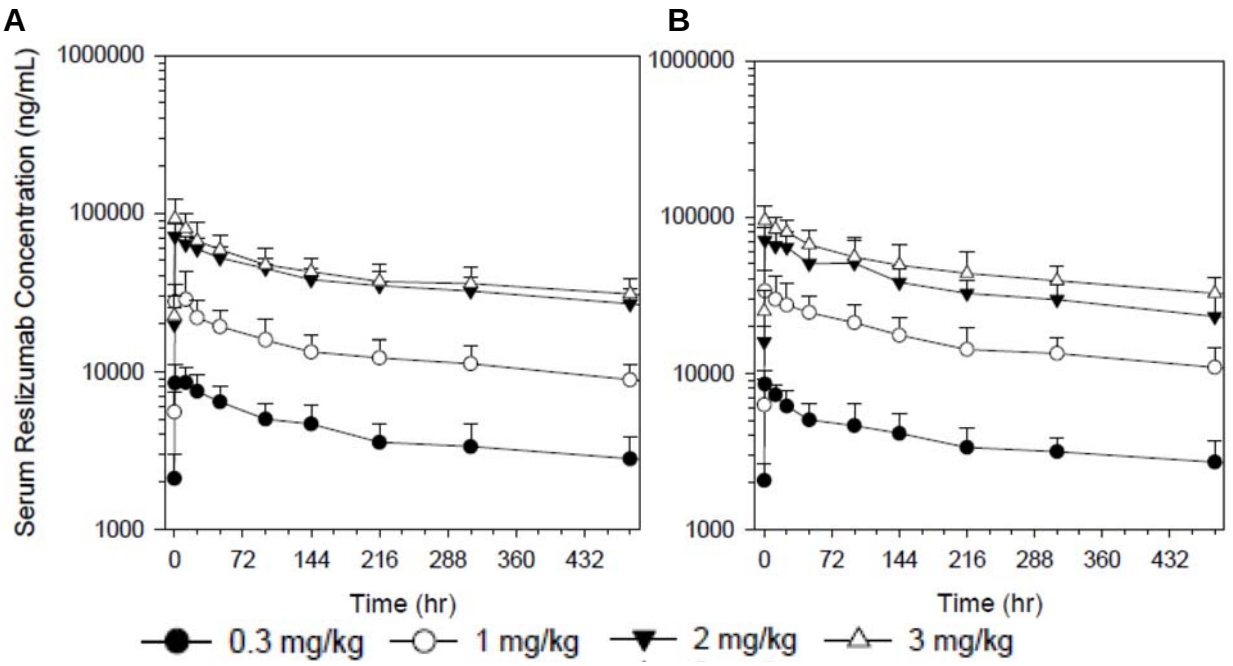

Figure 4.9 Mean (+SD) serum reslizumab concentration-time profiles of Japanese (A) and non-Japanese (B) healthy subjects following the fifth dose IV infusion of reslizumab (0.3, 1.0, 2.0, or 3.0 mg/kg). (Source: CSR 1102, page 83, Figure 5 and Page 85 Figure 6)

Table 4.15 Mean (SD) PK Parameters following Five Dose Reslizumab IV Infusion in Japanese and Non-Japanese Subjects

	0.3 mg/kg		1.0 mg/kg		2.0 mg/kg		3.0 mg/kg	
	J (N=8)	NJ (N=7)	J (N=7)	NJ (N=8)	J (N=10)	NJ (N=9)	J (N=19)	NJ (N=17)
C_{max} (µg/mL)	9.57 (2.32)	8.69(1.60)	32.1 (12.7)	34.9 (11.1)	72.3 (14)	80.4 (17.5)	93.3 (18.9)	96.2 (22.1)
T_{max}* (h)	12.00	0.87	0.83	6.44	0.85	0.85	0.83	0.85
AUC_{0-t} (µg·h/mL)	4252 (1377)	4016 (1235)	12913 (3981)	15581 (5405)	37056 (7372)	35309 (9397)	39787 (15495)	47956 (12544)
AUC_{τ} (µg·h/mL)	2514 (726)	2325 (630)	7888 (2113)	9719 (3007)	22422 (3183)	21602 (5256)	25367 (5345)	28442 (6306)
$T_{1/2}$#(Day)	28.0 (6.2)	29.9 (8.0)	31.5 (7.4)	25.7 (4.0)	25.3 (2.9)	25.6 (4.4)	25.5 (4.8)	25.8 (7.8)
CL (mL/h/kg)	0.130 (0.045)	0.136 (0.031)	0.134 (0.035)	0.114 (0.041)	0.091 (0.017)	0.098 (0.025)	0.124 (0.028)	0.110 (0.025)
Vz (mL/Kg)	124.0 (41.6)	139.5 (45.3)	151.3 (69.5)	102.5 (43.2)	80.2 (19.9)	86.7 (25.8)	103.3 (16.8)	94.2 (16.4)
R_{obs}	1.48 (0.32)	1.56 (0.40)	1.47 (0.38)	1.66 (0.37)	1.75 (0.39)	1.87 (0.67)	1.57 (0.40)	1.53 (0.32)

* Median
# Harmonic mean
J = Japanese, NJ = non-Japanese
Source: CSR 1102, page 84, Table 12 and page 86, Table 13

Immunogenicity Results:
Out of the 100 subjects in this study, none was observed to be ADA positive at the predose baseline, and 9 subjects were found to be ADA positive after treatment (Table 4.16). The ADA titers of those subjects were below1:6 (6 in linear scale). Five of the 9 ADA positive subjects were positive at 1 time point only. There was no apparent trend towards lower exposure (as assessed by either C_{max} or AUC) in subjects who were confirmed positive for ADA.

Table 4.16 Profile and Titers of Reslizumab ADA Positive Subjects

Dose	Subject Number	Japanese/non-Japanese	Visit 4, Period 3 (Titer)	Visit 7, Follow up 1 (Titer)	Visit 9, Follow up 3 (Titer)
0.3 mg/kg	003025	NJ	-	+ (2)	-
0.3 mg/kg	003059	J	-	-	+ (6)
0.3 mg/kg	004013	NJ	+ (3)	-	+ (1)[a]
0.3 mg/kg	004047	NJ	+ (2)	+ (2)	-
1 mg/kg	005069	NJ	+ (2)	-	-
2 mg/kg	004040	NJ	+ (3)	-	+ (2)
2 mg/kg	005070	NJ	+ (3)	+ (<1)[a]	-
3 mg/kg	003063	J	+ (4)	-	-
3 mg/kg	005002	J	+ (2)	-	-

Source: CSR 1102, page 833, Table 33

PD Results:

- The effect of reslizumab on serum IL-5

All the serum IL-5 values were within the normal range, with the exception of period 5 values for Subject 005085 (non-Japanese, 3.0 mg/kg reslizumab). For this subject, IL-5 level prior to period 5 dosing was high, 6.7 pg/mL (normal range 0 to 4.5 pg/mL), and for the postdose values up to day 3 after dosing values remained high, ranging between 5.8 and 8.9 pg/mL. At all subsequent time points (from day 7 onwards), values of IL-5 were within normal ranges for the subject.

- The effect of reslizumab on blood eosinophil count

The blood eosinophil counts at baseline was not well balanced among different groups with highest values (~180 cells/µL) obtained from 0.3 mg/kg group (Figure 4.10). The mean blood eosinophil counts from all the groups reduced to < 100 cells/µL at Day 3 following the first dose of reslizumab treatment. However, the reduction appeared less sustainable in 0.3 mg/kg group after 2 weeks.

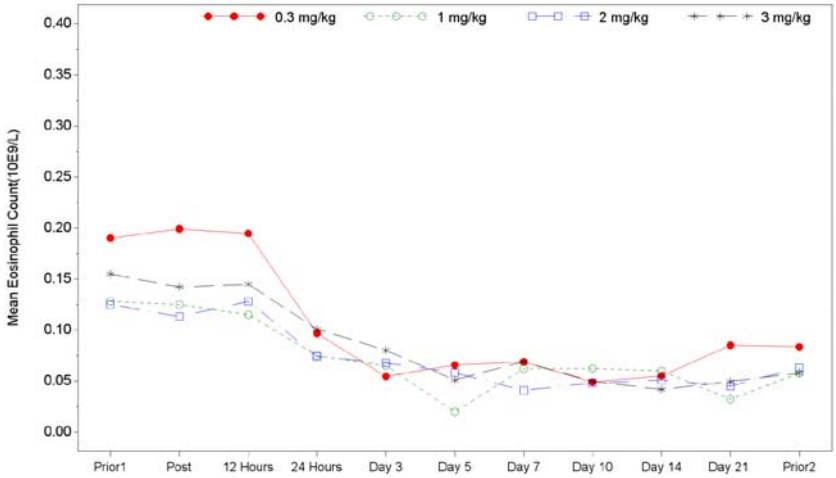

Figure 4.10 Mean blood eosinophil count by dose level following the first dose of reslizumab treatment. (Source: CSR 1102, page 96, Figure 13)

Safety Results:
There were no deaths in the study. Two serious adverse events were reported in one subject. The subject sustained serious adverse events of head injury and scalp laceration, both of which were considered not related to study drug. Overall, 29 (58%) Japanese subjects and 32 (64%) non-Japanese subjects reported at least 1 adverse event. There was no trend toward an increased incidence of adverse events with increased doses (Table 4.17). No ECG findings were reported as adverse events and no abnormal ECG findings were assessed as clinically significant by the investigators. No trend was observed towards an increase in QTcF with increasing reslizumab concentration. There was a Japanese subject had a single QTcF >450 msec with a concurrent change in QTcF interval from baseline of greater than 30 msec. No consistent trend of QTcF and QTcB trend were observed for this subject.

Table 4.17 Summary of Cardiocore ECG Safety Outlier Profile

	0.3 mg/kg	1 mg/kg	2 mg/kg	3 mg/kg
N	9	10	10	21
QTcF > 450 ms	2 (22%)	1 (10%)	0	1 (5%)
QTcF or QTcB > 480 ms	0	0	0	0
Change in QTcF > 30 ms	3 (33%)	0	2 (20%)	4 (19%)
Change in QTcF > 60 ms	0	0	0	0
QTcF > 450 ms and dQTcF > 30 ms	1 (11%)	0	0	0
QTc > 450 ms and dQTc > 60 ms	0	0	0	0

Source: adapted from CSR 1102, page 132, Table 32

Conclusions:
Reslizumab systemic exposures were similar between Japanese subjects and non-Japanese subjects following either single or multiple doses treatment. Systemic exposures as assessed by C_{max} and AUC increased in an approximately dose proportional manner over the range of 0.3 mg/kg through 3.0 mg/kg. Observed accumulation ratio ranged from 1.5 to 1.9 following 5 doses, Q28 days treatment. There was no apparent trend towards lower reslizumab exposure in ADA positive subjects.

Reslizumab reduced blood eosinophils at all dose levels.

No trend towards an increase in QTcF was observed with increasing reslizumab concentration in either Japanese or Non-Japanese subjects.

4.1.5 Study C38072/1107 (Study 1107)

Study Type: Phase 1, single-dose, BA study in healthy subjects
Study Dates: 06/04/2013 – 12/03/2013
Sponsor: Teva

Title:
A Randomized, Open-Label, Parallel-Group, Single-Dose Study to Characterize the Absolute Bioavailability of Reslizumab (220 mg) Following Subcutaneous Administration to Healthy Subjects

Objective:

- Primary

  To assess the absolute bioavailability of reslizumab following administration of a single 220 mg subcutaneous (SC) dose to healthy non-Japanese subjects as assessed by $AUC_{0\text{-}inf}$.

- Secondary
  - To characterize the PK profile of reslizumab following administration of a single 220 mg SC dose to healthy Japanese subjects by assessing serum concentration data over time.
  - To characterize the safety and tolerability of reslizumab following a single IV or SC dose of 220 mg to healthy non-Japanese subjects.

Study Design and Method:
This study was conducted in the US. This investigation was a randomized, open-label, single-dose, two-parallel-group, bioavailability study in 75 healthy subjects (15 Japanese and 60 non-Japanese). Single dose of reslizumab was administered as either IV infusion for 20 minutes or SC injection.

The Japanese subjects were required to be born in Japan, have a passport issued from Japan and have Japanese parents and grandparents. In order to tease out the body weight effect on reslizumab clearance during the comparison of PK between Japanese and non-Japanese subjects, the Sponsor selected 16 non-Japanese subjects as subcutaneous comparator set (SCS) who met the more stringent weight and age range criteria corresponding to the Japanese subjects; specifically, subjects 20 through 45 years of age weighing 50 through 80 kg with a BMI of less than 28.0 kg/m^2.

Blood samples (5 mL each) for PK were obtained pre-dose, and at 6, 12, and 24 hours post-dose on day 1. In addition, blood samples were collected on post-dose days 3, 5, 7, 10, 14 (±1 day), 21 (±1 day), 28 (±1 day), 42 (±2 days), 56 (±2 days), 84 (±2 days), 112 (±3 days), and 140 (±3 days).

Blood samples for measurement of anti-drug antibodies (ADA) were obtained prior to the dose of study drug and at the visits on days 14 (±1 day), 28 (±1 day), 84 (±2 days), and 140 (±3 days).

Serum samples were analyzed for reslizumab using a sandwich ELISA in which microtiter plates were pre-coated with recombinant human IL-5 to capture reslizumab. Samples (including standards and quality controls) were added and incubated on the plate. Mouse anti-human IgG4 conjugated with horseradish peroxidase detected the bound reslizumab. Tetramethylbenzidine, a substrate for horseradish peroxidase, developed a color that was detected and was proportional to the amount of reslizumab present in the sample.

Serum samples were analyzed for ADA using a validated homogeneous solution-based bridging ELISA. The analysis of anti-reslizumab antibody in subject serum consists of 3 tiers of assays for screening, confirmation, and titer analysis:

- All samples were first analyzed in the screening assay to detect the ADA.
- The screening positive samples were further analyzed in the confirmatory assay using immune-competition with an excess amount of reslizumab to characterize binding specificity to reslizumab.
- Positive samples with binding specificity to reslizumab were then analyzed in a titration assay for the determination of anti-reslizumab antibody titer.

A subject was classified as having a treatment-emergent ADA response if a sample was tested positive in the assay at any of the post-dose time points but not at the pre-dose time point, or post-dose ADA titer increased 4-fold or greater from a positive baseline ADA sample.

PK Endpoints:

- The observed C_{max} and T_{max}.
- $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$
- Percentage extrapolation calculated as $(AUC_{0\text{-}inf} - AUC_{0\text{-}t})/(AUC_{0\text{-}inf})x100$
- apparent serum terminal elimination rate constant (λz) and associated elimination half-life ($t_{½}$)
- Total serum clearance (CL) and apparent serum clearance following SC dose (CL/F)
- Volume of distribution (Vz), apparent volume of distribution following SC dose (Vz/F)
- Absolute bioavailability following SC administration (F) calculated as $(AUC_{0\text{-}inf})$ SC/$(AUC_{0\text{-}inf})$ IV (non-Japanese subjects only)

PD Endpoints:
Absolute and percent change of eosinophil count from baseline.

Immunogenicity Endpoints:
Anti-reslizumab antibodies were measured and the titer was determined for each confirmed positive sample.

PK Results:
In total 15 Japanese and 30 non-Japanese healthy subjects received reslizumab SC treatment. Another 30 non-Japanese healthy subjects received reslizumab IV treatment. All non-Japanese subjects are Caucasians. The mean body weight appeared slightly higher in non-Japanese subjects than in Japanese subjects (Table 4.18).

Table 4.18 Baseline Demographic Characteristics by Group

	Non-Japanese			Japanese
	IV (N=30)	SC (N=30)	SCS (N=16)	SC (N=15)
Age (year)	31.2 (8.8)	27.6 (7.9)	28.5 (5.6)	30.3 (7.6)
Body Weight (kg)	72.2 (15.0)	73.2 (9.6)	70.3 (8.5)	62.8 (10.0)
BMI (kg/m^2)	24.2 (2.8)	26.0 (2.5)	24.8 (2.2)	22.2 (2.8)

Mean (SD)
J = Japanese, NJ = non-Japanese
Source: CSR 1107, page 56, Table 6

- Bioavailability Results

Reslizumab concentration-time profiles following single dose 220 mg IV or SC administration in non-Japanese subjects are shown in Figure 4.11. T_{max} following SC administration was reached approximately Day 4. After that, the PK profile was similar for both routes of administration with a comparable long half-life (~25 days). A side-by-side comparison of PK parameters following 2 routes of administration are listed in Table 4.19.

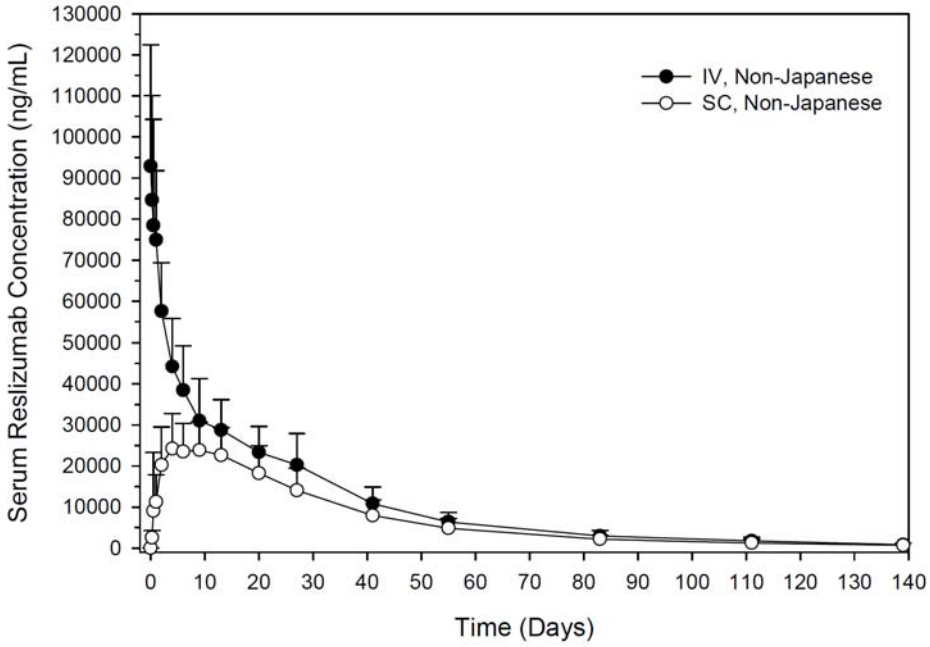

Figure 4.11 Mean (+SD) serum reslizumab concentration-time profiles following a single dose of 220 mg IV (N=30) or SC (N=30) administration in non-Japanese subjects. (Source: CSR 1107, page 63, Figure 3)

Table 4.19 Mean (SD) PK Parameters following Single-Dose IV or SC Administration of 220 mg Reslizumab in Non-Japanese Subjects

Variable Statistic	Non-Japanese	
	iv (N=30)	sc (N=30)
C_{max} (ng/mL)	99316.7 (29875.18)	29123.3 (12553.41)
t_{max} (min, max) (h)	0.4 (0.3, 24.1)	102.9 (12.0, 484.6)
$AUC_{0-\infty}$ (ng*h/mL)	35973.9 (8798.72)	24250.0 (8351.85)
AUC_{0-t} (ng*h/mL)	34288.5 (9014.79)	22508.1 (8916.38)
Extrapolation (%)	4.70 (8.634)	2.57 (1.814)
λ_z (1/h)	0.00119 (0.000270)	0.00113 (0.000206)
$t_{½}$ (h)	608.07 (121.614)	632.02 (109.730)
CL (mL/hr)	6.530 (1.8082)	–
CL/F (mL/h)	–	10.125 (3.3660)
V_z (L)	5.69 (1.859)	–
V_z/F (L)	–	9.14 (3.307)
V_{ss} (L)	4.59 (1.338)	–

Source: CSR 1107, page 64, Table 10

Mean reslizumab C_{max} following SC route was about 30% of the C_{max} following IV route. The absolute bioavailability of reslizumab following SC route was 67.4% (as assessed by mean $AUC_{0\text{-}inf}$ values).

- PK comparison between non-Japanese and Japanese subjects

PK parameters of reslizumab is similar following a single SC administration in Japanese (N=15) and BWI-matching non-Japanese subjects (SCS, N=16) except that T_{max} (~ 9 days) was delayed in Japanese subjects (Table 4.20). The mean C_{max} and $AUC_{0\text{-}inf}$ of Japanese subjects were 85% and 105% the values of non-Japanese subjects.

Table 4.20 Mean (SD) PK Parameters following Single-Dose SC Administration of 220 mg Reslizumab in Non-Japanese and Japanese Subjects

Variable Statistic	Non-Japanese SCS (N=16)	Japanese (N=15)
C_{max} (ng/mL)	32368.8 (14890.97)	27553.3 (8472.55)
t_{max} (min, max) (h)	99.8 (12.0, 483.9)	218.4 (95.0, 340.1)
$AUC_{0-\infty}$ (ng*h/mL)	24516.2 (7770.23)	25645.9 (8383.47)
$AUC_{0\text{-}t}$ (ng*h/mL)	22531.1 (9153.13)	24686.5 (7832.13)
Extrapolation (%)	2.07 (1.208)	3.37 (3.508)
λ_z (1/h)	0.00115 (0.000177)	0.00115 (0.000236)
$t_{½}$ (h)	619.67 (105.252)	624.50 (133.591)
CL (mL/hr)	–	–
CL/F (mL/h)	9.909 (3.2692)	9.786 (4.4768)
V_z (L)	–	–
V_z/F (L)	8.71 (2.794)	8.56 (3.376)
V_{ss} (L)	–	–

Source: CSR 1107, page 67, Table 12

Immunogenicity Results:

Out of the 75 subjects in this study, 2 (3%) were found to be treatment-emergent ADA positive, one subject following IV administration and one subject following SC administration. Both subjects were positive at only one time point and had low ADA titers (≤3). Subject 10567106 (non-Japanese SC) had a titer of 3 on day 14 and Subject 10567110 (non-Japanese IV) had a titer <1 on day 143. Subject 10567110 had a laboratory abnormality that met the criteria for potentially clinically significant eosinophilia (≥ 10% of WBC count) during screening and at final assessment.

PD Results:

- The effect of reslizumab on blood eosinophil count

Mean blood eosinophil counts at baseline were not well balanced either between IV (~200 cells/μL) and SC (~150 cells/μL) administration groups or non-Japanese SCS group (~110 cells/μL) and Japanese group (~110 cells/μL). Nevertheless, the mean blood eosinophil counts from all the groups were maximally reduced to ~50 cells/μL around day 28 (Figure 4.12).

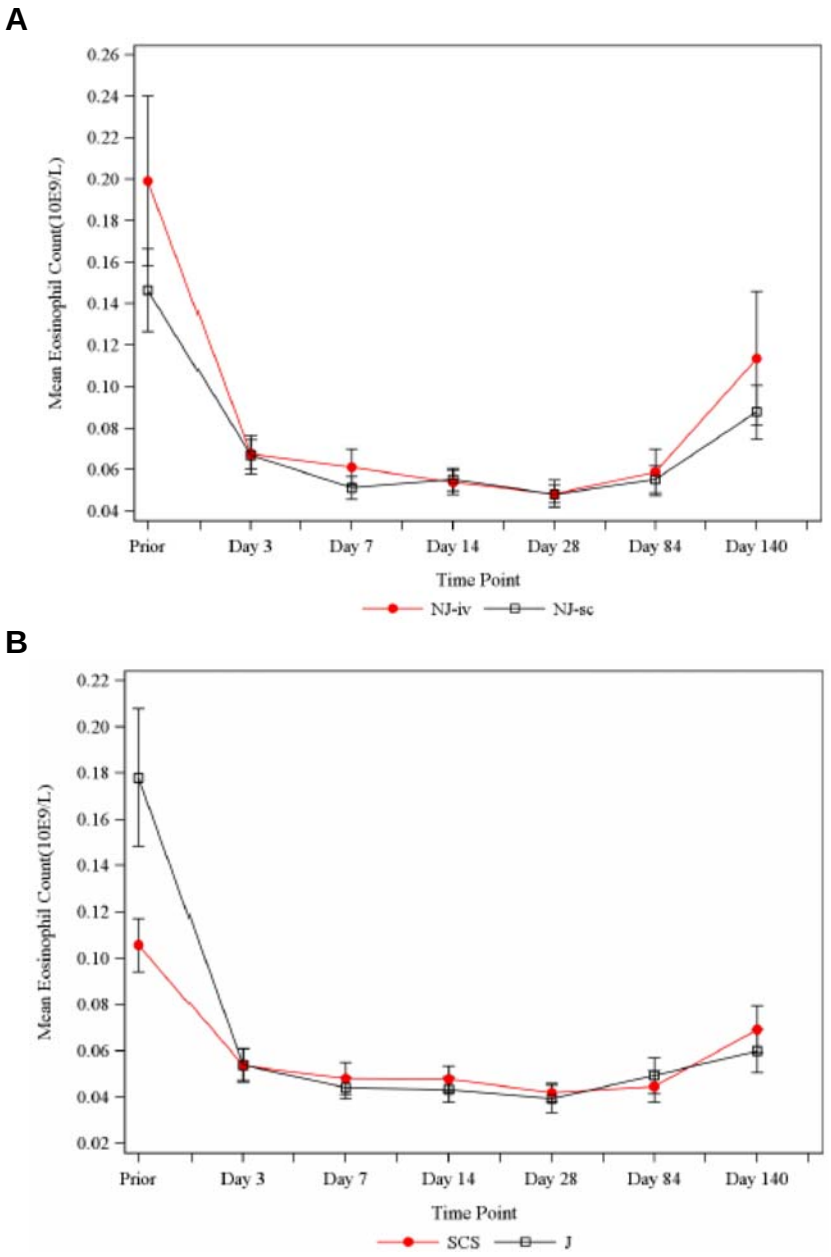

Figure 4.12 Mean (SE) blood eosinophil count by administration route in non-Japanese subjects (A) and race following SC administration (B). (Source: CSR 1107, page 69, Figure 7 and page 71 Figure 9)

Safety Results:

There were no deaths, serious adverse events, severe adverse events, or adverse events in the study. Two subjects had weakly positive ADA titers and were not associated with any safety findings. The overall incidence of adverse events was slightly higher in the non-Japanese sc group (43%) versus the non-Japanese IV group (33%), and similar between the non-Japanese SC (43%) and Japanese sc (40%) groups. No ECG findings were reported as adverse events. There were no clinically meaningful trends in mean changes from baseline to endpoint in ECG parameters in any treatment group. Subject 10567040, a 31-year-old Japanese female received reslizumab SC, had baseline QTcF of 450 msec, and increased to 451 msec on day 2. There were no reported cardiovascular adverse events or clinically relevant vital sign findings.

Conclusions:
The absolute bioavailability of reslizumab following single dose 220 mg SC administration was approximately 67%. There were no apparent trends towards differences in exposure between Japanese and non-Japanese subjects following SC reslizumab administration.

Only two subjects (3%) had low titre of ADA.

Reslizumab maximally reduced blood eosinophils counts to ~ 50 cells/µl in all treatment groups.

There were no clinically meaningful trends in mean changes from baseline to endpoint in ECG parameters in any treatment groups

4.1.6 Study C38072/3081 (Study3081)

Study Type: Phase 3 efficacy, safety, popPK, two-dose-level study in asthma patients
Study Dates: 02/07/2011 – 09/12/2013
Sponsor: Teva

Title:
A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12-75 Years of Age) With Eosinophilic Asthma

Objective:

- The primary objective was to determine whether reslizumab, at a dosage of 0.3 or 3.0 mg/kg administered once every 4 weeks for a total of 4 doses, was more effective than placebo in improving lung function in patients with eosinophilic asthma as assessed by the overall change from baseline in FEV1.

- The secondary objectives included:
  - Evaluation of reslizumab treatment effect on blood eosinophil counts compared with placebo.
  - Characterization of reslizumab PK using serum concentrations obtained prior to and after each infusion.
  - Characterization the relationship between serum concentrations of reslizumab and measures of efficacy and safety.
  - Assessment of immunogenicity by measurement of anti-reslizumab antibodies at baseline and at weeks 8 and 16 or early withdrawal.

Study Design and Method:
This investigation was a multicenter, randomized, double-blind, placebo-controlled, three-parallel-group, two IV dose levels study in approximately 300 asthmatic patients with inadequately controlled with medium to high dose ICS. In total 315 patients were randomized and 311 patients received at least one dose of study drug. 9 adolescents received at least one dose of reslizumab treatment. The IV doses were 0.3 or 3.0 mg/kg and the dosing interval was 4 weeks. The treatment duration was 16 weeks (total 4 doses).

Noteworthy inclusion criteria included:

- Patient was male or female, 12 through 75 years of age, with a previous diagnosis of asthma.
- The patient had an ACQ score of at least 1.5.
- The patient had airway reversibility of at least 12% to beta-agonist administration at screening.
- The patient was currently taking fluticasone at a dosage of at least 440 mcg daily (or equivalent). Patients' baseline asthma therapy regimen (including but not limited to inhaled corticosteroids, leukotriene antagonists, 5-lipoxygenase inhibitors, cromolyn) must have been stable for 30 days before screening, and continued without dosage changes throughout the study.
- The patient had a blood eosinophil count of at least 400/μL.

Noteworthy exclusion criteria included:

- The patient had known hypereosinophilic syndrome.
- The patient was a current smoker.
- The patient was currently using systemic corticosteroids.
- The patient had presence of or suspected parasitic infestation/infection.

Blood samples for PK analysis were collected at baseline, before and after each infusion at weeks 4, 8, and 12, and at week 16 or early withdrawal. Patients participating at centers in the US were asked to return to the study center for 2 additional visits for collection of blood samples for measurement of serum reslizumab concentration (1 visit to occur on day 2 or 3, and 1 visit to occur during week 2 or 3). In addition, attempts were made to collect a blood sample for measurement of serum reslizumab concentration from any patient who experienced a serious adverse event, or an adverse event leading to withdrawal from the study, or a worsening of asthma symptoms.

Serum reslizumab concentrations were determined at (b) (4), using a validated sandwich ELISA. Microtiter plates were pre-coated with recombinant human IL-5 to capture reslizumab. Samples (including standards and quality controls) were added and incubated on the plate. The bound reslizumab was detected by a mouse anti-human IgG4 horseradish peroxidase conjugate.

Serum reslizumab concentration data will be pooled with data from other studies and included in population PK and PD analyses.

ADA was only analyzed in the blood samples collected from reslizumab-treatment groups, but not placebo-treatment group. Blood samples were drawn for anti-reslizumab antibody analyses at baseline, and at weeks 8 and 16 or early withdrawal. Blood samples for anti-reslizumab antibody assessment were also to be obtained from all patients (inside or outside of the US) who experienced a serious adverse event, an adverse event that led to withdrawal, or an exacerbation of asthma symptoms.

The ADA analysis in human serum employed a validated homogeneous ELISA and it was performed in a 3-tier approach consisting of screening, confirmatory, and titer assays.

A patient was classified as having a treatment-emergent ADA response if a sample was tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample.

Efficacy/PD Endpoints:
Change from baseline to weeks 4, 8, 12, 16, and endpoint was measured for the Blood eosinophils count

PK Results:
The PK data from this study was pooled with data from other studies in a popPK meta-analysis and the results were presented in popPK report CP-11-006.

PD Results:

- Blood eosinophil counts

  Mean absolute blood eosinophil levels by treatment group from Day 1 to Week 16 are presented in Fig. 4.13. The mean eosinophil counts at baseline (pre-dose on Day 1) were 601, 644, and 599 cells/μL for placebo, 0.3 mg/kg, and 3 mg/kg treatment group, respectively. Blood eosinophils counts decreased significantly from baseline in both two active treatment groups comparing to placebo group at any time points between Week4 and Week 16 ($p<0.0001$). It appeared that the reduction plateau phase was reached at Week 4 and Week 8 for 0.3 mg/kg, and 3 mg/kg treatment group, respectively. The absolute values of blood eosinophil counts reduced maximally to 517, 208, and 48 cells/μL (or reduced by 14%, 68%, and 92%) for placebo, 0.3 mg/kg, and 3 mg/kg treatment group, respectively.

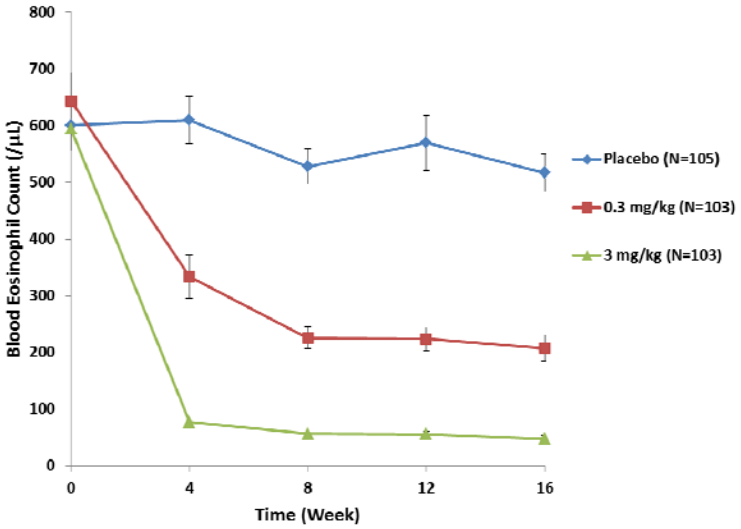

Figure 4.13 Arithmetic mean (±SE) of absolute blood eosinophil counts-time profile in different groups: placebo (blue, N=105), 0.3 mg/kg (brown, N=103), and 3 mg/kg (green, N=103. (Source: CSR 3081, page 351 - 355, Summary 15.24)

Immunogenicity Results:

ADA was only assessed in 589 analyzable blood samples obtained from reslizumab-treatment groups (102 subjects from 0.3 mg/kg group and 103 subjects from 3 mg/kg group) over 16-week treatment period. 38 (19%) patients had at least one collection time point positive in the ADA assay (Table 4.21). However, 16/38 patients were positive at baseline. Of these 16 patients, 11 patients were observed to be positive only at baseline; 4 patients were positive in both pre-dose and post-dose collection time points but had no appreciable (≥ 4 fold) titer increase after dosing. Therefore 23 patients (12 in 0.3 mg/kg group and 11 in 3 mg/kg group) or 11% patients had positive treatment-emergent ADA response. The median titer of the ADA in those patients was 7.20 and 6.96 in 0.3 mg/kg and 3 mg/kg group (with Week 8 and 16 data combined), respectively (Table 4.22).

Table 4.21 Summary of Immunogenicity Incidence by Treatment Group

Time Points	0.3 mg/kg N (%)	3 mg/kg N(%)
Week 1 (Baseline)	8/99 (8%)	8/98 (8%)
Week 8	8/90 (9%)	10/94 (11%)
Week 16	7/91 (8%)	5/89 (6%)
Positive at any time	20/102 (20%)	18/103 (17%)
Treatment-Emergent	12/102 (12%)	11/103 (11%)

Source: adapted from bioanalytical report of Study 3081, page 19, Table 9

Table 4.22 Titer of anti-Reslizumab Antibody in Confirmed Positive Subjects

Reslizumab dose	Pre-dose (Baseline)	Week 8 only	Week 16 only	Both week 8 and week 16	Early Withdrawal or Unscheduled
0.3 mg/kg	4.1 (2.1 – 26)	7.66 (3.44 - 10.5)	2.75 (2.63 - 2.86)	7.20 (3.24 - 13.1)	7.25 (4.85 - 26.1)
3.0 mg/kg	4.49 (1.18 - 15.9)	6.79 (3.04 - 13.1)	11.21 (8.92 - 13.5)	6.96 (2.66 - 10.8)	44.1[a] (NA)

For each time point, median titer (range) is provided.
Source: bioanalytical report of Study 3081, page 20, Table 10

Conclusions:

- Overall change from baseline in blood eosinophil counts over the 16 weeks of treatment showed significant reduction of eosinophil counts for both active treatment groups compared with placebo ($p<0.0001$).

- 16/203 (8%) of patients in the reslizumab treatment group were positive on the treatment-emergent ADA response. 12/102 (12%) and 11/103 (11%) patients were positive on the treatment-emergent ADA response in 0.3 mg/kg and 3.0 mg/kg treatment groups, respectively.

4.1.7 Study C38072/3082 (Study3082)

Study Type: Phase 3 efficacy, safety, popPK, placebo-controlled study in asthma patients
Study Dates: 04/12/2011 – 03/03/2014
Sponsor: Teva

Title:
A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma

Objective:

- The primary objective of this study was to demonstrate the efficacy of reslizumab at a dose of 3.0 mg/kg administered intravenously every 4 weeks over 12 months, as assessed by the reduction in frequency of clinical asthma exacerbations (CAEs) during 12 months.

- The secondary objectives included:
  - Change from baseline to week 16 in FEV1.
  - Change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) score to week 16.
  - Overall change from baseline in the Asthma Control Questionnaire (ACQ) score over 16 weeks.
  - Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks.

- PK objective
  - To characterize the pharmacokinetics of reslizumab by obtaining serum concentrations at baseline and weeks 4, 8, 12, 16, 24, 36, and 48
  - To characterize the relationship between serum concentrations of reslizumab and measures of efficacy and safety

- Immunogenicity objective

To evaluate immunogenicity by measurement of anti-reslizumab antibodies at baseline and at weeks 16, 32, 48, and 52, or early withdrawal

Study Design and Method:
This investigation was a multicenter, randomized, double-blind, placebo-controlled, two-parallel-group, fixed-dosage study in approximately 480 patients with inadequately controlled asthma. In total 244 and 245 patients were randomized into placebo and reslizumab treatment group, respectively. Among them, 7 and 6 adolescents were randomized into placebo and reslizumab treatment group, respectively. The IV dose was 3.0 mg/kg and the dosing interval was 4 weeks. The treatment duration was 48 weeks (total 13 doses).

Noteworthy inclusion criteria included:

- Patient was male or female, 12 through 75 years of age, with a previous diagnosis of asthma.
- The patient had at least 1 asthma exacerbation requiring oral, intramuscular, or intravenous corticosteroid use for at least 3 days over the past 12 months before screening.
- The patient had airway reversibility of at least 12% to beta-agonist administration.
- The patient had an ACQ score of at least 1.5 at the screening and baseline (before the 1st dose of study drug) visits.
- The patient was taking inhaled fluticasone at a dosage of at least 440 mcg, or equivalent, daily. Chronic oral corticosteroid use (no more than 10 mg/day prednisone or equivalent) was allowed.

The patient's baseline asthma therapy regimen (including, but not limited to, inhaled corticosteroids, oral corticosteroids up to a maximum dose of 10 mg prednisone daily or equivalent, leukotriene antagonists, 5-lipoxygenase inhibitors, or cromolyn) had to be stable for 30 days prior to screening and baseline and had to continue without dosage changes throughout the study.

- The patient had a blood eosinophil level of at least 400/μL at least once during the screening period prior to being randomized.

Noteworthy exclusion criteria included:

- The patient had known hypereosinophilic syndrome.
- The patient was a current smoker.
- The patient was using systemic immunosuppressive, immunomodulating, or other biologic agents within 6 months prior to screening.
- The patient had an active parasitic infection within 6 months prior to screening.

Blood samples (5 mL) for measurement of serum reslizumab concentrations were collected from all patients before each study drug infusion at baseline and at weeks 4, 8, 12, 16, 24, 36, and 48. Blood samples were also collected following completion of the infusion at baseline and weeks 16 and 36. Patients participating at centers in the US were asked to return to the study center for collection of additional blood samples for pharmacokinetics either on day 2 or day 3 and either at week 2 or at week 3 after the first infusion. Every effort was made to also obtain blood samples for serum reslizumab concentrations from all the patients experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms.

For the determination of reslizumab concentration in human serum, a sandwich ELISA was validated and used. Microtiter plates were pre-coated with recombinant human IL-5 to capture reslizumab. Samples (including standards and quality controls) were added and incubated on the plate. The bound reslizumab was detected by a mouse anti-human IgG4 horseradish peroxidase conjugate.

At the same time blood samples were drawn for analysis of serum reslizumab concentrations, blood was drawn for blood eosinophil count as part of the hematology laboratory tests.

Serum reslizumab concentration data will be pooled with data from other studies and included in population PK and PD analyses.

ADA was only analyzed in the blood samples collected from reslizumab-treatment groups, but not placebo-treatment group. Blood samples for anti-reslizumab antibody assessment were obtained at baseline and predose at weeks 16, 32, 48, and 52 or early withdrawal. Every effort was made to also obtain immunogenicity blood samples from patients (inside and outside of the US) experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms.

The ADA analysis in human serum employed a validated homogeneous ELISA and it was performed in a 3-tier approach consisting of screening, confirmatory, and titer assays.

A patient was classified as having a treatment-emergent ADA response if a sample was tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample.

Efficacy/PD Endpoints:
Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks

PK Results:
The PK data from this study was pooled with data from other studies in a popPK meta-analysis and the results were presented in popPK report CP-11-006.

PD Results:
Blood eosinophil counts
Mean absolute blood eosinophil levels by treatment group from baseline to Week 52 are presented in Fig. 4.14. The mean eosinophil counts at baseline (pre-dose on Day 1) were 624 and 696 cells/µL for placebo and 3 mg/kg reslizumab treatment group, respectively. Blood eosinophils counts decreased significantly from baseline in 3 mg/kg reslizumab treatment group comparing to placebo group at any time points between Week 4 and Week 52 ($p<0.0001$). The absolute values of blood eosinophil counts reduced maximally to 455 and 49 cells/µL (or reduced by 27% and 93%) for placebo and 3 mg/kg reslizumab treatment group, respectively.

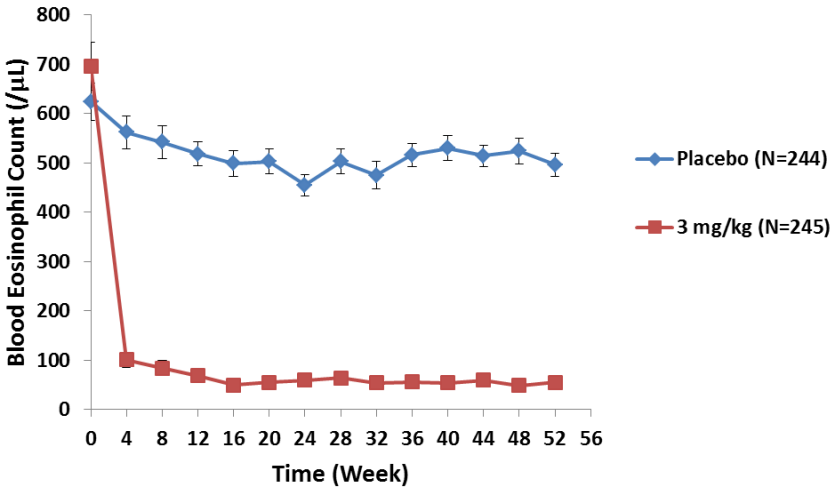

Figure 4.14 Arithmetic mean (±SE) of absolute blood eosinophil counts-time profile from placebo group (blue, N=244) and 3 mg/kg reslizumab group (brown, N=245). (Source: CSR 3082, page 577 - 590, Summary 15.21)

Immunogenicity Results:
ADA was only analyzed in 1215 analyzable samples obtained from 3 mg/kg reslizumab-treatment group (245 subjects) over 52-week treatment period. 12 (5%) patients had at least one collection time point positive in the ADA assay (Table 4.23). However, 4/12 patients were positive at baseline. Of these 4 patients, 3 patients were observed to be positive only at baseline; 1 patient was positive in both pre-dose and post-dose collection time points but had no titer increase after dosing. Therefore 8 patients (3%) were positive on treatment-emergent ADA response. Of these 8 patients, 5 patients were ADA positive only at one post-baseline visit. The median titer of the ADA in those patients ranged from 3.52 to 9.96 from Week 16 to Week 52 (Table 4.24). There was no evidence for the ADA titer to increase during the treatment period in the 3 patients who were ADA-positive at more than one visit.

Table 4.23 Summary of Immunogenicity Incidence in 3 mg/kg Reslizumab Group

Time Points	3 mg/kg Reslizumab N (%)
Week 1 (Baseline)	4/242 (2%)
Week 16	6/228 (3%)
Week 32	2/217 (1%)
Week 48	4/211 (2%)
Week 52	2/219 (1%)
Positive at any time	12/245 (5%)
Treatment-Emergent	8/245 (3%)

Source: adapted from bioanalytical report of Study 3082, page 1423, Summary 15.64

Table 4.24 Titer of anti-Reslizumab Antibody in Confirmed Positive Subjects

ADA response	Visit 2 (baseline)	Visit 6 (Week 16)	Visit 10 (Week 32)	Visit 14 (Week 48)	Visit 15 (Week 52)	Early Withdrawal /Unscheduled
n	4	6	2	5	2	0
Median Titer	18.9 (5.84 – 45.4)	3.85 (2.39 – 6.94)	9.96 (4.81 – 15.1)	3.52 (2.50 – 5.47)	4.69 (3.07 – 6.31)	NA

For each time point, median titer (range) is provided.
Source: bioanalytical report of Study 3082, page 19, Table 10

Blood eosinophil counts at each visit were compared between the 8 treatment-emergent ADA-positive patients and 237 ADA-negative patients (Figure 4.15). The overall pattern of blood eosinophil reduction by reslizumab in treatment-emergent ADA positive patients, as a group, was not different from patients who were ADA-negative, indicating no effect on reslizumab pharmacologic activity. The pattern of adverse events was also similar to that observed for the overall study population.

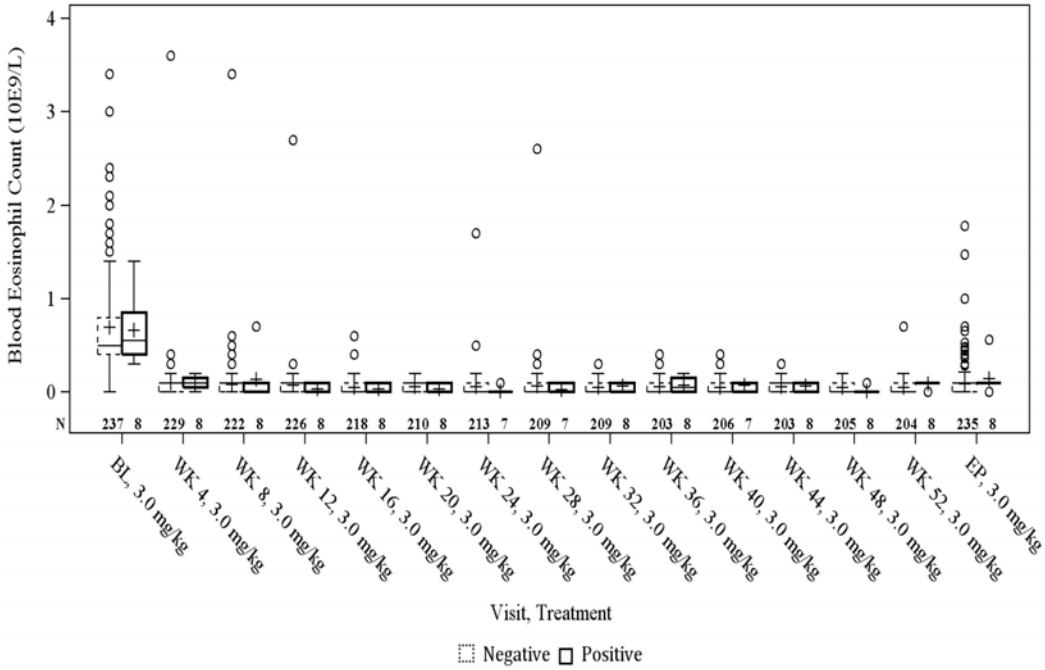

Figure 4.15 Box plots of blood eosinophil counts by visit and overall ADA status (8 positive and 237 negative patients). (Source: CSR 3082, page 201, Figure 18)

Conclusions:

- Blood eosinophils counts were significantly reduced from baseline in 3 mg/kg reslizumab treatment group compared with the placebo group [$p<0.0001$ at all measured time points (every 4 weeks from Week 4 to Week 52)].

- 8/245 (8%) of patients in the 3 mg/kg reslizumab treatment group were positive on treatment-emergent ADA response. The ADA titers were generally low.

4.1.8 Study C38072/3083 (Study3083)

Study Type: Phase 3 efficacy, safety, placebo-controlled study in asthma patients
Study Dates: 03/22/2011 – 04/03/2014
Sponsor: Teva

Title:
A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma

Objective:

- The primary objective of the study was to determine whether reslizumab, at a dose of 3 mg/kg administered intravenously (iv) every 4 weeks over 12 months, was more effective than placebo in reducing the number of clinical asthma exacerbations (CAEs) in patients with eosinophilic asthma as assessed by the frequency of CAEs.

- The secondary objectives included:
  - Change from baseline to week 16 in FEV1.
  - Change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) score to week 16.
  - Overall change from baseline in the Asthma Control Questionnaire (ACQ) score over 16 weeks.
  - Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks.

- Immunogenicity objective

To evaluate immunogenicity by measurement of anti-reslizumab antibodies at baseline and at weeks 16, 32, 48, and 52, or early withdrawal

Study Design and Method:
This investigation was a multicenter, randomized, double-blind, placebo-controlled, two-parallel-group, fixed-dosage study in approximately 460 patients with inadequately controlled asthma. In total 232 and 232 patients were randomized into placebo and reslizumab treatment group, respectively. Among them, 4 and 8 adolescents were randomized into placebo and reslizumab treatment group, respectively. The IV dose was 3.0 mg/kg and the dosing interval was 4 weeks. The treatment duration was 48 weeks (total 13 doses).

Noteworthy inclusion criteria included:

- Patient was male or female, 12 through 75 years of age, with a previous diagnosis of asthma.
- The patient had at least 1 asthma exacerbation requiring oral, intramuscular, or intravenous corticosteroid use for at least 3 days over the past 12 months before screening.
- The patient had airway reversibility of at least 12% to beta-agonist administration.
- The patient had an ACQ score of at least 1.5 at the screening and baseline (before the 1st dose of study drug) visits.
- The patient was taking inhaled fluticasone at a dosage of at least 440 mcg, or equivalent, daily. Chronic oral corticosteroid use (no more than 10 mg/day prednisone or equivalent) was allowed. The patient's baseline asthma therapy regimen (including, but not limited to, inhaled corticosteroids, oral corticosteroids up to a maximum dose of 10 mg prednisone daily or equivalent, leukotriene antagonists, 5-lipoxygenase inhibitors, or cromolyn) had to be stable for 30 days prior to screening and baseline and had to continue without dosage changes throughout the study.

- The patient had a blood eosinophil level of at least 400/μL at least once during the screening period prior to being randomized.

Noteworthy exclusion criteria included:

- The patient had known hypereosinophilic syndrome.
- The patient was a current smoker.
- The patient was using systemic immunosuppressive, immunomodulating, or other biologic agents within 6 months prior to screening.
- The patient had an active parasitic infection within 6 months prior to screening.

Blood samples for analysis of serum reslizumab concentrations were obtained from all patients (inside and outside of the US) experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms. Results of analyses of pharmacokinetics will be provided in a separate report.

ADA was only analyzed in the blood samples collected from reslizumab-treatment groups, but not placebo-treatment group. Blood samples were collected from all patients for the assessment of the presence of ADA at baseline and prior to the study drug infusion at the week 16, 32, 48, and 52 visits or early withdrawal visit. Additional blood samples for ADA assessment were obtained from all patients (inside or outside of the US) experiencing a serious adverse event, an adverse event leading to withdrawal, or an exacerbation of asthma symptoms.

The ADA analysis in human serum employed a validated homogeneous ELISA and it was performed in a 3-tier approach consisting of screening, confirmatory, and titer assays.

A patient was classified as having a treatment-emergent ADA response if a sample was tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample.

Efficacy/PD Endpoints:
Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks

PD Results:
Blood eosinophil counts
Mean absolute blood eosinophil levels by treatment group from baseline to Week 52 are presented in Fig. 4.16. The mean eosinophil counts at baseline (pre-dose on Day 1) were 688 and 610 cells/μL for placebo and 3 mg/kg reslizumab treatment group, respectively. Blood eosinophils counts decreased significantly from baseline in 3 mg/kg reslizumab treatment group comparing to placebo group at any time points between Week 4 and Week 52 ($p<0.0001$). The absolute values of blood eosinophil counts reduced maximally to 521 and 47 cells/μL (or reduced by 24% and 92%) for placebo and 3 mg/kg reslizumab treatment group, respectively.

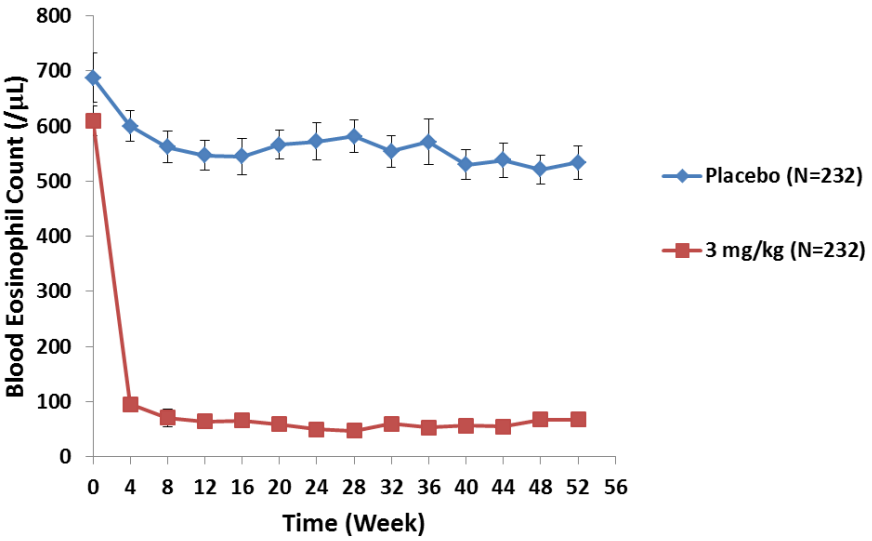

Figure 4.16 Arithmetic mean (±SE) of absolute blood eosinophil counts-time profile from placebo group (blue, N=232) and 3 mg/kg reslizumab group (brown, N=232). (Source: CSR 3083, page 554 - 567, Summary 15.21)

Immunogenicity Results:
ADA was only analyzed in 1119 analyzable samples obtained from 3 mg/kg reslizumab-treatment group (226 subjects) over 52-week treatment period. 23 (10%) patients had at least one collection time point positive in the ADA assay (Table 4.25). However, 10/23 patients were positive at baseline. Of these 10 patients, 7 patients were observed to be positive only at baseline; 1 patient was positive in both pre-dose and post-dose collection time points but had no titer increase after dosing. Therefore 15 patients (7%) were positive on treatment-emergent ADA response. Of these 15 patients, 3 patients were ADA positive only at one post-baseline visit. The median titer of the ADA in those patients ranged from 7.02 to 9.1 from Week 16 to Week 52 (Table 4.26). There was no trend for the number of ADA-positive patients to increase during the 12-month treatment period.

Table 4.25 Summary of Immunogenicity Incidence in 3 mg/kg Reslizumab Group

Time Points	3 mg/kg Reslizumab N (%)
Week 1 (Baseline)	10/205 (5%)
Week 16	11/207 (5%)
Week 32	11/201 (5%)
Week 48	11/199 (6%)
Week 52	11/201 (5%)
Positive at any time	23/226 (10%)
Treatment-Emergent	15/226 (7%)

Source: adapted from bioanalytical report of Study 3083, page 1343, Summary 15.62

Table 4.26 Titer of anti-Reslizumab Antibody in Confirmed Positive Subjects

ADA response	Visit 2 (baseline)	Visit 6 (Week 16)	Visit 10 (Week 32)	Visit 14 (Week 48)	Visit 15 (Week 52)	Early Withdrawal /Unscheduled
n	10	11	11	11	11	0
Median Titer	9.44 (1.88 – 39.9)	7.97 (2.87 – 104)	9.1 (2.43 – 39.8	7.75 (2.58 – 44.8)	7.02 (1.95 – 106)	NA

For each time point, median titer (range) is provided.
Source: bioanalytical report of Study 3083, page 19, Table 9

Blood eosinophil counts at each visit were compared between the 15 treatment-emergent ADA-positive patients and 211 ADA-negative patients (Figure 4.17). The overall pattern of blood eosinophil reduction by reslizumab in treatment-emergent ADA positive patients, as a group, was not different from patients who were ADA-negative, indicating no effect on reslizumab pharmacologic activity. The pattern of adverse events was also similar to that observed for the overall study population.

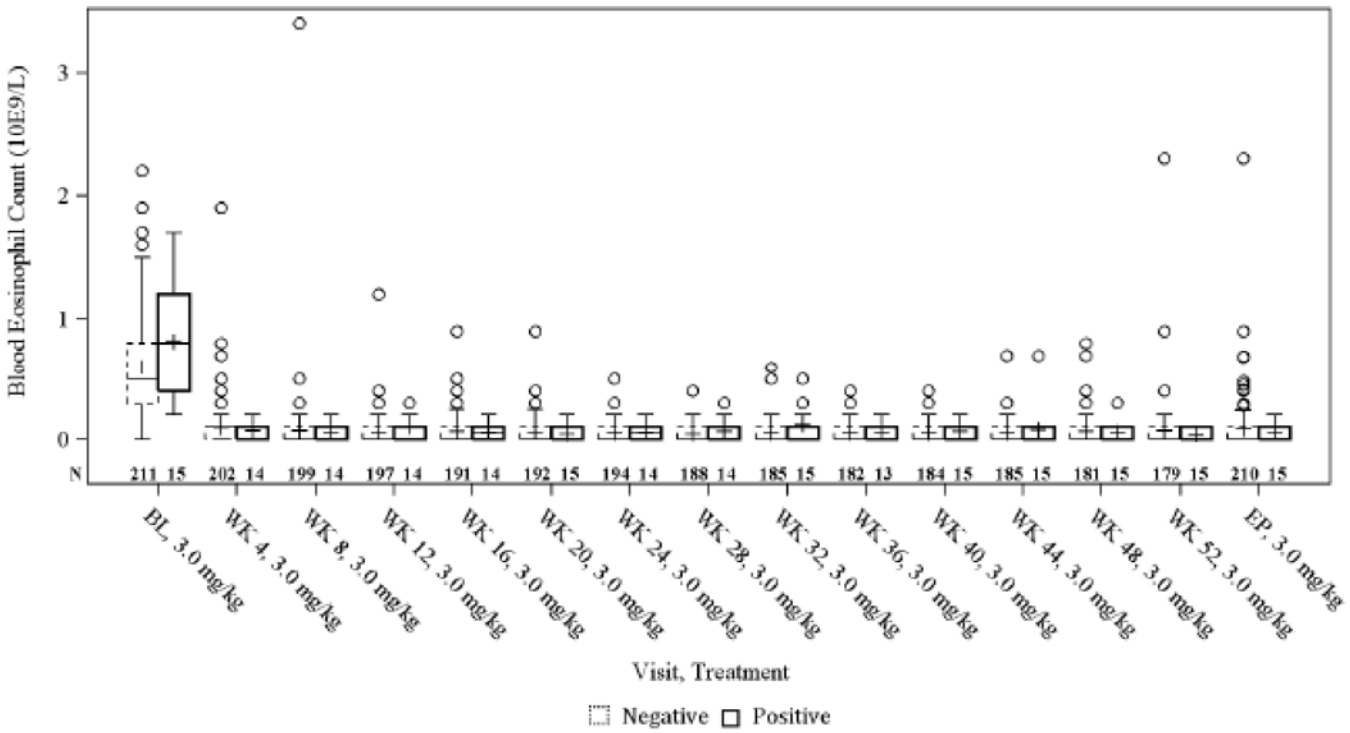

Figure 4.17 Box plots of blood eosinophil counts by visit and overall ADA status (8 positive and 237 negative patients). (Source: CSR 3083, page 207, Figure 18)

Conclusions:

- Blood eosinophils counts were significantly reduced from baseline in 3 mg/kg reslizumab treatment group compared with the placebo group [$p<0.0001$ at all measured time points (every 4 weeks from Week 4 to Week 52)].

- 15/226 (7%) of patients in the 3 mg/kg reslizumab treatment group were positive on treatment-emergent ADA response. The ADA titers were generally low.

4.1.9 Study C38072/3084 (Study3084)

Study Type: Phase 3 efficacy, safety, placebo-controlled study in asthma patients
Study Dates: 02/17/2012 – 08/14/2013
Sponsor: Teva

Title:
A 16-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) Treatment in Patients with Moderate to Severe Asthma

Objective:

- The primary objective of the study was to characterize the efficacy of reslizumab treatment, at a dosage of 3.0 mg/kg every 4 weeks for a total of 4 doses, in improving pulmonary function in relation to baseline blood eosinophil levels in patients with moderate to severe asthma, as assessed by the change from baseline to week 16 in forced expiratory volume in 1 second (FEV1).

- The secondary objectives included:
  - To characterize the efficacy of reslizumab treatment in relation to baseline blood eosinophil levels as assessed by the effect of reslizumab treatment at the planned time points, on the eosinophil count.
  - To characterize the efficacy of reslizumab treatment compared with placebo treatment in relation to baseline blood eosinophil levels as assessed by the effect of reslizumab treatment at the planned time points, on the eosinophil count.
  - .
  - Overall change from baseline in the Asthma Control Questionnaire (ACQ) score over 16 weeks.
  - Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks.

- Immunogenicity objective

To evaluate immunogenicity of reslizumab by determining the presence of antibodies to reslizumab during the screening period, at week 8, week 16 or early withdrawal, and at the end-of-study (EOS) follow-up visit (12 weeks ±7 days after the end of treatment [EOT] visit at week 16 or early withdrawal)

Study Design and Method:
This investigation was a multicenter, randomized, double-blind, placebo-controlled, two-parallel-group, fixed-dosage study in approximately 500 patients with moderate to severe asthma. In total data from 98 and 398 patients in placebo and reslizumab treatment groups, respectively, were analyzed (15 randomized patients from sites 864 and 909 were included as randomized, but not analyzed, since the participation of these sites was terminated during the course of the study). No adolescents were recruited in this study. The IV dose was 3.0 mg/kg and the dosing interval was 4 weeks. The study duration was 16 weeks (total 4 doses were administered).

Noteworthy inclusion criteria included:

- Patient was male or female, 18 through 65 years of age, with a previous diagnosis of asthma.
- The patient had an ACQ score of at least 1.5.
- The patient had airway reversibility of at least 12% to beta-agonist administration at screening.
- The patient was taking inhaled fluticasone at a dosage of at least 440 mcg, or equivalent, daily. The patients' baseline asthma therapy regimens (including, but not limited to, inhaled corticosteroids [ICSs], leukotriene antagonists, 5-lipoxengase inhibitors, cromolyn) must have

been stable for 30 days before screening and were expected to continue without dosage changes throughout study.

Noteworthy exclusion criteria included:

- The patient had known hypereosinophilic syndrome.
- The patient was a current smoker.
- The patient was using systemic immunosuppressive, immunomodulating, or other biologic agents within 6 months prior to screening.
- The patient had an active parasitic infection within 6 months prior to screening.
- The patient was currently using or had used systemic corticosteroids (included use of oral corticosteroids [OCSs]) within 30 days prior to the screening visit.

ADA was only analyzed in the blood samples collected from reslizumab-treatment groups, but not placebo-treatment group. Blood samples were collected from all patients for the assessment of the presence of ADA at baseline and prior to the study drug infusion at the week 8, 16, and 12 weeks after the EOT, or early withdrawal.

The ADA analysis in human serum employed a validated homogeneous ELISA and it was performed in a 3-tier approach consisting of screening, confirmatory, and titer assays.

A patient was classified as having a treatment-emergent ADA response if a sample was tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample.

Efficacy Endpoints:

The primary efficacy measure and variable for this study was the change from baseline to week 16 in FEV1. The secondary endpoints included blood eosinophil counts measured at weeks 4, 8, 12, 16, and follow-up, or upon early withdrawal

PD Results:

Blood eosinophil counts

Mean absolute blood eosinophil levels by treatment group and baseline eosinophil counts (<400 or ≥400 cells/μL) from baseline to Week 16 are presented in Fig. 4.18. The mean eosinophil counts at baseline were similar between placebo group and reslizumab group in both eosinophil high and low categories. Mean blood eosinophil counts remained relatively stable for placebo group in both categories. Blood eosinophils counts greatly reduced from baseline in both categories. The absolute values of blood eosinophil counts from reslizumab treatment group reduced maximally to 42 and 62 cells/μL in eosinophil low and high categories.

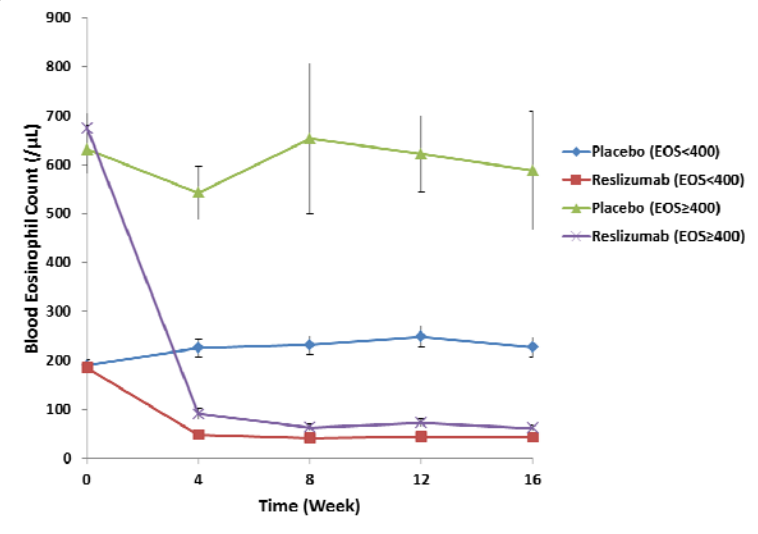

Figure 4.18 Arithmetic mean (±SE) of absolute blood eosinophil counts-time profile from placebo group with eosinophil counts<400 cells/µL (blue, N=77), placebo group with eosinophil counts ≥ 400 cells/µL (green, N=19), 3 mg/kg reslizumab group with eosinophil counts<400 cells/µL (brown, N=318), 3 mg/kg reslizumab group with eosinophil counts ≥400 cells/µL (purple, N=78). (Source: Reviewer's analysis)

Immunogenicity Results:
ADA was only analyzed in 1553 analyzable samples obtained from 3 mg/kg reslizumab-treatment group (395 subjects) over 16-week treatment period. 30 (8%) patients had at least one collection time point positive in the ADA assay (Table 4.27). However, 13/30 patients were positive at baseline. Of these 13 patients, 8 patients were observed to be positive only at baseline; 3 patients were positive in both pre-dose and post-dose collection time points but had no appreciable (≥ 4 fold) titer increase after dosing. Therefore 19 patients (5%) were positive on treatment-emergent ADA response. Of these 19 patients, 12 patients were ADA positive only at one post-baseline visit. The median titer of the ADA in those patients ranged from 4.75to 7.03 from Week 4 to follow-up visit (Table 4.28).

Table 4.27 Summary of Immunogenicity Incidence in 3 mg/kg Reslizumab Group

Time Points	3 mg/kg Reslizumab N (%)
Week 1 (Baseline)	13/388 (3%)
Week 8	15/361 (4%)
Week 16	9/337 (3%)
Positive at any time	30/395 (8%)
Treatment-Emergent	19/395 (5%)

Source: adapted from bioanalytical report of Study 3084, page 667, Summary 15.56

Table 4.28 Titer of anti-Reslizumab Antibody in Confirmed Positive Subjects

ADA response	Predose (Baseline)	Visit 4 (Week 8)	Visit 6 (Week 16, EOT)	Visit 7 (12 weeks after EOT)	Early Withdrawal or Unscheduled
n	13	15	9	8	2
Median Titer (Range)	6.51 (3.79 –16.8)	7.03 (1.85–40.8)	4.75 (1.38–56.4)	6.31 (<1–60.5)	18.05 (2.1–34)

For each time point, median titer (range) is provided.
Source: bioanalytical report of Study 3083, page 20, Table 10

Blood eosinophil counts at each visit were compared between the 19 treatment-emergent ADA-positive patients and 376 ADA-negative patients (Figure 4.19). The overall pattern of blood eosinophil reduction by reslizumab in treatment-emergent ADA positive patients, as a group, was not different from patients who were ADA-negative, indicating no effect on reslizumab pharmacologic activity. Eleven (57%) of the 19 ADA-positive patients reported adverse events, which was the same frequency of adverse event reporting for the overall reslizumab 3.0 mg/kg group. The adverse event profile in patients with a positive ADA test during the treatment period was not meaningfully different from the overall population.

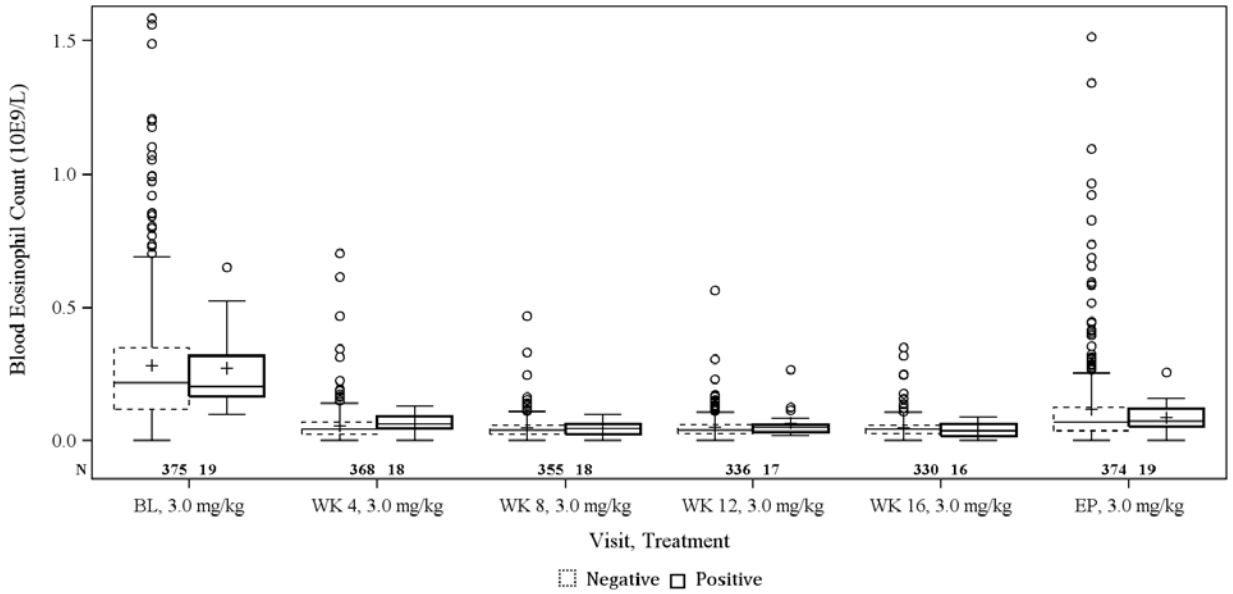

Figure 4.19 Box plots of blood eosinophil counts by visit and overall ADA status (19 positive and 376 negative patients). (Source: CSR 3084, page 171, Figure 12)

Conclusions:

- Blood eosinophils counts were greatly reduced from baseline in 3 mg/kg reslizumab treatment group compared with the placebo group. The absolute values of blood eosinophil counts from reslizumab treatment group reduced maximally to 42 and 62 cells/μL in eosinophil low and high categories.

- 19/395 (5%) of patients in the 3 mg/kg reslizumab treatment group were positive on treatment-emergent ADA response. The ADA titers were generally low.

4.1.6 In Vitro Study XT133130

Study Type: In vitro drug-drug interaction study in cultured human hepatocytes
Study Dates: 11/11/2013 – 12/12/2013

Title:
In vitro Evaluation of IL-5 and Anti-IL5 Antibody (Reslizumab) on Cell Viability and Cytochrome P450 Expression in Cultured Human Hepatocytes

Objective:
The objective of this experiment was to investigate the effects of treating a single primary culture of fresh human hepatocytes with IL-5 and the IL-5 antibody, reslizumab, on the expression of cytochrome P450 (CYP) enzymes, specifically to determine if there was scientific rationale for conducting a more complete in-vitro study.

Study Design and Method:
One fresh preparation of cultured human hepatocytes from 1 liver was treated once daily for 3 consecutive days with media containing DMSO (0.1% v/v, vehicle control for inducers), placebo buffer (2%, v/v, vehicle control for IL-6, IL-5, and reslizumab), 1 of 2 concentrations of IL-5 (100 or 400 pg/mL), reslizumab (200 μg/mL, about 2-fold of the C_{max} following 3 mg/kg IV administration in subject weighing 75 kg), CYP suppressor IL-6 (10 ng/mL), or 1 of 3 known human CYP inducers, namely, omeprazole (50 μM), phenobarbital (750 μM), and rifampin (20 μM). After treatment, the cells were harvested with Buffer RLT to isolate RNA, which was analyzed by qRT-PCR to assess the effects.

The potential of IL-5 and reslizumab to cause cytotoxicity was assessed based on the release of lactate dehydrogenase (LDH) into the culture medium (a measure of cell membrane integrity) and by daily microscopic evaluation of cellular morphology.

Results:

- Viability and morphology of cultured human hepatocytes

  At the time of isolation, the viability of the hepatocyte preparation was 82.2%. Prior to and during treatment, human hepatocyte cultures formed confluent monolayers with few intercellular spaces and, in general, were cuboidal and contained intact cell membranes and granular cytoplasm with 1 or 2 centrally located nuclei.

- The effect of IL-5 and Reslizumab on LDH

  Treatment of cultured human hepatocytes with all of the control articles, and up to 400 pg/mL IL-5 or 200 μg/mL reslizumab resulted in little or no increase in LDH activity (Figure 20). On the contrary, the hepatocytes treated with the non-ionic detergent Triton X-100 exhibited a marked increase in LDH activity.

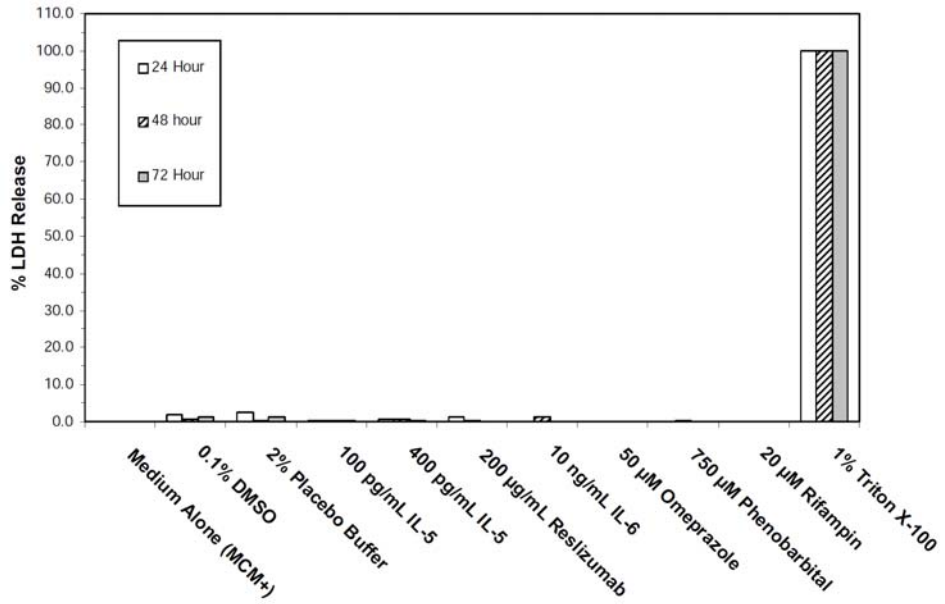

Figure 4.20 The effect of IL-5, reslizumab, IL-6, omeprazole, phenobarbital and rifampin on hepatocytes cytotoxicity. (Source: CSR 10DMW042, page 17, Figure 1)

- The effect of IL-5 and reslizumab on human CYP1A2, 2B6, and 3A4 mRNA levels

Treatment of cultured human hepatocytes with up to 400 pg/mL IL-5 and 200 µg/mL reslizumab caused minimal change (<16%) in CYP1A2, 2B6, and 3A4 mRNA levels (Table 4.29). On the contrary, CYP1A2 mRNA inducer omeprazole (50 µM) enhanced the mRNA level about 103-fold. CYP2A6 mRNA inducer omeprazole (50 µM) enhanced the mRNA level about 21-fold. CYP3A4 mRNA inducer rifampin (20 µM) enhanced the mRNA level about 16-fold. IL-6 reduced mRNA level of 1A2, 2B6, and 3A4 approximately 18%, 37% and 32%, respectively.

Table 4.29 Effect of Reslizumab on Three CYP Enzymes mRNA Levels in Human Hepatocytes

	CYP1A2 mRNA	CYP2B6 mRNA	CYP3A4 mRNA
0.1% DMSO	1.00	1.00	1.00
2% Placebo Buffer	1.00	1.00	1.00
100 pg/mL IL-5	1.32	0.890	0.928
400 pg/mL IL-5	0.990	0.954	0.963
200 µg/mL Reslizumab	0.844	1.05	0.862
10 ng/mL IL-6	0.817	0.629	0.676
50 µM Omeprazole	103	21.4	N/A
20 µM Rifampin	N/A	N/A	16.3

Provided as fold-change
Source: CSR 10DMW042, page 18, Table 4; page 19, Table 5; page 20 Table 5

Conclusion:

- Compared with vehicle controls, reslizumab did not increase cytotoxicity to human hepatocytes.

- Whereas the positive controls caused anticipated and appropriate decreases or increases in CYP mRNA levels, treatment of cultured human hepatocytes with up to 400 pg/mL IL-5 or 200 µg/mL reslizumab caused little or no changes (≤20% decrease or less than 1.5-fold increase) in CYP1A2, CYP2B6, or CYP3A4 mRNA levels.

4.2 Appendix – Pharmacometrics Review

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Are the PK parameters reported in the label supported by the population PK analysis submitted by the sponsor?

Yes, the PK parameters reported in the label are supported by the population PK (popPK) analysis submitted by the sponsor.

The PK parameters for reslizumab stated in the label are supported by the popPK analysis submitted by the sponsor (Report CP-11-006) and reproduced by the reviewer (Table 1). The final dataset (ph123pk3) for population PK analysis contained a total of 10314 serum reslizumab concentration measurements from 804 subjects (130 healthy volunteers, 16 patients with nasal polyposis, and 658 asthmatic patients) from 8 studies (Studies 350, 290, 10, 3081, 3082, 1102, 1107 and 1942).

During analysis of the PK samples from Studies C38072/1102, C38072/1107, 3081, and 3082, quantifiable values above the LLOQ were detected in both a proportion (46.3%) of subjects receiving placebo as well as in a subset (n=139) of pre-first dose samples in reslizumab treatment group. Therefore, an operational limit of quantitation (OLOQ) was predefined to designate concentration values below the LLOQ for the PK data from these 4 studies. A value of 420 ng/mL was selected as a rational cutoff (ie, less than approximately 5% of mean peak concentration observed following administration of a 0.3-mg/kg dose). As such, 30 post-dose sample (from Studies C38072/1102, C38072/1107, 3081, and 3082) with a measurable reslizumab concentration below 420 ng/mL was flagged as BLQ. In addition, 113 samples from 13 patients were excluded because their pre-dose concentrations were ≥420 ng/mL. As a result, a separate dataset (ph123pk6) without setting OLOQ was generated and analyzed independently.

The final PK model for IV reslizumab was a 2-compartment model with zero-order input and first-order elimination. The popPK results showed that the estimates of PK parameters were similar (difference < 3%) between two datasets by independent analysis (Table 2).

Table 1 Reslizumab PK Parameter Estimates and Standard Error from final PopPK Model

Parameter	Typical Value[1]	Inter-individual Variability[2]
CL (clearance, ml/hr)	7.16 (0.0971)	33.3% (6.54)
V1 (central volume, L)	3.13 (0.0369)	26.0% (16.0)
Q (distributional clearance, mL/hr)	10 (0.754)	97.2% (13.2)
V2 (peripheral volume, L)	2.05 (0.0687)	54.8% (10.1)

[1] Estimate (SE) for typical subject weighting 73 kg.
[2] CV (SE%)
Source: Adapted from Report CP-11-006, Page 9

Table 2 Comparison of Reslizumab PK Parameter Estimates between Two Datasets

Parameter	ph123pk3	ph123pk6*
CL (clearance, ml/hr)	7.16	7.19
V1 (central volume, L)	3.13	3.20
Q (distributional clearance, mL/hr)	10	9.85
V2 (peripheral volume, L)	2.05	2.05

* Dataset without setting OLOQ criteria and including 13 more subjects not listed in ph123pk3
Source: Adapted from Report CP-11-006, Page 100, Table 26

1.1.2 What are the effects of intrinsic factors on the PK of Reslizumab?

Sex, age and race were not significant covariates for the reslizumab PK. As body weight increased, the systemic clearance also increased.

- Sex: Gender did not significantly influence reslizumab PK. The geometric mean of post-hoc CL of male is approximately 12% higher than that of females (Figure 1).

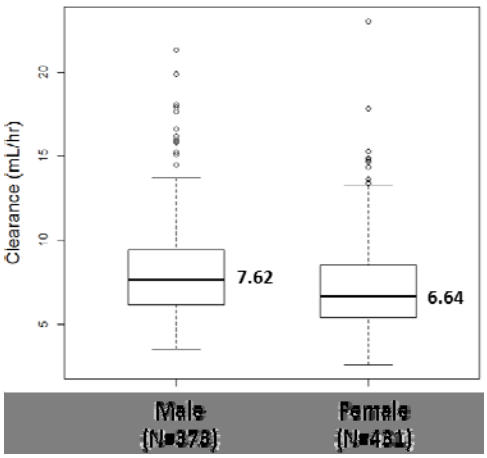

Figure 1 The effect of gender on reslizumab clearance. (Source: reviewer's analysis)

- Race: Race did not significantly influence reslizumab PK. The geometric mean of post-hoc CL of Blacks is approximately 22% higher than Whites; the CL of Asian is approximately 6% less than Whites (Figure 2).

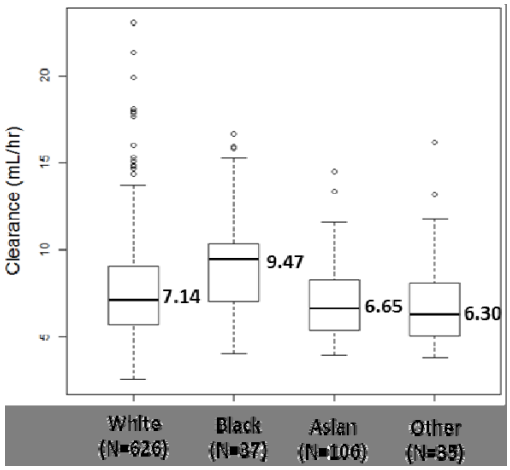

Figure 2 The effect of race on reslizumab clearance. Japanese population from Studies 1102 and 1107 was considered as Asian. (Source: reviewer's analysis)

- Age: There is no clear linear trend between CL and age (Figure 3A). The difference of geometric mean of CL values between adolescents and adults, elderly and adults was (b) (4)% and <3%, respectively (Figure 3B).

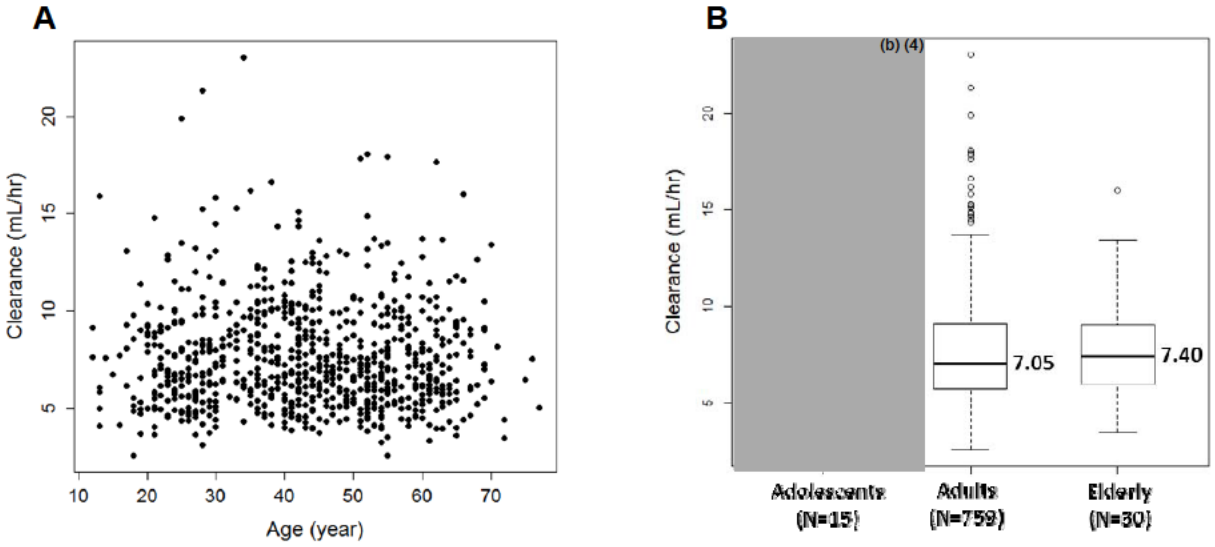

Figure 3 The effect of age on reslizumab clearance. (A) Scatter plot of age and CL (correlation coefficient = -0.03) and (B) box plot comparison of CL between adolescents (12 to less than 18 years), adults (18 to 65 years) and elderly (greater than 65 years). (Source: reviewer's analysis)

- Body weight: CL increased with body weight increase (Figure 4A). The power for body weight on CL is estimated to be 0.561 (SE=0.0457), whose introduction reduced objective function approximately 130. Due to the dose justification by body weight, the median value of model-predicted 3 mg/kg normalized $AUC_{ss\ (0\text{-}4wk)}$ was comparable between four body weight quartiles (Figure 5). The geometric mean of model-predicted 3 mg/kg normalized $AUC_{ss\ (0\text{-}4wk)}$ was 42% high in the fourth body weight quartile than the first quartile. V_1 (central volume of distribution) also increased with body weight increase (Figure 4B). The power for body weight on V_1 is estimated to be 0.606 (SE=0.0562), whose introduction also reduced objective function approximately 130.

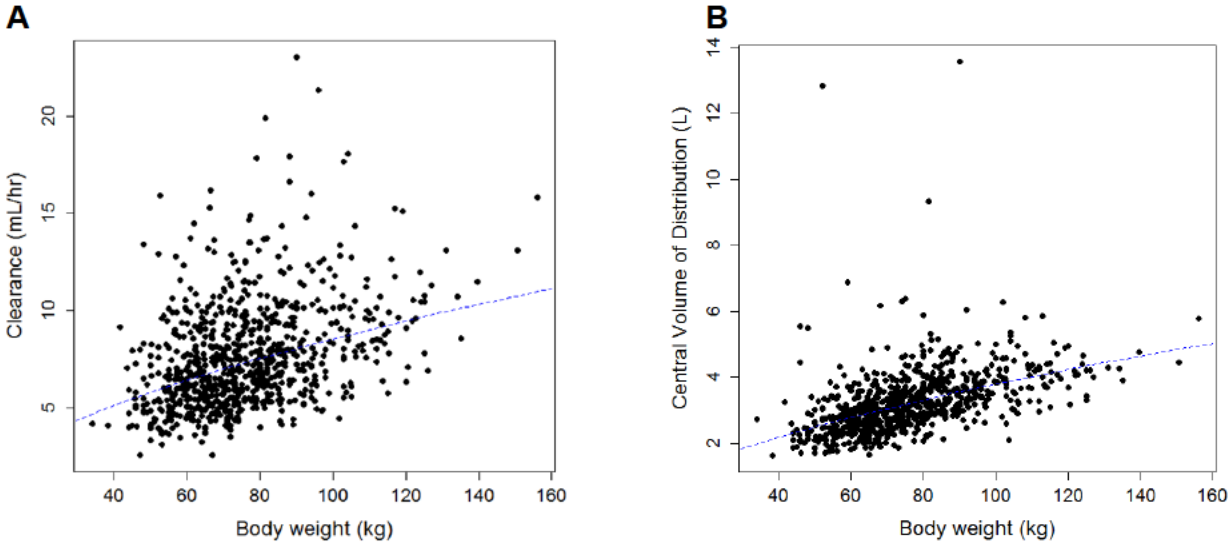

Figure 4 The effect of body weight on reslizumab CL (A) and V_1 (B). (Source: adapted from Report CP-11-006, page 149, Figure 19)

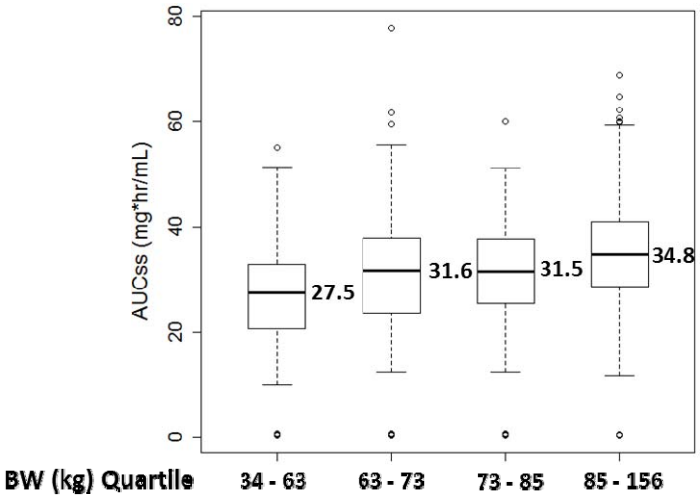

Figure 5 The effect of body weight on model-predicted 3 mg/kg normalized $AUC_{ss\ (0\text{-}4wk)}$. (Source: adapted from Report CP-11-006, page 153, Figure 22)

- Renal Impairment

No formal study was conducted to assess the effect of renal impairment on the reslizumab PK. To be noted, the creatinine clearance CRCL was calculated by using Cockcroft-Gault formula:
CRCL = [(140 − AGE) × WT] ÷ (72 × SCr)
Therefore, CRCL-CL relationship is confounded by body weight as shown in Figure 6.

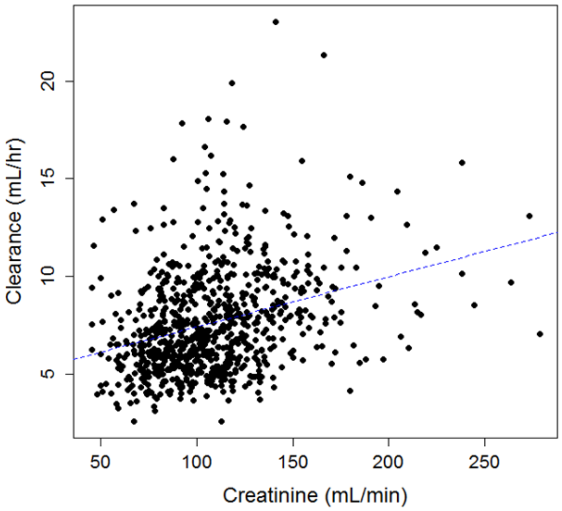

Figure 6 The effect of CRCL (calculated by Cockcroft-gault formula) on reslizumab CL (correlation coefficient = 0.31). (Source: Reviewer's analysis)

On the other hand, no clear trend was observed between reslizumab CL and the estimated glomerular filtration rate (eGFR). The eGFR was calculated by following formula, which is independent on the body weight:
$eGFR = 175 \times SerumCr^{-1.154} \times age^{-0.203} \times 1.212$ (if patients black) × 0.742 (if female)

The classification of renal function in this report was based on eGFR values as defined by FDA Guidance for Industry: Pharmacokinetics in Patients with impaired Renal Function. The geometric mean CL values were comparable between subjects with normal renal function and mild/moderate renal impairment (Figure 7, difference < 10%). There was only one subject (ID 70039 from Study 3081) with severe renal impairment.

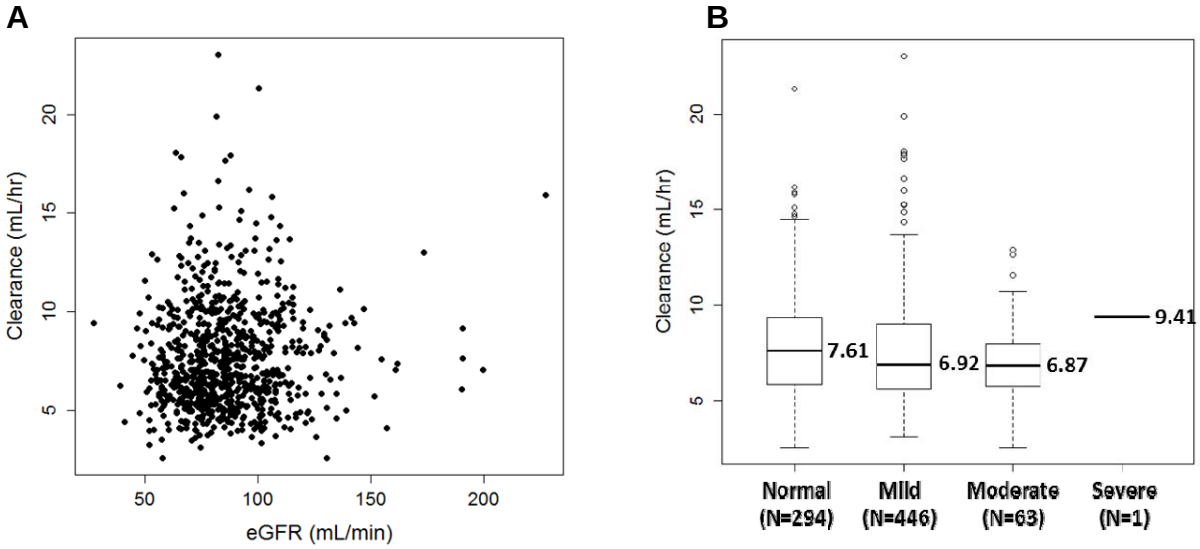

Figure 7 The effect of renal impairment on reslizumab CL. A, effect of eGFR on reslizumab CL (correlation coefficient = 0.06). B, box plot of reslizumab CL by renal function category [normal: EGFR ≥ 90 mL/min; mild impairment: 90 > EGFR ≥ 60 mL/min; moderate impairment: 60 > EGFR ≥ 30 mL/min; severe impairment: 30 > EGFR ≥ 15 mL/min] (Source: Reviewer's analysis)

- Hepatic Impairment

No formal study was conducted to assess the effect of hepatic impairment on the reslizumab PK. The classification of hepatic function in this report was based on NCI hepatic dysfunction grouping. There was no subject with severe hepatic impairment in this report. The geometric mean CL values were comparable between subjects with normal hepatic function and mild hepatic impairment (Figure 8, difference < 15%).

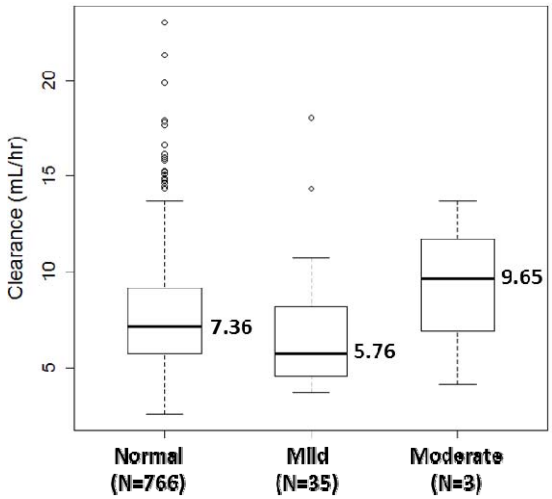

Figure 8 The effect of hepatic impairment on reslizumab CL (Source: Reviewer's analysis)

1.1.3 What are the effects of immunogenicity on the PK, efficacy, and safety of reslizumab?

There is no apparent impact of ADA on reslizumab PK, eosinophil response, and clinical efficacy in terms of FEV1 and CAE measurements.

- Effects on PK

A subject was classified as having a treatment-emergent ADA response if sample was tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample. The neutralizing antibody was not assessed in Phase 3 studies. The incidence of positive ADA response was approximately 6% (65/1071) in evaluated asthma patients from Phase 3 studies 3081, 3082, 3083 and 3084. Final dataset ph123pk3 included subjects from studies 1102, 1107, 3081, and 3082 that shared the same immunogenicity assay. Among them, 561 subjects had ADA results available and 41 were ADA-positive (7.3%). The geometric mean of reslizumab CL was comparable between ADA-positive and ADA negative subjects (Figure 9, difference < 10%).

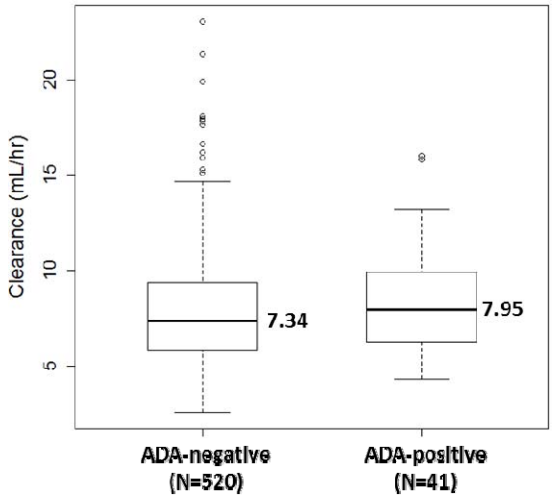

Figure 9 The effect of anti-reslizumab antibody on reslizumab CL (Source: Reviewer's analysis)

- Effects on PD

Blood eosinophil counts at each visit were compared between the ADA-negative and ADA-positive patients in studies 10, 3081, 3082, 3083, and 3084 utilizing the 3 mg/kg dose. The overall pattern of blood eosinophil suppression by reslizumab in treatment-emergent ADA-positive patients, as a group, was not different from ADA-negative patients.

- Effects on efficacy – clinical asthma exacerbation (CAE)

In studies 3082 and 3083, a total of 23 patients treated with 3 mg/kg reslizumab were ADA-positive (Table 3). Two of the ADA positive patients experienced at least 1 CAE (rate = 0.11) during the 52-week treatment period. Of 454patients who were ADA-negative, 149 had at least 1 CAE (rate = 0.95) during the 52-week treatment period. This data indicate no evidence of increase in CAEs due to the presence of ADA.

Table 3 CAE Rate Comparison by ADA Response from 3 mg/kg Reslizumab Treatment Group in Studies 3082 and 3083

	N of Patients	N of Patients with at least 1 CAE	Adjusted CAE Rate (95% CI)	CAE Rate Ratio (Positive/Negative)
ADA-Positive	23	2	0.11 (0.02, 0.53)	0.12 (0.03, 0.56)
ADA-Negative	454	149	0.95 (0.68, 1.31)	

Source: Adapted from integrated immunogenicity report, Page 42, Table 18

- Effects on efficacy – FEV1

In studies 3081, 3082 and 3083, FEV1 values over 16 week were available in 575 patients who received 3 mg/kg reslizumab treatment. Among them, 33 patients were ADA-positive (Table 4). Analysis showed there was no statistically significant difference in FEV1 between ADA positive and negative patients.

Table 4 FEV1 Change from Baseline Comparison over 16 Weeks by ADA Response from 3 mg/kg Reslizumab Treatment Group in Studies 3081, 3082 and 3083

	ADA-Positive Patients*	ADA-Negative Patients*	Treatment Difference (95% CI)
FEV1 Change (L) from Baseline over 16 Weeks	0.292 (33, 0.0815)	0.274 (542, 0.0546)	0.018 (-0.111, 0.147)
FEV1 Change (L) from Baseline at Week 16	0.254 (33, 0.0895)	0.280 (504, 0.0554)	-0.026 (-0.175, 0.123)

* Least square mean (N, SE)
Source: Adapted from integrated immunogenicity report, Page 43, Table 19

- Effects on safety

Overall, the adverse event profile in patients with positive ADA status during the treatment period was not meaningfully different from the ADA negative population.

Adverse events from studies 10, 3081, 3082, 3083, and 3084 were pooled to analyze the effect of ADA on safety. 7.2% (81/1131) patients were ADA-positive. The incidence of adverse events by system organ class was similar across ADA-positive (64% patients) and negative (66%) patients. The incidence of adverse events by most common adverse events (≥ 5%) was also similar across ADA-positive (64% patients) and negative (66%) patients.

1.1.4 What are the effects of co-medication on the PK of Reslizumab?

The popPK analysis evaluated the effects of two classes of common concomitant medications (systemic corticosteroid and leukotriene antagonist) on reslizumab PK. No significant effects were identified. The geometric mean of post-hoc CL of patients received systemic corticosteroid treatment is only 1.3% higher than those did not received treatment (Figure 10). The geometric mean of post-hoc CL of patients received leukotriene antagonist treatment is only 6.3% higher than those did not received treatment (Figure 10).

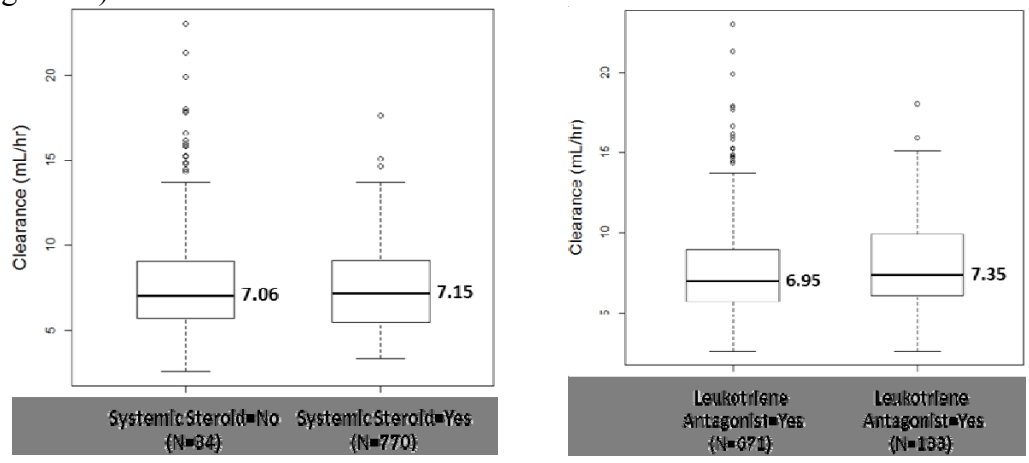

Figure 10 The effect of concomitant medications (Left: systemic corticosteroid; right: leukotriene antagonist) on reslizumab CL (Source: Reviewer's analysis)

1.1.5 What is the characteristic of exposure-response (E-R) relationship for efficacy? Does it support the proposed dose regimen?

The characteristic of E-R relationship of PD/efficacy is listed as following. It supports the proposed dose regimen.

- E-R relationship of PD (blood eosinophil count)

Yes, there is an E-R relationship for blood eosinophil count.

A total of 10063 blood eosinophil measurements from 958 patients (12 from Study 350; 75 from Study 290; 100 from Study 10; 304 from Study 3081; and 467 from Study 3082) were used for development of the population PK/PD model for blood eosinophil response (Figure 11).

The final PK/PD model was an indirect response model used to describe the relationship between reslizumab serum concentration and inhibition of peripheral blood eosinophil counts:

$$\frac{dR}{dt} = k_{in} \times \left(1 - \frac{I_{\max} \times C_{ij}}{IC_{50i} + C_{ij}}\right) - k_{out} \times R$$

Where:

R is blood eosinophil count;

k_{in} is the zero-order rate constant for production of blood eosinophil;

IC_{50i} is the concentration that produces 50% of maximal inhibition in the eosinophil production rate in the ith individual;

I_{max} is the maximal inhibitory capability of reslizumab (assumed maximal response is 1);

C_{ij} is the predicted reslizumab concentration in the ith individual at the jth time;

k_{out} is the first-order rate constant describing the rate of loss of blood eosinophil;

$k_{in} = k_{out} \times EOS_{baseline}$

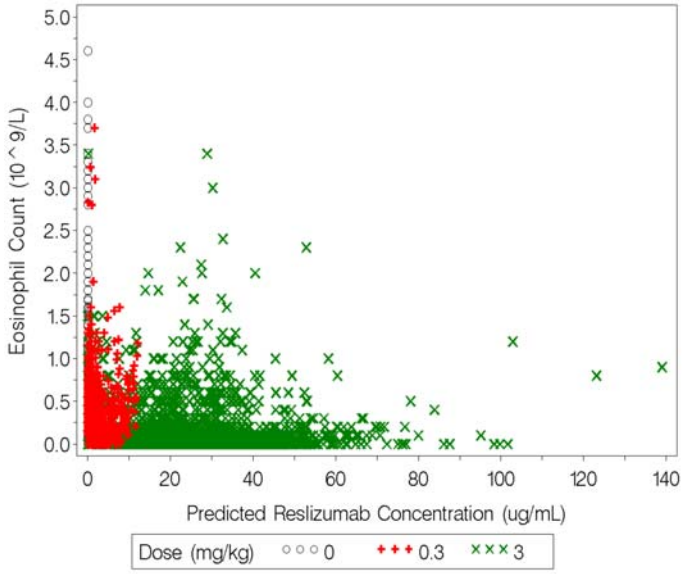

Figure 11 Scatterplot of blood eosinophil counts versus predicted reslizumab concentration, by dose. (Source: Report body CP-15-001, page 220, Figure 9)

The typical value for maximal inhibitory effect (I_{max}) of 0.949 indicates almost complete inhibition of the production of the blood eosinophil counts (Figure 12). In addition, the final estimate for IC_{50} of 0.773 µg/mL indicates that 50% maximal inhibition is achieved at a low concentration. Based on the IC_{50} value, the estimated IC_{90} concentration is 6.96 µg/mL. To put this IC_{50} estimate in perspective,

the PK model-predicted median $C_{av,ss}$ (µg/mL) values for reslizumab doses of 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, and 3 mg/kg were 0.7, 1.9, 4.8, 18.1, and 44.2 µg/mL, respectively.

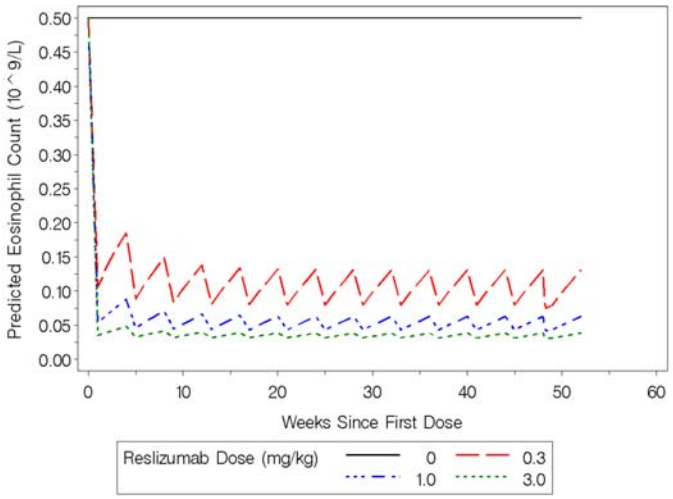

Figure 12 Model-predicted blood eosinophil counts from the final indirect response model (Source: Report body CP-15-001, page 36)

- E-R relationship of FEV1

Yes, there is an E-R relationship for FEV1.

A total of 27431 observations from 955 patients from Studies 290, 10, 3081, and 3082 were used for development of the population PK/PD model for FEV1 response. The final PK/PD model was comprised of a sigmoid maximum pharmacologic effect (E_{max}) time-course model including parameters estimating the baseline FEV1, maximum response in FEV1 (E_{max}), time to 50% of the maximum effect, and the sigmoidicity factor as shown in the 3 equations below:

$$FEV_{1ij} = BL_i + \frac{\left(E\max_i \times Week_{ij}^{0.275}\right)}{\left(13.3^{0.275} + Week_{ij}^{0.275}\right)}$$

$$BL_i = 2.48 - 0.0237 \times \left(Age_i - 47\right) - 0.597 \times SEXF_i - 0.387 \times RACB_i - 0.527 \times RACA_i - 0.340 \times RACO_i$$

$$E\max_i = 0.171 \times \left(\frac{BMI_i}{27}\right)^{-2.22} + 0.003379 \times C_{av,ss_i}$$

Where:

BL is the estimated baseline FEV1;
SEXF is an indicator variable for sex where 1=female and 0=male;
$C_{av,ss}$ is the estimated average reslizumab concentration at steady state;
RACB is for Black;
RACA is for Asian;
RACO is for non-White, non-Black, and non-Asian

Assuming the median reslizumab $C_{av,ss}$ of 0, 4.8 µg/mL and 44.2 µg/mL for placebo, 0.3 and 3 mg/kg, the model-predicted increases in FEV1 from baseline are 0.088, 0.096 and 0.164 L at Week 16, respectively (Figure 13). The observed FEV1 change from baseline was 0.052, 0.188, and 0.243 at Week 16 following placebo, 0.3 mg/kg and 3 mg/kg treatment, respectively (CSR 3081, page 112,

Table 22). The LS mean of FEV1 change from baseline was 0.138, 0.262, and 0.302 at Week 16 following placebo, 0.3 mg/kg and 3 mg/kg treatment, respectively (Study 3081).

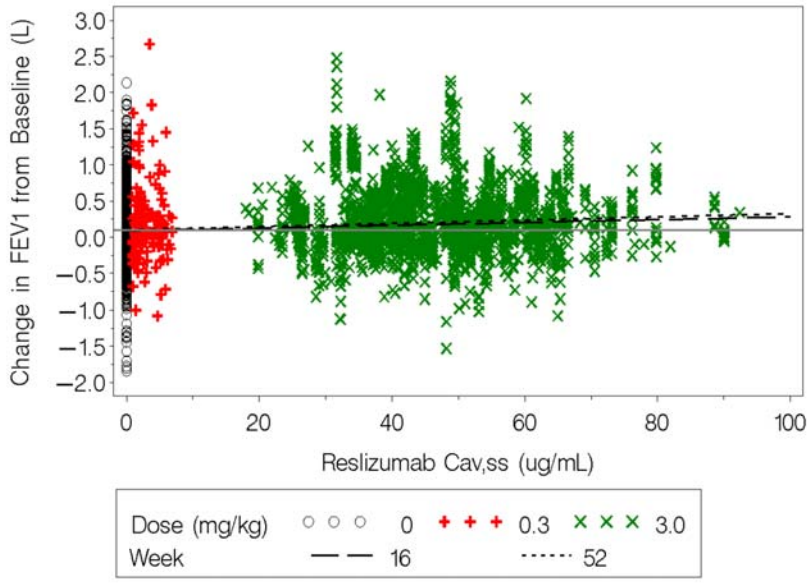

Figure 13 Scatterplot of FEV1 change from baseline versus predicted reslizumab concentration $C_{av,ss}$, by dose. The dashed line represent the model-predicted FEV1 for Weeks 16 and 52 assuming the median $C_{av,ss}$ for a Q4W dosing regimen for a White, female patient with median age (47 years) and BWI=27 kg/m^2. (Source: Summary-Clin-Pharm.pdf, page 58, Figure 22)

- E-R relationship of clinical asthma exacerbation (CAE)

No, there is no apparent trend for change in the rate of CAEs with increasing reslizumab exposure.

Exploratory data analysis for CAEs was performed using data from Study 3082 patients who received reslizumab and were included in the population PK analysis and placebo patients in the full analysis dataset. A total of 479 observations (236 on reslizumab and 243 on placebo) were included in the PK/PD dataset for CAE analysis. The rates of CAEs per year were higher in placebo group [1.4 (SD=1.8)] compared to 3 mg/kg treatment group patients [0.8 (SD=1.3)]. However, the number of patients at each level of CAEs per year is similar for the lowest exposure quartile (from 18.3 to 37.2 µg/mL) and the highest exposure quartile (54.1 to 92.4 µg/mL) (Table 5).

Table 5 Observed Frequency Distributions of CAE Rate, by Reslizumab Exposure Quartile for 3 mg/kg Treatment arm

Clinical asthma exacerbations per year	First $C_{av,ss}$ quartile [18.3, 37.2] (µg/mL)	Second $C_{av,ss}$ quartile (37.2, 44.4] (µg/mL)	Third $C_{av,ss}$ quartile (44.4, 54.1] (µg/mL)	Fourth $C_{av,ss}$ quartile (54.1, 92.4] (µg/mL)
[0, 0.5]	33	40	40	33
(0.5, 1.5]	12	11	9	11
(1.5, 2.5]	8	5	4	8
(2.5, 3.5]	2	3	3	2
(3.5, 4.5]	3	0	1	1
(4.5, 5.5]	0	0	1	2
(5.5, 6.5]	1	0	0	1
(6.5, 7.5]	0	0	1	0
(7.5, 9.36]	0	0	0	1

Source: Report CP-15-001, Page 13

- E-R relationship of asthma control questionnaire (ACQ) scores

Yes, there is an E-R relationship for ACQ7.

A total of 8016 observations from 875 patients from Studies 10, 3081, and 3082 were used for development of the population PK/PD model for ACQ score response. The final population PK/PD model for ACQ scores was an inhibitory sigmoid E_{max} time-course model including parameters estimating the baseline ACQ score, maximum reduction in ACQ score (E_{max}), time to 50% of the maximum effect, and the sigmoidicity factor as shown in the 2 equations below:

$$ACQ\ \ Score_{ij} = 2.61 + \frac{\left(E\max_i \times Week_{ij}^{1.35}\right)}{\left(2.9^{1.35} + Week_{ij}^{1.35}\right)}$$

$$E\max_i = -0.869 - 0.00517 \times C_{av,ss_i}$$

Where:

$C_{av,ss}$ is the estimated average reslizumab concentration at steady state;

Assuming the median reslizumab $C_{av,ss}$ of 0, 4.8 µg/mL and 44.2 µg/mL for placebo, 0.3 and 3 mg/kg, the model-predicted change of ACQ score from baseline are -0.790, -0.812, and -0.998 at Week 16, respectively (Figure 14). The LS mean of ACQ score change from baseline was -0.584, -0.795, and -0.935 at Week 16 following placebo, 0.3 mg/kg and 3 mg/kg treatment, respectively (CSR 3081, page 131, Table 32).

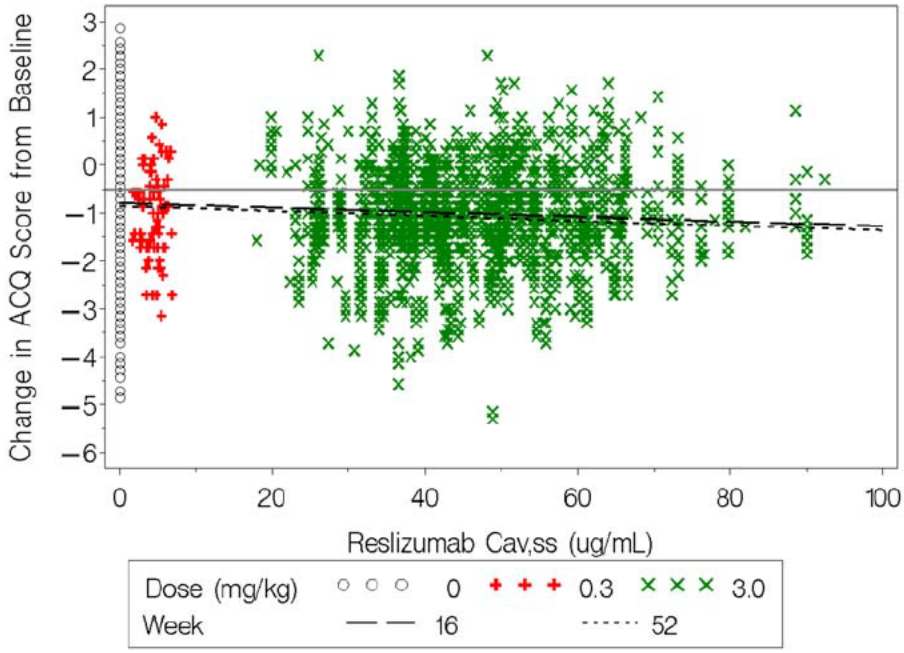

Figure 14 Scatterplot of Asthma Control Questionnaire change from baseline versus predicted reslizumab concentration $C_{av,ss}$ with final PK/PD model-predicted lines overlaid for Week 16 (dashed line) and 52 (dotted line). (Source: Report CP-15-001, Page 270, Figure 41)

1.1.6 What is the characteristic of exposure-response (E-R) relationship for safety? Does it support the proposed dose regimen?

The characteristic of E-R relationship of muscle disorder adverse events is listed as following. It supports the proposed dose regimen.

- E-R relationship of muscle disorder adverse events

There is no significant E-R relationship between $C_{av,ss}$ and muscle disorder AE.

Myalgia was considered as an adverse drug reaction for the Phase 3 clinical program, occurring in 0.55% (4/730) of placebo-treated patients and 0.97% (10/1028) of reslizumab 3 mg/kg-treated patients for Cohort 3 (Studies 10, 3081, 3082,3083 and 3084) (Summary of clinical safety.pdf, Page 65, Table 19). CPK elevations beyond the designated potentially clinically significant threshold for the ISS/SCS (CTCAE°grade 3: >5 × ULN) were observed more frequently during reslizumab 3.0 mg/kg treatment compared with placebo (2% and 1%, respectively). These values were generally transient and asymptomatic; there is no evidence of treatment-related myopathy, rhabdomyolysis, or myositis.

Because the myalgia incidence was less than 1% and PK information was unavailable from Studies 3083 and 3084, the E-R analysis was conducted in a separate pooled PK/PD data set. A total of 1100 patients with 59 muscle disorder AE records from Studies 10, 290, 3081, and 3082 were used for development of the population PK/PD model for muscle disorder AE. The occurrence of muscle disorder adverse events used in this analysis was defined by a broadly ranging muscle disorder category based on the standardized Medical Dictionary for Regulatory Activities queries. For clinical meaning of this muscle disorder classification, refer to primary review by medical reviewer Dr. Donohue.

Reviewer's comment:
The usage of (b) (4) *as reslizumab exposure-response analysis is not appropriate.* (b) (4)

Canonically, using observed C_{min} values would be more appropriate for this exposure-response analysis. Due to the 12-weekly dosing regimen in study 290 which had the highest incidence of muscle disorder AE, the C_{min} values were expected to be low from this study. Conceivably, the conclusion could be reversed based on C_{min} analysis. Indeed, the Sponsor did claim that "The median exposure measures for the patients who experienced muscle disorders were generally slightly higher as compared to the median for those patients who did not experience muscle disorders with the exception of C_{min} and steady-state C_{av}." (Source: Report CP-15-001, Page 13)

Reviewer conducted an independent exposure-response analysis based on the $C_{av,ss}$ and C_{min} values. No significant relationship was observed (Table 17 and 18). This confirmed the Sponsor's above claim.

In addition, there is no clear trend observed for dose-response relationship of muscle disorder adverse events (Table 7). The muscle disorder AE incidence was comparable between placebo and reslizumab 3mg/kg treatment (~ 5%). The incidence was lower (~ 3%) in 0.3 mg/kg treatment group and higher in (~ 10%) 1 mg/kg group. The majority of the muscle disorder AEs (approximately 70%) occurred during the first 90 days of treatment.

Table 7 Incidence of Muscle Disorder Adverse Events and Median Age by Reslizumab Dose

	Placebo	Reslizumab		
		0.3 mg/kg	1 mg/kg	3 mg/kg
Muscle Disorder AE*	26/466 (5.6%)	6/174 (3.4%)	7/73 (9.6%)	20/387 (5.2%)
Age (years)#	47 (12-75)	45.5 (13-72)	50 (19-77)	46 (12-76)

* Incidence
# Median (range)
Source: Reviewer's summary from aefirst.xpt

- E-R relationship of serum creatine phosphokinase

There is no significant E-R relationship for serum creatine phosphokinase.

The PK/PD safety analysis of CPK included a total of 3889 observations from 879 patients from Studies Res-5-0010, 3081, and 3082. The median baseline creatine phosphokinase, as well as on-treatment median creatine phosphokinase, was higher in the reslizumab-treated groups compared to placebo (Table 8). The change in CPK from baseline was -3.9, 10.4, and 11.1 U/L following placebo, 0.3 mg/kg and 3 mg/kg reslizumab treatment, respectively. No PK/PD modeling was performed for the safety lab CPK since no exposure-response relationship was apparent.

Table 8 Mean (SD) Serum Creatine Phosphokinase Means by Reslizumab Dose

	Placebo	Reslizumab	
		0.3 mg/kg	3 mg/kg
Patient Number	393	101	385
Baseline (U/L)	130.092 (128.239)	141.901 (110.849)	142.470 (124.063)
On Treatment (U/L)	123.895 (97.380)	148.984 (190.605)	149.542 (175.819)
Change from Baseline (U/L)	-3.906 (128.036)	10.419 (186.269)	11.055 (158.596)

Source: Adapted from Report CP-15-001, Page 187, Table 50 and Page 190, Table 53

1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in BLA 761033. This BLA is considered acceptable from a pharmacometrics perspective.

1.3 Label Statements

Please refer to Section 3 - Detailed Labeling Recommendations in clinical pharmacology review.

2. RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK analysis

The PK of reslizumab in healthy subjects and patients with asthma or nasal polyposis ranging in age from 12 to 77 years was well characterized by a 2-compartment model with zero-order input and first-order elimination. The key findings from sponsor's population PK analysis (Report CP-11-006) are summarized below:

- Disease status is unlikely to influence reslizumab PK, as the PK parameter estimates and predicted exposures were similar in healthy subjects and patients.
- The model-estimated typical values of CL and Vc for a 73-kg subject (representing the median body weight of the patient population in this analysis) were 7.16 mL/h and 3130 mL, respectively, resulting in a population mean terminal elimination half-life of approximately 568 hours or 23.7 days.
- Body weight was identified as a statistically significant predictor of CL and Vc, with both PK parameters increasing in a less than proportional manner with increasing body weight, such that the typical CL and Vc are predicted to increase by approximately 57% (from 5.92 to 9.01 mL/h) and 52% (from 2548 to 4013 mL), respectively, as subject weights range from the 5th percentile (52 kg) to 95th percentile (110 kg) of body weight observed in the PK analysis population.
- Age, sex, race (white, black or African-American, Asian, and other), baseline renal function (normal to moderately decreased), baseline liver function tests (normal and Grade 1/2 elevation), and concomitant use of either leukotriene antagonists or corticosteroids were all not found to be significant sources of IIV in reslizumab PK. The lack of a sufficient number of subjects in the analysis dataset with very poor renal function or high grades (3-4) of elevated liver function tests prevented an assessment of the impact of more severe renal or hepatic impairment on reslizumab PK.
- The covariate analysis showed that the presence of circulating anti-drug antibodies did not significantly alter the disposition of reslizumab.

- Overall, these findings suggest that weight-based dosing is appropriate for IV reslizumab administration to ensure consistent reslizumab exposures across the heterogeneous target patient population.

The PK parameter estimates from the Sponsor's final population PK model are listed in Table 9.

Table 9 Parameter Estimates from the Reslizumab Final Population Pharmacokinetic Model

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
CL: clearance (mL/h)	7.16	1.36	33.3 %CV	6.54
Power for weight on CL	0.561	8.15		
V_c: central volume of distribution (mL)	3130	1.18	26.0 %CV	16.0
Power for weight on V_c	0.606	9.28		
Q: distributional clearance (mL/h)	10.0	7.51	97.2 %CV	13.2
V_p: peripheral volume of distribution (mL)	2050	3.35	54.8 %CV	10.1
cov(IIV in CL, IIV in V_c)	0.0410	14.8	NA	NA
cov(IIV in V_p, IIV in V_c)	0.0332	22.4		
cov(IIV in V_p, IIV in CL)	0.129	8.83		
cov(IIV in Q, IIV in CL)	0.138	16.9		
cov(IIV in Q, IIV in V_p)	0.382	14.6		
RV (log scale, full-profile)	0.0398	5.70	0.199 SD	NA
RV (log scale, Phase 2 sparse)	0.337	39.6	0.581 SD	
RV (log scale, Phase 3)	0.107	9.15	0.327 SD	
Minimum value of the objective function=-14614.946				

Source: Report CP-11-006, Page 9

The standard goodness-of-fit plots for the final model run369 is shown in the Figure 15

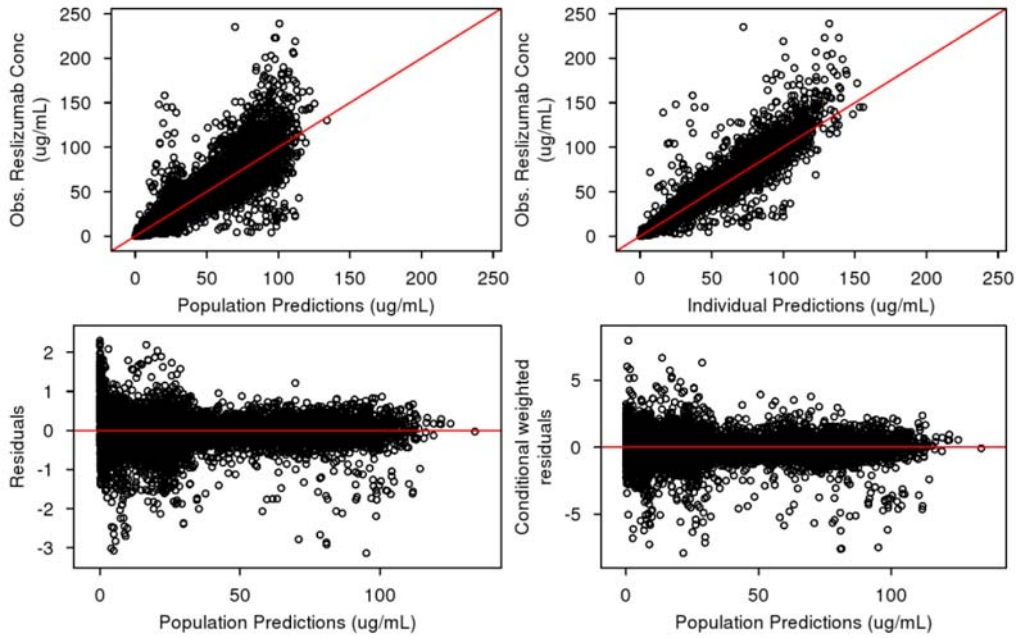

Figure 15 Goodness-of-fit plots for Reslizumab final population PK model. (Source: Report CP-11-006, Page 123, Figure 10)

Plots of model-predicted reslizumab concentration-time profiles for typical subjects with body weights representative of the 5th percentile (52 kg), median (73 kg), and 95th percentile (110 kg) of the weight

distribution in the PK analysis population are provided in Figure 16, overlaid on observed concentration data collected following multiple dosing (q4w) of 0.3, 1, 2, and 3 mg/kg IV reslizumab.

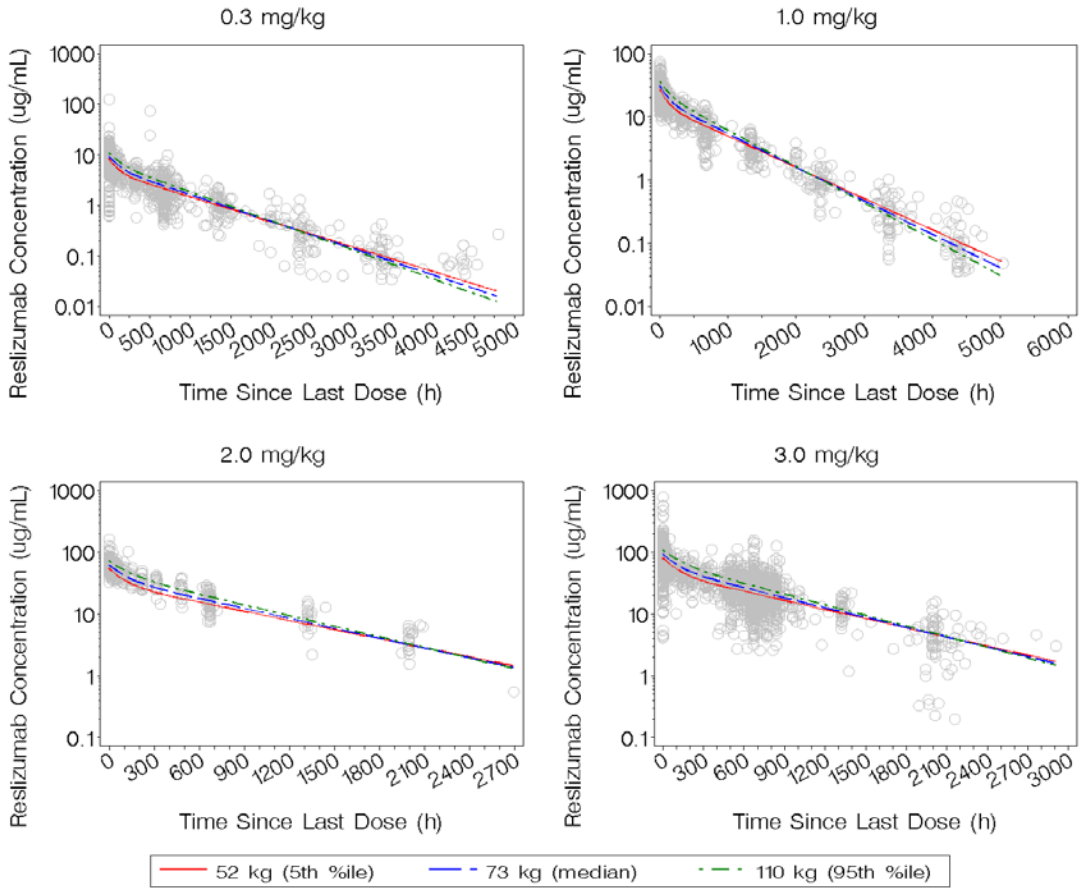

Figure 16 Model-predicted typical value PK profiles by body weight overlaid on observed reslizumab concentrations versus time since last dose following multiple dosing (q4w) of IV administration (Source: Report CP-11-006, Page 10)

Subsequent to final PK model development, the OLOQ criteria for exclusion of data (cutoff of 420 ng/mL) were evaluated based on FDA feedback from pre-BLA meeting. The original LLOQ of 20 ng/mL was reinstated and all samples previously excluded due to the OLOQ criteria (a total of 30 post-dose samples from 23 subjects included in the original model development dataset), as well as 113 samples from 13 subjects not included in the original model development dataset, were reincorporated into the analysis dataset. Pertinent PK models in the critical model development path (including base model, key covariate models, and final model) were re-estimated using the updated dataset and compared against the original modeling results. There were no differences in the covariates identified as significant predictors of PK and, in all models tested, only minor changes were observed in parameter estimates compared to the original models (Table 10). The strong concordance in model estimates provides supporting evidence that proactive utilization of the OLOQ criteria during model development did not contribute to any clinically meaningful differences in model results. As such, in accordance with the strategy agreed upon with the FDA, the dataset implementing the OLOQ was used as the final model analysis dataset and the individual estimates of exposure derived from the final model estimation (with the OLOQ cutoff implemented) were used for subsequent PK/PD and exposure-response evaluations.

Table 10 Comparison of Parameter Estimates from the Base and Final popPK Models with and without OLOQ Criteria Applied

Parameter	Base pharmacokinetic model		Final pharmacokinetic model	
	OLOQ criteria		OLOQ criteria	
	Applied	Not applied	Applied	Not applied
CL: clearance (mL/h)	7.26	7.28	7.16	7.186
Power for weight on CL	NE	NE	0.561	0.5837
V_c: central volume of distribution (mL)	3110	3190	3130	3203
Power for weight on V_c	NE	NE	0.606	0.6459
Q: distributional clearance (mL/h)	15.3	15.1	10.0	9.854
V_p: peripheral volume of distribution (mL)	2150	2120	2050	2045
IIV in CL	33.2 %CV	33.5 %CV	33.3 %CV	33.94 %CV
IIV in V_c	30.2 %CV	37.4 %CV	26.0 %CV	33.54 %CV
IIV in Q	NE	NE	97.2 %CV	97.71 %CV
IIV in V_p	45.0 %CV	41.5 %CV	54.8 %CV	55.71 %CV
cov(IIV in CL, IIV in V_c)	NE	NE	0.0410	0.05303
cov(IIV in V_p, IIV in V_c)			0.0332	0.04018
cov(IIV in V_p, IIV in CL)			0.129	0.1378
cov(IIV in Q, IIV in CL)			0.138	0.1440
cov(IIV in Q, IIV in V_p)			0.382	0.3971
RV (log scale, full-profile)	0.211 SD	0.211 SD	0.199 SD	0.2000 SD
RV (log scale, Phase 2 sparse)	0.566 SD	0.568 SD	0.581 SD	0.5839 SD
RV (log scale, Phase 3)	0.326 SD	0.405 SD	0.327 SD	0.4062 SD

Source: Report CP-11-006, Page 100, Table 26

2.2 E-R analysis

2.2.1 E-R analysis for blood eosinophil

The relationship between reslizumab concentration and inhibition of the blood eosinophil response was described by an indirect response PK/PD model including parameters for the zero-order rate constant for inhibition of EOS response, maximum inhibition of EOS response (I_{max}), reslizumab concentration associated with 50% maximal inhibition, and first-order rate constant for dissipation of inhibition of EOS response. The key findings from sponsor's PK/PD analysis for blood eosinophil count (Report CP-15-001) are summarized below:

- Lowering of EOS was predicted to be reslizumab exposure-dependent, with increasing magnitude of EOS lowering and duration of response with increasing dose, as well as decreased fluctuation at higher doses.
- Given the high estimated maximal inhibition of 0.949, the low estimated IC_{50} of 0.773 μg/mL relative to the steady-state average serum concentration for reslizumab 3 mg/kg, and long reslizumab elimination half-life, a dosage regimen of 3 mg/kg every 4 weeks would be anticipated to typically produce near maximal inhibition of the eosinophil response.

- Sensitivity to reslizumab inhibition of the blood eosinophil response (IC50) was not influenced in a statistically significant manner by age, body weight, sex, race (white, black or African-American, Asian, or other), concomitant leukotriene antagonists, anticholinergics, or theophylline.

The parameter estimates from the Sponsor's final PK/PD model are listed in Table 11.

Table 11 Parameter Estimates from the Final PK/PD Model for Blood Eosinophil Counts

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
k_{out}, 1/h	0.0388	8.64	NE	NA
I_{max}	0.949	0.600	NE	NA
IC_{50}, µg/mL	0.773	11.9	90.1 %CV	23.0
RV (Phase 1/2, full-profile EOS)	0.0685	21.3	0.262 SD	NA
RV (Phase 2, sparse EOS)	0.0334	20.3	0.183 SD	
RV (Phase 3, sparse EOS)	0.0773	11.4	0.278 SD	
Minimum value of the objective function=-16399.693				

Source: Report CP-15-001, Page 9

The visual predictive check for the final PK/PD model for blood eosinophil counts is shown in Figure 17.

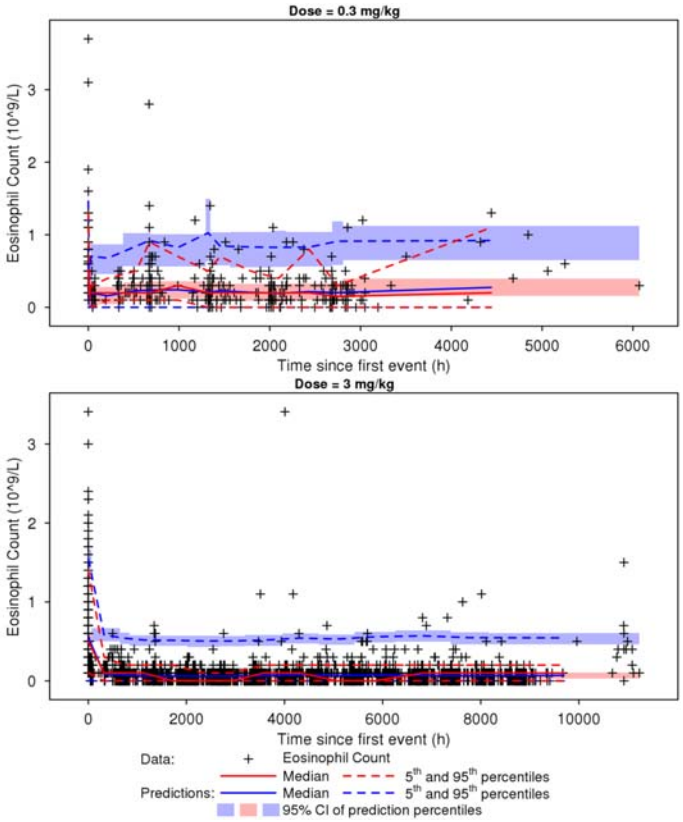

Figure 17 Visual predictive checks for the final PK/PD model for blood eosinophil counts overlaid on the observed data, sparse-profile data for doses of 0.3 mg/kg (upper panel) and 3 mg/kg (lower panel) (Source: Report CP-15-001, Page 219, Figure 8)

2.2.2 E-R analysis for FEV1

The final PK/PD model for FEV1 was a sigmoid E_{max} time-course model including parameters for the baseline FEV1, maximum response in FEV1 (E_{max}), time to 50% of the maximum effect, and a

sigmoidicity factor. The key findings from sponsor's PK/PD analysis for FEV1 (Report CP-15-001) are summarized below:

- A linear relationship best described the exposure-response relationship between E_{max} and reslizumab $C_{av,ss}$. As reslizumab $C_{av,ss}$ increases, the model-predicted FEV1 increases.

- Sex, race, and age were statistically related to baseline FEV1 whereby male sex, white race, and younger age were associated with higher baseline FEV1. Baseline BMI was statistically related to E_{max} whereby patients with lower BMI have higher predicted maximum FEV1 response.

- The FEV1 response to reslizumab was not influenced in a statistically significant manner by body weight, concomitant leukotriene antagonists, anticholinergics, or theophylline.

The parameter estimates from the Sponsor's final PK/PD model are listed in Table 12.

Table 12 Parameter Estimates from the Final PK/PD Model for FEV1

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
BL: baseline FEV_1 (L)	2.48	1.47	0.550 SD	5.19
BL: slope for age on baseline FEV_1 (L/y)	-0.0237	5.99		
BL: additive shift for sex on baseline FEV_1 (L)	-0.597	6.79		
BL: additive shift for black race on baseline FEV_1 (L)	-0.387	22.9		
BL: additive shift for Asian race on baseline FEV_1 (L)	-0.527	10.7		
BL: additive shift for other race on baseline FEV_1 (L)	-0.340	19.1		
EMAX: maximum FEV_1 response (L)	0.171	16.3	0.532 SD	12.7
EMAX: slope for $C_{av,ss}$ on E_{max} (L/µg/mL)	0.00379	24.2		
EMAX: power for BMI on E_{max} (L/kg/m^2)	-2.22	20.8		
T50: time to half maximal response (weeks)	13.3	9.21	NE	NA
S: Hill coefficient	0.275	8.49	172 %CV	10.2
Additive residual error	0.0558	4.92	0.236 SD	NA
Minimum value of the objective function=-12485.357				

Source: Report CP-15-001, Page 11

The visual predictive check for the final PK/PD model for blood eosinophil counts is shown in Figure 18.

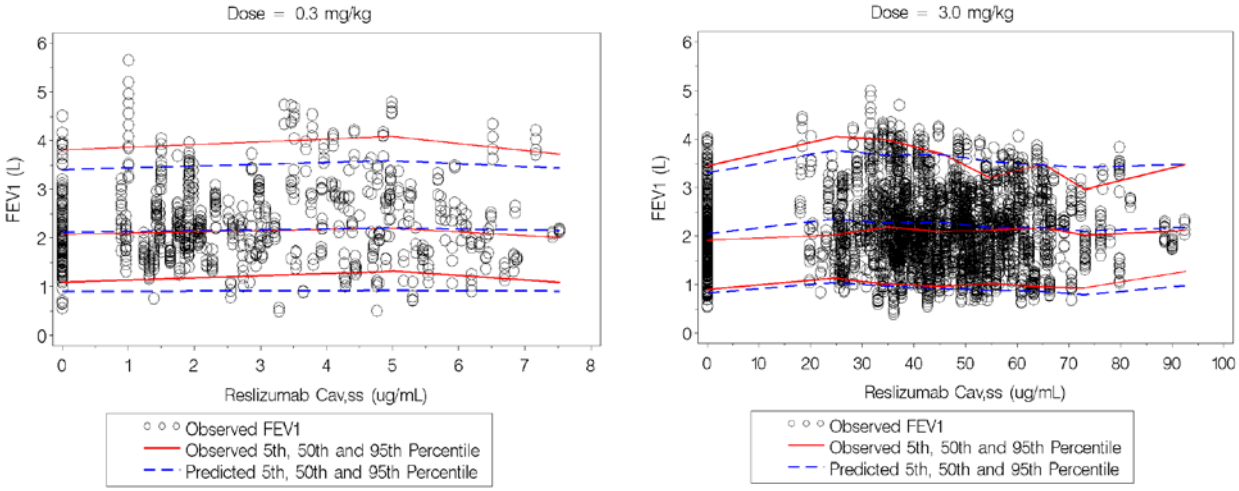

Figure 18 Visual predictive checks for the final PK/PD model for FEV1 overlaid on the observed data, doses of 0.3 mg/kg (left panel) and 3 mg/kg (right panel) (Source: Report CP-15-001, Page 243-4, Figure 24)

2.2.3 E-R analysis for ACQ7

The final PK/PD model for ACQ scores was a sigmoid E_{max} time-course model including parameters for the baseline ACQ7 score, maximum reduction in ACQ7 score (E_{max}), time to 50% of the maximum effect, and a sigmoidicity factor. The key findings from sponsor's PK/PD analysis for ACQ7 (Report CP-15-001) are summarized below:

- A linear relationship best described the exposure-response relationship between E_{max} and reslizumab $C_{av,ss}$. As reslizumab $C_{av,ss}$ increases, the ACQ7 score is predicted to decrease.

- ACQ7 scores were not influenced in a statistically significant manner by age, body weight, sex, race (white, black or African-American, Asian, or other), concomitant leukotriene antagonists, anticholinergics, or theophylline.

The parameter estimates from the Sponsor's final PK/PD model are listed in Table 13.

Table 13 Parameter Estimates from the Final PK/PD Model for FEV1

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
BL: baseline FEV_1 (L)	2.48	1.47	0.550 SD	5.19
BL: slope for age on baseline FEV_1 (L/y)	-0.0237	5.99		
BL: additive shift for sex on baseline FEV_1 (L)	-0.597	6.79		
BL: additive shift for black race on baseline FEV_1 (L)	-0.387	22.9		
BL: additive shift for Asian race on baseline FEV_1 (L)	-0.527	10.7		
BL: additive shift for other race on baseline FEV_1 (L)	-0.340	19.1		
EMAX: maximum FEV_1 response (L)	0.171	16.3	0.532 SD	12.7
EMAX: slope for $C_{av,ss}$ on E_{max} (L/µg/mL)	0.00379	24.2		
EMAX: power for BMI on E_{max} (L/kg/m^2)	-2.22	20.8		
T50: time to half maximal response (weeks)	13.3	9.21	NE	NA
S: Hill coefficient	0.275	8.49	172 %CV	10.2
Additive residual error	0.0558	4.92	0.236 SD	NA
Minimum value of the objective function=-12485.357				

Source: Report CP-15-001, Page 11

The visual predictive check for the final PK/PD model for blood eosinophil counts is shown in Figure 19.

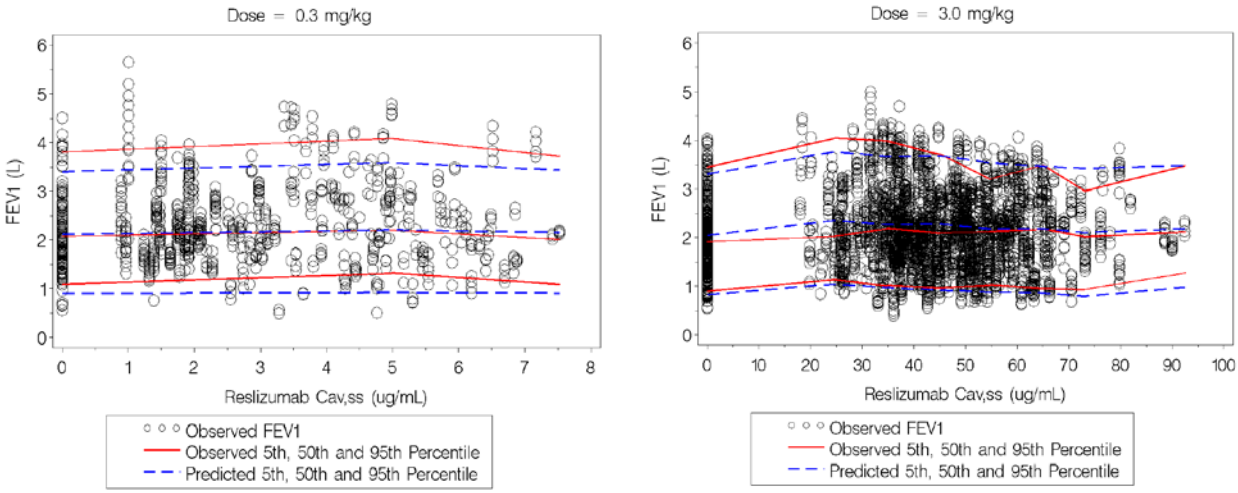

Figure 19 Visual predictive checks for the final PK/PD model for FEV1 overlaid on the observed data, doses of 0.3 mg/kg (left panel) and 3 mg/kg (right panel) (Source: Report CP-15-001, Page 243-4, Figure)

2.2.4 E-R analysis for muscle disorder AE

(b) (4)

The key findings from sponsor's PK/PD analysis for muscle disorder AE (Report CP-15-001) are summarized below:

- For a 47-year-old patient (median age), the predicted probability of muscle disorders is 0.04, 0.04, 0.04, and 0.07 at the median-predicted reslizumab concentration (0, 1.38, 1.44, and 24.81 µg/mL) associated with reslizumab doses of 0, 0.3, 1, and 3 mg/kg, respectively.

- No statistically significant influence of baseline weight, baseline BMI, sex, or race (white, black or African-American, Asian, or other) on the probability of muscle disorder AEs was found.

The estimates of maximum likelihood of effect of reslizumab concentration and age on muscle disorder incidence from the Sponsor's final PK/PD model are listed in Table 14.

Table 14 Summary of Effects of Reslizumab Exposure (C_{pred}) and Age on Occurrence of Muscle Disorder Adverse Events

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-4.2349	0.5375	62.0753	<.0001
(b) (4)					
AGE	1	0.0219	0.0103	4.4995	0.0339

Source: Report CP-15-001, Page 1357

3. RESULTS OF REVIEWER'S ANALYSIS

3.1 Introduction

Reviewer repeated and confirmed Sponsor's popPK and E-R analysis. Reviewer agreed with all the major conclusions drawn by the Sponsor. The discussions and comments were reflected in the Pharmacometrics Key Review Questions.

3.2 Objectives

The reviewer's analysis objectives are:

- To assess the effect of introduction of OLOQ (420 ng/mL) in the final data set (ph123pk3). The assessment will be based on the comparability of the PK parameter estimates between two datasets (ph123pk3 and ph123pk6).

- To confirm the E-R response for FEV1.

- To assess the validity of E-R response for muscle disorder AE.

- To generate figures and tables for the review convenience.

3.3 Methods

3.3.1 Software

Software: SAS9.3, R3.1.1, and NONMEM 7.3 were used for the reviewer's analysis.

3.3.2 Data Sets and Control stream

Review folder and Data set are summarized in Table 15

Table 15 Summary of Reslizumab Pharmacometrics Reviewer Folder and Data Set

Analysis Objective	Folder Location	Sponsor's Data Set	Adapted Data Set*	Sponsor's Control Stream	Adapted Control Stream*
Population PK Analysis	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Reslizumab_BLA761033_YR\popPK	ph123pk3.xpt ph123pk6.xpt	res420.csv res.csv	base-pk-model-01-ctl.txt final-pk-model-ctl.txt	run001 mod run003 mod
E-R for Blood Eosinophil Count	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Reslizumab_BLA761033_YR\EOS	pkpdeos3-nmdat.txt	EOS.csv	base-model-01-ctl.txt	run001 mod
E-R for FEV1	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Reslizumab_BLA761033_YR\EOS	fevall5.xpt	fevall.csv	fev1-final-model-ctl.txt	run004 mod run005 mod run006 mod
E-R for ACQ7	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Reslizumab_BLA761033_YR\ACQ	pkpdacq-nmdat.txt	ACQ.csv	acq-final-model-ctl.txt	run001 mod run002 mod
E-R for Muscle Disorder	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Reslizumab_BLA761033_YR\MD	aefirst.xpt	AEFIRST.sas7bdat	musc-lr-8-final-model.sas	CPRED.sas CAVSS.sas CMIN.sas

* Adapted for changes of directory, input and output format

3.4 Results

- To assess the effect of introduction of OLOQ

Instead of using two independent approach to develop the final model of each of the two datasets (ph123pk3 with OLOQ and ph123pk6 without OLOQ), the reviewer utilized the final model of data set ph123pk3 to analyze the data set ph123pk6. The estimates of the major PK parameters and their variability from two datasets are listed in Table 16. Generally the estimates from two data sets are comparable. Therefore Sponsor's approach by introduction of OLOQ in the final dataset is reasonable and acceptable.

Table 16 Comparison of Reslizumab PK Parameter Estimates between Two Datasets by Using the Final model for Data Set ph123pk3

Parameter	ph123pk3*	ph123pk6#
CL (clearance, ml/hr)	7.16	7.17
V1 (central volume, L)	3.13	3.14
Q (distributional clearance, mL/hr)	10	10
V2 (peripheral volume, L)	2.05	2.06
Inter-Subjective Variability for CL	33.3%	33.2%
Inter-Subjective Variability for V1	26.0%	26.2%
Inter-Subjective Variability for Q	97.2%	96.9%
Inter-Subjective Variability for V2	54.8%	54.8%

* Dataset with OLOQ
# Dataset without OLOQ (also contains 13 more subjects not listed in ph123pk3)

- To confirm the E-R response for FEV1

The Sponsor proposed a time-dependent E_{max} model for the E-R relationship for FEV1. The model presumes that E_{max} value is linear proportional to the $C_{avg,ss}$ value ($E_{max} \propto 0.003379 \times C_{avg,ss}$); and the FEV1 change from baseline follows a time-dependent increase E_{max} model. In order to evaluate the slope of Cavg,ss, reviewer fixed slope of 0 in the model and estimate the value of objective function in the new model (model 6). The objective function increased 17.635 for this slope-fixed model. Therefore, introduction of the slope for $C_{avg,ss}$ in the E_{max} model appeared statistically significant.

- To assess the validity of E-R response for muscle disorder AE

(b) (4)

Here reviewer used the (b) (4) $C_{av,ss}$ (Table 17) or C_{min} (Table 18) as reslizumab exposure variable. The results confirmed that there is no significant E-R relationship between $C_{av,ss}/C_{min}$ and muscle disorder AE.

Table 17 Summary of Effects of Reslizumab Exposure ($C_{av,ss}$) and Age on Occurrence of Muscle Disorder Adverse Events

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.9035	0.5247	55.3468	<.0001
CAVSS	1	-0.00107	0.00599	0.0317	0.8588
AGE	1	0.0222	0.0101	4.7927	0.0286

Source: reviewer's analysis; Control stream: CAVSS.sas; Output: CAVSS.pdf

Table 18 Summary of Effects of Reslizumab Exposure ($C_{av,ss}$) and Age on Occurrence of Muscle Disorder Adverse Events

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.8124	0.5212	53.4954	<.0001
CMIN	1	-0.0147	0.0117	1.5866	0.2078
AGE	1	0.0223	0.0101	4.8768	0.0272

Source: reviewer's analysis; Control stream: CAVSS.sas; Output: CMIN.pdf

4.3 Appendix – New Drug Application Filing Memo

Application Information			
BLA Number	761033	**SDN**	1
Applicant	Teva	**Submission Date**	**3/30/2015**
Generic Name	Reslizumab	**Brand Name**	Cinqair
Drug Class	Anti-IL-5 antibody		
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.		
Dosage Regimen	3 mg/kg once every 4 weeks		
Dosage Form	100 mg/10mL solution per vial	**Route of Administration**	intravenous injection
OCP Division	II	**OND Division**	DPARP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Yunzhao Ren MD, Ph.D.	Ping Ji, Ph.D.	
Pharmacometrics	Yunzhao Ren MD, Ph.D.		
Genomics			
Review Classification	☑ Standard ✗ Priority ✗ Expedited		
Filing Date	5/11/2015	**74-Day Letter Date**	6/12/2015
Review Due Date	12/3/2015	**PDUFA Goal Date**	3/30/2016

Application Fileability
Is the Clinical Pharmacology section of the application fileable? ☑ Yes ✗ No If no list reason(s)
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? ✗ Yes ☑ No If yes list comment(s)
Is there a need for clinical trial(s) inspection? ✗ Yes ☑ No If yes explain

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ✗ No	Clinical Pharmacology Summary	☑ Yes ✗ No
Bioanalytical and Analytical Methods	☑ Yes ✗ No	Labeling	☑ Yes ✗ No

Clinical Pharmacology Studies		
Study Type	**Count**	**Comment(s)**
In Vitro Studies		
✗ Metabolism Characterization		

✗ Transporter Characterization			
✗ Distribution			
☑ Drug-Drug Interaction		1	Study DM-2013-017
In Vivo Studies			
Biopharmaceutics			
☑ Absolute Bioavailability		1	Study C38072/1107
✗ Relative Bioavailability			
✗ Bioequivalence			
✗ Food Effect			
☑ Bioanalytical methods		5	Reports 02-30264, 172-1204, 256-0702, 256-0901A, C38072-Clin Pk-Inv-001
✗ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	Study C38072/1107
	☑ Multiple Dose	1	Study C38072/1102
Patients	☑ Single Dose	1	Study I96-350
	☑ Multiple Dose	6	StudiesP00290, Res-5-0010, C38072/3081, C38072/3082, C38072/3083, and P01942 (irrelevant indication)
✗ Mass Balance Study			
✗ Other (e.g. dose proportionality)			
Intrinsic Factors			
✗ Race			
✗ Sex			
✗ Geriatrics			
✗ Pediatrics			
✗ Hepatic Impairment			
✗ Renal Impairment			
✗ Genetics			
Extrinsic Factors			
✗ Effects on Primary Drug			
✗ Effects of Primary Drug			
Pharmacodynamics			
☑ Healthy Subjects		2	Studies C38072/1107 and C38072/1102
☑ Patients		3	Studies I96-350, P00290, and Res-5-0010
Pharmacokinetics/Pharmacodynamics			
✗ Healthy Subjects			
✗ Patients			
✗ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		1	Report C38072CP-11-006
☑ Exposure-Efficacy		1	Report C38072CP-15-001
☑ Exposure-Safety		1	Report C38072CP-15-001

Total Number of Studies/Reports	**In Vitro**	1	**In Vivo**	18

Total Number of Studies/Reports to be Reviewed		1		17

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/s/

YUNZHAO REN
12/16/2015

PING JI
12/16/2015

YANING WANG
12/16/2015

SURESH DODDAPANENI
12/17/2015