Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cinqaero

reslizumab

Procedure no: EMEA/H/C/003912/P46/008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

List of abbreviations and definition of terms

ACQ-6	Asthma Control Questionnaire-6
ADA	anti-drug antibody
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
anti-IL-5	anti-human interleukin-5
AQLQ +12	Asthma Quality of Life Questionnaire +12
AST	aspartate aminotransferase (SGOT)
BMI	body mass index
BUN	blood urea nitrogen
CAE	clinical asthma exacerbation
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
DoR	date of randomization
ECG	electrocardiogram
eDiary	electronic diary
EOT	end of treatment
EQ-5D	European Quality of Life 5-dimension health state utility index
FEF25%-75%	forced expiratory flow at 25% to 75% forced vital capacity
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high level term
ICS	inhaled corticosteroids
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
IWRS	Interactive Web Response System
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
mAb	monoclonal antibody
MMRM	mixed-effect model for repeated measures
NAb	neutralizing antibody
NB	negative binomial
OCS	oral corticosteroid
PCS	potentially clinically significant
PEF	peak expiratory flow
PP	per-protocol
PT	preferred term
QTc	QT interval corrected for heart rate
SABA	short-acting beta-agonist
SAP	statistical analysis plan
sc	subcutaneous
SD	standard deviation
SDR	statistical data review
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SMQ	standardized MedDRA queries
SNOT-22	Sinonasal Outcome Test-22
SOC	system organ class
ULN	upper limit of the normal range

Table of contents

1. Introduction

On 23 May 2018, the MAH submitted a completed paediatric clinical study C38072-AS-30027 for reslizumab (Cinqaero), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure EMEA/H/C/003912/P46/008.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that C38072-AS-30027 was part of a clinical development program for a subcutaneous formulation of reslizumab for which an extension application was planned for submission in May 2018. Since the extension application is no longer proceeding as planned, this study report is being submitted as a standalone study.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Reslizumab solution for subcutaneous (sc) injection (110 mg/mL in a prefilled syringe) is being developed for eosinophilic asthma in adolescent and adult patients. Study C38072/1107 evaluated the bioavailability of reslizumab sc compared to reslizumab iv in healthy subjects. A Phase 1 study in healthy adult subjects (C38072 PK 10071) was conducted to assess dose proportionality of sc reslizumab following single doses of 55, 110, and 220 mg, and to assess for effect of injection site (upper arm, abdomen, thigh) on the pharmacokinetics of sc reslizumab.

Two placebo-controlled phase 3 efficacy and safety studies of reslizumab 110 mg sc, administered every 4 weeks (q4w) in patients with eosinophilic asthma ≥12 years of age, have completed clinical conduct and Clinical Study Reports are in preparation (Studies C38072 AS-30025 and C38072-AS-30027). Eligible patients who complete these 2 studies have the opportunity to enter an open label, 36 week extension study (C38072 AS 30066).

2.3. Clinical aspects

2.3.1. Introduction

Reslizumab (CEP-38072) is a humanized anti-human interleukin-5 monoclonal antibody (anti-IL-5 mAb). Reslizumab works by binding to IL-5 and preventing its binding to the IL-5 receptor, thereby reducing circulating and tissue eosinophils.

Reslizumab injection for intravenous (iv) administration was first approved via the centralized procedure in the European Union under the tradename CINQAERO® on 16 August 2016, as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

In this application, results of subcutaneaous (sc) reslizumab in patients from 12 years of age were presented in the clinical study report of Study C38072-AS-30027. The MAH stated that Study C38072-AS-30027 is a stand-alone study.

No data for adolescents became available as the only one adolescents included was randomised to placebo group.

The study was not part of the Paediatric Investigation Plan according to the European Medicines Agency Decision P/0010/2018, dated 30 January 2018 on the acceptance of a modification of an agreed paediatric investigation plan for reslizumab (CINQAERO), (EMEA-001202-PIP02-13-M02).

2.3.2. Clinical study

Clinical study number and title

Study C38072-AS-30027:

Phase 3, 24-Week, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients with Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils;

Description

Study C38072-AS-30027 is a Phase 3, 24-Week, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Reslizumab Subcutaneous Dosing (110 mg Every 4 Weeks) in Patients with Oral Corticosteroid Dependent Asthma and Elevated Blood Eosinophils.

The study was conducted at 78 centers in 17 countries by 78 investigators.

Methods

Objective(s)

Primary Objective: determination of the ability of reslizumab (110 mg) administered subcutaneously (sc) once every 4 weeks to produce a corticosteroid-sparing effect (as demonstrated by percent reduction in daily oral corticosteroid [OCS] use) in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control.

Secondary Objective: evaluation of the clinical benefits of reslizumab in the context of OCS reduction.

Another efficacy objective of this study was to evaluate the effect of reslizumab on standard asthma control measures during tapering of OCS in patients with OCS-dependent asthma.

Target Biomarker Objective: evaluation of the effect of sc dosing of reslizumab on blood eosinophil counts.

Immunogenicity Objective: determination of the incidence of ADAs and neutralizing antibodies (NAbs) after sc dosing of reslizumab.

Pharmacokinetic Objective: characterisation of the PK of sc reslizumab in the study population.

Rapporteur's comment

The primary objective is a relevant objective for severe asthma patients.

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study in patients 12 years of age and older with OCS-dependent asthma and elevated blood eosinophils.

The study consisted of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and a late 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments.

During the optimization period, the patient's minimal effective OCS requirement was determined. The patient's previous OCS was standardized to an equivalent dose and regimen of prednisone to the nearest 2.5 mg daily.
For optimization, the OCS dose was reduced at 1-week intervals according to the algorithm of the protocol amendment 2, for up to 10 weeks or until there was a worsening of asthma signs and symptoms (minimum 1 day in optimization). When either a lung function or symptomatic deterioration occurred, the patient was to be returned to the previously effective OCS level, which would then constitute the minimally effective dose for the purpose of run-in. If this previously effective dose was no longer effective, the investigator could determine the clinically appropriate, minimally effective dose for the purpose of run-in. The optimization period was considered finished when patients experienced a worsening of asthma signs and symptoms, or if patients optimized to an OCS dose of <5 mg without a worsening of asthma signs and symptoms.

Patients could enter run-in (visit 12) on the same day as optimization ended if the patients were on the minimally effective prednisone dose (did not require a prednisone burst at end optimization). Patients whose minimal effective OCS dose remained between ≥5 and ≤40 mg of prednisone daily at the end of optimization could advance to run-in.

During run-in, patients continued maintained their minimally effective OCS dose and previous background asthma medications unchanged. The frequency of symptoms, use of inhaled reliever bronchodilator, night-time awakenings due to asthma requiring a rescue inhaler, and ambulatory lung function during the last 7 days of the run-in period constituted the baseline level of control for analysis and the basis for the OCS reduction algorithm used during the treatment period.

The patient's previous non-OCS background asthma controller medications were to be continued unchanged throughout the pre-randomization period and the entire study. At the beginning of the optimization period, asthma symptom diary and electronic peak flow meter were distributed, on which the patient recorded asthma symptoms, number of reliever bronchodilator inhalations, night-time awakenings due to asthma requiring rescue inhaler, and AM and PM PEF during optimisation period, run-in period and treatment period.

Figure 1 Overall Study Schema for Study C38072-AS-30027
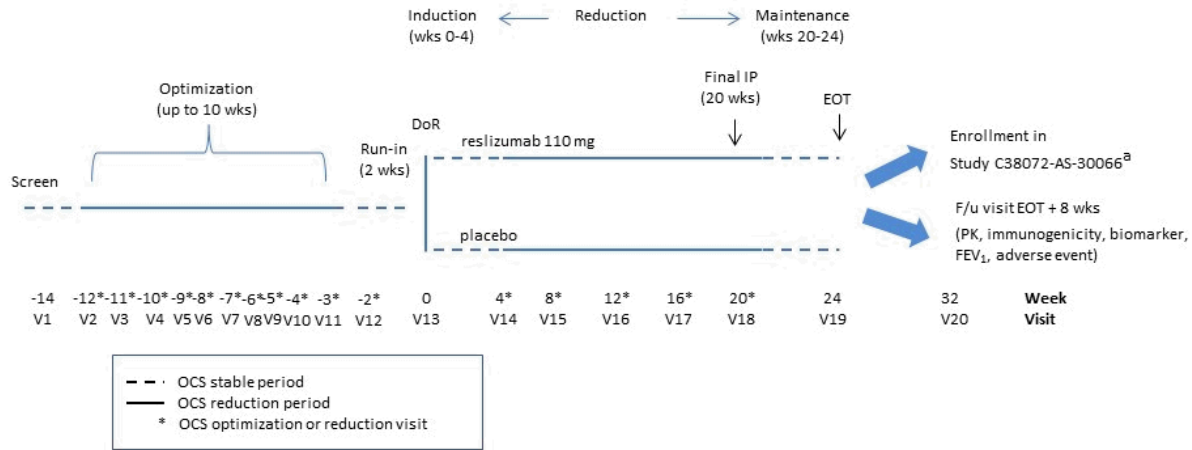
[a] If patients elected to enrol in the open-label, long-term extension safety study, C38072-AS-30066, they did not complete the early and/or late follow-up visits under the Study C38072-AS-30027 protocol, but instead completed the early and/or late follow-up visits at the end of Study C38072-AS-30066.
DoR=day of randomization; EOT=end of treatment; FEV1=forced expiratory volume in 1 second; F/u=follow up; IP=investigational product; OCS=oral corticosteroid; PK=pharmacokinetic; V=visit; wk=week.
Note: An additional, late follow-up for immunogenicity and PK testing was performed 28 weeks (±2 weeks) after the last dose of study drug (ie, approximately week 48).

Rapporteur's comment

The study design is previously described for mepolizumab (Nucala®) (Bel, 2014)[1]

Study population /Sample size

Diagnosis and Main Criteria for Inclusion (not all inclusive):

- The patient was male or female, 12 years of age and older, with a previous diagnosis of asthma.

    Patients 12 to <18 years of age were excluded from participating in South Korea, the Netherlands, and Argentina, and patients 66 years of age and older were excluded from participating in South Korea.

- Written informed consent had to be obtained before a diagnosis of asthma was confirmed on the basis of patient history and by demonstration of airway reversibility.

- The patient continued to require an average daily maintenance dose of OCS for asthma of between 5 and 40 mg of prednisone or equivalent during the 3 months before screening. Patients on an OCS dose of >40 mg at screening who the investigator believed may be able to decrease OCS dose to ≤40 mg during the optimization period could also be enrolled.

    Note: Every-other-day dosing that was within this daily average (i.e. 10 to 80 mg) was allowed.

- The patient had a documented blood eosinophil level of at least 300/µL during the previous 12 months while on at least medium total daily dose of inhaled corticosteroids based on the Global Initiative for Asthma 2016 clinical comparability table or ≥300/µL at screening while on chronic OCS or that became manifest during the OCS optimization period or at the week -2 visit (end of optimization period/beginning of run-in period).

---

[1] Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al; SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371(13):1189-97.

<u>Main Criteria for Exclusion</u> (not all inclusive):

- The patient had any clinically significant, uncontrolled medical condition (treated or untreated) that would interfere with the study schedule or procedures and interpretation of efficacy results or would compromise the patient's safety.

- The patient had another confounding underlying lung disorder (eg, chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis eosinophilic granulomatosis with polyangiitis [also known as Churg-Strauss syndrome], or allergic bronchopulmonary aspergillosis).

- The patient had a known hypereosinophilic syndrome.

- The patient required treatment for an asthma exacerbation within 4 weeks of screening.

- The patient was currently using any systemic immunosuppressive or immunomodulatory biologic agents (eg, anti-immunoglobulin E monoclonal antibody [mAb] or other mAb [eg, mepolizumab] or soluble receptor) or non-biologic (eg, methotrexate or cyclosporine), except maintenance OCS for the treatment of asthma. Previous use of such agents that occurred >5 half-lives from the screening visit could be allowed if approved by the medical monitor.

> ***Rapporteur's comment***
>
> The in- and exclusion criteria are acceptable.

Treatments

<u>Investigational Product</u>: Reslizumab 110 mg was administered sc once every 4 weeks through week 20, for a total of 6 doses.

<u>Placebo</u>: Matching placebo was administered sc once every 4 weeks through week 20, for a total of 6 doses.

Investigational product dosage regimen and duration of treatment sc dose and regimen were based on data from the iv program and sc data from Study C38072/1107.

Outcomes/endpoints

<u>Primary Efficacy Measure and Endpoint</u>:

The primary efficacy variable and endpoint for this study was the categorized percent reduction in the daily OCS dose during weeks 20 to 24, as compared with the dose at the end of the optimization phase. Percent reduction was categorized as follows: 90% to 100%; 75% to <90%; 50% to <75%; >0% to <50%; and no decrease in OCS, loss of baseline asthma control during weeks 20 through 24, or discontinuation of study drug.

Loss of baseline asthma control was defined as FEV1 less than 80% of baseline at the week 24 visit, clinically significant worsening in ACQ-6 score (change in score of 0.5) at the week 24 visit compared with baseline, and/or CAE during weeks 20 through 24.

A CAE was defined as a clinically judged deterioration in asthma control, as determined by the investigator and as evidenced by new or worsening asthma signs or symptoms based on the patient history, asthma control diary, physical examination, and/or ambulatory or clinic visit assessment of lung function AND that resulted in a medical intervention, including at least 1 of the following:

• use of systemic corticosteroids (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days)

• asthma-specific hospital admission

• asthma-specific emergency department visit

Additional medication and/or medical intervention that would satisfy the CAE definition occurring within 7 days of the last day of a prior CAE event was considered as part of the same event for analysis purposes.

The CAE start and stop dates were collected to determine the exacerbation duration. The start date of a CAE was the start date of the initial medical intervention (eg, use of systemic corticosteroids [injection or, if oral, at least a doubling from the current OCS dose for at least 3 days], asthma-specific hospital admission, or asthma-specific emergency department visit, whichever came first). The stop date was the last day of systemic corticosteroids (injectable), or for those with a doubling of the OCS dose, the stop date was the date when the patient returned to their baseline dose, or the last day of an asthma-specific hospitalization or emergency department visit, whichever was later. For patients receiving at least a doubling from their current dose of OCS for at least 3 days that did not return to baseline (dose before exacerbation), an asthma exacerbation stop date was the day that they have been on a new stable dose for at least 10 days.

Secondary Efficacy Measures and Endpoints:

- Proportion of patients achieving ≥50% reduction in OCS dose at weeks 20 to 24 relative to the OCS dose at the date of randomization (DoR)/baseline, while maintaining asthma control

- Proportion of patients achieving dose reduction to ≤5-mg daily dose at weeks 20 to 24, while maintaining asthma control

- Percent change from DoR/baseline in OCS dose at weeks 20 to 24

- Proportion of patients achieving <5 mg decrement in OCS dose (ie, the minimal and non-responders) at weeks 20 to 24, compared with the OCS dose at DoR/baseline, while maintaining asthma control

- Proportion of patients discontinuing OCS at weeks 20 to 24, while maintaining asthma control

- Annualized rate of clinical asthma exacerbations (CAEs) requiring a burst of systemic corticosteroid (injection or, if oral, at least a doubling from the current OCS dose for at least 3 days), an asthma-specific hospital admission, or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)

Other Pre-Specified Efficacy Measures and Endpoints:

- Time to first CAE

- Other clinic lung functions, including the following:

➢ Pre-bronchodilator forced expiratory volume in 1 second (FEV1): change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal

➢ Post-bronchodilator FEV1: change from DoR/baseline to weeks 4, 12, 20, and 24 or early withdrawal

➢ Ambulatory lung function: change in morning (AM) and evening (PM) peak expiratory flow from run-in baseline at each week through week 24 or early withdrawal

- Asthma Quality of Life +12 score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal

- Asthma Control Questionnaire (ACQ-6) score: change from DoR/baseline to weeks 4, 8, 12, 16, 20, and 24 or early withdrawal

- Change in total inhalations of reliever bronchodilator medication (eg, short-acting beta-agonist) (number of inhalations per 24 hours: day+night) from run-in baseline at each week through week 24 or early withdrawal

- Number of night-time awakenings due to asthma over the 24-week treatment period

- Change in total asthma symptom score from run-in baseline at each week through week 24 or early withdrawal

- European Quality of Life 5-dimension health state utility index score: change from DoR/baseline to week 24 or early withdrawal

- St George's Respiratory Questionnaire score: change from DoR/baseline to weeks 12 and 24 or early withdrawal

Clinical asthma exacerbation (CAE) is defined as requiring a burst of systemic corticosteroid (injection, or if oral, at least a doubling from the current OCS dose for at least 3 days); an asthma-specific hospital admission; or an asthma-specific emergency department visit during the treatment period (weeks 0 to 24)

Rapporteur's comment

Overall, the endpoints are generally accepted endpoints in asthma trials. The percentage reduction is calculated categorised. This is considered acceptable because this reflects the stepwise reduction (tapering) of OCS.

Prior and Concomitant Therapy

Excluding OCS, which was adjusted per protocol, the patient's baseline asthma therapy regimen (including, but not limited to, ICS, leukotriene antagonists, 5-lipoxygenase inhibitors, and cromolyn) was to be stable for 30 days before screening and to be continued without dosage changes throughout the study. Changes in background maintenance therapy were to be discussed with the medical monitor.

The following medications were allowed before and during this study:

- Inhaled fluticasone propionate at 880 µg or equivalent daily PLUS another controller(s) (eg, LABA, long-acting muscarinic antagonist [LAMA], leukotriene inhibitor, or theophylline) for at least 6 months before the screening visit. For a fixed-dose ICS/LABA preparation, the highest labelled dose in that region would satisfy this criterion.

- For patients 12 through <18 years of age, the ICS dose was to correspond to at least a medium total daily dose for the formulation.

- Allergen immunotherapy was allowed.

- Inhaled reliever medications were allowed as needed for the relief of intermittent asthma symptoms.

- Prior asthma medications such as ICS, leukotriene pathway modifiers, long-acting bronchodilators, and mast cell stabilizers could be taken concomitantly and were not to be altered during this study, unless patient safety was at risk.

The following medications were not allowed during this study:

- Patients were to refrain from using reliever inhalers for 6 hours before any study visit that included spirometry or airway reversibility testing, including the screening visit.

- If a patient was taking LABAs, these were to be withheld for 12 hours before any study visit that included spirometry or airway reversibility testing, including the screening visit.

- Any immunosuppressive or immunomodulatory agents (biological and non-biological), including, but not limited to, methotrexate, cyclosporine, and interferon (excluding systemic corticosteroids prescribed for asthma and maintenance allergen immunotherapy).

- All biologic therapies, including, but not limited to, Xolair® (omalizumab), mepolizumab, benralizumab, lebrikizumab, and anti-tumor necrosis factor mAbs.

- All non-biologic investigational drugs.

- Inhaled nicotine (including electronic cigarettes).

At each clinic visit after the screening visit, the investigator asked the patients whether they had taken any medications (other than study drug), including over-the-counter medications, vitamins, or herbal, or nutritional supplements, since the previous visit. Indication, dosage, and start and end dates were entered on the appropriate CRF.

Statistical Methods

Randomisation

Patients were randomized to reslizumab 110 mg sc or placebo in a 1:1 ratio. To achieve balance between treatment groups in the average daily OCS use/requirement and age, randomization was stratified by optimized, average daily OCS dose of >10 or ≤10 mg and age (12 to <18 years of age or ≥18 years of age) at baseline.

Sample size

The primary efficacy variable and endpoint for this study is the percent reduction in the daily OCS dose during weeks 20 to 24 as compared with the dose at the end of the optimization phase.

The study will be considered positive if the measure meets statistical significance at the respective predefined significance level. A statistically significant effect of reslizumab over placebo, as measured by the primary efficacy variable, is required to establish the efficacy of reslizumab treatment.

The sample size was calculated based on the following assumptions:

- Categorical reduction in OCS dose after 24 weeks of treatment will have the following distribution for the placebo group (based on Bel et al 2014):

  – 10.9% percent of subjects will have 90% to 100% reduction

  – 7.9% percent of subjects will have 75% to <90% reduction

  – 14.8% percent of subjects will have 50% to <75% reduction

  – 10.8% percent of subjects will have 0% to <50% reduction

- 55.6% percent of subjects will have no reduction, loss of asthma control, or discontinuation from study drug

- The overall odds ratio between reslizumab and placebo based on proportional odds model will be 2.63

- Alpha level of 0.05

Based on the above assumptions, a sample size of 76 subjects per group will provide 90% power to detect a significant effect of reslizumab over placebo on the probability for a higher categorical reduction of OCS dose.

Rapporteur's comment

The sample size calculation is based on the results as observed for mepolizumab (Nucala) (Bel, 2014).

Blinding

Patients were randomly assigned to treatment through an IRT. Using this system ensured a balance across treatment groups; no effort was made to maintain a balance among treatment groups within a study centre.

Patients and investigators remained blinded to treatment assignment during the study. The sponsor's personnel involved in the study were also blinded to the study drug identity after the run-in period until the database was locked for analysis and the treatment assignment was revealed, with the exception of the bioanalytical group (Biologics Assays and Technology) who were not blinded to facilitate PK and ADA sample analyses. Eosinophils and monocytes were redacted from the post-baseline differential cell count reports.

Both reslizumab and placebo were provided as clear solutions.

The intent-to-treat (ITT) analysis set included all randomly assigned patients and was used for all efficacy analyses, unless otherwise noted.

The safety analysis set included all patients who received at least 1 dose of study drug and was used for all safety analyses, unless otherwise noted.

The per-protocol analysis set was a subset of the ITT analysis set including only patients without major protocol violations and was used for sensitivity analysis for the primary endpoint.

An on-treatment approach was adopted as the primary analysis for the efficacy variables assessed by visit. In this analysis, the treatment period was defined from the first dose of study drug to the end of treatment (EOT) (week 24) visit for patients who completed treatment and from the first dose of study drug to the last dose of study drug (+4 weeks) for the patients who discontinued treatment early.

The assessment of safety in this study was based on measurements and events recorded during the treatment period (on-treatment). On-treatment assessments were defined as events and measurements occurring between the first dose of study drug and the EOT (week 24) visit for patients who completed treatment and between the first dose of study drug and the last dose of study drug +4 weeks for patients who discontinued treatment early.

A fixed-sequence multiple testing procedure was implemented to test the primary and secondary variables while controlling the overall type I error rate at 0.05. If the resulting 2-sided p-value from the primary comparison was ≤0.05, then the next comparison of interest (first secondary variable) was interpreted inferentially at 0.05. This process continued through the secondary variables until either all

comparisons of interest were interpreted inferentially or until the point at which the resulting 2-sided p-value for a comparison of interest was >0.05. At the point where p>0.05, no further comparisons were interpreted inferentially. The hierarchy of secondary endpoints is presented in the Statistical Analysis Plan.

No multiplicity adjustments were made for other efficacy and exploratory analyses.

Results

Recruitment/ Number analysed

Baseline data

A total of 273 patients with OCS-dependent severe eosinophilic asthma were screened; 180 patients were enrolled, and 177 patients were randomized in the study, all of whom received at least 1 dose of study drug.
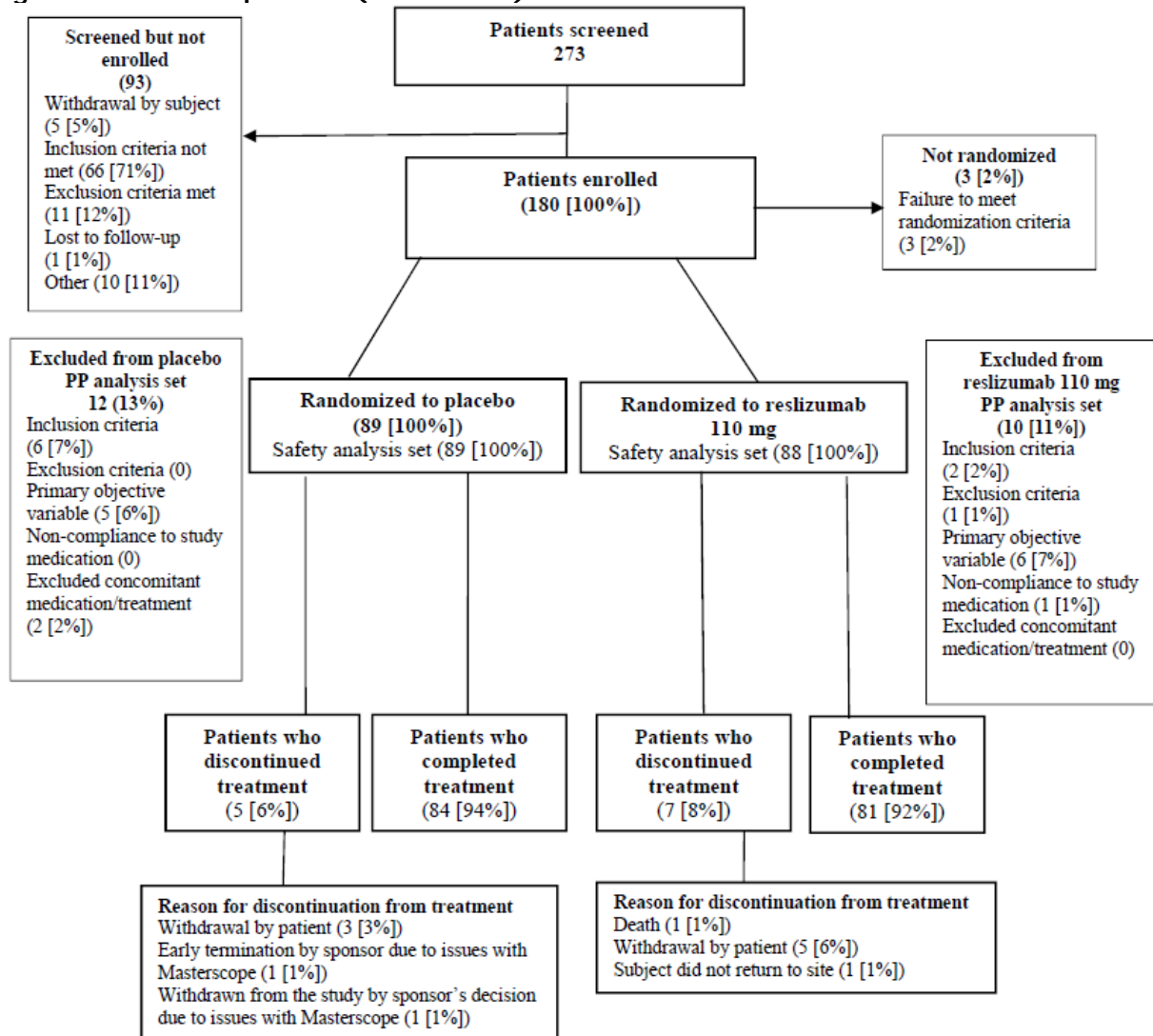
A total of 167 (94%) patients completed treatment (83 [93%] patients in the placebo group and 84 [95%] patients in the reslizumab group), and 10 (6%) patients discontinued treatment (6 [7%] patients in the placebo group and 4 [5%] patients in the reslizumab group).

A total of 167 (94%) patients completed the planned treatment phase (84 [94%] patients in the placebo group and 83 [94%] patients in the reslizumab group), and 10 (6%) patients discontinued the planned treatment phase (5 [6%] patients in both of the treatment groups).

The most frequent reason for discontinuation from treatment was withdrawal by patient. A total of 165 (93%) patients completed the study (84 [94%] patients in the placebo group and 81 [92%] patients in the reslizumab group), and 12 (7%) patients discontinued the study (5 [6%] patients in the placebo group and 7 [8%] patients in the reslizumab group).

Only one adolescent was included and was randomised to placebo group.

Figure 2 Patient Disposition (All Patients)

Screened but not enrolled (93)
Withdrawal by subject (5 [5%])
Inclusion criteria not met (66 [71%])
Exclusion criteria met (11 [12%])
Lost to follow-up (1 [1%])
Other (10 [11%])

Patients screened 273

Patients enrolled (180 [100%])

Not randomized (3 [2%])
Failure to meet randomization criteria (3 [2%])

Excluded from placebo PP analysis set 12 (13%)
Inclusion criteria (6 [7%])
Exclusion criteria (0)
Primary objective variable (5 [6%])
Non-compliance to study medication (0)
Excluded concomitant medication/treatment (2 [2%])

Randomized to placebo (89 [100%])
Safety analysis set (89 [100%])

Randomized to reslizumab 110 mg
Safety analysis set (88 [100%])

Excluded from reslizumab 110 mg PP analysis set (10 [11%])
Inclusion criteria (2 [2%])
Exclusion criteria (1 [1%])
Primary objective variable (6 [7%])
Non-compliance to study medication (1 [1%])
Excluded concomitant medication/treatment (0)

Patients who discontinued treatment (5 [6%])

Patients who completed treatment (84 [94%])

Patients who discontinued treatment (7 [8%])

Patients who completed treatment (81 [92%])

Reason for discontinuation from treatment
Withdrawal by patient (3 [3%])
Early termination by sponsor due to issues with Masterscope (1 [1%])
Withdrawn from the study by sponsor's decision due to issues with Masterscope (1 [1%])

Reason for discontinuation from treatment
Death (1 [1%])
Withdrawal by patient (5 [6%])
Subject did not return to site (1 [1%])

Source: Summary 15.1.1, Summary 15.1.2, Listing 16.2.1.1, Listing 16.2.1.2, and Listing 16.2.1.3.
ITT=intent-to-treat; PP=per protocol.
Note: Numbers in parentheses are numbers of patients.

Rapporteur's comment

Overall, discontinuation was similar in both groups. The reason for discontinuation was slightly different, but this is considered irrelevant.

Demographics

Overall, the mean age of patients was 54.3 years (53.1 years in the placebo group and 55.5 years in the reslizumab group), and majority of patients were female (117 [66%] patients: 57 [64%] patients in the placebo group and 60 [68%] patients in the reslizumab group) and White (152 [86%] patients: 80 [90%] patients in the placebo group and 72 [82%] patients in the reslizumab group).

The mean airway reversibility at screening was 25.3% overall, and 27% of patients reported historical airway reversibility. Mean baseline pre-bronchodilator forced expiratory volume in 1 second (FEV1) was 1.655 L, and mean baseline post-bronchodilator FEV1 was 1.885 L. Mean FEV1 at baseline (percent predicted) was 57.0%. Forty-seven percent of subjects had an eosinophil count of ≥400/μL at

baseline, and the mean eosinophil count at baseline was 500/µL (521/µL in the placebo group and 479/ µL in the reslizumab group). The mean OCS dose at baseline (optimized dose) was 10.37 mg in both treatment groups, and the mean duration of OCS use was 3.11 years.

Table 1 Baseline Characteristics (ITT Analysis Set)

Baseline characteristic	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Airway reversibility at screening (%)			
n	89	88	177
Mean (SD)	24.6 (20.53)	26.0 (25.86)	25.3 (23.28)
SE of mean	2.18	2.76	1.75
Median	21.0	19.0	21.0
Min, max	-8, 95	-4, 193	-8, 193
Airway reversibility at screening (mL)			
n	89	88	177
Mean (SD)	371.3 (263.70)	349.7 (322.02)	360.6 (293.50)
SE of mean	27.95	34.33	22.06
Median	335.0	259.5	294.0
Min, max	-95, 1233	-64, 1714	-95, 1714
Airway reversibility at screening, n (%)			
<12%	22 (25)	19 (22)	41 (23)
≥12%	67 (75)	69 (78)	136 (77)
Historical airway reversibility, n (%)			
Yes	24 (27)	23 (26)	47 (27)
No	3 (3)	8 (9)	11 (6)
Missing	62 (70)	57 (65)	119 (67)

Pre-bronchodilator FEV$_1$ at baseline (L)			
n	89	88	177
Mean (SD)	1.740 (0.657)	1.569 (0.653)	1.655 (0.659)
SE of mean	0.070	0.070	0.050
Median	1.690	1.475	1.540
Min, max	0.700, 4.140	0.680, 4.560	0.680, 4.560
Post-bronchodilator FEV$_1$ at baseline (L)			
n	89	88	177
Mean (SD)	1.987 (0.683)	1.781 (0.708)	1.885 (0.701)
SE of mean	0.072	0.075	0.053
Median	1.910	1.615	1.780
Min, max	0.860, 4.430	0.740, 4.530	0.740, 4.530
FEV$_1$ at baseline (% predicted)			
n	89	88	177
Mean (SD)	58.7 (19.79)	55.2 (16.72)	57.0 (18.36)
SE of mean	2.10	1.78	1.38
Median	56.3	54.7	55.7
Min, max	26, 109	24, 105	24, 109
Eosinophil at baseline (1×10^9/L)			
n	89	88	177
Mean (SD)	0.521 (0.4914)	0.479 (0.3883)	0.500 (0.4424)
SE of mean	0.0521	0.0414	0.0333
Median	0.380	0.370	0.380
Min, max	0.01, 3.18	0.01, 2.25	0.01, 3.18
Eosinophil at baseline, n (%)			
<300/µL	33 (37)	28 (32)	61 (34)
300-<400/µL	13 (15)	19 (22)	32 (18)
≥400/µL	43 (48)	41 (47)	84 (47)
Historical eosinophil, n (%)			
Yes	70 (79)	62 (70)	132 (75)
No	19 (21)	26 (30)	45 (25)

Age at asthma onset, years			
n	89	88	177
Mean (SD)	32.9 (17.85)	32.8 (17.71)	32.9 (17.73)
SE of mean	1.89	1.89	1.33
Median	35.0	36.0	35.0
Min, max	0, 66	0, 70	0, 70
Age at asthma onset, n (%)			
<40 years	54 (61)	57 (65)	111 (63)
≥40 years	35 (39)	31 (35)	66 (37)
OCS dose at baseline (mg)			
n	89	88	177
Mean (SD)	10.37 (6.435)	10.37 (6.807)	10.37 (6.604)
SE of mean	0.682	0.726	0.496
Median	10.00	10.00	10.00
Min, max	5.0, 37.5	5.0, 40.0	5.0, 40.0
OCS dose at baseline, n (%)			
≤10 mg	69 (78)	68 (77)	137 (77)
>10 mg	20 (22)	20 (23)	40 (23)
Duration of OCS use, n (%)			
<5 years	74 (83)	72 (82)	146 (82)
≥5 years	15 (17)	16 (18)	31 (18)
Phadiatop test, n (%)			
Positive	47 (53)	47 (53)	94 (53)
Negative	39 (44)	40 (45)	79 (45)
Missing	3 (3)	1 (1)	4 (2)
Smoking status, n (%)			
Current	0	0	0
Former	13 (15)	12 (14)	25 (14)
Never	76 (85)	76 (86)	152 (86)

Source: Summary 15.1.4.1, Summary 15.1.4.4, Listing 16.2.4.2, and Listing 16.2.4.7.
FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; max=maximum; min=minimum; OCS=oral corticosteroid; SD=standard deviation; SE=standard error.
Notes: All spirometry variables represent pre-bronchodilator measurements, except for FEV_1 as indicated. Historical eosinophil indicates whether the patient had a documented blood eosinophil level of at least 300/µL during the previous 12 months. Historical airway reversibility indicates whether patient had a documented FEV_1 reversibility of 12% or a provocation concentration producing a 20% fall in FEV_1 for methacholine of ≤8 mg/mL during the previous 24 months.

Consistent with the target population of this study, all patients reported a history of asthma. The mean time since diagnosis was 20.1 years for the placebo group and 22.3 years for the reslizumab group. Twenty-nine percent of patients overall missed school or work due to asthma in the past 12 months (23 [26%] patients in the placebo group and 28 [32%] patients in the reslizumab group). Patients in the placebo and reslizumab groups missed an average of 22.13 and 31.04 days of school or work, respectively, due to asthma in the past 12 months.
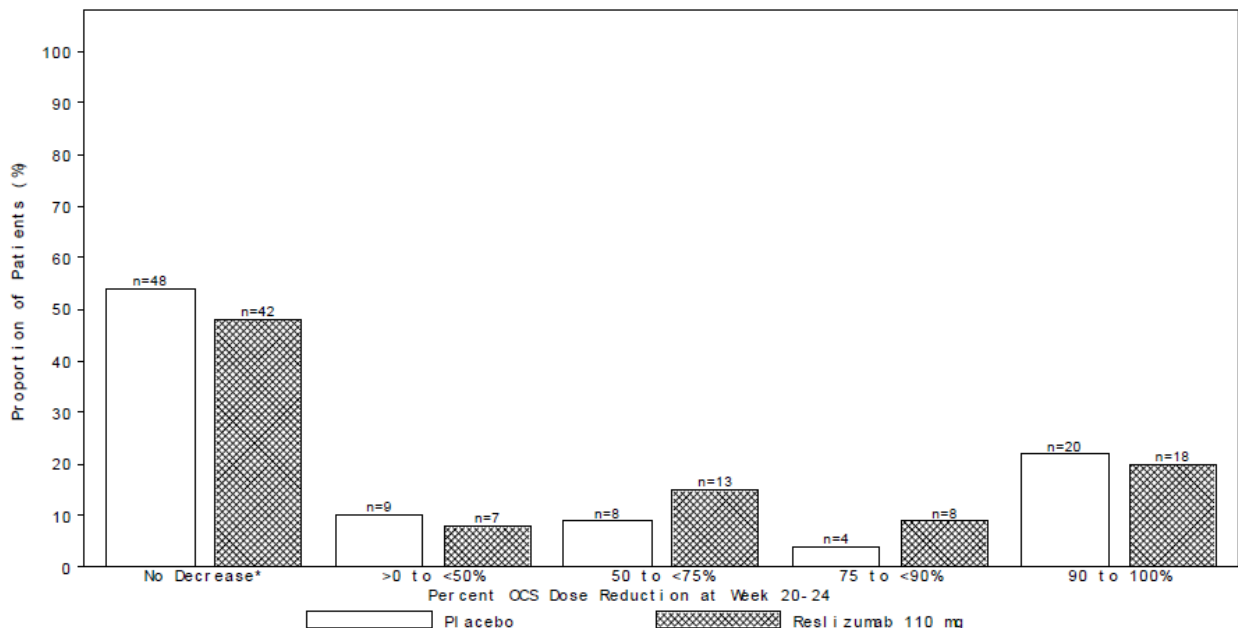
Efficacy results

Primary efficacy endpoint

The primary efficacy endpoint was the 5-level categorized percent reduction in OCS dose during weeks 20 to 24, as compared with the optimized dose at baseline. The primary efficacy endpoint was not met. There was no significant difference between placebo and reslizumab across the 5-level categorized percent reductions in the daily OCS dose during weeks 20 to 24 compared with the OCS dose at the end of the optimization phase (reslizumab versus placebo odds ratio for reduction of OCS use at weeks 20 to 24 was 1.23 [95% confidence interval [CI]: 0.702, 2.157; p-value=0.468]).

Approximately 20% of patients in both treatment groups reduced OCS use by 90% to 100% during weeks 20 to 24 (placebo 22% and reslizumab 20%). A larger percentage of patients in the reslizumab group reduced OCS use by 75% to <90% (placebo 4 [4%] patients and reslizumab 8 [9%] patients) and by 50% to <75% (placebo 8 [9%] patients and reslizumab 13 [15%] patients). Nine (10%) patients in the placebo group and 7 (8%) patients in the reslizumab group reduced OCS use by 0% to <50%. Approximately 50% (placebo 48 [54%] patients and reslizumab 42 [48%] patients) showed no decrease in OCS use (or loss of baseline asthma control) during weeks 20 to 24.

Figure 3 Proportion of Patients in Each OCS Dose Reduction Category (Primary) at Weeks 20 to 24 by Treatment Group (ITT Analysis Set)

Source: Graph 17.1.1.
*No decrease in OCS, loss of baseline asthma control during weeks 20 to 24, or discontinuation from study drug.
ITT=intent-to-treat; OCS=oral corticosteroid.

The results of the sensitivity analyses and subgroup analyses were similar to those for the primary efficacy endpoint. The Reslizumab versus placebo odds ratio (95% CI) with Multiple imputations including data retrieved post-dropout was 1.28 (0.728, 2.241) (p = 0.393) and for the PP analysis set 1.07 (0.585, 1.975) (p= 0.816).

Secondary efficacy endpoints

Secondary efficacy endpoints were not interpreted inferentially because the primary endpoint was not met.

REDUCTION IN ORAL CORTICOSTEROID

Results for secondary efficacy endpoints related to change in OCS use were similar to the primary efficacy analysis.

Thirty-six percent of patients in the placebo group and 44% of patients in the reslizumab group reduced OCS dose by at least 50% at weeks 20 to 24. The reslizumab versus placebo odds ratio (95% CI) was 1.45 (0.786, 2.683; nominal p-value=0.234).

Thirty-four (38%) patients in the placebo group and 37 (42%) patients in the reslizumab group reduced the OCS dose to ≤5 mg at weeks 20 to 24. The reslizumab versus placebo odds ratio (95% CI) was 1.45 (0.786, 2.683; nominal p-value=0.234)

A decrease in OCS dose was observed in both treatment groups over the treatment period. The percent change (LS mean) from randomization/baseline in OCS dose at weeks 20 to 24 was -40.34 for the placebo group and -58.08 for the reslizumab group. The treatment difference (reslizumab minus placebo) (95% CI) at weeks 20 to 24 was -17.75% (-38.986, 3.494%) (nominal p-value=0.101).

Table 2 Secondary Analyses of Categorized OCS Dose Reduction at Weeks 20 to 24 (ITT Analysis Set)

Variable Statistic	Placebo (N=89)	Reslizumab 110 mg (N=88)	Reslizumab versus placebo odds ratio (95% CI)	P-value
At least 50% reduction from baseline	89	88	1.45 (0.786, 2.683)	0.234
Yes	32 (36)	39 (44)	—	—
No[a]	57 (64)	49 (56)	—	—
OCS dose ≤5 mg	89	88	1.19 (0.631, 2.229)	0.596
Yes	34 (38)	37 (42)	—	—
No[a]	55 (62)	51 (58)	—	—
OCS dose=0 mg	89	88	0.82 (0.371, 1.818)	0.628
Yes	20 (22)	18 (20)	—	—
No[a]	69 (78)	70 (80)	—	—
At least 5 mg reduction from baseline	89	88	1.36 (0.722, 2.562)	0.341
Yes	31 (35)	36 (41)	—	—
No[a]	58 (65)	52 (59)	—	—

Source: Summary 15.2.1.6 and Listing 16.2.6.2.
[a] Patients listed as "no" had a result that did not meet the threshold, experienced loss of baseline asthma control during weeks 20 to 24, or discontinued from study drug.
CI=confidence interval; ITT=intent-to-treat; OCS=oral corticosteroid.
Notes: All data were included; missing data were included as non-responders. Odds ratio, confidence interval, and p-value were based on a logistic regression model adjusted for treatment, stratification factors (age group and OCS dose group), duration of OCS use, and baseline value.

Rapporteur's comment

As for the primary endpoint, the results of the secondary endpoints addressing OCS reduction were only a slightly in favour of reslizumab, as observed for the responders. However, these similar results to the primary endpoints are not unexpected as they are strongly related to the primary endpoint.

CLINICAL ASTHMA EXACERBATIONS

Forty-three (48%) patients in the placebo group and 38 (43%) patients in the reslizumab group had at least 1 CAE reported while on study treatment. The mean (SD) frequency of CAEs observed during the treatment period was 0.8 (0.98) in the placebo group and 0.6 (0.77) in the reslizumab group.

When exacerbation duration was excluded from the offset variable, the adjusted CAE rate (95% CI) was 1.86 (1.283, 2.682) in the placebo group and 1.51 (1.052, 2.177) in the reslizumab group. The reslizumab versus placebo CAE rate ratio (95% CI) was 0.82 (0.504, 1.321) (nominal p-value=0.407). When exacerbation duration was not excluded from the offset variable, the adjusted CAE rate (95% CI) was 1.64 (1.183, 2.283) in the placebo group and 1.41 (1.010, 1.981) in the reslizumab group. The reslizumab versus placebo CAE rate ratio (95% CI) was 0.86 (0.553, 1.340) (nominal p-value=0.506).

The time to first CAE was similar for both treatment groups. The Kaplan-Meier estimate of the probability of not experiencing a CAE by week 24 (95% CI) was 0.52 (0.41, 0.62) for the placebo group and 0.57 (0.46, 0.67) for the reslizumab group. The reslizumab versus placebo hazard rate ratio (95% CI) was 0.80 (0.519, 1.247) (nominal p-value=0.330).

Table 3 Frequency of Clinical Asthma Exacerbations (ITT Analysis Set)

Variable Statistic	Placebo (N=89)	Reslizumab 110 mg (N=88)
Number of patients with at least 1 CAE (%)	43 (48%)	38 (43%)
Frequency of CAE during treatment period		
Mean (SD)	0.8 (0.98)	0.6 (0.77)
SE of mean	0.10	0.08
Median	0.0	0.0
Min, max	0, 4	0, 3
Analysis: excluding exacerbation duration from the offset[a]		
Adjusted CAE rate	1.86	1.51
95% CI	(1.283, 2.682)	(1.052, 2.177)
CAE rate ratio (reslizumab vs placebo)	0.82	
95% CI	(0.504, 1.321)	
P-value	0.407	
Analysis: not excluding exacerbation duration from the offset[b]		
Adjusted CAE rate	1.64	1.41
95% CI	(1.183, 2.283)	(1.010, 1.981)
CAE rate ratio (reslizumab vs placebo)	0.86	
95% CI	(0.553, 1.340)	
P-value	0.506	

Source: Summary 15.2.9.1 and Listing 16.2.6.13.

[a] For this analysis, the offset variable was calculated as the logarithm of follow-up duration minus the summed duration of exacerbations during the follow-up.

[b] For this analysis, the offset variable was calculated as the logarithm of follow-up duration.

CAE=clinical asthma exacerbation; CI=confidence interval; EOT=end of treatment; ITT-intent-to-treat; max=maximum; min=minimum; OCS=oral corticosteroid; SD=standard deviation; SE=standard error.

Notes: Count events between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. Adjusted CAE rates, CAE rate ratio, confidence interval, and p-value were based on a negative binomial regression model adjusted for stratification factors (OCS dose group), age, number of prior exacerbations, and an offset variable.

Rapporteur's comment

The results of the secondary endpoints addressing clinical asthma exacerbation were numerically in favour of reslizumab. However the duration of the study would not been long enough for measuring pulmonary exacerbations accurately.

PULMONARY FUNCTIONS TESTS

The exploratory and other clinical efficacy endpoints, including change in FEV1, did not show a statistically significant difference between the placebo and reslizumab groups.

FEV1

The increases from baseline observed in pre- and post-bronchodilator FEV1 from DoR/baseline to week 24 or early withdrawal were similar for the placebo and reslizumab treatment groups.

The LS mean (±SE) change in pre-bronchodilator FEV1 from baseline to the Week 24 was 0.241 (0.142) L for the placebo group and 0.222 (0.145) L for the reslizumab group. The reslizumab-placebo treatment difference (95% CI) was -0.019 (-0.122, 0.085) L (nominal p-value=0.724). The LS mean (±SE) change from DoR/baseline to week 24 or early withdrawal in post-bronchodilator FEV1 was 0.113 (0.135) L for the placebo group and 0.131 (0.139) L for the reslizumab group. The reslizumab-placebo treatment difference (95% CI) was 0.018 (-0.082, 0.117) L (nominal p-value=0.729).

The LS mean (±SE) change in pre-bronchodilator FEV1 from baseline to the Week 32 was 0.391 (0.194) L in the placebo group and 0.277 (0.201) L in the reslizumab group. The reslizumab-placebo treatment difference (95% CI) was -0.114 (-0.237, 0.008) (nominal p-value=0.067). The LS mean (±SE) change in post-bronchodilator FEV1 was 0.280 (0.179) L in the placebo group and 0.211 (0.185) L in the reslizumab group. The reslizumab-placebo treatment difference (95% CI) was -0.069 (-0.183, 0.045) (nominal p-value=0.233).

Figure 4 Pre-Bronchodilator FEV1 (L): LS Mean (±SE) Change from Baseline to Each Visit by Treatment Group (ITT Analysis Set)
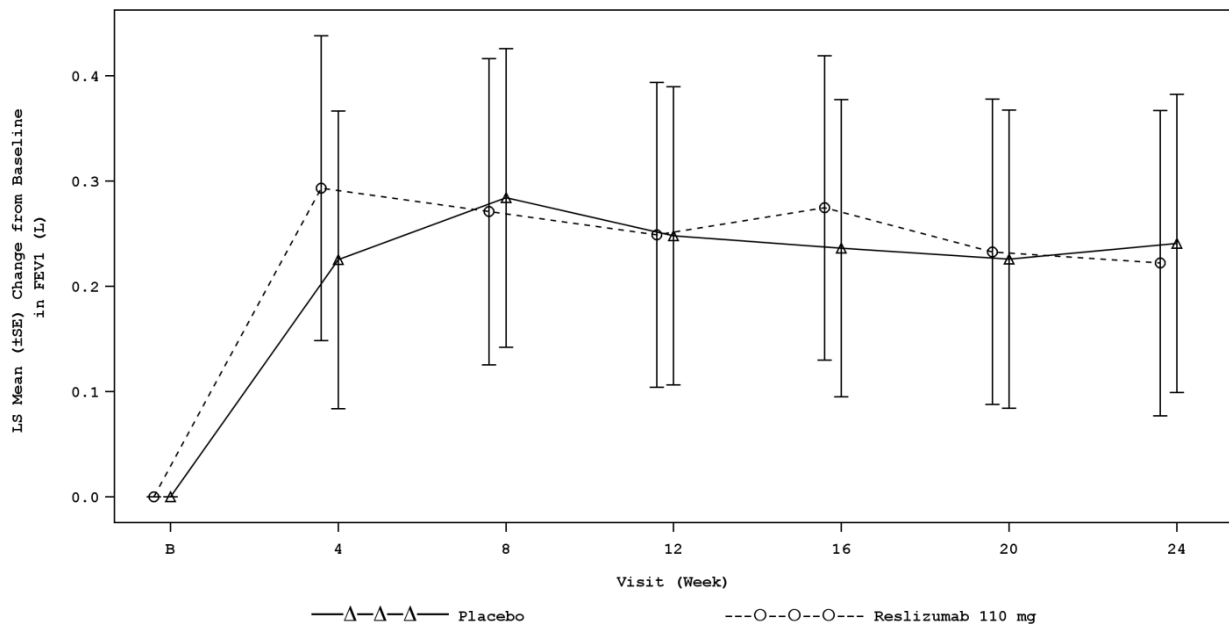
Rapporteur's comment

The results of the secondary endpoints addressing pulmonary function did not show a difference between reslizumab and placebo, although the study duration was long enough for measuring pulmonary function.

QUALITY OF LIFE AND PATIENT-REPORTED OUTCOMES

Rapporteur's comment

For PRO the responder analyses are considered very important because these questionnaires are validated for individual scores and not for comparisons on groups level.

The Applicant refers for responder analyses for the PRO to Summary 15. This is not found in the documentation. The Applicant is requested to submit the module summary 15 with all the referred results.

The quality-of-life endpoints did not show differences between the treatment groups.

ACQ-6:

Higher ACQ-6 scores are an indication of poorer asthma control. Overall ACQ-6 scores decreased in both treatment groups from DoR/baseline to week 24 or early withdrawal. The LS mean (±SE) change in ACQ-6 score was -0.45 (0.389) in the placebo group and -0.62 (0.397) in the reslizumab group. At week 24, the reslizumab-placebo treatment difference (95% CI) was -0.17 (-0.458, 0.114) (nominal p-value=0.238).

Figure 5 ACQ-6 (0-6): LS Mean (±SE) Change from Baseline to Each Visit by Treatment Group (ITT Analysis Set)
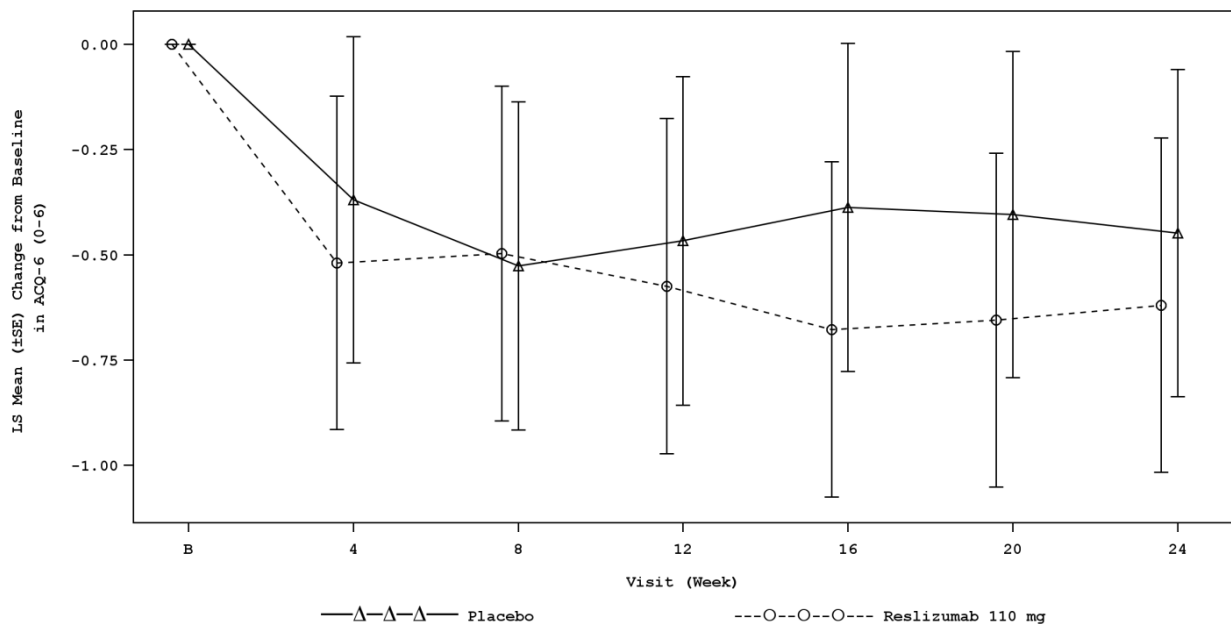
Source: Graph 17.4.1 and Summary 15.2.4.1.
ACQ-6=6-item Asthma Control Questionnaire; B=baseline; ITT=intent- to- treat; LS=least squares; SE=standard error.
Notes: The ACQ-6 is a 6-item instrument; each item is scored on a scale of 0 to 6 (higher scores are an indication of poorer asthma control). The ACQ-6 score is the mean of the 6 questions.

The proportion of patients who achieved a ≥0.5-unit decrease in ACQ-6 score from baseline was similar in both treatment groups. At week 24, 38 (46%) patients in the placebo group and 39 (47%) patients in the reslizumab group had achieved a decrease in ACQ-6 score ≥0.5 units (nominal p-value=0.831).

AQLQ

Higher AQLQ +12 scores indicate improved quality of life. An increase in overall AQLQ +12 score was observed in both treatment groups during the study.

The LS mean (±SE) change in AQLQ +12 score from DoR/baseline to week 24 was 0.67 (0.396) in the placebo group and 0.92 (0.407) in the reslizumab group. The reslizumab-placebo treatment difference (95% CI) was 0.25 (-0.056, 0.551) (nominal p-value=0.110).

The proportion of patients who achieved a ≥0.5-unit increase in AQLQ +12 score from baseline was similar in both treatment groups during the study (Summary 15.2.3.2). When assessed from DoR/baseline to week 24, an increase of ≥0.5 units was observed in 34 (42%) patients in the placebo group and 36 (47%) patients in the reslizumab group (nominal p-value=0.459).

SGRQ

The SGRQ scores are expressed as a percentage of overall impairment, where 100 represents the worst possible health status, and 0 represents the best possible health status. Overall SGRQ scores decreased from DoR/baseline in both treatment groups on study, with a slightly larger decrease observed over time in the reslizumab group.

At week 24, the LS mean (±SE) change was -7.6 (6.59) in the placebo group and -10.1 (6.73) in the reslizumab group at week 24. The reslizumab-placebo treatment difference (95% CI) at week 24 was -2.5 (-7.00, 2.01) (nominal p-value=0.276).

The SGRQ domain scores, including domains of Symptoms, Activity, and Impact, were similar to the overall SGRQ scores and are summarized in Summary 15.2.5.1. The proportion of patients who achieved a ≥4.0-unit decrease from baseline to each visit in SGRQ score is summarized in Summary 15.2.5.2.

SNOT-22

Higher SNOT-22 scores represent worse quality of life and lower SNOT-22 scores represent improvement in quality of life. Changes in SNOT-22 score from DoR/baseline to week 24 were similar between treatment groups over time.

At week 24, the LS mean (±SE) change was -0.11 (0.163) in the placebo group (n=19) and -0.10 (0.157) in the reslizumab group (n=21). The reslizumab-placebo treatment difference (95% CI) in SNOT-22 score at week 24 was 0.00 (-0.447, 0.451) (nominal p-value=0.993).

Rapporteur's comment

For PRO the responder analyses are considered very important because these questionnaires are validated for individual scores and not for comparisons on groups level.

These responder analyses of the quality-of-life endpoints, as far as available, did not show relevant differences between the treatment groups.

The Applicant is requested to submit the module summary 15 with all the referred results.


BIOMARKER VARIABLES

Blood eosinophil counts

Blood eosinophil counts decreased in both treatment groups between baseline and week 4 and remained below baseline until the follow-up visit.

The mean (SD) change in blood eosinophil counts from DoR/baseline to week 24 was -0.144 10^9/L (0.5040) in the placebo group and -0.385 10^9/L (0.3570) in the reslizumab group.

Figure 6 Blood Eosinophil Counts (109/L): Mean (±SE) Change from Baseline to Each Visit by Treatment Group (ITT Analysis Set)
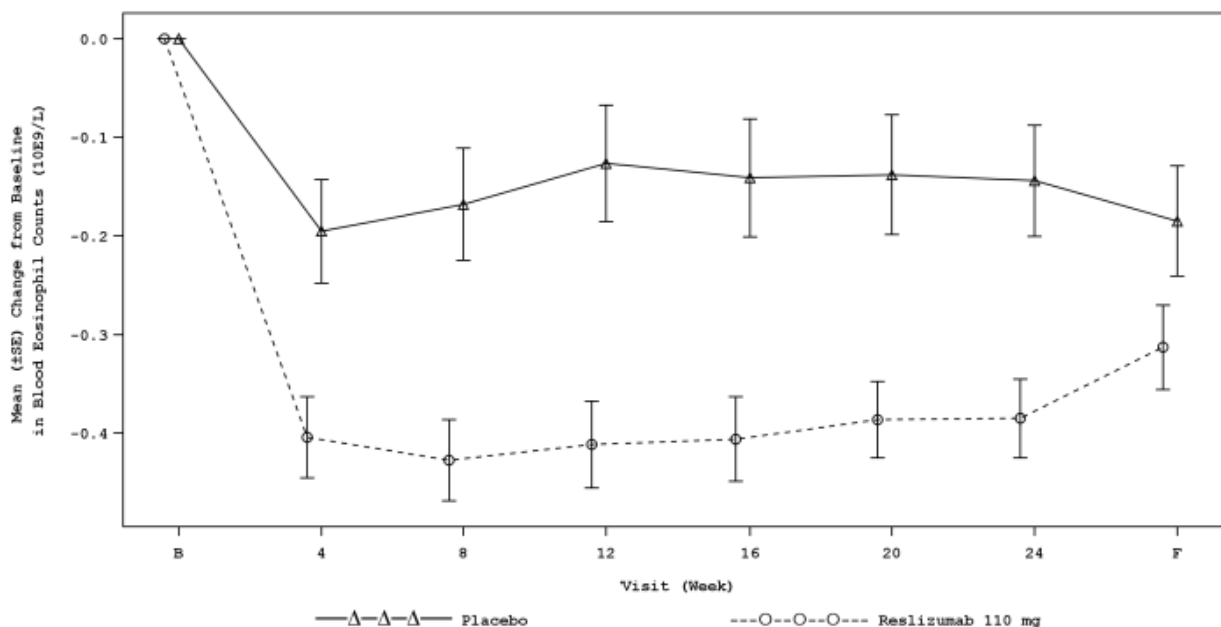
Source: Graph 17.8.
B=baseline; F=follow-up; ITT=intent-to-treat; SE=standard error.

> **Rapporteur's comment**
>
> The difference in mean (SD) change in blood eosinophil counts from DoR/baseline to week 24 was between reslizumab and placebo was -0.241 10^9/L, indicating that sc reslizumab 110 mg q4w effectively reduced peripheral eosinophils as expected, based on the mechanism of action of an anti-IL-5 mAb.
>
> However, this difference is smaller than observed in the two pivotal registration trials, in which the differences were - 0.475 and - 0.476 10^9/L. In these trials reslizumab was administered intravenously.

Immunogenicity

A summary of the ADA assay data collected under this protocol is presented in Table 4.

Table 4 Serum Samples Collected for Anti-Drug Antibody Analysis (ITT Analysis Set)

Sample collection visit	Placebo (N=89)	Reslizumab 110 mg (N=88)
Number of patients with samples collected during the treatment period (visits 13-19) and/or early withdrawal	89	88
Number of patients with samples collected at the follow-up visit (visit 20)	68	64
Number of patients with samples collected at the late follow-up visit (visit 21)	18	21

Source: Report C38072-AS-30027-ADA-BAR-01-Interim.
ITT=intent-to-treat.

Eleven of the 88 (13%) reslizumab-treated patients had treatment-emergent ADA responses (Table 5); a patient was classified as having a treatment-emergent ADA response if a sample tested positive at a post-baseline visit, which was not positive at the baseline visit, or if the titre increased at least 4-fold at a post-baseline visit relative to the positive baseline sample. Eight of the 11 patients had an ADA-positive sample at a single post-dose sampling time. Three patients had ADA-positive samples at 2 sampling times, which were at most 8 weeks apart, followed by ADA-negative samples at subsequent time points.

In 4 patients, the ADA sample collected prior to drug administration tested positive. Two of these patients did not have a post-dose ADA-positive result at any time point available and were therefore considered to be negative for treatment-emergent ADA. The other 2 patients had post-dose ADA-positive samples; however, the titre of the response did not increase at least 4-fold over the pre-dose ADA titre and was also determined to be negative for treatment-emergent ADA.

The anti-reslizumab antibody titers were generally low and ranged from 1.94 to 27.0 in linear scale.

Table 5 Subjects With Treatment-Emergent Positive ADA Results Including Titres (ITT Population)

Subject	Visit (Week)								Subject ADA Response
	13 (Pre-dose)	14 (Week 4)	15 (Week 8)	16 (Week 12)	19 (Week 24)	20 (Week 30)	21 (Week 48)	Unscheduled	
	–	–	–	–	+ (3.68)	–	–	NA	Treatment Emergent
	–	+ (7.22)	+ (7.57)	–	–	–	TBD	NA	Treatment Emergent
	–	+ (4.70)	–	–	–	TBD	TBD	NA	Treatment Emergent
	–	–	–	–	+ (3.88)	TBD	TBD	NA	Treatment Emergent
	–	+ (6.13)	–	–	–	TBD	TBD	NA	Treatment Emergent
	–	+ (4.49)	–	+ (3.42)	–	–	TBD	–	Treatment Emergent
	–	+ (3.57)	+ (3.92)	–	–	–	TBD	NA	Treatment Emergent
	–	–	+ (5.80)	–	–	–	–	–	Treatment Emergent
	–	–	–	+ (8.50)	–	–	TBD	NA	Treatment Emergent
	–	+ (3.42)	–	–	–	TBD	TBD	NA	Treatment Emergent
	–	–	–	–	+ (5.01)	–	TBD	NA	Treatment Emergent

Source: Report C38072-AS-30027-ADA-BAR-01-Interim.
ADA=anti-drug antibody; ITT=intent-to-treat; NA=not applicable; TBD=to be determined as sample was not available at time of reporting.
Note: + sign indicates ADA positive; numbers in parenthesis indicate titer in linear scale; - sign indicates ADA negative.

Impact of Anti-Drug Antibody on Clinical Outcomes

The clinical outcome results for patients with post-baseline positive ADA results (Table 6) were comparable to those for the overall reslizumab group.

None of the ADA-positive samples were identified as having neutralizing activity; therefore, no patients had developed a NAb response.

Table 6 Clinical Outcomes for Patients with Post-Baseline Treatment-Emergent Positive ADA Status (ITT Analysis Set)

Statistic	Positive post-baseline treatment-emergent ADA status N=11 (%)
Number of patients experiencing at least 1 CAE	3 (27%)
Categorized percent OCS reduction (5-level response) at weeks 20 to 24	
90% to 100%	2 (18%)
75% to <90%	1 (9%)
50% to <75%	2 (18%)
>0% to <50%	0
No decrease	6 (55%)
Mean change (SD) from baseline to week 24 in pre-bronchodilator FEV_1	-0.015 (0.152)
Mean change (SD) in blood eosinophil count from baseline to week 24	-0.202 (0.1173)
Mean (ng/mL) (SD) reslizumab concentration	5715.38 ng/mL (2353.93)

Source: Summary 15.2.1.5.2, Summary 15.2.2.6.2, Summary 15.2.10.1.3, Summary 15.3.7.5, and Listing 16.2.6.1.
ADA=anti-drug antibody; CAE=clinical asthma exacerbation; FEV_1=full expiratory volume after 1 second; OCS=oral corticosteroid; SD=standard deviation.

Rapporteur's comment

There was no difference with the overall population and ADA positive patients for CAE and categorized percentage OCS reduction. However, there was a difference for FEV1 and blood eosinophil counts:

- The LS mean (±SE) change in pre-bronchodilator FEV1 from baseline to the Week 24 was 0.222 (0.145) L for the reslizumab group and -0.015 for the ADA + reslizumab treated patients.

- The mean (SD) change in blood eosinophil counts from DoR/baseline to week 24 was -0.385 10^9/L (0.3570) in the reslizumab group and -0.202 (0.1173) for the ADA + reslizumab treated patients.

There were too few ADA positive patients to unequivocally interpret the effect of the development of ADAs on efficacy.

Safety results

Exposure

Exposure to study drug was similar for the placebo and reslizumab treatment groups. The mean duration of exposure was 166.2 days, and 92% of patients received all 6 planned injections.

Adverse Events

Forty-seven (53%) patients in the placebo group and 57 (65%) patients in the reslizumab group reported at least 1 adverse event.

Adverse events considered to be treatment related by the investigator were reported in 3 (3%) patients in the placebo group and 7 (8%) patients in the reslizumab group. Four (4%) patients in the placebo group and 10 (11%) patients in the reslizumab group had serious adverse events during the treatment period; none were considered treatment related. There was 1 death reported in the study (a 61-year-old male in the reslizumab group who had sudden death suspected to be due to pulmonary embolism based on the assessment of the physician who registered the death, which occurred 7 days after the first reslizumab dose); it was not considered by the investigator to be related to study drug. During the study, 1 patient (placebo group) was discontinued from treatment due to a non-serious adverse event (Table 7).

No specific patterns were identified in the subgroups.

Table 7 Overview of Adverse Events (Safety Analysis Set)

Adverse event category	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Patients with at least 1 AE	47 (53)	57 (65)	104 (59)
Patients with at least 1 treatment-related AE	3 (3)	7 (8)	10 (6)
Patients with at least 1 SAE	4 (4)	10 (11)	14 (8)
Patients with at least 1 treatment-related SAE	0	0	0
Patients with at least 1 SAE resulting in death	0	1 (1)	1 (<1)
Patients with at least 1 AE leading to discontinuation	1 (1)	0	1 (<1)
Patients with at least 1 AE related to OCS withdrawal	2 (2)	3 (3)	5 (3)
Patients with at least 1 AE related to OCS use	2 (2)	5 (6)	7 (4)

Source: Summary 15.3.2.1.1.
AE=adverse event; EOT=end of treatment; OCS=oral corticosteroid; SAE=serious adverse event.
Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. Treatment-related adverse events or adverse events related to OCS use included events with missing relationship to study drug or OCS use, respectively.

Overall, in the Safety Analysis Set, the SOCs with adverse events reported most frequently (≥8% overall) were Infections and Infestations (39% overall); Respiratory, Thoracic and Mediastinal Disorders (14% overall); General Disorders and Administration Site Conditions (9% overall); Musculoskeletal and Connective Tissue Disorders (8% overall); and Nervous System Disorders (8% overall).

SOCs in which more adverse events were reported in the reslizumab group compared with the placebo group (at least 5% higher) were Respiratory, Thoracic, and Mediastinal (placebo 11% and reslizumab 17%); General Disorders and Administration Site Conditions (placebo 6% and reslizumab 13%); and Musculoskeletal and Connective Tissue Disorders (placebo 4% and reslizumab 11%).

The most commonly reported adverse events (≥5% in either treatment group) were viral upper respiratory tract infection, asthma, bronchitis, headache, influenza, injection site pain, and rhinitis allergic. A summary of commonly reported adverse events (≥2% in either treatment group) is presented in
Table 8.

Events that occurred more frequently in the reslizumab group compared with the placebo group (at least 5% higher) were viral upper respiratory tract infection (13% and 6%, respectively) and rhinitis allergic (5% and 0%, respectively).

Events that occurred more frequently in the placebo group compared with the reslizumab group included respiratory tract infection viral (4% and 2%, respectively).

Table 8: Adverse Events Occurring in ≥2% in Either Treatment Group (Safety Analysis Set)

MedDRA preferred term	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Patients with at least 1 adverse event	47 (53)	57 (65)	104 (59)
Viral upper respiratory tract infection	5 (6)	11 (13)	16 (9)
Asthma	6 (7)	8 (9)	14 (8)
Bronchitis	4 (4)	6 (7)	10 (6)
Headache	3 (3)	4 (5)	7 (4)
Influenza	2 (2)	4 (5)	6 (3)
Injection site pain	1 (1)	4 (5)	5 (3)
Rhinitis allergic	0	4 (5)	4 (2)
Gastroenteritis	0	3 (3)	3 (2)
Muscle spasms	0	3 (3)	3 (2)
Nausea	0	3 (3)	3 (2)
Rhinitis	0	3 (3)	3 (2)
Acute sinusitis	3 (3)	2 (2)	5 (3)
Asthenia	0	2 (2)	2 (1)
Blood urea increased	0	2 (2)	2 (1)
Bronchitis bacterial	0	2 (2)	2 (1)
Chest injury	0	2 (2)	2 (1)
Conjunctivitis allergic	0	2 (2)	2 (1)
Contusion	1 (1)	2 (2)	3 (2)
Cough	1 (1)	2 (2)	3 (2)
Depression	0	2 (2)	2 (1)
Drug hypersensitivity	0	2 (2)	2 (1)
Dyspnoea	0	2 (2)	2 (1)
Hypercholesterolaemia	0	2 (2)	2 (1)
Myalgia	1 (1)	2 (2)	3 (2)
Pain in extremity	0	2 (2)	2 (1)
Pharyngitis	3 (3)	2 (2)	5 (3)
Respiratory tract infection	1 (1)	2 (2)	3 (2)
Respiratory tract infection viral	4 (4)	2 (2)	6 (3)
Urinary tract infection	2 (2)	2 (2)	4 (2)
Vomiting	0	2 (2)	2 (1)
White blood cell count increased	0	2 (2)	2 (1)

Source: Summary 15.3.2.22.2
EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities.
Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. System organ class and preferred terms (within system organ class) are sorted in descending order of incidence for the reslizumab treatment group. Patients are counted only once in each preferred term and only once in each system organ class. MedDRA version 20.0 was used.

Severity of Adverse Events

Most adverse events for patients in both treatment groups were mild or moderate in severity.

Severe adverse events occurred more frequently in the reslizumab group than in the placebo group; 4 (4%) patients in the placebo group and 11 (13%) patients in the reslizumab group had severe adverse events (Table 9). Severe adverse events occurring in at least 2 patients were asthma (2% of patients each in both treatment groups) and injection site pain (2% of patients in the reslizumab group). All other occurrences of severe adverse events occurred in 1 (1%) patient.

Table 9: Summary of Severe Adverse Events by Preferred Term (Safety Analysis Set)

MedDRA preferred term	Number (%) of patients	
	Placebo (N=89)	Reslizumab 110 mg (N=88)
Number of patients with at least 1 severe adverse event	4 (4)	11 (13)
Asthma	2 (2)	2 (2)
Injection site pain	0	2 (2)
Acute sinusitis	0	1 (1)
Bronchitis	0	1 (1)
Cellulitis	0	1 (1)
Drug hypersensitivity	0	1 (1)
Headache	0	1 (1)
Inguinal hernia	0	1 (1)
Muscle spasms	0	1 (1)
Pain in extremity	0	1 (1)
Pneumonia	0	1 (1)
Syncope	0	1 (1)
Sudden death	0	1 (1)
Haematoma	1 (1)	0
Pneumonia bacterial	1 (1)	0

Source: Summary 15.3.2.2.2 and Listing 16.2.7.1.1.
EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities.
Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. System organ class and preferred terms (within system organ class) were sorted in descending order of incidence for the reslizumab treatment group. Patients were counted only once in each preferred term and only once in each system organ class. MedDRA version 20.0 was used. If a patient reported an adverse event more than once, the greatest severity was presented.

Attribution of Adverse Events

Adverse events considered to be treatment related by the investigator were reported more frequently in the reslizumab group (7 [8%] patients) than in the placebo group (3 [3%] patients), and most of treatment-related adverse events in the reslizumab group were injection site reactions (Table 10). Treatment-related injection site pain was reported by 1 (1%) patient in the placebo group and 4 (5%) patients in the reslizumab group. Treatment-related myalgia was reported by 1 (1%) patient in both

the placebo and reslizumab groups. All other treatment-related adverse events were reported by 1 (1%) patient.

Table 10: **Treatment-Related Adverse Events by Preferred Term (Safety Analysis Set)**

MedDRA preferred term	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Number of patients with at least 1 treatment-related adverse event	3 (3)	7 (8)	10 (6)
Injection site pain	1 (1)	4 (5)	5 (3)
Myalgia	1 (1)	1 (1)	2 (1)
Asthenia	0	1 (1)	1 (<1)
Alopecia	1 (1)	0	1 (<1)
Fatigue	0	1 (1)	1 (<1)
Headache	0	1 (1)	1 (<1)
Injection site swelling	0	1 (1)	1 (<1)
Pruritus generalised	1 (1)	0	1 (<1)

Source: Summary 15.3.2.3.1.
EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities.
Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. System organ class and preferred terms (within system organ class) were sorted in descending order of incidence for the reslizumab treatment group. Patients were counted only once in each preferred term and only once in each system organ class. MedDRA version 20.0 was used. Treatment-related adverse events included events with missing relationship to study drug.

> **Rapporteur's comment**
>
> There was only a relevant difference between reslizumab ad placebo for Injection site pain.
>
> This difference may be due to the administration method as such difference was not observe with I.V. administration.

Adverse Events Occurring Within 24 Hours of Study Drug Administration

The overall proportion of adverse events occurring within 24 hours after study injection was the same for both treatment groups (8 [9%] patients in each group). Injection site pain was the most common adverse event reported within 24 hours after study drug injection (1 [1%] patient in the placebo group and 4 [5%] patients in the reslizumab group). Most adverse events that occurred within 24 hours after study drug injections were mild or moderate in severity. Two (2%) patients in the reslizumab group had severe adverse events that occurred with 24 hours after study drug injections, including injection site pain (2 [2%] patients) and pain in extremity (1 [1%] patient).

Adverse Events by ADA Status

All eleven reslizumab-treated patients with treatment-emergent ADA responses reported at least 1 adverse event similar to the adverse events reported by patients with ADA-negative responses, the most frequently reported SOC for patients with ADA-positive responses was Infections and Infestations.

In general, the percentages of patients with positive or negative ADA treatment-emergent responses who experienced an adverse event were similar for most SOCs and PTs. Except for Headache and Allergic rhinitis, which were reported by 2 patients each, all adverse events were reported by single positive ADA patients.

Under the Immune System Disorders SOC, 1 event of drug hypersensitivity and 1 event of food allergy were reported, neither of which were considered related to study drug or led to discontinuation of treatment.

Rapporteur's comment

Overall, the pattern was similar between patients with ADA and patients without ADA. However, the number of patients was limited in this trial.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There was 1 death during the study in the reslizumab group.

A total of 14 (8%) patients experienced serious adverse events during the treatment period of the study (4 [4%] patients in the placebo group and 10 [11%] patients in the reslizumab group).

Adverse events leading to discontinuation from treatment were reported by 1 patient in the placebo group.

Adverse events of special interest, administration site reactions, anaphylaxis and hypersensitivity, malignancies, opportunistic infections and helminth infections, muscle disorders, and increased CPK levels are discussed below.

Deaths

There was 1 death during the study in the reslizumab group. This event was not considered related to the study drug.

A 61-year-old white male in the reslizumab group died 7 days after the first reslizumab sc injection. The patient was in his usual health until approximately 5 minutes before his death. The death was reported as sudden death not otherwise specified, possibly due to pulmonary embolism based on the diagnosis of the physician who registered the death, and was considered by the investigator as unrelated to study drug. An autopsy was not performed.

No other adverse events were reported for this patient during the study.

Other Serious Adverse Events

Fourteen (8%) patients had 1 or more treatment-emergent serious adverse events during the treatment period in this study (4 [4%] patients in the placebo group and 10 [11%] patients in the reslizumab group [Table 11]). Serious adverse events were most frequently reported in the SOCs of Respiratory, Thoracic, and Mediastinal Disorders (2 [2%] patients in the placebo group and 3 [3%] patients in the reslizumab group) and Infections and Infestations (1 [1%] patient in the placebo group and 3 [3%] patients in the reslizumab group). Serious adverse events reported in other SOCs occurred in 1 (1%) patient each. None of the serious adverse events reported during the study were assessed as related to the study drug by the investigator, including the SAE of drug hypersensitivity, which was secondary to an allergic reaction to co-trimoxazole.

Table 11: Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System organ class MedDRA preferred term	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Number of patients with at least 1 serious adverse event	4 (4)	10 (11)	14 (8)
Respiratory, Thoracic and Mediastinal Disorders	2 (2)	3 (3)	5 (3)
Asthma	2 (2)	3 (3)	5 (3)
Infections and Infestations	1 (1)	3 (3)	4 (2)
Cellulitis	0	1 (1)	1 (<1)
Influenza	0	1 (1)	1 (<1)
Pneumonia	0	1 (1)	1 (<1)
Pneumonia bacterial	1 (1)	0	1 (<1)
Gastrointestinal Disorders	0	1(1)	1 (<1)
Inguinal hernia	0	1 (1)	1 (<1)
General Disorders and Administration Site Conditions	0	1 (1)	1 (<1)
Sudden death	0	1 (1)	1 (<1)
Immune System Disorders	0	1 (1)	1 (<1)
Drug hypersensitivity	0	1 (1)	1 (<1)
Nervous System Disorders	0	1 (1)	1 (<1)
Syncope	0	1 (1)	1 (<1)
Injury, Poisoning and Procedural Complications	1 (1)	0	1 (<1)
Contusion	1 (1)	0	1 (<1)
Facial bones fracture	1 (1)	0	1 (<1)
Fibula fracture	1 (1)	0	1 (<1)
Foot fracture	1 (1)	0	1 (<1)
Head injury	1 (1)	0	1 (<1)
Rib fracture	1 (1)	0	1 (<1)

Source: Summary 15.3.2.4 and Listing 16.2.7.3.

EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities.

Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. System organ class and preferred terms (within system organ class) were sorted in descending order of incidence for the reslizumab treatment group. Patients were counted only once in each preferred term and only once in each system organ class. MedDRA version 20.0 was used.

Rapporteur's comment

Overall, the pattern was similar between patients treated with reslizumab and patients treated with placebo, although in total more SAEs occurred in patients treated with reslizumab.

Overall, this difference has no consequence.

Discontinuation Due to Adverse Events

One patient in the placebo group discontinued from treatment due to an adverse event of generalized pruritus.

Protocol- and SAP-Defined Adverse Events of Special Interest

Six cases of hypersensitivity were reported during the study: 2 events of drug hypersensitivity (to concomitant medications), both in the reslizumab group; 2 events of food/supplement allergy, 1 event in each treatment group; and 1 event each of allergy to arthropod bite (reslizumab group) and pruritus generalized (placebo group). No events of hypersensitivity were considered by the investigator to be related to study drug.

> A patient in the reslizumab group had a serious event of drug hypersensitivity 22 days after the third sc injection and on the day of starting co-trimoxazole for a respiratory infection. The investigator considered the event of drug hypersensitivity to be a serious allergic reaction to concomitant use of co-trimoxazole and not related to study drug. The event was considered severe and resolved 1 day after onset.

> A patient in the reslizumab group had a non-serious event of drug hypersensitivity 8 days after the sixth sc injection and on the same day as the first dose of penicillin. The investigator considered the event of drug hypersensitivity to be an allergic reaction to concomitant use of penicillin and not related to study drug. The event was considered moderate in severity and resolved the same day as onset.

> A patient in the reslizumab group had a non-serious adverse event of food allergy (allergic reaction due to wheat beer consumption) 3 days after the second sc injection and the same day that the patient consumed the wheat beer. The investigator considered the event of allergic reaction to be due to a pre-existing known food allergy and not related to study drug. The event was considered mild in severity and resolved the same day as onset.

> A patient in the reslizumab group had a non-serious adverse event of allergy to arthropod bite 32 days after the fourth sc injection. The investigator considered the event of allergy to arthropod bite to be not related to study drug. The event was considered mild in severity and resolved 14 days after onset.

> A patient in the placebo group had a non-serious adverse event of systemic urticaria (possible allergic reaction to concomitant use of an effervescent tablet with vitamin C plus zinc) 23 days after the fifth sc injection and on the same day that the effervescent tablet was consumed). The investigator considered the event of systemic urticaria as not related to study drug. The event was considered moderate in severity and resolved the next day.

> A patient in the placebo group had a non-serious adverse event of pruritus generalized on the same day as the fourth sc injection. The investigator considered the event of pruritus generalized to be related to study drug. The event was considered moderate in severity, and administration of study drug was permanently discontinued due to the event. The event resolved 2 days after onset.

Rapporteur's comment

It is stated that no events of hypersensitivity were considered by the investigator to be related to study drug. However, it seems that the case of the last patient above described was considered the event being related to study drug, because the study drug as permanently discontinued.

Therefore, it is considered that the event was drug related. After deblinding it turned out The study drug was placebo.

Adverse events with terms falling under the anaphylactic reaction SMQ (broad criteria) occurred in 12 (13%) patients in the placebo group and 12 (14%) patients in the reslizumab group (Summary 15.3.2.14.1). The most common reported terms were asthma (6 [7%] patients in the placebo group and 8 [9%] patients in the reslizumab group), cough (1 [1%] patient in the placebo group and 2 [2%] patients in the reslizumab group) and dyspnoea (no patients in the placebo group and 2 [2%] patients in the reslizumab group). No events fell under the PTs under anaphylactic reaction SMQ-narrow (Summary 15.3.2.14.2). All adverse event terms in the anaphylactic SMQ were considered by the investigator as unrelated to study drug.

Rapporteur's comment

Hypersensitivity ad anaphylactic reaction are known adverse events of reslizumab.

Adverse events with terms falling under the anaphylactic reaction SMQ (broad criteria) overlap with symptoms of asthma exacerbation. Therefore, the interpretation of anaphylactic reaction is hampered. However, anaphylactic reaction SMQ-narrow is considered more informative. According to the Applicant no events felt under anaphylactic reaction SMQ-narrow. However, the source is lacking in the dossier. The Applicant is request to provide module summary 15.

Malignancies

No malignancies or events of opportunistic infections or helminth infections were reported during this study.

Muscle Disorders

Muscle disorders included muscle disorder HLGT and blood creatine phosphokinase increased PTs and occurred in 5 (6%) patients in the placebo group and 6 (7%) patients in the reslizumab group (Table 12).

There were 3 cases of myalgia in the study (1 subject in the placebo group and 2 subjects in the reslizumab group), 2 of which was considered to be related to study drug (1 [1%] patient in each treatment group). All other muscle disorder events were considered by the investigator as unrelated to study drug.

> A patient in the reslizumab group had a non-serious adverse event of myalgia 11 days after the first sc injection. The investigator considered the event of myalgia as related to OCS withdrawal and use, and not related to study drug. The event was considered moderate in severity and resolved 3 days after onset.

> Another patient in the reslizumab group had a non-serious adverse event of myalgia 47 days after the sixth sc injection. The investigator considered the event of myalgia as not related to study drug and not related to OCS use or withdrawal. The event was considered moderate in severity and resolved 22 days after onset.

> Another patient in the placebo group had a non-serious adverse event of myalgia after an sc injection (date of the event onset not specified). The investigator considered the event of

myalgia as possibly related to study drug and not related to OCS use or withdrawal. The event was considered moderate in severity and ongoing when the patient completed the study.

Table 12 Muscle Disorders (Safety Analysis Set)

MedDRA high-level term MedDRA preferred term	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Number of patients with at least 1 adverse event (under muscle disorder HLGT and/or blood CPK increased PT)	5 (6)	6 (7)	11 (6)
Muscle-related signs and symptoms NEC	0	3 (3)	3 (2)
Muscle spasms	0	3 (3)	3 (2)
Muscle pains	1 (1)	2 (2)	3 (2)
Myalgia	1 (1)	2 (2)	3 (2)
Skeletal and cardiac muscle analyses	4 (4)	1 (1)	5 (3)
Blood creatine phosphokinase increased	4 (4)	1 (1)	5 (3)

Source: Summary 15.3.2.17.
CPK=creatine phosphokinase; EOT=end of treatment; HLGT=high-level group term; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified.
Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. High-level term and preferred terms (within high-level term) were sorted in descending order of incidence for the reslizumab treatment group. Patients were counted only once in each preferred term and only once in each high-level term. MedDRA version 20.0 was used. Muscle disorders included Muscle Disorder HLGT and Blood Creatine Phosphokinase Increased preferred terms.

Rapporteur's comment

Muscle disorders, blood creatine phosphokinase increased and myalgia are known adverse events of reslizumab.

Muscle disorders and myalgia are also symptoms caused by OCS withdrawal. Therefore, the interpretation of these symptoms are hampered by this overlap.

Given the low number of events and the quite similar frequency, changes in the existing SmPC are not considered necessary.

Administration Site Reactions

Administration site reactions were reported in 4% of the safety analysis set (2 [2%] patients in the placebo group and 5 [6%] patients in the reslizumab group) and included events of injection site pain, bruising, and swelling. A greater percentage of patients in the reslizumab group (5%) reported events of injection site pain (compared with 1% in the placebo group). The majority of administration site reactions were mild or moderate in severity. All events of injection site pain and swelling were considered by the investigator as related to the study drug. Injection site bruising was considered by the investigator as unrelated to the study drug.

The adverse event profile of patients with positive or negative ADA treatment-emergent responses was similar. Two patients with positive post-baseline ADA values reported adverse events under the Immune System Disorders SOC. One event of drug hypersensitivity and 1 event of food allergy were reported, neither of which was considered related to study drug or led to discontinuation of treatment.

Clinical Laboratory Assessments

Three patients in the placebo group and 1 patient in the reslizumab group had post-baseline PCS CPK values that were reported as adverse events. All CPK elevations were transient and normalized by the end of the study, except for 1 case for 1 patient in the placebo group on day 171 (CPK value of 801 U/L, which was ≥3.1 but <10× ULN and an increase of >0 from baseline) (Listing 16.2.8.2 and Listing 16.2.8.6). None of the PCS CPK values were assessed as related to study drug or lead to discontinuation.

CPK values ≥3.1×ULN were considered adverse events. Four patients in the placebo group (5 events) and 1 patient in the reslizumab group had adverse events of blood CPK increased, including the PCS CPK values described above, all of which were assessed as not related to study drug and considered resolved.

> ***Rapporteur's comment***
>
> Creatine phosphokinase increased is a known adverse event of reslizumab. Given the low number of events and the fact that are more events were observed in the placebo group, changes in the existing SmPC are not considered necessary.

Vital Signs, Electrocardiogram, and Physical Examination Findings

There were no clinically meaningful trends in vital signs measurements, electrocardiogram results, or physical examination findings.

Pharmacokinetics

Pharmacokinetic data of reslizumab was generated and is included in the population pharmacokinetic analysis that will be reported separately (Report CP-17-15).

> ***Rapporteur's comment***
>
> Report CP-17-15 was not submitted yet, so conclusions can be made.

2.3.3. Discussion on clinical aspects

Therapeutic Context

Reslizumab is a humanized anti-human interleukin-5 monoclonal antibody (anti-IL-5 mAb). Reslizumab works by binding to IL-5 and preventing its binding to the IL-5 receptor, thereby reducing circulating and tissue eosinophils.

The iv reslizumab 3-mg/kg dose was shown to be effective at reducing CAE rate and improving lung function and asthma control in 4 placebo-controlled trials of the Phase 3 BREATH program. The 110-mg sc dose proposed for the reslizumab sc program was selected based on exposure projected to be equivalent to approximately 1 mg/kg iv in an average-sized person and assuming the bioavailability observed in Study C38072/1107 (67%).

Modelling and simulation prior to the start of the Phase 3 sc program showed that predicted steady-state trough serum concentrations of reslizumab following administration of the to-be-studied 110 mg sc dosing regimen, based on the assumed bioavailability of 67%, were expected to fall within the range of exposures that produced meaningful effects on both blood eosinophils and FEV1 in patients with eosinophilic asthma.

Design and conduct of the study

The current study C38072-AS-30027 was a Phase 3, 24-week double-blind, placebo-controlled, parallel-group efficacy and safety study in patients with OCS-dependent asthma and elevated blood eosinophils. This study sought to determinate the ability to produce a corticosteroid-sparing of sc reslizumab 110 mg administered every 4 weeks

The study consisted of a screening period of up to 2 weeks, followed by an optimization period of up to 10 weeks, a run-in period of at least 2 weeks, a 24-week double-blind treatment period, an 8-week follow-up period, and a late 16-week follow-up period to collect drug wash-out samples for immunogenicity assessments. During the optimization period, the patient's minimal effective OCS requirement was determined. The During the optimization period, the patient's minimal effective OCS requirement was determined.

The primary efficacy endpoint was the 5-level categorized percent reduction in OCS dose during weeks 20 to 24, as compared with the optimized dose at baseline. Percent reduction was categorized as follows: 90% to 100%; 75% to <90%; 50% to <75%; >0% to <50%; and no decrease in OCS, loss of baseline asthma control during weeks 20 through 24, or discontinuation of study drug.

The current study was designed to evaluate the OCS-sparing effect of sc reslizumab in a population with more severe asthma at baseline compared to the patients included in the registration trials in which low dose OCS ($\leq$ 10 mg) was allowed, but not required.

A sample size of 76 subjects per group was calculated to provide 90% power to detect a significant effect (overall odds ratio 0f 2.63) of reslizumab over placebo on the probability for a higher categorical reduction of OCS dose, based on the publication for mepolizumab (Bel et al 2014).

Efficacy data

The results of the primary efficacy analysis were not statistically significant, and therefore the primary endpoint of this study was not met. The reslizumab versus placebo odds ratio (95% CI) for reduction of OCS use at weeks 20 to 24 was 1.23 (0.702, 2.157; p-value=0.468).
The results of the sensitivity analyses were similar to those for the primary efficacy endpoint.
Results of subgroup analyses for the primary endpoint were similar to the results of the primary efficacy analysis.

Secondary efficacy endpoints were not interpreted inferentially because the primary endpoint was not met. The percentage of patients who experienced at least 1 CAE (48% and 43% in the placebo and reslizumab groups, respectively) was similar between treatment groups. The mean (SD) frequency of CAEs during the treatment period was lower for the reslizumab group (0.8 [0.98] for the placebo group and 0.6 [0.77] for the reslizumab group) but was not statistically significant.

Results for secondary efficacy endpoints related to change in OCS use were similar to the primary efficacy analysis.

The exploratory and other clinical and quality-of-life endpoints including change in FEV1 did not show neither a clinically relevant nor a statistically significant difference between the placebo and reslizumab groups.

Decreases from baseline in blood eosinophil counts were larger in the reslizumab group than in the placebo group, but were lower compared to the results of the pivotal registration trials with I.V. administration.

None of the ADA-positive samples were identified as having neutralizing activity; therefore, no patients had developed a Nab response.

No data for adolescents became available as the only one adolescents included was randomised to placebo group.

Safety data

The majority of patients in both treatment groups received study treatment for ≥ 5 months and received ≥ 6 sc injections.

Overall, 59% of patients in the safety analysis set had at least 1 adverse event during the study; adverse events with a frequency ≥5% in either treatment group included viral upper respiratory tract infection, asthma, bronchitis, headache, influenza, injection site pain, and rhinitis allergic. The frequency of these events was higher in the reslizumab group.

Treatment-related adverse events occurred more frequently in the reslizumab group (8%) compared with the placebo group (3%). The most frequently reported treatment-related adverse event was injection site pain.

Serious adverse events were reported in 11% in the reslizumab group compared to 4% in the placebo group, with the majority in single patients and with events that are expected for adult patients with eosinophilic asthma.

Treatment-emergent ADA responses were observed in 11 of the 88 (13%) reslizumab-treated patients, all transient. The anti-reslizumab antibody titres were generally low. Two patients with positive post-baseline ADA values reported adverse events under the Immune System Disorders SOC. One event of drug hypersensitivity and 1 event of food allergy were reported, neither of which was considered related to study drug or led to discontinuation of treatment.

Six cases of hypersensitivity were reported during the study: 2 in the placebo group and 4 in the reslizumab group. No hypersensitivity events were considered related to reslizumab. One patient in the placebo group with an event of generalized pruritus discontinued treatment permanently. Events under the anaphylactic reaction and hypersensitivity SMQs (narrow and broad) were reported in a similar incidence in both treatment groups, with the most common events related to underlying asthma disease (eg, asthma, cough) and pre-existing allergic conditions (eg, allergic rhinitis).

No malignancies or events of opportunistic infections or helminth infections were reported.

Muscle disorders, including blood CPK increased, were reported at a similar frequency in both treatment groups (6% overall).

Administration site reactions were reported in both treatment groups with a greater percentage of patients in the reslizumab group, mainly due to more reports of injection site pain.

One death occurred during the study (event of sudden death, possibly pulmonary embolism), which was considered by the investigator and sponsor as unrelated to reslizumab.

3. Rapporteur's overall conclusion and recommendation

The primary efficacy endpoint of reduction in OCS dose was not met: there was no statistically significant improvement in efficacy measures. However, a modest reduction in blood eosinophil levels was observed in the reslizumab group.

The reasons for not achieving the objective of this study may be the lower exposure compare to the I.V. administration. The model-predicted effects of body weight and age of population pharmacokinetic analysis are suggestive for a considerably higher absolute bioavailability for lighter and younger patients, which may be relevant for the adolescents and children. However, the expected response may have also been too high (overall odds ration 2.63), but in the pulmonary function test endpoints and quality of life endpoint did not show a relevant difference, suggesting that the exposure may have been too low.

Subcutaneous reslizumab 110 mg every 4 weeks s.c. was well tolerated in patients with OCS-dependent asthma and elevated blood eosinophils. The adverse events reported during the study are consistent with the expected profile for a population of adult patients with OCS-dependent asthma and elevated blood eosinophils.

The submitted clinical study data with reslizumab sc did not influence the benefit risk evaluation of the registered reslizumab 10 mg/ml IV formulation in adults. Since the sc formulation is not being developed anymore and sc administration is not included in the current registration dossier for Cinqaero, no update of the SmPC is considered necessary for Study C38072-AS-30027 submitted under Article 46 of Regulation (EC) No1901/2006, as amended. No data for adolescents became available as the only one adolescent included was randomised to placebo group.

To be noted: in paediatric investigation plan EMEA-0012-02-PIP02-13, the development of a subcutaneous formulation in paediatric patients aged 6-<12 was specifically requested, since the reslizumab mechanism of action was expected to be relevant in children with EA ages 6 through 11 years, and these patients would be better served by a sc formulation administered via a thin needle, rather than by an iv infusion, due to the inconvenience and pain associated with iv infusions. Stopping development of the sc formulation in children aged 6-11 has, therefore, consequences for the existing agreed paediatric investigation plan, and should be discussed within the PDCO.

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1) The Applicant refers for responder analyses and safety findings for the PRO to Summary 15. This is not found in the documentation. The Applicant is requested to submit the module summary 15 with all the referred results.

2) The Applicant stated that the pharmacokinetic data of reslizumab was generated and is included in the population pharmacokinetic analysis that will be reported separately (Report CP-17-15). However, Report CP-17-15 was not submitted. The Applicant is requested to submit Report CP-17-15 with their responses.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

QUESTION 1:

Based on the data submitted, the MAH should provide module Summary 15 with all the referred results and Report CP-17-15 as part of this procedure. (See section "Additional clarification requested.")

Teva's Response:

The Clinical Study Report (CSR) submitted was incomplete, omitting Summary 15. A complete C38072-AS-30027 CSR, which includes all the Section 15 summaries and graphs referred to in the CSR body, is now submitted with this response.

In addition, it was noted that Table 26 (and its source, Summary 15.3.2.22.2) included adverse events with an incidence of ≥2% in the reslizumab treatment group rather than adverse events with an incidence of ≥2% in either treatment group, as indicated in the table title. The table content has been corrected in the CSR erratum provided with this response.

Adverse events:

A greater percentage of patients in the reslizumab group (65%) reported adverse events in comparison to patients in the placebo group (53%).

Overall, in the Safety Analysis Set, the system organ classes (SOCs) with adverse events reported most frequently (≥8% overall) were Infections and Infestations (39% overall); Respiratory, Thoracic and Mediastinal Disorders (14% overall); General Disorders and Administration Site Conditions (9% overall); Musculoskeletal and Connective Tissue Disorders (8% overall); and Nervous System Disorders (8% overall) (Summary 15.3.2.2.1).

SOCs in which more adverse events were reported in the reslizumab group compared with the placebo group (at least 5% higher) were Respiratory, Thoracic, and Mediastinal (placebo 11% and reslizumab 17%); General Disorders and Administration Site Conditions (placebo 6% and reslizumab 13%); and Musculoskeletal and Connective Tissue Disorders (placebo 4% and reslizumab 11%).

The most commonly reported adverse events (≥5% in either treatment group) were viral upper respiratory tract infection, asthma, bronchitis, hypertension, upper respiratory tract infection, headache, influenza, injection site pain, and rhinitis allergic. A summary of commonly reported adverse events (≥2% in either treatment group) is presented in Table 26.

Events that occurred more frequently in the reslizumab group compared with the placebo group (at least 5% higher) were viral upper respiratory tract infection (13% and 6%, respectively) and rhinitis allergic (5% and 0%, respectively).

Events that occurred more frequently in the placebo group compared with the reslizumab group (at least 5% higher) included hypertension (6% and 1%, respectively) and upper respiratory tract infection (6% and 1%, respectively).

Table 26: Adverse Events Occurring in ≥2% in Either Treatment Group (Safety Analysis Set)

MedDRA preferred term	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Patients with at least 1 adverse event	47 (53)	57 (65)	104 (59)
Viral upper respiratory tract infection	5 (6)	11 (13)	16 (9)
Asthma	6 (7)	8 (9)	14 (8)
Bronchitis	4 (4)	6 (7)	10 (6)
Headache	3 (3)	4 (5)	7 (4)
Influenza	2 (2)	4 (5)	6 (3)
Injection site pain	1 (1)	4 (5)	5 (3)
Rhinitis allergic	0	4 (5)	4 (2)
Gastroenteritis	0	3 (3)	3 (2)
Muscle spasms	0	3 (3)	3 (2)
Nausea	0	3 (3)	3 (2)
Rhinitis	0	3 (3)	3 (2)
Acute sinusitis	3 (3)	2 (2)	5 (3)
Asthenia	0	2 (2)	2 (1)
Blood urea increased	0	2 (2)	2 (1)
Bronchitis bacterial	0	2 (2)	2 (1)
Chest injury	0	2 (2)	2 (1)
Conjunctivitis allergic	0	2 (2)	2 (1)
Contusion	1 (1)	2 (2)	3 (2)
Cough	1 (1)	2 (2)	3 (2)
Depression	0	2 (2)	2 (1)
Drug hypersensitivity	0	2 (2)	2 (1)
Dyspnoea	0	2 (2)	2 (1)
Hypercholesterolaemia	0	2 (2)	2 (1)
Myalgia	1 (1)	2 (2)	3 (2)
Pain in extremity	0	2 (2)	2 (1)
Pharyngitis	3 (3)	2 (2)	5 (3)
Respiratory tract infection	1 (1)	2 (2)	3 (2)
Respiratory tract infection viral	4 (4)	2 (2)	6 (3)
Urinary tract infection	2 (2)	2 (2)	4 (2)
Vomiting	0	2 (2)	2 (1)
White blood cell count increased	0	2 (2)	2 (1)
Arthralgia	2 (2)	1 (1)	3 (2)
Blood creatine phosphokinase increased	4 (4)	1 (1)	5 (3)
Chronic sinusitis	2 (2)	1 (1)	3 (2)

Conjunctivitis	2 (2)	1 (1)	3 (2)
Herpes zoster	2 (2)	1 (1)	3 (2)
Hypertension	5 (6)	1 (1)	6 (3)
Sinusitis noninfective	2 (2)	1 (1)	3 (2)
Upper respiratory tract infection	5 (6)	1 (1)	6 (3)
Anxiety	2 (2)	0	2 (1)
Cholelithiasis	2 (2)	0	2 (1)
Diabetes mellitus	3 (3)	0	3 (2)
Diarrhoea	2 (2)	0	2 (1)
Dizziness	3 (3)	0	3 (2)
Dysgeusia	3 (3)	0	3 (2)
Insomnia	2 (2)	0	2 (1)
Sinusitis	2 (2)	0	2 (1)

Source: Article 46 Response Table 1.

EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities.

Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. System organ class and preferred terms (within system organ class) are sorted in descending order of incidence for the reslizumab treatment group. Patients are counted only once in each preferred term and only once in each system organ class. MedDRA version 20.0 was used.

Assessment of the response

The MAH submitted the requested Summary 15.

The affected items concerned the PRO and adverse events sections; relevant sections will be discussed hereunder.

PRO

The submitted summary data confirmed the initially data provided. No changes are made in the assessment.

Although some small differences were observed between subgroups, no conclusions can be drawn given the primary analysis was not met and the small number of patients in some subgroups.

Incidence of Adverse Events

The MAH also submitted corrected results of the adverse events. Following events are added compared to the previous table:

MedDRA preferred term	Number (%) of patients		
	Placebo (N=89)	Reslizumab 110 mg (N=88)	Total (N=177)
Arthralgia	2 (2)	1 (1)	3 (2)
Blood creatine phosphokinase increased	4 (4)	1 (1)	5 (3)
Chronic sinusitis	2 (2)	1 (1)	3 (2)

Conjunctivitis	2 (2)	1 (1)	3 (2)
Herpes zoster	2 (2)	1 (1)	3 (2)
Hypertension	5 (6)	1 (1)	6 (3)
Sinusitis noninfective	2 (2)	1 (1)	3 (2)
Upper respiratory tract infection	5 (6)	1 (1)	6 (3)
Anxiety	2 (2)	0	2 (1)
Cholelithiasis	2 (2)	0	2 (1)
Diabetes mellitus	3 (3)	0	3 (2)
Diarrhoea	2 (2)	0	2 (1)
Dizziness	3 (3)	0	3 (2)
Dysgeusia	3 (3)	0	3 (2)
Insomnia	2 (2)	0	2 (1)
Sinusitis	2 (2)	0	2 (1)

Source: Article 46 Response Table 1.
EOT=end of treatment; MedDRA=Medical Dictionary for Regulatory Activities.
Notes: Data were included between the first dose of study drug and the EOT visit for completed patients, and between the first dose of study drug and 4 weeks after the last dose of study drug for patients who discontinued treatment early. System organ class and preferred terms (within system organ class) are sorted in descending order of incidence for the reslizumab treatment group. Patients are counted only once in each preferred term and only once in each system organ class. MedDRA version 20.0 was used.

As adverse events are added with a higher frequency in placebo group than in reslizumab group, the overall conclusion is not affected by this addition.

Issue resolved.

QUESTION 2:

The Applicant stated that the pharmacokinetic data of reslizumab was generated and is included in the population pharmacokinetic analysis that will be reported separately (Report CP-17-15). However, Report CP-17-15 was not submitted. The Applicant is requested to submit Report CP-17-15 with their responses.

Teva's Response:

The population pharmacokinetics analysis report updated with data from the reslizumab treatment groups of the studies of the fixed-dose reslizumab sc program (ie, Studies C38072/1107, C38072-PK-10071, C38072-AS-10069, C38072-AS-30025, and C38072-AS-30027) has now been finalised (Report CP-17-15; report date, 31 July 2018) and is provided as requested.

Synopsis of Report CP-17-15:

Report Title:
Population Pharmacokinetic Modeling in Support of the Reslizumab Subcutaneous Administration Development Program in Pediatric, Adolescent, and Adult Patients

Objectives:
The goal of this analysis was to establish a population pharmacokinetic (PK) model to describe the PK of reslizumab, including an assessment of the effects of baseline demographic characteristics (including organ function), concomitant medications, and the presence of anti-drug antibodies (ADAs) on the PK of reslizumab following intravenous (iv) or subcutaneous (sc) administration.

The objectives of the population PK analyses described herein were to:
☐ Update and refine the previously developed population PK model for reslizumab using prior knowledge of reslizumab iv PK and data from Studies C38072-AS-10069, C38072-PK-10071, C38072-AS-30025, and C38072-AS-30027 following sc administration.
☐ Characterize the effect of covariates on the PK variability and evaluate the model performance using visual predictive check (VPC) methodology.
☐ Generate individual reslizumab exposure measures for use in pharmacokinetic/pharmacodynamic (PK/PD) analyses.

Data Description:
Data from 6 Phase 1 studies (I96-350, P01942, C38072/1102, C38072/1107, C38072-AS-10069, C38072-PK-10071), 2 Phase 2 studies (P00290 and Res-5-0010), and 4 Phase 3 studies (C38072/3081, C38072/3082, C38072-AS-30025, and C38072-AS-30027) were pooled for the population PK analysis of reslizumab. Participants in Phase 1 Studies C38072/1102 and C38072/1107 were healthy non-Japanese and Japanese men and women. Participants in Phase 1 Study C38072-PK-10071 were healthy adult men and women. Participants in Phase 1 Study C38072-AS-10069 were children (6 to <12 years of age) with asthma. Participants in Phase 1 Study I96-350 were adult men and women with severe asthma. Participants in Phase 1 Study P01942 were adult men and women with nasal polyps. Participants in Phase 2 Studies P00290 and Res-5-0010 were adult men and women with moderate to severe asthma that was not well controlled. Participants in Phase 3 Studies C38072/3081 and C38072/3082 were men and women, aged 12 to 75 years with eosinophilic asthma (blood eosinophil count ≥400/μL). Participants in Phase 3 Study C38072-AS-30025 were men and women >12 years of age with uncontrolled asthma (blood eosinophil count ≥300/μL). Participants in Phase 3 Study C38072-AS-30027 were men and women >12 years of age with corticosteroid dependent asthma (blood eosinophil count ≥300/μL).

Dose Administration:

A single dose of iv reslizumab was given in Phase 1 Study I96-350 (0.03 mg/kg iv bolus, 0.1 mg/kg iv bolus, 0.3 mg/kg iv infusion, or 1 mg/kg iv infusion), Phase 1 Study P01942 (1 mg/kg or 3 mg/kg iv infusion), and in one dose arm of Phase 1 Study C38072/1107 (220 mg iv infusion). In Phase 1 Study C38072/1102, 5 iv doses of reslizumab were given 4 weeks apart (0.3, 1, 2, or 3 mg/kg iv infusion). In Phase 2 Study P00290, 2 iv doses of reslizumab were given 12 weeks apart (0.3 mg/kg or 1 mg/kg iv infusion). Four iv doses of reslizumab were given 4 weeks apart in Studies Res-5-0010 (3 mg/kg iv infusion) and C38072/3081 (0.3 mg/kg or 3.0 mg/kg iv infusion). In Study C38072/3082 (3.0 mg/kg iv infusion), 13 doses of iv reslizumab were given 4 weeks apart. Generally, the duration of iv infusions ranged from 20 to 50 minutes, but may have varied from subject to subject. A single dose of sc reslizumab was given in Phase 1 Study C38072-AS-10069 (33, 110, or 165 mg administered in the upper arm). A single dose of sc reslizumab was given in Phase 1 Study C38072-PK-10071 (55, 110, or 220 mg administered in the upper arm; 110 mg administered in the abdomen; 110 mg administered in the thigh). A single dose of sc reslizumab was given in one dose arm of Phase 1 Study C38072/1107 (220 mg sc administered in the upper arm). In Study C38072-AS-30025, 13 doses of sc reslizumab (110 mg sc) were given 4 weeks apart; sequential administration via the upper arm, abdomen, and thigh was repetitively used for each consecutive dose (patients were assigned to 1 of 3 different dose arms, each beginning the dosing sequence at 1 of the 3 differentanatomical injection sites). In Study C38072-AS-30027 (110 mg sc administered in the upper arm), 6 doses of sc reslizumab were given 4 weeks apart.

Pharmacokinetic Sample Collection Plans, by Study:

Study number/ Phase	Pharmacokinetic sampling plan
C38072-AS-10069/ Phase 1	Prior to first dose and on days 3 (±1 day), 7 (±2 days), 14 (±2 days), 28 (±3 days), 56 (±3 days), and 84 (±7 days)
C38072-PK-10071/ Phase 1	Predose; 6 and 12 hours postdose on day 1; 24 and 36 hours postdose on day 2; and on days 3, 5, 7, 10, 14 (±1), 21 (±1), 28 (±1), 42 (±2), 56 (±2), and 84 (±2)
C38072-AS-30025/ Phase 3	Prior to first dose; weeks 1 (patients in US centers only), 2, 4, 8, 12, 16, 20, 32, 48, 52, or early withdrawal; and at approximately week 60 and week 76 for ADA assessment
C38072-AS-30027/ Phase 3	Prior to first dose; weeks 4, 8, 12, 16, 20, and 24 or early withdrawal; and at approximately week 32 and week 48
C38072/1102/ Phase 1	Periods 1, 5: before and after infusion; 12 and 24 hours after start of infusion; and on days 3, 5, 7, 10, 14, and 21 Periods 2, 4: before and after infusion; 12 and 24 hours after start of infusion Period 3: before and after infusion; 12 and 24 hours after the start of infusion; and on day 3
C38072/1107/ Phase 1	Predose (0 hours); 6, 12, and 24 hours postdose; and on 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)
C38072/3081/ Phase 3	Baseline, before and after each infusion at weeks 4, 8, and 12, and at week 16 or early withdrawal. US study sites: also at day 2-3 and week 2-3 Also from patients with serious adverse drug reaction or CAE
C38072/3082/ Phase 3	Baseline and before each infusion at weeks 4, 8, 12, 16, 24, 36, and 48 Following completion of the infusion at baseline and weeks 16 and 36 US study sites: also at day 2-3 and week 2-3 Also from patients experiencing a serious adverse drug reaction or CAE
I96-350/ Phase 1	All groups: Predose (0 hours) and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours after dose Groups 1 and 2: days 8, 15, 30, 60, 90, and 120+ Groups 3-5: days 8, 15, 30, 60, 90, 120, 150, and 180
P00290/ Phase 2	Prior to 1st dose (0 hours); 1 and 4 hours after dose; day 4; and weeks 2, 4, and 9. week 12 prior to 2nd dose (0 hours); 1 and 4 hours after 2nd dose; weeks 12.5, 14, 16, 20, 26, 32, and 38
P01942/ Phase 1	Predose (0 hours); 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, and 48 hours after dose; and at weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, and 36
Res-5-0010/ Phase 2	Day 0, weeks 4, 8, 12, and 15

ADA=anti-drug antibody; CAE=clinical asthma exacerbation; iv=intravenous; n=number of subjects; sc=subcutaneous; US=United States

Population Pharmacokinetic Analysis Methodology: The overall procedures followed for the development of the population PK model for reslizumab were:

1) exploratory data analysis;

2) base structural model development via application and refinement of previously developed final population PK model using prior iv data pooled with sc data from Studies C38072-AS-10069, C38072-PK-10071, and C38072-AS-30027; 3) evaluation of covariate effects using forward selection; 4) full multivariable model evaluation (including application, re-estimation, and refinement of PK model using dataset updated with Study C38072-AS-30025 data);

5) backward elimination of covariates (including all available iv/sc data);

6) final model refinement;

and 7) model evaluation.

Stationary covariates evaluated were age, race, sex, baseline body weight, baseline body mass index, baseline renal function, baseline liver function tests, baseline serum albumin, baseline peripheral blood eosinophil count, patient status, and ADA status. Time varying concomitant medications evaluated were beta-agonists, leukotriene antagonists, and oral or injectable corticosteroid classes. The final PK model was validated using a simulation based, prediction-corrected VPC methodology to assess concordance between the model based simulated data and the observed data.

Population Pharmacokinetic Analysis Results:

A total of 12906 serum reslizumab concentration measurements from 1057 subjects (10438 concentrations from 816 subjects receiving iv reslizumab and 2468 concentrations from 241 subjects receiving sc reslizumab) were used for development of the base population PK model and covariate forward selection procedure. After inclusion of Study C38072-AS-30025 data, a total of 15020 serum reslizumab concentration measurements from 1293 subjects (10438 concentrations from 816 subjects receiving iv reslizumab and 4582 concentrations from 477 subjects receiving sc reslizumab) were used for the covariate backward elimination procedure and final population PK model development. In total, the analysis population used for thefinal population PK model included 249 healthy volunteers from Phase 1 Studies C38072/1102, C38072/1107, and C38072-PK-10071; 36 pediatric patients from Phase 1 Study C38072-AS-10069; 40 patients from Phase 1 Studies I96-350 and P01942; 196 patients from Phase 2 Studies P00290 and Res-5-0010; 450 patients from Phase 3 Studies C38072/3081 and C38072/3082; and 322 patients from Phase 3 Studies C38072-AS-30025 and C38072-AS-30027. The final analysis dataset included 79 patients between 12 and 17 years of age, inclusive, with the remainder of patients ranging in age from 18 to 83 years (median: 43 years). The analysis population was primarily Caucasian (78%), with relatively equivalent gender distributions (44.5% male, 55.5% female).

The final population PK model for reslizumab was a 2-compartment model with zero order input for iv doses, firstorder absorption for sc doses (with absolute bioavailability [F1] estimated separately for Study C38072/1107 versus all other sc data), and first order elimination. Interindividual variability was estimated for the first-order absorption rate constant (Ka), clearance (CL), central volume of distribution (Vc), distributional clearance (Q), and peripheral volume of distribution (Vp), which were each described using an exponential error model. The residual variability (RV) was estimated using separate log error models applied to full profile iv data (Studies I96-350, P01942, C38072/1102, C38072/1107, and P0290), Phase 2/3 sparse iv data (Studies Res-5-0010, C38072/3081, and C38072/3082), full profile sc data (Studies C38072-AS-10069, C38072-PK-10071, and C38072/1107), and Phase 3 sparse sc data (Studies C38072-AS-30025 and C38072-AS-30027).

Covariate analysis identified body weight as a significant predictor of F1, CL, Vc, and Vp, and age as a significant predictor of F1. Each covariate effect was described according to a power function. Based on the equations provided below, the typical CL, Vc, and Vp parameter values are predicted to increase less than proportionally with increasing body weight, while the typical F1 is predicted to decrease less than proportionally with increasing body weight and increasing age. No other covariates were found to be significant descriptors of variability in reslizumab PK.

$$\tilde{F}1_i = \left[(0.633 \times ST_{1107}) + (0.413 \times ST_{SC})\right] \times \left(\frac{WTKG_i}{73}\right)^{-0.367} \times \left(\frac{AGE_i}{43}\right)^{-0.161}$$

$$\tilde{CL}_i = 7.11 \times \left(\frac{WTKG_i}{73}\right)^{0.560}$$

$$\tilde{V}_{c_i} = 3080 \times \left(\frac{WTKG_i}{73}\right)^{0.636}$$

$$\tilde{V}_{P_i} = 2100 \times \left(\frac{WTKG_i}{73}\right)^{0.389}$$

Where:

$\tilde{F}1_i$ is the typical value of absolute bioavailability in the ith subject;

$\tilde{CL}_i$ is the typical value of clearance (mL/h) in the ith subject;

$\tilde{V}_{c_i}$ is the typical value of central volume of distribution (mL) in the ith subject;

$\tilde{V}_{P_i}$ is the typical value of peripheral volume of distribution (mL) in the ith subject;

ST_{1107} is a dichotomous indicator flag for Study C38072/1107 (1 = C38072/1107, 0 = other sc studies);

ST_{SC} is a dichotomous indicator flag for dedicated sc studies (1 = Studies C38072-AS-10069, C38072-PK-10071, C38072-AS-30027, and C38072-AS-30025, 0 = otherwise);

AGE_i is the age (y) in the ith subject; and

$WTKG_i$ is the body weight (kg) in the ith subject.

The final PK model parameter estimates and their associated precisions (%RSE) are presented in the table below. All fixed effect parameters (cardinal PK and covariate effect parameters) and random effect parameters (interindividual variability [IIV] and RV) were estimated with good precision (%RSE ≤ 20.5% and ≤30.0%, respectively). Using body weights representative of the 5th and 95th percentiles observed in this analysis dataset population, the typical CL, Vc, and Vp would range from 5.62 mL/h, 2359 mL, and 1784 mL, respectively, for a subject weighing 48 kg up to 8.90 mL/h, 3974 mL, and 2454 mL, respectively, for a subject weighing 109 kg. The mean apparent terminal elimination half life for a typical subject based upon final population mean parameter estimates is estimated at approximately 23 days.

Parameter Estimates and Standard Errors from the Reslizumab Final Population Pharmacokinetic Model

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude[a]	%SEM
K_a: First-order absorption rate constant (1/h)	0.0140	7.79	60.6 %CV	13.7
F1: Absolute bioavailability for Study 1107	0.633	4.73	NE	NA
F1: Absolute bioavailability for all sc studies	0.413	2.05		
F1: Power for body weight on F1	-0.367	19.5	NA	NA
F1: Power for age on F1	-0.161	20.5		
CL: Central clearance (mL/h)	7.11	1.26	32.0 %CV	4.88
CL: Power for body weight on CL	0.560	8.03		
V_c: Central volume of distribution (mL)	3080	1.15	26.1 %CV	10.3
V_c: Power for body weight on V_c	0.636	7.69		
Q: Distributional clearance (mL/h)	12.4	5.83	109 %CV	12.5
V_p: Peripheral volume of distribution (mL)	2100	2.96	51.3 %CV	8.24
V_p: Power for body weight on V_p	0.389	18.6	NA	NA
cov(IIV in CL, IIV in V_c)[b]	0.0325	12.4	NA	NA
cov(IIV in Q, IIV in V_c)[b]	-0.118	20.3		
cov(IIV in Q, IIV in CL)[b]	0.0580	30.0		
cov(IIV in V_p, IIV in CL)[b]	0.103	8.63		
cov(IIV in V_p, IIV in Q)[b]	0.362	11.4		
RV (log scale, iv full-profile)	0.0402	5.69	0.201 SD	NA
RV (log scale, iv Phase 2/3)	0.103	8.72	0.320 SD	
RV (log scale, sc full-profile)	0.0367	17.3	0.192 SD	
RV (log scale, sc Phase 3)	0.0397	14.1	0.199 SD	
Minimum value of the objective function = -22285.667				

Source: d2pk\tables\doc\final-pooled-pk-model_r203770.docx.

[a] The calculated shrinkage in the η estimate distributions were as follows: 9.51% for IIV in K_a, 5.75% for IIV in CL, 25.6% for IIV in V_c, 39.9% for IIV in Q, and 29.1% for IIV in V_p.

[b] The calculated correlation coefficients (r^2) of the off-diagonal omegas were as follows: 0.152 for cov(IIV in CL, IIV in V_c), 0.170 for cov(IIV in Q, IIV in V_c), 0.0274 for cov(IIV in Q, IIV in CL), 0.390 for cov(IIV in V_p, IIV in CL), 0.416 for cov(IIV in V_p, IIV in Q).

%CV=coefficient of variation expressed as a percentage; IIV=interindividual variability; iv=intravenous; NA=not applicable; NE=not estimated; RV=residual variability; sc=subcutaneous; SD=standard deviation; %SEM=standard error of the mean expressed as a percentage

The calculated shrinkage in the epsilon estimate distributions for RV were as follows: 8.24% for full-profile iv data, 9.9% for sparse Phase 2/3 iv data, 14.0% for full-profile sc data, and 10.7% for sparse Phase 3 sc data.

The prediction-corrected VPC model evaluation indicated that overall, as well as by study, the central tendency in the reslizumab concentration time-course and the magnitude of variability is being described well by the final population PK model.

Prediction-Corrected Visual Predictive Check of the Final Population Pharmacokinetic Model for Reslizumab Following Intravenous and Subcutaneous Administration

CI=confidence interval; Pred Corr=prediction corrected
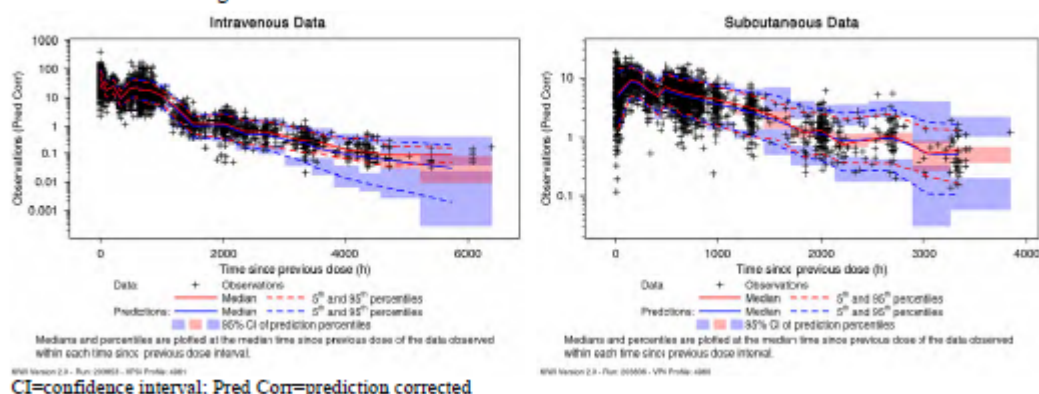
The Population Pharmacokinetic Conclusions:

☐ The PK of reslizumab in healthy volunteers and patients with eosinophilic asthma, nasal polyposis, uncontrolled asthma, or oral corticosteroid-dependent asthma ranging in age from 6 to 83 years were well characterized by a 2-compartment model with zero order input for iv dosing, first-order absorption (with absolute bioavailability) for sc dosing, and first-order elimination kinetics.

☐ 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, Vc, and Vp for a 73 kg subject were 7.11 mL/h, 3080 mL, and 2100 mL, respectively, resulting in a population mean t½ of approximately 559 hours or 23.3 days.

☐ Body weight was identified as a statistically significant predictor of CL, Vc, and Vp, with each PK parameter increasing in a less than proportional manner with increasing body weight, such that the typical CL, Vc, and Vp are predicted to increase by approximately 58% (from 5.62 mL/h to 8.90 mL/h), 68% (from 2359 mL to 3974 mL), and 38% (from 1784 mL to 2454 mL), respectively, as subject weights range from the 5th percentile (48 kg) to 95th percentile (109 kg) of body weight observed in the PK analysis population.

☐ Body weight and age were identified as statistically significant predictors of F1, with F1 decreasing in a less than proportional manner with increasing body weight or increasing age. Based on the combined influence of both covariates and using the 5th and 95th percentiles of observed age and body weight in the sc population, the typical F1 is predicted to decrease by approximately 53%, from 0.70 in a 9-year-old subject weighing 35 kg to 0.33 in a 70-year-old subject weighing 106 kg.

☐ 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), serum albumin, baseline peripheral eosinophil count, and concomitant use of beta agonists, leukotriene antagonists, or corticosteroids were 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 ADAs did not significantly alter the disposition of reslizumab.

Assessment of the response

The MAH submitted the requested Report CP-17-15 including the population pharmacokinetic analysis including pharmacokinetic date from 6 Phase 1 studies (I96-350, P01942, C38072/1102,

---

C38072/1107, C38072-AS-10069, C38072-PK-10071), 2 Phase 2 studies (P00290 and Res-5-0010), and 4 Phase 3 studies (C38072/3081, C38072/3082, C38072-AS-30025, and C38072-AS-30027).

The PK of reslizumab following iv infusion, iv bolus injection, or sc injection demonstrated linear elimination over the dose ranges of 0.03 to 3.0 mg/kg for iv and 33 to 220 mg for sc. The disposition of reslizumab was well described by a 2-compartment model with zero-order input for iv dosing, first-order absorption with absolute bioavailability for sc dosing, and first-order elimination kinetics. The magnitude of estimated random, unexplained IIV in CL and Vc reflects the moderate range expected (32.5 and 26.2 %CV, respectively), particularly given the different routes of administration, the wide range of ages and body weights in the analysis population, and in light of the amount of observed between-subject variability in both the observed full PK profiles as well as in the sparse PK data.

With the exception of body weight and age, all other covariates that were explored either did not achieve statistical significance or did not sufficiently explain (ie, reduce) a considerable proportion of IIV (at least 5%) on the PK parameter tested.

In this analysis population, neither baseline mild or moderate renal impairment nor baseline elevated liver function tests (Grade 1-2) were associated with altered reslizumab PK. Which is in line whith the expected monoclonal antibody characteristics of reslizumab. The presence of circulating ADA against reslizumab did not seem to result in or produce decreases in reslizumab exposures.

The only concomitant medication classes with sufficient prevalence in this PK population to allow meaningful analysis were the beta agonists, leukotriene antagonists, and corticosteroids. None of these co-administered classes were identified as a significant covariate for reslizumab PK; this is in line with the expectation that small-molecule drugs would not impact reslizumab PK.

The population typical values of CL, Vc, and Vp were best described by power functions of body weight. The estimates of the power term values were fairly similar for each PK parameter (0.560 for CL, 0.636 for Vc, and 0.389 for Vp) indicating that the typical values of CL, Vc, and Vp all increase in a less-than-proportional manner with increasing body weight. In general the t½ remaine unchanged over the observed body weight range evaluated in this analysis population.

However, increasing body weight for a given fixed dose amount, results in reduced reslizumab serum exposures regardless of route of administration. For sc-dosed drug, the model-predicted effects of body weight and age on F1 (each producing a reduction in F1 with increasing body weight and/or advancing age) suggest a considerably higher absolute bioavailability for lighter and younger patients. In turn, reslizumab exposures are predicted to be proportionally lower in older and particularly heavier patients.

The POP-PK analysis is of sufficient quality. The findings in this report do not influence the overall clinical outcome. The submitted summary data confirmed the initially data provided. No changes are made in the assessment.

Issue resolved.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

None

Clinical studies

Product Name: Reslizumab Solution for Injection   Active substance: Reslizumab

Study title	Study number	Date of completion*	Date of submission of final study report
A single-dose, open-label, parallel group study to characterize the pharmacokinetics, pharmacodynamics, immunogenicity, safety, and tolerability of reslizumab following subcutaneous administration in children with asthma (6 to less than 12 years of age)	C38072-AS-10069 (PIP Study 3)	15 February 2017	March 2018 Article 46 stand alone submission
A Phase 3, 24-week, double-blind, placebo-controlled, parallel-group, efficacy and safety study of reslizumab subcutaneous dosing (110 mg every 4 weeks) in patients with oral corticosteroid dependent asthma and elevated blood eosinophils	C38072-AS-30027	04 December 2017	Pending
A 52-week double-blind, placebo-controlled, parallel-group efficacy and safety study of reslizumab 110 mg fixed, subcutaneous dosing in patients with uncontrolled asthma and elevated blood eosinophils	C38072-AS-30025 (PIP Study 2)	31 January 2018	Pending
An open-label extension study of reslizumab 110-mg fixed, subcutaneous dosing in patients 12 years of age and older with severe eosinophilic asthma	C38072-AS-30066	22 February 2018	Pending
Double-blind, randomised, placebo-controlled trial to evaluate the safety and efficacy of reslizumab as add-on to best standard of care in children from 6 to less than 12 years of age with uncontrolled severe asthma and elevated blood eosinophils	not applicable (PIP Study 4)	not started	Pending

*=last patient last visit for end of trial as defined in the protocol