EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CINQAERO

International non-proprietary name: reslizumab

Procedure No. EMEA/H/C/003912/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

% predicted FEV_1	actual FEV_1 divided by standard predicted FEV_1 times 100%
ACQ	Asthma Control Questionnaire
ADA	anti-drug antibody
ADR	adverse drug reaction
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-IgE	anti-immunoglobulin E (omalizumab)
anti-IL-5 mAb	anti-human interleukin-5 monoclonal antibody
AQLQ	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ASUI	Asthma Symptom Utility Index
ATC	Anatomical Therapeutic Chemical
AUC	area under the serum versus time curve
AUC	area under the serum concentration-time curve for 1 dosing interval (τ) of a multiple dose regimen
AUC0-D28	area under the concentration-time curve from time 0 to day 28 after study drug administration
AUCss(0 4wk)	area under the reslizumab serum concentration versus time curve at steady state
BAL	bronchoalveolar lavage
BBB	Blood Brain Barrier
BLA	Biologics License Application
BMI	body mass index
BRAL-1	brain-linked protein-1
BSE	Bovine Spongiform Encephalopathy
BW	body weight
CAE	clinical asthma exacerbation
CAP	Centralised Authorisation Procedure
Cav,ss(0 4wk)	average reslizumab serum concentration at steady state
Cc	Cubic Centimetre
cGMP	Current Good Manufacturing Practices
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
Cmax	maximum drug concentration
Cmax,ss(0 4wk)	maximum drug concentration at steady state
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPK	creatine phosphokinase
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
CYP	cytochrome P450
diff.	difference
DLP	Data Lock Point
DP	Drug Product
DS	Drug Substance
e.g.	example given
ECG	electrocardiogram
EG	eosinophilic gastroenteritis
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
EOT	end of treatment

ER	emergency room
ERA	environmental risk assessment
EU	European Union
EURD	EU Reference Dates
F0	parental generation
F1	first generation offspring
FDA	Food and Drug Administration
FEF	Forced Expiratory Flow
FEF25%-75%	forced expiratory flow during the middle half of the forced vital capacity
FEV	Forced Expiratory Volume
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	Gastroesophageal Reflux Disease
GGT	gamma-glutamyl transpeptidase
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	healthcare professional
HES	hypereosinophilic syndrome
HLGT	high level group term
HLT	high level term
hpf	high power field
ia	intra-arterial
IC50	inhibitory concentration of 50%
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin-G
IIV	interindividual variability
IL-5	interleukin-5
im	intramuscular
INN	International Non-proprietary Name
ip	intraperitoneal
IP	Investigational Product
IRT	Interactive Response Technologies
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent-to-treat
iv	intravenous
IVRS	interactive voice response system
J	Japanese
KM	Kaplan-Meier
LABA	long-acting beta-agonist
LFT	Liver Function Test
LLOQ	low lower limit of quantitation
LS	least squares
LTRA	leukotriene receptor antagonist
mAB	Monoclonal Antibody
MAH	Marketing Authorisation Holder
max	maximum
MDRD	Modification of Diet in Renal Disease
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MID	minimal important difference
min	minimum
mL	Millilitre
mM	Millimolar
MMRM	mixed-effect model for repeated measures

n	number (subpopulation)
NA	not applicable
NAEPP	National Asthma Education and Prevention Program
NB	negative-binomial
NJ	non Japanese
No.	number
NOEL	No-observed-effect level
NP	nasal polyposis
NR	not reported
NZW	New Zealand white
OCS	oral corticosteroid
OLE	Open Label Extension
PBRER	Periodic benefit-risk evaluation report
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PhV	pharmacovigilance
PIL	Patient Information Leaflet
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PND	postnatal day
PopPK	population pharmacokinetics
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PT	Preferred Term
Pts	Patients
Q	distributional clearance
RMP	Risk Management Plan
Robs	observed accumulation ratio (i.e. AUC□ (period 5)/AUC0-28 (period 1))
RR	Relative Risk
Rss	steady-state accumulation ratio (i.e. AUC□ (period 5)/AUC0-inf (period 1))
RU	response units
RV	residual variability
SA	scientific advice
SABA	short-acting beta-agonist
SAP	Statistical Analysis Plan
sc	subcutaneous
SCE	Summary of Clinical Efficacy
SD	standard deviation
SE	standard error
SMQ	standardized Medical Dictionary for Regulatory Activities query
SOC	System Organ Class
SPC, SmPC	Summary Of Product Characteristics
Teva	Teva Global Branded Pharmaceutical Products R & D, Inc.
tmax	time to maximum observed drug concentration
TSE	transmittable spongiform encephalopathy
UK	United Kingdom
ULN	upper limit of normal
URTI	upper respiratory tract infection
US(A)	United States (of America)
Vc	volume of distribution in central compartments
Vp	volume of distribution in peripheral compartments
Vss	steady-state volume of distribution
Vz	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
λz	terminal rate constant for elimination

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharmaceuticals Limited submitted on 30 June 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for CINQAERO through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

CINQAERO is indicated to reduce exacerbations, relieve symptoms and improve lung function in adult patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The applicant indicated that reslizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0017/2015 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0017/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance reslizumab in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 November 2010, 24 July 2014 and 26 February 2015. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: USA.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: David Lyons

- The application was received by the EMA on 30 June 2015.
- The procedure started on 23 July 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2015.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC/CHMP members on 23 October 2015.
- During the meeting on 19 November 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 February 2016.
- The Rapporteurs circulated the Joint CHMP and PRAC Assessment Report on the applicant's responses to the List of Questions to all CHMP/PRAC members on 05 April 2016.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 14 April 2016.
- The Rapporteurs circulated an updated Joint CHMP and PRAC Assessment Report to all CHMP/PRAC members on 22 April 2016.
- During the CHMP meeting on 28 April 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 May 2016
- The Rapporteurs circulated the Joint CHMP and PRAC Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP/PRAC members on 09 June 2016.
- The Rapporteurs circulated an updated Joint CHMP and PRAC Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP/PRAC members on 17 June 2016.
- During the meeting on 20-23 June, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to CINQAERO.

2. Scientific discussion

2.1. Introduction

Problem statement

Asthma is a common, heterogeneous disease characterised by inflammation and clinically defined by respiratory symptoms such as shortness of breath, coughing, wheezing, and chest tightness together with variable expiratory airflow limitation. In addition, asthma is often characterized by airway hyperresponsiveness to direct or indirect stimuli (Global Initiative for Asthma [GINA] 2014).

Many factors can influence the development of asthma or trigger asthma-related symptoms, including those related to the individual patient and factors related to the environment surrounding the patient with asthma (Bacharier et al 2008, Ege et al 2011, GINA 2014, Vijverberg et al 2011).

The goals of asthma treatment are control of symptoms and prevention of exacerbations with minimal drug-related side effects. Well-controlled asthma is indicated by symptoms that occur less frequently than twice per week (including the need for reliever use), normal lung function, no awakenings due to asthma, and no activity limitation due to asthma.

Asthma that is uncontrolled is not the same as severe asthma. Classification of the severity of asthma is based on the level of treatment required to control symptoms. The intensity of treatment is defined by step-wise treatment recommendations (GINA).

Asthma severity in clinical can be assessed when the patient has been on regular controller treatment for months.

- Mild asthma is asthma that is well controlled with step 1 or step 2 treatment,
- Moderate asthma is asthma that is well controlled with step 3 treatment,
- Severe asthma is asthma that requires step 4 or step 5 treatment.

“Asthma control” refers to the extent to which the manifestations of asthma have been reduced or removed by treatment.

Asthma control has two domains: symptom control and future risk of adverse outcomes. Future risks are characterised by identifying whether a patient is at risk of adverse asthma outcomes, particularly exacerbations fixed airflow imitation and side effects of medication. Asthma symptom control and exacerbation risk may have different causes and may need different treatment options.

The majority of patients with asthma can achieve good symptom control and minimal exacerbations with regular controller treatment. However, some patients remain uncontrolled due to truly refractory asthma. For these patients, who remain inadequately controlled on medium-to-high dose ICS plus a long-acting beta-agonist (LABA), there are few therapeutic alternatives beyond the add-on treatment with oral corticosteroids (OCSs) and/or (for patients with perennial allergies) anti-immunoglobulin E (anti-IgE). Adverse effects of prolonged high-dose inhaled or systemic corticosteroid use are well known and include, among others, infection, adrenal suppression, cataract formation, osteoporosis, and aggravation of diabetes.

From the already authorised asthma treatments, omalizumab, a recombinant humanised mAb (IgG1) is recommended for use in GINA Step 5 (add-on treatment for allergic asthma), but only a small proportion of

patients with severe asthma are appropriate candidates for its use based on specific weight and IgE levels in addition to a positive test for a perennial allergen. Anti-IgE has demonstrated modest efficacy on asthma exacerbations in patients with allergic asthma, with small and highly variable effects on lung function (Busse et al 2001, Hanania et al 2011, Humbert et al 2005, Solér et al 2001).

Eosinophilic Asthma Phenotype

The failure of guideline-based, stepped-care therapy to adequately control a substantial proportion of asthma patients has been attributed to heterogeneity in aetiology (e.g., allergic, non-allergic, or occupational), severity, physiologic parameters (e.g., reversible or fixed obstruction), and underlying inflammatory pathology (Bradding and Green 2010, Gibson 2009).

Eosinophilic asthma has emerged as a distinctive asthma phenotype (Walford and Doherty 2014, Wenzel et al 1999, Wenzel 2012). Eosinophilic asthma has been associated with the key pathophysiological and clinical features of asthma, including airway remodelling with associated persistent airflow limitation and poor clinical control with risk of asthma exacerbation (Balzar et al 2005, Green et al 2002, Jatakanon et al 2000, Petsky et al 2012, Robinson 1995, Saglani et al 2007, ten Brinke et al 2001, Wenzel et al 1999). Inhaled corticosteroids reduce the number of airways eosinophils, but despite treatment, airway eosinophilia may still persist. Recent large epidemiological surveys indicate that elevated blood eosinophil levels are an independent risk factor for future asthma exacerbations (Malinovschi et al 2013, Tran et al 2014, Zeiger et al 2014), and this observation has been incorporated into the most recent expert asthma guidance (GINA 2015).

The anti IL-5 antibody mepolizumamb (Nucala) was authorised in the European Union in December 2015 as add-on treatment for severe refractory eosinophilic asthma.

About the product

Reslizumab (CINQAERO) is a humanized anti-human interleukin-5 monoclonal antibody (anti IL-5 mAb) of the immunoglobulin-G4 kappa (IgG4/κ) isotype. It works by binding to IL-5 thereby preventing its binding to the IL-5 receptor and consequently reduces circulating and tissue eosinophils.

Reslizumab contains the complementarity determining regions (CDRs) of the original rat anti-human IL-5 antibody 39D10 grafted onto a human framework which is produced in the murine myeloma NS0 expression system.

Proposed indication

CINQAERO is indicated to reduce exacerbations, relieve symptoms and improve lung function in adult patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

Proposed posology

The recommended dose of reslizumab is 3.0 mg/kg every 4 weeks, given as an intravenous infusion.

Of note, the initial development studies were performed by Schering-Plough (Schering), and included evaluations of non-clinical safety, pharmacology, and pharmacokinetics (PK). Schering also performed clinical studies in patients with asthma and in patients with nasal polyposis. Ception Therapeutics (later owned by Cephalon) subsequently continued the development of reslizumab for the treatment of eosinophilic esophagitis in paediatric subjects, asthma, and other eosinophil-mediated diseases. At present, Teva Pharmaceutical Industries (Teva) has taken ownership of the molecule.

Type of Application and aspects on development

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

The reslizumab i.v. clinical program comprises fourteen clinical studies, including six Phase 3 studies, four Phase 2 studies, and four Phase 1 studies; thirteen of these studies are completed, and one study (Study 3085) was ongoing at the time of data cut-off (01 September 2014) and is currently concluding. Besides studies in patients with an eosinophilic asthma phenotype which is the subject of the current MAA, studies have been performed in other patients populations as well (patients with eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic gastroenteritis, and nasal polyposis). These are included in support of safety.

CHMP guidance for development of asthma treatment is available in the form of a revised Note for guidance on clinical investigation of medicinal products for treatment of asthma (CHMP/EWP/2922/01 Rev.1 – released in December 2015).

The Applicant obtained feedback on the development of reslizumab for asthma three times (November 2010, July 2014 and February 2015). The first advice concerned the intravenous formulation; the other advices are related to a subcutaneous formulation which is not part of the current MAA.

The CHMP gave advice related to the use of a combined pharmacokinetic and toxicology study in monkey using both iv and sc administration, to support sc administration in humans. Further, the CHMP considered that the 26 week study in a transgenic mouse model was adequate to describe the overall carcinogenicity potential of reslizumab, but advised the Applicant to provide a comprehensive review on the role of IL-5 and eosinophils in tumour biology and/or anti-tumour responses. The Applicant was also advised to address the cross-reactivity of reslizumab with human and Cynomolgus brain tissue further.

The requested SA for the i.v. formulation concerned the selection of study population, choice of the primary and key secondary endpoints, proposed efficacy analyses, collection of safety data, and inclusion of adolescent patients (12-17 years of age). It was highlighted that a 6-month study duration might be too short for the exacerbation studies. Further, it was advised to reduce the upper limit for the oral steroid criterion from planned 10mg/day, since this increases the risk of the recruitment of essentially untreatable patients with a high risk for dropouts. Overall, the amended programme (extension of study duration to 12 months, studying additional doses) was considered acceptable to support an indication in the given subpopulation of asthma patients. As a response to the EMA advice, an additional study (Study 3084) was conducted in patients with asthma who were unselected for blood eosinophils to ensure that the phenotype of the target population could be sufficiently defined, since the degree of correlation between blood eosinophilia and sputum eosinophilia had not been fully established.

Notably, at the time of the SA the Applicant has presented a criterion of 2 exacerbations/previous year as inclusion criterion. The inclusion criteria for the submitted pivotal exacerbation studies has been changed to 1 exacerbation in the previous year. Further, the primary endpoint was changed during the studies and FEV1 was ultimately not included in the primary endpoint in either of the exacerbation studies as presented at the time of SA; however, it was analysed as the first key secondary endpoint in each study.

2.2. Quality aspects

2.2.1. Introduction

The active substance of CINQAERO is reslizumab, a humanized recombinant monoclonal antibody (mAb) of the IgG 4 subtype produced in NS0 cells. Reslizumab binds specifically to interleukin-5 (IL-5), thereby neutralizing the biological activity of this cytokine.

Reslizumab is formulated in an acetate buffer solution containing sodium acetate, sucrose. The finished product is supplied as a 10 mg/ml concentrate for solution for infusion.

2.2.2. Active Substance

General information

Reslizumab is a humanized anti-human interleukin-5 monoclonal antibody (anti-IL-5 mAb) of the immunoglobulin-G4 kappa (IgG4/κ) isotype, which contains the complementarity determining regions (CDRs) (i.e., antigen-binding regions) of the original rat antihuman antibody 39D10 grafted onto a human framework.

Reslizumab has a characteristic IgG4 structure including two identical heavy chains and two identical light chains linked by 16 disulfide bonds (4 inter-chain disulfide bonds and 12 intrachain disulfide bonds). The two post-translational modifications are the conserved N-linked glycosylation on the CH2 domain of the heavy chain at asparagine 293 (Asn293) and loss of C-terminal lysine residue of the heavy chain. N-linked oligosaccharides of reslizumab are core fucosylated, bi-antennary, and complex type glycans, as expected for IgG4 antibodies derived from NS0 cell lines.

Reslizumab has a theoretical molecular mass of 146,776 Da calculated for the antibody with two C terminally clipped lysine residues and two G1F glycans.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Reslizumab is expressed in a NS0 murine myeloma cells which has been engineered for product expression using a glutamine synthetase promotor system. The cGMP Master Cell Bank was established in 1994. The MCB was used to prepare multiple working cell banks (WCB), providing a conventional two-tiered cell bank system. The MCB and the currently used serum-free WCB (established in 2006) have been tested to confirm their identity and purity in accordance with the ICH guidelines Q5A and Q5D. The Applicant has demonstrated the genetic stability of the cell banks. No adventitious agents, with the exception of A- and C-type retrovirus-like particles in the MCB, were detected.

Other Manufacturer Working Cell Banks were initially prepared and used for the production of reslizumab active substance tested in the toxicology and Phase 1 clinical studies. A summary of the characterization and safety test results of these cell banks have been provided.

Manufacturing process

Reslizumab active substance is manufactured at Lonza Biologics Inc. Portsmouth, NGH 03810, USA (Lonza US).

One production bioreactor leads to one bulk active substance lot. Bulk active substance lots are not combined at the active substance stage.

The upstream manufacturing process starts with cells from a single ampoule of the WCB are propagated via two steps: Inoculum Expansion, and Cell Culture. The final cell culture production in the bioreactor is followed by the Primary Recovery step.

The purification of Reslizumab consists of three chromatography column steps, three concentration and diafiltration steps and two viral control steps (a low pH viral inactivation step and a viral reduction filtration step). The purification starts with affinity-chromatography and is subsequently followed by a low pH treatment step, ultrafiltration/diafiltration (UF/DF) concentration, anion exchange chromatography, UF/DF concentration, cation exchange chromatography, viral reduction filtration and concentrated with a final UF/DF. Excipients are added to reslizumab and the bulk is then 0.22 µm filtered into sterile disposable containers. The containers are stored at 2-8°C pending batch disposition.

There are no process intermediates in the reslizumab active substance manufacturing process. For each step the manufacturing details are indicated (e.g. the temperature, load, reuse of filters/resin, cleaning and storage of resin/filters, holding time/temperature of the intermediate step).

Reprocessing is allowed for the viral reduction filtration and the final 0.22 µm filtration before filling.

Process controls

The Applicant has provided a list of critical quality attributes which were deemed to be appropriate. In order to identify critical process parameters (CPPs), the Applicant developed the control strategy by conducting two risk assessments; the first was based on a risk matrix where the risk of deviation and the risk to quality were considered. The second was a Failure Modes and Effects Analysis (FMEA) which considered severity, occurrence and detection. Information derived from both risk assessments and the studies that were triggered by risk assessments over the course of development were utilized as a whole to determine potential criticality of process parameters in the current process. Following the risk assessment, small scale experiments were used to test the criticality of the identified potential CPPs. Appropriate data were provided to show that these small scale studies were representative of the full scale manufacturing process. Overall the data used to justify the designation of process parameters as critical or non-critical was acceptable and the identified list of CPPs was endorsed.

Process validation

The active substance manufacturing process was validated according to a defined process validation master plan. Three consecutive active substance batches were manufactured at the commercial scale in 2008. One of these Batches was run at extended cell generation numbers near the edge of the process limit for cell generations as defined in the fermentation process description.

During the process validation additional in process samples were collected and assayed for purity by isoelectric focusing (IEF), reduced and non-reduced sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), Gel permeation high performance liquid chromatography (GP-HPLC) and for residual process impurities. Analytical testing and characterization was performed to assess the quality of the process validation batches.

As a part of process validation, resin reuse and cleaning, viral clearance, impurity clearance, viral filtration reprocessing, final filtration reprocessing and bulk active substance shipping were also validated at either manufacturing-scale or laboratory-scale using scaled-down models representative of the proposed manufacturing scale. Where appropriate, results from supporting validation studies (e.g., hold time studies, membrane re-use, resin re-use, etc.) are included for each relevant unit operation.

Reprocessing across the viral filter and reprocessing of the 0.22 µm filtration step have been validated.

Based on review of the release and additional characterization data, it can be concluded that the validated process can produce active substance batches that are consistent in quality and conform to the reference standard.

A continued process verification system is in place. Three batches have been produced under this protocol in 2014 and also demonstrate that the active substance manufacturing process is consistent and all in-process controls are within acceptable ranges specified. Process changes introduced after manufacture of the process validation batches in 2008 have been described and are considered minor.

Characterisation

Reslizumab has been well characterised using several orthogonal approaches and all relevant aspects of primary, secondary and tertiary structure, charge variants, aggregation, purity, potency have been examined.

The primary structure of reslizumab was well characterized with respect to complete sequence verification, terminal sequences, post-translational modifications, disulfide bond linkage, monosachride composition and glycan structure using a variety of analytical approaches. The secondary and tertiary structures of reslizumab were evaluated using multiple biophysical techniques. The high order structure analysis shows reslizumab predominantly contains β-sheets and buried tryptophans, indicating a folded and well defined structure.

SDS-PAGE, GP-HPLC, IEF and to a limited extent the potency assay are stability indicating. A thermal stress study (55 °C up to 4 weeks) was performed to provide more insight into the degradation pathway of reslizumab. Degradation in the form of aggregation, fragmentation and deamidation was observed and to a much lesser extent deglycosylation and oxidation.

Specification

Specifications have been established to ensure the identity, purity, biological activity (potency), safety, and consistency of the reslizumab active substance.

A cell-based method has been used to determine the potency of reslizumab for lot release and stability testing. For this cell-based method, reslizumab binds to interleukin-5 (IL-5), which prevents IL-5 from binding to the IL-5 receptor on the target cells. By blocking IL-5 binding to the IL-5 receptor, cell proliferation is inhibited. The bioassay measures the relative potency of reslizumab by measuring the number of viable cells in culture after addition of reslizumab in various concentrations and IL-5 at a constant concentration.

The proposed commercial release and stability specification for reslizumab were based on the current understanding of process capability and assay variability, and are also supported by clinical experience and product intended use.

Methods and validation

The analytical procedures used for release and shelf life testing of the active substance have been appropriately described. The suitability of these analytical procedures for their intended purposes was established through either verification (compendial) or validation (non-compendial).

Adequate validation reports have also been provided for the methods used during development and for assessment of active substance and finished product stability.

Reference Material

The reference standards are representative of the manufacturing procedure and are used for active substance as well as finished product testing. The results of release and characterisation testing have been provided for the three reference standards used so far. An adequate qualification protocol for future working standards has been provided, as well as stability protocols for the current reference standard and future reference standards.

Stability

Results from long-term stability studies of the process validation batches have been provided. Additional stability studies were conducted at accelerated and stressed storage conditions, and at -80°C to explore the stability of reslizumab finished product at frozen storage conditions. The accelerated and stressed storage condition stability data indicate that SDS-PAGE, GP-HPLC, IEF, BIAcore and the Potency bioassay are capable of detecting changes in the product over time at increased temperature and humidity..

Comparability exercise for Active Substance

The manufacturing process has evolved throughout development and included the original Schering manufacturing process, the Ception process by Lonza UK and the current commercial manufacturing process at 5000L scale by Lonza US. Adequate comparability studies including comparison to Schering lots, scale change and site change (Lonza UK to Lonza US) have been provided. Comparability is considered demonstrated.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished medicinal product is a sterile, unpreserved, clear to slightly opalescent aqueous solution for infusion supplied in 10 ml single-use vials containing 100 mg of reslizumab. The product is packaged in a type I clear, borosilicate glass vial, stoppered with a rubber stopper and sealed with an aluminium flip-off seal. The finished product is diluted with saline prior to use. The active substance and finished product formulation differ only in the active ingredient concentration (12 mg/ml and 10 mg/ml respectively). The active substance is diluted in a quantity of the same acetate-sucrose buffer system used for the active substance.

The formulation of the finished product has remained unchanged from clinical studies to proposed commercial formulation.

The robustness of the finished product formulation has been considered by varying the formulation. Many (heavy) visual particulates were found when the product is formulated at a combination of high pH and sodium acetate content.

As particles are observed routinely in the finished product, it is recommended that an in-line filter be used at the point of administration and the Applicant has performed in-line filtration studies demonstrating that no visible particles are observed after in-line filtration (0.22 μm filter). A compatibility study demonstrated that the recommended in-line filters do not impact on product quality.

Manufacture of the product and process controls

The manufacturing process has been adequately described and includes a standard formulation and aseptic filling process that consists of buffer formulation and bioburden reduction filtration, bulk active substance pooling, formulation and sterile filtration, filling and capping, and final 100% inspection and packaging.

Appropriate in-process tests are performed on pooled bulk active substance, after initial dilution, final dilution, before sterile filtration and during filling. There are no process intermediates. Appropriate hold times at various

stages of manufacture have been set. Raw materials and container components (including filters) are adequately defined.

Process validation studies were carried out and four commercial scale process validation batches were manufactured. Hold time periods were validated and appropriate process parameters were established. The process validation batches passed all in-process control tests and complied with finished product specifications. Distribution/Agitation/shaking studies support the quality of the finished product in the proposed primary and secondary container closure systems. The sterilising filters were qualified in terms of microbial retention and extractables/leachables.

The excipients used are compendial. There are no novel excipients or excipients of human or animal origin.

Product specification

The finished product specification includes test methods for identity, protein concentration, biological activity (potency), purity, safety and pharmaceutical properties. The release panel of testing methods and the corresponding criteria are applicable to both release and stability.

The analytical procedures used for release and shelf life testing of the finished product have been appropriately described. The suitability of these analytical procedures for their intended purposes was established through either verification (compendial) or validation (non-compendial).

Given that the finished product formulation is the same as the active substance and there is only a minimal difference in concentration between finished product and active substance prior to dilution for analysis and no difference in concentration following dilution for analysis, the active substance validations are considered to demonstrate suitability of the analytical procedures for analysis of both active substance and finished product.

Batch analysis data have been presented for eight 100 mg/vial batches. The batch analysis data presented are considered satisfactory.

Stability of the product

Stability studies have been carried out in line with relevant guidance. The primary stability study encompasses three process validation batches that were also used in the phase 3 studies. Samples maintained in the inverted as well as samples in the upright position were included to determine the effects of the closure on product quality. These studies indicate no relevant changes in any of the attributes after 36 months of storage at the recommended long-term storage condition 2-8°C.

Based on the data provided the claimed shelf life of 36 months at 2-8 °C protected from light is considered acceptable for the finished product. The quality of the diluted product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Container closure system

The suitability of the container closure has been discussed. Materials meet compendial requirements and suitability of the container closure has been demonstrated by real time, accelerated and stressed stability studies. Dye ingress and sterility testing on stability confirms the integrity of the container closure. Extractable and leachable studies have also been carried out; results are summarised and indicate that there is no

significant accumulation of leachables in aged finished product stored at the recommended storage conditions. The microbial attributes of the finished product are adequately discussed including procedures in place to minimise the risk of microbial contamination and the results of microbial ingress challenge studies. The data supports the appropriateness of the proposed container closure. Compatibility studies have been provided and are considered adequate.

Adventitious agents

There are no materials of biological origin used in routine manufacture of the finished product. Cell banks have been extensively tested for adventitious as well as endogenous agents. The low probability of adventitious agent transmission via raw materials was confirmed by the information presented and, along with the negative full adventitious agent test results, provides evidence of a low risk of transmission of viral or TSE agents.

Viral clearance studies were performed for the chromatography steps (, the low pH viral inactivation step, and the nanofiltration step using appropriate model viruses. These studies provide evidence that the production process could remove adventitious virus contamination and the overall inactivation/removal capacity is regarded as sufficient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The descriptions of the manufacture and control of the active substance and finished product presented were sufficiently and adequately detailed. Information on development, manufacture and control of the active substance and finished product has been provided in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, which leads to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure additional data have been presented on the designation of critical quality attributes and the risk assessment strategies used to assign potential critical process parameters. The proposed control strategy is well described and supported by appropriate data.

The Applicant is recommended to re-evaluate the active substance and finished product specifications when data from additional lots are available.

Regarding the residual host cell proteins ELISA the Applicant is recommended to further substantiate that the anti-HCP antibodies recognize a broad range of HCPs representative of the manufacturing process.

Several active substance manufacturing processes were used in the course of development. The Applicant has provided assurance that sufficient batches have been included in the comparability studies to demonstrate comparability across all processes.

The microbial retention study for the sterile filtration was performed at 2-8°C to mimic the product temperatures experienced at beginning of final filtration/filling process of the finished product. The Applicant has committed to conduct a microbial retention study at 25°C during the entire duration of the filtration process for confirmation.

The finished product may contain visible proteinaceous particles. These have been present in the finished product formulation since early development and have been observed at all formulation conditions that include variations of pH, excipient concentrations and protein concentrations. A number or orthogonal methods confirmed the proteinaceous nature of the visible particulates. Data has also been provided which confirm that the visible/sub-visible particulates observed after transportation are proteinaceous in nature and are removed (visible) or reduced (sub-visible) by the use of an in-line filter.

Furthermore, visible proteinaceous particles have been observed for clinical and validation lots at release and stability. During clinical development, over 400 patients were administered finished product batches without the use of an in-line filter. In over 2000 subjects treated with reslizumab, regardless of the utilization of in-line filter, low-titer anti-drug antibodies (ADA) were detected in 5% asthma patients receiving reslizumab at 3 mg/kg with no apparent impact on efficacy or safety.

In the robustness studies an increase in visual particulates was found when the product is formulated at a combination of a slightly higher pH and sodium acetate content. The applicant indicated that acetate level is controlled via manufacturing (buffer preparations) and detection controls (pH, conductivity) and data have been provided showing that the dispensed amounts are well centred around the target values and that the allowed pH ranges and conductivity ranges are met. The Applicant is recommended to evaluate appropriate implementation of pH and conductivity as IPC tests for the UF/DF diafiltration buffer and excipient buffer steps.

The Applicant has committed to developing a method to control the number of visible proteinaceous particles in each vial by comparison with vials with spiked bead. Specific acceptance criteria will be developed and will be introduced as part of the 100% manual inspection and during appearance testing as part of release and stability testing. In the interim period visible proteinaceous particles will be controlled by monitoring particulates using the same absorbance method as was done during development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance and the finished product have been appropriately characterised and in general satisfactory documentation has been provided. The results indicate that the active substance as well as the finished product can be reproducibly manufactured. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal safety studies with reslizumab were performed in compliance with Good Laboratory Practice (GLP) regulations.

2.3.2. Pharmacology

The activity of reslizumab has been studied in vitro using IL-5 receptor binding assays, surface plasmon resonance (BIAcore) analysis, and by examining IL-5 mediated cell-based response. Additional *in vitro* studies have been performed to characterize the binding of reslizumab to IL-5 and to study reslizumab binding to non-targeted tissues and biological substances. In vivo, the biological activity of reslizumab has been measured

in monkeys, rabbits, guinea pigs, and mice using antigen or human IL-5-induced bronchoprovocation as methods to induce pulmonary eosinophilia and airway hyper-responsiveness.

Reslizumab material from early batches produced by Schering was used in almost all pharmacology studies, with the exception of study BDR-2014-045-BAR-WC (surface plasmon resonance analysis) and DRR-2013-001 (PD effect in transgenic mouse) that were conducted with reslizumab material produced by the Applicant.

Primary pharmacodynamic studies

In vitro activity and IL-5 binding

The affinity of the binding to human IL-5 was indistinguishable between reslizumab and its parental antibody 39D10 (Study D26740). Reslizumab has similar binding affinity for human, monkey and mouse IL-5 (BDR-2014-045-BAR-WC). The binding affinity of reslizumab in the rat has been demonstrated by surface plasmon resonance analysis and revealed a similar affinity of reslizumab for rat IL-5 albeit lower than that for human IL-5.

In vitro tissue cross reactivity

In human tissue, binding was observed in spinal cord, brain and optic nerve. No binding was seen to peripheral nerves, or any other human tissue examined. Similarly, binding of reslizumab was seen in the spinal cord, cerebellum, cerebrum, and optic nerve of monkey tissue. The affinity of reslizumab for this antigen in monkeys compared to humans is unknown. No binding was seen in corresponding mouse tissues (P6330) or in tissue from guinea pig (P6669).

Further examination of the CNS staining pattern in monkey tissue showed that reslizumab predominately stained cerebrum white matter, cerebellum white matter and granular cell layer, and spinal cord white and grey matter. Myelinated portions of brain stained most intensely (SN96408). Data from human tissue are more limited, but while staining of cerebellum white matter and granular cell layer is seen, this was not seen for the trigeminal nerve (SN99372). Binding to the human brain link protein-1 (BRAL-1) is found to be the likely cause for the observed staining (D38271). Subsequent studies suggest that this binding to BRAL-1 is an artefact with no significant binding of reslizumab to BRAL-1 detected using surface plasmon resonance analysis or subsequent orthogonal immunohistochemical staining.

In vivo pharmacology in asthma models

Numerous studies in pre-sensitised animal models have been performed to study the effect of reslizumab on airway eosinophilia and hyperreactivity induced by allergen challenge.

Reslizumab (1 mg/kg ip) reduced the increase in eosinophils in broncho-alveolar lung (BAL) fluid observed in a pulmonary allergic response in B6D2F1/J mouse significantly, and equivalent to 39D10 (D26555). The effect was also confirmed in the mouse strains used for repeat dose toxicity (CD-1, D27201) and carcinogenicity testing (transgenic hRAS2, DRR-2013-001). Both the magnitude and the duration of the effect appeared to be dose-related. An ip dose of 10 mg/kg reslizumab was shown to inhibit allergic pulmonary eosinophilia in mice for up to 8 weeks (D27785).

In sensitised guinea pig, reslizumab induced a dose dependent reduction of airway eosinophilia and reactivity starting at doses of 0.03 mg/kg ip and 1 mg/kg ip, respectively. Complete inhibition of antigen-induced

hyperreactivity was produced by 30 mg/kg reslizumab (D27175). Results suggest that the effect may be partly mediated by a high dose IgG stabilising effect on mast cells (D27508). Furthermore, the effect of reslizumab in guinea pigs appeared to be IL-5 specific (D27630, D27174). The lack of effect of reslizumab on circulating lymphocytes or granulocytes in guinea pigs may suggest an advantage compared to peroral treatment with corticosteroids (D26956).

In vivo activity of reslizumab is also demonstrated in NZW rabbit (5 mg/kg iv), the 2nd species used in embryofoetal development studies (D27530), and in Cynomolgus monkey (0.3 mg/kg iv) that was used in repeat dose toxicity testing (D26751). In monkeys, the duration of reslizumab was extended and detectable even after 6 months (D26968).

Doses shown to have a pharmacological effect in animals are mainly comparable to clinical use (3 mg/kg BW), but toxicokinetic data are not available.

Secondary pharmacodynamic studies

Studies limited to investigating the effect of reslizumab in a murine model for allergic conjunctivitis (DRR-2013-006) and eosinophilic oesophagitis (Res-4-0002) support that reslizumab selectively affects eosinophilic recruitment, without a significant effect on basophils or mast cells.

Safety pharmacology programme

Reslizumab administered iv at a dose of 100 mg/kg (600 mg/m2) to rats (DS-2014-080) and 25 mg/kg (300 mg/m2) to monkeys (SN96333) did not elicit effects on the most important parameters related to organ functions (cardiovascular, CNS, or gastrointestinal). The doses tested in rats and monkeys are 5.4-fold and 2.7-fold higher than the proposed human therapeutic dose of 3 mg/kg (111 mg/m2) on a body surface area basis, respectively. After iv administration of reslizumab (5 or 25 mg/kg) to monkeys, there was no immunohistochemical evidence of binding of reslizumab to CNS tissues and the concentration in cerebrospinal fluid (CSF) was <0.1 µg/mL (SN96333). Additionally, macro- and microscopic examinations of a IL-5 knockout mice did not identify any differences that may indicate a human concern related to use of reslizumab (D28658). There were also no differences detected in a modified Irwin test on IL-5 knockout and IL-5 positive controls (D28259). Based on literature data, eosinophils does not appear to be essential in animal immune defence against a parasitic infection.

In a preliminary renal safety pharmacology study, findings of haematuria and increased protein levels in the urine were evident following iv administration of 100 mg/kg reslizumab (D27240). In a subsequent study (DS-2014-081) reslizumab did not significantly affect urinalysis or urine chemistry parameters suggesting that the previously seen haematuria and proteinuria was a consequence of the hypotonic vehicle used in the initial formulation. However, an examination of the data from this report shows very high variability in the values for one group (Group 1), with a standard deviation that is very similar to the mean value which appears to be the result of inclusion of an outlier with a urine volume value and a specific gravity value indicative that this sample was contaminated with water.

Pharmacodynamic drug interactions

Reslizumab had an additive effect with oral prednisolone for suppression of BAL fluid eosinophilia in allergic B6D2F1/J mice (D26940).

2.3.3. Pharmacokinetics

The pharmacokinetic studies were mainly conducted in the species and strains used during nonclinical safety testing (CD-1 mice, NZW rabbits, and Cynomolgus monkeys). In addition, one pharmacokinetic study was performed in Sprague Dawley rats.

Serum and CSF samples were quantified for reslizumab or anti-drug antibodies (ADAs) by the use of one or several of the following validated methods: A biological assay, an ELISA assay, or a Biosensor assay. The methods used for detection of anti reslizumab antibodies are however sensitive to the concomitant presence of reslizumab, and the usefulness is therefore limited.

Absorption

Systemic exposures to reslizumab in serum following single or repeated iv dose administration increased dose proportionally or slightly more than dose proportionally, and did not appear to be sex-dependent. The mean elimination half-life (t½) observed in most of the nonclinical PK studies generally ranged from approximately 8 to 18 days after iv administration, and after repeated dosing some accumulation was observed in animals, as expected. In humans, the half-life is 24 days. The long half-life is compatible with the proposed dosing regimen (every 4 weeks). Generally, a low volume of distribution was observed in mouse, rat and rabbit.

In the studies where anti-reslizumab antibodies (ADA) were detected, the ADA response correlated with decreased serum reslizumab concentrations in some animals, although not all (SN96264 (mouse), DS-2009-030, D26751, 96265 (Cynomolgus monkey), SN95457 (NZW rabbit). Epitope mapping indicate that the anti-reslizumab antibodies bind to the variable region of reslizumab.

Distribution

Absorption data suggest that distribution mainly is limited to the vascular system in both animals and humans. Low penetration of the blood-brain barrier (<0.1 µg/mL in CSF) by reslizumab following iv administration of 25 mg/kg was observed in Study P6670. Specific distribution studies have not been conducted.

Metabolism

The metabolic degradation of antibodies is expected to occur via normal proteolytic mechanisms. In line with ICH S6, studies on metabolism are not required.

Excretion

The lack of specific excretion studies is acceptable since the predicted mechanism of elimination is via proteolysis. Relatively low concentrations of reslizumab (~6-8% of corresponding serum concentrations) were detected in the milk of lactating mice dosed iv with reslizumab (DS-2010-020).

Pharmacokinetic drug interactions

Published literature indicates that cytokines can be involved regulation of CYP450 enzymes (Mahmood and Green, J Clin Pharmacol 2007 Dec; 47 (12) 1540-54). The applicant has conducted an in vitro study in human hepatocytes to investigate potential direct cytotoxicity of IL-5 and reslizumab, and to investigate the effect on expression of selected CYP450 enzymes (DM-2013-017). Results do not indicate any potential for a significant effect on hepatocyte viability, or on CYP450 expression, by reslizumab, or IL-5. Reslizumab is considered to be very specific for IL-5, and no further studies with respect to pharmacokinetic drug interaction potential is considered necessary.

2.3.4. Toxicology

The nonclinical toxicology program to support this application, was designed in accordance with the International Conference on Harmonization (ICH) guidelines for the preclinical testing of biologicals (S6 Preclinical Safety Evaluation of Biotechnology derived Pharmaceuticals), and includes standard single dose studies in mice, rats, and Cynomolgus monkeys; 1- and 6-month repeat-dose iv toxicity studies in mice and monkeys; in vitro genetic toxicology tests, an in vivo carcinogenicity study in rasH2 transgenic mice, a full reproductive toxicity evaluation linked to a juvenile toxicity study in mice; a single-dose intrathecal toxicokinetic study in monkeys; cross reactivity studies; and local tolerance studies in rats and rabbits. Although the current application relates to the iv route of administration, an iv to sc toxicokinetic bridging study was performed in monkeys to support ongoing clinical trials by the sc route.

The majority of the pivotal toxicity studies were conducted in the period 1996-1999, using early batches of reslizumab produced by Schering (single and repeat dose toxicity, fertility, embryo-foetal development, local tolerance). The peri- and postnatal development with juvenile toxicity study, the 6 month carcinogenicity study in transgenic mice, and the iv/sc bridging study were however conducted with reslizumab produced by Ception (also used in phase 2 clinical trials).

Single dose toxicity

Three GLP-compliant single dose toxicity studies followed by a 14 days observation period have been conducted, using mouse, rat and monkey. The studies and the main findings are summarized in Table 4. Toxicokinetic data were not collected in any of the studies.

Table 1 Single dose toxicity studies with reslizumab

Study ID/GLP	Species/ Sex/Number/ Group	Dose (mg/kg)/Route	Observed max non-lethal dose (mg/kg)	Major findings
P6147 (GLP)	CD-1 Mouse 5/sex/group	0/500 iv	≥500	No drug-related findings for clinical signs, body weight, food consumption, or gross necropsy observations.
P6146 (GLP)	CD Rat 5/sex/group	0/500 iv	≥500	No drug-related findings for clinical signs, body weight, food consumption, or gross necropsy observations.
P6144 (GLP)	Cynomolgus monkey	0/100 iv	≥100	No drug-related findings for clinical signs, body weight, food consumption, or gross necropsy observations.

Repeat dose toxicity

Repeat-dose toxicity studies in mouse and monkey have been conducted with reslizumab from early batches produced by Schering. The studies are summarized in Table 5, and further described below.

Table 2 Repeat dose toxicity studies with reslizumab

Study ID/GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg) /Route /manufacturer	Major findings	NOEL/ NOAEL (mg/kg/day)

P6190 (GLP) 1 month	CD-1 mouse 20-40/sex/group	0/1/5/25 iv on days 1 and 15 4-5 weeks recovery	3 incidental deaths, one in each treatment group. 25 mg/kg (M): Minimal reduction in BW, lymphocyte counts and spleen and thymus weight. No histopathological correlates.	5 in M ≥ 25 in F
DS-2011-017 (GLP) 1 month	001178-W (Wild Type) CByB6F1-Tg(HRAS)2Jic mouse 10/sex/group	0/250/500 iv on days 1, 15, and 29 No recovery groups	Only pharmacological effects on eosinophils and total serum protein at both dose levels.	≥ 500
SN96264 (GLP) 6 months	Crl:CD-1 (ICR)BR VAF/Plus mouse 10/sex/group	0/2/10/25 iv once every 4 weeks (7 doses) Necropsy 5 weeks after last dose. No recovery groups.	3 incidental deaths in treatment groups. No other findings.	≥ 25
P6188 (GLP) 1 month	Cynomolgus monkey 4-6/sex/group	0/1/5/25 iv on days 1 and 15 7 weeks recovery	None	≥ 25
Res-4-0006 (GLP) 1 month	Juvenile Cynomolgus monkey (1.4-2.3 years) 6/sex/group	0/1/15 iv weekly (4 doses) 4 weeks recovery	Only reversible pharmacological effects on eosinophils at 15 mg/kg.	≥ 15
P6749 (GLP) 6 months	Cynomolgus monkey 7-12/sex/group	0/1/5/25 iv once every 4 weeks (7 doses) 3 months recovery	Transient postdose reaction in one high dose animal (salivation, emesis, recumbency). No findings on neurological examinations in any animals.	≥ 25

DS-2009-030 (GLP) 6 months	Cynomolgus monkey 8 M/group	0/1/5/25 sc or 1 iv once every 28 days (6 doses) 6 weeks recovery	An increase in eosinophil counts from several animals in the reslizumab-dosed groups (1 mg/kg iv, 1 mg/kg sc, and 5 mg/kg sc) was considered of uncertain relationship to reslizumab administration. Eosinophilic infiltrates and mucosal hyperplasia of the jejunum in a single animal in the 1 mg/kg iv. Local reaction at the injection site observed in one animal in the 25 mg/kg group.	Not established

Genotoxicity

Table 3 In vitro genotoxicity tests conducted with reslizumab

Type of test/study ID/GLP	Test system	Concentration range/ Metabolising system
Gene mutations in bacteria Study: P6214 (GLP)	*S. typhimurium* TA97a, TA98, TA100 TA102, TA1535; *E. Coli* WP2uvrA.	313-5000 µg/plate +/- S9
Chromosome aberration study Study: P6269 (GLP)	Human peripherial blood lymphocytes from two donors	31.3 or 125-1000 µg/ml +/- S9

Carcinogenicity

Table 4 Carcinogenicity study conducted with reslizumab

Study ID /GLP	Dose/Route	Exposure (AUC)	Species/No. of animals
DS-2012-005 (GLP)	0/100/250/516 mg/kg iv injection once every 2 weeks for 26 weeks	TK data not available	001178-T (hemizygous) CbyB6F1-Tg(HRAS)2Jic mice 25/sex/group

TK: Toxicokinetic

A 6 month carcinogenicity study with reslizumab in transgenic 001178-T (hemizygous) mice that carries the human prototype c-Ha-ras gene was conducted following discussions between Cephalon and FDA in 2010. Based on literature data that points to roles for IL-5 and eosinophils in tumour immune surveillance, the FDA considered that there was a need for assessment of carcinogenic potential. During the SA procedure in 2014, the CHMP agreed that the already conducted study DS-2012-005, previously discussed with the FDA, was adequate to describe the overall carcinogenicity potential of reslizumab.

At initiation of dosing, animals were 8-9 weeks old. A total of 14 doses of reslizumab (100, 250 or 516 mg/kg), or placebo, were administered iv every 2 weeks during the study. Females given 516 mg/kg/dose were slightly more likely to be observed as hunched, thin, or with few faeces relative to the remaining reslizumab and control groups. No evidence of reslizumab-related haematopoietic neoplasia was noted. At all reslizumab dose levels, reslizumab administration was associated with lower absolute eosinophil, white blood cell and lymphocyte count. No reslizumab-related macroscopic or microscopic findings were noted in the pathology examination at necropsy. Microscopic findings in animals given the positive control article reflected a robust carcinogenic response characterized by the occurrence of numerous neoplasms consistent with the expected effect of N-methyl- N-nitrosourea [MNU] in rasH2 mice, and no evidence of reslizumab-related oncogenicity was noted.

Reproduction Toxicity and developmental toxicity

Reproductive and developmental toxicity studies with reslizumab were carried out in CD-1 mice (fertility, general reproductive performance, and postnatal development; maternal toxicity, embryo-foetal toxicity, and teratogenicity; and, pre- and postnatal development) and NZW rabbits (maternal toxicity, embryo-foetal toxicity, and teratogenicity). In addition, a number of F1 generation mouse pups from the pre-/postnatal study were administered reslizumab from postnatal (PND) 14 to PND 70 and assessed for effects of the test article on systemic toxicity in juvenile mice. Most of the studies were conducted with reslizumab manufactured by Schering, with the exception of the pre- and postnatal study where newer batches of reslizumab from Ception were used (see discussion in section 2.3.6). Bioactivity of reslizumab in NZW rabbit was confirmed in pharmacology studies.

Table 5 Reproduction and developmental toxicity studies with reslizumab

Study ID/ Study type/ / GLP	Species/Sex/ Number/Group	Dose (mg/kg) /Route /manufacturer	Dosing period	Major findings	NOAEL (mg/kg
Fertility					
P6370 Preliminary iv fertility and postnatal study (GLP, except for the antigen challenge evaluation).	CD-1 mouse M/10 F/20	0/2/10/50 iv *Schering*	M: 1st day of 2-week premating period, and on 1st day of mating period. F: same as M plus on day 6 of presumed pregnancy and on day 2 post parturition	None, including no effects on changes in total or differential white blood counts in the 4-week old offspring. Absolute eosinophil counts in the offspring were comparable to the control mice, and there had been no effect on the ability of sensitized offspring (F1) to mount an eosinophilic response to OVA antigen challenge.	≥ 50 Toxicokinetic not included
P6981 Intravenous Fertility	CD-1 mouse M/25 F/25	0/2/10/50 iv *Schering*	M: Dosed on day 28 and day 14 prior	None	F0 Males: ≥50 mg/kg; F0 Females:

Study of reslizumab in Mice (GLP)			to mating, on first day of mating, and on day 14 after start of mating. F: Dosed on day 14 prior to mating, on 1st day of mating, and on day 14 after start of mating for females that did not mate during the 1st or 2nd week. Those that mated during the 2nd week were dosed on GD 0.		≥50 mg/kg Mean serum conc. at NOAEL: M: 208 µg/ml F: ND
Embryo-foetal development					
D27256 Pilot Intravenous Embryo-Foetal Development Study of reslizumab (Anti IL-5) in Mice (non-GLP)	CD-1 mouse F/8	0/2/10/50 iv *Schering*	Once on day 6 after mating.	The 50 mg/kg group had an increased incidence of resorptions (12.1% vs 3.7% in controls) which was possibly test-article related. NOEL = 10 mg/kg	F0: ≥50 mg/kg F1: 10 mg/kg Toxicokinetic not included
P6378 Intravenous Embryo-Foetal Development Study of reslizumab in Mice (GLP)	CD-1 mouse F/25	0/2/10/50 iv *Schering*	Once on day 6 after mating	None.	F0: ≥50 mg/kg F1: ≥50 mg/kg Toxicokinetic not included
D27243 Pilot Intravenous Embryo-Foetal Development Study of reslizumab in Rabbits (non-GLP)	New Zealand White rabbit F/4	0/2/10/50 iv *Schering*	Once on day 7 after mating	The 50 mg/kg group had a reduced pregnancy Rate (2 of 4 were pregnant).	F0: 10 mg/kg F1: ≥50 mg/kg Toxicokinetic not included
P6379 Intravenous Embryo-Foetal Development Study of reslizumab in Rabbits	New Zealand White rabbit F/20	0/2/10/50 iv *Schering*	Once on day 7 after mating	None	F0: ≥50 mg/kg F1: ≥50 mg/kg Toxicokinetic not included

(GLP)					
Peri & postnatal					
DS-2010-020 Perinatal/Postnatal Reproduction, Development, and Juvenile Toxicity Study of Intravenous Reslizumab in Mice, Including a Postnatal Behavioral/Functional Evaluation (GLP)	CD-1 mouse F0: F/30 F1: M/16-17; F/15-16	F0: 0/10/50 iv F1: 0/10/25 iv *Ception*	F0: GDs 6, 18 and DL 14 (mice that delivered a litter) F1: PNDs 14, 42 and 70	Peri & postnatal: F1: Statistically significant increase in normal movement in the home cage (50 mg/kg/dose female mice on PND 77±2). Relation to treatment considered doubtful. Juvenile: None	F0: 50 mg/kg/dose; F1 Developmental Replicate: 50 mg/kg/dose; F1 Juvenile Toxicity Phase: 25 mg/kg/dose

Overall, there were no reslizumab related findings with respect to male or female fertility in mouse, general reproductive performance, embryo-foetal development or teratogenicity in mouse and rabbit. There were also no findings suggesting an effect on peri- post natal development, or juvenile toxicity, in mouse. In the postnatal and juvenile groups endpoints included growth, development, sexual maturation, fertility, reproductive performance, behaviour and learning, haematology and clinical chemistry. Reslizumab is excreted into milk in mouse, reaching a concentration approximately 6-8% of the concentration in maternal serum.

Local Tolerance

The results from four local tolerance studies where reslizumab manufactured by Schering was administered via subcutaneous (SN98072), intravenous (SN98568), intramuscular (SN98071) or intraarterial (P6233) route, and a pain-on injection study (SN98070) did not show any reslizumab related increase in irritation and pain.

Other toxicity studies

Antigenicity and immunotoxicity

Reslizumab is a humanised protein and therefore expected to have antigenic properties in animals, which indeed was observed in some animals (formation of antibodies to reslizumab).

No dedicated studies on immunotoxicity have been conducted. IgG4 does not activate the complement system.

Impurities

No dedicated studies on impurities have been conducted.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant claims a waiver for environmental risk assessment (ERA) studies for reslizumab based on the following:

- Reslizumab is a recombinant humanized anti-IL-5 mAb of the IgG4/κ isotype. Proteins are biodegradable both in the body and in the environment and are usually excreted from the body after endogenous proteolytic degradation. It is the Applicant's opinion that proteins such as reslizumab are exempt from the requirement of preparing an Environmental Assessment.
- Reslizumab is indicated for a very small population of eosinophilic asthma patients.

As stated in the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447), antibodies are unlikely to pose a significant risk to the environment. Based on this, the Applicant's justification for not submitting an ERA for reslizumab is considered acceptable to the CHMP, although the size of the patient population in itself is not a ground for waiver.

2.3.6. Discussion on non-clinical aspects

Pharmacology

IL-5 binding activity has been satisfactorily demonstrated in a combination of in vitro and in vivo studies for mouse, monkey and rabbit. The binding affinity of reslizumab in the rat, the species in which several safety pharmacology studies were performed, has been determined using surface plasmon resonance technology and revealed a similar affinity of reslizumab for rat IL-5 albeit lower than that for human IL-5.

Testing of reslizumab in different animal models on asthma supports a therapeutic potential for reslizumab in airway eosinophilic conditions. It is however noted that the effect of reslizumab on eosinophils in circulation has not been investigated in any of the non-clinical pharmacology studies included in the dossier. However, the applicant refers to literature data pointing to an inhibitory effect of TRFK-5 (rat anti-mouse IL-5) on allergen-induced increase in bone marrow eosinophils in mice (Kung et al 1995).

The observation of binding of reslizumab to human and monkey CNS tissue in vitro resulted in a cause for concern related to potential adverse effects. This topic has been further addressed by the applicant by further investigations of CNS distribution in vivo, a study with intrathecal administration in monkey, and inclusion of neurological endpoints (functional and histopathological) in several in vivo studies in rat and monkey (see safety pharmacology and toxicology). Taken together, reslizumab is, due to the high molecular weight, not expected to reach CNS in animals or humans with an intact blood brain barrier, and results from different non-clinical studies with reslizumab in rodents and monkey do not predict neurotoxicity. The applicant has performed additional studies to further investigate the binding of reslizumab to BRAL-1, which was previously identified as the antigen to which reslizumab was binding in the CNS tissue. Surface plasmon resonance analysis revealed no binding of reslizumab to recombinant hBRAL-1 and subsequent orthogonal immunohistochemical staining revealed no BRAL-1 binding in CNS tissue suggesting that the earlier findings may have been artefacts and that reslizumab does not bind with any significant affinity to BRAL-1.

Pharmacokinetics

Specific distribution studies have not been conducted. For a monoclocal antibody, distribution studies are in general not considered necessary and given that the efficacy of reslizumab is the result of systemic inhibition of eosinophil activation, this is appropriate.

General toxicology

Overall, there were no adverse findings in the single and repeat dose toxicity studies that could be related to reslizumab in either species. Also, no CNS-related effects have been revealed during thorough investigations in animals.

The choice of species for general toxicity testing is justified in terms of pharmacological responsiveness.

In most general toxicity studies, neither toxicity, nor reduction of blood eosinophils, could be detected. However, the fully humanised IL-5 IgG1 antibody mepolizumab was reported to induce a > 80% reduction in blood eosinophils in monkeys administered repeated monthly doses ≥ 5 mg/kg (Hart TK, Cook RM, Zia-Amirhosseini P, Minthorn E, Sellers TS, Maleeff BE, Eustis S, Schwartz LW, Tsui P, Appelbaum ER, Martin EC, Bugelski PJ, Herzyk DJ, J Allergy Clin Immunol, 2001 Aug;108(2):250-7). In theory, the lack of an expected pharmacological effect could be due to production of neutralising antibodies developing in response to repeated dosing. Indeed, at weeks 13 and 25, a few monkeys in the 6 months study P6749 cleared reslizumab completely prior to the next dosing. However, for most animals this was not the case. It is therefore agreed that these infrequent cases does not invalidate the results of the studies. It is also noted that in the studies where a pharmacological effect actually was observed, reslizumab manufactured by Ception was used. In the pharmacology studies and other repeat dose toxicity studies performed earlier, material from Schering was administered. However, when 1 mg/kg Ception material was administered iv every 28 days for 6 months to monkeys, no reduction in blood eosinophils could be detected (DS-2009-030), which is consistent with the lack of effect on circulating eosinophils noted following iv administration of 1 mg/kg Schering substance every 4 week in the standard 6-month toxicity study in monkeys (Study P6749). This comparison supports the fact that there is no significant difference in pharmacological activity between reslizumab produced by Schering and Ception. It is acknowledged that it may be more difficult to detect a reduction of circulating eosinophils in healthy animals, than in BAL fluid in allergic animals, or in patients with elevated eosinophils. In healthy mice and monkeys, an inhibitory effect on circulating eosinophils could only be detected in studies where reslizumab was administered weekly (Res-4-006), or at high monthly doses (≥ 250 mg/kg, DS-2011-017).In addition, a reduction in blood eosinophils was seen in the 6 month carcinogenicity study (monthly iv doses ≥ 250 mg/kg).

With the exception of the study in juvenile monkeys (Res-4-0006), AUC values have not been calculated in monkeys (due to few sampling points). In these studies, Cmax levels have been used for interspecies comparison during assessment. Considering the long half-life of reslizumab, AUC may have been a more appropriate parameter for exposure. The interspecies comparison is further complicated by the fact that different dosing intervals are compared, and the fact that ADA formation cannot be quantitated in the presence of reslizumab. Under these conditions, animal exposure at NOAEL equal to, or slightly in excess, of expected human therapeutic exposure must be interpreted cautiously. One exception is however the 1 month study DS-2011-017 in 001178 Wild Type mouse, where high doses leading to a reslizumab exposure at least 50 fold higher compared to humans resulted in a reduction of eosinophils.

Genotoxicity

Reslizumab was assessed for genotoxic potential in two in vitro tests, the bacterial mutagenicity (Ames) test in Salmonella typhimurium and Escherichia coli, and a chromosomal aberration study in human peripheral blood lymphocytes. In both tests, negative results were reported.

As outlined in ICH S6 (R1), standardised genotoxicity studies routinely conducted for pharmaceuticals are not considered appropriate for biotechnology-derived pharmaceuticals. The Ames test and chromosomal aberration assay conducted by the applicant are considered redundant and do not give any useful information. Monoclonal

antibodies in general are not considered to entail any potential for interaction with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of reslizumab has been tested in a transgenic rasH2 mouse model, in accordance with Scientific advice from the FDA. In 2014, the Applicant received support on the adequacy of the study design by the CHMP during an EMA scientific advice procedure.

During the SA, the CHMP advised the Applicant to provide a comprehensive review on the role of IL-5 and eosinophils in tumour biology and/or anti-tumour responses. This has been addressed in the submitted non-clinical overview. Taken together, there is conflicting evidence on the role of eosinophils and IL-5 in the promotion or suppression of tumours, and results seem to depend on the particular model used. Most important, no model using IL-5 deficient animals has demonstrated an increased risk of spontaneous tumours. Models in experimental systems of induced tumours showed contradictory results and often indicated a protective rather than tumour promoting effect in IL-5 deficient mice.

In conclusion, iv administration of reslizumab to rasH2 hemizygous CByB6F1- Tg(HRAS)2Jic mice at doses up to the maximum-feasible dose (516 mg/kg) once every 2 weeks for 26 weeks (14 doses) was well tolerated. No evidence of reslizumab-related oncogenicity, mortality, haematopoietic neoplasia, or macroscopic or microscopic organ/tissue findings was noted. A pharmacological effect on blood eosinophils was observed, and a robust carcinogenic response induced by the positive control agent confirms the model. At the high dose level a safety margin of at least 50 compared to the clinical dose (3 mg/kg) can be extrapolated from a different toxicology study, which is considered acceptable by CHMP.

Reproductive and developmental toxicity

In the embryo-foetal development studies in CD-1 mouse and NZW rabbit, toxicokinetic data were not collected, and a pharmacological effect has not been demonstrated. IgG antibodies can be transferred from the mother to the foetus, but transfer is very low during the first part of the pregnancy. In mouse, little is known concerning transfer of human IgG4 specifically, but the FcRn is observed to be present in the yolk sac from GD10-11 (Christopher J. Bowman, William J. Breslin, Anu V. Connor, Pauline L. Martin, Graeme J.Moffat, Lakshmi Sivaraman, M. Belen Tornesi, and Simon Chivers, Birth Defects Research (Part B) 98:459–485 (2013)). This may allow transfer of IgG to the foetus relatively earlier in mouse, compared to humans and rabbits. In rabbits, the majority of IgG transport from mother to foetus takes place from GD 15 (Pentsuk and van der Laan, Birth Defects Research (Part B) 86:328-344 (2009)). For all species, transfer increases during gestation. Given that transfer of reslizumab from mother to foetus during the period of organogenesis is expected to be very low in humans, the lack of data on actual foetal exposure in the embryofoetal development studies can be accepted. Maternal exposure data for mouse can be extrapolated from other studies. The limited PK-information from rabbit is considered a deficiency, but not essential for assessment since systemic exposure is assumed after iv administration.

Exposure of the F1 post weaning group in the peri- and post-natal study is expected to occur via transfer from mother to foetus during the late part of the pregnancy and/or via milk. Since the first sampling of blood was done on PND 14, foetal exposure during pregnancy cannot be quantitated. The reslizumab concentration in milk was shown to be 6-8% of the maternal serum concentration. Although the serum exposure in pups was low at PND 14, the increase up to PND 21 confirms relevant exposure via milk. This is expected since the mouse is known to have a postnatal uptake of IgG via FcRn in the small intestine until weaning. This is in contrast to the human situation, where uptake of IgG from milk in neonates only occurs 1-2 days after birth (Pentsuk and van der Laan, Birth Defects Research (Part B) 86:328-344 (2009)).

Use during pregnancy and breastfeeding have been included as missing information in the RMP. In addition, information on pregnancy exposure and breastfeeding is included in the SmPC.

Juvenile animals were exposed to reslizumab serum concentrations in the clinical range, but there were no changes in haematology at the end of the recovery phase. This indicates a lack of pharmacological effects during exposure on PND 14, 42 and 70, or that effects were reversible. A conclusion is impossible to draw due to lack of haematology samples during the exposure phase. Overall, the comprehensive PPND study that also includes exposure of juveniles from PND 14-70, has not revealed any adverse findings on growth and development, fertility and reproductive capacity, learning, behaviour, or motor activity.

Local tolerance

It is noted that reslizumab batches used in all local tolerance studies, with the exception of P6223, did not contain any aggregates. However, results are in line with data from toxicity studies in mouse and Cynomolgus monkey, as well as studies on reproductive and developmental toxicity studies in mouse and rabbit. Batches used in these studies, and in study P6223, are reported to contain up to 0.2% aggregates at batch release. Furthermore, clinical safety data collected for newer reslizumab material produced by Ception and the Applicant does not point to local adverse effects in patients.

Antigenicity and immunotoxicity

Since reslizumab is a humanised antibody, it is expected that all non-human species may produce anti-drug antibodies. ADA formation was only detected in a few animals across repeat dose toxicity studies. However, the number of ADA-positive animals may have been underestimated, due to interference of the antibody determination with circulating levels of the antigen. The most reliable estimation of the number of animals with ADA is therefore from the recovery phases of studies in which the serum levels of reslizumab were near or below the LLOQ of the assay.

An antigenic effect of reslizumab in animals is only considered of relevance for the interpretation of the results in non-clinical studies with repeated dosing, and not predictable for potential antigenicity in humans. Humans are considered the only relevant and appropriate species for determining antibody responses against reslizumab.

There were no indications of suppressed immune status in general toxicity studies. The Applicant refers to literature reports on the role of IL-5 and eosinophils for animal host defence against helminthic parasites. Taken together, animal models support a potentially complementary, but not essential role for eosinophils in immune defence against helminthic parasites. The lack of dedicated immunotoxicity studies is accepted. See Section 2.6 for further discussion on this point.

Impurities

Changes in manufacturing processes for proteins may affect the pharmacological activity, pharmacokinetics or safety profile of the product. No obvious differences between different reslizumab lots used throughout the non-clinical program have been established by the applicant.

No dedicated studies on impurities have been conducted. Given the general lack of systemic pharmacological and toxicological effects in mouse and monkey, animal models are not expected to be able to prove minor differences between lots with respect to impurities. Further qualifying studies in animals are therefore not considered to provide any useful information.

Environmental risk assessment

As stated in the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447), antibodies are unlikely to pose a significant risk to the environment. Based on this, the Applicant's justification for not submitting an ERA for reslizumab is considered acceptable.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical dossier is in accordance with ICH S6. Overall, the primary pharmacodynamic studies provided adequate evidence of rezlisumab binding activity. The general pharmacology studies support a therapeutic potential for reslizumab in airway eosinophilic conditions.

From the pharmacokinetic point of view, specific distribution studies have not been conducted. For a monoclocal antibody, distribution studies are in general not considered necessary and given that the efficacy of reslizumab is the result of systemic inhibition of eosinophil activation, this is appropriate.

Overall, the repeat dose toxicity studies revealed no adverse findings that could be related to reslizumab. Also, no CNS-related effects have been revealed during thorough investigations in animals.

From a non-clinical perspective, the data presented by the Applicant is satisfactory.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The main clinical studies in support of the target populations are two long-term phase 3 placebo-controlled studies in patients with eosinophilic asthma with the primary objective to reduce the frequency of clinical asthma exacerbations (study 3082 and 3083). One short-term phase 3 trial (study 3081) in patients with eosinophilic asthma was designed to assess primarily the impact of two doses of reslizumab on FEV1. Additional studies include the open-label long-term safety and efficacy study 3085, a short-term phase 3 study (3084) in patients with asthma and unselected for blood eosinophil level and a proof-of-concept phase 2 study (Res-5-0010) in patients with eosinophilic asthma.

Table 6 Synopsis of studies within the clinical development program for reslizumab

Study Number/ Duration	Primary Objective	Design	Dose reslizumab	Healthy subjects /patients	N Treated and Completed M/F (enrolled) Age range (years)
Efficacy and safety studies (primary to the indication of eosinophilic asthma)					
C38072/3081 16 weeks	Efficacy, safety	Phase 3 R, DB, PG, PC	0.3 mg/kg or 3.0 mg/kg iv every 4 weeks	Asthma, EOS ≥400/µL inadequately controlled with medium to high dose ICS	311 treated 265 completed M 132/F 183 12-71 years
C38072/3082 12 months	Efficacy, safety	Phase 3 R, DB, PG, PC	3.0 mg/kg iv every 4 weeks	Asthma, EOS ≥400/µL inadequately controlled with medium to high dose ICS, previous exacerbation	488 treated 433 completed M 186/F 303 12-75 years
C38072/3083 12 months	Efficacy, safety	Phase 3 R, DB, PG, PC	3.0 mg/kg iv every 4 weeks	Asthma and EOS ≥400/µL inadequately controlled with medium to high dose ICS previous exacerbation	464 treated 401 completed M 170/F 294 12-75 years
C38072/3084 16 weeks	Efficacy, safety	Phase 3 R, DB, PG, PC	3.0 mg/kg iv every 4 weeks	Asthma (moderate to severe)	492 treated 409 completed M 181/F 315 18-65 years
C38072/3085 Up to 104 weeks (2 years)	Safety, efficacy	Phase 3 NR, OL, long-term extension study 3081, 3082, 3083	3.0 mg/kg iv every 4 weeks	Asthma (moderate to severe) and EOS ≥400/µL	1051 treated 156 completed M 406/F 646 12-77 years
Other studies supporting the indication of eosinophilic asthma					
I96-350 Single dose	Safety, PK	Phase 1 R, DB, PC, rising single-dose,	0.03 mg/kg 0.10 mg/kg	Asthma, persistent (severe)	32 treated 31 completed M 18/F 14 20-65 years
P00290 12 weeks	Efficacy, safety	Phase 2; R, evaluator-blind, PG, PC	0.3 mg/kg 1.0 mg/kg Iv at day 1 and week 12	Asthma, persistent (moderate to severe)	211 treated 173 completed M 107/F 108 19-77 years
Res-5-0010 16 weeks	Efficacy, safety	Phase 2; R, DB, PG, PC	3.0 mg/kg iv every 4 weeks	Asthma; poorly controlled and eosinophilic airway inflammation	106 treated 94 completed M 43/F 63 19-69 years

Study Number/ Duration	Primary Objective	Design	Dose reslizumab	Healthy subjects /patients	N Treated and Completed M/F (enrolled) Age range (years)
Studies in healthy volunteers supporting safety					
C38072/1102 20 weeks	Safety, PD and PK	Phase 1: R, OL	0.3 mg/kg 1.0 mg/kg 2.0 mg/kg 3.0 mg/kg every 4 weeks	Healthy Volunteers Japanese and non-Japanese	100 treated 82 completed
C38072/1107 Singel dose	Safety, PK, PD	Phase 1 R, OL	Non-Janapese: 220 mg iv 220 mg sc Japanese: 220 mg sc	Healthy Volunteers Japanese and non-Japanese	75 treated; 45 s.c and 30 i.v. 70 completed
Additional studies supporting safety					
P01942 Single dose	Safety, PK	Phase 1 R, evaluator-blind, PG, PC	1.0 mg/kg 2.0 mg/kg	Nasal polyposis	24 treated 24 completed M 16/F 8 18-63 years
NIH Protocol 01-I-0155 Up to 24 weeks	Safety, efficacy	Phase 2 OL, uncontrolled, single and repeat-dose	1.0 mg/kg every 4 weeks	HES or EG	8 on single dose 5 on 5 to 6 doses 8 completed M 4/F 4 30-53 years
Res-5-002 15 weeks	Safety, efficacy	Phase 2b/3 R, DB, PG, PC	1.0 mg/kg 2.0 mg/kg 3.0 mg/kg Every 4 weeks	Eosinophilic esophagitis	226 treated 194 completed M 172/F 54 5-18 years
Res-5-004 16 weeks	Safety, efficacy	Phase 3 OL, extension	1.0 mg/kg dose increase to 3.0 mg/kg every 4 weeks	Eosinophilic esophagitis	190 treated 112 completed M 148/F 42 5-19 years

R=randomized; PG=parallel-group; DB=double-blind, PG=parallel-group, PC=placebo-controlled; M=male; F=female; EOS=eosinophils; iv=intravenous; ICS=inhaled corticosteroids; NIH=National Institute of Health

2.4.2. Pharmacokinetics

Absorption

After a single i.v. infusion of reslizumab over 20 to 50 minutes, mean peak serum concentrations of 78 µg/ml were typically observed either at the end of the infusion or at the next time point after the end of the infusion. Serum reslizumab concentrations generally decline from peak in a biphasic manner. Reslizumab pharmacokinetics in healthy adults and patients does not appear to be different to a relevant extent.

No apparent deviation from dose-proportional reslizumab PK was noted over the dose range of 0.3 mg/kg to 3.0 mg/kg. Lineair PK in this dose range was observed probably due to aspecific non-target mediated clearance.

Upon multiple dose administration of reslizumab, the serum concentration-time curves were qualitatively similar to that observed after a single dose, with accumulation of approximately 1.5 to 1.9 fold. This observed degree

of accumulation for reslizumab is in line with the expected accumulation considering an elimination half-life of approximately 24 days and dosing every 28 days (4 weeks).

Inter-individual variability following multiple doses was approximately 20% to 30% for both Cmax and AUC.

Distribution

As expected for a monoclonal antibody, reslizumab has a small volume of distribution (approximately 5 L for a typical patient), suggesting minimal distribution to the extravascular tissues.

Elimination

The CL estimate from the final PopPK model was 7.16 mL/h for the typical patient (an individual weighing 73 kg, representing the median body weight in the analysis dataset population). Reslizumab has a long terminal t½ of approximately 24 days. Similar to other monoclonal antibodies, reslizumab is believed to be degraded by enzymatic proteolysis into small peptides and amino acids.

Low albumin serum levels have been reported to result in increased clearance of monoclonal antibodies. The Applicant investigated the effect of albumin on the PK of reslizumab, however, no data were available for low albumin levels (<3.5 g/dl). No data were available for IL-5 levels, and as such, IL-5 levels could not be evaluated as a covariate in the popPK model.

Intra- and inter-individual variability

Interindividual variability of reslizumab pharmacokinetics under steady state conditions is small to moderate, between 20 and 30%.

Special populations

Reslizumab is an antibody with a molecular mass of 147 kDa and is therefore not expected to be excreted in urine. Further, no direct effect of hepatic function on the pharmacokinetics of reslizumab is expected either because antibodies are principally cleared by catabolism. The expected lack of effect of mild renal or hepatic impairment is confirmed by the PopPK analysis. With respect to renal function, in the PopPK analysis, the majority of individuals had either normal renal function (36.6%) or mildly decreased renal function (55.5%). A small proportion (7.9%) had moderately decreased renal function and only 1 subject (<1%) had severely decreased renal function. Renal function was assessed using an estimate of glomerular filtration rate based on a Modification of Diet in Renal Disease (MDRD) equation. There were insufficient data to assess the impact of severe renal impairment on the pharmacokinetics of reslizumab. With respect to hepatic impairment, in the PopPK analysis, the majority of the population (95.3%, n=766) exhibited normal liver function tests at baseline, 4% (n=35) exhibited mildly increased and 0.4% (n=3) moderately increased liver function tests. The results indicate that exposures are generally consistent across the liver function test groups, although exposure values increased slightly in patients with mild elevated liver function tests. Liver function was assessed using the National Cancer Institute Organ Dysfunction Working Group Liver Function Classification, in which classification of liver dysfunction is based on a combination of total bilirubin and aspartate aminotransferase. There were insufficient data to assess the impact of moderate hepatic impairment on the pharmacokinetics of reslizumab. No further formal studies in patients with renal and hepatic impairment are considered necessary.

Results of the PopPK analysis demonstrated that age, gender, race (Caucasian, Black, Asian), have no notable impact on the pharmacokinetics of reslizumab. No marked differences in reslizumab exposure were observed between adults and older subjects.

Table 7 Age Categories (≥65 years) in Reslizumab Population Pharmacokinetic Analysis

Age 65-74 (Older subjects number/ total number [%])	Age 75-84 (Older subjects number/ total number [%])	Age 85+ (Older subjects number/ total number[%])
40/804 [5.0%]	3/804 [0.4%]	0/804 [0%]

The PopPK analysis also demonstrated no clearly reduced exposure to reslizumab in patients who developed antibodies to reslizumab (i.e. were ADA positive).

No data in children are currently provided. Data in adolescents from PopPK study CP-11-006 suggest a slightly lower exposure in adolescents when dosed with 3 mg/kg.

PopPK analyses indicated that heavier body weight results in more rapid clearance and larger volume of distribution, potentially resulting in reduced exposure at higher weight when flat dosing would be applied. Exposure data upon weight-based dosing (3 mg/kg) suggests that the proposed weight-based posology yields relatively comparable exposure at all weight ranges.

Pharmacokinetic interaction studies

No formal clinical drug interaction studies have been performed with reslizumab. *In vitro* data (Study DM-2013-017) indicate that IL-5 and reslizumab are unlikely to affect CYP1A2, 3A4 or 2B6 activity.

2.4.3. Pharmacodynamics

Mechanism of action

Reslizumab binds to human interleukin 5 (IL-5), a key cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils. IL-5 is the most potent and specific cytokine for the eosinophil lineage and is responsible for cellular expansion, release from the bone marrow into the peripheral blood, and survival following a variety of triggers, typically TH2 stimuli.

By targeting IL-5, reslizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signalling and the over-expression of peripheral blood and tissue eosinophils. Neutralizing IL-5 reduces the promotion, growth and survival of eosinophils, although complete blood eosinopenia is not achieved due to redundant signalling by IL-3 and GM-CSF through a common β-sub-unit.

Primary and Secondary pharmacology

PK/PD analyses were provided in order to investigate potential dose-response and exposure response relationships, in support of the current application.

Based on the PK/PD analyses provided, the proposed 3 mg/kg dosing regimen is anticipated to produce near maximal inhibition of the eosinophil response. The model predicted decrease in eosinophil counts with this dosing regimen corresponds with a dose dependent increase in predicted FEV1. Improvement in FEV1 appeared to be more pronounced as exposure increases. A corresponding decrease in model predicted ACQ values is observed with increase in dose. As systemic exposure to reslizumab increases, the ACQ score decreases. These findings confirm that the observed exposure related changes in eosinophil levels and FEV1 are associated with an exposure-related improvement in symptoms.

Though I_{max} and IC_{50} for peripheral blood eosinophilia seem to occur at blood reslizumab below the ones expected at the proposed therapeutic dose, it is clear that administration of reslizumab (3.0 mg/kg) causes a reduction in blood eosinophils, which in turn is correlated with clinical benefit (i.e. improvement in FEV_1 and ACQ scores, see section 'Dose-response studies and main clinical studies'). This supports the correlation between peripheral blood eosinophil count and clinical benefit.

Reslizumab being a large molecule is considered to have a low risk for QT-mediated proarrhythmia. In Study C38072/1102, triplicate ECGs were collected at each pharmacokinetic time point and were compared to baseline. There was no apparent trend toward an increase in QTcF with an increase in the serum concentration of reslizumab. Overall, values of mean increases of QTcF were minimal and without indication of a relationship to increasing dose, expected time of maximal concentration, or increasing duration of exposure to reslizumab. As a result, repeat iv doses of up to 3.0 mg/kg reslizumab are considered to have minimal potential to cause cardiac repolarization changes. In Study C38072/1102, no ECG findings were reported as adverse events and no abnormal ECG findings were assessed as clinically significant by the investigators.

Myalgia was determined to be an adverse drug reaction for the proposed reslizumab dose (3 mg/kg) and regimen (every 4 weeks), based on an incidence slightly greater than placebo in controlled trials and clinical plausibility. Therefore, an exploration of the relationship between reslizumab exposure across a broad series of muscle disorder adverse event codes was conducted. An exposure-response correlation was observed with the model predicted probability of experiencing a muscle disorder adverse event increasing with increase in model-predicted reslizumab concentration.

No apparent differences in reslizumab pharmacodynamics were observed between Japanese and non-Japanese subjects. The Applicant discussed the possibility for relevant genetic differences related to IL-5 in different ethnic populations. All missense variants characterized in IL-5 are rare or very rare across European, East Asian, South Asian, African, and Latino.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics or reslizumab has been investigated to a reasonable extent. In general, pharmacokinetic characteristics of reslizumab are in line with those for other monoclonal antibodies, i.e., a small volume of distribution and a long elimination half-life was observed.

Results of the PopPK analysis demonstrated that age, gender, race (Caucasian, Black, Asian), have no notable impact on the pharmacokinetics of reslizumab.

No data in children are currently provided. Data in adolescents from PopPK study CP-11-006 suggest a slightly lower exposure in adolescents when dosed with 3 mg/kg. A PIP has been agreed in order to obtain data in the paediatric population between 6 and 18 years of age.

Exposure data upon weight-based dosing (3 mg/kg) suggests that the proposed posology yields relatively comparable exposure at all weight ranges. Additional analyses provided by the Applicant indicated that this relationship holds up to obese patients. Therefore, there is no need for capping of the dose at a certain weight.

Antibodies have a low potential for pharmacokinetic drug interactions as they are not metabolised by liver cytochrome P450 (CYP) or other drug metabolizing enzymes. Further, and it is unlikely that they have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction. This presumed lack of relevant

drug-drug interactions is confirmed by the exploratory in vitro data and PopPK analyses conducted by the Applicant. This information is adequately reflected in the SmPC.

However, reslizumab has not been studied in patients concurrently taking immunosuppressant medicinal products other than oral corticosteroids; therefore, the safety and efficacy profile of reslizumab in these patients is unknown. Use in combination with immunosuppressant drugs therapy is included as missing information in the RMP. This information is also reflected in the SmPC.

In addition, the SmPC states that reslizumab has not been studied in patients receiving live vaccines. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving reslizumab or the response to new immunisations in patients receiving reslizumab. Effect on vaccination and the use of live/attenuated vaccines has been added as missing information in the RMP.

Pharmacodynamics

The mechanism of action is through blockage of the IL-5 receptor by reslizumab. Reslizumab occupies a region on human IL-5 that is essential for its interaction with the receptor and thereby blocks IL-5 bioactivity.

Based on the PK/PD analyses provided, the proposed 3 mg/kg dosing regimen is anticipated to produce near maximal inhibition of the eosinophil response.

PK/PD analyses further indicate that there is no apparent trend toward an increase in QTcF with increasing serum concentrations of reslizumab. The modelled probability of experiencing a muscle disorder adverse event increases with increasing reslizumab concentration.

2.4.5. Conclusions on clinical pharmacology

Reslizumab is a humanised monoclonal antibody (IgG4, κ) against the human interleukin-5 (IL 5). Reslizumab binds specifically to IL 5 and interferes with IL 5 binding to its cell surface receptor. IL 5 is a key cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils. Reslizumab binds human IL 5 with picomolar affinity blocking its biological function; consequently survival and activity of eosinophils are reduced.

Pharmacokinetics or reslizumab has been investigated to a reasonable extent. In general, pharmacokinetic characteristics of reslizumab are in line with those for other monoclonal antibodies, i.e., a small volume of distribution and a long elimination half-life was observed.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study 3081

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

Methods

The primary objective of the study was to determine whether reslizumab, at a dosage of 0.3 or 3.0 mg/kg administered once every 4 weeks for a total of 4 doses, was more effective than placebo in improving lung function in patients with eosinophilic asthma as assessed by the overall change from baseline in forced expiratory volume in 1 second (FEV1).

Adult patients (aged 12- 75 years) with a previous diagnosis of asthma were included. Other main inclusion criteria were an ACQ score of at least 1.5, airway reversibility of at least 12% after beta-agonist administration, current blood eosinophil level of at least 400/μL and inhaled fluticasone at a dosage of at least 440 mcg, or equivalent, daily. Patients' baseline asthma therapy regimen must have been stable for 30 days before screening, and continued without dosage changes throughout the study.

The main exclusion criteria were known hypereosinophilic syndrome, other lung conditions (including a.o. COPD, Churg-Strauss syndrome), current smoker (smoked within the past 6 months), other systemic immunosuppressive or immunomodulating therapies, use of other biologic agents, comorbidity that could interfere with the study or compromise patients' safety, uncontrolled comorbidity, history of concurrent immunodeficiency (a.o. human immunodeficiency virus [HIV] or acquired immunodeficiency syndrome), current use of systemic corticosteroids (including use of oral corticosteroids), infections (including parasitic infection).

The study consisted of a 2- to 4-week screening period, a 16-week double-blind treatment period, including a final evaluation 4-weeks after the final infusion (end-of-treatment visit), and an end-of-study visit that occurred 90 (±7) days after the end-of-treatment visit. Thereafter, patients could enrol the open-label, long-term study or return for an assessment 90 (±7) days after their end-of-treatment visit in this study.

Eligible patients were randomly assigned to study drug treatment (reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg, or placebo) with a 1:1:1 ratio. Randomization was stratified according to the occurrence of previous asthma exacerbations within the past 12 months (yes or no) and age (12 to 17 years or 18 years of age or older) at baseline. An asthma exacerbation was defined by 1 of the following: 1) a reduction in FEV1 of 20% or greater, 2) a hospitalization because of asthma, 3) emergency treatment because of asthma, or 4) use of prednisone or systemic corticosteroids for 3 days or more.

The primary efficacy variable was the overall change from baseline in FEV1 over 16 weeks of treatment. Secondary efficacy variables were change from baseline over 16 weeks for ACQ score, FVC, FEF25%-75%, ASUI score, SABA use, blood eosinophil count, and % predicted FEV1. Change in AQLQ score from baseline to week 16 was also included as a secondary endpoint. Further, pharmacokinetics, immunogenicity, and safety and tolerability were evaluated.

All efficacy analyses were performed on the FAS (all randomized patients who were treated with at least 1 dose of study drug). The primary variable was analyzed using a mixed-effect model for repeated measures (MMRM) with fixed effects (treatment, stratification factors, sex, visit, interaction of treatment and visit), covariates (height, baseline value), and patient as the random effect for the repeated measurements. The overall treatment effect was analysed using a 2-sided t test at the significance level of 0.05. A hierarchical testing procedure (in the order of 3.0 mg/kg first) was used to control the Type I error for the 2 comparisons of reslizumab to placebo.

Results

A total of 315 were enrolled in the study and 311 received at least 1 dose of study drug (placebo: n=105, Reslizumab 0.3 mg/kg: n=103; Reslizumab 3.0 mg/kg: n=103). A total of 81%, 88%, and 83% of patients

completed the study for the placebo, 0.3 mg/kg and 3.0 mg/kg treatment group. Post-hoc analyses showed that most patients were classified as GINA step 4 (79%), followed by GINA step 3 (17%) and <1% as GINA step 5.

A total of 50 out of 311 (16%) patients withdrew from the study; (12 [12%] receiving 0.3 mg/kg reslizumab treatment, 18 [17%] receiving 3.0 mg/kg reslizumab treatment, and 20 [19%] receiving placebo treatment). The most frequent reason for withdrawal was adverse events, which occurred for 1 (<1%) patients in the 0.3 mg/kg reslizumab treatment group, 7 (7%) patients in the 3.0 mg/kg reslizumab treatment group, and 9 (9%) patients in the placebo treatment group.

Baseline demographic and disease state characteristics were generally similar between patients in each treatment group. The mean age was 43.9 years, 58% were female, 81% were white and mean weight was 76.2kg. The overall randomized population had a mean percent predicted FEV1 of 70.1%, AQLQ score of 4.349 and ACQ score of 2.514. About 56% of the patients experienced an exacerbation of asthma within the past 12 months and most patients (78%) used LABA in addition to ICS. The mean daily dosage for inhaled corticosteroids at baseline was 756.7 μg (range 320 - 2400), 756.3 μg (range: 320 – 1800) and 813.5 μg (range: 400 – 3400) in the placebo, reslizumab 0.3 mg/kg and reslizumab 3.0 mg/kg treatment group, respectively. About 87% of patients used a long-acting beta-agonist, in addition to the required ICS (randomised population). Comparable results were obtained for the FAS.

The overall change from baseline (LS mean) in FEV1 over 16 weeks was 0.126 L, 0.242 L, and 0.286 L for the patients in the placebo, 0.3 mg/kg reslizumab, and 3.0 mg/kg reslizumab treatment groups, respectively.

Both doses showed a statistical significant improvement in FEV1 compared to placebo; the treatment difference was 0.160 L (95%CI: 0.060-0.259) and 0.115 L (95%CI: 0.016-0.215) for reslizumab 3 mg/kg and 0.3 mg/kg, respectively (Table 11). Improvements were seen after the first dose and were sustained through 16 weeks.

The statistically significant improvement in FEV1 was confirmed for the reslizumab 3.0 mg/kg group with other measures of pulmonary function, including FVC, FEF25%-75%, and % predicted FEV1 (latter not shown) (Table 12) No treatment effect on FVC and FEF25%-75% was observed for patients in the reslizumab 0.3 mg/kg treatment group.

Improvements in ACQ, AQLQ, and ASUI scores, decreases in frequency of SABA use, and decreases in blood eosinophils were also seen for patients in the reslizumab treatment groups.

Except for asthma symptom score and SABA use, the changes from baseline in each of these endpoints were more consistent and larger for the reslizumab 3.0 mg/kg treatment group compared with the reslizumab 0.3 mg/kg treatment group.

Table 8 Change from baseline in FEV1 over 16 weeks by treatment group (Full Analysis Set – 3081)

Variable (unit)	Statistic	Treatment groups		
		Placebo (N=105)	Reslizumab 0.3 mg/kg (N=103)	Reslizumab 3.0 mg/kg (N=103)
Baseline FEV_1 (liters)	Mean	2.222	2.157	2.169
	SD	0.8125	0.8506	0.7815
	SE of mean	0.0793	0.0838	0.0770
	Median	2.120	2.060	2.140
	Min, max	0.600, 4.510	0.560, 4.500	0.570, 4.022
Change in FEV_1 (liters) over 16 weeks[a]	n[b]	103	101	102
	LS mean	0.126	0.242	0.286
	SE of LS mean	0.0549	0.0556	0.0548
	Treatment difference (active –placebo)	NA	0.115	0.160
	SE of difference	NA	0.0508	0.0507
	95% CI	NA	(0.016, 0.215)	(0.060, 0.259)
	p-value	NA	0.0237	0.0018

a=protocol defined endpoint; b=denotes number of patients who contributed at least once to the analysis. FEV1=forced expiratory volume in 1 second; sd=standard deviation; se=standard error; min=minimum; max=maximum; LS=least square; CI=confidence interval; NA=not applicable.

Table 9 Summary of Rezlizumab treatment effect – Secondary endpoints (Full analysis set- study 3081).

	LS mean change over 16 weeks			Treatment difference (95% CI) p-value	
Statistic	**Placebo (N=105)**	**Reslizumab 0.3 mg/kg (N=103)**	**Reslizumab 3.0 mg/kg (N=103)**	**Reslizumab 0.3 mg/kg**	**Reslizumab 3.0 mg/kg**
ACQ score Baseline mean (sd)	2.471 (0.8301)	2.499 (0.8903)	2.591 (0.8861)		
LS mean change (SE)	-0.494 (0.1231)	-0.732 (0.1250)	-0.853 (0.1233)	-0.238 (-0.456, -0.019) 0.0329	-0.359 (-0.577, -0.140) 0.0014
AQLQ score Baseline mean (sd)	4.374 (1.2047)	4.479 (1.2266)	4.164 (1.2233)		
LS mean change (SE) at week 16	0.779 (0.1817)	1.057 (0.1881)	1.138 (0.1829)	0.278 (-0.036, 0.591) 0.0822	0.359 (0.047, 0.670) 0.0241
FVC (L) Baseline mean (sd)	3.288 (1.0503)	3.289 (1.1232)	3.199 (1.0097)		
LS mean change (SE)	0.172 (0.0614)	0.220 (0.0623)	0.301 (0.0613)	0.048 (-0.058, 0.155) 0.3731	0.130 (0.023, 0.237) 0.0174
FEF25%-75% (L/s) Baseline mean (sd)	1.657 (0.9201)	2.337 (8.9642)	1.705 (1.5396)		
LS mean change (SE)	-0.145 (0.1342)	-0.114 (0.1361)	0.089 (0.1342)	0.030 (-0.209, 0.270) 0.8020	0.233 (-0.005, 0.472) 0.0552

ASUI score Baseline mean (sd)	0.674 (0.1897)	0.675 (0.2061)	0.657 (0.1913)		
LS mean change (SE)	0.082 (0.0218)	0.132 (0.0221)	0.129 (0.0218)	0.051 (0.012, 0.089) 0.0094	0.047 (0.009, 0.085) 0.0160
SABA (puff/day) Baseline mean (sd)	2.3 (2.20)	1.9 (2.45)	2.3 (2.58)		
LS mean change (SE)	-0.3 (0.28)	-1.0 (0.28)	-0.9 (0.27)	-0.648 (-1.152, -0.144) 0.0119	-0.624 (-1.126, -0.121) 0.0151
Eosinophil count (10^9/L) Baseline mean (sd)	0.601 (0.4331)	0.644 (0.4926)	0.595 (0.3931)		
LS mean change (SE)	-0.035 (0.0271)	-0.358 (0.0277)	-0.529 (0.0270)	-0.323 (-0.370, 0.275) 0.0000	-0.494 (-0.542, -0.447) 0.0000

ACQ= asthma control questionnaire, AQLQ=asthma quality of life questionnaire, FVC=forced vital capacity, EF25%-75%=forced expiratory flow at 25% to 75% forced vial capacity, ASUI=asthma symptom utility index, SABA=short-acting beta-agonist.

2.5.2. Main studies

Study 3082: A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma.

Study 3083: A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma.

The Applicant submitted two pivotal phase 3 studies (study 3082 and 3083) with identical design and objectives. This approach was previously discussed and agreed during scientific advice.

The studies consisted of a 2- to 4-week screening period and a 52-week treatment period, including a final evaluation at week 52 (end-of-treatment visit; 4 weeks after the final infusion at week 48). After the end-of-treatment visit, patients either enrolled in an available open-label, long-term study or returned for a follow-up assessment 90 (±7) days after the end-of-treatment visit. Both studies were multicentre studies conducted in the EU, US and Asian-Pacific region.

Methods and results are therefore presented combined.

Methods

Study Participants

Adult patients (aged 12- 75 years) with a previous diagnosis of asthma were included. The patient had at least 1 asthma exacerbation requiring oral, intramuscular, or intravenous corticosteroid use for at least 3 days over the past 12 months before screening. Other main inclusion criteria were an ACQ score of at least 1.5, airway reversibility of at least 12% after beta-agonist administration, current blood eosinophil level of at least 400/µL and inhaled fluticasone at a dosage of at least 440 mcg, or equivalent, daily. Chronic oral corticosteroid use (no more than 10 mg/day prednisone or equivalent) was allowed. Patients' baseline asthma therapy regimen must have been stable for 30 days before screening, and continued without dosage changes throughout the study.

The main exclusion criteria were known hypereosinophilic syndrome, other lung conditions (including a.o. COPD, Churg-Strauss syndrome), current smoker, other systemic immunosuppressive or immunomodulating therapies, use of other biologic agents, comorbidity that could interfere with the study or compromise patients' safety, uncontrolled comorbidity, history of concurrent immunodeficiency (a.o. human immunodeficiency virus [HIV] or acquired immunodeficiency syndrome), infections within a predefined period (parasitic infection, infections requiring hospitalization or antibiotics within 4 weeks prior to screening, water-borne parasites), asthma exacerbation within 4 weeks of screening or during screening period.

Treatments

Investigational Product: Reslizumab was provided as a sterile solution for infusion presented as 100 mg (10 mL) per vial, formulated at 10 mg/mL in sodium acetate, sucrose.

Placebo: Placebo was provided as a sterile solution for infusion presented as 10 mL per vial, formulated in sodium acetate, sucrose, and was used in a manner identical to that of reslizumab.

Patients were administered intravenously over 15 to 30 minutes reslizumab at a dosage of 3.0 mg/kg or placebo at baseline and once every 4 weeks relative to baseline over 48 weeks.

Objectives

The primary objective was to demonstrate the efficacy of reslizumab, at a dose of 3.0 mg/kg administered intravenously every 4 weeks over 12 months, as assessed by the reduction in frequency of clinical asthma exacerbations (CAEs) during 12 months. Secondary objectives were to demonstrate the efficacy of reslizumab based on overall change in FEV1 over 16 weeks and change to week 16, overall change in Asthma Quality of Life Questionnaire (AQLQ) over 16 weeks and change to week 16, time to first CAE, overall change in Asthma symptom utility index (ASUI) over 16 weeks, overall change in use of short-acting beta-agonist (SABA) over 16 weeks and overall change in blood eosinophil count over 16 and 52 weeks.

Outcomes / endpoints

The primary endpoint was the frequency of CAEs per patient over 52 weeks. An asthma exacerbation as defined as a worsening of asthma that required the following medical intervention:

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

The above criteria had to be corroborated with at least 1 other measurement to indicate worsening in the clinical signs and symptoms of asthma, as follows:

- decrease in FEV1 by 20% or more from baseline
- decrease in the PEFR by 30% or more from baseline on 2 consecutive days
- worsening of symptoms or other clinical signs per physician evaluation of the event

Secondary endpoints

- Change from baseline to week 16 in FEV1
- Overall change from baseline in FEV1 over 16 weeks
- Change from baseline in AQLQ score to week 16
- Overall change from baseline in ACQ score over 16 weeks
- Time to 1st CAE
- Overall change from baseline in ASUI score over 16 weeks
- Overall change from baseline in short-acting beta-agonist use over 16 weeks
- Overall change from baseline in blood eosinophil count over 16 weeks and 52 weeks

Further, pharmacokinetics, immunogenicity, and safety and tolerability were evaluated. Adverse events of special interest were adverse events related to 1.asthma exacerbation, 2. the administration route or potential safety issues with this class of medications (related to study drug infusion, hypersensitivity reactions, malignancies, adverse events in patients with anti-drug antibodies) and 3. Identified after medical review phase 3 safety studies: increase in serum creatine phosphokinase.

Sample size

For the study 3082, 480 patients (240 patients per treatment group) were planned to be enrolled.

For the study 3083, 460 patients (230 patients per treatment group) were planned to be enrolled.

Randomisation

All patients were randomly assigned to 1 of 2 treatment groups, either 3.0 mg/kg of reslizumab or placebo, using Interactive Response Technology (IRT). Randomization was stratified by oral corticosteroid use (yes or no) at study enrolment and by region (US or other). Study drug was administered by intravenous infusion once every 4 weeks (±7 days) relative to baseline for a total of 13 doses (48 weeks). Patients and investigators remained blinded to treatment assignment during the study. Because of the expected effect of reslizumab on blood eosinophil count, eosinophil count data were redacted from hematology results during the treatment period. In addition, the sponsor's clinical personnel involved in the study were also blinded to the study drug identity until the database was locked for analysis and the treatment assignment revealed.

The set of randomized patients (assigned to a treatment group regardless of whether or not patients received any study drug) was used for all study population summaries and efficacy analyses unless otherwise noted.

Blinding (masking)

Patients were randomly assigned in a double-blind fashion to reslizumab or matching placebo (1:1 ratio) via Interactive Response Technology (IRT) at the baseline visit. In order to maintain the blind, each patient received a specific volume of reslizumab or placebo solution determined by the patient's body weight.

Randomization was stratified by oral corticosteroid use (yes or no) at study enrolment and by region (United States [US] or other).

Statistical methods

Analysis sets

Randomised set: All patients who were randomly assigned to a treatment group at enrolment, regardless of whether or not a patient received any study drug. The set of randomized patients was used for all study population summaries and efficacy analyses unless otherwise noted.

Safety analysis set: All patients who received at least 1 dose of study drug. The safety analysis set was used for all safety analyses unless otherwise noted.

Full analysis set (FAS): includes all randomized patients who were treated with at least 1 dose of study drug.

Data from assessments of pulmonary function, SABA use, and the ACQ, AQLQ, and ASUI at a scheduled visit were excluded from the FAS if the assessments were preceded by usage within 7 days of a limited subset of medications that could significantly confound interpretation of the efficacy parameters at the visit. These medications included the addition of a long-acting beta-agonist, a long-acting muscarinic antagonist, or an oral or systemic corticosteroid, if not taken at baseline. If taken at baseline, an increase in a chronic, maintenance dose of the oral or systemic corticosteroid was included.

The FEV1 subpopulation analysis set includes all patients in the FAS with % predicted FEV1 ≤85% at baseline.

Statistical analyses

Primary endpoint – Frequency of clinical asthma exacerbations

Clinical asthma exacerbations that occurred between the completion of the first dose of study drug and 2 weeks after the end of treatment (week 52 or early withdrawal visit) were counted towards the CAEs for analysis. The frequency of CAEs was analysed using the generalized linear model (GLM) for data from the negative binomial distributions that is commonly referred to as the negative binomial (NB) regression model. The primary NB model included the treatment group and randomization stratification factors (baseline usage of oral corticosteroid [yes or no] and geographical region [US or other]) as model factors and the logarithm of follow up time excluding the summed duration of CAE events as an offset variable. This offset variable adjusted the CAE rate for total duration of patient exposure to study drug when not experiencing a CAE. The ratio of CAE rate between the treatment groups and its 95% confidence interval (CI) were estimated from the NB model. Treatment effect was tested using the likelihood based Chi-square test at the 0.05 significance level. The primary analysis of CAEs was based on the adjudicated data.

Sensitivity analyses primary endpoint: A low dropout rate in this study was anticipated (<5%) because all patients maintained their background therapies throughout the study. The primary analysis model was unbiased if the missing data mechanism appeared to be random. To assess the robustness of the primary NB model, a sensitivity analysis was performed using a multiple imputation procedure for missing data (Little and Rubin 2002). This analysis imputed values for CAE and exposure for patients who withdrew early from treatment. Imputation was done separately for patients considered as Missing at Random (MAR) (i.e., for reasons other than asthma exacerbation and lack of efficacy: imputation from the same stratum and treatment group) and for patients Missing Not at Random (MNAR) (i.e., for asthma exacerbation and lack of efficacy: imputation is drawn from placebo patient within the same stratum).

The primary analysis was also repeated using an offset that did not exclude the summed duration of exacerbations from the follow-up time in the offset calculation

Secondary analyses of the primary efficacy variable included the frequency of CAEs requiring courses of oral or systemic corticosteroids (oral or parenteral) prescribed for 3 or more days. The frequency of asthma exacerbations resulting in hospitalization or a visit to the emergency room was also analysed. These variables were analysed similarly to the primary efficacy variable. The frequency of asthma exacerbations as recorded by the investigator on the CAE eCRF page, ie, non-adjudicated CAEs, was also analysed.

Secondary and other efficacy variable analyses

Secondary endpoints were analysed using a mixed effect model for repeated measures (MMRM) with treatment group, visit, treatment and visit interaction, and stratification factors as fixed effects and patient as a random effect. Covariates for baseline values were also included in the model; for pulmonary function test analyses, covariates for height and sex were included as well.

The Kaplan-Meier method was used to estimate and compare the distributions of time to CAE between reslizumab and placebo. The hazard ratio and p-value were estimated using the stratified Cox regression model.

Analysis of the change from baseline to endpoint in pulmonary function tests was performed using an analysis of covariance (ANCOVA) model with fixed effects for treatment, oral corticosteroids use at enrolment (yes or no), region (US or other), sex, and covariates for height and baseline value. Analysis of the change in AQLQ score from baseline to endpoint was performed using the same ANCOVA model as for pulmonary function tests with the exception of inclusion of sex and height in the model. The stratified Cochran-Mantel-Haenszel test was used to analyse the proportion of patients achieving at least a 0.5 reduction from baseline in ACQ score and the proportion of patients achieving at least a 0.5 improvement from baseline in AQLQ score.

Multiple comparisons and multiplicity

A pre-specified, fixed sequence multiple testing procedure was implemented to test the primary and secondary efficacy variables while controlling the overall Type I error rate at 0.05. At the point where $p>0.05$, no further comparisons were interpreted inferentially.

Results of testing the frequency of CAEs specifically requiring systemic corticosteroids could be interpreted inferentially at an alpha level of 0.05 provided that results of all tests for secondary variables were significant.

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

Results

Participant flow

Most randomised patients completed the studies (86%-89%) (Table 13). Reasons for withdrawal were comparable between treatment groups; the main reason being withdrawal of consent. Withdrawal due to adverse events was low (2%-4%).

Table 10 Patient disposition by treatment group (Studies 3082 and 3083, all patients)

Analysis group, n(%)	Study 3082			Study 3083		
	Placebo	Reslizumab 3.0 mg/kg	Total	Placebo	Reslizumab 3.0 mg/kg	Total
Screened (all patients)			1486			1111
Randomised	244 (100)	245 (100)	489 (100)	232 (100)	232 (100)	464 (100)
Randomised, not treated	1 (<1)	0	1 (<1)	0	0	0
Safety analysis set	243 (>99)	245 (100)	488 (>99)	232 (100)	232 (100)	464 (100)
Full analysis set	243 (>99)	245 (100)	488 (>99)	232 (100)	232 (100)	464 (100)
FEV1 subpopulation analysis set	205 (84%)	218 (89%)	423 (87%)	185 (80)	180 (78)	365 (79)
Completed study*	215 (88)	218 (89)	433 (89)	199 (86)	202 (87)	401 (86)
Withdrew from study	29 (12)	27 (11)	56 (11)	33 (14)	30 (13)	63 (14)
Adverse event	8 (3)	4 (2)	12 (2)	9 (4)	8 (3)	17 (4)
Lack of efficacy	0	0	0	4 (2)	2 (<1)	6 (1)
Consent withdrawn	14 (6)	11 (4)	25 (5)	15 (6)	11 (5)	26 (6)
Protocol violation	2 (<1)	3 (1)	5 (1)	1 (<1)	2 (<1)	3 (<1)
Lost to follow-up	3 (1)	2 (<1)	5 (1)	2 (<1)	3 (1)	5 (1)
Noncompliance with study procedures	0	1 (<1)	1 (<1)	3 (1)	4 (2)	7 (2)
Noncompliance with study medication	0	1 (<1)	1 (<1)	0	0	0
Other	2 (<1)	5 (2)	7 (1)	1 (<1)	3 (1)	4 (<1)

* Patients were considered to have completed the study if they completed the treatment phase and the 90-day follow-up period or enrolled in the open-label extension study (study 3085)

Recruitment

For study 3082, the first patient was enrolled on 12 April 2011; the last patient last visit was on 03 March 2014.

For study 3083, the first patient was enrolled on 22 March 2011 and the last patient's last visit was on 03 April 2014.

Conduct of the study

About one-fourth of the patients reported at least 1 protocol violation, no markedly differences were seen between treatment groups. The most commonly reported violations were related to inclusion criteria (ACQ score less than 1.5) and GCP guidelines (e.g. signing wrong version IC, reporting serious AE beyond pre-defined time period, or physical exam categories not documented). Most patients remained in the study based on the decision of the sponsor.

Baseline data

Demographic characteristics are summarized in Table 14. Treatment groups were balanced with regard to age (mean: 47 years), sex, (42% male) and race (73% white).

Table 11 Demographic and baseline characteristics (study 3082 and 3083, randomised set)

Demographics	**Study 3082**			**Study 3083**		
	Placebo (N=244)	**Reslizumab 3.0 mg/kg (N=245)**	**Total (N=489)**	**Placebo (N=232)**	**Reslizumab 3.0 mg/kg (N=232)**	**Total (N=464)**
Age (years)						
Mean (sd)	46.7 (14.83)	46.6 (13.82)	46.6 (14.32)	47.5 (13.75)	46.4 (13.79)	47.0 (13.76)
Range	12, 75	12, 76	12, 76	12, 75	12, 74	12, 75
Sex, n (%)						
Male	83 (34)	103 (42)	186 (38)	82 (35)	88 (38)	170 (37)
Female	161 (66)	142 (58)	303 (62)	150 (65)	144 (62)	294 (63)
BMI, kg/m2	N=242	N=245	N=487			
Mean (sd)	28.0 (6.16)	27.7 (6.26)	27.9 (6.20)	27.0 (5.05)	27.0 (5.26)	27 (5.15)
Range	16.0, 47.6	15.3, 53.7	15.3, 53.7	17.5, 47.0	17.4, 52.3	17.4, 52.3
Race , n (%)						
White	182 (75)	173 (71)	355 (73)	169 (73)	168 (72)	337 (73)
Black	20 (8)	14 (6)	34 (7)	4 (2)	6 (3)	10 (2)
Asian	33 (14)	50 (20)	83 (17)	21 (9)	16 (7)	37 (8)
American Indian or Alaskan Native	0	0	0	4 (2)	7 (3)	11 (2)
Pacific Islander	0	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)

The number of adolescents and elderly included is limited (about 5%). Only few patients were included in the age group 12-17 yrs (n=11 on placebo and n=14 on reslizumab) which precludes a meaningful interpretation

and adolescents are currently not included in the indication. The number of elderly patients was limited (≥ 65 years: n=87) as can be expected for an asthmatic population.

Patients were stratified for US and OCS use at baseline. A total of 15% and 7% of the patients were enrolled in the US for studies 3082 and 3083, respectively, whereas 35.6% and 59.7% were enrolled in the EU. According to IVRS (used for analyses), 19% and 12% of patients used OCS at enrolment for studies 3082 and 3083. These numbers were somewhat lower based on CRF; 13% and 9%, respectively.

Disease state characteristics, including asthma exacerbation frequency, airway reversibility, FEV1, were generally similar between the 2 treatment groups at baseline for both studies (Table 15). Patients were inadequately controlled as demonstrated by a mean ACQ score of 2.7 and 2.6 points at baseline and FEV1 % predicted of 64.3% and 69.2% in studies 3082 and 3083, respectively. The mean number of prior asthma exacerbations was 2. Within study 3082, patients were receiving inhaled corticosteroids at baseline at a mean dose of 836 µg per day, approximately 15% were receiving concomitant low-dose oral corticosteroids, and more than 85% were receiving concomitant long-acting beta-agonist therapy. Within study 3083, patients were receiving inhaled corticosteroids at baseline at a mean dose of 806 µg per day. At least 82% of randomized patients in either treatment group used long-acting beta-agonists at baseline and about 12% used oral corticosteroids.

Table 12 Baseline disease characteristics (Randomised Set- study 3082 and 3083)

Baseline characteristic	Study 3082			Study 3083		
	Placebo (n=244)	3.0 mg/kg (n=245)	Total (N=489)	Placebo (n=232)	3.0 mg/kg (n=232)	Total (n=464)
AE last 12 months n(%)	N=242	N=242	N=484	N=232	N=231	N=463
Mean (sd)	2.1 (2.31)	1.9 (1.63)	2.0 (1.0)	2.0 (1.78)	1.9 (1.58)	1.9 (1.68)
Range	1.0, 20.0	1.0, 12.0	1.0, 20.0	1.0, 12.0	1.0, 10.0	1.0, 12.0
Time since most recent AE (months)	N=241	N=242	N=483	N=232	N=232	N=464
Mean (sd)	5.3 (3.26)	5.2 (3.11)	5.3 (3.18)	5.3 (2.82)	5.8 (3.28)	5.6 (3.07)
Range	0.7, 13.6	0.8, 13.4	0.7, 13.6	0.9, 13.0	0.8, 19.7	0.8, 19.7
Airway reversibility (%)	N=244	N=245	N=489	N=232	N=232	N=464
Mean (sd)	26.3 (18.1)	26.1 (15.47)	26.2 (16.82)	28.7 (23.75)	28.1 (16.06)	28.4 (20.25)
Range	-7.5, 127.3	1.9, 98.1	-7.5, 127.3	6.1, 257.3	11.5, 96.2	6.1, 257.3
FEV1 (L)	N=244	N=245	N=489	N=232	N=232	N=464
Mean (sd)	1.928 (0.7908)	1.894 (0.7258)	1.911 (0.7583)	2.004 (0.6682)	2.129 (0.7848)	2.066 (0.7307)
Range	0.340,	0.550,	0.340,	0.640,	0.490,	0.490,

	4.680	3.940	4.680	3.970	4.570	4.570
% predicted FEV1	N=244	N=245	N=489	N=232	N=232	N=464
Mean (sd)	65.0 (19.80)	63.6 (18.55)	64.3 (19.18)	68.0 (18.93)	70.4 (20.98)	69.2 (19.99)
Range	18.0, 113.6	19.0, 131.0	18.0, 131.0	26.0, 132.0	20.0, 167.0	20.0, 167.0
FVC (L)	N=244	N=245	N=489	N=232	N=232	N=464
Mean (sd)	3.015 (1.1298)	2.959 (0.9628)	2.987 (1.0488)	3.000 (0.9148)	3.187 (1.0471)	3.093 (0.9865)
Range	0.350, 10.50	1.080, 5.890	0.350, 10.50	1.060, 5.790	0.620, 6.290	0.620, 6.290
FEF25%-75% (L/s)	N=241	N=240	N=481	N=231	N=231	N=462
Mean (sd)	1.567 (3.8223)	1.259 (0.8094)	1.413 (2.7668)	1.860 (6.9954)	1.508 (0.8829)	1.684 (4.9834)
Range	0.220, 59.00	0.210, 4.280	0.210, 59.00	0.000, 107.0	0.230, 5.200	0.000, 107.0
ACQ score	N=244	N=245	N=489	N=232	N=232	N=464
Mean (sd)	2.763 (0.8782)	2.657 (0.8541)	2.710 (0.8670)	2.605 (0.7943)	2.570 (0.8876)	2.587 (0.8415)
Range	0.143, 5.429	0.429, 5.286	0.143, 5.429	0.86, 5.57	0.14, 5.43	0.14, 5.57
AQLQ overall score	N=242	N=243	N=485	N=231	N=229	N=460
Mean (sd)	4.159 (1.0883)	4.303 (1.1208)	4.231 (1.1059)	4.223 (1.0794)	4.352 (1.0220)	4.287 (1.0521)
Range	1.406, 7.000	1.719, 6.969	1.406, 7.000	1.656, 6.438	2.188, 7.000	1.656, 7.000
ASUI overall score	N=241	N=241	N=482	N=229	N=228	N=457
Mean (sd)	0.613 (0.2029)	0.633 (0.1938)	0.623 (0.1984)	0.649 (0.1919)	0.664 (0.2005)	0.656 (0.1961)
Range	0.079, 1.000	0.083, 0.982	0.079, 1.000	0.095, 1.000	0.040, 1.000	0.040, 1.000
Blood eosinophil count (109/L)	N=244	N=245	N=489	N=232	N=232	N=464
Mean (sd)	0.624 (0.5903)	0.696 (0.7677)	0.660 (0.6852)	0.688 (0.6824)	0.610 (0.4115)	0.649 (0.5642)

Range	0.000, 6.200	0.000, 9.700	0.000, 9.700	0.000, 7.400	0.000, 2.200	0.000, 7.400
LABA use at baseline						
Yes	207 (85)	214 (87)	421 (86)	192 (83)	190 (82)	382 (82)
Beta agonist use past 3 days						
Yes n (%)	188 (77)	170 (69)	358 (73)	181 (78)	182 (78)	363 (78)
Daily average number of puffs	N=241	N=242	N=483	N=201	N=204	N=405
Mean (sd)	2.7 (3.18)	2.4 (2.82)	2.6 (3.01)	2.7 (2.41)	2.9 (2.82)	2.8 (2.62)
Range	0.0, 25.0	0.0, 20.0	0.0, 25.0	0.0, 20.0	0.0, 20.0	0.0, 20.0
OCS use						
Yes n (%)	40 (16.4)	24 (9.8))	64 (13.1)	18 (7.8)	24 (10.3)	42 (9.1)
Total daily ICS dose at baseline (µg)	N=241	N=240	N=481	N=231	N=229	N=460
Mean (sd)	847.7 (442.13)	824.1 (380.28)	836.0 (412.17)	756.9 (274.23)	856.0 (588.40)	806.2 (460.56)
Range	200, 3200	200, 2280	200, 3200	160, 2000	160, 7000	160, 7000

Numbers analysed

For study 3082 data from 489 patients were analyzed for efficacy and data from 488 patients were analyzed for safety.

For study 3083 from 464 patients were analyzed for efficacy and data from 464 patients were analyzed for safety.

Outcomes and estimation

The mean duration of the treatment phase was about 340 days for both studies. About 78%-83% of patients received ≥13 complete infusions.

The primary analysis demonstrated a statistically significant reduction in CAE frequency for patients in the reslizumab 3.0 mg/kg group compared with placebo (Table 16). The reslizumab versus placebo CAE rate ratio (95% CI) was 0.5010 (95% CI: 0.3726, 0.6737; p<0.0001) and 0.4063 (95% CI: 0.2819, 0.5855; p<0.0001) for studies 3082 and 3083, respectively. These data indicate a 50% - 59% reduction in adjudicated CAE events per patient year by reslizumab 3.0 mg/kg. Sensitivity analyses showed comparable results.

The most common medical intervention for a CAE in the placebo and reslizumab groups was treatment with an oral systemic corticosteroid which also showed a statistical significant difference with placebo. Number of patients with a hospitalization or emergency visits was limited (between 4%-9% across both studies) and the difference with placebo was not statistically significant.

Table 13 Overall summary of CAE frequency over 52 weeks by treatment group (studies 3082 and 3083, randomised set).

	Study 3082		Study 3083	
Variable	Placebo (N=244)	Reslizumab 3.0 mg/kg (N=245)	Placebo (N=232)	Reslizumab 3.0 mg/kg (N=232)
Number of patients with at least 1 CAE, n (%)	132 (54.1)	92 (37.6)	105 (45.3)	59 (25.4)
Mean (SD) frequency of CAEs during the treatment period	1.34 (1.760)	0.72 (1.217)	1.01 (1.672)	0.46 (0.957)
Adjusted CAE rate (95% CI)	1.8036 (1.3715, 2.3720)	0.9037 (0.6778, 1.2048)	2.1147 (1.3291, 3.3645))	0.8591 (0.5488, 1.3451)
CAE rate ratio (95% CI) p-value	0.5010 (0.3726, 0.6737) <0.0001a		0.4063 (0.2819, 0.5855) <0.0001a	
Number of patients with at least 1 CAE requiring systemic corticosteroid, n (%)	118 (48.4)	80 (32.7)	92 (39.7)	49 (21.1)
Mean (SD) frequency of CAEs requiring systemic corticosteroid during the treatment period	1.12 (1.607)	0.55 (1.053)	0.80 (1.434)	0.35 (0.819)
CAE rate ratio (95% CI) p-value	0.4499 (0.3255, 0.6220) <0.0001		0.3893 (0.2621, 0.5782) <0.0001	
Number of patients with at least 1 CAE requiring oral corticosteroids, n (%)	117 (48.0%)	77 (31.4%)	86 (37.1%)	46 (19.8%)
Mean (SD) frequency of CAEs requiring oral corticosteroids during the treatment period	1.09 (1.590)	0.53 (1.022)	0.75 (1.417)	0.34 (0.817)
CAE rate ratio (95% CI) p-value	0.4384 (0.3158, 0.6085) <0.0001		0.4027 (0.2660, 0.6096) <0.0001	
Number of patients with at least 1 CAE resulting in hospitalization or a visit to the ER, n (%)	21 (8.6)	22 (9.0)	12 (5.2)	9 (3.9)
Mean (SD) frequency of CAEs resulting in hospitalization or a visit to the ER during the treatment	0.17 (0.720)	0.10 (0.341)	0.06 (0.249)	0.04 (0.194)

period				
CAE rate ratio (95% CI) p-value	0.6595 (0.3210, 1.3550) 0.2572		0.6886 (0.2878, 1.6479) 0.4020	

a This treatment group comparison was controlled for Type I error.
CAE=clinical asthma exacerbation; CI=confidence interval; ER=emergency room; SD=standard deviation.
Notes: The CAEs counted were those that occurred between the completion of the first dose of study drug and 2 weeks after the end EOT/early withdrawal visit. Adjusted CAE rates and CIs, CAE rate ratios and CIs, and p-values were based on NB regression model adjusted for stratification factors (baseline usage of OCS [yes or no] and geographical region [US or other]).

The median time to first CAE could not be estimated for the reslizumab treatment group in either study because less than 50% of patients in that group experienced a CAE. The KM estimates of probability of not experiencing a CAE by week 52 were higher in patients receiving reslizumab 3.0 mg/kg than in patients receiving placebo in Studies 3082 (61.3% vs 44.2%) and 3083 (73.2% vs 51.9%). Furthermore, as demonstrated by the hazard ratio, the likelihood of experiencing a CAE at any time during the 52-week treatment period for patients in the reslizumab treatment group was reduced by 42.5% (p<0.0001) in study 3082, and 51.4% (p<0.0001) in study 3083.

A summary of the secondary efficacy endpoints is shown in

Table **17.**

Efficacy was seen at the first time point and sustained over time. No significant effect was seen on use of short acting beta-agonist therapy over 16 weeks. Treatment effects on FEV1 increase were observed at the first observation period of 4 weeks and were sustained throughout the study. There was a statistically significant improvement compared to placebo; the treatment difference was 0.126 L and 0.093 L, respectively. Statistical significant improvements were also seen for other measures of asthma control based on the overall score (AQLQ, ACQ and ASUI). At the same time, the proportion of responders (minimal of ≥0.5 point improvement ACQ or AQLQ) was increased compared to placebo. For instance, the proportion of ACQ responders in the reslizumab 3.0 mg/kg and placebo groups was 77% and 64% (p=0.0022) at week 52, respectively in study 3082. Corresponding data for study 3083 were 81% and 62% (p=<0.0001) at week 52 in the reslizumab and placebo group, respectively.

Table 14 Treatment effect of reslizumab over 16 weeks and 52 weeks on measures of asthma control (Studies 3082 and 3083, randomised set).

	Study 3082				Study 3083			
	LS mean change over 16 weeks		LS mean change over 52 weeks		LS mean change over 16 weeks		LS mean change over 52 weeks	
Efficacy variable[a]	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizu-mab
FEV1 (L) (SE)	0.110 (0.031)	0.248 (0.030)	0.109 (0.031)	0.235 (0.030)	0.094 (0.041)	0.187 (0.041)	0.111 (0.042)	0.201 (0.041)
LS mean diff. (95% CI)	0.137 (0.076, 0.198)		0.126 (0.064, 0.188)		0.093 (0.030, 0.155)		0.090 (0.026, 0.153)	

	Study 3082				Study 3083			
	LS mean change over 16 weeks		LS mean change over 52 weeks		LS mean change over 16 weeks		LS mean change over 52 weeks	
Efficacy variable[a]	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizu-mab
p-value	<0.0001[b]		p<0.0001		0.0037[b]		0.0057	
ACQ score (SE)	–0.676 (0.066)	–0.941 (0.065)	–0.764 (0.0650)	–1.020 (0.0644)	–0.660 (0.0875)	–0.857 (0.0872)	–0.800 (0.0860)	–1.042 (0.0856)
LS mean diff. (95% CI) p-value	–0.266 (-0.399, -0.132) 0.0001[b]		–0.255 (-0.390, -0.121) 0.0002		–0.196 (-0.327, -0.066) 0.0032b		–0.242 (-0.372, -0.112) 0.0003	
AQLQ total score (SE)[a]	0.695 (0.088)	0.933 (0.088)	0.789 (0.082)	1.091 (0.081)	0.777 (0.1152)	0.987 (0.1158)	0.889 (0.1119)	1.123 (0.1117)
LS mean diff. (95% CI) p-value	0.238 (0.048, 0.428) 0.0143		0.302 (0.137, 0.467) 0.0004		0.209 (0.025, 0.393) 0.0259[b]		0.234 (0.070, 0.398) 0.0052	
ASUI score (SE)	0.109 (0.012)	0.167 (0.012)	0.127 (0.011)	0.188 (0.011)	0.080 (0.0161)	0.115 (0.0161)	0.113 (0.0147)	0.149 (0.0146)
LS mean diff. (95% CI) p-value	0.058 (0.034, 0.083) 0.0001[b]		0.061 (0.038, 0.084) 0.0001		0.035 (0.011, 0.059) 0.0037[b]		0.036 (0.014, 0.057) 0.0011	
SABA (puffs/day) (SE)	–0.36 (0.158)	–0.64 (0.156)	–0.42 (0.151)	–0.58 (0.149)	–0.44 (0.233)	–0.50 (0.230)	–0.55 (0.215)	–0.73 (0.209)
LS mean diff. (95% CI) p-value	–0.276 (-0.57, 0.045) 0.0919[b]		–0.152 (-0.467, 0.163) 0.3435		–0.062 (-0.411, 0.287) 0.7263[b]		–0.180 (-0.502, 0.142) 0.2732	
Blood eosinophils (109 cells/L) (SE)	–0.118 (0.0232)	–0.584 (0.0230)	–0.127 (0.0168)	–0.582 (0.0167)	–0.076 (0.0268)	–0.555 (0.0266)	–0.076 (0.0233)	–0.565 (0.0231)
LS mean diff. (95% CI)	–0.466		–0.455		–0.479		–0.489	

	Study 3082				Study 3083			
	LS mean change over 16 weeks		LS mean change over 52 weeks		LS mean change over 16 weeks		LS mean change over 52 weeks	
Efficacy variable[a]	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizumab	Placebo	Reslizu-mab
p-value	(-0.514, -0.418) 0.0001		(-0.491, -0.419) 0.0001		(-0.519, -0.439) 0.0001		(-0.525, -0.472) 0.0001	

a Values shown are LS mean changes over the specified period from baseline apart from the week 16 AQLQ values, which represent the change to week 16 (week 16 was the first time point where AQLQ was assessed).
b This treatment group comparison was controlled for Type I error.
ACQ=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; ASUI=Asthma Symptom Utility Index; diff.=difference; FEF25%-75%=forced expiratory flow during the middle half of the forced vital capacity; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; LS=least squares; NR=not reported; % predicted FEV1=actual FEV1 divided by standard predicted FEV1 times 100%; SABA=short-acting beta-agonist.

Ancillary analyses

Efficacy data from the main studies were pooled for the placebo and reslizumab 3.0 mg/kg groups. The Integrated 16-Week Population included data up to 16 weeks from all 3 placebo-controlled Phase 3 studies (i.e., Studies 3081, 3082, and 3083) and was utilized to evaluate short-term asthma control (e.g., FEV1, ACQ). The Integrated 52-Week Population included data through 52 weeks from the two 52-week placebo-controlled Phase 3 studies (ie, Studies 3082 and 3083) and was utilized primarily to evaluate future asthma risk (i.e. CAEs).

The 52-week integrated population was also used to evaluate the influence of intrinsic patient factors and of factors extrinsic to the patient. Data from the integrated 52-week population are shown here.

The demographics were generally similar between the studies (Table 18).

Table 15 Demographic characteristic by treatment group (Integrated 52-week population, randomized set).

Demographics	**Integrated Week 52 population**		
	Placebo (N=476)	**Reslizumab (N=477)**	**Total (N=953)**
Age (years)			
Mean (sd)	47.1 (14.30)	46.5 (13.79)	46.8 (14.05)
12-17 years	11 (2)	14 (3)	25 (3)
18-64 years	420 (88)	431 (9)	851 (89)
⩾65 years	45 (9)	32 (7)	77 (8)
Sex, n (%)			
Male	165 (35)	191 (40)	356 (37)
Female	311 (65)	286 (60)	597 (63)
Race, n (%)			
White	351(74)	341 (71)	692 (73)
Black	24 (5)	20 (4)	44 (5)
Asian	54 (11)	66 (14)	120 (12)
Other	47 (10)	50 (10)	97 (10)
Geographical region, n(%)			
US	52 (11)	53 (11)	105 (11)
Europe	234 (49)	217 (45)	451 (47)
Other	190 (40)	207 (44)	397 (42)

Results of the pooled analysis demonstrate that reslizumab reduced the rates of CAEs over 52 weeks, CAEs requiring systemic corticosteroid treatment for ≥3 days, and CAEs requiring hospitalization or a visit to the ER in each of the individual studies; the latter not reaching statistical significance (Table 19).

In the Integrated 52-Week Population, reslizumab-treated patients saw a 54% reduction in the CAE rate compared with placebo-treated patients (CAE rate ratio [95% CI]=0.4613 [0.3662, 0.5811], p<0.0001).

Table 16 Summary of CAEs overall and by medical intervention (adjudicated data, studies 3082 and 3083 and integrated 52-week population, Randomized set).

	Study 3082		Study 3083		Integrated 52-Week Population	
Variable	Placebo (N=244)	Reslizumab 3.0 mg/kg (N=245)	Placebo (N=232)	Reslizumab 3.0mg/kg (N=232)	Placebo (N=476)	Reslizumab 3.0 mg/kg (N=477)
Number of patients with at least 1 CAE, n (%)	132 (54.1)	92 (37.6)	105 (45.3)	59 (25.4)	237 (49.8)	151 (31.7)
Adjusted CAE rate	1.8036	0.9037	2.1147	0.8591	1.8118	0.8359
CAE rate ratio (95% CI)	0.5010 (0.3726, 0.6737)		0.4063 (0.2819, 0.5855)		0.4613 (0.3662, 0.5811)	
Number of patients with at least 1 CAE requiring systemic corticosteroid, n (%)	118 (48.4)	80 (32.7)	92 (39.7)	49 (21.1)	210 (44.1)	129 (27.0)
Adjusted CAE rate	1.6040	0.7217	1.6602	0.6463	1.5387	0.6572
CAE rate ratio (95% CI)	0.4499 (0.3255, 0.6220)		0.3893 (0.2621, 0.5782)		0.4271 (0.3324, 0.5488)	
Number of patients with at least 1 CAE requiring OCS, n (%)	117 (48.0)	77 (31.4)	86 (37.1)	46 (19.8)	203 (42.6)	123 (25.8)
Adjusted CAE rate	1.5909	0.6974	1.6049	0.6462	1.5044	0.6431
CAE rate ratio (95% CI)	0.4384 (0.3158, 0.6085)		0.4027 (0.2660, 0.6096)		0.4275 (0.3304, 0.5531)	
Number of patients with at least 1 CAE resulting in hospitalization or a visit to the ER, n (%)	21 (8.6)	22 (9.0)	12 (5.2)	9 (3.9)	33 (6.9)	31 (6.5)
Adjusted CAE rate	0.2073	0.1367	0.0473	0.0325	0.1169	0.0773
CAE rate ratio (95% CI)	0.6595 (0.3210, 1.3550)		0.6886 (0.2878, 1.6479)		0.6615 (0.3763, 1.1628)	

CAE=clinical asthma exacerbation; CI=confidence interval; ER=emergency room; OCS=oral corticosteroid

The results for the secondary endpoints based on the integrated week 52 population are shown in Table 20. The overall improvement in FEV1 is 117 ml over 16 weeks. The data on FEV1 and other symptomatic endpoints are consistent with the individual results. The improvements sustain over 52 weeks.

Table 17 Change from baseline over 16 weeks and 52 weeks in secondary endpoints by treatment group (Integrated 52-week population, randomized set) (Compiled by CHMP).

Statistic	Placebo (N=476)		Reslizumab 3.0 mg/kg (N=477)		Treatment difference (95% CI) p-value
Over 16 weeks	n		n		
FEV1 L LS mean change (SE)	468	0.109 (0.0245)	473	0.226 (0.0242)	0.117 (0.073, 0.160) <0.0001
ACQ score LS mean change (SE)	469	-0.672 (0.0158)	472	-0.905 (0.0514)	-0.232 (-0.325, -0.139) <0.0001
AQLQ score* LS mean change (SE)	445	0.711 (0.0689)	441	0.937 (0.0688)	0.226 (0.094, 0.359) 0.0008
ASUI score LS mean change (SE)	462	0.101 (0.0095)	465	0.149 (0.0095)	0.048 (0.030, 0.065) <0.0001
SABA (puff/day) LS mean change (SE)	426	-0.372 (0.1312)	420	-0.566 (0.1298)	-0.194 (-0.430, 0.043) 0.1081
Eosinophil count (10^9/L LS mean change (SE)	467	-0.098 (0.0175)	473	-0.574 (0.0174)	-0.476 (-0.507, -0.444) <0.0001
Over 52 weeks	n		n		
FEV1 L LS mean change (SE)	468	0.115 (0.0244)	473	0.224 (0.0240)	0.110 (0.066, 0.154) <0.0001
ACQ score LS mean change (SE)	469	-0.769 (0.0511)	472	-1.019 (0.0506)	-0.250 (-0.343, -0.156) <0.0001
AQLQ score LS mean change (SE)	452	0.813 (0.0653)	449	1.084 (0.0650)	0.272 (0.155, 0.388) <0.0001
ASUI score LS mean change (SE)	462	0.122 (0.0088)	465	0.171 (0.0087)	0.049 (0.033, 0.065) <0.0001
SABA (puff/day) LS mean change (SE)	432	-0.445 (0.1235)	432	-0.608 (0.1216)	-0.163 (-0.389, 0.063) 0.1571
Eosinophil count (10^9/L) LS mean change (SE)	467	-0.101 (0.0140)	473	-0.576 (0.0139)	-0.475 (-0.501, -0.450) <0.0001

* Analyzed at week 16

ASUI=Asthma Symptom Utility Index; CI=confidence interval; ISE=Integrated Summary of Efficacy; MMRM=mixed-effect model for repeated measures; NA=not applicable.

Notes: All inferential statistics were derived from an MMRM with treatment, study, visit, treatment-by-visit interaction, and stratification factors as fixed factors; a covariate for baseline value; and patient as a random effect. Unstructured covariance structure was assumed for the repeated measures.

Blood eosinophil level after discontinuation

Decreases in blood eosinophil counts were seen with reslizumab 3 mg/kg following the first dose and maintained through 52 weeks of treatment with no signs of tachyphylaxis.

Table 18 Change from Baseline to Follow-up in Blood Eosinophil Count (109 cells/L) by Treatment Group (Integrated 52-Week Population, Randomized Set)

Time point Statistic	Placebo (N=476)	Reslizumab3.0 mg/kg (N=477)
Baseline	N=476	N=477
Mean (sd)	0.655 (0.6369)	0.654 (0.6214)
Week 16	N=428	N=433
Mean (sd)	0.521 (0.4305)	0.058 (0.0906)
Week 52	N=405	N=407
Mean (sd)	0.514 (0.3842)	0.061 (0.1376)
Follow-up	N=39	N=36
Mean (sd)	0.612 (0.7491)	0.394 (0.3792)

Within the limited subset of patients who discontinued treatment and had a follow-up visit approximately 4 months after the last dose showed recrudescence of blood eosinophil counts. This is consistent with the prolonged half-life of reslizumab (24 to 30 days).

Subgroup analyses – Clinical asthma exacerbations

The frequency of CAEs over 52 weeks in the Integrated 52-Week Population was analyzed by age group, sex, race, geographical region, ADA results, OCS use at baseline, LABA use at baseline, and LTRA use at baseline (Table 22). Favourable results were seen for all subgroups except for patients 12 to 17 years (n=25), black patients (n=44), patients of other races (n=97) and patients enrolled in the US (n=105).

Table 19 Frequency of CAEs During the 52-Week Treatment Period by Subset and Treatment Group-Adjudicated Data (Integrated 52-Week Population, Randomized Set).

	Placebo (N=476)			Reslizumab 3.0 mg/kg (N=477)			Reslizumab 3.0 mg/kg vs placebo
Subgroup	No. of patients	No. of patients with at least 1 CAE	Adjusted CAE rate (95% CI)	No. of patients	No. of patients with at least 1 CAE	Adjusted CAE rate (95% CI)	CAE rate ratio (95% CI)
Age							
12-17 years	11	6	1.37 (0.57, 3.28)	14	8	2.86 (1.02, 8.09)	2.09 (0.82, 5.36)
18-64 years	420	199	1.72 (1.32, 2.24)	431	134	0.80 (0.61, 1.05)	0.47 (0.36, 0.60)
≥65 years	45	32	2.65 (1.31, 5.37)	32	9	0.87 (0.43, 1.78)	0.33 (0.15, 0.71)
Sex							
Male	165	79	1.67 (1.16, 2.42)	191	56	0.78 (0.54, 1.14)	0.47 (0.32, 0.69)
Female	311	158	1.86 (1.34, 2.57)	286	95	0.86 (0.62, 1.19)	0.46 (0.35, 0.62)
Race							
White	351	182	1.60 (1.22, 2.10)	341	100	0.65 (0.49, 0.87)	0.41 (0.31, 0.53)
Black	24	12	0.62 (0.20, 1.98)	20	12	0.75 (0.22, 2.51)	1.20 (0.62, 2.31)
Asian	54	22	4.96 (1.10, 22.38)	66	20	1.57 (0.38, 6.43)	0.32 (0.14, 0.69)
Other	47	21	1.37 (0.49, 3.83)	50	19	1.32 (0.49, 3.58)	0.96 (0.51, 1.83)
Geographical region							
US	52	23	0.83 (0.45, 1.52)	53	27	0.93 (0.52, 1.68)	1.13 (0.64, 1.98)
Europe	234	115	1.56 (1.21, 2.02)	217	47	0.46 (0.33, 0.64)	0.29 (0.20, 0.43)
Other	190	99	1.81 (1.38, 2.39)	207	77	0.89 (0.66, 1.19)	0.49 (0.35, 0.68)
At least 1 positive postbaseline ADA result[a]							
Yes	NA	NA	NA	23	2	0.11 (0.02, 0.53)	0.12 (0.03, 0.56)[b]
No	NA	NA	NA	454	149	0.95 (0.68, 1.31)	
OCS use at baseline							
Yes	73	44	2.04 (1.07, 3.89)	73	25	0.65 (0.34, 1.24)	0.32 (0.18, 0.55)
No	403	193	1.40 (1.11, 1.76)	404	126	0.69 (0.55, 0.87)	0.50 (0.39, 0.64)
LABA use at baseline							
Yes	383	198	1.84 (1.42, 2.37)	397	122	0.83 (0.63, 1.08)	0.45 (0.35, 0.58)
No	93	39	1.63 (0.75, 3.52)	80	29	0.84 (0.40, 1.75)	0.51 (0.29, 0.89)
LTRA use at baseline							
Yes	112	73	2.89 (1.91, 4.36)	97	33	0.89 (0.57, 1.39)	0.31 (0.20, 0.48)
No	364	164	1.39 (1.04, 1.85)	380	118	0.80 (0.60, 1.06)	0.58 (0.44, 0.75)

Source: ISE, Summary 5.3.2.1 and Summary 5.14.2.1.

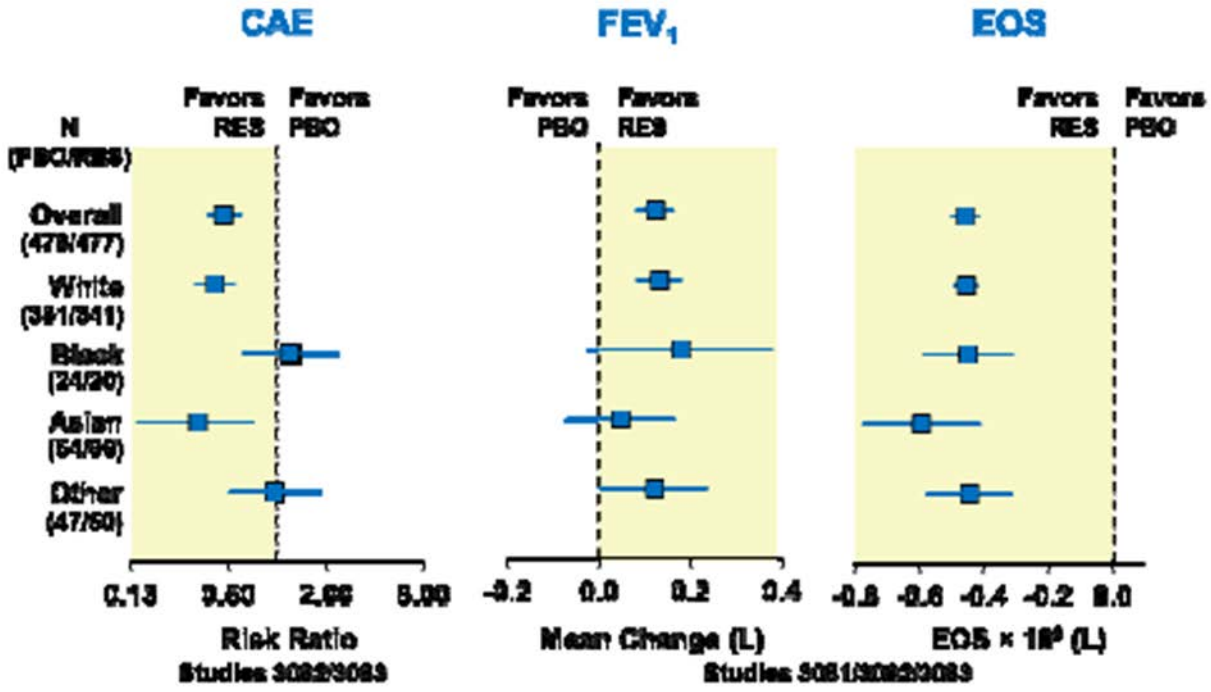
[a] Anti-drug antibodies were not assessed in placebo-treated patients.

[b] Clinical asthma exacerbation rate ratio (95% CI) is reported for the comparison of CAE rates in patients in the reslizumab 3.0 mg/kg treatment group with positive postbaseline ADA result versus patients in the reslizumab 3.0 mg/kg treatment group with negative postbaseline results.

ADA=anti-drug antibodies; CAE=clinical asthma exacerbations; CI=confidence interval; EOT=end of treatment; ISE=Integrated Summary of Efficacy; LABA=long-acting beta-agonist; LTRA=leukotriene receptor antagonist; NA=not applicable; NB=negative binomial; OCS=oral corticosteroid; US=United States.

Notes: The CAEs counted were those that occurred between the completion of the first dose of study drug and 2 weeks after the EOT/early withdrawal visit. Adjusted CAE rates and CIs and CAE rate ratio and CI were based on NB regression model adjusted for stratification factors (baseline usage of OCS [yes or no] and geographical region [US or other]).

Changes in the physiological measures of FEV1 and blood eosinophil counts in all 4 race subgroups were observed with reslizumab (Figure 3).



Source: CAE – ISE Table 47; EOS – Advisory Committee Summary 59; FEV_1 – ISE Summary 6.7.1.1.

Other category=Hispanic, Mexican, Mexican-American, Middle Eastern, Indian, Spanish, Mulate, and Latin American.

CAE=clinical asthma exacerbation; EOS=eosinophils; FEV_1=forced expiratory volume in 1 second; PBO=placebo; RES=reslizumab.

Figure 1: Reslizumab Effect by Race

A post-hoc analysis was performed for the primary endpoint stratified for the number of exacerbations in the previous year. Overall, 58% and 59% had one CAE and 18% and 22% had two prior CAE in the preceding year for placebo and reslizumab treated patients, respectively. Fourteen percent and 10% had ≥4 CAEs in the preceding year for placebo and reslizumab, respectively. The results show that reslizumab reduced CAE rate ratios for all values of number of exacerbations in the preceding year, with reductions of 32%, 56%, 61%, and 64% for 1, 2, 3, and ≥4 exacerbations in the preceding year, respectively.

Post-hoc analyses subgroup of patients with severe eosinophilic asthma (GINA step 4/5)

At the CHMP's request, post-hoc analyses were presented for the severe eosinophilic asthma population based on the integrated data from studies 3082 and 3083 using the GINA classification. Within both studies, most patients were characterised as GINA step 4 (68% in study 3082 and 70% in study 3083) with a minority being classified as GINA step 5 (13% in study 3082 and 9% in study 3083). The remaining population was classified as GINA step 3 (11% and 16% for study 3082 and 3083, respectively). Overall, about 80% of the population was classified as GINA step 4/5.

The outcomes for the primary and main secondary endpoints are summarized in the Table below for the subgroup of patients with GINA 4/5.

Table 20 Summary of primary and main secondary endpoints (change from baseline over 16 and 52 weeks) for the GINA 4/5 subgroup (Study 3082, 3083 and Integrated study population)

	Study 3082		Study 3083		Integrated studies 3082 and 3083	
Efficacy variable	**Placebo**	**Reslizumab**	**Placebo**	**Reslizumab**	**Placebo**	**Reslizumab**
No. of patients with at least 1 CAE	116/202	74/194	84/178	43/189	200/380	117/383
CAE rate ratio (95%CI)	0.50 (0.37, 0.69)		0.34 (0.23, 0.52)		0.44 (0.34, 0.56)	
FEV_1 (L)	N=199	N=192	N=174	N=189	N=373	N=381
Week 16 LS mean diff. (95% CI)	0.182 (0.114, 0.249)		0.099 (0.027, 0.171)		0.143 (0.094, 0.192)	
	N=199	N=192	N=174	N=189	N=373	N=381
Week 52 LS mean diff. (95% CI)	0.159 (0.092, 0.227)		0.092 (0.019, 0.166)		0.129 (0.080, 0.179)	
ACQ score	N=199	N=192	N=175	N=189	N=374	N=381
Week 16 LS mean diff. (95% CI)	-0.379 (-0.524, -0.234)		-0.252 (-0.399, -0.105)		-0.321 (-0.424, -0.218)	
	N=199	N=192	N=175	N=189	N=374	N=381
Week 52 LS mean diff. (95% CI)	-0.348 (-0.496, -0.200)		-0.301 (-0.448, -0.153)		-0.330 (-0.433, -0.226)	
ASUI score	N=196	N=189	N=173	N=188	N=369	N=377
Week 16 LS mean diff. (95% CI)	0.071 (0.044, 0.098)		0.048 (0.021, 0.075)		0.061 (0.041, 0.080)	
	N=196	N=189	N=173	N=188	N=369	N=377
Week 52 LS mean diff. (95% CI)	0.073 (0.047, 0.098)		0.053 (0.029, 0.078)		0.064 (0.046, 0.082)	
AQLQ	N=190	N=181	N=168	N=178	N=358	N=359
Week 16 LS mean diff. (95% CI)	0295 (0.089, 0.501)		0.280 (0.078, 0.482)		0.295 (0.151, 0.438)	
	N=191	N=185	N=171	N=180	N=362	N=365
Week 52 LS mean diff. (95% CI)	0.340 (0.160, 0.519)		0.339 (0.157, 0.521)		0.346 (0.219, 0.473)	

Of note, favorable beneficial effects were also observed in patients with GINA 3 as well; CAE rate ratio was 0.60 (95% CI: 0.30, 1.19). For the main secondary endpoints, numerical improvements was seen for FEV1 as well (mean change from baseline: 0.090, 95% CI: -0.019, 199), but this was less obvious for patient reported outcomes.

Post-hoc analysis in patients with refractory asthma and in patients with non-refractory asthma

At the CHMP's request, a post-hoc analysis of reslizumab efficacy in patients with refractory asthma and in patients with non-refractory asthma was performed.

Based on the definition and available data, 306 (32%) out of 953 patients for the integrated Studies 3082/3083 population met the definition of refractory asthma, and 647 (68%) patients were non-refractory.

The results of the primary endpoint and the main secondary endpoints are shown below. The post-hoc analyses show clinically relevant reductions in annual rate of exacerbation in both the refractory (59%) and non-refractory (49%) subgroup. The results are supported by the effects on lung function and patient reported outcomes.

Table 21 Summary of primary and main secondary endpoints (change from baseline over 16 and 52 weeks) for the refractory and non-refractory population (Integrated study population)

	Over 16 weeks		Over 52 weeks	
Efficacy variable	**Placebo (N=467)**	**Reslizumab (N=477)**	**Placebo (N=467)**	**Reslizumab (N=477)**
Overall population			237/476	151/477
CAE rate ratio (95% CI)			0.46 (0.37, 0.58)	
Refractory			96/161	54/145
CAE rate ratio (95% CI)			0.41 (0.28, 0.60)	
Non-refractory			141/315	97/332
CAE rate ratio (95% CI)			0.51 (0.38, 0.68)	
FEV1 (L) treatment diff (95% CI)				
Overall population	0.117 (0.073, 0.160)		0.110 (0.066, 0.154)	
Refractory	0.166 (0.084, 0.248)		0.158 (0.076, 0.240)	
Non-refractory	0.090 (0.039, 0.141)		0.085 (0.032, 0.137)	
ACQ7 treatment diff (95% CI)				
Overall population	-0.232 (-0.325, -0.139)		-0.250 (-0.343, -0.156)	
Refractory	-0.270 (-0.447, -0.093)		-0.295 (-0.471, -0.119)	
Non-refractory	-0.207 (-0.315, -0.099)		-0.221 (-0.329, -0.113)	
ASUI treatment diff (95% CI)				
Overall population	0.048 (0.030, 0.065)		0.049 (0.033, 0.065)	
Refractory	0.070 (0.035, 0.104)		0.070 (0.038, 0.102)	
Non-refractory	0.036 (0.016, 0.055)		0.038 (0.020, 0.055)	
AQLQ treatment diff (95% CI)				
Overall population	0.226 (0.094, 0.359)		0.272 (0.155, 0.388)	
Refractory	0.324 (0.101, 0.547)		0.432 (0.233, 0.632)	
Non-refractory	0.176 (0.013, 0.339)		0.185 (0.044, 0.326)	

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 Summary of efficacy for trial 3081

Title: A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12-75 Years of Age) with Eosinophilic Asthma				
Study identifier	3081			
Design	Randomized double-blind placebo-controlled parallel group multicenter study Stratified for previous exacerbation (yes/no) and age (12-17 years / ≥18 years) Patients were randomized 1:1:1 to treatment groups			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks Not applicable Ongoing	
Hypothesis	Superiority - both doses compared to placebo			
Treatments groups	Placebo		IV infusion every 4 weeks over 16 weeks N randomized=105	
	Reslizumab 0.3 mg/kg		IV infusion every 4 weeks over 16 weeks N randomized=104	
	Reslizumab 3.0 mg/kg		IV infusion every 4 weeks over 16 weeks N randomized=106	
Endpoints and definitions	Primary endpoint	FEV1	Forced-expiratory volume in 1 second Change from baseline in FEV1 over 16 weeks	
	Secondary endpoint	ACQ	Asthma Control Questionnaire score Change from baseline over 16 weeks	
	Secondary endpoint	AQLQ	Asthma Quality of Life Questionnaire score Change from baseline at week 16	
	Secondary endpoints	FVC FEF25%-75% ASUI SABA use Blood eosinophil count % predicted FEV1	Results for the other secondary endpoints were not repeated in the Table	
Database lock	Last patient completed on 12 September 2013			
Results and Analysis				
Analysis description	**Primary Analysis - Superiority of both doses over placebo**			
Analysis population and time point description	Full Analysis Set (randomized patients that received at least 1 dose of study drug). Overall change from baseline over 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
	Number of subject	105	103	103

	FEV1 (L) LS mean change SE	 0.126 0.0549	 0.242 0.0556	 0.286 0.0548
Effect estimate per comparison	Primary endpoint: FEV1	Comparison groups	Reslizumab 0.3 mg/kg versus placebo	Reslizumab 3.0 mg/kg versus placebo
		Difference LS means	0.115	0.160
		95% CI	(0.016, 0.215)	(0.060, 0.259)
		P-value	0.0237	0.0018
Analysis description	**Secondary analysis- Change from baseline in ACQ and AQLQ score for both doses compared to placebo**			
Analysis population and time point description	Full Analysis Set (randomized patients that received at least 1 dose of study drug). Overall change from baseline over 16 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
	Number of subjects	105	103	103
	ACQ score LS mean change SE	 -0.494 0.1231	 -0.732 0.1250	 -0.853 0.1233
	AQLQ score LS mean change SE	 0.779 0.1817	 1.057 0.1881	 1.138 0.1829
Effect estimate per comparison		Comparison groups	Reslizumab 0.3 mg/kg versus placebo	Reslizumab 3.0 mg/kg versus placebo
	ACQ score	Difference LS means	-0.238	-0.359
		95% CI	(-0.456, -0.019)	(-0.577, -0.140)
		P-value	0.0379	0.0014
	AQLQ score	Difference LS means	0.278	0.359
		95% CI	(-0.036, 0.591	(0.047, 0.670
		P-value	0.0822	0.0241

Table 23 Summary of efficacy for trial 3082

Title: A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma.		
Study identifier	3082	
Design	Randomised double-blind placebo-controlled parallel group study Randomisation (1:1) was stratified by oral corticosteroid use and region (US or other)	
	Duration of main phase:	52 weeks
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Ongoing
Hypothesis	Superiority of reslizumab 3.0 mg/kg over placebo in reduction of frequency of clinical asthma exacerbations over 12 months	

Treatments groups	Placebo		IV infusion every 4 weeks over 52 weeks N randomized=244
	Reslizumab 3.0 mg/kg		IV infusion every 4 weeks over 52 weeks N randomized=245
Endpoints and definitions	Primary endpoint	CAE	Frequency of clinical asthma exacerbation defined as either systemic corticosteroids use or a two-fold increase in ICS for ≥3 days, or an asthma-related emergency visit/hospitalization accompanied by a worsening in clinical signs and symptoms of asthma.
	Secondary endpoint	FEV1	Change from baseline in FEV1 over 16 weeks
	Secondary endpoint	ACQ	Asthma control questionnaire Change from baseline over 16 weeks
	Secondary endpoint	AQLQ	Asthma quality of life questionnaire Change from baseline to week 16
	Secondary endpoints	Not presented	Time to first CAE Overall change from baseline in asthma symptom utility index (ASUI) score over 16 weeks Overall change from baseline in SABA use over 16 weeks
Database lock	Last patient visit 03 March 2014		

Results and Analysis

Analysis description	**Primary Analysis – clinical asthma exacerbation over 52 weeks** Adult patients (aged 12- 75 years) with a previous diagnosis of asthma and at least 1 asthma exacerbation over the past 12 months before screening were included. Patients had a current blood eosinophil level of at least 400 cells/μL and were uncontrolled despite a medium-to-high dose ICS (inhaled fluticasone of at least 440 μg/daily, or equivalent).		
Analysis population and time point description	Randomised population (≈ intention-to-treat population) 52 weeks		
Descriptive statistics and estimate variability	Treatment group	Placebo	Reslizumab 3.0 mg/kg
	Number of subjects	N=244	N=245
	CAE Number with at least 1 CAE (%) Adjusted CAE rate (95% CI)	132 (54.1) 1.8036 (1.3715, 2.3720)	92 (37.6) 0.9037 (0.6778, 1.2048)
Effect estimate per comparison	Primary endpoint	Comparison groups	Reslizumab versus Placebo
		CAE rate ratio	0.5010
		95% CI	0.3726, 0.6737
		P-value	<0.0001

Notes	Missing or invalid values were not imputed in the primary analysis. Sensitivity analyses imputing missing data showed comparable results. One quarter of the patients had protocol violations, a per-protocol analysis is requested to assess the impact on the primary and key secondary endpoints.		
Analysis description	**Secondary analyses change from baseline over 16 weeks**		
Descriptive statistics and estimate variability	Treatment group	Placebo	Reslizumab 3.0 mg/kg
	Number of subjects	N=244	N=245
	FEV1 (L) LS mean change SE	 0.110 0.031	 0.248 0.030
	ACQ (units) LS mean change SE	 -0.676 0.066	 -0.941 0.065
	AQLQ (units) LS mean change* SE	 0.695 0.088	 0.933 0.088
	Blood eosinophil count (10^9/L) LS mean change SE	 -0.118 0.0232	 -0.548 0.0230
Effect estimate per comparison	Secondary endpoint	Comparison groups	Reslizumab versus Placebo
	FEV1	LS mean difference	0.137
		95% CI	0.076, 0.198
		P-value	<0.001
	ACQ	LS mean difference	-0.266
		95% CI	-0.399, -0.132
		P-value	0.0001
	AQLQ	LS mean difference	0.238
		95% CI	0.048, 0.428
		P-value	0.0143
	Blood eosinophil count (10^9/L)	LS mean difference	-0.466
		95% CI	-0.514, -0.418
		P-value	<0.0001
Notes	Analyses for FEV1, ACQ and AQLQ were controlled for Type 1 error * Change from baseline at week 16		

Table 24 Summary of efficacy for trial 3083

Title: A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma.			
Study identifier	3083		
Design	Randomised double-blind placebo-controlled parallel group study Randomisation (1:1) was stratified by oral corticosteroid use and region (US or other)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable Ongoing
Hypothesis	Superiority of reslizumab 3.0 mg/kg over placebo in reduction of frequency of clinical asthma exacerbations over 12 months		
Treatments groups	Placebo		IV infusion every 4 weeks over 52 weeks N randomized=232
	Reslizumab 3.0 mg/kg		IV infusion every 4 weeks over 52 weeks N randomized=232
Endpoints and definitions	Primary endpoint	CAE	Frequency of clinical asthma exacerbation defined as either systemic corticosteroids use or a two-fold increase in ICS for ≥3 days, or an asthma-related emergency visit/hospitalization accompanied by a worsening in clinical signs and symptoms of asthma.
	Secondary endpoint	FEV1	Change from baseline in FEV1 over 16 weeks
	Secondary endpoint	ACQ	Asthma control questionnaire Change from baseline over 16 weeks
	Secondary endpoint	AQLQ	Asthma quality of life questionnaire Change from baseline to week 16
	Secondary endpoints	Not presented	Time to first CAE Overall change from baseline in asthma symptom utility index (ASUI) score over 16 weeks Overall change from baseline in SABA use over 16 weeks Overall change from baseline in blood eosinophil count over 16 and 52 weeks
Database lock	Last patient visit 03 April 2014		
Results and Analysis			
Analysis description	**Primary Analysis – clinical asthma exacerbation over 52 weeks** Adult patients (aged 12- 75 years) with a previous diagnosis of asthma and at least 1 asthma exacerbation over the past 12 months before screening were included. Patients had a current blood eosinophil level of at least 400 cells/μL and were uncontrolled despite a medium-to-high dose ICS (inhaled fluticasone of at least 440 μg/daily, or equivalent).		
Analysis population and time point description	Randomised population (≈ intention-to-treat population) 52 weeks		

Descriptive statistics and estimate variability	Treatment group	Placebo	Reslizumab 3.0 mg/kg
	Number of subjects	N=232	N=232
	CAE Number with at lease 1 CAE (%) Adjusted CAE rate (95% CI)	105 (45.1) 2.1147 (1.3291, 3.3645)	59 (25.4) 0.8591 (0.5488, 1.3451)
Effect estimate per comparison	Primary endpoint	Comparison groups	Reslizumab versus Placebo
		CAE rate ratio	0.4063
		95% CI	0.2819, 0.5855
		P-value	<0.0001
Notes	Missing or invalid values were not imputed in the primary analysis. Sensitivity analyses imputing missing data showed comparable results. One quarter of the patients had protocol violations, a per-protocol analysis is requested to assess the impact on the primary and key secondary endpoints.		
Analysis description	**Secondary analyses change from baseline over 16 weeks**		
Descriptive statistics and estimate variability	Treatment group	Placebo	Reslizumab 3.0 mg/kg
	Number of subjects	N=232	N=232
	FEV1 (L) LS mean change SE	 0.094 0.041	 0.187 0.041
	ACQ (units) LS mean change SE	 -0.660 0.088	 -0.857 0.087
	AQLQ (units) LS mean change* SE	 0.777 0.115	 0.987 0.116
	Blood eosinophil count (10^9/L) LS mean change SE	 -0.076 0.027	 -0.555 0.027
Effect estimate per comparison	Secondary endpoint	Comparison groups	Reslizumab versus Placebo
	FEV1	LS mean difference	0.093
		95% CI	0.030, 0.155
		P-value	0.0037
	ACQ	LS mean difference	-0.196
		95% CI	-0.327, -0.066
		P-value	0.0032
	AQLQ	LS mean difference	0.209

		95% CI	0.025, 0.393
		P-value	0.0259
	Blood eosinophil count (10^9/L)	LS mean difference	-0.479
		95% CI	-0.519, -0.439
		P-value	<0.0001
Notes	Analyses for FEV1, ACQ and AQLQ were controlled for Type 1 error * Change from baseline at week 16		

Clinical studies in special populations

No clinical studies were performed in special populations. See sections 2.4.2 and 2.5.3.

Supportive studies

Study 3084: A 16-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) Treatment in Patients With Moderate to Severe Asthma.

Adult patients (aged 18-65 years) with a diagnosis of asthma and an ACQ score of at least 1.5, airway reversibility of at least 12% to beta-agonist administration and currently taking fluticasone at a dosage of at least 440 mg daily (or equivalent) were included in the study. Patients were unselected for blood eosinophil level. The primary objective was to characterize the efficacy of reslizumab treatment 3.0 mg/kg (every 4 weeks) in improving pulmonary function in relation to baseline blood eosinophil levels, based on change from baseline to week 16 in FEV1. Secondary efficacy endpoints were pulmonary function as measured by FEV1, % predicted FEV1, FVC, and FEF25%-75% at specified time points. In addition SABA use, ACQ and blood eosinophil count was measured. In addition, safety was assessed. Eligible patients were randomly assigned (1:4) to receive an infusion of placebo or reslizumab (3.0 mg/kg) every 4 weeks for 12 weeks.

A total of 496 patients were randomly assigned to treatment and analysed. The treatment groups (3.0 mg/kg reslizumab treatment group and placebo) were similar in regard to age (mean 44.9 and 45.1 years, respectively), race (65% and 74% white, respectively). A similar percentage of patients had an asthma exacerbation within the last 12 months prior to randomization, 40% and 41%, respectively. A minority of patients had baseline eosinophils ≥ $0.4x10^9$/L (Placebo: n=19/97 (19.6%), Reslizumab: n=77/395 (19.5%)).

The primary efficacy analysis (linear regression) failed to show a significant interaction between baseline blood eosinophil count and change in FEV1 at week 16: slope difference (active–placebo) was 0.3007 (SE=0.2559, p=0.2407). Secondary efficacy analyses showed small numerical improvements for the overall population compared to placebo, with substantially larger improvements in the ≥400/µL subgroup.

Study 3085: An Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Reslizumab (3.0 mg/kg) as Treatment for Patients With Eosinophilic Asthma Who Completed a Prior Teva-Sponsored Study in Eosinophilic Asthma

Patients included in study 3085 had completed study 3081, 3082, or 3083 or received at least two doses of study drug in study 3081. The primary objective was to obtain long-term safety data (up to 24 months). Secondary objective was to study the long-term efficacy of reslizumab based on change from baseline in pulmonary function tests (FEV1, % predicted FEV1, FVC, FEF25%-75%) and other measures of asthma control (SABA use,

ASUI ACQ and AQLQ). In addition, blood eosinophils were assessed. Patients were expected to participate in this study for up to 27 months.

A total of 1052 patients with eosinophilic asthma were enrolled in this study, 1051 (>99%) patients received at least 1 dose of reslizumab and were evaluated for safety. Four hundred-eighty (46%) patients received reslizumab for the first time. A total of 50 (5%) patients completed the 104-week treatment period and follow-up. A total of 1002 (95%) patients discontinued the study prior to completion, and 896 of these (85% of enrolled patients) did not complete the study due to early termination of the open-label study by the Sponsor. Indeed, the study was prematurely terminated with the rationale that the primary study objective had been sufficiently met that the enrolment had substantially exceeded the original planned sample size and the primary study objective, in terms of open-label safety events for patient exposure to an investigational product with an unconfirmed benefit/risk profile, would have been substantially met at that time.

Considering the previous studies, 277 patients (49%) had ≥24 months of treatment with reslizumab. Overall, the mean age of patients in the study was 47.2 years. Sixty-one percent of patients in the study were female, 77% were white, and 19% were Hispanic or Latino.

For the reslizumab-experienced group, baseline lung function was maintained through the treatment period; values at endpoint were similar to baseline. For instance for FEV1, there was no change from baseline at week 4 and a change of 0.010 L at week 48. Trends for improvement in pulmonary function, asthma symptoms, and overall quality of life scores were observed in reslizumab-naïve patients who were new to therapy. Reslizumab treatment produced a decrease in blood eosinophil levels in reslizumab-naïve patients, similar to the levels in reslizumab-experienced patients after the first dose. In an open label phase 3 extension study, low titre, frequently transient anti reslizumab antibodies were detected in 49 out of 1,014 asthma patients (5%) who received 3 mg/kg reslizumab for up to 36 months.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The in-and exclusion criteria for the dose-response study (3081) and pivotal trials (3082 and 3083) were largely similar, except that patients in the pivotal trials patients had to have at least one exacerbation in the previous year and oral corticosteroid use was allowed. Patients were inadequately controlled despite treatment with at least medium- to-high dose of inhaled corticosteroids (440 μg/day fluticasone propionate or equivalent). The minimal ICS dose corresponds to a 500 μg/day metered dose which is at the high end of the medium dose range for GINA step 3 (>250-500 μg/day). Therefore patients included could range from GINA step 3 to GINA step 5. This corresponds to a formerly called moderate (GINA 3) to severe (GINA 4 and 5) asthma population. In principle, a positive benefit-risk needs to be demonstrated for each grade of asthma severity to be included in the claimed indication. The pivotal studies were placebo controlled which is acceptable for a “severe” eosinophilic asthma population (GINA 4/5). For a population encompassing GINA 3, other treatment options are available (e.g. addition of LABA or increased dose of ICS) and an active controlled trial might be more appropriate in this population as recommended within the CHMP guideline. Post-hoc analyses were performed for the patient population classified as GINA 4/5 to assess the primary and main secondary endpoints in the severe eosinophilic asthma population.

At baseline patients were symptomatic. An additional post hoc sensitivity analyses was made to assess the benefit in the refractory patient population. The refractory patient population was defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2000 workshop; the high-dose ICS was based on

the 2014 severe ATS/ERS guidance table, which accommodates more recent formulations (Chung et al 2014). The benefits of reslizumab were assessed in this population as well.

Given the difficulties in measurement of sputum eosinophilia requiring access to specialised laboratories with trained personnel, the elevation of blood eosinophils was selected as a practical surrogate of sputum eosinophilia for the Phase 3 reslizumab studies. Although the correlation between blood eosinophilia and sputum eosinophilia is poor, this is acceptable as the measurement of sputum eosinophils has not been sufficiently standardised and is not widely available. Hence, this approach is considered acceptable. Asthmatic patients with an eosinophilic phenotype which could benefit from reslizumab were selected based on elevated blood eosinophil count (≥ 400 cells / μL).

The lowering effect of reslizumab on blood eosinophil count might hamper the blinding of the study. Several measurements were taken by the sponsor to avoid unblinding of personnel involved in collection of efficacy data such as redacting eosinophil count data from the haematology results. The CHMP is of the opinion that appropriate strategies to maintain the blind were put in place by the Applicant.

The use of the negative binomial model for exacerbation rate is considered acceptable, as it describes the population as a mixture of subpopulations with fixed rates (Poisson distributions). The sensitivity analysis for the primary outcome based on missing data assumes that patients withdrawing for reasons other than asthma exacerbation or lack of efficacy are missing at random, which is reasonable. For patients missing for imputation asthma exacerbation or lack of efficacy, the imputing data from the placebo group is conservative. Therefore, the overall imputation strategy is considered acceptable. The rest of the statistical methods is considered standard and acceptable.

Endpoints

Study 3081: The primary endpoint (change in FEV1 over 16 weeks) and secondary endpoints (lung function tests, asthma symptoms and quality of life) are considered appropriate. Effect on blood eosinophil count is considered an appropriate PD parameter. Only two doses were explored with the lower dose of 0.3 mg/kg assumed to be a minimally effective dose. The addition of an intermediate dose might have completed the dose-exploration phase.

The pivotal studies 3082 and 3083 were of 1 year duration, a sufficient duration to measure the improvement in exacerbations. The frequency of clinical asthma exacerbations per patient year is a clinically relevant endpoint for a controller medication (CHMP/EWP/2922/01 Rev.1). The definition (defined as either systemic corticosteroids use or a two-fold increase in ICS for ≥3 days, or an asthma-related emergency visit/hospitalization accompanied by a worsening in clinical signs and symptoms of asthma) is appropriate. The exacerbation definition included the “increase of ICS ⩾ 3 days” which is appropriate according the draft guideline of asthma (CHMP/EWP/2922/01 Rev.1). Lung function based on FEV1 is considered an important key secondary endpoint. Other secondary parameters assessing lung function, asthma symptoms and blood eosinophil count provide relevant information as well. Within their Day 121 response, the applicant clarified that lung function measurements were not pre-specified, which might enhance variability within these measurements. However, over 92% (study 3082) and 83% (study 3083) of the sites used the ATS/ERS 2005 criteria. The withdrawal times for spirometry were pre-specified for SABAs and LABAs, but not for other medications such as anticholinergics and xanthine derivatives. Post-hoc analyses showed that 10% of patients used anti-cholinergics and up to 12% used xanthine derivatives. Given the randomised blinded design of the study, the potential use of these drugs near the time of spirometry is not considered to bias assessment of the secondary endpoints in favour of reslizumab.

No data are currently available on the possibility to reduce concomitant controller medication like OCS.

The overall design of studies, although slightly different at the time of SA, was in line with the CHMP scientific advice and deemed acceptable (see Section 2.1).

During the assessment, the Applicant removed some published literature references listed in Annex A of the marketing authorisation application as it could not be excluded that the underlying data may be subject to data protection. The CHMP carefully considered the removal of the concerned references and concluded that it did not impact the integrity of the dossier and the evaluation performed.

Efficacy data and additional analyses

Dose finding

From the patient population (n=315) included in the dose-finding study (3081) about 56% experienced an exacerbation in the past 12 months. Post-hoc analyses showed that most patients were classified as GINA step 4 (79%), followed by GINA step 3 (17%) and <1% as GINA step 5. A statistical and clinical significant change from baseline in FEV1 over 16 weeks was shown for both the low and high dose compared to placebo (0.3 mg/kg: 0.115 L, 95%CI: 0.016-0.215; 3.0 mg/kg: 0.160 L, 95%CI: 0.060-0.259). The overall treatment effect was numerically larger for patients in the reslizumab 3.0 mg/kg treatment group. A similar pattern was seen for secondary endpoints. These results support the use of reslizumab 3.0 mg/kg within the range of investigated doses.

Pivotal studies

The pivotal phase 3 studies (3082 and 3083) included a total of 953 patients. The mean number of exacerbations in the previous year was 2.0, most patients used a second controller at baseline (>80%) and about 15% used OCS at baseline. Post-hoc analyses showed that overall 69% of patients were classified as GINA 4 and 11% as GINA 5, consistent with a severe eosinophilic asthma population. The remaining part (13%) was classified as GINA 3. Further, almost 60% of patients had 1 CAE in the past year and about 20% had experienced 2 CAEs, frequencies of previous exacerbations were in general balanced between treatment groups.

Over 85% completed the study and few patients withdrew due to lack of efficacy (<1%) or adverse events (<5%), showing that the treatment was well tolerated. However, about one quarter of patients had protocol violations in both studies. The applicant clarified within their Day 121 response that a conservative approach was taken as all protocol deviations were classified as violations. There was no apparent clustering of violations in certain centres and no indications of GCP misconduct that would trigger an inspection.

Both studies showed a statistical and clinically relevant reduction in clinical asthma exacerbations (CAE); the reduction in CAE rate during the first year was 50% and 59% in study 3082 and 3083, respectively. Most CAEs was based on systemic corticosteroid use, which indicate severe exacerbations: in that case the reduction of exacerbation was 55% and 61%, respectively. Sensitivity analyses showed comparable results suggesting a robust effect. A post-hoc sensitivity analysis on the per protocol population yielded results comparable to the primary analysis (46% and 60% reduction in CAE rate for study 3082 and study 3083, respectively). No statistical significant effect was shown for CAE based on an emergency visit or hospitalization, which may be explained by limited numbers.

The results of the primary analysis are supported by a clinically relevant effect on FEV1; the mean increase over 16 weeks compared to placebo was 0.137 L and 0.093 L for study 3082 and 3083 ($p<0.05$), respectively. Besides an improvement in lung function, patients reported statistically significant fewer asthma symptoms and reported an improved quality of life compared to placebo. An effect was seen as early as 4 weeks after start of treatment and maintained throughout the study period. The combination - an improvement in exacerbations, symptoms and lung function - indicates an overall better inflammatory control. Results of the FAS, which

excluded data that may have been affected by a restricted concomitant asthma medication were consistent with that of the primary analysis using the ITT population.

Efficacy was accompanied by a reduction in the number of blood eosinophil count, which support that the improvement in lung function was obtained because of better inflammatory control. A return towards baseline values of blood eosinophil count was demonstrated within a limited number of patients (n=36 combined data) but blood eosinophil counts were still reduced at 4 months after stop of treatment.

Subgroup analyses of the primary endpoint showed consistent results across gender, age except for adolescents, black patients and patients of other races and patients enrolled in the US.

The adolescent population was small (n=25 combined) and is not part of the indication. Paediatric patients < 18 years old have been added as a missing information in the RMP and the SmPC adequately reflects this information.

The lack of effect in subgroups such as black patients and US population could be explained by a lower background rate of exacerbations and an overall better asthma control according to the applicant. However, these finding remains unexplained. There are currently no indications of genetic factors to be involved in a lower response in these subpopulations. In addition, the improvements observed in FEV1 in these subpopulations are reassuring. Non-white patients have been added as topic for missing information to the RMP.

A post-hoc analysis showed that reslizumab reduced CAE rate ratios for all values of number of exacerbations in the preceding year, with a 32% reduction in patients with 1 prior CAE and a 56% to 64% in patients with 2, 3 or ≥4 previous CAE .

A post-hoc analysis was performed according to the GINA classification in order to identify the benefit in the subgroup of patients with severe eosinophilic asthma based on GINA classification4/5. The overall results of the primary and main secondary endpoints yielded similar results as the primary analysis, with numerically higher treatment effects for this subgroup. The largest effects were seen in the subgroup GINA 5 The overall reduction in CAE rate for GINA 4/5 was 56% (RR: 0.44, 95% CI: 0.34, 0.56) compared to 54% (RR: 0.46, 95% CI: 0.37, 0.58) for the total population based on the integrated data from studies 3082 and 3083.

Beneficial effects were also observed in patients classified as GINA 3 based on CAE and FEV1, but less obvious for patient reported outcomes. Within this patient group, however, additional treatment options are available such as the addition of LABA's. As no data are available on the effect of reslizumab compared to LABA, the patients with GINA 3 are excluded from the indication.

In addition, a post-hoc analysis was performed in patients with refractory asthma, based on the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2000 workshop definition and baseline characteristics that were available in the Studies 3082 and 3083 databases. These analysis showed that 306 (32%) out of 953 patients for the integrated Studies 3082/3083 population met the definition of refractory asthma. Reslizumab produced clinically meaningful reductions in the annual rate of asthma exacerbation in the refractory (59%) and non-refractory (49%) population as well (integrated Studies 3082/3083 population). These results were supported by the main secondary endpoints. Overall, the results show a consistent picture of efficacy of reslizumab in the included study population, which is considered mainly a severe eosinophilic asthma population.

The presence of ADA did not appear to impact efficacy.

The number of elderly patients was limited as can be expected for an asthmatic population. Current clinical data do not indicate a differential effect supported by PK and no additional follow-up measurements are currently deemed necessary. Elderly patients > 75 years old has been added as a missing information to the RMP.

Use of other immunosuppressive or immunomodulatory agents was not allowed. This information is adequately reflected in the SmPC and has been added as a missing information to the RMP.

Preliminary results of the long-term follow-up study 3085 support efficacy in the long-term.

Lack of efficacy in an overall asthma population unselected for blood eosinophil count (study 3084) support that reslizumab is only effective in an eosinophilic asthma phenotype.

Finally, for patients on a high medium ICS dose + second controller, the maintenance treatment can be increased to a high dose ICS + LABA. The expected benefit is small because of the flat dose response of inhaled corticosteroid. However, some patients may still benefit. In addition, an increase in inhalation therapy is considered more convenient for the patient compared to reslizumab's 4 weekly intravenous drug administration. Therefore, the CHMP requested the Applicant to restrict the indication to patients are still inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment. The Applicant accepted the CHMP's revised indication as follows:

"*CINQAERO is indicated 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*."

2.5.4. Conclusions on the clinical efficacy

Reslizumab at a dose of 3.0 mg/kg once every 4 weeks has shown a clinically relevant reduction in the frequency of exacerbations in asthmatic patients who are inadequately controlled despite medium-(high end) to-high dose ICS (at least 440 µg of inhaled fluticasone propionate or equivalent total daily dose) with elevated blood eosinophil levels ≥ 400 cells/µL and who mostly used a second controller medication.

Further, reslizumab improved lung function and asthma symptom, outcome measurements which support that a better inflammatory control has been achieved. Most patients were severe eosinophilic asthma patients (GINA 4/5) for which limited other treatment options exist. A clinically relevant treatment effect was also shown independent of the number of previous exacerbations and in the refractory asthmatic population.

No statistical significant effect was shown for CAE based on an emergency visit or hospitalization.

Beneficial effects were also observed in patients classified as GINA 3 based on CAE and FEV1, but less obvious for patient reported outcomes. Within this patient group, however, additional treatment options are available such as the addition of LABA's. As no data are available on the effect of reslizumab compared to LABA, the patients with GINA 3 are excluded from the indication.

No data are currently available on the possibility to reduce concomitant controller medication like OCS.

Some patients on a medium dose of ICS may benefit from an increase in ICS dose and this is considered more convenient for the patient compared to intravenous administration with reslizumab. Therefore the CHMP requested the Applicant to restrict the indication as follows:

CINQAERO is indicated 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 (see section 5.1)

The Applicant accepted the CHMP's revised indication.

2.6. Clinical safety

The evaluation of safety includes 14 studies that were conducted with reslizumab treatment.

Apart from study NIH 01-10155, all studies were integrated into 6 cohorts in the Integrated Summary of Safety (ISS). The exclusion of these patients is considered acceptable, because the number of patients in study NIH 01-10155 was low, i.e. 8 patients, and the investigated dose is lower than the recommended dose, i.e. <0.1 mg/kg. Cohorts 3, 4, and 6 were presented as the primary focus of the safety evaluation.

- Cohort 3 (N=1861): This cohort included all exposed patients from placebo-controlled asthma Studies Res-5-0010, 3081, 3082, 3083, and 3084, where patients received at least 1 dose of study drug up to 52 weeks.
- Cohort 4 (N=1611): This cohort included all reslizumab-treated patients from Cohort 3, plus the data from the open-label extension Study 3085 as of 01 September 2014 (N=1596; continuously exposed to 3.0 mg/kg. Cohort 4 is supportive for long term safety as it included also open label study 3085.
- Cohort 6 (N=2187): This cohort included all exposed patients and healthy subjects in sponsored reslizumab studies (any dose, any regimen). It is intended to help capture rare events.

Other cohorts created were: Cohort 1 containing the same studies as Cohort 3 but only up to 16 weeks, Cohort 2 including the 52 weeks studies 3082 and 3083 and Cohort 5 including all asthma patients exposed to reslizumab, regardless of dose and regimen.

In order to assess the safety of the intended population i.e. all asthma patients with baseline or screening blood eosinophils ≥400/µL and using the proposed marketed dose of reslizumab 3.0 mg/ an additional cohort was created "targeted cohort". Only the adverse event data and the long-term safety (exposure to reslizumab for >12 and >24 months) were analysed.

This overview will emphasize on the safety data presented in Cohort 3, considering these data as the main data.

Patient exposure

A total of 2195 patients or healthy subjects have been exposed to at least 1 dose of reslizumab. Of these, 1659 subjects received the recommended dose.

In Cohort 6 (all reslizumab Studies except Study NIH 01-10155) the total patient-years exposure for these 2187 reslizumab-treated patients was 2155.3 years. The mean duration of treatment for reslizumab-treated patients was 360.0 days (range: 1 to 1340 days).

Overall exposure and long term exposure are sufficient as in total 922 patients were treated for greater than 12 months of which 759 patients with reslizumab (Cohort 4). Moreover, 237 asthma patients were treated for at least 24 months. A total of 1006 asthma patients were treated with reslizumab for at least 6 months.

Extension, open-label study 3085, was intended to obtain additional safety data for reslizumab 3.0 mg/kg for up to 24 months. It has been prematurely terminated with the rationale that the primary study objective had been sufficiently met that the enrolment had substantially exceeded the original planned sample size and the primary study objective, in terms of open-label safety events for patient exposure to an investigational product with an unconfirmed benefit/risk profile, would have been substantially met at that time.

A total of 50 (5%) patients completed the 104-week treatment period and follow-up, while 1002 (95%) discontinued the study prior to completion, of which 896 (85%) due to early termination.

Table 25 Study Drug Exposure by Treatment Group- Safety Analysis Set

	Placebo (N=730)	Reslizumab 0.3 mg/kg (N=103) Cohort 3 (placebo controlled)	Reslizumab 3.0 mg/kg (N=1028) Cohort 3 (placebo controlled)	All reslizumab (N=1131)	Reslizumab 3.0 mg/kg (N=1596) (Cohort 4, placebo controlled and uncontrolled)
Patient-years exposure	516.7	31.3	612.5	643.8	1593.339
Duration of treatment phase (days)					
N	730	103	1028	1131	1596
Mean	258.5	111.1	217.6	207.9	364.6
SD	130.73	21.94	128.94	126.87	255.98
Median (min, max)	363.0 (14.0, 473.0)	113.0 (16.0, 196.0)	120.0 (1.0, 512.0)	119.0 (1.0, 512.0)	315.0 (1.0, 1012.0)
Duration of treatment phase, n (%)					
≥1 month	713 (98)	102 (>99)	1021 (>99)	1123 (>99)	1578 (99)
≥2 months	697 (95)	97 (94)	992 (96)	1089 (96)	1526 (96)
≥4 months	487 (67)	20 (19)	533 (52)	553 (49)	1112 (70)
≥6 months	436 (60)	2 (2)	438 (43)	440 (39)	994 (62)
≥12 months	388 (53)	0	389 (38)	389 (34)	743 (47)
≥24 months	0	0	0	0	213 (13)
≥30 months	0	0	0	0	9 (<1)
≥36 months	0	0	0	0	0
Number of complete infusions [a]					20219

Source: ISS Adhoc Summary 11.1

[a] A complete infusion is defined as at least 75% of planned dose.

min, max=minimum, maximum; SD=standard deviation; SE=standard error.

Note: Percentages are based on the number of patients in each treatment group.

Overall exposure and long term exposure are sufficient as in total 922 patients were treated for longer than 12 months (Cohort 6) and 994 asthma patients were treated with reslizumab for at least 6 months, 743 patients were treated with reslizumab for at least 12 months (Cohort 4). Moreover, 213 asthma patients were treated for at least 24 months.

In spite of the vast number of discontinuations due to early termination of study 3085 a sufficient number of data is available for the purpose of assessing long term safety in the complete clinical package. From that point of view there is no objection against the early termination.

Demographics and baseline

Overall, a total of 62% were women and 38% were men, consistent with the demography of the adult and adolescent asthma population. The proportion of White patients in the combined reslizumab population (71%) was slightly lower than in the placebo population (75%). The higher proportion of White patients in the placebo group yielded a lower proportion of Black patients as compared with the all reslizumab group (8% compared to 13%, respectively). Within the reslizumab treated patients, patients in the reslizumab 0.3 mg/kg treatment group were 71% non-Hispanic and non-Latino, whereas non-Hispanic and non-Latino patients accounted for 85% of the reslizumab 3.0 mg/kg treatment group population.

At baseline, assessments of respiratory function status (ACQ score, airway reversibility, FEV1, AQLQ, ASUI, and occurrence of asthma exacerbation within the last 12 months) were similar between reslizumab- and placebo-treated patients and indicative of an inadequately controlled asthma population.

Mean eosinophil count was slightly lower in reslizumab 3.0-mg/kg-treated patients (0.498 × 109/L) compared with placebo-treated patients (0.586 × 109/L). In Cohort 3, 1463 of the 1861 patients (78.6%) had eosinophil counts ≥400 cells/µL at screening or baseline. In Cohort 4, 1300 of the 1611 patients (80.7%) treated with reslizumab had eosinophil counts ≥400 cells/µL at screening or baseline.

Adverse events

In Cohort 3, the overall pattern of adverse events by frequency, severity, and relationship to study drug was similar between the placebo and reslizumab 3.0 mg/kg treatment groups (Table 29).

Table 26 Overview of Adverse Events for Cohort 3—Asthma, Placebo-Controlled Up To 52 Weeks (Studies Res-5-0010, 3081, 3082, 3083, and 3084)

	Number (%) of patients	
	Placebo (N=730)	**Reslizumab 3.0 mg/kg (N=1028)**
Patients with at least 1 adverse event	**589 (81)**	**690 (67)**
Mild adverse events	144 (20)	252 (25)
Moderate adverse events	369 (51)	368 (36)
Severe adverse events	76 (10)	70 (7)
Patients with at least 1 treatment related adverse event	**95 (13)**	**122 (12)**
Mild treatment related adverse events	53 (7)	77 (7)
Moderate treatment related adverse events	41 (6)	38 (4)
Severe treatment related adverse events	1 (<1)	7 (<1)
Patients who withdrew from a clinical study due to an adverse event	40 (5)	48 (5)
Patients who died	1 (<1)	0
Patients with at least 1 serious adverse event	66 (9)	65 (6)
Patients with at least 1 treatment-related serious adverse event	1 (<1)	5 (<1)

Cohort 1 containing data up through 16 weeks shows that the adverse event trends observed from Cohort 3 are also apparent at an earlier time point in the course of reslizumab treatment.

There is also no difference in the frequencies of the (serious) adverse events, treatment-related adverse events and discontinuations due to an adverse event between Cohort 3 and targeted Cohort 3 (i.e. patients with Eosinophils at east 400/µL at Screening and/or Baseline).

The long term exposure to reslizumab did not result in notable differences in adverse event incidence between Cohort 4 (overall 74% in reslizumab 3.0 mg/kg) and Cohort 3 (67% in Reslizumab 3.0 mg/kg).

Common Adverse Events

A total of 690 (67%) of the 1028 patients in the reslizumab 3.0 mg/kg group and 589 (81%) of the 730 patients in the placebo group reported at least 1 adverse event during the course of the individual study periods. There was no adverse event preferred term (PT) reported for reslizumab that occurred with a frequency greater than 1 percentage point higher than that of the corresponding placebo frequency.

For all events, the incidence of events was similar or lower for the reslizumab group versus the placebo treatment group with the exception of Neoplasm, benign, malignant and unspecified SOC, in which a slightly higher incidence was reported in the reslizumab 3.0 mg/kg group (11 [2%] patients) than in the placebo group (4 [<1%] patients).

The most commonly reported adverse event in the reslizumab 3.0 mg/kg treatment group was asthma (232 [23%] patients in reslizumab treatment group compared with 289 [40%] patients in the placebo treatment group); asthma worsening was to be reported as adverse event, per protocol.

The next most common PTs (reported in >5% of patients in the reslizumab 3.0 mg/kg treatment group) were nasopharyngitis (103 [10%] and 103 [14%] patients in the reslizumab 3.0 mg/kg and placebo treatment groups, respectively), upper respiratory tract infection (URTI; 96 [9%] and 69 [10%] patients, respectively), headache (78 [8%] and 62 [9%] patients, respectively), and sinusitis (57 [6%] and 51 [7%] patients, respectively).

The incidence of all common adverse events (>2%) was the same or higher in the placebo group compared to the reslizumab treatment group with the exception of oropharyngeal pain (reslizumab 3.0 mg/kg 2.6% and placebo 2.2%, respectively).

Table 27 Adverse Events (at Least 2%) in Descending Order in the Reslizumab 3.0 mg/kg Treatment Group by Preferred Term and Treatment Group (Cohort 3 and targeted Cohort 3)

MedDRA Preferred Term	Number (%) of patients Cohort 3	
	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Patients with at least 1 AE	**589 (80.7)**	**690 (67.1)**
Asthma	289 (39.6)	232 (22.6)
Nasopharyngitis	103 (14.1)	103 (10.0)
Upper respiratory tract infection	69 (9.5)	96 (9.3)
Headache	62 (8.5)	78 (7.6)
Sinusitis	51 (7.0)	57 (5.5)
Bronchitis	52 (7.1)	34 (3.3)
Urinary tract infection	24 (3.3)	34 (3.3)
Back pain	25 (3.4)	33 (3.2)
Influenza	37 (5.1)	33 (3.2)
Rhinitis allergic	22 (3.0)	28 (2.7)
Oropharyngeal pain	16 (2.2)	27 (2.6)
Pharyngitis	25 (3.4)	23 (2.2)
Cough	23 (3.2)	22 (2.1)
Dyspnoea	20 (2.7)	22 (2.1)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory activities.
Notes: Preferred Terms are sorted by descending order of incidence for the reslizumab 3.0 mg/kg group.

Adverse events occurring more frequently in the 3.0 mg/kg reslizumab group than in the placebo group was seen infrequently and in no cases was the difference between the groups more than 0.5%. (Table 31).

Table 28 Adverse Events Occurring in at Least 1% of Patients in the Reslizumab 3.0 mg/kg Treatment Group and More Frequently Than in the Placebo Group, by Preferred Term and Treatment Group (Cohort 3)

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

[i] Urinary tract infection occurred in 3.31% of patients in reslizumab 3.0 mg/kg and in 3.28% of patients on placebo.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory activities.

In Cohort 4, the frequency of adverse events by SOC was slightly higher than was observed in Cohort 3 for the reslizumab-treated groups. A total of 1172 (73%) of the 1596 patients with continuous exposure to reslizumab 3 mg/kg reported at least 1 adverse event during the course of the individual study periods in this cohort. The overall most common adverse events reported were asthma, nasopharyngitis, URTI, headache, and sinusitis. Given the increased length of observation and length of exposure, yet in the events rates (which weigh heavily in the duration of exposure) the same magnitude of increase was not seen.

In the "targeted Cohort 3", the proportion of patients with at least 1 AE incidence was higher than in Cohort 3; a total of 517 (72%) of the 717 patients in the reslizumab 3.0 mg/kg group and 524 (81%) of the 643 patients in the placebo group reported at least 1 adverse event during the course of the individual study periods.

Severe Adverse Events

Overall, severe adverse events did not occur at a high incidence in either group (70 [7%] and 76 [10%] patients in the reslizumab 3.0 mg/kg and placebo groups, respectively).

The SOCs with the highest incidence of severe events were consistent with the overall adverse event frequency.

The severe adverse event with the highest incidence was asthma (19 [2%] and 27 [4%] patients in the reslizumab 3.0 mg/kg and placebo groups, respectively). All other severe adverse events were reported with an incidence <1%. The most frequently reported severe events following asthma were headache, pneumonia, back pain, sinusitis and influenza.

Treatment-Related Adverse Events

Overall a low number of treatment related adverse events were observed, 122 (12%) and 95 (13%) patients in the reslizumab 3.0 mg/kg and placebo groups, respectively. The proportions of events in the reslizumab-treated and placebo groups were similar. Very few events occurred in ≥5 patients (<1%) in the reslizumab 3.0 mg/kg group.

The most frequent treatment-related adverse events in Cohort 3 were headache, asthma, nausea, fatigue, and increased blood creatine phosphokinase (CPK).

Table 29 Treatment-Related Adverse Events (at Least 3 Patients in Any Treatment Group) by Preferred Term and Treatment Group (Cohort 3—Studies Res-5- 0010, 3081, 3082, 3083, and 3084, Safety Analysis Set)

MedDRA 15.0 Preferred Term	Number (%) of patients	
	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Patients with at least 1 treatment-related AE	95 (13)	122 (12)
Headache	18 (2)	19 (2)
Asthma	5 (<1)	8 (<1)
Fatigue	6 (<1)	7 (<1)
Nausea	4 (<1)	7 (<1)
Blood creatine phosphokinase increased	2 (<1)	6 (<1)
Dizziness	11 (2)	4 (<1)
Infusion site pain	3 (<1)	4 (<1)
Somnolence	1 (<1)	4 (<1)
Myalgia	2 (<1)	3 (<1)
Pruritus	2 (<1)	3 (<1)
Weight increased	1 (<1)	3 (<1)
Oropharyngeal pain	1 (<1)	3 (<1)
Urticaria	1 (<1)	3 (<1)

MedDRA 15.0 Preferred Term	Number (%) of patients	
	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Anaphylactic reaction	0	3 (<1)
Diarrhoea	3 (<1)	2 (<1)
Dysgeusia	5 (<1)	1 (<1)
Paraesthesia	3 (<1)	1 (<1)
Infusion site haematoma	4 (<1)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory activities.

CPK elevations were observed for:

- Blood creatine phosphokinase increased was reported as an adverse event in 20 (1.9%) patients on reslizumab 3.0 mg/kg vs. 12 (1.6%) patients on placebo.
- CPK elevation greater than 5 times the upper limit of normal (ULN) per laboratory data occurred in 25 (2.4%) patients on reslizumab 3.0 mg/kg vs. 10 (1.4%) patients on placebo.
- CPK elevation greater than 10 times the upper limit of normal (ULN) per laboratory data occurred in 8 (0.77%) patients on reslizumab 3.0 mg/kg vs. 3 (0.41%) patients on placebo.

Severe treatment-related adverse events were <1% in both groups (7 [<1%] and 1 [<1%] patients in the reslizumab 3.0 mg/kg and placebo groups, respectively).

Analysis of treatment-related serious adverse events resulted in a very low number of events (5 [<1%] and 1 [<1%] patients in the reslizumab 3.0 mg/kg and placebo groups, respectively).

In the reslizumab 3.0 mg/kg group, treatment-related serious adverse events of anaphylactic reactions were reported by 3 patients, and one event each of osteoarthritis and lung adenocarcinoma. The only treatment-related serious adverse event reported for placebo patients was 1 case of erysipelas.

Because the difference is mainly driven by a difference in anaphylactic reaction, this is considered of concern, in spite of the low numbers.

Adverse Events of Special Interest

Infusion reactions, administration site reactions, hypersensitivity/anaphylaxis, malignancies, infections, and musculoskeletal/CPK abnormalities were designated as adverse events of special interest based on potential effects of the anti-IL-5 mechanism of action and on individual study results.

Infusion reactions and administration site reactions

In Cohort 3, adverse events occurring during or within 24 hours were reported in 30% (306/1028) of patients receiving reslizumab 3.0 mg/kg compared with 39% (282/730) of patients receiving placebo. The most frequently reported event occurring within 24 hours of the infusion was asthma (6% and 14% in the reslizumab 3.0 mg/kg and placebo treatment groups, respectively).

Administration Site Reactions (HLGT) occurred at the same frequency of 2% in the reslizumab 3.0 mg/kg treatment group and in the placebo treatment group. None of the administration site reactions/events were severe, serious, or resulted in discontinuation.

Hypersensitivity and anaphylaxis

In Cohort 3, the incidence of broad anaphylaxis events as well as broad and narrow angioedema events was higher in placebo-treated patients, compared with patients treated with reslizumab.

Five relevant cases in the reslizumab group (<1%) and no cases in the placebo group were observed. Three out of the five anaphylactic reactions (i.e. 3 out of 1028 patients treated with reslizumab) were reported as treatment-related serious adverse events, had a temporal link to infusion, were assessed as related to reslizumab, and resulted in discontinuation of reslizumab treatment. These reactions were observed during or within 20 minutes after completion of the reslizumab infusion and were reported as early as the second dose of reslizumab. They were fully resolved with standard treatment with no residual effect. Manifestations included skin or mucosal involvement, dyspnoea, wheezing, gastrointestinal symptoms and chills.

Two cases occurred on the second infusion, and 1 case occurred on the twelfth infusion. The two other anaphylactic reactions concerned other reasons; were not temporally linked to reslizumab infusion, were associated to pre-known food allergy and immunotherapy, and did not result in discontinuation of reslizumab.

All cases were observed in ADA-negative female patients (2 of whom had medical history of hypersensitivity/anaphylaxis).

There were no other related cases of anaphylaxis reported for the reslizumab 3.0 mg/kg dose in any other Cohort.

Malignancies

In literature, it is suggested that eosinophils possibly play immunomodulatory role in some tumours Therefore, agents lowering peripheral blood and tissue eosinophils could potentially have indirect effects on tumour biology. The papers referred to by the Applicant showed conflicting results; there was not enough evidence to assume either a protective or a suppressive effect on tumour growth by (depletion) of eosinophils. There is no definitive biological evidence that neutralisation of interleukin (IL)-5 or reduction of eosinophil number or function is associated with malignancy.

For reslizumab itself, in the entire clinical program, a total of 24 patients were diagnosed with malignancy: 3 placebo-treated patients and 21 reslizumab-treated patients (6 patients in placebo-controlled studies and 15 patients in the open-label extension [OLE] Study 3085).

In the placebo controlled studies, malignancy was reported in 6 of 1028 (<1%) patients in the reslizumab 3.0 mg/kg treatment group and 2 of 730 (<1%) patients in the placebo treatment group. There was no malignancy in the reslizumab 0.3 mg/kg treatment group.

An additional 13 patients reported malignant neoplasm during the open-label extension Study 3085 by 01 September 2014 cut-off date for data integration, thus overall, there were 22 events of malignancy in 19 patients on reslizumab in Cohort 4. Two additional malignancy cases were not included in this table i.e. 1 ovarian epithelial cancer and 1 borderline ovarian neoplasm from the ongoing Study 3085, which were reported after 01 September 2014.

The most commonly reported malignancies in reslizumab-treated patients were skin cancers, reported by 8 patients (5 patients with NMSC and 3 patients with localized cutaneous malignant melanoma). There were 13 non-skin cancers reported; 8 of these were of the most common tissue types of cancer in the general adult population (i.e. lung, breast, prostate, and colon). The remaining 5 malignancies included 1 anal cancer, 1 diffuse large B-cell lymphoma and 1 plasmacytoma (diagnosed after 147 days on the drug) (Table 33).

These observed malignancies in the reslizumab clinical development program presented a diverse range of common tissue types that would be expected in a primarily adult population.

Table 30 Adverse Events of Malignant Neoplasm by Preferred Term and Treatment Group (Cohort 4 - Studies Res-5-0010, 3081, 3082, 3083, 3084, and 3085, Safety Analysis Set)

System Organ Class MedDRA Preferred Term	All reslizumab 3.0 mg/kg patients (N=1596[a])		
	No. of events	No. (%) of patients	Events/100 PY (PY=1593.34)
Patients with at least 1 malignant neoplasm	22	19 (1)	1.38
Patients with at least 1 malignant neoplasm excluding non-melanoma skin cancer	15	15(<1)	0.94
Basal cell carcinoma	5	3 (<1)	0.314
Breast cancer	3	3 (<1)	0.188
Malignant melanoma	2	2 (<1)	0.126
Prostate cancer	2	2 (<1)	0.126
Anal cancer	1	1 (<1)	0.063
Colon cancer	1	1 (<1)	0.063
Keratoacanthoma	1	1 (<1)	0.063
Lung adenocarcinoma	1	1 (<1)	0.063
Lung neoplasm malignant	1	1 (<1)	0.063
Lymphoma	1	1 (<1)	0.063
Malignant melanoma in situ	1	1 (<1)	0.063
Metastases to lung	1	1 (<1)	0.063
Plasmacytoma	1	1 (<1)	0.063
Squamous cell carcinoma	1	1 (<1)	0.063

One patient was diagnosed with prostate cancer and skin SCC. Another patient was diagnosed with 3 skin BCC lesions.

Four of the 19 patients diagnosed with malignancy had a medical history of malignancy. In 2 of these patients, the malignancy diagnosed during the study was a reoccurrence of their previous malignancy. One case of colon cancer had a diagnosis of familial adenomatous polyposis.

Out of the total number, 8 malignancies in reslizumab-treated patients were diagnosed within 6 months from initiation of reslizumab. An additional 6 malignancies (4 at the cut off date September 2014) were diagnosed between 6 and 12 months after initiation of the study drug (Table 34).

Two of the malignancies in the OLE Study 3085 were diagnosed within less than 6 months of exposure to study drug leaving 14 patients diagnosed with a malignancy after 6 months exposure to reslizumab.

No malignancies occurred in children or adolescent patients in any reslizumab study.

Table 31 Incidence of Malignant Tumors by Interval of Time to First Malignancy Occurrence (Including Non-Melanoma Skin Cancer) Safety Analysis Set Cohort 4

Exposure	Cohort 4-Reslizumab 3.0 mg/kg N=1596 (PY=1593.34)		
	No. of patients in interval	No. of patients with malignancy	% of patients
Overall malignancies	1596	19	1.19
0 - ≤6 months	1596	8	0.50
>6 - ≤12 months	994	4	0.40
>12 - ≤18 months	740	3	0.41
>18 - ≤24 months	468	4	0.85
>24 - < 30 months	212	0	0

To put the findings into perspective, they are compared to large epidemical databases Surveillance, Epidemiology, and End Results (SEER) and Clinical Practice Research Datalink (CPRD):

- the SEER database do not include non-melanoma skin cancer (NMSC), melanoma in-situ, and recurrences of previously diagnosed malignancies
- the CPRD database do not include recurrences of previously diagnosed malignancies

The comparison of reslizumab clinical studies malignancy rates to the SEER database and to the CPRD demonstrated a higher (yet not statistically significant) rate in the reslizumab studies.

When comparing with the incidence rates in the SEER, the overall malignancy rates indicated that the observed number of malignancies among patients in Cohorts 3 and 4, treated with reslizumab 3.0 mg/kg, was higher than the expected values; the standardized incidence ratio (SIR) of observed to expected number of events in Cohorts 3 and 4 were 1.54 (95% CI: 0.50-3.58, p=0.229) and 1.33 (95% CI: 0.69-2.32, p=0.199), respectively. When excluding the malignancies diagnosed within 6 months of study enrolment, the standardized incidence ratio (SIR) of observed to expected number of events in Cohorts 4 was 0.66 (95% CI: 0.24-1.45, p=0.885).

When comparing with the CPRD, the SIRs of malignancies in reslizumab-treated patients in Cohorts 3 and 4 were 1.51 (95% CI: 0.56-3.30, p=0.209) and 1.56 (95% CI: 0.91-2.50, p=0.052), respectively, indicating a higher than expected number of malignancies with cut-off of dates September 2014. With cut-off date February 2015, the SIR of malignancies in reslizumab-treated patients in Cohort 4 is 1.72 (95% CI: 1.04-2.69, p=0.018). When excluding the malignancies diagnosed within 6 months of study enrolment, the standardized incidence ratio (SIR) of observed to expected number of events in Cohorts 3 and 4 were 0.25 (95% CI: 0.01-1.41, p=0.981) and 0.92 (95% CI: 0.44-1.69, p=0.648), respectively.

Infections

Forty-five percent of patients in Cohort 3 had at least 1 adverse events reported under the SOC of Infections and Infestations and the HLGT of Microbiology and Serology Investigation A higher incidence of events indicative of infection was reported in the placebo treatment group (53%, event rate 162.56 per 100 patient-years) compared with the reslizumab 3.0 mg/kg treatment group (41%, event rate 130.86 per 100 patient-years). The specific types of infections and incidence were generally similar across treatment groups. A similar incidence of

infections was reported in all reslizumab-treated patients in Cohort 4 (50%, event rate 123.594 per 100 patient-years). The most commonly reported events indicative of infection were nasopharyngitis (14%), urinary tract infection (URTI) (12%), sinusitis (7%), and bronchitis (6%). Overall, the events reported are consistent with what is expected in a patient population with an underlying condition of asthma.

The Phase 3 studies were conducted in regions where helminthic parasite infections are prevalent, including South and Central America, Africa, and Asia. There were no helminthic parasitic infections reported or difference between treatment groups with adverse events that could be associated with gastrointestinal helminthic infections.

Musculoskeletal system

Myalgia occurred at a greater frequency in reslizumab 3.0 mg/kg-treated patients (10 (0.97%)) than placebo-treated patients (4 (0.55%)) in Cohort 3. There was a slightly higher incidence of adverse events reported under the Musculoskeletal and Connective Tissue Disorders SOC within the 24 hours of infusions in the reslizumab group compared with placebo group (23 [2.2%] patients and 11 [1.5%] patients, respectively). In general, these events were mild, transient, and did not recur with continuing reslizumab treatment. There was 1 discontinuation for myalgia each in the placebo and reslizumab 3.0 mg/kg treatment groups, and there were no related reports of myopathy, myositis, or rhabdomyolysis.

Searches of the safety data for a broad-based group of terms associated with muscle disorders showed a similar incidence in the reslizumab 3.0 mg/kg group (83 [8.1%] patients) compared to the placebo group (75 [7.8%] patients). The results of population pharmacokinetics/pharmacodynamics analyses suggest a relationship between reslizumab exposure and musculoskeletal adverse events; however, the model was influenced by 5 overweight/obese female patients with high reslizumab concentrations and non-specific complaints.

The possible relationship between CPK elevations and an increase of clinical adverse events of myalgia was analysed posthoc.

Table 32 Musculoskeletal Adverse Events and Significant CPK Elevations by Treatment Group

Category	Asthma Placebo-controlled Studies (Cohort 3)	
	Placebo (N=730) n (%)	Reslizumab 3.0 mg/kg (N=1028) n (%)
Patients fall into ≥1 category	65 (9)	99 (10)
Musculoskeletal SOC or CPK adverse event evaluation - serious adverse event or discontinuation due to an adverse event	3 (<1)	8 (<1)
Musculoskeletal and Connective Tissue Disorders SOC starting on day of infusion	11 (2)	23 (2)
Broad muscle adverse events[a]	57 (8)	83 (8)
CPK >10 × ULN	3 (<1)	8 (<1)

Myalgia and CPK elevations are known in other drugs such as statins. Hence, possible pharmacodynamic interactions with potentially myotoxic medications were investigated at the CHMP request in a posthoc analyses for the incidence of elevated CPK in patients who were concomitantly treated with potentially myotoxic medications. A higher incidence of patients with CPK elevations was observed for on any drug associated with

toxic myopathies elevated (10%, placebo; 13%, reslizumab 3.0 mg/kg). This seems mostly driven by patients concomitantly treated with statins: CPK Grade 2 was more frequently observed in the reslizumab group (9%, placebo; 14%, reslizumab 3.0 mg/kg).

Serious adverse events and deaths

Serious adverse events

Serious adverse events were generally infrequent (reslizumab 65 (6%), placebo 66 (9%)), and no apparent trends were observed between the reslizumab-treated patients and their placebo comparators (cohort 3). Asthma was the most common serious adverse event reported.

Table 33 Serious Adverse Events (>1 Patient in Any Treatment Group) by System Organ Class, Preferred Term, and Treatment Group (Cohort 3—Studies Res-5-0010, 3081, 3082, 3083, and 3084, Safety Analysis Set)

System Organ Class **MedDRA 15.0 Preferred Term, n (%)**	**Number (%) of patients**	
	Placebo (N=730)	Reslizumab 3.0 mg/kg (N=1028)
Patients with at least 1 serious adverse event	**66 (9)**	**65 (6)**
Respiratory, thoracic, and mediastinal disorders	27 (4)	26 (3)
Asthma	23 (3)	23 (2)
Infections and infestations	22 (3)	18 (2)
Pneumonia	7 (<1)	7 (<1)
Sinusitis	2 (<1)	2 (<1)
Bronchitis	2 (<1)	0
Urinary tract infection	2 (<1)	0
Injury, poisoning, and procedural complications	11 (2)	8 (<1)
Fall	0	2 (<1)
Road traffic accident	3 (<1)	2 (<1)
Contusion	2 (<1)	0
Immune system disorders	0	4 (<1)
Anaphylactic reaction	0	4 (<1)
General disorders and administration site conditions	0	3 (<1)
Chest pain	0	2 (<1)

MedDRA=Medical Dictionary for Regulatory activities.

Serious adverse events that were reported by more than 1 patient in the reslizumab group and were not reported in the placebo group included chest pain (4 [<1%] patients), anaphylaxis reactions (4 [<1%] patients), and falls (2 [<1%] patients).

Treatment-related serious adverse events of anaphylactic reactions were reported by 3 patients in the reslizumab 3.0 mg/kg group. One event each of osteoarthritis and lung adenocarcinoma was reported in the reslizumab 3.0 mg/kg group. The only treatment-related serious adverse event reported for placebo patients was 1 case of erysipelas.

In the targeted cohort 3, the pattern was similar.

In Cohort 4, the overall serious adverse event rate was slightly higher (137 (9%)) than what was observed in Cohort 3 reslizumab 3.0 mg/kg patients 6% and the same as Cohort 3 placebo patients (9%). Asthma was reported in 38 (2%) of the 1611 patients in the reslizumab treatment group. The next most common PTs (reported in ≥3 patients in the reslizumab treatment group) were pneumonia (8 [<1%] patients), anaphylactic

reaction (4 [<1%] patients), chest pain (3 [<1%] patients), breast cancer (3 [<1%] patients), and sinusitis (3 [<1%] patients).

The increase in overall SAE incidence compared to Cohort 3 is likely attributable to the longer period of adverse event reporting as well as an increased number of unique serious adverse events within the Neoplasms Benign, Malignant, and Unspecified SOC and a more diversified array of events observed in the Respiratory, Thoracic and Mediastinal Disorders SOC. The slight increase in overall incidence of SAE is a result of the accumulation of diverse, low-frequency events over time.

Deaths

There were 3 deaths during open label Study 3085 with reslizumab treatment 3.0 mg/kg ; all these events were not considered related to the study drug: 1 patient due to progressive anal cancer, 1 patient due to hemoptysis, aspiration pneumonia, and cardio-respiratory arrest, and 1 patient who died at home with cardiac arrest reported as the cause of death. All these events were not considered related to the study drug.

Additionally, 1 death occurred in Study 3082 in the placebo group on day 56 of treatment, 1 month after the second placebo infusion, most probably due to accidental combined drug intoxication.

No deaths occurred in any treatment groups in the other studies.

Laboratory findings

All clinical laboratory evaluations were performed on Cohort 3 except for Study Res-5-0010, since different laboratory normal ranges and clinical significance criteria were used in Study Res-5-0010, and the time of final assessment (week 15) was different than the other studies in the cohort.

Serum chemistry parameters

In Cohort 3 without Study Res-5-0010, serum chemistry parameters were similar at baseline between the placebo and reslizumab 3.0 mg/kg treatment groups, with the exception of CPK (mean CPK 142.8 U/L [median 105.0 U/L]) and 132.5 U/L [median 97.0 U/L] in the reslizumab 3.0 mg/kg group and in the placebo group, respectively.

Serum chemistry tests were similar at baseline for both treatment groups and remained comparable at endpoint. Shifts in serum chemistry variable values from the normal range at baseline to outside the normal range occurred infrequently.

A total of 69 (10%) patients in the placebo group and 95 (10%) patients in the reslizumab 3.0 mg/kg group had potentially clinically significant (PCS) abnormal serum chemistry values. There was a slightly higher incidence in shifts to abnormal high in the reslizumab group compared to the placebo group in ALT, ALP, and GGT. However, a slightly higher incidence of patients with PCS abnormalities was observed in the placebo group for alanine aminotransferase (ALT) (13 [2%] patients) and gamma-glutamyltransferase (25 [4%] patients) compared to the reslizumab 3.0 mg/kg group (13 [1%] patients and 32 [3%] patients, respectively). Given the absence of any obvious imbalance in the relevant SOCs or HLT, the pattern of ALT and AST abnormalities are not considered clinically meaningful.

PCS abnormalities in CPK occurred more frequently in the reslizumab 3.0 mg/kg group for overall and for CPK elevation greater than 5 times and 10 times the upper limit of normal (ULN) (refer to the section above).

Hematology parameters

In Cohort 3 without Study Res-5-0010, hematology parameters were generally similar at baseline between the placebo and reslizumab 3.0 mg/kg treatment groups, and mean changes from baseline to endpoint were low. Changes that did occur in hematology variables were generally similar in the placebo and reslizumab 3.0 mg/kg treatment groups, with the exception of the pharmacological effect of reslizumab on eosinophil count.

In general, no clinically meaningful differences were observed between the treatment groups in the number (%) of patients with potentially clinically important hematology abnormalities, the types of abnormalities, and the time points at which abnormalities were reported. The eosinophil count was the only exception, accounting for the vast majority of potentially clinically important abnormal hematology values (388 (58%) patients in the placebo group and 97 (10%) patients in the reslizumab 3.0 mg/kg group).

The incidence of shifts to PCS hematology abnormalities were relatively low in both groups (<1%), with the exception of shifts to PCS-elevated eosinophils, which ranged between 3% and 6% in the placebo group and 0% and 2% in reslizumab group.

Urinalysis Parameters

In Cohort 3 (without Study Res-5-0010), there were no meaningful trends in mean changes from baseline for any urinalysis variables: 380 (23%) patients had potentially clinically important abnormal urinalysis values, 165 (25%) patients in the placebo group and 215 (22%) patients in the reslizumab 3.0 mg/kg group. This difference was due to a higher incidence in the placebo group (11%) in PCS urine blood compared to the reslizumab group (8%).

Vital signs

There was no evidence of any trends in changes from baseline to endpoint (with and without follow-up) in pulse or systolic and diastolic blood pressure values after treatment with reslizumab 3.0 mg/kg, and no apparent trends when compared to the placebo group.

The incidence of PCS abnormal vital signs values was similar between the reslizumab-treated (192 (19%) patients) and placebo groups (160 (22%) patients). PCS low body temperature was the most common PCS value with the largest difference between the 2 groups with a slightly higher incidence in placebo (128 [18%] patients) compared to reslizumab 3.0 mg/kg patients (135 [13%]).

Analysis of vital sign shifts relative to baseline tended to reduce the frequency of PCS values compared with those observed PCS value during the treatment period. No adverse trends were observed.

Body temperature was the measure that had the greatest frequency of changes from a baseline high PCS/normal value to a low PCS value (28 [3%] and 26 [4%] patients in the reslizumab 3.0 mg/kg and placebo groups, respectively). As the incidences of low body temperature between treatment groups were balanced and not associated with any specific adversity, they are not considered to be clinically meaningful.

No other shifts occurred in ≥1% of patients in either group at endpoint.

Electrocardiographic Parameters

In the Cohort 3 patients (excluding Study Res-5-0010), ECG values in the reslizumab-treated and placebo groups were comparable for mean heart rate, PR interval, QRS interval, QT interval, QTc interval (Bazett and Fridericia), and RR interval measurements at baseline and endpoint. Shifts from normal to abnormal occurred with comparable frequency in the reslizumab-treated and placebo treatment groups. None of the shifts in the reslizumab-treated patients were considered by the investigator to be clinically meaningful.

Combined absolute interval prolongations plus change from baseline in QRS and PR Interval were similarly low for both the reslizumab-treated and placebo treatment groups.

Absolute QTc interval prolongations at baseline and endpoint occurred with comparable frequency in both groups. The change from baseline in QTc interval and combined absolute QTc interval prolongations plus change from baseline values were low overall and generally lower in the reslizumab-treated patients at week 52 and endpoint.

In the other studies, a Japanese subject had a single QTcF >450 msec with a concurrent change in QTcF interval from baseline of greater than 30 msec. There were no reported cardiovascular adverse events or clinically relevant vital sign findings temporally related to this ECG finding. In addition, there were no medical history or laboratory findings to account for the QTcF findings.

Safety in special populations

Age

The Applicant has provided safety data for following age categories: 12 to 17 years age group, 18 to 64 years age group and 65 years and older age group. Only adult patients up to 75 years of age were allowed to be included.

In both 18 to 64 years age group and 65 years and older groups lower incidences of overall adverse events were reported in reslizumab (50%-68%) compared to placebo-treated patients (80%-86%).

Overall, the adverse events (PT) reported were comparable across age groups. The most frequently reported adverse events across age ranges were asthma (18%-42% in reslizumab 3.0 mg/kg and 31%-57% in placebo), and nasopharyngitis (10%-26% in reslizumab 3.0 mg/kg and 13%-31% in placebo). ,

The frequency of all of these adverse event categories was similar or lower in reslizumab-treated patients compared to placebo-treated patients in the age group >65 years, as well as compared to placebo in the age group 18 to 65 years of age apart from vascular disorders. For vascular disorders, the adverse events were reported for 4 (9%) reslizumab 3.0 mg/kg-treated patients and 3 (5%) placebo-treated patients for >65 years of age group. The following table represents the adverse events in subgroups of the adult population Age ≤65 and Age > 65.

Experience in paediatric patients is limited. The data did not indicate a difference in the safety profile of reslizumab in paediatric patients compared with that in adult patients.

Table 34 Selected Adverse Events per CHMP Request by Age Group and Treatment (Cohort 3)

	Ages 18 to 65 years n (%)		Age >65 years n (%)	
	Placebo N=658	Reslizumab 3.0 mg/kg N=965	Placebo N=56	Reslizumab 3.0 mg/kg N=44
Patients with at least 1 adverse event	528 (80)	652 (68)	48 (86)	22 (50)
Serious adverse events – Total	52 (8)	61 (6)	11 (20)	4 (9)
- Fatal	1 (<1)	0	0	0
- Hospitalization/ prolong existing hospitalization	45 (7)	54 (6)	10 (18)	4 (9)
- Life-threatening	1 (<1)	7 (<1)	0	0
- Disability/ incapacity	3 (<1)	0	0	0
- Other (medically significant)	12 (2)	10 (1)	1 (2)	0
Adverse events leading to discontinuation	39 (6)	48 (5)	1 (2)	0
Psychiatric disorders (SOC)	19 (3)	21 (2)	2 (4)	0
Nervous system disorders (SOC)	99 (15)	120 (12)	13 (23)	1 (2)
Accidents and injuries (SMQ)	49 (7)	54 (6)	5 (9)	2 (5)
Cardiac disorders (SOC)	30 (5)	17 (2)	5 (9)	1 (2)
Vascular disorders (SOC)	16 (2)	28 (3)	3 (5)	4 (9)
CNS vascular disorders (SMQ)	2 (<1)	4 (<1)	0	0
Infections and infestations (SOC)	340 (52)	391 (41)	38 (68)	16 (36)
Anticholinergic syndrome (SMQ)	43 (7)	45 (5)	9 (16)	2 (5)
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	26 (4)	26 (3)	8 (14)	1 (2)

Furthermore, a review of adverse events reported at a higher frequency in the older age group did not reveal any significant differences between reslizumab- and placebo-treated patients.

Other populations

Apart for age, the Applicant has performed safety analyses in following subpopulation: gender, race, post-baseline anti-drug antibody status, baseline eosinophil count and medication at baseline

There were more female patients (1103 (62%)) included than male patients 708 (38%). In general, reported adverse events showed the same pattern as in the overall population apart. Anaphylactic reactions were reported for 5 (1%) female patients in the reslizumab 3.0 mg/kg group with no cases reported in male or placebo patients. This might be explained by the larger number of females enrolled in the clinical trials and the potential for females to be at higher risk for allergic reactions.

Of the overall population, 1357 (73%) were white, 212 (11%) were black, 138 (7%) were Asian, and 154 (9%) were 'other' race. In general, the adverse event profile was similar across races.

However, in contrast with the lower incidences of adverse events of reslizumab 3.0 mg/kg in the white and black race categories compared with placebo, a similar incidence of adverse events was observed in Asian patients and those with a race category of 'other'. The differences in these incidences between reslizumab- and placebo-treated patients in different race subgroups were most likely due to a smaller number of patients in the latter two race subgroups.

Same differences were seen between races for reporting adverse events in the SOCs; black patients reported adverse events at higher frequency in the reslizumab 3.0 mg/kg group compared to the placebo group e.g. in Gastrointestinal Disorders SOC (13% reslizumab 3.0 mg/kg and 11% placebo), while in Asian patients this appeared in the Metabolism and Nutrition Disorders SOC (11% reslizumab 3.0 mg/kg and 5% placebo).

The incidence of adverse events was lower in the reslizumab 3.0 mg/kg group (56%-60% reslizumab 3.0 mg/kg was than in the placebo group (69%-71%0 placebo), irrespective of baseline eosinophil count. The adverse events (PT) reported were comparable across baseline eosinophil count subgroups and treatment groups.

Adverse Events by medication at baseline

Oral corticosteroid use at baseline

Of the overall population, 146 (7.8%) patients received oral corticosteroid use (OCS) at baseline.

The most frequently reported adverse events across baseline OCS use subgroups were asthma, nasopharyngitis, headache, and upper respiratory tract infection.

A higher incidence of patients with use of OCS at baseline had adverse events reported in some SOCs in the reslizumab 3.0 mg/kg group compared to the placebo group in contrast to patients without use of OCS at baseline.

In the OCS at baseline group, there was a higher incidence of pneumonia in the reslizumab-treated patients (five of 73 reslizumab treated patients) compared to placebo (one of the 73 placebo patients). The reports of pneumonia were mainly associated with asthma exacerbations with an infective component. Two pneumonia cases in patients treated with OCS at baseline were considered serious; 1 was placebo-treated, 1 was reslizumab 3.0 mg/kg-treated patient, and none resulted in early termination of therapy.

However, the incidence of pneumonia according to baseline OCS is different when using IVRS or CRF reporting. Only with IVRS there is a difference with more reports in the reslizumab group (5 patients vs 1 patient in the placebo-group).

Of the two cases treated with reslizumab, one patient was diagnosed with lung adenocarcinoma 2 weeks after the pneumonia event, and 1 patient developed "hospital acquired pneumonia". Both cases are explained by the comorbidity: lung carcinoma is a well-known risk factor for pneumonia and hospital admission for hospital acquired pneumonia.

The 4 additional non-serious pneumonia events (1 in a placebo-treated patient and 3 in reslizumab-treated patients) did not involve hospitalisation and were of mild (2 cases) or moderate (2 cases) severity.

Furthermore, in the overall population as well as in patient population without OCS at baseline such higher incidence of pneumonia in the reslizumab-treated patients has not been observed.

***Long-acting beta-agonist at baseline and* Leukotriene Inhibitor use at baseline**

A total 1308 (70%) of patients received long-acting beta-agonist (LABA) at baseline. In general, the adverse event profile was similar in reslizumab- and placebo-treated patients irrespective of use of LABA at baseline. Of

the overall population, 357 (19%) of patients were using leukotriene inhibitors at baseline. In general, the adverse event profile between reslizumab- and placebo-treated patients was similar irrespective of use of leukotriene inhibitors.

Immunological events

Immunogenicity

The immunogenicity of reslizumab has been assessed in all the clinical studies. In general, the incidence of anti-reslizumab response as well as the antibody titer is low.

An ADA- status was considered positive:

- if a sample tested positive at any post-dose time point if negative at baseline, or
- if a post-dose ADA titer increased 4 fold or greater from the positive ADA baseline.

The ADA incidence in 4 of the Phase 3 studies (3081, 3082, 3083, and 3084) was 5% for the 3.0 mg/kg dose group. The ADA titers in these studies were low, with the highest titer at 106 with an average percentage of transient ADA response of 40%.

Impact of ADA Response on efficacy

There were too few ADA positive patients to unequivocally interpret the effect of the development of ADAs on CAE, but so far there is no indication of a negative effect of the presence of ADA on the exacerbation rate.

In studies 3081, 3082 and 3083, 34 patients who received 3.0 mg/kg reslizumab were ADA positive. There were no differences observed in the improvements in FEV1 over 16 weeks between ADA positive and negative patients.

Blood eosinophil counts in ADA-positive patients continued decreasing over reslizumab treatment period in a way similar to ADA-negative patients, indicating that the presence of ADA did not reduce reslizumab clinical effect.

Impact of ADA Response on safety

The incidence of adverse events was similar across ADA-positive (52 [64%] patients) and negative (697 [66%]) patients and treatment groups. The most frequently occurring SOC (reported in >20% of ADA-positive and negative patients) were Infections and Infestations and Respiratory, Thoracic and Mediastinal Disorders.

The adverse events (PT) reported were comparable across ADA status and treatment groups. The most frequently reported adverse events across ADA status were asthma, nasopharyngitis, and headache. There were no reports of anaphylaxis, hypersensitivity reactions, or myalgia as adverse events in ADA-positive patients.

There was no association of a positive ADA response with hypersensitivity reactions to reslizumab, including the reported anaphylactic reactions, all of which were ADA-negative. In addition, there was no indication of adverse events related to an immune complex disorder (eg, renal dysfunction and rash).

Anaphylaxis and hypersensitivity

Beyond the 3 anaphylactic reactions, the frequency of hypersensitivity and potential hypersensitivity reaction was similar between the placebo and reslizumab groups. These reactions were not associated with a positive ADA response and did not result in discontinuation of study drug treatment.

Safety related to drug-drug interactions and other interactions

There is currently no evidence in the literature discussing drug-drug interactions associated with IL-5 or anti-IL-5 antibodies and there are no data to suggest that IL-5 is involved in the regulation of enzymes or pathways responsible for drug metabolism.

In the population PK analysis, there appeared to be no impact of common concomitant medications (leukotriene antagonists, systemic corticosteroids, prednisone, and montelukast) on reslizumab exposure. However, in the analyses of adverse events by baseline concomitant asthma medications a higher incidence of pneumonia was seen in the reslizumab-treated patients compared to placebo in the OCS at baseline group. The differences have been explained by the comorbidity.

Discontinuation due to adverse events

In Cohort 3, the same frequency of patients reported at least 1 adverse event leading to discontinuation; 48 (5%) of the 1028 patients in the reslizumab 3.0 mg/kg group and 40 (5%) of the 730 (5%) patients in the placebo group respectively.

Asthma leading to discontinuation was reported in 28 (3%) of the 1028 patients in the reslizumab 3.0 mg/kg treatment group and in 21 (3%) of the 730 patients in the placebo group. Anaphylactic reaction (3 [<1%] and 0 patients in the reslizumab 3.0 mg/kg and placebo groups, respectively) was the only additional adverse event reported in >2 patients in the reslizumab 3.0 mg/kg group and not reported in the placebo group that led to discontinuation.

There were no apparent trends in adverse events within the Infections and Infestations SOC: 3 (<1%) patients in the placebo group discontinued due to bronchitis events (with no incidence in the reslizumab 3.0 mg/kg group), and 2 (<1%) patients in the placebo group discontinued due to sinusitis events, with 1 (<1%) patient reporting sinusitis in the reslizumab 3.0 mg/kg group. In Cohort 1, the most frequently observed SOCs and PTs were similar to data at 52 weeks.

In Cohort 4, adverse events leading to discontinuation occurred in a similar frequency (65 [4%] of the 1611 reslizumab treated patients) and in the same main SOCs compared with Cohort 3 (reslizumab 3.0 mg/kg and placebo 5% each). Asthma leading to discontinuation was most frequently reported in 29 (2%) of the 1611 patients in the reslizumab treatment groups.

However, the number of discontinuations in Cohort 4 is mainly driven by the results of Cohort 3; only 5% of the patients in the additional study 3085 completed this study because of early termination of this study. A conclusion on continuation of treatment beyond one year of treatment cannot be drawn.

2.6.1. Discussion on clinical safety

Overall exposure and long term exposure are sufficient; 1659 subjects received the recommended dose and in total 922 patients were treated for greater than 12 months of which 759 patients with reslizumab. A total of 1006 asthma patients were treated with reslizumab for at least 6 months, while 237 asthma patients were treated for at least 24 months.

In Cohort 3 (all exposed patients from placebo-controlled asthma studies), the overall pattern of adverse events by frequency, severity, and relationship to study drug was similar between the placebo and reslizumab 3.0 mg/kg treatment groups.

The reporting of at least 1 AE was higher in the placebo group (81%) than in the reslizumab 3.0 mg/kg group (67%). The incidence of events was always similar or lower for the reslizumab group apart from Neoplasm, benign, malignant and unspecified SOC.

When an adverse event preferred term (PT) was reported more frequently for reslizumab, it occurred never with a frequency more than 0.5 % higher than that of the corresponding placebo frequency.

The long term exposure (> 1 year) to reslizumab did not indicate a notable increase in adverse event incidence. The small increase in incidences of the most frequently occurring SOCs (reported in >15% of patients) could be appointed to the longer observation time.

The most commonly reported adverse event was asthma, lower in the reslizumab treatment indicating an effect in the reslizumab treatment group. The type and incidence of events were as to be expected in a moderate to severe, predominantly adult asthma population, i.e. events of URTI. The next most common PTs (reported in >5% of patients in the reslizumab 3.0 mg/kg treatment group) were nasopharyngitis and upper respiratory tract infection.There are no indications that the AEs increase one-sidedly over the time.

Overall, severe adverse events occurred in 7% and 10% in the reslizumab 3.0 mg/kg and placebo groups, respectively. Asthma was seen with the highest incidence, being lower in the reslizumab 3.0 mg/kg group. The most frequently reported severe events following asthma were pneumonia, cough, sinusitis and influenza, all with comparable frequency.

The proportions of treatment related adverse events in the reslizumab-treated and placebo groups were similar (12% - 13%). The most frequent treatment-related adverse events were headache, asthma, nausea, fatigue, and increased blood creatine phosphokinase (CPK). The difference in number of serious treatment related adverse events between reslizumab 3.0 mg/kg and placebo group is driven by a difference in anaphylactic reaction, which is considered of concern, in spite of the low numbers.

Infusion reactions and administration site reactions were adverse events occurring during or within 24 hours. The most frequently reported event occurring within 24 hours of the infusion was asthma. Administration Site Reactions (HLGT) occurred at the low same frequency (2%). None of the administration site reactions/events were severe, serious, or resulted in discontinuation.

Anaphylaxis occurred in five cases in the reslizumab group (<1%) and no cases in the placebo group. Three of the 5 cases had a temporal link to infusion, were assessed as related to reslizumab, and resulted in discontinuation of reslizumab treatment. All cases were observed in ADA negative female patients. Two cases were not temporally linked to reslizumab infusion, and were attenuated to pre-known food allergy and immunotherapy, and did not result in discontinuation of reslizumab. This information is adequately reflected in the SmPC and as an important identified risk in the RMP.

In the entire clinical program, a total of 24 patients were diagnosed with malignancy: 3 placebo-treated patients and 21 reslizumab-treated patients (6 patients in placebo-controlled studies and 15 patients in the open-label extension [OLE] Study 3085). In 2 patients, the malignancy diagnosed during the study was a reoccurrence of their previous malignancy. The most commonly reported malignancies in reslizumab-treated patients were skin cancers, reported by 8 patients (5 patients with NMSC and 3 patients with localized cutaneous malignant melanoma). There were 13 non-skin cancers reported; 8 of these were of the most common tissue types of cancer in the general adult population (i.e. lung, breast, prostate, and colon). A comparison of reslizumab malignancy rates with general population databases and asthma patients' database (SEER and CPRD, respectively) demonstrated a higher (yet not statistically significant) rate in the reslizumab studies. Out of the total number, 8 malignancies in reslizumab-treated patients were diagnosed within 6 months from initiation of

reslizumab. Because malignancy is unlikely to be causally associated with reslizumab, when the malignancies, particularly solid tumours, are diagnosed within 6 months of study enrolment sensitivity analyses for the comparison of reslizumab malignancy rates with SEER and CPRD were performed. After excluding patients with malignancy within 6 months of a minimum reslizumab exposure, the Standardized Incidence Ratio values were near or below 1 and remained statistically non-significant. Furthermore, as worst case scenario an analysis including the 2 additional patients from study 3085 who were already under surveillance during the placebo controlled phase, would have been preferred but are not considered essential. This information is adequately reflected in the SmPC and as an important potential risk in RMP.

A higher incidence of events indicative of infection was reported in the placebo treatment group compared with the reslizumab 3.0 mg/kg treatment group. The most commonly reported events indicative of infection were consistent with what is expected in an asthma patient population. No helminthic parasitic infections were reported. As eosinophils are possibly involved in the response to helminth infections, adequate warning is included in the SmPC and this information is included as an important identified risk in the RMP.

In all the analyses, CPK is repeatedly observed in a higher frequency than in placebo: overall and CPK elevation greater than 5 times the upper limit of normal (ULN) per laboratory data and CPK elevation greater than 10 times the upper limit of normal (ULN) per laboratory data. As the difference for CPK elevation greater than 5 times the upper limit of normal (ULN) per laboratory data exceeds the 1% difference between reslizumab and placebo and also other measurements show higher number in the reslizumab group. This information has been reflected in the SmPC.

Myalgia occurred at a greater frequency in reslizumab 3.0 mg/kg-treated patients (n=10, 0.97% versus n=4; 0.55%). In general, these events were mild, transient, and did not recur with continuing reslizumab treatment. There was 1 discontinuation for myalgia in each group. Based on the provided data, a relationship between myalgia and CPK elevation can neither concluded nor excluded. However, both myalgia and “blood creatine phosphokinase increased” are included in the SmPC.

Because myalgia and CPK elevations are known in other drugs such as statins, potential interactions were investigated with potentially myotoxic medications. No patterns can be distinguished for a pharmacodynamic relation between reslizumab and a drug known with an increase of clinical adverse events of myalgia as analysed by CPK elevations. Therefore, a pharmacodynamic interaction does not seem to be likely. This is supported by the facts that drug-drug interactions are not plausible given the properties of reslizumab (a monoclonal antibody) and its specificity for soluble interleukin-5.

Serious adverse events appeared in 65 (6%) patients in reslizumab group and in 66 (9%) patients in placebo group without a specific trend. Asthma was the most common serious adverse event reported.

Serious adverse events reported by more than 1 patient in the reslizumab group and not reported in the placebo group were rare, and included chest pain (4 [<1%] patients), anaphylaxis reactions (4 [<1%] patients), and falls (2 [<1%] patients).

The increase in overall SAE incidence for the exposure > 1 year is likely attributable to the longer period of reporting. The slight increase in overall incidence of SAE is a result of the accumulation of diverse, low-frequency events over time.

The 3 deaths during open label Study 3085 with reslizumab treatment 3.0 mg/kg were not considered related to the study drug. Additionally, 1 death occurred in Study 3082 in the placebo group, most probably due to accidental combined drug intoxication.

The laboratory findings are overall sufficient similar and do not raise concerns.

In the data presented for the different age groups, no specific trend is seen. The frequency of adverse event categories specific for elderly was overall similar or lower in reslizumab-treated patients compared to placebo-treated patients in the age group >65 years, as well as compared to placebo in the age group 18 to 65 years of age except for vascular disorders.

The Applicant has not requested an indication in the paediatric population. Limited data are available in patients > 12 years old and no data in patients <12 years old.

As there are no data in patients >75 years old and in patients <12 years old, the lack of these data is included in the missing information of RMP and is adequately reflected in the SmPC.

A higher proportion of patients with use of OCS at baseline in the reslizumab group reported adverse events in several SOCs e.g. respiratory tract (URTI, dyspnoea) in contrast to patients without use of OCS at baseline. Moreover, pneumonia was reported more frequently in patients with OCS at baseline. Detailed information on the severity of pneumonia cases showed that only 2 cases in the reslizumab treated patients were considered serious. Moreover, they were due to comorbidity.

The incidence of the titer of ADAs is low. There was no association of a positive ADA response with hypersensitivity reactions or indication of adverse events related to an immune complex disorder. In addition, there is also no apparent impact of ADA on reslizumab PK, eosinophil response, and clinical efficacy in terms of FEV1 and CAE measurements, indicating a lack of neutralizing activity. The overall safety profile, including anaphylaxis, of ADA positive patients was similar to ADA negative patients. Hence, long term exposure, including long-term immunogenicity was added as a missing information in the RMP and this information is adequately reflected in the SmPC.

Results of population pharmacokinetic analysis confirm that concomitant use of either leukotriene antagonists or systemic corticosteroids does not affect the pharmacokinetics of reslizumab. Reslizumab has not been studied in patients concurrently taking immunosuppressant medicinal products other than OCS; therefore, the safety profile of reslizumab in these patients is unknown. Use in combination with immunosuppressant drugs therapy is included as missing information in the RMP. This information is also reflected in the SmPC.

Withdrawal from the studies due to a treatment related AEs was overall low (5%) and comparable between reslizumab and placebo.

Section 4.8 of the SmPC was built applying the following principle: the AEs were captured with “arithmetic cut-off rules” and then assessed for potential relatedness to reslizumab.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall exposure was sufficiently investigated. The overall pattern of adverse events by frequency, severity, and relationship to study drug was similar between the placebo and reslizumab 3.0 mg/kg treatment groups. The most commonly reported adverse event was asthma, consistently lower reported in all categories of AEs in the reslizumab treatment indicating an effect in the reslizumab treatment group. The incidence of severe adverse events as well as the incidence of treatment related adverse events was low and comparable. Severe treatment-related adverse events were <1% in both groups.

Anaphylaxis occurred in five cases in the reslizumab group (<1%) of which 3 treatment related. This information is adequately reflected in the SmPC and as an important identified risk in the RMP.

A higher incidence of malignancies in patients in the reslizumab group during the placebo controlled phase and the possibly higher frequency compared with the SEER and to the CPRD was observed but after excluding malignancies diagnosed within 6 months from initiation of reslizumab SIR values were near or below 1 and remained statistically non-significant. A drug-related causality is considered unlikely based on the preponderance of common tissue types without a clustering of a particular tumour type or atypical tumours, and the similar malignancy rates in both treatment groups in the PCTs after excluding malignancies that were diagnosed within less than 6 months of reslizumab treatment) and the results of the comparisons with SEER and CPDR. However, malignancy will be continued to be monitored and evaluated via routine pharmacovigilance and in a long-term non interventional post authorisation safety study and it will be considered as an adverse event of special interest in future clinical studies.

2.7. Risk Management Plan

Safety concerns

Table 35 Summary of Safety Concerns Associated with Reslizumab in the Target Population

Summary of Safety Concerns	
Important identified risks	Severe hypersensitivity reactions, including anaphylactic or anaphylactoid reactions
Important potential risks	Parasitic (helminth) infections Malignancy
Missing information	Paediatric patients < 18 years old Elderly patients >75 years old Use during pregnancy Use in breastfeeding Long term exposure, including long-term immunogenicity Use in combination with immunosuppressant drugs therapy Effect on vaccination and the use of live/attenuated vaccines Patients with non-white race

Pharmacovigilance plan

Table 36 Table of On-going and Planned Studies in the Post-authorisation Pharmacovigilance Development Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Study Number C38072-AS-30025 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 (Phase 3) (Category 3)	Determine the effect of reslizumab (110 mg) administered subcutaneously every 4 weeks on clinical asthma exacerbations in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on standard-of-care asthma therapy and to evaluate the safety and immunogenicity of reslizumab.	Important identified risk: Severe hypersensitivity reactions, including anaphylactic or anaphylactoid reactions. Important potential risks: Parasitic (helminth) infections, Malignancy. Missing information: Paediatric patients <18 years old, Elderly patients >75 years old, Use during pregnancy, Effect on vaccination and the use of live/attenuated vaccines, Patients with non-white race	Ongoing	Final study report completion planned for 1Q 2018
Study Number C38072-AS-30027 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 (Category 3)	Determine the ability of reslizumab (110 mg) administered subcutaneously once every 4 weeks to produce a corticosteroid-sparing effect in patients with OCS-dependent asthma and elevated blood eosinophils, without loss of asthma control and to evaluate the safety of sc dosing of reslizumab and tapering of OCS. Study will also evaluate the potential of sc dosing of reslizumab to raise anti-drug antibodies (ADAs).	Important identified risk: Severe hypersensitivity reactions, including anaphylactic or anaphylactoid reactions. Important potential risks: Parasitic (helminth) infections, Malignancy. Missing information: Paediatric patients <18 years old, Elderly patients >75 years old, Use during pregnancy, Effect on vaccination and	Ongoing	Final study report completion planned for 1Q 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
		the use of live/attenuated vaccines, Patients with non-white race		
Active Pregnancy Surveillance Programme (Category 3)	The primary objective of the reslizumab active pregnancy surveillance is to characterize risks related to reslizumab exposure during pregnancy, i.e. assess foetal and maternal outcomes.	Missing information: Use during pregnancy, Use in breastfeeding	Planned	Annually with the PSUR. Protocol will be provided within 4 months after EC decision.
A long-term non-interventional study comparing the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab (Category 3)	Study will compare the risk of malignancy in severe asthma patients treated with reslizumab and patients not treated with reslizumab using an existing healthcare database.	Important potential risk: Malignancy	Planned	Interim reports with the PSURs, at least annually Protocol will be provided within 6 months after EC decision.

Risk minimisation measures

Table 37 Summary of Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Severe hypersensitivity reactions, including anaphylactic or anaphylactoid reactions	Labelling information (SmPC Section 4.2, 4.3, 4.4, 4.8, and 6.6) and PIL. Prescription only medicine.	None
IMPORTANT POTENTIAL RISKS		
Parasitic (helminthic) infections	Labelling information (SmPC Section 4.4) and PIL. Prescription only medicine.	None
Malignancy	Labelling information (SmPC Section 4.8). Prescription only medicine	None
MISSING INFORMATION		
Paediatric patients < 18 years old	Labelling information (SmPC Section 4.2, 4.8, 5.1 and 5.2) and PIL. Prescription only medicine.	None
Elderly patients >75 years old	Labelling information (SmPC Section 4.2 and 5.2). Prescription only medicine.	None
Use during pregnancy	Labelling information (SmPC Section 4.6) and PIL. Prescription only medicine.	None
Use in breastfeeding	Labelling information (SmPC Section 4.6) and PIL. Prescription only medicine.	None
Long term exposure, including long-term immunogenicity	Labelling information (SmPC Section 4.2, and 5.1). Prescription only medicine.	None
Use in combination with immunosuppressant drugs therapy	Labelling information (SmPC Section 4.5) and PIL. Prescription only medicine.	None
Effect on vaccination and the use of live/attenuated vaccines	Labelling information (SmPC Section 4.5) and PIL. Prescription only medicine.	None
Patients with non-white race	Labelling information (SmPC Section 5.2). Prescription only medicine.	None

These routine risk minimisation measures are considered sufficient to minimise the risks of the product in the revised indication.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Reslizumab is a humanised anti-IL-5 mAb which binds to IL-5, a cytokine responsible for amongst others differentiation and activation of human eosinophils. The subsequent reduction in circulating and tissue eosinophils could be beneficial in asthma patients with an eosinophilic phenotype. It is to be given every 4 weeks by i.v. infusion as an add-on to standard of care.

The goals of asthma treatment are control of symptoms and prevention of exacerbations.

Proposed initial indication

CINQAERO is indicated to reduce exacerbations, relieve symptoms and improve lung function in adult patients with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

Proposed revised indication

CINQAERO is indicated 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 (see section 5.1)

The recommended dose, based on body weight, is 3 mg/kg, given once every four weeks.

The main studies in support of clinical efficacy of reslizumab consist of two pivotal randomised, placebo-controlled, double-blind studies of identical design (studies 3082 and 3083) with a study duration of one year to measure the effects one exacerbations. The data are supported by one short-term (16 weeks) randomised, placebo-controlled, double-blind, dose-response study (study 3081).

Benefits

Beneficial effects

Reslizumab showed a consistent reduction in, severe, exacerbations compared with placebo among studies. The proportion of patients with at least one CAE decreased from 54.1% to 37.6% and from 45.3% to 25.4% in study 3082 and 3083, respectively. The reslizumab versus placebo CAE rate ratio was 0.5010 (95% CI: 0.3726, 0.6737; study 3082) and 0.4063 (95% CI: 0.2819, 0.5855; study 3083), corresponding to a 50% - 59% reduction in CAE events per patient year. Sensitivity analyses support the robustness of the results. Most patients (>80%) were treated with systemic corticosteroids for ≥3 days, indicating a severe exacerbation.

In addition, reslizumab showed a statistically significant and clinically relevant improvement in lung function based on FEV1. The treatment difference in LS mean change from baseline over 16 weeks with placebo was 0.137 L (95%CI: 0.076, 0.198) and 0.93 L (95% CI: 0.030, 0.155) for study 3082 and 3083, respectively. A treatment effect was observed at the first observation period of 4 weeks and sustained throughout the study. Statistical significant improvements were also seen in asthma symptoms and quality of life, and accompanied by a reduction in blood eosinophils.

Subgroup analyses of the primary endpoint showed consistent results for gender, number of prior asthma exacerbations, presence of ADA and specific types of baseline asthma medication.

Long-term data up to two years supports maintenance of effect based on lung function and asthma symptoms (study 3085).

Most patients (about 80%) suffered from severe eosinophilic asthma based on GINA 4/5 classification. Post-hoc analyses showed that the reduction of CAE (56%) in this subgroup was comparable to that of the overall population (based on integrated data studies 3082 and 3083). Also for the main secondary outcomes (lung function and quality of life), results were comparable to that of the overall population with numerical higher treatment effects. In addition, post-hoc analyses showed a clinical relevant treatment effect in both the refractory and non-refractory population, reduction in CAE rate was 59% and 49%, respectively and supported with improvements in the secondary outcome measures.

Uncertainty in the knowledge about the beneficial effects

Beneficial effects regarding the exacerbation rate and lung function were observed in patients classified in GINA 3 as well. However, in these patients additional treatments are available like the addition of LABA to the ICS dose. The clinical data did not provide a direct comparison between reslizumab and LABA. Therefore, the benefit of reslizumab over currently approved therapy is not established and these patients are excluded from the indication.

No statistical significant effect was shown for CAE based on an emergency visit or hospitalization.

Data in elderly (≥65 years: n=32) in the pivotal trials are limited. The adolescent population was small (n=14) and subgroup analyses of the primary endpoint did not show results in this population. Adolescents are excluded from the indication.

Subgroup analyses of the primary endpoint did not show a significant improvement for black patients and patients of other races and patients enrolled in the US.

No data are currently available on the possibility to reduce concomitant controller medication like OCS.

The inclusion was limited to patients with eosinophilic asthma (current blood eosinophil level of at least 400/µL), because the beneficial effects of anti-IL5 therapy like reslizumab is limited to this asthma phenotype. Indeed,

the lack of efficacy in an overall asthma population unselected for blood eosinophil count (study 3084) support that reslizumab is only effective in an eosinophilic asthma phenotype.

Finally, for patients on a high medium ICS dose + second controller, the maintenance treatment can be increased to a high dose ICS + LABA. The expected benefit is small because of the flat dose response of inhaled corticosteroid. However, some patients may still benefit. In addition, an increase in inhalation therapy is considered more convenient for the patient compared to reslizumab's 4 weekly intravenous drug administration. Therefore, the CHMP requested the Applicant to restrict the indication to patients are still inadequately controlled despite high dose inhaled corticosteroid ICS and another controller. The Applicant accepted the CHMP's revised indication.

Risks

Unfavourable effects

The most frequently reported AEs were asthma (39.6% on placebo, and 22.5% on reslizumab), nasopharyngitis (14.1% on placebo and 10.0% on reslizumab) and upper respiratory tract infections (9.5% on placebo and 9.3% on reslizumab).

Most commonly reported treatment-related treatment related AEs were headache (2%) and asthma, fatigue, nausea, and blood creatinine kinase increase (<1%).

Serious treatment emergent AEs were reported at comparable frequencies in both treatment groups (9% on placebo and 6% on reslizumab); the most commonly reported in the reslizumab treated group were asthma (2%), pneumonia and anaphylactic reaction (<1% each).

Serious-treatment related effects occurred only in 5 patients in the reslizumab group including 3 anaphylactic reactions, and one event each of osteoarthritis and lung adenocarcinoma. No deaths occurred while on reslizumab during the first year, while 3 deaths were reported during the open-label study, all not considered related to the study drug.

Withdrawal from the studies due to a treatment related AEs was overall low (5%) and comparable between reslizumab and placebo.

Overall 5 cases of anaphylaxis were seen in the reslizumab-treated group, of which 3 were considered treatment-related. Administration site reactions occurred at the same frequency of 2% in the reslizumab and placebo treated group. This information is adequately reflected in the SmPC and as an important identified risk in the RMP.

The number of malignancies was higher in the reslizumab treated group (n=6) compared to placebo (n=2) in the first year of follow-up. An additional 15 patients reported malignant neoplasm during the open-label study. Most commonly reported type of malignancies that occurred in more than 1 patient were basal cell carcinoma (n=3), breast cancer (n=3), malignant melanoma (n=2) and prostate cancer (n=2). In order to put the findings into perspective, the results were compared with large epidemical databases i.e. Surveillance, Epidemiology, and End Results (SEER) and Clinical Practice Research Datalink (CPRD). The comparison of reslizumab clinical studies malignancy rates to the SEER database and to the CPRD demonstrated a higher (yet not statistically significant) rate in the reslizumab studies.

Additionally, a possibly higher frequency compared with the SEER and to the CPRD was observed but after excluding malignancies diagnosed within 6 months from initiation of reslizumab standardized incidence rates (SIR) values were near or below 1 and remained statistically non-significant.

Malignancy will be continued to be monitored and evaluated via routine pharmacovigilance and in a long-term non interventional post-authorisation safety study and it will be considered as an adverse event of special interest in future clinical studies. In addition, this information is adequately reflected in the SmPC.

Myalgia occurred at a greater frequency in reslizumab 3.0 mg/kg-treated patients compared to placebo (n=10, 0.97% versus n=4; 0.55%). In general, these events were mild, transient, and did not recur with continuing reslizumab treatment. There was 1 discontinuation for myalgia in each group.

The ADA incidence in 4 of the Phase 3 studies (3081, 3082, 3083, and 3084) was 5% for the 3.0 mg/kg dose group. The ADA titers in these studies were low, with the highest titer at 106 with an average percentage of transient ADA response of 40%.

Uncertainty in the knowledge about the unfavourable effects

A comparison of reslizumab malignancy rates with general population databases and asthma patients' database (SEER and CPRD respectively) demonstrated a higher (but not statistically significant) rate in the reslizumab studies. This rate appeared to normalise after excluding patients with malignancy within 6 months of a minimum reslizumab exposure of 6 months. Whether reslizumab is associated with an increased risk of malignancies can neither be concluded nor excluded as the numbers are low. This uncertainty also exists in literature on the role that eosinophils possibly play immunomodulatory role in some tumours as the data show conflicting results on the role of eosinophils). In the nonclinical studies, there was no evidence of a mutagenic or carcinogenic effect of reslizumab. However, malignancy will be continued to be monitored and evaluated via routine pharmacovigilance and in a long-term non interventional post-authorisation safety study and it will be considered as an adverse event of special interest in future clinical studies. In addition, this information is adequately reflected in the SmPC.

Based on the provided data, a relationship between myalgia and CPK elevation can neither be concluded nor excluded. However, both myalgia and "blood creatine phosphokinase increased" are included in the SmPC.

Analyses of potential interactions with potentially myotoxic medications demonstrated a higher incidence of patients with CPK elevations for on any drug associated with toxic myopathies but mostly driven by patients (with normal CPK at baseline) concomitantly treated with statins. Therefore, a pharmacodynamic interaction does not seem to be likely. This is supported by the fact that drug-drug interactions are not plausible given the properties of reslizumab (a monoclonal antibody) and its specificity for soluble interleukin-5.

Regarding the limited data available on the safety profile in patients above 65 years of age, the frequency adverse event categories was similar or lower in reslizumab-treated patients compared to placebo-treated patients apart from vascular disorders. There were no significant differences between reslizumab- and placebo-treated patients in the age groups 18-65 years and >65 years.

Patients on OCS at baseline reported higher frequencies of events of respiratory tract while on reslizumab compared to placebo and the population without OCS. Only two cases of pneumonia in the reslizumab treated patients were considered serious while they were confounded by comorbidity. A (pharmacodynamic) interaction is not likely.

The current data indicate that immunogenicity is low and does not appear to impact efficacy and/or safety.

No information is available on the use of reslizumab in patients concomitantly taking immunosuppressants and the impact on the safety profile. Use in combination with immunosuppressant drugs therapy is included as missing information in the RMP. This information is also reflected in the SmPC.

Patients with helminthic infections which were excluded from the studies. As eosinophils are possibly involved in the response to helminth infections, adequate warning is included in the SmPC and this information is included as an important identified risk in the RMP.

Effects table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects*						
Asthma exacerbation All	Number of asthma exacerbation per patient (95% CI) Adjusted rate	Per patient year	0.8359 (0.6536, 1.0689)	1.8118 (1.4227, 2.3073)	Rate ratio: 0.46 (95% CI 0.36-0.58), p<0.0001 Consistent among the two pivotal studies Sensitivity analyses confirm robustness data <u>GINA 4/5 subgroup</u> Rate ratio: 0.44 (95% CI 0.34-0.56), p<0.0001 Relevant treatment effect in refractory and non-refractory population	
FEV1	Mean change in FEV1 from baseline (SE)	L	0.226 (0.0242)	0.109 (0.0245)	LS mean difference: 0.110 L (95% CI: 0.066-0.154), p<0.0001 Difference is clinically relevant Secondary endpoints confirm the improved anti-inflammatory control	
ACQ	Mean change in asthma control questionnaire score from baseline (SE)		-0.905 (0.0514)	-0.672 (0.0158)	LS mean difference: -0.250 (95% CI: -0.343, -0.156), p<0.0001	
AQLQ	Mean change in asthma quality of life questionnaire score from baseline (SE)		0.937 (0.0688)	0.711 (0.0689)	LS mean difference: 0.272 (95% CI: 0.155, 0.388), p<0.0001	
Blood eosinophil count	Mean change in blood eosinophil count from baseline (SE)	10^9 cells/L	-0.574 (0.0174)	-0.098 (0.0175)	LS mean difference: -0.475 (95% CI: -0.50, -0.45), p<0.0001	
Unfavourable Effects**						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Nasopharyngitis Upper respiratory infections		%	10.0 9.3	14.1 9.5	Common adverse events, expected in the asthmatic patient population	
Pneumonia		%	7%	1%	All severities of pneumonia in patients with OCS at baseline. Pharmacodynamic interaction unlikely	
Anaphylactic reactions		%	<1	0	N=3/5 treatment-related and serious adverse events leading to discontinuation	
Myalgia		%	0.97	0.55	Absolute number low (n=10). Events were mild and transient. Considered treatment-related	
Malignancies		%	<1	<1	Reslizumab (n=6) compared with placebo (n=2) in placebo-controlled phase. In the extension study 3085, 15 additional malignancies were reported. Broad range of malignancies. Causal relationship unlikely. No indications found in non-clinical data	
ADA	Anti-drug antibodies	%	5	NA	No impact on efficacy or safety. Long-term follow up needed	
CPK	elevation >5 times ULN	N (%)	25 (2.4%)	10 (1.4%)	Relation with myalgia unclear	

Abbreviations: OCS: oral corticosteroids, CPK: creatine phosphokinase, ULN: upper limit of normal
Notes: *Pooled analysis of studies 3082 and 3083; ** Pooled analysis of studies 3081, 3082, 3083 and 3084

Benefit-risk balance

Importance of favourable and unfavourable effects

Reslizumab add-on to standard of care showed a consistent clinically relevant 54% reduction in the frequency of severe exacerbations per patient year. This is considered of clinical relevance in an asthma population, which remains uncontrolled despite medium-to-high dose of ICS (at least 440 µg of inhaled fluticasone propionate or equivalent total daily dose), the current cornerstone controller treatment. Severe exacerbations constitute a major burden to the patient, both in terms of morbidity and mortality with a negative impact on quality of life. Besides a reduction in exacerbation frequency, symptomatic improvement was demonstrated based on additional relevant symptomatic clinical endpoints. Furthermore, reslizumab showed a clinically relevant

improvement in lung function (overall FEV1 increase of 117 ml). Thereby, the drug meets the criteria of both asthma control and reduction in exacerbations which are set for controller medication within clinical guidelines. The anti-inflammatory mechanism of action is supported by the strong reduction in blood eosinophil count.

The pivotal studies included an asthma population that could be classified as GINA 3-5. The inclusion was limited to patients with eosinophilic asthma (current blood eosinophil level of at least 400/µL), because the beneficial effects of anti-IL5 therapy like reslizumab is limited to this asthma phenotype.

Most patients (>80%) used LABA in addition to a high medium or high dose ICS (GINA 4/5) representing a severe asthma population; only few therapeutic alternatives beyond the add-on treatment with oral corticosteroids (OCSs) and/or (for patients with perennial allergies) anti-immunoglobulin E (anti-IgE) are available in this patient population with persistent eosinophilia. The use of OCS is limited by their well-known side effects, whereas anti-IgE has demonstrated modest efficacy on asthma exacerbations in patients with allergic asthma, but with small and highly variable effects on lung function.

Some patients on a medium dose of ICS may benefit from an increase in ICS dose and this is considered more convenient for the patient compared to intravenous administration with reslizumab. Therefore the CHMP requested the Applicant to restrict the indication as follows:

CINQAERO is indicated 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 (see section 5.1)

The Applicant accepted the CHMP's revised indication.

Patients classified as GINA 3 were using a medium to high dose ICS without additional controller. Although reslizumab showed beneficial effects in this patient group, the effect has not been compared with the standard of care, i.e. the addition of LABA to treatment. Therefore, the B/R for reslizumab cannot be established in the GINA 3 subgroup of patients and these patients are excluded from the indication.

Overall, reslizumab treatment was well tolerated and there were few discontinuations due to adverse events i.e. anaphylactic reactions and asthma worsening. The majority of adverse events associated with reslizumab e.g. myalgia and CPK elevations, were mild to moderate and transient. Serious adverse events, which were few, included anaphylactic reactions. These resolved upon discontinuation of treatment. Immunogenicity appears low based on the current data.

At the moment, it is uncertain whether there is an increased risk for malignancies related to reslizumab exposure. More patients in the reslizumab group developed malignancies compared to placebo treated patients, but the numbers were low. Comparisons with large epidemical databases (SEER, CPRD) were reassuring as well as literature and non-clinical studies. However, malignancy will be continued to be monitored and evaluated via routine pharmacovigilance and via a long-term post-authorisation safety study and it will be considered as an adverse event of special interest in future clinical studies. In addition, this information is adequately reflected in the SmPC.

Benefit-risk balance

The observed reduction in (severe) asthma exacerbations and improvement in lung function which is supported by other parameters of asthma control outweighs the risks of reslizumab in patients with severe eosinophilic asthma (GINA 4/5) which constitute about 80% of the current study population. The risks associated with reslizumab therapy are considered low in view of the safety profile discussed earlier on, and although the

number of malignancies appear to be higher there are currently no reasons to suspect causality. This will be further followed-up post marketing.

Discussion on the benefit-risk balance

Based on the pivotal studies, clinical relevant efficacy has been demonstrated in a severe eosinophilic asthma population as most patients (80%) can be defined as GINA step 4/5. Additional post-hoc analyses showed also a clinical relevant treatment effect in both the refractory and non-refractory population. Beneficial effects were observed in the exacerbation rate supported with lung function and patient derived outcomes.

Nevertheless, considering the safety profile of CINQAERO, a positive benefit-risk balance for a population, which can still be treated with an increased dose of inhaled corticosteroids or addition of another controller, was not endorsed by the CHMP. Therefore, at the CHMP's request, the Applicant accepted to restrict the indication to patients with severe eosinophilic asthma inadequately controlled despite high dose inhaled corticosteroids plus another controller.

Regarding the limited data for elderly patients between 65 years and 75 years of age the available information showed comparable pharmakinetics, efficacy and safety compared to adults below 65 years. Therefore, it is currently concluded that the information is sufficient and does not have to be pursued as missing information.

The beneficial effect of reslizumab has been demonstrated in asthma patients with an eosinophilic phenotype (based on blood eosinophil count ≥ 400 cells/μL) and with at least one previous asthma exacerbation; clinical relevant efficacy was demonstrated over the range of prior asthma exacerbations.

The overall safety profile indicates a good tolerability. Concomitant use with immunosuppressants, risk of helminthic infections and anaphylactic reactions are properly addressed in the SmPC and can be followed up post-marketing as part of routine pharmacovigilance activities and in the randomised clinical trials C38072-AS-30025 and C38072-AS-30027. Long term exposure, including long-term immunogenicity is also included as missing information in the RMP.

The relationship between reslizumab and malignancies has been explored extensively. A drug-related causality is considered unlikely based on the preponderance of common tissue types without a clustering of a particular tumour type or atypical tumours, and the similar malignancy rates in both treatment groups in the PCTs after excluding malignancies that were diagnosed within less than 6 months of reslizumab treatment and the results of the comparisons with SEER and CPDR. However, malignancy will be continued to be monitored and evaluated via routine pharmacovigilance and in a long-term non interventional post-authorisation study and it will be considered as an adverse event of special interest in future clinical studies. In addition, this information is adequately reflected in the SmPC.

The overall B/R of reslizumab is positive for the following proposed indication "*CINQAERO is indicated 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 (see section 5.1)*".

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of CINQAERO in the treatment of severe eosinophilic asthma inadequately controlled

despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment as add on therapy in adult patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that reslizumab is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0017/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.