Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Reslizumab

Proprietary Product Name: Cinqair / Cinqaero

Sponsor: Teva Pharma Australia Pty Ltd

June 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AERD	Aspirin exacerbated respiratory disease
anti-IgE	Anti-immunoglobulin E (omalizumab)
anti-IL-5 mAb	Anti-human interleukin-5 monoclonal antibody
AQLQ	Asthma Quality of Life Questionnaire
ASUI	Asthma Symptom Utility Index
AUC	Area under the curve
BRAL-1	Brain link protein-1
CAE	Clinical asthma exacerbation
CDRs	Complementarity determining regions
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Peak plasma concentration
CMI	Consumer Medicine Information
CNS	Central nervous system
CPD	Certified Product Details
CPK	Creatine phosphokinase
CPRD	Clinical Practice Research Datalink
CYP	Cytochrome P450
EE	Eosinophilic oesophagitis
EMA	European Medicines Agency
FDA	Food and Drug Administration

Abbreviation	Meaning
FEF 25%-75%	Forced expiratory flow during the middle half of the forced vital capacity
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
HAPLN2	Proteoglycan link protein 2
IC_{50}	Half maximal inhibitory concentration
ICS	Inhaled corticosteroid
IgG4/k	Immunoglobulin G4 kappa
IL-5	Interleukin-5
IM	Intramuscular
INN	International Non-proprietary Name
IP	Intraperitoneal
IRT	Interactive Response Technology
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ISI	Integrated Summary of Immunogenicity
ITT	Intent to treat
IV	Intravenous
K_d	Dissociation constant
LABA	Long acting beta-agonist
LAMA	Long acting muscarinic antagonist

Abbreviation	Meaning
LS	Least squares
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
NB	Negative binomial
NIH	National Institute of Health
OCS	Oral corticosteroid
PFT	Pulmonary function tests
Ph. Eur.	European Pharmacopeia
PI	Product Information
PIP	Paediatric Investigation Plan
PD	Pharmacodynamic
PK	Pharmacokinetic
% predicted FEV1	Actual FEV1 divided by standard predicted FEV1 times 100%
PO	Orally
PopPK	Population pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
RR	Rate ratio
SABA	Short-acting beta-agonist
SC	Subcutaneous
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics

Abbreviation	Meaning
SD	Standard deviation
SOC	System Organ Class
Teva	Teva Branded Pharmaceutical Products R and D, Inc.
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New chemical (biological) entity
Decision:	Approved
Date of decision:	17 July 2017
Date of entry onto ARTG	25 July 2017
Active ingredient:	Reslizumab
Product names:	Cinqair; Cinqaero
Sponsor's name and address:	Teva Pharma Australia Pty Ltd Locked Bag 2053 North Ryde BC NSW 1670
Dose form:	Concentrated solution
Strength:	100 mg/10 mL
Container:	Vial
Pack size:	1 vial
Approved therapeutic use:	*Cinqair/Cinqaero is indicated as add on therapy in adult patients with severe eosinophilic asthma (blood eosinophil count ≥ 400 cells/μL) (see Clinical Trials).*
Route of administration:	Intravenous infusion
Dosage:	The recommended dose of Cinqair, based on body weight, is 3.0 mg/kg, given once every 4 weeks. Cinqair is intended for long term treatment. For additional information on dosage please see the Product Information.
ARTG numbers:	277278; 277279

Product background

This AusPAR describes the application by Teva Pharma Australia Pty Ltd (the sponsor) to register Cinqair (and the additional trade name Cinqaero) reslizumab 100 mg/10 mL concentrated solution for intravenous infusion for the following indication:

> *Cinqair/Cinqaero (reslizumab) 100 mg/10 mL is indicated as add on treatment in adult patients with severe eosinophilic asthma.*

Severe asthma is defined as that which requires treatment with high dose inhaled glucocorticoids plus a second controller and/or systemic glucocorticoids to prevent asthma from being 'uncontrolled' or which remains uncontrolled despite this therapy.

Patients with eosinophilic asthma do not respond to inhaled glucocorticoids and require systemic glucocorticoids to control their asthma. They are less likely to be atopic/ allergic. They have high levels of blood and tissue eosinophils and high levels of exhaled nitric oxide.

From the already authorised asthma treatments, omalizumab, a recombinant humanised monoclonal antibody (mAb) (IgG1) is recommended for use in Global Initiative for Asthma (GINA) Step 5 (add on treatment for allergic asthma);[1] but only a small proportion of patients with severe asthma are appropriate candidates for its use.

The anti- interleukin 5 (IL-5) antibody, mepolizumab (Nucala) was registered in Australia in February 2016 for use as add on treatment for on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over.

Reslizumab is a humanised anti-human IL-5 mAb (anti IL-5 mAb), produced in mouse myeloma cells (NS0) by recombinant DNA technology. Reslizumab works by specifically binding to soluble circulating human IL-5 and prevents it binding to the IL-5 receptor complex expressed on the eosinophil surface. IL-5 a key cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils is thereby inhibited. The mode of action of reslizumab consequently reduces circulating and tissue eosinophils.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 25 July 2017.

At the time the TGA considered this application; a similar application had been approved or was under consideration in the countries/regions, as outlined in Table 1.

Table 1: International regulatory status

Country/Region	Date of submission/approval	Approved indication
USA	Application: BLA 761033 Submitted: 29.03.2015 Approved: 23.03.2016	Cinqair is indicated for the add on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.
European Union (Centralised)*	Application: EMEA/H/C/003912 Submitted: 30.06.15 Approved: 16.08.2016	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.
Canada	Application: NDS File HC6-024-e179932, control # 185873 Submitted: 29.06.2016	CinqairTM (reslizumab) is indicated as add on maintenance treatment in adult patients with severe

[1] The Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org/

Country/Region	Date of submission/approval	Approved indication
	Approved: 20.07.2016	eosinophilic asthma who: · are inadequately controlled with medium to- high dose inhaled corticosteroids and an additional asthma controller(s) (for example, LABA) and · have a blood eosinophil count of ≥ 400 cells/µL at initiation of the treatment.
Russia	Submitted: 21.12.2015	
Switzerland	Submitted: 31.05.2016	
Israel	Submitted: 31.05.2016	
South Korea	Submitted: 03.08.2016	
Peru	Submitted: 25.10.2016	
Brazil	Submitted: 18.11.2016	
Chile	Submitted: 27.12.2016	
Turkey	Submitted: 29.03.2017	

* A variation was submitted on 9 November 2016 for the reslizumab European Union marketing authorisation in order to introduce a vial based dosing regimen for patients weighing between 35 and 199 kg and a new presentation of the product (25 mL vial). This variation is currently under assessment.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>.

II Submission timeline

Table 2: Registration timeline for Submission PM-02916-02101-1-5

Description	Date
Submission dossier accepted and 1st round evaluation commenced	29 July 2016
First round evaluation completed	3 January 2017
Sponsor provides responses on questions raised in first round evaluation	1 March 2017
Second round evaluation completed	6 April 2017

Description	Date
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	26 April 2017
Sponsor's pre-Advisory Committee meeting response	16 May 2017
Advisory Committee meeting	6 to 7 April 2017
Registration decision	17 July 2017
Entry onto ARTG	25 July 2017
Number of TGA working days from submission dossier acceptance to registration decision*	201

* Statutory timeframe 255 working days

II. Quality findings

Introduction

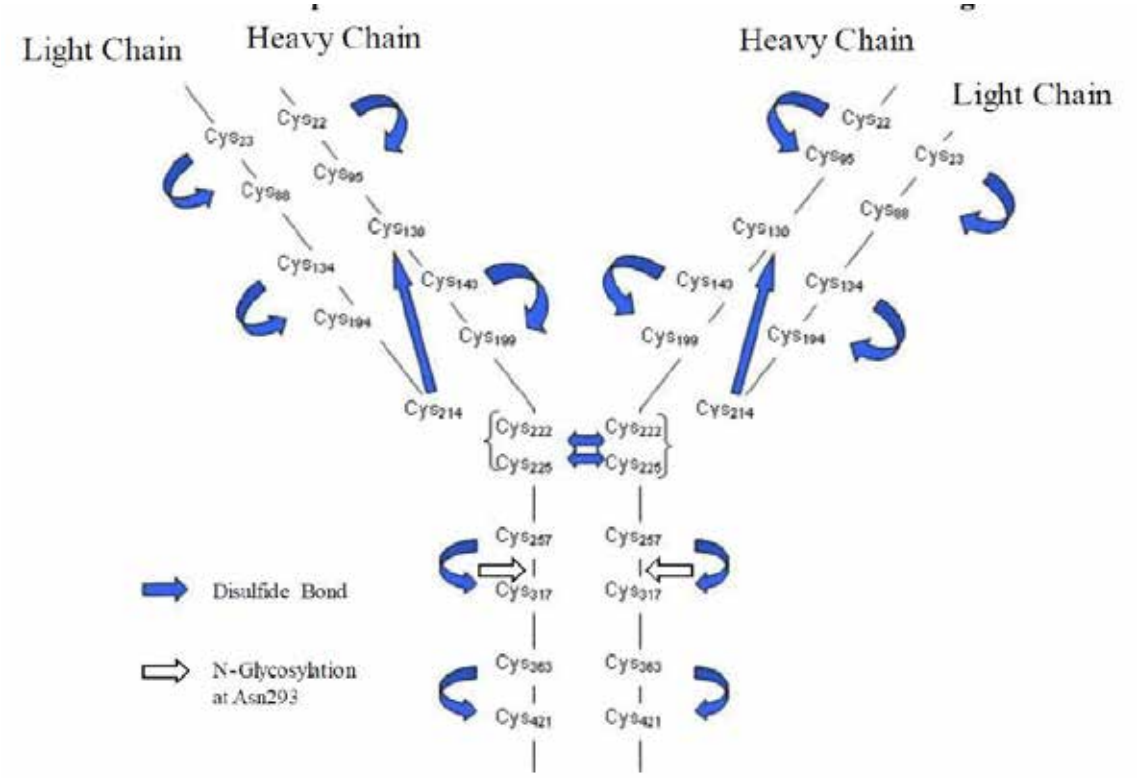
Reslizumab is a humanised anti-human anti-IL-5 mAb of the immunoglobulin-G4 kappa (IgG4/κ) isotype, which contains the complementarity determining regions (CDRs) (that is, antigen binding regions) of the original rat anti-human antibody 39D10 grafted onto a human framework.

An amino acid sequence for both heavy and light chains has been predicted from the translation of the nucleotide sequence for the gene of the reslizumab antibody. The completely verified amino acid sequences for the heavy chain and light chain of reslizumab was provided. There are 2 heavy chain post translational modifications identified as the conserved N-linked glycosylation on the CH_2 domain of the heavy chain at asparagine 293 (Asn293) (N) and loss of C-terminal lysine residue (K) of the heavy chain.

Reslizumab has a theoretical molecular mass of 146,776 Da calculated for the antibody with 2 C-terminally clipped lysine residues and 2 G1F glycans.

Reslizumab has a characteristic IgG4 structure including 2 identical heavy chains and 2 identical light chains linked by 16 disulphide bonds (4 inter chain disulphide bonds and 12 intra chain disulphide bonds).

Figure 1: Structural representation of reslizumab Di-sulphide bond linkage



The figure shows the general structure with the confirmed di-sulphide bond linkages. The glycosylation site at Asn293 is also indicated. Disulphide linkages in reslizumab are identical to the native wild type human IgG4 antibody. No miss linkages have been detected. 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 specifically binds to soluble circulating human IL-5 and prevents its binding to the IL-5 receptor present on eosinophils, thereby inhibiting their activation, proliferation and ameliorating disease state. Reslizumab has a low Fc receptor binding profile as expected.

Drug substance (active ingredient)

Reslizumab is produced in mouse myeloma cells (NS0) by recombinant DNA technology. The purified reslizumab drug substance is a clear to opalescent, colourless to yellow solution formulated with 20 mM sodium acetate, 7% sucrose at pH 5.5 with a target protein concentration of 12 mg/mL.

Drug product

The manufacture of reslizumab drug product employs a standard formulation and aseptic filling process that consists of 5 major operations:

- buffer formulation and bio-burden reduction filtration;
- bulk drug substance (BDS) pooling;
- formulation (BDS Dilution) and sterile filtration;
- filling and capping; and
- final 100% inspection and packaging.

The drug product is manufactured at a10 mg/mL strength and a batch size of 240 L.

The specifications comply with specific monographs as listed as well as with relevant general monographs including European Pharmacopeia (Ph. Eur.) monograph 520 (parenteral preparations), Ph. Eur. monograph 2031 (monoclonal antibodies for human use) and Ph. Eur. monograph 2034 (substances for pharmaceutical use).

All analytical procedures are validated.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data indicate that the product is not photostable.

Taken together, the stability data gathered to date on reslizumab drug product support a 36 month expiration dating period for the drug product when stored in the proposed container closure system at the intended storage temperature of 2 to 8°C.

Chemical and physical in-use stability has been demonstrated at 2°C to 8°C and at 25°C in sodium chloride 0.9% solution for infusion for up to 16 hours when protected from light.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Cinqair/Cinqaero reslizumab concentrated solution for infusion 100 mg/10 mL. However, the Delegate is advised of the following:

1. The evaluator considers the storage condition for the product to be '36 months when stored at 2°C to 8°C. Refrigerate. Do not freeze'. Temperature excursions during shipping should not be approved and where temperature excursions do occur affected batches should be quarantined until an application to vary has been considered by the TGA. This approach has been agreed to by the sponsor.
2. Good Manufacturing Practice (GMP) certification for a number of manufacturing sites has yet to be confirmed (under review by TGA). Registration of this product should not be approved until GMP issues are resolved. The sponsor continues to negotiate with TGA's Manufacturing Quality Branch on GMP certification issues.
3. The evaluator is concerned that the source and nature of the visible particles seen in drug product is not fully explained. There appears to be no detectable effect on potency associated with the presence of particles and oddly the presence of particles does not seem to be associated with any other measurement of degradation. The presence of a final filter at the point of injection to remove particulates somewhat addresses the evaluator's concern but does not necessarily adequately address the issue of what the particulates are and what other changes in drug product may be associated with their presence. This information could be provided to TGA post market area for their reference. The sponsor has provided additional information which further mitigates the risk but is none the less brought to the attention of the Delegate.

Proposed conditions of registration

Batch release testing and compliance with Certified Product Details (CPD):

1. It is a condition of registration that goods which do not meet all Australian Market Authorisation requirements must not be supplied in Australia. This includes, but is not limited to, good which:
    a. differ from their approved ARTG entry and CPD;

b. have not been maintained at the approved storage conditions, or where applicable within the permitted temperature excursion ranges, as recorded in the ARTG entry and on the CPD;

c. have not been tested against the approved Australian specifications;

d. any other deviation from the Market Authorisation requirements.

Where there is evidence that failure to comply with Australian Market Authorisation requirements does not result in goods of unacceptable quality, sponsors may seek an exemption from this condition by applying to temporarily vary the conditions of registration (for the affected batches) under s.28 of the Act.

2. It is a condition of registration that, as a minimum, each batch of Cinqair/Cinqaero reslizumab concentrated solution for infusion 100 mg/10 mL strength imported into/manufactured in Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

3. The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

III. Nonclinical findings

Introduction

The sponsor has applied to register a new biological entity, reslizumab (Cinqair; Cinqaero), a humanised monoclonal antibody (IgG4, kappa) against human IL-5. Cinqair/Cinqaero is proposed to be used as add on treatment in adult patients with severe eosinophilic asthma, involving intravenous (IV) administration at a dose of 3 mg/kg once every 4 weeks.

The scope of nonclinical studies conducted met the relevant TGA adopted guideline.[2] All pivotal safety related studies were performed according to Good Laboratory Practice (GLP), except for the safety pharmacology study that investigated effects on the cardiovascular system. Overcoming this particular deficiency, monitoring of cardiovascular function was included in 2 GLP compliant general repeat dose toxicity studies.

The studies investigating the general repeat dose toxicity of reslizumab were deficient due to inappropriate dose selection, with testing of far higher doses justified and feasible. This deficiency is largely overcome by the carcinogenicity study, though. Doses tested in the reproductive toxicity studies were also inappropriately low. Also, the nonclinical testing program would have benefitted from more routine toxicokinetic analyses.

[2] ICH S6 [R1] - ICH guideline for the preclinical safety evaluation of biotechnology-derived pharmaceuticals

Pharmacology

Primary pharmacology

IL-5 is the major haematopoietic cytokine responsible for the proliferation, differentiation, activation, survival and recruitment of eosinophils. By binding to IL-5, reslizumab is designed to reduce IL-5 receptor activation, leading to a reduction in the number of blood and pulmonary eosinophils.

Reslizumab was shown to bind to human IL-5 with high affinity *in vitro*, with a dissociation constant (K_d) of 81 pM observed. In cell based functional experiments, reslizumab inhibited the binding of human IL-5 to its receptor (half maximal inhibitory concentration (IC_{50}), 0.28 nM) and inhibited proliferation of TF-1 cells (a human erythroleukaemic cell line) induced by human IL-5 (IC_{50}, 45 pM). Affinity of the antibody for mouse and monkey IL-5 was similar compared with human; while the affinity of reslizumab for rat IL-5 was approximately 7 times lower than for the human form.

In vivo, prior treatment with reslizumab (administered IV, intraperitoneal (IP) or intramuscular (IM) as a single dose) was shown to significantly attenuate the increase in eosinophils in bronchoalveolar lavage fluid induced by antigen challenge in sensitised mice, guinea pigs and cynomolgus monkeys, with the drug acting in a dose dependent manner. Long lasting efficacy was evident, with statistically significant inhibition of eosinophilia demonstrated for up to 4 to 8 weeks post dose in mice (2 to 10 mg/kg) and up to 6 months in monkeys (0.3 mg/kg). Airway hyper reactivity in sensitised guinea pigs was significantly decreased by reslizumab at ≥ 1 mg/kg IP, and antigen induced bronchoconstriction was significantly reduced in the species at 30 mg/kg IP (but not at 10 mg/kg). In rabbits, IV administration of reslizumab was shown to attenuate the influx of eosinophils into the skin following cutaneous antigen challenge.

In other nonclinical efficacy studies, reslizumab significantly decreased eosinophils in the oesophagus (and also blood) in a mouse model of eosinophilic oesophagitis, but did not effectively reduce ocular hyperaemia in a mouse model of allergic conjunctivitis (consistent with greater involvement of basophils and mast cells compared with eosinophils).

Combination treatment with reslizumab and prednisolone (2 mg/kg IP + 5 mg/kg orally (PO)) produced roughly additive inhibition of antigen-induced pulmonary eosinophilia in sensitised mice. No additional inhibition, though, was seen at a lower dose of prednisolone (2.5 mg/kg PO).

Cross reactivity

Immunohistochemical studies examining cross reactivity; involving a suitably comprehensive panel of tissues; revealed binding of reslizumab in human central nervous system (CNS) tissues (cerebellum, cerebrum, spinal cord and optic nerve), that was not attributable to the presence of IL-5. A similar binding pattern was evident in CNS tissues from the cynomolgus monkey, while no specific binding was noted with CNS tissues from the mouse or guinea pig. The cross reactive antigen was identified as brain link protein-1 (BRAL1), a structural protein involved in cell matrix interactions.[3] BRAL1 (also known as hyaluronan and proteoglycan link protein 2 (HAPLN2)) contains a CRRR motif similar to the ERRR binding epitope recognised by reslizumab. BRAL1 knockout mice show abnormal diffuseness of hyaluronan-associated extracellular matrix in the nodes of Ranvier (that is, there is an altered ionic diffusion barrier at the myelin sheath gaps of

[3] Kwok J.C., et al. (2011) Extracellular matrix and perineuronal nets in CNS repair. *Dev. Neurobiol.* 71**:** 1073–1089.

axons) and a marked decrease in conduction velocity in the spinal cord.[4] The toxicological significance of the cross reactivity finding is discussed below.

Safety pharmacology

In dedicated safety pharmacology studies, reslizumab had no acute effects on CNS, cardiovascular, renal or gastrointestinal function in rats at 100 mg/kg IV; effects on the respiratory system were not examined. Given the much lower affinity of reslizumab for its IL-5, the rat is not an ideal species to have used for these investigations. Addressing these deficiencies, the general repeat dose toxicity program in cynomolgus monkeys included examination of neurological, cardiovascular, respiratory and renal functional endpoints, with no adverse effects observed (tested up to 25 mg/kg IV). Further support for inhibition of IL-5 activity by reslizumab not having effects on the major physiological systems is offered by observations of IL-5 knockout mice, which appear normal; as well as previous safety findings for the existing anti-IL-5 antibody, mepolizumab (Nucala).

Pharmacokinetics

Following IV administration, reslizumab displayed a long serum half-life in laboratory animal species (approximately 14 days in mice, approximately 8 days in rats, approximately 12 days in rabbits and approximately 7 days in monkeys), but shorter than in humans (approximately 24 days). Exposure was generally dose proportional or slightly greater than dose proportional in animals; humans, similarly, showed dose proportional exposure. Subcutaneous (SC) administration was associated with approximately 80% bioavailability in mice and complete bioavailability in rats.

As expected for an antibody, reslizumab appeared to be largely confined to the plasma compartment. The steady state volume of distribution values approximated serum volume in mice and was about double the serum volume in the rabbit. No specific tissue distribution studies were conducted, but limited penetration of the blood-brain barrier by reslizumab is evident based on only very low levels of the drug (< 0.1 μg/mL) being detected in cerebrospinal fluid samples of monkeys following dosing at 25 mg/kg IV (compared with serum concentrations that were hundreds or thousands of times higher).

No metabolism or excretion studies were submitted, which is acceptable given the protein nature of the drug.

Pharmacokinetic drug interactions

Experiments with cultured human hepatocytes revealed no notable effect of reslizumab (200 μg/mL) on cytochrome P450 (CYP) CYP1A2, 2B6 or 3A4 expression.

Toxicology

Acute toxicity

Single dose toxicity studies, conducted by the IV route and featuring 14 days observation post dose, were conducted in mice (500 mg/kg), rats (500 mg/kg) and cynomolgus monkeys (100 mg/kg). No deaths occurred and no other overt toxicity was observed, indicating a low order of acute toxicity for reslizumab.

[4] Bekku Y., et al. (2010) Bral1: its role in diffusion barrier formation and conduction velocity in the CNS. *Neurosci.* 30**:** 3113–3123.

Repeat-dose toxicity

Pivotal repeat dose toxicity studies of 6 months duration were conducted by the IV route in mice and cynomolgus monkeys. These studies involved administration of up to 25 mg/kg at 4 week intervals; the dosing frequency matching that proposed clinically. Additional repeat dose toxicity studies were of shorter duration (4 weeks) and involved weekly or fortnightly IV administration up to the same dose level in monkeys and up to 500 mg/kg in mice. A 6 month study in monkeys by the SC route; involving administration up to 25 mg/kg once every 4 weeks, and with an additional 1 mg/kg IV group; was also submitted.

Species selection and study duration for the pivotal repeat dose toxicity studies were appropriate. However, the pivotal studies did not employ appropriate dose levels. The highest tested doses were not constrained by toxicity nor produced a maximal pharmacological effect, and they yielded only very low or modest multiples of the serum area under the curve (AUC) in patients at the maximum recommended human dose (approximately 1.5 to 3; see below), falling far short of the approximately 10 fold exposure multiple recommended in the relevant TGA adopted guideline.[2]

Relative exposure

Animal: human exposure multiples are calculated below for selected repeat dose toxicity studies based on comparison of serum AUC values, adjusted for differences in dosing frequency where appropriate (that is, multiplied by 2 to account for fortnightly compared with monthly dosing). The pivotal monkey study featured only limited toxicokinetic sampling and serum AUC values were not determined. Consequently, relative exposure achieved in that study has been estimated from more extensive toxicokinetic data obtained in the 6 month SC study (with SC administered drug assumed to be fully bioavailable). The guideline states that 'whenever possible, systemic exposure should be monitored during the toxicity studies'.[2]

Table 3: Relative exposure in selected repeat dose toxicity studies

Species		Study duration [Study no.]	Dose (mg/kg);IV		AUC0–t (µg·h/mL)	Exposure ratio#
Mouse	(001178-W)	4 weeks [DS-2011-017]	250	Q14D	1422500	94
			500		2180500	144
	(CD-1)	6 months [SN96264] (pivotal)	2	Q28D	5840	0.2
			10		22100	0.7
			25		45500	1.5
Monkey (cynomolgus)		6 months [P6749] (pivotal)	1	Q28D	1170†	0.04
			5		5270†	0.2
			25		96400†	3.2
Human (Population PK model)		steady state[CP-11-006]	[3 mg/kg]	Q28D	30362	–

= animal:human serum AUC0–t (adjusted for differences in dosing frequency, where appropriate); animal values are for the sexes combined, obtained on the last sampling occasion; † = values are estimates based on data obtained in the 6 month monkey SC toxicity study (Study DS-2009-030).

Major effects

There were no toxicologically significant findings in the pivotal mouse and monkey studies, with no observed adverse effect levels of 25 mg/kg IV every 4 weeks established in both species (relative exposure, 1.5 in mice and 3.2 in monkeys). Some serum samples were found to be positive for anti-reslizumab antibodies, but the reliable detection of anti-drug antibodies was impaired by the presence of free drug in serum. In any case, an adequate number of animals remained exposed to reslizumab.

Treatment was not associated with obvious reductions in serum eosinophil counts in the pivotal mouse or monkey studies, but such changes were seen in mice dosed at ≥ 250 mg/kg IV every 2 weeks (in a study that did not include histopathological examination) and in monkeys at ≥ 1 mg/kg IV weekly and 25 mg/kg SC every 4 weeks.

Addressing deficiencies in the general repeat dose toxicity program, much higher doses were used in a study investigating the carcinogenic potential of reslizumab. Transgenic mice received up to 516 mg/kg reslizumab IV every 2 weeks for 6 months (estimated relative exposure, approximately 150, based on toxicokinetic data obtained in a 4 week study in wildtype mice), with no effect on mortality or bodyweight gain, and no treatment related macroscopic or (neoplastic/non neoplastic) microscopic lesions found. Pharmacological activity of reslizumab was evident at all dose levels tested, based on significant reductions in serum eosinophil counts observed at the end of the study.

Of particular note, no CNS toxicity was evident in animals with repeated IV or SC dosing. Much higher exposure of the CNS was obtained in a study in monkeys where reslizumab was administered intrathecally (at 0.07 mg/kg; single dose), bypassing the blood-brain barrier. Reslizumab concentrations measured in the cerebrospinal fluid of monkeys approached or exceeded the serum peak concentration (C_{max}) in patients at the maximum recommended human IV dose. Functional neurological assessment and histopathological examination of CNS tissues, conducted 1 and 4 weeks post dose, revealed no effect of reslizumab. These findings support the cross reactivity of reslizumab with BRAL1 as being of no toxicological significance.

Genotoxicity

While standard genotoxicity studies are not recommended to be conducted for biotechnology derived products under the guideline;[2] the sponsor did submit studies investigating bacterial mutagenicity and chromosomal aberrations in vitro (in human lymphocytes). Both studies were appropriately designed and conducted, and returned negative results for reslizumab. As a large protein, the drug would not be expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of reslizumab was investigated in a 6 month study in transgenic mice (rasH2 model). The study was mostly appropriately designed and conducted. The study did not include toxicokinetic analyses or examination of potential anti-drug antibodies. Nevertheless, very high exposure multiples are seen to have been obtained based on data from a 4 week study in wildtype mice, and continued pharmacological activity is evident based on reduced circulating eosinophil counts at the end of the study.

No carcinogenic activity was observed with reslizumab up to the highest dose tested (516 mg/kg IV once every 2 weeks), estimated to yield approximately 150 times the systemic exposure in patients at the maximum recommended human dose (based on toxicokinetic data obtained in a 4 week study in wildtype mice).

Reproductive toxicity

Reproductive toxicity studies with reslizumab covered all stages. Species selection was appropriate, with the mouse used as the main species, and the rabbit used as the second, non rodent species for further investigation of potential effects on embryofetal development. Administration was by the clinical route (IV). The timing/duration of treatment was appropriate, with doses given once only or every 2 weeks or so, so that there was exposure during the critical periods. Again, the studies did not include toxicokinetic sampling to allow for the determination of serum AUC values, in contrast to the recommendation for routine monitoring of systemic exposure in toxicity studies in the guideline.[2]

Relative exposure

Animal: human exposure multiples achieved at the highest doses used in the definitive reproductive toxicity studies are estimated in Table 4, shown below. Animal AUC values used for the calculations were obtained in other studies. Only modest multiples of the clinical AUC were reached.

Table 4: Relative exposure in definitive reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg); IV		AUC0–t (µg·h/mL)	Exposure ratio#
Mouse (CD-1)	Fertility	50	Q14D	119133a	3.9
	Embryofetal development		single dose		
	Pre-/postnatal development		approximately Q14D		
Rabbit (NZW)	Embryofetal development	50	single dose	113899b	3.8
Human (Population PK model)	steady state [CP-11-006]	3	Q28D	30362	–

only data for the highest tested doses are shown; a = estimate based on mean calculated AUC0–14 d in mice at 50 mg/kg IV in Single dose pharmacokinetic studies Res-4-0026 and SN00150); b = estimate based on calculated AUC0–14 d in rabbits at 50 mg/kg IV in Single dose pharmacokinetic Study P6613; # = animal:human serum AUC0–t

Excretion of reslizumab in milk was demonstrated in mice. Drug concentrations in the milk of lactating animals were approximately 6 to 8% of the serum concentration.

No adverse effects on male or female fertility, embryofetal development or pre/postnatal development were observed with reslizumab in mice up to the highest dose tested (50 mg/kg; estimated relative exposure, approximately 4), and embryofetal development was also unaffected in the rabbit (≤ 50 mg/kg; estimated relative exposure, approximately 4).

The maximum dose levels used in these studies were not constrained by toxicity; higher doses should have been tested in accordance with recommendations in the guideline.[5]

Pregnancy classification

The sponsor had proposed Pregnancy Category B1 for reslizumab.[6] Although the submitted studies on embryofetal development are limited in some regards (which would ordinarily warrant a B2 categorisation);[7] considering that the available nonclinical data do not indicate an adverse effect of reslizumab with use in pregnancy, that significant placental transfer of an IgG4 antibody is not anticipated in humans during the period of organogenesis, and noting the normal development of mice lacking IL-5, assignment to Pregnancy Category B1 is considered to be acceptable.

Local tolerance

Reslizumab solution was well tolerated by the IV route in rabbits, as well as by other routes (intramuscular and intra-arterial in rabbits; subcutaneous and subplantar in rats), in a series of specialised local tolerance studies. The administered strength, 10 mg/mL, matches that of the concentrated commercial solution. Cinqair/Cinqaero is to be diluted in saline prior to patient administration. The strength tested in animals is approximately 3 times higher than that for infusion in a 70 kg patient (according to administration instructions in the proposed PI document).

Reslizumab was also seen to be well tolerated locally in the general repeat dose toxicity studies and in the mouse carcinogenicity study (tested up to 103 mg/mL IV in mice; and 10 mg/mL IV and 110 mg/mL SC in monkeys).

Paediatric use

Cinqair/Cinqaero is to be indicated for use in adult patients only.

A study in juvenile mice, involving monthly IV administration at up to 25 mg/kg for a total of 3 doses, revealed no toxicity or adverse effects on development by reslizumab, but the highest tested dose is predicted to have yielded only a very low multiple (1.5) of the clinical systemic exposure. A 4 week study in juvenile monkeys, where reslizumab was given at up to 15 mg/kg IV weekly, also showed no toxicity, and was associated with higher exposure ratios (approximately 8 fold; based on serum AUC and adjusting for the higher dosing frequency in animals compared with patients). Finally, while dosing commenced when animals were young adults, the mouse carcinogenicity study does provide support that reslizumab does not target developing systems, even at doses associated with very high multiples of the clinical exposure (approximately 150).

Comments on the nonclinical safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for reslizumab detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

[5] ICH S5 (R2): ICH Harmonised tripartite guideline. Detection of toxicity to reproduction for medicinal products and toxicity to male fertility S5(R2).
[6] Pregnancy Category B1 is defined as "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage."
[7] Pregnancy Category B2 is defined as "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage"

Nonclinical summary and conclusions

- The conduct of the nonclinical program for reslizumab was not fully in accordance with the relevant TGA adopted guideline.[2]
- IL-5 is the major cytokine responsible for the proliferation, differentiation, activation, survival and recruitment of eosinophils. In vitro, reslizumab was shown to bind to human IL-5 with picomolar affinity, to inhibit the binding of IL-5 to its receptor, and to inhibit IL-5-stimulated cell proliferation in a human cell line. In vivo, it attenuated pulmonary eosinophilia induced by antigen challenge in multiple laboratory animal species (mice, guinea pigs and cynomolgus monkeys), acting with a long duration of action. Roughly additive inhibition was seen with reslizumab in combination with prednisolone in a study in sensitised mice (although this depended on the steroid dose).
- The main laboratory animal species used in the toxicity program; mouse, cynomolgus monkey and rabbit; were shown to be pharmacodynamically responsive to reslizumab. In particular, the antibody's affinity for mouse and monkey IL-5 was demonstrated to be similar compared with that for the human form. The rat was used in some of the safety studies, but reslizumab recognised its form of IL-5 less well.
- Reslizumab was found to display cross reactivity with brain link protein-1 (BRAL1; monkey and human forms), a structural protein involved in cell matrix interactions.
- No effects on neurological, cardiovascular, respiratory, renal or gastrointestinal function were seen with reslizumab in dedicated safety pharmacology studies or in general repeat dose toxicity studies that included monitoring of relevant functional endpoints.
- Reslizumab exhibited a long serum half-life in laboratory animal species (as in humans) following IV administration. Entry into the CNS following IV dosing was shown to be minimal in monkeys.
- Single dose toxicity studies in mice, rats and monkeys demonstrated a low order of acute toxicity for reslizumab.
- Pivotal repeat dose toxicity studies of 6 months duration; involving IV administration once every 4 weeks were conducted in mice and monkeys. While no toxicologically significant effects were observed, the studies did not use appropriately high doses, with only low multiples of the clinical systemic exposure obtained at the maximum dose level tested (25 mg/kg in both species; yielding 1.5 times (mice) and approximately 3 times (monkeys) the serum AUC in patients; with this falling well short of the approximately 10 fold exposure multiple recommended in the absence of toxicity or saturated pharmacology in the guideline.[2] While not ideal, a 6 month carcinogenicity study in transgenic mice, which employed far higher doses and more frequent administration (516 mg/kg IV every two weeks; yielding approximately 150 times the clinical exposure) offers adequate support for the general safety of reslizumab.

- No toxicological significance is seen to be attached to the finding of BRAL-1 cross reactivity by reslizumab. This is based on pharmacokinetic grounds (with the antibody predicted to only minimally enter the CNS in patients) and the absence of CNS toxicity observed in laboratory animal species (including in a monkey study where intrathecal administration was employed to produce high exposure in the CNS).
- Reslizumab was not genotoxic in assays for bacterial mutagenicity and clastogenicity in vitro, and not carcinogenic in an adequately conducted study in transgenic mice.
- Male and female fertility (mice), embryofetal development (mice and rabbits) and pre/postnatal development (mice) were unaffected by reslizumab. Again, the maximum dose level tested in the reproductive toxicity studies (estimated to yield up to approximately 4 times the systemic exposure of patients), fell short of level recommended in the relevant ICH guideline.[2]
- Pregnancy Category B1, as proposed by the sponsor, is considered to be acceptable. This is based on information on the role of the pharmacological target in development evident from IL-5 knockout animals, and anticipated limited placental transfer of an IgG4 antibody in humans during the period of organogenesis, supplementing the sponsor's (limited) embryofetal study data.
- Reslizumab was shown to be well tolerated locally following administration by the clinical route (IV) in animals, as well as by various other parenteral routes.
- Inappropriately low dose selection in the general repeat dose toxicity studies and in the reproductive toxicity studies is considered to be a significant deficiency of the nonclinical package, but not a critical one, with adequate support for safety obtained from other sources.
- There are no nonclinical objections to registration of Cinqair/Cinqaero for the proposed indication.
- The nonclinical evaluator also made comments about the PI but these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Reslizumab is a humanized anti-human IL-5 monoclonal antibody (anti IL-5 mAb) of the immunoglobulin-G4-kappa (IgG4/k) isotope, produced in mouse myeloma cells (NS0) by recombinant DNA technology. Reslizumab works by binding to IL-5, thereby preventing binding of IL-5 to the IL-5 receptor and consequently reduces circulating and tissue eosinophils.

The sponsor's proposed indication:

> *'Reslizumab is indicated as add on treatment in adult patients with severe eosinophilic asthma'.*

Dosage forms and strengths

Concentrated solution for intravenous infusion, vial, 100 mg/10 mL.

Dosage and administration

The recommended dose of Cinqair, based on body weight, is 3.0 mg/kg, given once every 4 weeks as an intravenous infusion. Cinqair is intended for long term treatment. A decision to continue Cinqair therapy should be made at least annually based on disease severity and level of exacerbation control.

Information on the condition being treated

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 hyper-responsiveness to direct or indirect stimuli (Global Initiative for Asthma (GINA) 2014).[8]

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.[8,9,10,11]

[8] GINA 2014. Global Initiative for Asthma (GINA) Report, 2014. The Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org/
[9] Bacharier L, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63: 5-34.
[10] Ege M, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med* 2011; 364: 701-709.
[11] Vijverberg S, et al. Biomarkers of therapy responsiveness in asthma: pitfalls and promises. *Clin Exp Allergy* 2011; 41: 615-629

Eosinophilic asthma has emerged as a distinctive asthma phenotype.[12,13,14] Eosinophilic asthma is associated with tissue and sputum eosinophilia, thickening of the basement membrane zone, and often by corticosteroid responsiveness.[15,16] 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.[17,18,19,20,21,22,23,24] Inhaled corticosteroids (ICS) 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;[25,26,27] and this observation has been incorporated into the most recent expert asthma guidance.[28]

Current treatment options

For moderate to severe asthma 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 (OCS) and/or (for patients with perennial allergies) anti-immunoglobulin E (anti-IgE (omalizumab)). 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 monoclonal antibody (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

[12] Walford H, and Doherty T. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma Allergy 2014;7: 53-65.
[13] Wenzel S, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999; 160: 1001-1008.
[14] Wenzel S. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; 18: 716-725.
[15] Berry M, et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax* 2007; 62: 1043-1049.
[16] Fahy J. Eosinophilic and neutrophilic inflammation in asthma: insights from clinical studies. *Proc Am Thorac Soc* 2009; 6: 256-259.
[17] Balzar S, et al. Increased TGF-beta2 in severe asthma with eosinophilia. *J Allergy Clin Immunol* 2005; 115: 110-117.
[18] Green R, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360: 1715-1721.
[19] Jatakanon A, et al. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000; 161: 64-72.
[20] Petsky H, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 2012; 67: 199-208.
[21] Robinson D. Eosinophils and asthma. What do measurements tell us? *Clin Exp Allergy* 1995 25: 795-798.
[22] Saglani S, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007; 176:858-864.
[23] Brinke A, et al. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med* 2001; 164: 744-748.
[24] Wenzel S, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999; 160: 1001-1008.
[25] Malinovschi A, et al. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol* 2013; 132: 821-827.
[26] Tran T, et al. High blood eosiniphil count is associated with more frequent asthma attack in asthma patients. *Ann Allergy Asthma Immunol* 2014; 113: 19-24.
[27] Zeiger R, et al. Real-time asthma outreach reduces excessive short-acting beta2-agonist use: a randomized study. *J Allergy Clin Immunol Pract* 2014; 2: 445-456.
[28] GINA 2015 Global Initiative for Asthma (GINA) REPORT, 2015. The Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org/

asthma exacerbations in patients with allergic asthma, with small and highly variable effects on lung function.[29,30,31,32] Thus, there is a substantial unmet need for patients who are inadequately controlled by current standard of care therapy.

The anti-IL-5 antibody mepolizumab (Nucala) was authorised in the US in November 2015 as add on maintenance treatment for patients with severe asthma aged 12 years and older and with an eosinophilic phenotype. Mepolizumab was authorised in the European Union in December 2015 as add on treatment for severe refractory eosinophilic asthma in adults and in Australia in February 2016 as add on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over.

Clinical rationale

Cinqair/Cinqaero (reslizumab) 100 mg/10 mL is indicated as add on treatment in adult patients with severe eosinophilic asthma. Reslizumab is a humanized anti-IL-5-mAb of the IgG4/$_K$ isotype, developed 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. Reslizumab works by binding specifically to IL-5 and interferes with IL-5 binding to its cell surface receptor on the eosinophil surface, thereby inhibiting IL-5 which is a key cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils.

Reslizumab specifically addresses an unmet medical need for an effective, targeted, and well tolerated therapy for patients with asthma and elevated blood eosinophils who continue to be substantially impacted by their disease, despite use of an ICS based controller regimen.

Contents of the clinical dossier

The submission contained the following clinical information:

- Pharmacokinetic (PK) studies: Four studies that provided PK data:
  - Study I96-350
  - Study C38072/1102
  - Study C38072/1107
  - Study P01942.
- Pharmacodynamic (PD) studies: Two studies that provided PD data:
  - Study C38072/1102
  - Study C38072/1107.
- Population pharmacokinetic (PopPK) studies: One PopPK analyses:
  - Study CP-11-006 PopPK
- Safety and efficacy studies:

[29] Busse W, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001; 108: 184-190.
[30] Hanania N, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011; 154: 573-582
[31] Humbert M, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60: 309-316
[32] Solér M, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18: 254-261. Erratum in: Eur Respir J 2001; 18: 739-740.

- Main studies; 5 efficacy and safety studies primary to the indication of eosinophilic asthma:
  - Study C38072/3081; dose finding study
  - Study C8072/3082; pivotal study
  - Study C8072/3083; pivotal study,
  - Study C8072/3084; study unselected for blood eosinophils,
  - Study C8072/3085; long term study.
- Supportive; 3 efficacy/safety studies supporting the indication of eosinophilic asthma:
  - Study I96-350
  - Study P00290
  - Study Res-5-0010.
- Two Phase I studies in healthy volunteers supporting safety:
  - Study C38072/1102
  - Study C38072/1107.
- Four studies in other patient populations (eosinophilic oesophagitis (EE), hypereosinophilic syndrome, eosinophilic gastroenteritis, and nasal polyposis).

· An Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS) and Integrated Summary of Immunogenicity (ISI).

Paediatric data

Cinqair is not indicated for use in paediatric patients less than 18 years of age. The safety and effectiveness in paediatric asthma patients (aged 17 years and younger) have not been established.

The development program has enrolled a limited number of adolescents. This limits the interpretation of the safety data.

Cinqair was evaluated in 39 patients aged 12 to less than 18 years with asthma in two 52 week exacerbation studies and one 16 week lung function study. In the exacerbation studies, patients were required to have at least 1 asthma exacerbation requiring systemic corticosteroid use in the year prior to study entry. In these studies, the asthma exacerbation rate was higher in adolescent patients treated with Cinqair than placebo (Cinqair n = 14, rate 2.86, 95% confidence interval (CI) (1.02 to 8.09) and placebo n = 11, rate 1.37, 95% CI (0.57 to 3.28): rate ratio 2.09, 95% CI (0.82 to 5.36)).

The sponsor submitted a paediatric study plan to the US FDA in August 2014. The agreed paediatric study plan included a deferral of studies for the population of pre-schoolers (0 through 5 years of age) and children (6 through 11 years of age). The need for any additional studies in the preschool population (0 through 6 years) will be determined later. The paediatric study requirement for ages 0 to 11 years was waived because there is evidence strongly suggesting that the drug product would be ineffective in this paediatric group. Reslizumab was not found to be effective in children 12 to 17 years of age.

The EMA has given the decision on the agreement of a Paediatric Investigation Plan (PIP) and the granting of a deferral and waiver (birth to less than 6 years of age) in January 2015. The agreed completion of all the studies and trials included in the PIP is March 2020.

Good clinical practice

The clinical program was conducted in full accordance with the Good Clinical Practice (GCP): Consolidated Guideline (approved by the International Conference on Harmonisation), applicable national and local laws and regulations, and relevant Health Authority Guidance for Industry, including the European Directive for Clinical Trials.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5: Studies providing pharmacokinetic information

Study ID Duration	Primary objective	Design	Dose of reslizumab	Healthy volunteers or patients	Number; gender Age range
I96-350 Single dose	Safety, PK	Phase I R, DB Rising single dose	0.03, 0.10, 0.30 and 1.0 mg/kg	Asthma, severe	32 treated; 31 completed M and F 20 to 65 years
C38072/1102 20 weeks	Safety, PK, PD	Phase I R, OL	0.3, 1.0, 2.0 and 3.0 mg/kg Every 4 weeks	Healthy volunteers Japanese and non-Japanese	100 treated 82 completed M and F 20 to 45 years
C38072/1107 Single dose	Safety, PK, PD	Phase I R, OL	220 mg IV 220 mg SC	Healthy volunteers Japanese and non-Japanese	75 treated 70 completed M and F 18 to 45 years
P01942 Single dose	Safety, PK	Phase I R, evaluator blinded	1.0 and 3.0 mg/kg	Nasal polyposis	24 treated 24 completed M and F 18 to 63 years

OL = open label; DB = double blind; R = randomised; M = Male; F = Female

For the full evaluation of pharmacokinetics please see Attachment 2.

Evaluator's conclusions on pharmacokinetics

The following summary was adapted from the EMA Assessment Report;[33] and the FDA Clinical Review of Reslizumab.[34]

[33] EMA. Assessment Report: Cinqaero, Reslizumab. Procedure No. EMEA/H/C/003912/0000, 23 June 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003912/WC500212252.pdf

[34] FDA Clinical Review of Reslizumab. Available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm499687.pdf)

Peak serum concentrations occur at the end of the infusion. They decline in a biphasic manner.

The mean observed accumulation ratio of reslizumab following multiple doses of administration ranged from 1.5 to 1.9 fold. This is in line with the elimination half-life of about 24 days and dosing every 28 days.

PK was dose proportional (linear) across the dose range of 0.3 mg/kg to 3.0 mg/kg.

The volume of distribution of reslizumab is approximately 5 L, suggesting minimal distribution to the extravascular tissues. This is similar to other monoclonal antibodies.

Reslizumab clearance is approximately 7 mL/hour. Similar to other monoclonal antibodies, reslizumab is degraded by enzymatic proteolysis into small peptides and amino acids.

Because reslizumab binds to a soluble target, it is not expected to go through a target mediated clearance.

The PopPK analysis did not show any effect of renal or hepatic impairment on the PK of reslizumab (only data points for mild renal or hepatic impairment were available). Renal or hepatic impairment is not expected to have an effect on the PK of reslizumab: it has a molecular mass of 147 kDa and therefore is not excreted in the urine; it is cleared by catabolism and not by the liver. There were insufficient data to confirm a lack of effect of moderate/severe renal or hepatic impairment on PK.

The PopPK analysis did not show any material difference in the PK of reslizumab by age (adults < 65 years versus 65 + years) or gender.

No data for children were submitted. PopPK data suggest a slightly lower exposure when adolescents are dosed at 3.0 mg/kg.

At a fixed dose, patients with higher body weight have more rapid elimination; however, weight based dosing (3.0 mg/kg) provides similar exposure across patients with different body weights.

Pharmacodynamics

For the clinical evaluation of pharmacodynamics please see Attachment 2.

Evaluator's conclusions on pharmacodynamics

Mechanism of action

Reslizumab is a humanized monoclonal antibody ($IgG4/_K$) against the human 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, thereby reducing the survival and activity of eosinophils.

Pharmacodynamic effects

Effect on sputum eosinophils

The effect of reslizumab in patients with asthma and elevated sputum eosinophil counts (at least 3%) was evaluated in a 15 week, Phase II, randomised, double blind, placebo controlled clinical study with reslizumab 3.0 mg/kg. Sputum eosinophils were measured in a subset of 38 adult patients at the end of therapy. In this study, the percentage of

sputum eosinophils was reduced from a mean baseline value of 17.4% (standard deviation (SD): 15.9%) by 82% at the end of therapy in the reslizumab group.

Effect on blood eosinophils

In clinical studies with reslizumab 3.0 mg/kg, decreases in blood eosinophil counts were seen following the first dose and maintained through 52 weeks of treatment with no signs of tachyphylaxis. In pooled data, mean eosinophil counts were 655 μL^{-1} (n = 476) and 654 μL^{-1} (n = 477) for the placebo and reslizumab treatment groups at baseline and were 514 μL^{-1} (n = 405) and 61 µL-1 (n = 407) at Week 52. Eosinophils began to return towards baseline in those reslizumab patients completing a 90 day follow-up assessment (394 μL^{-1}, n = 36). Decreases in blood eosinophils were related to reslizumab levels.

The reduction in blood eosinophil counts by reslizumab in anti-reslizumab antibody positive patients was not different from patients who were anti-reslizumab antibody negative.

Dosage selection for the pivotal studies

Study C38072/3081 was the only study in the intended asthma population to perform dose finding. However, it included only 2 doses, at a 10 fold difference. Data from Study C38072/3081 could not meaningfully inform Phase III dose selection, because all Phase III trials were initiated before Study C38072/3081 was completed.

The sponsor's rationale for choosing the higher dose is that improvement in Asthma Quality of Life Questionnaire (AQLQ) (assessed only at Week 16 and endpoint in this study, p = 0.0241), forced vital capacity (FVC) (p = 0.0174) and FEF 25% to 75%;[35] (p = 0.0552) were observed only for the reslizumab 3.0 mg/kg dose. Hence, the sponsor considered that dosing of reslizumab at 0.3 mg/kg was less effective in treating the small airways where asthma pathology predominantly resides.

The paucity of dose finding data is a limitation of the reslizumab program, particularly in light of the need to weigh potential benefit with the risks observed. The 0.3 mg/kg dose of reslizumab showed a statistically significant evidence of efficacy for forced expiratory volume in 1 second (FEV1) in Study C38072/3081. It is unknown whether a lower dose may have demonstrated a more favourable benefit-risk profile.

Efficacy

Studies providing efficacy data

Studies C38072/3081, C38072/3082, C38072/3083, C38072/3084 and C38072/3085 provided evaluable efficacy data.

Study C38072/3081 was a dose finding study; studies C38072/3082 and C38072/3083 were the pivotal studies; Study C38072/3084 was a study in moderate to severe asthma patients unselected for blood eosinophil levels; Study C38072/3085 was an open label extension study (long term study).

[35] FEF 25% to 75% = forced expiratory flow during the middle half of the forced vital capacity

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

Table 6 (continued): 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)
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 = randomised; PG = parallel group; DB = double blind, PC = placebo controlled; OL = open label; M = male; F = female; EOS = eosinophils; NIH = National Institute of Health.

Evaluator's conclusions on efficacy

In summary, the results of the studies comprising the clinical efficacy program provide evidence for the efficacy of IV reslizumab 3.0 mg/kg administered once every 4 weeks for the treatment asthma in adult patients with elevated eosinophils who are not well controlled by medium to high dose ICS (440 µg/day fluticasone propionate or equivalent) and who mostly (82 to 87%) used a second controller medication (that is patients already on ICS based standard of care therapy).

Reslizumab treatment resulted in statistically significant reduced exacerbations, relieved asthma symptoms, and improved lung function in the patient population. These outcome changes were clinically significant. Most patients were severe eosinophilic asthma patients (GINA Stages 4/5) for which limited other treatment options exist. The endpoints comply with the adopted EU guidelines.

No statistical significant effect was shown for clinical asthma exacerbation (CAE) based on an emergency visit or hospitalisation. This may suggest that reslizumab treatment was effective in reducing moderate exacerbations but not severe exacerbations.

The population was representative of the Australian asthma population.

Data in the elderly (≥ 65 years (n = 32)) in the Studies C38072/3082 and C38072/3083 were limited.[36] The adolescent population was small (n = 14);[37] and subgroup analyses of

[36] n = 32 is in the treatment arm of the studies
[37] n = 14 is in the treatment arm of the studies

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. The treatment effect was larger in patients who were using a leukotriene receptor antagonist (LTRA) at Baseline (69% versus 42%). This may indicate that it is a marker of asthma severity (that is, a patient who is using multiple controller concomitant medications) or possibly a marker of patients with asthma with allergic rhinosinusitis/nasal polyposis (where LTRAs may also be used).

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

The open label extension study (Study C38072/3085) in patients previously treated with reslizumab as part of one of the Phase III safety and efficacy studies in eosinophilic asthma resulted in maintained asthma control (as assessed by FEV1 and other lung function parameters, ACQ, ASUI, and AQLQ[38]) as a group. There was a trend towards improving asthma control in the group of patients previously treated with placebo as part of one of the Phase III safety and efficacy feeder studies and who received open label reslizumab 3.0 mg/kg during this extension study.

Safety

Studies providing safety data

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

Apart from Study NIH 01-I-0155, 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-I-0155 was low, that is 8 patients, and the investigated dose is lower than the recommended dose that is, 1.0 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, C38072/3081, C38072/3082, C38072/3083, and C38072/3084, 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 C38072/3085 as of 1 September 2014 (n = 1,596; continuously exposed to 3.0 mg/kg). Cohort 4 is supportive for long term safety as it included also open label Study C38072/3085.
- Cohort 6 (n = 2187): This cohort included all exposed patients and healthy subjects in sponsored reslizumab studies (any dose, any regimen) except Study NIH 01-I-0155. It is intended to help capture rare events.

The clinical evaluation focussed on the safety data presented in Cohort 3, considering these data as the main data. For the full safety evaluation please see Attachment 2.

[38] ACQ: Asthma Control Questionnaire; ASUI: Asthma Symptom Utility Index; AQLQ: Asthma Quality of Life Questionnaire

Patient exposure

A total of 2,195 patients or healthy subjects have been exposed to at least 1 dose of reslizumab in these studies. Considering all studies (except for Study NIH 01-I-0155) in the reslizumab clinical development program, 1,189 patients were treated for at least 6 months, 922 patients were treated for greater than 12 months, 371 patients were treated for greater than 24 months, and 64 patients were treated for greater than 36 months. The maximum exposure in the program was 1,340 days (44 months). Healthy subjects and patients with asthma, EE, nasal polyposis, eosinophilic gastroenteritis, or hypereosinophilic syndrome were included in these studies.

Analyses will focus primarily on one cohort that is Cohort 3, as this is the largest placebo controlled cohort of pooled data that utilized the proposed dose (3.0 mg/kg) and regimen (every 4 weeks) for up to 52 weeks. Displays of this cohort analyses presented will provide a comparison between placebo and reslizumab 3.0 mg/kg. This cohort (n = 1,861) included all asthma patients who received at least 1 dose of study drug in controlled studies through 52 weeks. The treatment groups summarised in Table 7 (see below) include placebo and all reslizumab (0.3 mg/kg + 3.0 mg/kg). The total patient-years exposure was 613 patient-years for the 1,028 patients treated with reslizumab 3.0 mg/kg and 517 patient-years for the 730 patients in the placebo group. The mean duration of treatment was 218 days (range: 1 to 512 days) for patients treated with reslizumab 3.0 mg/kg and was 259 days (range: 14 to 473 days) for patients in the placebo group.

Patients in Cohort 3 were exposed to up to 13 infusions during the course of study treatment. Of the 1,028 patients treated with reslizumab 3.0 mg/kg, a total of 438 patients (43%) were treated for at least 6 months (equating to 7 infusions), and 389 (38%) were treated for greater than or equal to 12 months (equating to 13 infusions). Of the 730 patients in the placebo group, a total of 436 patients (60%) were treated for at least 6 months (equating to 7 infusions), and 388 (53%) were treated for greater than or equal to 12 months (equating to 13 infusions). Greater than 98% of reslizumab 3.0 mg/kg and placebo patients received a complete infusion.

Table 7: Study drug exposure in controlled trials; Safety population, Cohort 3

	Placebo (N=730)	Reslizumab (N=1131)
Patient-years exposure	517	644
Duration of treatment (days), mean ± SD	259 ± 131	208 ± 127
Duration of treatment n (%)		
≥ 6 months	436 (60)	440 (39)
≥ 12 months	388 (53)	389 (34)

Extension, open label Study C38072/3085, 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. In spite of the vast number of discontinuations due to early termination of Study C38072/3085 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. Cohort 4 included all reslizumab treated patients from Cohort 3, plus the data from the open label extension Study C38072/3085 as of 1 September 2014.

Study drug exposure for randomized patients in the reslizumab treatment groups in the Safety analysis set for Cohort 4, without reslizumab 0.3 mg/kg treated patients included, is

presented in Table 8. The total patient-years exposure for these 1,596 patients treated with 3.0 mg/kg reslizumab was 1,593 patient-years. The mean duration of treatment for these patients was 365 days (range: 1 to 1,012 days).

Patients in Cohort 4 were exposed to up to 36 complete infusions during the course of study treatment. The total number of complete infusions (defined as at least 75% of planned dose) for 3.0 mg/kg reslizumab treated patients in Cohort 4 was 20,219. Of the 1,596 patients: a total of 994 patients (62%) were treated for at least 6 months (equating to 7 infusions); 743 (47%) were treated for greater than or equal to 12 months (equating to 13 infusions); 213 (13%) of these patients were treated for greater than or equal to 24 months (equating to 26 infusions). Greater than 95% of these patients received a complete infusion.

Table 8: Study drug exposure; Safety analysis set, Cohort 4 (without reslizumab 0.3 mg/kg treated Patients)

Statistic	Reslizumab 3.0 mg/kg (N=1596)
Patient-years exposure	1593.339
Duration of treatment phase (days)	
n	1596
Mean	364.6
SD	255.98
SE of mean	6.41
Median (min, max)	315.0 (1.0, 1012.0)
Duration of treatment phase, n (%)	
≥1 month	1578 (99)
≥2 months	1526 (96)
≥4 months	1112 (70)
≥6 months	994 (62)
≥12 months	743 (47)
≥24 months	213 (13)
≥30 months	9 (<1)
≥36 months	0
Number of complete infusions [a]	20219

Source: ISS Table 12 [a] A complete infusion is defined as at least 75% of planned dose. Note: Percentages are based on the number of patients in each treatment group. min, max=minimum, maximum * Control = Comparator

For the full evaluation of the safety information please see Attachment 2.

Post marketing data

No post marketing data are available.

Evaluator's conclusions on safety

The overall extent of exposure in the safety database with respect to the number of patients and duration of treatment is adequate. 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 events were symptoms attributed to asthma, which were consistently lower 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 were treatment related. This information is adequately reflected in the PI and as an important identified risk in the Risk Management Plan (RMP).

The incidence of myalgia was slightly increased in reslizumab treated patients versus placebo treated patients (0.97% versus 0.55%, respectively); there was 1 discontinuation for myalgia from each of the treatment groups. There was no apparent relationship between changes in creatine phosphokinase (CPK) and exposure to reslizumab. There was no event of related myositis or myopathy (for example, rhabdomyolysis) in the IV reslizumab program.

There were no deaths related to reslizumab.

Reslizumab is an immunomodulator, and thus malignancy is a safety issue of special concern. A higher incidence of malignancies in patients in the reslizumab group during the placebo controlled phase and the possibly higher frequency compared with the surveillance, epidemiology, and end results (SEER) and to the Clinical Practice Research Datalink (CPRD) was observed. The sponsor considered that a drug-related causality is 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 placebo controlled trials after excluding malignancies that were diagnosed within less than 6 months of reslizumab treatment and the results of the comparisons with the SEER and CPRD. However, malignancy will be continued to be monitored and evaluated via routine pharmacovigilance and will be considered as an adverse event of special interest in future clinical studies.

First round benefit-risk assessment

First round assessment of benefits

Table 9: First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Demonstrated a consistent reduction in asthma exacerbations compared to placebo in studies. The proportion of patients with at least one CAE decreased from 54% to 38% and from 45% to 25% in Studies C38072/ 3082 and C38072/3083, respectively (pooled data: 50% to 32%) that is for 100 patients treated with reslizumab for 1 year, one could expect to prevent 18 CAE. The reslizumab versus placebo CAE rate ratio was 0.50 (95% CI: 0.37, 0.67; Study C38072/3082) and 0.41 (95% CI: 0.28, 0.59; Study C38072/3083), corresponding to a 50% to 59% reduction in CAE events per patient year. Overall, reslizumab treatment demonstrated a clinically meaningful effect in the reduction of CAE.	**Strengths:** Long-term data up to two years supports maintenance of effect based on lung function and asthma symptoms (Study C38072/3085). Immunogenicity rates were low. **Uncertainties:** It is unknown whether the beneficial effects on exacerbation rate and lung function observed in a patient population that were mostly GINA Stages 4/5 are also relevant to GINA Stage 3. In these patients, other treatment options include the addition of a LABA or an increase in ICS dose. The clinical data did not provide a direct comparison between the benefits of

Indication	
Demonstrated a statistically significant and clinically relevant improvement in lung function based on FEV1. The treatment difference in least squares (LS) mean change from Baseline over 16 weeks with placebo was 0.137 L (95% CI: 0.08, 0.198) and 0.093 L (95% CI: 0.003, 0.155) for Studies C38072/3082 and C38072/3083, respectively. A treatment effect was observed at the first observation period of 4 weeks and sustained throughout the study. Statistically significant and clinically relevant improvements were also seen in asthma symptoms and quality of life, and accompanied by a reduction in blood eosinophils.	reslizumab added to moderate dose ICS versus moderate dose ICS with LABA or high dose ICS. No statistical significant effect was shown for CAE based on an emergency visit or hospitalization. This may suggest that reslizumab treatment was effective in reducing moderate exacerbations but not severe exacerbations. When reslizumab treatment is ceased, it is uncertain what happens with the asthma control.

First round assessment of risks

Table 10: First round assessment of risks

Risks	Strengths and Uncertainties
Anaphylaxis occurred in 5 cases in the reslizumab group (< 1%) of which 3 were 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 PI and as an important identified risk in the RMP. Malignancies: 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. This information is adequately reflected in the PI. 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. Data in elderly (≥ 65 years: n = 32) in the	**Uncertainties:** 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. No information is available on the use of reslizumab in patients concomitantly taking immunosuppressants and the impact on the safety profile. This information is also reflected in the PI. Patients with parasitic (helminth) infections were excluded from the studies. As eosinophils are possibly involved in the response to helminth infections, adequate warning is included in the PI and this information is included as an

Risks	Strengths and Uncertainties
Studies C38072/3082 and C38072/3083 were 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. However the lack of efficacy observed may be that the study was not powered sufficiently to detect a difference. Further studies in children and adolescents would be warranted.	important identified risk in the RMP. No data are currently available on the possibility to reduce concomitant controller medication like OCS. No data are currently available in its use in patients with renal or hepatic failure. No formal clinical drug interaction studies have been performed with reslizumab. There is very limited data in its use in pregnant women.

First round assessment of benefit-risk balance

The benefit-risk balance of reslizumab for the proposed usage is favourable although a more defined population (that is patients on medium to high dose ICS plus another controller) should be considered.

The patient population studied were mostly GINA Stages 4/5 (80%), that is on treatment with inhaled ICS plus another treatment. The efficacy in GINA Stage 3 patients is uncertain, and for this subgroup of patients other treatments are available. LABAs and LTRAs have been available for many years and therefore safety is better established.

There are questions about the most appropriate treatment regime. A minimal number of doses were studied. Clearly, 3.0 mg/kg was more efficacious than 1.0 mg/kg or 0.3 mg/kg but it is unknown if 1.5 mg/kg, 2.0 mg/kg or 2.5 mg/kg for example, would be more efficacious. The duration of treatment is also not clearly established. It appears efficacy reaches a peak at a month and then stabilises. There is no recommendation as to whether patients then need to remain on treatment to receive benefits or could be weaned off treatment and the benefits preserved. If long term treatment is needed, there remain questions as to the safety of reslizumab over 5, 10 and 20 years and whether there is a change in immunogenicity or the development of treatment resistance over that time.

The risks associated with reslizumab therapy are considered low in view of the safety profile discussed earlier on. The main concern is about the safety imbalance in malignancies. This will require monitoring post market.

Overall, the observed reduction in 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 Stages 4/5).

First round recommendation regarding authorisation

At this stage, the clinical evaluator has no major concerns against approving reslizumab for registration however, would recommend a revised indication.

Reslizumab is indicated as:

> *'an add on maintenance treatment in adult patients with severe eosinophilic asthma with a blood eosinophil count of ≥ 400 cells/µL who are inadequately controlled on medium to high dose inhaled corticosteroids in combination with at least another controller'.*

This recommendation is subject to a satisfactory response to the questions and amendments to the PI.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For details of the clinical questions the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The second round assessment of benefits of reslizumab is unchanged as a result of the sponsor's responses including the clarification of the chosen eosinophil count threshold of ≥ 400 cells/µL and the inclusion of a more defined population (that is patients on medium to high dose ICS plus another controller) in the indication.

Second round assessment of risks

The sponsor has clarified concerns regarding immunogenicity. However, the duration of therapy and long term efficacy and safety beyond 36 months remain unknown.

Second round assessment of benefit-risk balance

Overall, the benefit-risk balance of reslizumab for the sponsor's proposed revised indication is favourable.

Second round recommendation regarding authorisation

At this stage, the clinical evaluator has no major concerns against approving reslizumab for registration for the sponsor's proposed revised indication:

> *'Cinqair is indicated as add on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite medium to high dose inhaled corticosteroids in combination with at least another controller (see Clinical Trials)'.*

This recommendation is subject to a satisfactory response to the amendments to the PI.

V. Pharmacovigilance findings

Risk management plan evaluation

Summary

- The sponsor has submitted an application to register a new biological entity, reslizumab (Cinqair/Cinqaero). Cinqair is proposed to be used for the treatment of severe eosinophilic asthma in adults. The proposed dosing regimen involves intravenous infusion of 3.0 mg/kg once every four weeks (dosage and administration).
- The sponsor has submitted EU-RMP version 1.2 (dated 20 May 2016; data lock point (DLP) 15 May 2016) and ASA dated 23 June 2016 in support of this application. The

sponsor has submitted the updated EU-RMP version 1.4 (dated 21 June 2016; DLP 20 June 2016) with ASA dated 14 February 2017 with its post first round response.

- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below:

Table 11: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Severe hypersensitivity reactions, including anaphylactic or anaphylactoid reactions	ü 4	ü 1	ü	–
Important potential risks	Parasitic (helminth) infections	ü	ü 1	ü	–
	Malignancy	ü	ü 1, 3	ü	–
Missing information	Paediatric patients < 18 years old	ü	ü 1	ü	–
	Elderly patients > 75 years old	ü	ü 1	ü	–
	Use during pregnancy	ü 4	ü 1, 2,	ü	–
	Use in breastfeeding	ü 4	ü 2	ü	–
	Long-term exposure, including long term immunogenicity	ü	–	ü	–
	Use in combination with immunosuppressant drugs therapy	ü	–	ü	–
	Effect on vaccination and the use of live/attenuated vaccines	ü	ü 1	ü	–
	Patients with non-white race	ü	ü 1	ü	–

1) Phase III clinical trials; 2) Active pregnancy surveillance program; 3) Long-term non-interventional study; 4) Specific event follow-up forms as a part of routine pharmacovigilance

The sponsor has proposed routine and additional pharmacovigilance to monitor the safety concerns.[39]

Routine risk minimisation has been proposed by the sponsor to mitigate all the safety concerns.[40]

Post-Round 2

The sponsor has updated the PI content as proposed by the clinical evaluator in response to the second round evaluation reports. There is no outstanding RMP issue for this submission.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available

[39] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[40] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is: Implement EU-RMP version 1.4 (dated 21 June 2016; DLP 20 June 2016) with ASA dated 14 February 2017 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Introduction

Background

Reslizumab is a humanized anti-human IL-5 monoclonal antibody (anti IL-5 mAb) of the immunoglobulin-G4-kappa (IgG4/$_K$) isotope, produced in mouse myeloma cells (NS0) by recombinant DNA technology. Reslizumab works by binding to IL-5, thereby preventing the binding of IL-5 to the IL-5 receptor and consequently reduces circulating and tissue eosinophils.

Severe asthma is defined as that which requires treatment with high dose inhaled glucocorticoids plus a second controller and/or systemic glucocorticoids to prevent asthma from being 'uncontrolled' or which remains uncontrolled despite this therapy.

Patients with eosinophilic asthma do not respond to inhaled glucocorticoids and require systemic glucocorticoids to control their asthma. They are less likely to be atopic/allergic. They have high levels of blood and tissue eosinophils and high levels of exhaled nitric oxide. These features may occur in association with severe sinus disease, nasal polyposis, and in a minority aspirin exacerbated respiratory disease (AERD).

Overseas registrations

Reslizumab has been approved for use in Europe with the following indications:

> *'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)'.*

Reslizumab has also been approved in the USA and Canada with the following indications:

> *'Cinqair the add on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype'.*

Other similar agents on the ARTG to treat severe asthma

An anti-IL-5 antibody, mepolizumab (Nucala) was registered in Australia in February 2016 as add on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over. Reslizumab has a different International non-proprietary name (INN) from mepolizumab as it has a different immunoglobulin isotype (IgG4/$_K$ compared with IgG1).

Omalizumab, (Xolair), a recombinant humanised monoclonal antibody (mAb) (IgG1) was considered by ADEC at its December 2005 meeting and recommended for approval for the management of adult and adolescent patients with moderate allergic asthma, who are already being treated with inhaled steroids and who have raised serum immunoglobulin E

levels. It was also recommended for approval in children at its October 2010 meeting. The currently registered indications in Australia are as follows:

> *'Allergic Asthma*
>
> *Children 6 to < 12 years of age*
>
> *In children aged 6 to < 12 years, Xolair is indicated as add on therapy to improve asthma control in patients with severe allergic asthma who have documented exacerbations despite daily high dose inhaled corticosteroids, and who have immunoglobulin E levels corresponding to the recommended dose range.*
>
> *Adults and adolescents ≥ 12 years of age*
>
> *Xolair is indicated for the management of adult and adolescent patients with moderate to severe allergic asthma, who are already being treated with inhaled steroids, and who have serum immunoglobulin E levels corresponding to the recommended dose range'.*

Quality

Reslizumab is a humanised anti-human interleukin-5 monoclonal antibody (anti-IL-5 mAb) of the immunoglobulin-G4 kappa ($IgG4/_K$) isotype, which contains the complementarity determining regions (CDRs) (that is, antigen binding regions) of the original rat antihuman antibody 39D10 grafted onto a human framework. A diagrammatic representation is shown in Figure 1.

Reslizumab drug product (DP) is a preservative free, sterile aqueous solution presented as 100 mg in a single use 10 mL glass vial. Drug product is formulated as 10 mg/mL reslizumab in 20 mM sodium acetate, 7% sucrose, pH 5.5. The drug product is diluted in sterile 0.9% sodium chloride solution prior to infusion.

Reslizumab drug substance is expressed in a murine myeloma NS0 cell line (SHP1), which has been engineered for high product expression using a glutamine synthetase promoter system. The manufactured antibody has a theoretical molecular weight of 147 kDa and is composed of 2 heavy chains and 2 light chains.

There are no objections on quality grounds to the approval of Cinqair, Cinqaero reslizumab concentrated solution for infusion 100 mg/10 mL. However the evaluator had the following concerns:

- The storage conditions for the product are: 36 months when stored at 2°C to 8°C. Refrigerate. Do not freeze. The evaluator concluded that temperature excursions during shipping should not be approved and where temperature excursions do occur affected batches should be quarantined until an application to vary has been considered by the TGA. This approach has been agreed to by the sponsor and included in the conditions of registration.
- GMP certification for a number of manufacturing sites has yet to be confirmed (under review by TGA). Registration of this product should not be approved until GMP issues are resolved. The sponsor continues to negotiate with TGA's Manufacturing Quality Branch on GMP certification issues and these are being resolved.
- The evaluator is concerned that the source and nature of the visible particles seen in drug product is not fully explained. There appears to be no detectable effect on potency associated with the presence of particles and oddly the presence of particles does not seem to be associated with any other measurement of degradation. The presence of a final filter at the point of injection to remove particulates somewhat addresses the evaluator's concern but does not necessarily adequately address the

issue of what the particulates are and what other changes in DP may be associated with their presence. This information could be provided to TGA post-market area for their reference.

Recommended conditions of registration

1. It is a condition of registration that goods which do not meet all Australian Market Authorisation requirements must not be supplied in Australia. This includes, but is not limited to, good which:

   a. differ from their approved ARTG entry and Certified Product Details (CPD);

   b. have not been maintained at the approved storage conditions, or where applicable within the permitted temperature excursion ranges, as recorded in the ARTG entry and on the CPD;

   c. have not been tested against the approved Australian specifications;

   d. any other deviation from the Market Authorisation requirements.

   Where there is evidence that failure to comply with Australian Market Authorisation requirements does not result in goods of unacceptable quality, Sponsors may seek an exemption from this condition by applying to temporarily vary the conditions of registration (for the affected batches) under s.28 of the Act.

2. It is a condition of registration that, as a minimum, each batch of Cinqair, Cinqaero Reslizumab Concentrated Solution for Infusion 100 mg/10 mL strength imported into/manufactured in Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

3. Certified Product Details

   The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Nonclinical

The evaluator mentions that IL-5 is the major cytokine responsible for the proliferation, differentiation, activation, survival and recruitment of eosinophils. In vitro, reslizumab was shown to bind to human IL-5 with picomolar affinity, to inhibit the binding of IL-5 to its receptor, and to inhibit IL-5-stimulated cell proliferation in a human cell line. In vivo, it attenuated pulmonary eosinophilia induced by antigen challenge in multiple laboratory animal species (mice, guinea pigs and cynomolgus monkeys), acting with a long duration of action.

The evaluator also mentions that the animals used in the toxicity programme were pharmacodynamically responsive to reslizumab. Reslizumab was found to display cross reactivity with brain link protein-1 (BRAL1; monkey and human forms), a structural protein involved in cell matrix interactions.

There were no significant effects observed in the safety and general toxicity studies. Single dose toxicity studies in mice, rats and monkeys demonstrated a low order of acute toxicity for reslizumab.

The evaluator states that the pivotal repeat dose toxicity studies were of 6 months duration and were conducted in mice and monkeys. Though no toxicity was observed, the studies used low doses, low multiples of the clinical systemic exposure obtained at the maximum dose level tested (25 mg/kg) in both species; yielding 1.5 times (mice) and approximately 3 times (monkeys) the serum AUC in patients; this fell short of the approximately 10 fold exposure multiple recommended in the absence of toxicity or saturated pharmacology in the guideline.[2] A 6 month carcinogenicity study in transgenic mice, which employed far higher doses and more frequent administration (516 mg/kg IV every 2 weeks; yielding approximately 150 times the clinical exposure), offers adequate support for the general safety of reslizumab.

No toxicological significance is seen to be attached to the finding of BRAL-1 cross reactivity by reslizumab.

Reslizumab was not genotoxic in assays for bacterial mutagenicity and clastogenicity in vitro, and not carcinogenic in an adequately conducted study in transgenic mice.

Male and female fertility (mice), embryofetal development (mice and rabbits) and pre/postnatal development (mice) were unaffected by reslizumab. Again, the maximum dose level tested in the reproductive toxicity studies (estimated to yield up to approximately 4 times the systemic exposure of patients), fell short of level recommended in the relevant ICH guideline.[2]

Pregnancy Category B1, as proposed by the sponsor, is considered to be acceptable, the evaluator.**Error! Bookmark not defined.**

The evaluator states that a significant deficiency in the non-clinical package was the, 'inappropriately low dose selection in the general repeat dose toxicity studies and in the reproductive toxicity studies"; however, the evaluator concludes that it is not critical as safety is obtained from other sources.

The PI amendments proposed by the evaluator have been incorporated by the sponsor.

Overall, there are no objections to the registration for the proposed indication.

Clinical

Pharmacokinetics

Four studies are included in the evaluation. The evaluator mentions that the pharmacokinetics summary is adapted from EMA Assessment Report;[33] and the FDA Clinical Review of Reslizumab.[34]

After a single IV 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. The serum concentrations generally decline from peak in a biphasic manner. Reslizumab pharmacokinetics in healthy adults and patients does not appear to be different to a significant extent.

There was dose proportionality observed over the dose range of 0.3 mg/kg to 3.0 mg/kg.

Serum concentration time curves after multiple dosing were similar to that observed after single dosing with an accumulation ratio of approximately1.5 to 1.9 fold. This is in line with the elimination half-life of about 24 days and dosing every 28 days.

The volume of distribution of reslizumab is approximately 5 L, suggesting minimal distribution to the extravascular tissues. This is similar to other monoclonal antibodies.

Reslizumab clearance is approximately 7 mL/hour. Similar to other monoclonal antibodies, reslizumab is 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 effect of albumin on the pharmacokinetics of reslizumab was investigated, but no data were available for albumin levels below 3.5 g/dL. No data were available for IL-5 levels.

The clinical evaluator mentions that, 'the PopPK analysis did not show any effect of renal or hepatic impairment on the pharmacokinetics of reslizumab, however only data points for mild renal or hepatic impairment were available. Renal or hepatic impairment is not expected to have an effect on the pharmacokinetics of reslizumab: it has a molecular mass of 147 kDa and therefore is not excreted in the urine; it is cleared by catabolism and not by the liver. There were insufficient data to confirm a lack of effect of moderate/severe renal or hepatic impairment on pharmacokinetics'. There were no significant effect in the pharmacokinetics of reslizumab by age (adults < 65 years versus 65 + years) or gender.

At a fixed dose, patients with higher body weight have more rapid elimination; however, weight based dosing (3.0 mg/kg) provides similar exposure across patients with different body weights.

Pharmacodynamics

Effect on sputum eosinophils: The effect of reslizumab in patients with asthma and elevated sputum eosinophil counts (at least 3%) was evaluated in a 15 week, Phase II, randomised, double blind, placebo controlled clinical study with reslizumab 3.0 mg/kg. In this study, the percentage of sputum eosinophils was reduced from a mean baseline value of 17.4% (SD: 15.9%) by 82% at the end of therapy in the reslizumab group.

Effect on blood eosinophils: In clinical studies with reslizumab 3.0 mg/kg, decreases in blood eosinophil counts were seen following the first dose and maintained through 52 weeks of treatment with no signs of tachyphylaxis. In pooled data, similar results were observed. Decreases in blood eosinophils were related to reslizumab levels.

Dose finding studies

Study P00290 was a Phase II, multicentre, randomised, evaluator blind, placebo controlled, parallel group study in 211 patients (at least 18 years of age) with severe, persistent asthma of at least 1 year duration. Patients received one of 3 treatments: reslizumab 0.3 mg/kg, reslizumab 1.0 mg/kg or matching placebo. No significant differences were noted for the comparison of 0.3 mg/kg or 1.0 mg/kg reslizumab versus placebo for any of the efficacy parameters evaluated.

Study 38072/3081 was a 16 week, randomised, double blind placebo controlled study to evaluate the efficacy and safety of reslizumab (0.3 or 3.0 mg/kg). Results for the primary endpoint, change from baseline in FEV1 over 16 weeks, demonstrated statistically significant improvement at both dose levels, with a larger treatment effect observed for the higher dose (0.160 L versus 0.115 L). Greater magnitude of improvement was reported with the higher dose, in patient reported measures of asthma control such as the asthma control questionnaire.

A significant deficiency in this study was that only two doses were used; the doses used were of a tenfold difference and thus, not sensitive to identify a dose separation. This study was conducted concurrently with the pivotal studies and could not feasibly contribute to dose selection. The Delegate has not considered this further as it is only a 16 week dose finding study.

The paucity of dose finding studies was a major limitation in the clinical development program.

Efficacy

Pivotal Studies 38072/3082 and 38072/3083

The clinical evaluator has considered these studies together as their design was essentially the same. Both studies were Phase III, multicentre, randomised, double blind, placebo controlled, parallel group studies to evaluate the efficacy, safety, and immunogenicity of treatment with reslizumab, at a dosage of 3.0 mg/kg administered IV once every 4 weeks relative to baseline, in asthma patients (12 through 75 years of age) with an eosinophilic phenotype. The study enrolled patients with asthma and serum eosinophil counts > 400/ µL, inadequately controlled with medium to high dose ICS with or without other treatments, and a history of previous exacerbations (details of the inclusion and exclusion criteria are included in Attachment 2 Section 7.2.1.2). These patients would correspond to GINA Stages 3 to 5. After the end of treatment visit, patients enrolled in an available open label, long term study (Study C38072/3085) or returned for an assessment 90 (± 7) days after their end of treatment visit.

The primary efficacy variable was frequency of asthma exacerbations per patient during the 52 week treatment period. The criteria used to define exacerbation are described in Attachment 2 Section 7.2.2.4. There are also multiple secondary endpoints described in Section 7.2.2.4.

Patients were randomly assigned in a double blind manner to reslizumab or matching placebo (1:1 ratio) via interactive response technology (IRT) at the baseline visit.

Sample size calculations are detailed Attachment2 Section 7.2.2.7. A total of 460 patients, 230 patients per group, provided approximately 90% power at the significance level 0.05 to detect a 33% reduction in clinical asthma exacerbation (CAE) rate by reslizumab as compared with placebo. This power estimate was based on computer simulations with data generated from the negative binomial (NB) distributions. For the Study C38072/3082, 480 patients (240 patients per treatment group) were planned to be enrolled. For the Study C38072/3083, 460 patients (230 patients per treatment group) were planned to be enrolled.

The patient disposition table extracted from the evaluation report is given below in Table 12.

Table 12: Patient disposition by treatment group (Studies C38072/3082 and C38072/3083, 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)

Within each study, subject demographics and baseline characteristics generally were balanced among the 2 treatment groups.

The studies had the following limitations:

- The number of adolescents and elderly included is limited (about 5%). Only few patients were included in the age group 12 to 17 years (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 = 77) as can be expected for an asthmatic population.
- The study population included patients with poorly controlled asthma on moderate to high dose ICs with or without other medications. Approximately 85% were using LABA. Thus, in some patients, additional treatment with LABA may have been considered prior to using reslizumab
- The number of patients completing the study was around 89% due to protocol variations.
- the definition of exacerbations was broad:

  'Frequency of clinical asthma exacerbation defined as either systemic corticosteroids use or a two fold increase in inhaled corticosteroid (ICS) for ≥ 3

days, or an asthma related emergency visit/hospitalisation accompanied by a worsening in clinical signs and symptoms of asthma'.

Primary efficacy endpoint

'Compared to placebo, the mean rate of asthma exacerbation was statistically significantly reduced among patients administered reslizumab in both studies. The point estimate for exacerbation rate ranged from 0.86 to 0.90 per year in reslizumab-treated patients versus 1.80 to 2.11 per year in placebo patients. The overall reduction was 54% (rate ratio (RR): 0.46, 95% CI 0.37, 0.58) for the total population based on the integrated data from Studies C38072/3082 and C38072/3083. The proportion of patients who did not experience an asthma exacerbation during the entire treatment period was higher in the reslizumab group (63% and 75%) compared with the placebo group (46% and 55%), in Studies C38072/3082 and C38072/3083, respectively'.

The subgroup analysis for CAEs is discussed in Attachment 2 (see Section 7.2.2.13). These were analysed by age group, sex, race, geographical region, anti-drug antibody (ADA) results, OCS use at Baseline, LABA at baseline, and so on. 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).

In relation to secondary efficacy endpoints (see Attachment 2, Table 11), treatment effects on FEV1 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 overall symptom scores (AQLQ, ACQ and ASUI). The proportion of responders (minimal of ≥ 0.5 point improvement ACQ or AQLQ) was increased with reslizumab compared to placebo. 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 C38072/3082. Corresponding data for Study C38072/3083 were 81% and 62% (p = < 0.0001) at week 52 in the reslizumab and placebo group, respectively. The evaluator considered these changes to be clinically significant. Details are found in Attachment 2, Table 11.

Supporting studies

Studies 38072/3084, Res-5-0010, 0002, 0004, NIH Protocol 01-1-015

Study 38072/3084

This is a study conducted on subjects with moderate to severe asthma, unselected for blood eosinophils; the duration was also short, 16 weeks. Primary efficacy variable was the change from baseline, FEV1.

The results for the overall population (unselected for baseline eosinophils) was change in baseline FEV1 over 16 weeks; this study did not show a significant treatment effect (0.076 L, p = 0.0697 and 0.068 L, p = 0.1719, respectively). Likewise, no treatment effect was observed at week 16 for the group of patients with a baseline eosinophil count < 400/µL as a group (0.033 ml, p = 0.5422).

The primary efficacy analysis, a linear regression model, did not show a significant interaction between baseline blood eosinophil count and change in FEV1 at Week 16.

Long term Study C38072/3085

Patients included in Study C38072/3085 (an open label extension study) had completed Study C38072/3081, C38072/3082 or C38072/3083 or received at least two doses of study drug in Study C38072/3081. The primary objective was to obtain long term safety data (up to 24 months). The secondary objective was to study the long term efficacy of

reslizumab based on change from baseline in pulmonary function tests (PFT) (FEV1, % predicted FEV1, FVC, FEF 25%-75%)[41] and other measures of asthma control (short-acting beta-agonist (SABA) use, ASUI, ACQ and AQLQ).

This study was prematurely terminated based on 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 the reslizumab experienced group, baseline lung function was maintained through the treatment period; values at endpoint were similar to baseline. 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.

Overall efficacy conclusions

The evaluator states that:

> *'the results of the studies comprising the clinical efficacy program provide evidence for the efficacy of IV reslizumab 3.0 mg/kg administered once every 4 weeks for the treatment asthma in adult patients with elevated eosinophils who are not well controlled by medium to high dose ICS (440 µg/day fluticasone propionate or equivalent) and who mostly (82 to 87%) used a second controller medication (that is patients already on ICS based standard of care therapy).*
>
> *Reslizumab treatment resulted in statistically significant reduced exacerbations, relieved asthma symptoms, and improved lung function in the patient population. These outcome changes were clinically significant. Most patients were severe eosinophilic asthma patients (GINA Stages 4/5) for which limited other treatment options exist.[8] The endpoints comply with the adopted EU guidelines'.*

The limitation was the data on the elderly (≥ 65 years: n = 32) in the Studies C38072/3082 and C38072/3083 was small in number. The adolescent population was also small (n = 14) and subgroup analyses of the primary endpoint did not show results in this population. However, adolescents are excluded from the indication.

Safety

A total of 2,195 patients or healthy subjects have been exposed to at least 1 dose of reslizumab in the clinical development program. Considering all studies (except for Study NIH 01-I-0155) in the reslizumab clinical development program, 1,189 patients were treated for at least 6 months, 922 patients were treated for greater than 12 months, 371 patients were treated for greater than 24 months, and 64 patients were treated for greater than 36 months. The maximum exposure in the program was 1,340 days (44 months).

In 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 placebo and reslizumab 3.0 mg/kg treatment groups; see Attachment 2, Section 8.3.1.2.

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 incidences of events was similar or lower for the reslizumab group, apart from neoplasm, benign, malignant and unspecified system organ class (SOC); see Attachment 2, Table 22.

[41] FEV1: forced expiratory volume in 1 second, % predicted FEV1: actual FEV1 divided by standard predicted FEV1 times 100%; FVC: forced vital capacity, FEF 25%-75%: forced expiratory flow during the middle half of the forced vital capacity

The long term exposure (> 1 year) to reslizumab did not indicate a notable increase in adverse event incidence.

The most commonly reported AE was asthma, lower in the reslizumab group. The type and incidence of events were as to be expected in a moderate to severe, predominantly adult asthma population, that is, events of upper respiratory tract infection (URTI). The next common Preferred Terms (PTs) (> 5%) were nasopharyngitis and URTI. They were evenly distributed between groups, see Attachment 2; Table 23.

Severe events occurred in 7% and 10% in the reslizumab and placebo groups. Asthma, pneumonia, cough, sinusitis and influenza were reported.

The percentage of treatment related adverse events in the reslizumab treated and placebo groups were similar (12% to 13%). The most frequent treatment related adverse events were headache, asthma, nausea, fatigue and increased blood creatine phosphokinase (CPK). Increased blood CPK were associated with myalgia.

Administration site reactions were similar between groups (2%). None were serious and resulted in discontinuation.

There were five cases of anaphylaxis in the reslizumab group (< 1%) and no cases in the placebo group were observed. Three out of the five anaphylactic reactions (that is 3 out of 1,028 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 shortly 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.

Malignancies are discussed in Section 8.4.9 of Attachment 2. A total of 24 patients were diagnosed with malignancy: 3 placebo treated patients and 21 reslizumab treated patients. In the reslizumab group, in 2 patients, it was a recurrence of previous malignancy. The most commonly reported malignancies in reslizumab treated patients were skin cancers (n = 8). There were 13 non-skin cancers reported; 8 of these were of the most common tissue types of cancer in the general adult population (that is lung, breast, prostate, and colon). The remaining 5 malignancies also included 1 anal cancer, 1 diffuse large B-cell lymphoma and 1 plasmacytoma.

The evaluator mentions that there were no clusters of specific types of malignancies that would suggest an immunosuppressive mechanism. However there is a need to monitor the rate of malignancy due to the concern of a potential immunomodulatory role of reslizumab.

A clinically significant imbalance in CPK elevations was observed. Potentially clinically significant 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). See Attachment 2, Section 8.4.3.

Myalgia occurred marginally in greater frequency with reslizumab (0.97% versus 0.55%). These were mild, transient and did not recur with continuing reslizumab treatment.

Serious adverse events appeared in 6% in reslizumab group and 9% in placebo. There was no specific trend observed. Asthma was the most common serious event reported.

There were three deaths during the open label Study 3085 and were not considered related to the study drug.

There were no significant laboratory abnormalities.

Overall, the evaluator concludes that the safety profile is acceptable.

Clinical evaluator's recommendation

The evaluator recommends that the risk benefit profile for the revised indication is acceptable.

Risk management plan

The sponsor has proposed routine and additional pharmacovigilance to monitor the safety concerns. Routine risk minimisation has been proposed by the sponsor to mitigate all the safety concerns. An outstanding concern was that the evaluator recommended that Cinqair be prescribed by a specialist experienced in the diagnosis and treatment of severe asthma. This was in line with the Nucala PI.

Table 11 (see above) shows the summary of safety concerns and the pharmacovigilance and risk minimisation strategies.

Suggested wording of condition of registration:

- Implement EU-RMP version 1.4 (dated 21 June 2016; DLP 20 June 2016) with ASA dated 14 February 2017 and any future updates as a condition of registration.

Risk-benefit analysis

The major issue affecting the registration of the product is the GMP clearance. Registration cannot proceed until this is resolved.

1. The indication has been revised to:

   'Cinqair is indicated as add on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite medium to high dose inhaled corticosteroids in combination with at least another controller (see Clinical Trials)'.

   as per the clinical evaluator's recommendation (and is in line with the EU indication).

2. The efficacy profile is acceptable to support the revised indication.

3. The safety signals identified in the pivotal studies were anaphylaxis, raised CPK and malignancy. These have been satisfactorily addressed in the draft PI. The concern of the evaluator regarding the potential for severe hypersensitivity reaction is addressed by the statement:

   'Cinqair should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis. The patient has to be observed over the duration of the infusion and for an appropriate period of time afterwards. Patients should be instructed in how to recognise symptoms of serious allergic reactions'.

4. The definition of eosinophilic asthma is based on more than blood eosinophil count, but also clinical phenotype (resistant to inhaled steroids, older age at presentation). Some clinicians use a lower blood eosinophil count of > 150 cells/µL. The evaluator initially recommended that the cut-off regarding ≥ 400 cells/µL blood eosinophils be included in the indication as this was an inclusion criterion in the pivotal studies.

   The sponsor states that patients with blood eosinophilic count ≥ 400 cells/µL are expected 'to experience the greatest clinical improvement from reslizumab therapy'. The sponsor maintains that 'patients with eosinophilic asthma who require daily maintenance corticosteroid therapy and have a blood eosinophil count < 400 cells/µL may also benefit from reslizumab. Therefore, the treating physician should use their discretion as to whether or not a patient has the eosinophilic asthma phenotype and is an appropriate candidate for reslizumab treatment'.

It is noted that the registered indication for another anti-IL-5 agent Nucala, mepolizumab does not specify this cut-off.

5. Prescribing should occur in consultation with a specialist in light of the severity of asthma and need to be sure of the diagnosis prior to treatment. However it is recognised that a GP is usually the main doctor responsible for the management of patients with asthma.

   The following wording is proposed:

   'Cinqair should be prescribed by a medical practitioner in consultation with a specialist respiratory physician, experienced in the diagnosis and treatment of severe asthma'.

6. It is noted that particulate matter is present in the drug product. Use with a filter is recommended. This concern should be highlighted to the RMP team.

The Committee for Medicinal Products for Human Use (CHMP) report had the following comments about the particles in the drug product:

The robustness of the drug product formulation has been considered by varying the formulation as follows: protein concentration 9 to 11 mg/mL, sodium acetate concentration 15 to 25 mM, sucrose concentration 6% to 8% and pH 5 to 6. This study raises concerns on the robustness of the formulation and its control as many (heavy) visual particulates were found at the higher buffer concentration (25 mM sodium acetate; target is 20 mM) and pH (6.0; target is 5.5).

As particles are observed routinely in the drug 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.

It does not appear that the formulation study considered specific efforts to reduce the levels of visible particles present in the drug product and adequate justification as to why the presence of these particles should be accepted has not been provided. Further information is requested in relation to these points. Furthermore, the characterisation studies carried out to verify the proteinaceous nature of the particles are considered insufficient. The applicant has been asked to investigate further methods to characterise the particles as proteinaceous in nature and to demonstrate the absence of non-proteinaceous material in the particles. Following transportation, the particles continue to be present in the vials, though qualitatively appear to be disintegrated into slightly smaller particles. It is stated that these particles are in the sub-visible range. It should be confirmed that the drug product complies with the specification for sub-visible particles after shipping (in accordance with Ph. Eur. 2.9.19) and that the smaller visible particles (present after agitation) are also removed by the proposed in-line filter.

Delegate's considerations

Questions to the sponsor

1. Please update the TGA in relation to the outstanding GMP clearances. This submission cannot proceed to registration until these issues are resolved.
2. Please comment on the nature of the solid particles in the drug product. What size are these? What would be the anticipated outcome for a patient if a filter was not used to administer reslizumab?

Summary

· Eosinophilic asthma is one of several asthma phenotypes. It is characterised by asthma refractory to inhaled steroids.

- The pivotal studies, patients had blood eosinophils ≥ 400 /µL as an inclusion criterion. This is not included in the proposed indication. Other agents used to treat eosinophilic asthma have used different criteria for eosinophils in the clinical trials
- Efficacy has been established in comparison with high dose ICS and another controller.
- There are no major safety concerns.
- The solution for injection contains solid particles. These have no apparent effect on efficacy or safety. Use with a filter is recommended.

Proposed action

The Delegate had no reason to say, at this time, that the application for reslizumab for the treatment of eosinophilic asthma should not be approved for registration.

The Delegate proposed to register Cinqair/ Cinqaero reslizumab, concentrated solution for intravenous infusion, vial, 100 mg/10 mL, for the indication:

> *'Cinqair / Cinqaero is indicated as add on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite medium to high dose inhaled corticosteroids in combination with at least another controller (see Clinical Trials)'.*

The PI will require some amendments in relation to dosing and administration.

The Delegate endorsed the conditions imposed by the quality evaluator and the RMP evaluator

Request for ACPM advice

1. Should the indication specify the blood eosinophilic count of ≥ 400 cells/µL?
2. Do you agree that prescribing occur in consultation with specialists in light of the need for accurate diagnosis, severity of asthma, and the potential to cause anaphylaxis?
3. Does the committee have experience with other products containing particulate matter. How practical is a filter? Is the PI adequate?

Response from sponsor

The sponsor acknowledges the Delegate's view that Cinqair/ Cinqaero has a positive risk-balance for the indication proposed:

> *'Cinqair [Cinqaero] is indicated as add on therapy in patients with severe eosinophilic asthma inadequately controlled despite medium to high dose inhaled corticosteroids in combination with at least another controller (see Clinical Trials)'.*

Product background

Reslizumab is a humanised antihuman interleukin-5 monoclonal antibody (anti-IL-5-mAb) of the immunoglobulin-G4 kappa (IgG4/k) isotype, developed to reduce exacerbations, relieve symptoms and improve lung function in adult patients with asthma and elevated numbers of eosinophils who are inadequately controlled on inhaled corticosteroids.

Sponsor comments: questions to ACM

1. Should the indication specify the blood eosinophilic count of ≥ 400 cells/µL?

The sponsor addressed the use of a specific blood eosinophilic count of ≥ 400 cells/µL in the response to the first round clinical efficacy Question 1. It is the sponsor's view that, with regard to eosinophil threshold, that proposed indication in patients with 'severe

eosinophilic asthma' provides sufficient identification of the appropriate patient for reslizumab without unnecessarily restricting access in patients who may have a lower blood eosinophil count for whom their disease is still mediated by eosinophils.

The sponsor notes that the Nucala (mepolizumab) Australian Product Information does not describe specific eosinophil count values in the approved indication wording, with specific starting and maintenance counts of ≥ 150 cells/µL and ≥ 300 cells/µL, respectively, presented under the 'Clinical Trials' heading only.

2. *Do you agree that prescribing occur in consultation with specialists in light of the need for accurate diagnosis, severity of asthma, and the potential to cause analphylaxis?*

The sponsor has agreed to and adopted the wording proposed by the Delegate with regard to specialist respiratory physician prescribing, evident in the Australian PI provided in the response:

> *'Cinqair should be prescribed by a medical practitioner in consultation with a specialist respiratory physician, experience in the diagnosis and treatment of severe asthma'.*

The proposed reference to medical practitioner in addition to specialist is underpinned by experience within the clinical development program. In Phase III clinical studies investigating reslizumab in patients with eosinophilic asthma, a number of the investigators were either family practitioners or general practitioners. While it is acknowledged that the majority of prescribers will be specialists in the respiratory field, 'medical practitioner' best reflects the potential range of prescribers within the diverse Australian health system, providing particularly for continuity of care in remote and regional settings.

3. *Does the committee have experience with other products containing particulate matter? How practical is a filter? Is the PI adequate?*

The sponsor directs the ACM to review the response provided in this document to 'Questions to the sponsor', Question 2 (below).

Questions to the sponsor

1. *Please update the TGA in relation to the outstanding GMP clearances. This submission cannot proceed to registration until these issues are resolved.*

All open GMP certification activities have been resolved. All sites have acceptable GMP currency allowing for the reslizumab application for registration to progress to approval.

2. *Please comment on the nature of the solid particles in the drug product. What size are these? What would be the anticipated outcome for a patient if a filter was not used to administer reslizumab?*

Details regarding the nature and size of the solid particles and their potential impact on patient safety were submitted to the TGA as part of the initial application dossier, with the source of visible particles readdressed in the sponsor's response to the TGA's second round evaluation dated 6th April. The relevant content is excerpted below for the ease of review.

   a. *Nature and particle size*

'Reslizumab drug product may contain proteinaceous particles which is a known phenomenon for many biologics therapeutics. Reslizumab particles have been thoroughly characterized and their physical and chemical properties are well understood."…."The size of the visible particles was determined to be around 100 µm' … 'the number of visible proteinaceous particles are typically > 10 particles per vial'.

   b. *Administration in the absence of an in-line filter*

"Consideration was given during clinical development to potential impact on patient safety due to the presence of particles, which have been observed in a majority of the reslizumab drug product lots. The current practice requires the use of an in-line filter, prior to administration of reslizumab. However, in early clinical development, there were a few drug product lots that were used without an inline filter. In over 2,000 subjects treated with reslizumab, low-titre, frequently transient anti-reslizumab antibodies were detected in 5% asthma patients receiving reslizumab at 3 mg/kg with no apparent impact on systemic exposure, clinical pharmacodynamics, efficacy or safety. Accordingly, the applicant considered the visible particles in the drug product as acceptable, with no noticeable impact on safety during early clinical development and no demonstrable impact on product quality over the proposed shelf life. The use of an in-line filter will ensure that the proteinaceous particles are not included during product administration, thereby removing this as a specific concern for patient safety."

Pre-ACM response: sponsor's comments on status of suspected unexpected serious adverse reactions (SUSAR)

Teva Pharma Australia advises that there have been no SUSARs associated with reslizumab since the data cut-off for the Integrated Safety Summaries dated 1 September 2014.

Teva submit for ACM's information the latest Periodic Safety Update Report (PSUR) (No. 923/03/17 dated 13 April 2017) for the period 16 August 2016 to 16 February 2017.

Pre-ACM response: sponsor's comments on foreign labelling

The Australian application for registration of reslizumab concentrated solution for intravenous infusion (100 mg/10 mL) was based upon a dossier submitted to, and subsequently approved in, the European Union. As such, the Australian PI for Cinqair is based upon the Cinqaero Summary of Product Characteristics (SmPC) for the equivalent European registration. The format and content of information presented in Cinqair (AU) is consistent with that of Cinqaero (EU).

For ACM's reference, the European SmPC for Cinqaero and United States Prescribing Information for Cinqair are provided.

Advisory committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Cinqair/Cinqaero vial containing 100 mg/10 mL of reslizumab to have an overall positive benefit-risk profile for the amended indication:

> *'Cinqair is indicated as add on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite medium to high dose inhaled corticosteroids in combination with at least another controller (see Clinical Trials)'.*

In making this recommendation the ACM:

- noted patients with eosinophilic asthma do not respond to inhaled glucocorticoids and require systemic glucocorticoids to control their asthma. They are less likely to be atopic/allergic and have high levels of blood and tissue eosinophils.
- recommends that GMP clearance is resolved to the satisfaction of TGA.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA; and
- negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Should the indication specify the blood eosinophilic count of ≥ 400 cells/µL?*

The ACM agreed that the indication specify the blood eosinophilic count of ≥ 400 cells/µL. ACM noted that submitted data clearly shows effect is only evident when the blood eosinophilic count is above 400 cells/µL.

2. *Should the prescribing be restricted to specialists?*

The ACM agreed that prescribing by medical practitioners occur in consultation with specialist respiratory physician experienced in the diagnosis and treatment of severe asthma due to the need for accurate diagnosis, severity of asthma, and the potential to cause anaphylaxis.

3. *Please comment on the concerns about the solid particles in the drug product and advice to use with a filter.*

The ACM agreed that a filter is recommended and that the concerns about the solid particles in the drug product be highlighted in the risk management plan and PI.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Additional comments

The ACM noted the imbalance in malignancies between the reslizumab and placebo group. No such imbalance was observed with the other drug in this class mepolizumab. The relatively short duration of the trial and the broad range in malignancies were noted. There was a comment that reslizumab may unmask malignancies in patients. It was recommended the Delegate reconsider risk mitigation strategies.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cinqair/Cinqaero reslizumab 100 mg/ 10 mL concentrated solution for intravenous infusion indicated for:

> *'Cinqair/Cinqaero is indicated as add on therapy in adult patients with severe eosinophilic asthma (blood eosinophil count ≥ 400 cells/µL) (see Clinical Trials)'.*

Specific conditions of registration applying to these goods

- The reslizumab EU Risk Management Plan (RMP), version 1.4, dated 21 June 2016 (data lock point 20 June 2016) with Australian Specific Annex, dated 14 February 2017, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Batch Release Testing and Compliance with Certified Product Details:

1. It is a condition of registration that goods which do not meet all Australian Market Authorisation requirements must not be supplied in Australia. This includes, but is not limited to, good which:
    a. differ from their approved ARTG entry and Certified Product Details (CPD);
    b. have not been maintained at the approved storage conditions, or where applicable within the permitted temperature excursion ranges, as recorded in the ARTG entry and on the CPD;
    c. have not been tested against the approved Australian specifications;
    d. any other deviation from the Market Authorisation requirements.
2. It is a condition of registration that, as a minimum, each batch of Cinqair and Cinqaero reslizumab concentrated solution for infusion 100 mg/10 mL strength imported into/manufactured in Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Attachment 1. Product Information

The PI for Cinqair approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>. The PI for Cinqaero is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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