



Australian Government

Department of Health

Therapeutic Goods Administration

# Australian Public Assessment Report for mepolizumab (rch)

Proprietary Product Name: Nucala

Sponsor: GlaxoSmithKline Australia Pty Ltd

**March 2017**

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- 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.

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## Common abbreviations

Abbreviation	Meaning
ACS	Asthma control score
ACQ	Asthma control questionnaire
ACSOM	Advisory Committee on the Safety of Medicines
ADA	Antidrug antibody
ADEC	Australian Drug Evaluation Committee
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Aminotransferase
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
AUEC <sub>eos(0-Day 84)</sub>	Area under the absolute blood eosinophil time curve to Day 84 for subset of subjects with blood eosinophil data
BMI	Body mass index
BSV	Between subject variability
CD	Circular dichroism
CI	Confidence interval
cIEF	Capillary Isoelectric Focusing
CL	Plasma clearance
CL/F	Apparent plasma clearance
C <sub>max</sub>	Maximum plasma concentration
CMI	Consumer Medicines Information
CSR	Clinical study report
cumAUC <sub>(0-Day 84)</sub>	Cumulative plasma mepolizumab AUC to Day 84
cumAUC <sub>(0-Day 140)</sub>	Cumulative plasma mepolizumab AUC to Day 140

Abbreviation	Meaning
EC <sub>50</sub>	Concentration associated with 50% maximal effect
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Emergency department
ED <sub>50</sub>	Dose associated with 50% maximal effect attributable to drug
eDiary	Electronic diary
EGPA	Eosinophilic granulomatosis with polyangiitis
EoE	Eosinophilic oesophagitis
ELISA	Enzyme linked immunosorbent assay
E <sub>max</sub>	Maximum change from baseline in blood eosinophils
eNO	Exhaled nitric oxide
EQ-5D	EQ-5D health outcomes questionnaire
ERS	European Respiratory Society
F	Absolute bioavailability
FDA	Food and Drug Administration (USA)
FeNO	Fractional exhaled nitric oxide
FEV <sub>1</sub>	Forced expiratory volume in one second
GCP	Good clinical practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
H	Hour/s
HES	Hypereosinophilic syndrome
IC <sub>50</sub>	Concentration associated with 50% maximal effect
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IDMC	Independent Data Monitoring Committee

Abbreviation	Meaning
ID <sub>50</sub>	Dose associated with 50% of the maximal inhibition effect
IgE	Immunoglobulin E
IL-5	Interleukin-5
IRB	Institutional Review Board
ISS	Integrated Summary of Safety
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive voice response system
KA	Absorption rate constant
LABA	Long acting beta 2 agonist
LFT	Liver function test
LLQ	Lower limit of quantification
Max <sub>eos</sub>	Maximum reduction from baseline in blood eosinophils (between Day 0 and last quantifiable measurement)
Max <sub>speos</sub>	Maximum reduction from baseline in percent sputum eosinophils
MCID	Minimal clinically important difference
MDP1	Mepolizumab drug product 1
MDP2	Mepolizumab drug product 2
MDS1	Mepolizumab drug substance 1
MDS2	Mepolizumab drug substance 2
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
NAC	National Asthma Council (Australia)
OCS	Oral corticosteroid
OLE	Open label extension
OR	Odds ratio
PC	Placebo controlled multiple dose studies

Abbreviation	Meaning
PCMDA	Placebo controlled multiple dose asthma studies
PCSA	Placebo controlled asthma studies
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PK	Pharmacokinetic(s)
Proportional inhibition AUEC <sub>speos(0-Day 84)</sub>	Area above the percent sputum eosinophil time curve to Day 84 as a proportion of the total area under the baseline percent sputum eosinophil level to Day 84
Ppb	Part per billion (µg/L)
PBRB	Periodic Benefit-Risk Evaluation Report
PP	Per protocol
PSUR	Periodic Safety Update Report
PT	Preferred term
PY	Patient year
QOL	Quality of life
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Risk Assessment Plan
RMP	Risk Management Plan
RR	Relative risk
RUCAM	Roussel Uclaf Causality Assessment Method
SABA	Short acting beta 2 agonist
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics



Abbreviation	Meaning
$t_{1/2}$	Terminal half life
TBL	Total bilirubin
Tmax	Time to maximum plasma concentration
Tmax <sub>eos</sub>	Time to first occurrence of maximum reduction from baseline in blood eosinophil levels (between Day 0 and last quantifiable measurement)
Tmax <sub>speos</sub>	Time to maximum reduction in percent sputum eosinophil levels
Trep <sub>eos</sub>	Time to $\geq 50\%$ eosinophil repletion
TSANZ	Thoracic Society of Australia and New Zealand
UK	United Kingdom
US	United States
ULN	Upper limit of normal
VAS	Visual analogue scale
V1	Volume of central compartment
V2	Volume of peripheral compartment
V2/F	Apparent volume of the central compartment
V3/F	Apparent volume of the peripheral compartment
WFI	Water for injection
wmean <sub>eos(0–Day 84)</sub>	Weighted mean absolute blood eosinophil levels (Day 0 to 84)
wmean <sub>eos(84–Day 140)</sub>	Weighted mean absolute blood eosinophil levels (Day 84 to 140)
wmean <sub>eos(0–tlast)</sub>	Weighted mean absolute blood eosinophil levels (Day 0 to last quantifiable measurement)
wmean <sub>speos(0–Day 84)</sub>	Weighted mean percent sputum eosinophil levels (Day 0 to 84 or last day with available eosinophil data prior to Day 84)
w/v (%)	Weight/Volume (Percentage)

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	25 January 2016
<i>Date of entry onto ARTG</i>	02 February 2016
<i>Active ingredient(s):</i>	Mepolizumab (rch)
<i>Product name(s):</i>	Nucala
<i>Sponsor's name and address:</i>	GlaxoSmithKline Australia Pty Ltd (GSK) PO Box 18095 Melbourne VIC 8003, Australia
<i>Dose form(s):</i>	Powder for injection
<i>Strength(s):</i>	100 mg
<i>Container(s):</i>	Vial
<i>Pack size(s):</i>	One single-use vial per pack (WFI not included)
<i>Approved therapeutic use:</i>	<i>Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over see Clinical Trials)</i>
<i>Route(s) of administration:</i>	Subcutaneous (SC) injection
<i>Dosage:</i>	100 mg every 4 weeks
<i>ARTG number:</i>	232028

### Product background

This AusPAR describes the application by the sponsor to register a new biological entity, mepolizumab (Nucala) for the following proposed indication:

*Nucala is indicated as an add-on treatment for severe eosinophilic asthma in patients aged 12 years and over identified by either a blood eosinophil count  $\geq 150$  cells/ $\mu$ L at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu$ L in prior 12 months, with a history of exacerbations and/or dependency on systemic corticosteroids.*

Mepolizumab is a recombinant humanised monoclonal antibody (mAb), which targets human interleukin-5 (IL-5). IL-5 is a protein that plays an important role in the growth and survival of eosinophils involved in eosinophilic asthma.

The product is proposed to be used as an add-on treatment for severe eosinophilic asthma in patients aged  $\geq 12$  years, with a dosage regimen of 100 mg subcutaneously (SC) every 4 weeks.

The proposed Product Information (PI) submitted with the original application stated the following in regard to Dosage and Administration:

*Nucala should be administered by a health care professional.*

*Following reconstitution, Nucala should only be administered as a subcutaneous injection (SC) (for example upper arm, thigh, or abdomen) (see Use and Handling).*

*Adults and adolescents (12 years or older):*

*The recommended dose is 100 mg of Nucala administered by SC injection once every 4 weeks.*

*Children (below 12 years):*

*The safety and efficacy of Nucala have not been established in children less than 12 years of age.*

*Elderly (65 years or older):*

*No dosage adjustment is recommended in patients 65 years or older (see Pharmacokinetics and Special Patient Populations).*

*Renal impairment:*

*Dose adjustments in patients with renal impairment are unlikely to be required (see Pharmacokinetics and Special Patient Populations).*

*Hepatic impairment:*

*Dose adjustments in patients with hepatic impairment are unlikely to be required (see Pharmacokinetics and Special Patient Populations).*

## Regulatory status

At the time the TGA considered this application, a similar application was under consideration in the European Union (EU), United States (US), and Canada. Table 1.

**Table 1: List of countries in which a similar application have been approved**

Country/ region	Submission date	Status	Indications (approved or requested)
EU - centralised procedure	3 November 2014	Approved 2 December 2015	<i>Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients (see section 5.1).</i>
USA	4 November 2014	Approved 4 November 2015	<i>Nucala is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. [See Clinical Studies (14).]  <b>Limitations of Use</b>  <i>Nucala is not indicated for treatment of other eosinophilic conditions.  Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.</i></i>
Canada	18	Approved 3	<i>Nucala (mepolizumab) is indicated as</i>

Country/ region	Submission date	Status	Indications (approved or requested)
	November 2014	December 2015	<i>add-on maintenance treatment of adult patients with severe eosinophilic asthma who are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g LABA), and have a blood eosinophil count of <math>\geq 150</math> cells/<math>\mu</math>L (0.15 GI/L) at initiation of treatment with NUCALA™ OR <math>\geq 300</math> cells/<math>\mu</math>L (0.3 GI/L) in the past 12 months.</i>

## Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared 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. Quality findings

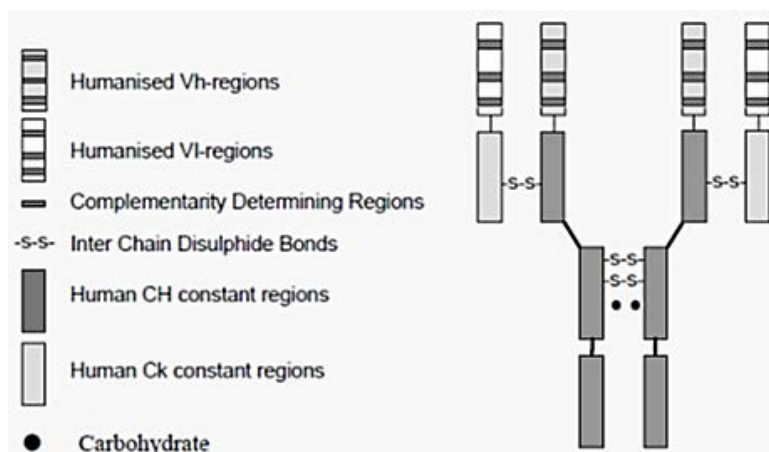
### Drug substance (active ingredient)

#### Structure

Mepolizumab has a typical immunoglobulin G (IgG) structure consisting of two light and two heavy chains. The heavy chain contains 449 amino acids with an estimated molecular mass of approximately 49 kilo Daltons (kD) and the light chain contains 220 amino acids with an estimated molecular mass of approximately 24 kDa. Both heavy chains are glycosylated at asparagine 299 with complex biantennary oligosaccharides. The polypeptide molecular mass is 146 kDa and the carbohydrate molecular mass is approximately 3 kDa resulting in a total estimated molecular mass of 149 kDa for mepolizumab.

The schematic structure of the drug substance is shown in Figure 1.

**Figure 1: The schematic structure of mepolizumab**



**Manufacture**

Mepolizumab is produced from engineered CHO cells in an essentially animal-component free medium. The manufacturing process consists of two parts: cell culture and purification. The cell culture process starts with a seed train and gradual expansion over 3 stages and eventual seed into a batch fermentation tank. Mepolizumab is then separated from cell debris through the harvest procedure.

The purification is a multi-step process that involves several chromatography steps, virus inactivation steps and virus filtration. The resultant filtrate is formulated by concentration and diafiltration using tangential flow ultrafiltration (TFUF). Mepolizumab bulk substance undergoes filtration then dispensed into containers, frozen and stored until transported to the finished product manufacturing site under validated shipment conditions.

**Specifications**

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use were listed. Appropriate validation data have been submitted in support of the test procedures.

**Formulation**

Mepolizumab drug product is a white lyophilized powder manufactured from the bulk drug substance solution containing 75 mg/mL mepolizumab, sodium phosphate dibasic heptahydrate, sucrose and polysorbate 80 at pH 7.0. The drug product is filled and lyophilized in 10 mL Type 1 clear glass vials, sealed with grey bromobutyl rubber single vent stoppers and aluminium overseals with red flip-off caps. The reconstituted drug product is a clear-to-opalescent, colourless-to-pale-yellow or pale-brown solution.

**Manufacture**

The drug product manufacturing process begins with thawing of individual containers of the bulk drug substance followed by mixing each of the containers individually. Bulk drug substance is then pooled, mixed, sterilized by filtration, filled into vials and lyophilized.

**Specifications**

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product.

**Stability**

Stability data have been generated under real time and accelerated/stressed conditions to characterise the stability profile of the product. Photostability data indicates that the product is relatively insensitive to light exposure. However protection from light exposure is recommended as an additional control. The shelf life is *'24 months, store at 2°C to 8°C (refrigerate, do not freeze.), protect from light'*.

In reference to the following requirement outlined in the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (updated 31 July 2013), Guidance 14 'Stability testing for prescription medicines', 14.4 'Specific requirements on stability of biological medicines', which stipulates that *'Supply of a medicine that has undergone temperature excursions outside the approved storage temperature during transport may only occur if appropriate temperature stress/cycling stability data, covering the temperature excursion range and duration, have been evaluated and approved by the TGA.'*

*Temperature excursion stability data should be obtained by placing samples exposed to temperature stress/cycling treatments at an early stage of shelf life, then maintained at the approved storage conditions for the full shelf life'*, it is recommended that temperature excursions outside of the long term storage conditions be limited to brief periods for

biological medicines, unless stability of the product have been confirmed at the end of its shelf life following the temperature excursion as described in the guidance above.

In-use stability data have also been submitted. The reconstituted product does not contain a preservative, therefore it is recommended to use the product as soon as practicable after reconstitution and discard any remaining after 6 hours.

## **Biopharmaceutics**

A bioavailability and bioequivalence study has been submitted. As it is a monoclonal product, pharmaceutical chemistry evaluator did not evaluate this study.

## **Quality summary and conclusions**

All quality issues have been solved except for four Good Manufacturing Practice (GMP) clearance certificates which are still under application. The evaluator recommends that Nucala (mepolizumab) (rch) 100 mg Powder for Injection (Aust R 232028) not be approved until all GMP certificates are current.

The following condition of registration is recommended to the Delegate:

### **Batch release testing by Laboratories Branch**

It is a condition of registration that, as a minimum, the first five independent batches of Nucala (mepolizumab) (rch) 100 mg Powder for Injection (AUSTR 232028) imported into 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 (LB).

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of units to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. Three vials of each batch for testing by the Therapeutic Goods Administration LB together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

## **III. Nonclinical findings**

### **Introduction**

The nonclinical data were appropriate for a biological medicine and addressed the requirements of the relevant International Conference on Harmonisation (ICH) guideline (S6(R1)). The critical safety studies were Good Laboratory Practice (GLP)-compliant. The investigation of toxicity was limited by mepolizumab only having pharmacological activity in monkeys and not the other laboratory animal species tested (mouse, rat, guinea pig, rabbit and dog). Some pharmacology and toxicity studies in mice used a homologue antibody that was active against murine IL-5.

## Pharmacology

### Primary pharmacology

IL-5 is the major haematopoietic cytokine responsible for the proliferation, differentiation, activation, survival and recruitment of eosinophils. This involves binding of IL-5 to the alpha chain of the IL-5 receptor (IL-5R $\alpha$ ), with the IL-5/IL-5R $\alpha$  complex then forming a heterodimer with the  $\beta$  chain of the receptor leading to signal transduction<sup>1</sup>. By binding to IL-5, mepolizumab is designed to reduce IL-5 receptor activation, leading to a reduction in the number of blood and pulmonary eosinophils.

Mepolizumab was shown to bind to human (h) IL-5 with high affinity in vitro, with the binding affinity ( $K_D$ ) estimated to be approximately 100 pM. X-ray crystallography data indicate that two mepolizumab Fabs bind to one IL-5 dimer, with binding occurring in a region associated with the binding of IL-5 to IL-5R $\beta$ . Mepolizumab was shown to inhibit the binding of hIL-5 to hIL-5R $\alpha$  expressed on *Drosophila* cells in vitro, with an 50% inhibitory concentration ( $IC_{50}$ ) value of 0.94 nM; this is consistent with steric hindrance by the antibody.

In vitro in functional assays, mepolizumab inhibited IL-5-induced differentiation of human and monkey bone marrow cells to eosinophils with similar potency ( $IC_{50}$  values approximately 100 pM). In experiments with a human erythroleukemic cell line (TF-1.28) and murine pre-B cells (B13), mepolizumab inhibited cell proliferation in response to human IL-5 ( $IC_{50}$  values of 73 and 31 pM in the respective cell lines) as well as to monkey IL-5, but not to IL-5 from mouse, rat, rabbit or dog. Non-humanised mepolizumab ('mAb 2B6') had no significant effect on lung eosinophil counts in guinea pigs exposed to an aerosol-borne antigen and did not alter peripheral eosinophil counts, or inhibit eosinophilia induced by IL-2 (involving downstream release of cytokines, including IL-5), in rabbits. These findings are consistent with the very high degree of homology between human and monkey IL-5, and considerably lower homology for other common laboratory animal species, so that mepolizumab is only pharmacologically active in primates.

In vivo, mepolizumab (1 mg/kg SC) decreased peripheral eosinophil counts in healthy cynomolgus monkeys, with 50% maximal efficacy associated with a plasma concentration of 1.43  $\mu$ g/mL. However, the relative reductions (81 to 96%) of blood eosinophils reported in this study must be viewed with caution due to the low baseline eosinophil values. Mepolizumab was shown to prevent the increase in blood eosinophils induced by recombinant human IL-2 (and involving IL-5 release) in monkeys. However, it is noted that the animals used in the study were not hypereosinophilic at the time when mepolizumab was given, with IL-2 treatment initiated only after treatment with mepolizumab. Finally, of relevance to the proposed indication, in a monkey model of asthma, mepolizumab (10 mg/kg intravenously (IV)) inhibited the antigen-induced increase in lung eosinophil count, as well as reducing peripheral eosinophils by approximately 25%.

### Secondary pharmacodynamics and safety pharmacology

Secondary pharmacology studies revealed binding of mepolizumab in human immune tissues, with binding generally restricted to T-lymphocytes, eosinophils and dendritic cells. The pattern of binding did not indicate potential off-target binding in humans.

One GLP-compliant specialised safety pharmacology study was conducted, which assessed the effects of 10 and 100 mg/kg IV mepolizumab on the respiratory, cardiovascular

<sup>1</sup> Zaks-Zilberman M., Harrington A.E., Ishino T. and Chaiken I.M: Interleukin-5 receptor subunit oligomerization and rearrangement revealed by fluorescence resonance energy transfer imaging. *J. Biol Chem* 2008 May 9;283(19)

(excluding electrocardiogram [ECG]) and renal systems in cynomolgus monkeys. The general repeat-dose toxicity studies in monkeys included ECG and urinalysis examination (at doses up to 100 mg/kg/month intravenously [IV]). There were no treatment-related effects on the respiratory or renal systems. Potential effects of mepolizumab on central nervous system (CNS) function were not investigated in specialised experiments, but as no adverse clinical signs were apparent in repeat-dose studies this is considered acceptable, and no relevant concern is held.

Single IV administration of mepolizumab at  $\leq 100$  mg/kg to male monkeys did not result in significant changes in blood pressure or heart rate for 3 h post-dose (estimated to yield plasma levels of mepolizumab more than 100-times higher than the clinical peak plasma concentration [ $C_{max}$ ]). There were no effects of mepolizumab on ECG parameters at repeated doses of up to 100 mg/kg/month. It is noted that the ECG testing was performed long after dosing (21 to 26 days). In general, it would be more appropriate to perform the ECG testing around the time of the  $C_{max}$  (that is, shortly after dosing here) to better explore the potential effects of the drug, but the plasma mepolizumab levels around the time of the ECG assessment were sufficiently high, giving a relative exposure of  $> 37$  times the clinical  $C_{max}$ . Accordingly, no relevant concern is held for QT prolongation in patients.

## Pharmacokinetics

Following subcutaneous injection, mepolizumab had a long time to peak plasma concentration ( $T_{max}$ ) (1 to 4 days) in both cynomolgus monkeys and humans. Exposure to mepolizumab was dose-proportional in monkeys and humans. Complete bioavailability was observed after SC dosing. Plasma half-life was long in monkeys (11 to 14 days) and humans (16 to 21 days) following SC administration. Consistent with the long plasma half-life, accumulation of mepolizumab was observed after repeated dosing.

As an antibody, mepolizumab is expected to be largely confined to the plasma compartment. However, the volume of distribution indicated some distribution to tissues in cynomolgus monkeys. A low level of distribution to the bronchoalveolar fluid was shown in monkeys. Mepolizumab may also distribute to target tissues based on an in vitro study that showed tissue binding to leukocytes in bone marrow, lymph nodes, spleen and lymphoid nodules of the tonsils in human tissues.

No specific studies on the metabolism and excretion of mepolizumab were conducted, and are not required. The fate of antibodies within the body is generally understood to involve catabolism and subsequent amino acid recycling. Mepolizumab did not alter expression of cytochrome P450 isozyme CYP3A4 in human hepatocytes in an in vitro study.

Based on the similarity in pharmacokinetics compared to humans and pharmacological activity in the species, the cynomolgus monkey is a suitable animal model for assessing the toxicity of mepolizumab.

## Toxicology

### Acute toxicity

Acute toxicity was assessed following a single dose of 3 mg/kg (IV bolus) or 304 mg/kg (IV infusion) of mepolizumab in cynomolgus monkeys. No adverse clinical signs or mortality was observed. The maximum non-lethal dose of 304 mg/kg IV yielded plasma levels of mepolizumab 394- and 171-times higher than the anticipated clinical  $C_{max}$  and area under the plasma concentration versus time curve (AUC), respectively. These data indicate a low order of acute toxicity for mepolizumab.



## Repeat-dose toxicity

Two repeat-dose toxicity studies were conducted in cynomolgus monkeys in which mepolizumab were administered by monthly IV or SC dosing for 2 and 6 months. The duration of the pivotal study and the use of cynomolgus monkeys as the only animal species is appropriate (ICH guideline S6). The proposed route of administration in humans is by SC injection, which was only used in one dose group in the 6-month study. However, as exposure was similar between IV and SC dosing this is not considered a deficiency. The dosing schedule used in the repeat-dose studies was the same as that proposed for clinical use (once every 4 weeks).

## Relative exposure

Exposure ratios have been calculated based on animal: human plasma  $AUC_{0-4wk}$ . Human reference values are from Clinical Study MEA115588, which predicted steady state  $AUC_{0-4wk}$  values for the proposed clinical dose and route. These predicted values were consistent with those measured in a study that involved administration of 250 mg mepolizumab SC (Clinical Study SB-240563/017). AUC values for monkeys are for the sexes combined and at steady state, measured after the fifth dose of mepolizumab. Moderate to high relative exposure levels were achieved in the animals (Table 2).

**Table 2: Relative exposure in the pivotal repeat-dose toxicity study**

Species	Study duration	Dose per 4 weeks (mg/kg)	Route	$AUC_{0-4\text{ wk ss}}$ (mg*h/mL)	Exposure ratio
Monkey (Cynomolgus)	6 months [RSD-100X0L]	10	SC	61	7.4
		10	IV	68	8.2
		100	IV	809	99
Human (severe asthma)	Predicted steady state [MEA115588]			8.2	-

# = animal: human plasma  $AUC_{0-4\text{ wks}}$  at steady state (monkeys) or predicted steady state (humans)

## Major toxicities

Mepolizumab was well tolerated in cynomolgus monkeys at doses up to 100 mg/kg/month IV for six months. No treatment-related changes were observed in clinical, immunological, histopathological and other examinations at any dose (relative exposure based on AUC;  $\leq 99$ ), except for decreases in circulating and pulmonary eosinophils. Similarly, there were no apparent adverse effects in a 2-month study of cynomolgus monkeys with IL-2-induced eosinophilia that were treated with mepolizumab at  $\leq 50$  mg/kg/month IV.

The reduction in circulating and pulmonary eosinophil counts in treated monkeys reflects the intended pharmacological effect of the drug. There was no clear treatment-related effect on mature or immature bone marrow eosinophils in the animals. In the 2-month study, the decreased circulating eosinophil counts were shown to be reversible within approximately 10 weeks of cessation of treatment.

Following SC administration of mepolizumab to monkeys, the decreases in peripheral and bronchoalveolar lavage eosinophil counts were similar to the same IV dose (consistent

with similar toxicokinetics), and toxicological profiles were also similar between these two groups.

### **Genotoxicity**

Genotoxicity studies were not conducted, which is appropriate as protein medicines are unlikely to interact directly with deoxyribonucleic acid (DNA), as indicated in ICH guideline S6.

### **Carcinogenicity**

Carcinogenicity studies were not conducted, which is appropriate for this product, consistent with ICH guideline S6.

### **Reproductive toxicity**

Due to the absence of pharmacological activity in rodents or rabbits, a combined embryofetal and pre-/postnatal development study was performed with mepolizumab in monkeys. In this GLP-compliant study, females were treated IV once monthly during gestation, and allowed to deliver naturally; lactating mothers were not dosed with mepolizumab. In addition, a fertility and embryofetal development study was conducted in mice using the mepolizumab homologue, SB 264091, which cross-reacts with murine IL-5. Overall, the reproductive toxicity studies are limited with respect to ICH guideline S5. No necropsies were performed (maternal or infant) in the monkey study, and behaviour, maturation and reproduction in offspring were not assessed. Considering also the modest number of monkeys used and offspring available for examination, the reproductive toxicity studies performed with mepolizumab are of limited predictive value.

### **Relative exposure**

Relative exposure to mepolizumab in cynomolgus monkeys during gestation was moderate to high (Table 3).

**Table 3: Relative exposure in reproductive toxicity study**

Species	Study	Dose per 4 weeks (mg/kg)	Route	AUC <sub>0-4 wks</sub> (mg*h/mL)	Exposure ratio
Monkey (Cynomolgus)	Embryofetal and pre-/postnatal development [CD2003/01020/00]	10	IV	39	4.7
		100	IV	254	31
Human (severe asthma)	Steady state [MEA115588]	100 mg	SC	8.2	-

# = animal: human plasma AUC<sub>0-4 wks</sub>.

## **Nonclinical summary**

- The nonclinical submission contained an adequate set of studies investigating the pharmacology, pharmacokinetics and toxicity of the drug, in line with requirements

for a biological medicine indicated in ICH guideline S6. Critical studies were GLP-compliant.

- In vitro studies showed that mepolizumab binds to human IL-5 with subnanomolar affinity and blocks binding of IL-5 to its receptor with an  $IC_{50}$  of approximately 1 nM. Mepolizumab was shown to inhibit IL-5-induced differentiation of human and monkey bone marrow cells to eosinophils and inhibit the proliferation of IL-5-sensitive cell lines. Mepolizumab binds to human and monkey IL-5, but does not recognise IL-5 from other common laboratory animal species (mouse, rat, guinea pig, rabbit and dog).
- In vivo, mepolizumab (1 mg/kg SC) decreased peripheral eosinophil counts by 81 to 96% in cynomolgus monkeys. Mepolizumab also prevented induction of eosinophilia by IL-2 (involving downstream release of IL-5) in the species.
- In vitro binding of mepolizumab in human tissues was restricted to lymphoid tissues (bone marrow, lymph nodes, the spleen and lymphoid nodules of the tonsils).
- There were no drug-related effects on respiratory rate, blood pressure, heart rate or urinalysis parameters in monkeys following single IV injection of mepolizumab at doses up to 100 mg/kg (> 100 times the clinical  $C_{max}$ ). No effects on ECG were apparent in monkeys after repeated dosing when plasma levels of mepolizumab were > 37-times the clinical  $C_{max}$ .
- The plasma kinetics of mepolizumab was shown to be similar between cynomolgus monkeys and humans. As expected for an antibody,  $T_{max}$  was long (1 to 4 days), as was  $t_{1/2}$  (11 to 14 days in monkeys; 16 to 21 days in humans), following SC administration. Mepolizumab exposure was dose-proportional, and showed accumulation with repeated dosing. The volume of distribution suggested some distribution outside the plasma compartment, with low levels detected in bronchoalveolar fluid in monkeys.
- A single-dose study in cynomolgus monkeys showed a low order of toxicity for mepolizumab.
- Mepolizumab was well tolerated in repeat-dose toxicity studies, conducted in cynomolgus monkeys. The pivotal study involved monthly administration by the IV ( $\leq 100$  mg/kg) or SC (10 mg/kg) route for 6 months (relative exposure based on AUC,  $\leq 99$ ). There were no treatment related findings apart from the expected pharmacological effect of reduced eosinophil counts (peripheral and pulmonary).
- Genotoxicity and carcinogenicity studies were not performed and are not required for this monoclonal antibody. The effect of mepolizumab on tumour surveillance is currently unknown.
- In pregnant monkeys, administration of mepolizumab throughout gestation ( $\leq 100$  mg/kg/month IV; relative exposure,  $\leq 31$ ) was not seen to adversely affect embryofetal or pre/postnatal development. However, examination of skeletal and visceral malformations was not performed. Mepolizumab was detected in the plasma of infants of monkeys that had been treated during pregnancy, with levels 2 to 3 times higher than in mothers at the same time point. Excretion in milk occurred at low levels; significant placental transfer was apparent. Fertility was unaffected in male and female mice treated with a murine-active homologue of mepolizumab, and there was no clear treatment-related increase in fetal malformations in the species.
- Mepolizumab was well tolerated locally in monkeys, including in experiments with the clinical formulation.
- Anti-mepolizumab antibodies developed at a low incidence in treated monkeys.
- There was no evidence of immunotoxicity in monkeys that received repeated doses of mepolizumab, except for the pharmacological effect on eosinophils. In addition, a

mepolizumab homologue with activity in mice did not compromise host defence to parasitic infection.

## **Nonclinical conclusions and recommendation**

There were no major deficiencies in the nonclinical data. However, the extent of the nonclinical investigations was limited by pharmacological activity being restricted to monkeys.

Nonclinical pharmacology studies offered support for use for the proposed indication. IL-5 is recognised to be the major cytokine responsible for the proliferation, differentiation, activation, survival and recruitment of eosinophils, and mepolizumab was shown to bind to human IL-5 with high affinity and potently inhibit its activity in vitro in cell-based functional assays. It was shown to be effective in vivo in monkeys with antigen and IL-2-induced eosinophilia.

No clinically relevant hazards were identified, and no target organs for toxicity of mepolizumab were identified, at very high multiples of the clinical exposure.

Reproductive toxicity studies and published effects in IL-5 deficient mice did not identify any obvious concerns for reproductive toxicity and Pregnancy Category B1 is considered acceptable.

There are no nonclinical objections to registration of Nucala for the proposed indication.

## **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**

#### **Clinical rationale**

According to World Health Organization (WHO) estimates, there are up to 235 million asthmatic patients worldwide and up to 10% of these cannot achieve control with inhaled therapies alone. According to the National Asthma Council<sup>2</sup>, over 2 million Australians (or approximately 1 in 10 adults and children) have asthma with up to 400 asthma-related deaths annually. The rate of asthma has declined in children but it has remained stable in adults. Asthma management plans are based on preventive therapies such as low dose inhaled corticosteroids (ICS) and reliever medications such as short and long acting inhaled beta 2 agonists (LABAs). However, despite widespread acceptance of ICS preventers in Australia, up to 5% of patients suffer severe refractory asthma with frequent exacerbations and emergency department (ED) admissions, and disproportionate use of health care resources. Oral corticosteroids (OCS) are commonly required in patients with severe asthma. However, OCS are poorly tolerated and compliance with therapy is often suboptimal, particularly when given in high doses during exacerbations. The well understood consequences of long term OCS merit any alternative therapy which allows OCS dose reduction or cessation.

Asthma is associated with airway inflammation, airway narrowing and reversible airway obstruction. It is a heterogeneous disease with several phenotypes. However, it is

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<sup>2</sup> [www.nationalasthma.org.au](http://www.nationalasthma.org.au)

commonly associated with eosinophil infiltration of lung tissues and the severity of asthma is broadly correlated with airway eosinophil levels<sup>3</sup>. There is an inconsistent relationship between sputum eosinophilia and lung function and airway hyperresponsiveness<sup>4</sup>. However, there is a much closer relationship between eosinophilic inflammation and the risk of severe asthma exacerbations<sup>5</sup>. IL-5 promotes eosinophil growth, activation, survival and migration from bone marrow to the lung. Mepolizumab is the first humanised IgG1 antibody inhibitor of IL-5 which is hoped will reduce exacerbation rates in patients with severe eosinophilic asthma who have inadequate symptom control on daily OCS therapy. In support of this concept, two recently published randomised, placebo controlled, Phase III trials of reslizumab, a monoclonal antibody inhibitor of IL-5, have shown improved asthma control with reduced exacerbation rates in patients with moderate to severe eosinophilic asthma poorly controlled on high dose ICS therapy<sup>6</sup>.

## Guidance

The Phase III clinical program for mepolizumab for severe eosinophilic asthma was developed with feedback from the regulatory authorities of the EU, Japan, United Kingdom (UK), Sweden and Canada. The approach proposed to define the 100 mg SC dose was supported. A single OCS sparing study was also supported in principle. At the United States (US) Pre-Biologics License Application Meeting in January 2014, the FDA stated that the submission package was suitable for filing. A TGA planning letter was issued on 15 December 2014.

## Contents of the clinical dossier

### *Scope of the clinical dossier*

The submission contained the following clinical information:

- 2 clinical pharmacology studies, including 2 that provided pharmacokinetic data and 2 that provided pharmacodynamic data.
- 1 population pharmacokinetic analyses.
- Two pivotal efficacy/safety exacerbation studies (MEA112997 and MEA115588).
- One pivotal OCS reduction study (MEA115575).
- Two ongoing extension studies (MEA115666 and MEA115661).
- One dose-finding study (MEA114092).
- One Phase II study in patients with moderately severe asthma (006).
- An Integrated Summary of Efficacy and an Integrated Summary of Safety.

In addition the submission contained an Application letter, Application form, Draft Australian PI and Consumer Medicines Information (CMI), FDA-approved product label, European Summary of Product Characteristics (SmPC), a Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

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<sup>3</sup> Bousquet J, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990; 323:1033-1039

<sup>4</sup> Crimi E, et al. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. *Am J Respir Crit Care Med* 1998; 157:4-9

<sup>5</sup> Green RH, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360:1715-1721

<sup>6</sup> Castro M, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; S15:42-49

**Paediatric data**

The submission included limited paediatric data.

**Good clinical practice**

All studies were conducted according to the principles of International Conference on Harmonisation- Good Clinical Practice (ICH GCP).

**Pharmacokinetics (PKs)****Studies providing pharmacokinetic data**

- Study SB-240563/018, which assessed the bioavailability following administration at 3 SC sites and 1 intramuscular site relative to IV administration of single 250 mg doses of SB-240563 to healthy volunteers;
- Study SB-240563/001, which assessed the safety, PKs and effect on the early and late phase response to allergen challenge of rising doses of SB-240563 in male patients with mild asthma;
- Study SB-240563/017, which assessed tolerability and PKs of three 250 mg SC doses of SB-240563 in male and female patients with asthma;
- Study SB-240563/035, which assessed the safety and PKs of SB-240563 in male patients with mild asthma; and
- Study SB-240563/036, which assessed the effect of 750 mg SB-240563 (Anti-IL-5) on clinical features, cutaneous late phase reactions and bronchial, nasal, skin, bone marrow and blood eosinophils in male and female patients with atopic asthma.
- Study MEA114092, which assessed the ascending single and multi-SC dose, bioavailability and pharmacodynamics (PD) in adults with asthma.
- Study 2014N210473\_00, which was a population PK analysis comparing asthmatic adult and paediatric pharmacokinetics following IV administration.
- Study MEA115705, which assessed the pharmacokinetics of a single ascending IV dose in healthy Japanese males.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

**Evaluator's conclusions on pharmacokinetics*****Absorption, distribution, metabolism and excretion***

- Following a single SC administration of 250 mg mepolizumab in the abdomen, arm or thigh the mean mepolizumab plasma concentration-time profiles were similar in shape and the  $T_{max}$  ranged from 5 to 7 days.
- In healthy subjects, following SC administration of 250 mg mepolizumab in the abdomen, arm or thigh, the absolute bioavailability of mepolizumab was 0.64, 0.75 and 0.71, respectively.
- In subjects with asthma, the absolute bioavailability of mepolizumab following SC administration of 12.5, 125 or 250 mg mepolizumab in the upper arm was 0.81, 0.82 and 0.64, respectively.

- No food studies have been undertaken as the SC administration route is unaffected by food.
- In subjects with asthma, following SC doses of 12.5 mg, 125 mg or 250 mg mepolizumab in the upper arm on three occasions (every 4 weeks), mepolizumab AUC and  $C_{max}$  values increased in a less than dose proportional manner following each of the three monthly SC doses.
- In healthy subjects, following three SC doses of 250 mg mepolizumab in the anterior, lateral abdominal wall, the mean AUC and  $C_{max}$  were approximately 65% and 80%, respectively, higher after the third dose than following the first dose.
- In subjects with asthma administered three SC doses of 12.5, 125 or 250 mg mepolizumab given at monthly intervals,  $C_{max}$  was approximately 68%, 68% and 69% higher, respectively, after the third dose than the first dose and  $AUC_{0-tau}$  was 73%, 74% and 64% higher, respectively.
- PPK analysis in subjects with asthma indicated that following SC administration, mepolizumab plasma concentration-time data was well described by a two compartment model with first order absorption and first order elimination. The volume of distribution at steady state, for a subject weighing 70 kg, was equal to the plasma volume plus the interstitial space, indicating that there was limited drug distribution into the tissues.
- In asthmatic subjects following SC administration, mepolizumab was cleared slowly with an estimated clearance of 0.31 L/day and the CL/F and V/F were dose independent.

#### ***Intra- and inter-individual variability***

The results of a PPK analysis indicated that the inter-subject variability on CL/F, V<sub>2</sub>/F and KA following SC administration of mepolizumab in the upper arm were 58%, 59% and 87%, respectively, and there was an estimated residual variability of 0.333.

#### ***Special populations***

- No PK studies examined the effects of hepatic or renal impairment on the PKs of mepolizumab; however, as mepolizumab is an IgG these factors are unlikely to affect mepolizumab PKs.
- No studies examined the effects of age and race on mepolizumab PKs following SC injection.
- Following IV injection, there was close correlation between mepolizumab PKs in adult and paediatric populations.
- Following IV injection, increases in  $AUC_{0-inf}$  and  $C_{max}$  were dose-proportional in Japanese males.

#### ***Drug-drug Interactions***

- Mepolizumab has a low potential for drug-drug interactions.

#### ***Limitations of PK studies***

- None of the submitted studies examined the PKs of mepolizumab following SC administration in healthy subjects.
- Data regarding the effects of race and age on mepolizumab PKs is available following IV administration only, even though the PKs of mepolizumab are clearly different following dosing via the SC and IV routes.

- No studies have been conducted comparing SC administration of the clinical trial form of mepolizumab (MDS1) and the formulation proposed for marketing (MDS2), nor has a request for a biowaiver been presented as part of the evaluation materials.

#### ***Questions regarding the PK studies***

Two forms of mepolizumab drug substance were primarily used in the clinical trials (MDS1 and MDS2). Studies (MEA115705, MEA114092, SB-240563/018 and SB-240563/017) used MDS1. However, no PK studies contained in the evaluation materials examined the bioequivalence between SC doses of MDS1 and the proposed commercial formulation, that is MDS2, and no biowaiver has been applied for.

Can the sponsor please justify why no bridging study between the trial and commercial formulations of mepolizumab has been conducted and/or why no application for a biowaiver has been made?

## **Pharmacodynamics (PDs)**

### **Studies providing pharmacodynamic data**

None of the PK/PD studies examined the PDs of mepolizumab following SC administration in healthy subjects or the PD effects of the proposed commercial presentation of mepolizumab (MDS2) and only Study MEA114092 examined the mepolizumab PDs following SC administration of the clinical trial formulation of mepolizumab (MDS1) in asthmatic adults. None of the PD studies had deficiencies that excluded their results from consideration.

### **Evaluator's conclusions on pharmacodynamics**

#### ***Mechanism of action***

- Mepolizumab inhibits the bioactivity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

#### ***Effect on blood eosinophils***

- Following a single SC administration of 12.5 mg, 125 mg or 250 mg mepolizumab, there was a pronounced decrease in blood eosinophils levels in all 3 SC dosage groups.
- The decrease, based on  $AUEC_{eos(0 \text{ to Day } 84)}$ <sup>7</sup>, appeared to be dose-related with the 12.5 mg SC dose having a weaker effect than the 125 mg dose. Following the highest SC dose (250 mg) however, there was little evidence of a greater effect on blood eosinophils levels beyond that seen at the 125 mg dose level.
- The decrease in blood eosinophils was relatively stable up until Day 28 post dose when the subjects received a second SC dose of mepolizumab.
- By Day 140, following 3 doses of mepolizumab given once every 4 weeks, blood eosinophil levels had not completely returned to pre-dose and the percentage of subjects who reached  $\geq 50\%$  blood eosinophil repletion by Day 140 ranged from 7% to 9% in the groups receiving SC doses of  $\geq 125$  mg. By contrast, 38% of subjects receiving the 12.5 mg dose had reached  $\geq 50\%$  blood eosinophil repletion by Day 140.

<sup>7</sup> Area under the absolute blood eosinophil time curve to Day 84 determined using the linear trapezoidal rule, for subset of subjects with blood eosinophil data to Day 84.



- The SC dose of mepolizumab that induced 90% of the maximum inhibitory effect attributable to the drug at Week 12 was estimated to be 99 mg, whereas, the dose inducing 50% of the maximum inhibitory effect at week 12 was estimated to be 11 mg SC.

#### ***Effect on induced sputum***

- There was a dose dependent decrease in sputum eosinophils following SC doses of 12.5 mg and 125 mg mepolizumab. At the highest doses (250 mg) the decrease in sputum eosinophils was similar to that seen at the 125 mg dose.
- The geometric mean proportional inhibition ( $AUEC_{\text{speos}(0 \text{ to Day } 84)}$ ) was highest following the 250 mg SC dose of mepolizumab (0.693), whereas, the weighted ( $\text{mean}_{\text{speos}(0 \text{ to Day } 84)}$ ) (1.368%) and ( $\text{Max}_{\text{speos}}$ ) percent sputum eosinophil values (0.025%) were lowest following the 125 mg SC dose.

#### ***Effect on total and free IL-5***

- Following a single SC dose of 12.5 mg, 125 mg or 250 mg mepolizumab, serum total IL-5 levels increased from baseline in almost all subjects up to Day 28. Following 3 doses, serum total IL-5 levels remained constant up to Day 140 in all groups except in the 12.5 mg SC group. After Day 70 a decrease in serum total IL-5 levels was observed in the 12.5 mg SC cohort although levels did not return to baseline by Day 140.
- A general increase over time in the percentage of subjects with measurable serum free IL-5 was observed in the 12.5 mg SC group as well as on Days 112 and 140 in the other treatment groups.

#### ***Time course of PD effects***

- Following SC doses of mepolizumab in subjects with asthma, there was a pronounced decrease in blood eosinophils levels from baseline by the first post-dose measurement on Day 3.
- The  $T_{\text{max}_{\text{speos}}}$  following a single SC administration of 12.5 mg, 125 mg or 250 mg mepolizumab ranged from 33.6 to 50.6 days.
- Depletion in induced sputum was observed from the first post-dose measurement on Day 7.

#### ***Relationship between drug concentration and PD effects***

- There was a clear relationship between blood eosinophil levels and plasma concentrations of mepolizumab.
- The  $IC_{50}^8$  for the inhibition of blood eosinophils was 1.26  $\mu\text{g}/\text{mL}$ .
- No clear relationship was observed between serum total IL-5 and mepolizumab plasma concentrations.

#### ***Limitations of PD studies***

- None of the submitted PK/PD studies have examined the PDs of the formulation of mepolizumab proposed for marketing.
- No thorough QT analysis has been conducted following SC doses of mepolizumab.

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<sup>8</sup> Concentration associated with 50% maximal effect

## Dosage selection for the pivotal studies

### Study MEA112997 (DEWAM)

For details see Attachment 2.

## Efficacy

### Studies providing efficacy data

The following studies provided efficacy data:

- Study MEA115588
- Study MEA115575
- Study MEA115661
- Study MEA115666
- Study 006

For details of these studies see Attachment 2.

### Evaluator's conclusions on efficacy

Mepolizumab is indicated as add-on treatment for severe eosinophilic asthma in patients aged 12 years and over identified by either a blood eosinophil count  $\geq 150$  cells/ $\mu\text{L}$  at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu\text{L}$  in the prior 12 months, with a *'history of exacerbations and/or dependency on systemic corticosteroids.'*

The pivotal placebo controlled study in patients with severe eosinophilic asthma demonstrated a statistically significant and clinically meaningful benefit for mepolizumab compared with placebo. In the 100 mg SC group of MEA115588, there was an exacerbation rate reduction of 53% ( $p < 0.001$ ), and a reduction of 61% in exacerbations requiring hospitalisation and/or emergency department (ED) visits. The treatment duration was only 32 weeks but the interim analyses of the open label extension studies demonstrated that efficacy was sustained long term. Similar exacerbation rate reductions were also demonstrated with the 75 mg IV doses in MEA115588 and MEA112997 (47% and 48%, respectively). In MEA115575, there was a 32% reduction in exacerbation rates compared with placebo despite significant OCS dosage reductions.

Blood eosinophils were suppressed by all doses of mepolizumab and this effect was sustained for at least 32 weeks. Blood eosinophils at screening have been shown to be an accurate biomarker with exacerbation rate reductions greater in patients with high eosinophil counts and most usefully in those with  $\geq 150$  cells/ $\mu\text{L}$ . Exacerbation rate reductions were associated with improved lung function. In the mepolizumab 100 mg SC group of MEA115588, pre- and post-bronchodilator FEV<sub>1</sub> increases of 98 mL and 138 mL were demonstrated. These differences were statistically significant and clinically meaningful. Asthma symptoms measured by ACQ and SGRQ were also improved.

The overall benefit of mepolizumab was observed in patients with or without concurrent maintenance OCS. However, in MEA115588 there was no meaningful response in patients with maintenance OCS treated with mepolizumab 100 mg SC. Mepolizumab also permitted clinically meaningful OCS dose reductions without loss of asthma control. In MEA115575, a 50% reduction in median OCS dose from baseline was achieved in the mepolizumab group compared with 0% in the placebo group during a four week maintenance period. However, a further analysis of MEA115661 is required to confirm that this benefit is

sustained. There were no important differences observed in subgroups based on age, gender, race, and body weight. However, more data are required to support use in adolescents.

The efficacy of mepolizumab is supported by a recently published study of reslizumab, another monoclonal IL-5 inhibitor<sup>6</sup>. Two duplicate placebo controlled Phase III studies with large patient numbers assessed exacerbation rate reductions in patients with moderate to severe asthma inadequately controlled on ICS, and with blood eosinophils  $\geq 400$  cells/ $\mu$ L. In both studies, patients receiving reslizumab had significant reductions in the frequency of asthma exacerbations [RR 0.50 (95% CI: 0.37, 0.67) and RR 0.41 (0.28, 0.59), both  $p < 0.0001$ ] compared with those receiving placebo.

The efficacy outcomes in the submission appear to be based on a selection of exploratory studies rather than a coherent Phase III trial program. In the various pivotal and supportive studies, the patient populations differed with respect to eosinophil criteria, maintenance OCS use, mepolizumab dose and delivery, and efficacy outcomes. In addition, several analyses were retrospective. The dose selection process was not ideal and the lowest effective dose was determined retrospectively with a PK/PD study. Relatively few patients received the 100 mg SC dose proposed for marketing and the single pivotal study had an observation period of only 32 weeks. Despite these limitations, there appears little doubt that mepolizumab improves outcomes in patients with severe eosinophilic asthma, and that blood eosinophils are a clinically useful biomarker. However, the heterogeneous studies do not support the proposed indication in several respects. This has caused confusion with different labels proposed for the EU, US, Canada and Australia, presumably following feedback from the respective authorities.

## Safety

### Studies providing safety data

The following studies provided evaluable safety data:

#### *Pivotal efficacy studies*

In the pivotal efficacy studies MEA115588 and MEA115575 the following safety data were collected:

- General AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by preferred term (PT), system organ class (SOC) and treatment group.
  - AEs of particular interest included infusion reactions, serious cardiac, vascular and thromboembolic adverse events, malignancies and infections.
- Laboratory tests, including clinical chemistries and haematology, were performed at central laboratories.
- Vital signs.
- Electrocardiogram (ECG).

#### *Dose-response and efficacy studies*

The following dose-response and non-pivotal efficacy studies provided safety data: MEA112997, MEA115661, MEA115666, and 006. A summary of all 19 mepolizumab studies performed in all doses and indications is shown in Table 4.

**Table 4: Summary of safety studies- study groupings for analysis of safety**

Study Grouping	Studies Included	
<b>Asthma</b>		
Placebo-controlled Severe Asthma Studies (PCSA)	MEA112997, MEA115588, MEA115575	
Open-label Extension Severe Asthma Studies <sup>1</sup> (OLE)	MEA115661, MEA115666	
Placebo-controlled Multiple-dose Asthma Studies (PCMDA)	Severe asthma	MEA112997, MEA115588, MEA115575
	Moderate asthma	SB-240563/006
	Asthma PK/PD	SB-240563/017, SB-240563/036
<b>All Indications</b>		
All Studies (ALL)	Severe asthma	MEA112997, MEA115588, MEA115575, MEA115661, MEA115666
	Moderate asthma	SB-240563/006
	Asthma PK/PD	MEA114092, SB-240563/017, SB-240563/036, SB-240563/001, SB-240563/035
	HES	MHE100185, MHE100901, MHE104317 (Compassionate Use <sup>3</sup> )
	EoE	MEE103226, MEE103219 <sup>2</sup>
	Atopic Dermatitis	SB-240563/045
	Healthy Subjects	SB-240563/018, MEA115705
Placebo-controlled Multiple-dose Studies (PC)	Severe asthma	MEA112997, MEA115588, MEA115575
	Moderate asthma	SB-240563/006
	Asthma PK/PD	SB-240563/017, SB-240563/036
	HES	MHE100185
	EoE	MEE103226
	Atopic Dermatitis	SB-240563/045

1. These studies are currently ongoing; interim safety results are presented in this Safety Summary. 2. Conducted in paediatric subjects. 3. Includes ongoing open label studies MHE112000 and MHE112562 PK/PD= pharmacokinetic/pharmacodynamics; HES = hypereosinophilic syndrome; EoE = eosinophilic esophagitis

### Patient exposure

In addition to patients with severe asthma, the sponsor has conducted exploratory studies of mepolizumab for other indications including moderate asthma, hypereosinophilic syndrome, eosinophilic oesophagitis, and atopic dermatitis (Table 5). In this overall population, 2022 patients (or healthy subjects) received at least one dose of mepolizumab and a further 661 received placebo. Overall, 1229 patients with severe eosinophilic asthma received at least one dose of mepolizumab. Of these, 1018 received mepolizumab 100 mg SC in randomised, placebo controlled studies, or long term extension studies. In the 1018 patients treated with mepolizumab 100 mg SC, total treatment exposure was 789 patient years (PYs). A total of 576 patients (57%) were treated for up to 12 months and 442 patients (43%) were treated for 12 to less than 24 months. Patients who received mepolizumab 100 mg SC were given a mean of 10 treatments. A total of 915 patients were given at least one dose of mepolizumab in the severe asthma studies; 263 received mepolizumab 100 mg SC and 344 received 75 mg IV (Table 6). In the severe asthma group, the all dose treatment exposure was 687.4 patient/years with a mean of nine treatments given.

**Table 5: Patient exposure**

Indication	Number (%) of Subjects						Total <sup>2</sup>
	Placebo	Mepolizumab					
		100 SC	75 IV	250 IV	750 IV	All Doses <sup>1</sup>	
All	661	1018	361	294	568	2022	2331
Asthma	581 (88)	1018 (100)	355 (98)	275 (94)	285 (50)	1596 (79)	1863 (80)
Severe Asthma	412 (62)	1018 (100)	344 (95)	152 (52)	156 (27)	1229 (61)	1327 (57)
HES	42 (6)	0	0	0	256 (45) <sup>3</sup>	256 (13)	260 (11)
EoE	6 (<1)	0	0	0	0	64 (3)	70 (3)
Atopic Dermatitis	23 (3)	0	0	0	20 (4)	20 (<1)	43 (2)
Healthy Volunteers	9 (1)	0	6 (2)	19 (6)	7 (1)	86 (4)	95 (4)

**Table 6: Patient exposure- summary of duration of exposure and number of treatments administered (severe asthma studies, safety population)**

Treatments administered	Placebo N=412	Mepolizumab				
		100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Mean (SD)	8.9 (3.05)	7.2 (1.48)	9.5 (3.04)	12.0 (2.67)	11.8 (2.90)	9.7 (3.19)
Min. Max	1, 14	1, 8	1, 14	1, 14	1, 14	1, 14
Treatment Exposure						
Total Subject-Years <sup>1</sup>	284.02	147.48	254.25	142.19	143.50	687.43
Exposure (months)						
Mean (SD)	8.3 (2.83)	6.7 (1.39)	8.9 (2.81)	11.2 (2.48)	11.0 (2.70)	9.0 (2.97)
Median	7.5	7.4	7.6	12.0	12.0	7.6
Min. Max	1, 13	1, 8	1, 13	1, 13	1, 14	1, 14
Range of Exposure (months)						
<12, n (%)	288 (70)	263 (100)	217 (63)	22 (14)	26 (17)	528 (58)
12 - <24, n (%)	124 (30)	0	127 (37)	130 (86)	130 (83)	387 (42)

Note: Studies included MEA112997, MEA115588 and MEA115575 1. Sum across subjects of (treatment stop date to treatment start date +29)/365.25

## Safety issues with the potential for major regulatory impact

### *Liver toxicity*

No significant issues were identified. In all clinical studies, 15 (< 1%) patients were withdrawn due to potential hepatic toxicity. In the placebo controlled severe asthma studies, standard protocol-defined LFT stopping criteria occurred in ten patients, five during treatment and five post-treatment. Three (< 1%) patients met the criteria in the placebo and mepolizumab 75 mg IV groups, and two (1%) in each in the mepolizumab 250 mg IV and 750 mg IV groups. In the OLE studies, three events were reported on-treatment, one post-treatment, and one with unknown timing. No event met the criteria for Hy's law<sup>9</sup>.

### *Haematological toxicity*

No significant issues were identified.

<sup>9</sup> Hy's law: Patients with all 3 of these are Hy's law cases: 1. Hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo. 2. Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum total bilirubin (TBL) to > 2xULN, without initial findings of cholestasis (elevated serum ALP). 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury. (Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research [CDER], Center for Biologics Evaluation and Research [CBER], July 2009)

***Serious skin reactions***

No significant issues were identified.

***Cardiovascular safety***

Severe cardiac events were uncommon in the placebo and mepolizumab groups of the severe asthma studies. However, safety concerns were raised by an excess of ischaemic events in the mepolizumab group compared with placebo in MEA112997. This finding was not confirmed by the independent data monitoring committees (IDMCs) in subsequent studies and the sponsor reasonably argues that this observation was a chance event.

***Unwanted immunological events***

No significant issues were detected. All therapeutic antibodies have the potential to induce anti-drug antibodies (ADAs) although the incidence is usually low and of no clinical significance. In the placebo-controlled severe asthma studies, 6% of patients treated with mepolizumab 100 mg SC and 2% of patients treated with IV mepolizumab developed ADAs. However, most were transient and low titre. Stopping and restarting treatment in MEA115666 did not increase immunogenicity and ADAs were not related to hypersensitivity reactions.

**Postmarketing data**

Not applicable.

**Evaluator's conclusions on safety**

In patients with severe eosinophilic asthma, the safety profile of mepolizumab was comparable to placebo. This was apparent for all doses tested with a flat dose response relationship in the 75 mg to 750 mg IV dose range. This wide safety window supports the use of a unit 100 mg SC dose without the need for mg/kg dosing.

In the pivotal Studies MEA115588 and MEA11575 and in the dose ranging Study MEA112997, the incidence of AEs was similar in the mepolizumab 75 mg IV and 100 mg SC, and placebo groups. Compared with placebo, SAEs and withdrawals due to AEs were lower in the mepolizumab groups compared with placebo. No deaths attributed to mepolizumab were reported. The most commonly observed AEs were headache and nasopharyngitis. As expected, injection site reactions were reported more frequently in the mepolizumab 100 mg SC group (8%) compared with placebo (3%). However, most were mild or moderate and no anaphylactic reactions considered related to mepolizumab treatment by the investigators were reported. There was no evidence of an increased risk of AEs of special interest, including serious or opportunistic infections, malignancies, cardiac, vascular, ischaemic, and thromboembolic events. ADAs were reported in 6% of patients given mepolizumab 100 mg SC but the titres were low or transient and no neutralising ADAs were reported. No differences in the safety profile of mepolizumab were observed in the OLEs. In the Phase III studies<sup>6</sup> the safety profile of reslizumab was also comparable to placebo. The most common AEs were upper respiratory infections and pharyngitis.

As with most therapeutic antibodies, no significant off-target adverse reactions have been identified, and the frequency of injection site reactions was as expected. Anaphylactic reactions cannot always be predicted but none were reported and the risks and management are well understood by clinicians. With the exception of helminthic infections, IL-5 inhibition is not expected to increase the risk of serious infections and no other risks of special interest were observed.

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## First round benefit-risk assessment

### First round assessment of benefits

The benefits of mepolizumab in the proposed usage are:

- An approximately 50% reduction in the rate of asthma exacerbations, including clinically significant exacerbations, exacerbations requiring ED visits, and exacerbations requiring hospitalisation. The percentage reduction equates to an absolute rate reduction of one exacerbation per year in the severe asthma population. This absolute reduction can be considered clinically meaningful as asthma exacerbations are potentially life-threatening, cause considerable morbidity and increase OCS exposure.
- At screening in MEA112997 and MEA115588, near fatal asthma exacerbations in the previous 12 months were reported by 11% and 7% of patients. Although deaths were infrequent in the study program, mepolizumab has the potential to reduce asthma deaths in patients inadequately controlled on maximal doses of other therapies.
- A useful average reduction in the daily dose of OCS was achieved in MEA115575. Compared with placebo, patients treated with mepolizumab were able to reduce their median daily OCS dose by approximately 50%, and approximately 50% of mepolizumab patients were able to reduce their daily OCS dose to  $\leq 5$  mg. This is a significant benefit given the well understood, dose-related toxicity of long term OCS therapy. However, whether or not this OCS reduction is sustained depends on the outcome of an analysis of long-term efficacy in MEA115661.
- Compared with placebo, FEV<sub>1</sub> increased by  $> 50$  ml in the pivotal studies (although the difference was not statistically significant in MEA112997). The improvement in lung function was associated with improved asthma control measured by ACQ-5, and improved quality of life measured by SGRQ.
- Efficacy rates were maintained with long term treatment with no evidence of tolerance and immunogenicity rates were low.
- The safety profile of mepolizumab was comparable to placebo. Local and systemic injection reactions were generally mild and the rates were comparable to other therapeutic antibodies.
- There is a high therapeutic index with doses of up to 750 mg sharing a safety profile similar to placebo. This is reassuring when treating patients with low body weight. It also justifies the fixed dose of 100 mg SC rather than a dosage based on mg/kg.

### First round assessment of risks

The risks of mepolizumab in the proposed usage are:

- Systemic allergic reactions and local injection site reactions: however, the rates comparable to those of other therapeutic proteins and the risk of anaphylaxis are low. These reactions are now well understood and they are easily manageable in all but exceptional cases.
- Immunogenicity: however, the rates were low and no long term tolerance was observed.
- Serious and opportunistic infections: however, the rates were comparable to placebo.
- Malignancies: however, the rates were low and comparable to background levels in the general community. IL-5 inhibition is not expected to increase the rate of

malignancies. However, the risk cannot be quantified without continued observation over longer time periods.

- The number of adolescents treated with mepolizumab is too small to assess efficacy or safety in patients aged 12 to 17.
- The maintenance of the effect of OCS dose reduction was not adequately evaluated with only a four week follow-up.

### **First round assessment of benefit-risk balance**

The benefit-risk balance is favourable although further data are required to support the proposed indication. With this caveat, mepolizumab reduces the rate of clinically significant exacerbations in patients with severe eosinophilic asthma. It also enables reduction in the dose of maintenance OCS therapy but long term data are required to confirm this observation. With the exception of injection reactions, the safety profile of mepolizumab is comparable to placebo.

### **First round recommendation regarding authorisation**

Authorisation is not recommended for the indication *'as add-on treatment for severe eosinophilic asthma in patients aged 12 years and over identified by either a blood eosinophil count  $\geq 150$  cells/ $\mu$ L at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu$ L in the prior 12 months, with a history of exacerbations and/or dependency on systemic corticosteroids'*

A favourable safety profile has been established in a large number of patients given mepolizumab in doses of up to 750 mg IV. However, insufficient efficacy data have been submitted:

- To support the indication *'with a history of exacerbations AND dependency on systemic steroids'*, the sponsor has provided a Phase IIb dose ranging study (MEA112997) in which only 33% of patients were receiving maintenance OCS at baseline. A least effective dose based on exacerbation rates was not established.
- A single pivotal Phase III study (MEA115588) was provided. The EMA guideline CPMP/EWP/2330/99 recommends that *'in cases when the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling...'*. The external validity of MEA115588 has not been established as the overall efficacy rate was driven largely by patients who were not receiving OCS. Only 144 (30%) patients were receiving maintenance OCS at screening (44 placebo, 48 mepolizumab 75 mg IV and 52 mepolizumab 100 mg SC). The treatment benefit in this population was notably less, and not statistically significant in the 100 mg SC group. The study was not powered to show a treatment difference in the maintenance OCS population and patient numbers in the other pre-specified subgroups were low. Overall, MEA115588 should be considered a Phase IIb exploratory study in a mixed patient population and it did not meet the criteria for a pivotal Phase III trial.
- Insufficient data were provided to support use in adolescents.
- The blood eosinophil criteria for initiation of treatment in the target population (patients receiving maintenance OCS) have not been convincingly established.
- No data have been provided to support the indication *'with a history of exacerbations OR dependency on systemic steroids'*. Patients in the steroid sparing study (MEA115575) had a significant history of exacerbations. Despite the encouraging results, MEA115575 should be considered an exploratory Phase II study as the effects



of steroid reduction were studied in limited patient numbers for only four weeks. Insufficient long term efficacy data have been provided.

## Clinical questions

Additional expert input was not required.

### Pharmacokinetics

#### Question 1

As mentioned in the Formulation Development section of this report, two forms of mepolizumab drug substance were primarily used in the clinical trials (MDS1 and MDS2). Studies MEA115705, MEA114092, SB-240563/018 and SB-240563/017 all used MDS1. However, no PK studies contained in the evaluation materials examined the bioequivalence between SC doses of MDS1 and the proposed commercial formulation, that is MDS2, and no biowaiver has been applied for. Can the sponsor please justify why no bridging study between the trial and commercial formulations of mepolizumab has been conducted and/or why no application for a biowaiver has been made?

### Pharmacodynamics

No questions.

### Efficacy

#### Question 1

The study population in MEA112997 comprised patients with severe uncontrolled refractory asthma, with eosinophil markers assessed as a post hoc exploratory secondary objective. Given that mepolizumab specifically inhibits IL-5 and hence reduces eosinophil numbers and function, why was the relationship between treatment and blood eosinophil numbers not thoroughly examined prospectively?

#### Question 2

In MEA112997, 33% of patients reportedly received maintenance OCS at screening (Table 15 in Attachment 2). However, in Section 5.4 of the Clinical Study Report (CSR), the reported number was 188 (31%). Please clarify.

#### Question 3

In MEA112997, it is not clear from Table 15 in Attachment 2 if all patients met at least one of the inclusion criteria for severe eosinophilic asthma. The proportion of patients with blood eosinophils, sputum eosinophils and eNO are presented as Y/N without units of measurement. Moreover, one or more of the parameters were not present, or were unknown, in a large proportion of patients. As an example, blood eosinophils were not recorded in 14% of the total group. As baseline haematology was reportedly performed by a central laboratory, and presumably eosinophil counts were included in the panel, please explain why blood eosinophil counts were not available for all patients.

In the same table, 30% of patients had '*Lack of asthma control*' at screening. This patient group had deterioration of asthma control following a  $\leq 25\%$  reduction in the regular maintenance dose of ICS or OCS, as defined in the inclusion criteria. However, it seems improbable that 30% of patients with severe refractory asthma would have had their ICS or OCS reduced by  $\geq 25\%$  in the previous year as part of normal clinical practice. Please confirm that Institutional Review Board (IRB) approval was given if these patients did undergo a trial of steroid reduction to meet the entry criteria.

**Question 4**

In MEA112997 and MEA115588, the inclusion criteria included a history of exacerbations. In MEA115575, patients were not required to have a history of exacerbations but 84% reported at least one event with a mean of 3.1 events in the previous year. Please suggest how MEA115575 study supports the specific wording of the proposed indication '.....or dependency on systemic corticosteroids'.

**Question 5**

- a. In the MEA115588 CSR, the sponsor states that patients who did not have  $\geq 150$  cells/ $\mu\text{L}$  at baseline '*had a reduced positive response to mepolizumab in terms of exacerbation frequency*'. However, in Table 32 in Attachment 2 the data suggest no meaningful response with RR ratios of 0.93 (95% CI: 0.42, 2.04) and 0.90 (0.43, 1.86) in the 75 mg IV and 100 mg SC groups, respectively. Please justify the first statement. It appears that only patients with  $\geq 150$  cells/ $\mu\text{L}$  at screening had a positive response in which case  $\geq 150$  cells/ $\mu\text{L}$  could be used in isolation as a useful biomarker of response.
- b. The data in the same table offer scant support for the use of  $\geq 300$  cells/ $\mu\text{L}$  in the previous 12 months as a sole treatment criterion in the proposed indication. MEA115588 is the most useful study supporting the use of blood eosinophils as a biomarker. Based on Table 32 in Attachment 2 please provide a justification to support the use of  $\geq 300$  cells/ $\mu\text{L}$  as a stand-alone criterion in the proposed indication.
- c. In MEA112997 and all other studies, the potentially confounding effect of corticosteroid-induced eosinophil suppression in patients receiving maintenance OCS was not addressed. It is possible that patients with the most poorly controlled asthma (commonly those receiving OCS) will fail to meet the eosinophil criteria in the proposed indication simply because they are receiving OCS. Please provide a comparison of eosinophil counts at screening in patients both with and without maintenance OCS use. Please use this analysis to further justify the eosinophil criteria for patients receiving OCS in the proposed indication.

**Question 6**

In MEA115661, a total of 65 patients received mepolizumab 100 mg SC in the steroid reduction feeder Study MEA115575 compared with 349 patients who received 75 mg IV or 100 mg SC in MEA115588 (Table 27 in Attachment 2). Overall, efficacy was sustained long term but the results are driven primarily by patients in the MEA112997 study who did not participate in a steroid reduction protocol. Sustained efficacy cannot be determined in patients who successfully reduced the maintenance dose of OCS for only 4 weeks. Please provide a separate analysis of the MEA115575 subgroup in MEA115661, including as a minimum the final maintenance dose of OCS and exacerbation rates.

**Question 7**

Up to 25% of asthmatics smoke but current smokers were excluded from the severe asthma studies. Please comment on eosinophil function in asthmatic smokers and the potential value of mepolizumab in this population.

**Question 8**

Table 39 in the MEA115575 CSR (not included in this summary) reports a higher percentage of ADRs in the mepolizumab 100 mg SC group (30%) than in the placebo group (18%). However, the absolute numbers of ADRs reported in each group appear to be comparable. Please clarify.

**Question 9**

In the ME115588 CSR, in the text 24% of patients were taking continuous OCS at screening but 30% are reported in the CSR Table 7 (table not included in this summary). Please clarify.

**Safety****Question 1**

In Study MEA112997, cardiac and vascular disorders were identified a priori as AEs of special interest. Please briefly describe any theoretical cardiovascular risks specifically related to IL-5 inhibition on which this concern might have been based.

**Question 2**

Nasopharyngitis as a PT was amongst the most common AEs reported in the clinical trial program but it is not reported as such in the PI. Presumably the omission relates to relative risk but please confirm or otherwise.

**Question 3**

In MEA112997, there were no meaningful changes in mean serum creatinine from baseline to Week 52 in the placebo or mepolizumab groups. There were no clinically meaningful changes in serum creatinine throughout the treatment period in the placebo group but isolated, significant increases were reported in the mepolizumab groups (Table 68 in Attachment 2). Please provide a brief narrative for these events as no comments are provided in the CSR.

**Second round evaluation of clinical data submitted in response to questions**

The sponsor's responses to the Clinical questions and the evaluator's comments on the sponsor's responses are detailed in Attachment 2.

**Second round benefit-risk assessment**

Authorisation is recommended for the proposed indication with wording amended from the first version:

*Nucala is indicated as an add-on treatment for severe asthma with eosinophilic inflammation in patients aged 12 years and over with a history of exacerbations and/or dependency on systemic corticosteroids. Patients should have a blood eosinophil count  $\geq 150$  cells/ $\mu$ L at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu$ L in the prior 12 months.*

Most concerns raised in the first round have been addressed by the sponsor in response to the clinical questions, most notably by providing the final data for the steroid sparing effect in Study MEA115575.

Efficacy and safety have not been established in the limited number of adolescent patients studied. However, the risks associated with maintenance OCS are well established and cannot be ignored. Despite the paucity of data, a steroid sparing effect with a reduction in exacerbation rates alters the risk-benefit balance in favour of mepolizumab treatment. This assessment applies only to adolescents receiving maintenance OCS as defined in the indication.

The sponsor has not justified use in patients with asthma well controlled by OCS as nearly all patients in MEA115575 had a history of exacerbations. Despite the lack of direct

evidence in patients without exacerbations, this small subgroup can reasonably be expected to benefit from the steroid sparing effects of mepolizumab.

## V. Pharmacovigilance findings

### Risk management plan (RMP)

The sponsor submitted a Risk Management Plan (EU-RMP version 01 data lock point 10 July 2014), with an Australian Specific Annex version 1.0 dated November 2014 which was reviewed by the RMP evaluator and evaluation comments are summarised below.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 9.

**Table 7: Summary of safety concerns**

Important identified risks	Systemic Allergic and Non-Allergic Reactions Local Injection Site Reactions
Important potential risks	Immunogenicity Alterations in immune response (infections) Alterations in immune response (malignancies) Alterations in cardiovascular safety Exaggerated response of symptoms upon cessation of treatment with mepolizumab
Important missing information	Limited data in pregnant and lactating patients Limited data in patients $\leq 18$ years of age Patients with parasites or at high risk of parasitic infections Limited data in long-term safety of 100 mg SC dose

### Pharmacovigilance plan

Routine pharmacovigilance has been proposed in the EU-RMP to monitor all the safety concerns. This includes targeted follow-up questionnaires for the following:

- Identified risks: systemic allergic/hypersensitivity and non-allergic reactions;
- Potential risks: immunogenicity, alterations in cardiovascular safety.

Specifically, the sponsor has listed the following adverse events to be monitored using the targeted follow-up questionnaires in the ASA:

- Hypersensitivity/anaphylaxis
- Myocardial infarction/unstable angina
- Cerebrovascular events: stroke and transient ischemic attack
- Deep vein thrombosis/pulmonary embolism
- Peripheral arterial thromboembolism

The sponsor also plans to conduct a pharmacokinetic/pharmacodynamics study to monitor the safety of mepolizumab in children of 6 to 11 years of age; and a pregnancy surveillance study in the USA and Canada to monitor the safety of mepolizumab during pregnancy.

### Risk minimisation plan

The sponsor proposes routine risk minimisation for all the safety concerns except the important potential risks '*alterations in immune response (malignancy)*', '*alterations in cardiovascular safety*', '*exaggerated response of symptoms upon cessation of treatment*' for which no risk minimisation is considered necessary. The sponsor proposes no additional risk minimisation.

### Advisory committee on the safety of medicines (ACSOM) questions

Any issues raised in the RMP report that are not adequately addressed by the sponsor's response are likely to be referred to ACSOM.

### Reconciliation of issues outlined in the RMP report

Table 8 summarises recommendation of the RMP evaluation report and the sponsor's responses to the issues raised.

**Table 8: Reconciliation issues outlined in the RMP evaluation report**

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the non-clinical and clinical evaluators. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The responses to the requests and/or Nonclinical and Clinical Evaluation Reports have been reviewed and the company confirms that an update to the RMP in respect of these is not required.	The evaluator assumes what the sponsor means is that the non-clinical and clinical evaluators are satisfied with the relevant parts of the EU-RMP. It is noted that an updated EU-RMP and ASA have been provided with the sponsor's response.
2. It is noted that the following safety concerns that have been identified with the use of other interleukin	a) Everds and Tarrant <sup>10</sup> discuss haematotoxicity caused by biotherapeutic agents, which can be directly related to the activity of the drug or indirectly due to autoimmunity, biological cascades, antidrug antibodies, or other immune system	The sponsor's response is acceptable.

<sup>10</sup> Everds NE, Tarrant JM: Unexpected hematologic effects of biotherapeutics in nonclinical species and in humans. Toxicol Pathol 2013 Feb;41(2)

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>antagonists, including IL-5 antagonists, are missing from the above list:</p> <ol style="list-style-type: none"> <li>Blood dyscrasia;</li> <li>Use in patients with severe renal impairment.</li> </ol> <p>The sponsor should provide justification as to why these safety concerns are not relevant to the use of mepolizumab, or include them in the list of safety concerns in the ASA.</p>	<p>responses. Most hematologic toxicities of biotherapeutics are not based on drug class, but instead are species specific, immune-mediated, and of low incidence. Despite the potential for hematologic toxicity in most biotherapeutics, the risk-benefit profile is favourable; hematologic effects are readily monitorable and managed by dose modification, drug withdrawal, and/or therapeutic intervention.</p> <p>Mepolizumab is a humanised IgG1 monoclonal antibody that blocks human interleukin-5 from binding to the IL-5 receptor complex expressed on eosinophil cell surface and thus inhibits signalling. Neutralisation of IL-5 with mepolizumab temporarily reduces blood and sputum eosinophils. In the mepolizumab severe asthma development program, hematologic profiles (that is complete blood counts) were extensively evaluated in over 2000 subjects and no signals or trends were noted with the exception of the expected (on target) decrease in blood eosinophil levels. Furthermore, the immunogenicity profile of mepolizumab has been extensively evaluated. In the placebo-controlled Severe Asthma Studies, 15 subjects out of 263 (6%) treated with 100 mg SC and 13 subjects out of 652 (2%) treated with IV mepolizumab had anti-mepolizumab antibodies after having received at least one dose. Antibodies were low titre and mostly transient; 50% of these subjects had only one positive test result. There were no signals for immune-mediated responses (that is hypersensitivity reactions or serum sickness) associated with positive anti-mepolizumab antibody status.</p> <p>GSK will continue to collect and evaluate haematology data. Once mepolizumab is available commercially, GSK routinely employs a robust pro-active process for identifying safety signals in the postmarketing environment with four main components:</p> <ol style="list-style-type: none"> <li>Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.</li> <li>Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.</li> </ol>	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p>3. Systematic, regular review of the literature.</p> <p>4. Regular review of aggregate observational data.</p> <p>Sources screened for signals include the GSK safety database, the GSK disproportionality analysis tool for Signal Management, global scientific literature, clinical study data, epidemiology study data, and observational databases.</p> <p>Considering the absence of a signal in the hematologic profile of mepolizumab to date, GSK does not consider haematotoxicity a safety concern. It is GSK's position that continued monitoring and evaluation of new data in ongoing and planned clinical trials coupled with GSK's robust post-marketing surveillance and safety signal detection processes are adequate for monitoring for new evidence of hematologic toxicity.</p> <p>*A safety signal is defined as a report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance (CIOMS VI).</p> <p>b) Mepolizumab is a humanised IgG1 monoclonal antibody characterized by a large molecular weight of 149.2 kDa that precludes its elimination by glomerular filtration. Consequently, changes in renal function are not anticipated to impact the elimination of mepolizumab.</p> <p>From a population PK analysis of Phase III severe asthma data, there was no evidence that patients with creatinine clearance values between 50–80 mL/min have reduced mepolizumab clearance compared with creatinine clearance values &gt;80 mL/min. Data is however, limited in patients with creatinine clearance values ≤50 mL/min.</p> <p>Additionally, the population PK model predicts that the effect of creatinine clearance on mepolizumab exposure in the different renal impairment categories; defined as 10, 50 and 80 mL/min (compared with a typical value of 112 mL/min), are increases of 35%, 10% and 4%, respectively. These increases are not considered clinically significant, particularly in the context of the safety profile of mepolizumab. The Company therefore does not consider severe renal impairment a safety concern.</p>	
3. The sponsor should provide an update to	GSK will provide a finalized protocol by 2Q2016. The table below includes the	The sponsor's response is

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>the protocol of the pregnancy study once it has been finalised. This should include key milestones and the dates on which reports are scheduled to be submitted in Australia.</p>	<p>planned timeline for major milestones. RMP evaluator: Table not included here.</p>	<p>acceptable.</p>
<p>4. Considering the different indications applied in the EU and in Australia, the sponsor should provide its plan on enhanced surveillance to monitor the safety of mepolizumab in patients between 12 and 18 years of age, or provide justification as to why enhanced surveillance is not necessary in this patient group.</p>	<p>GSK conducts signal detection throughout the product lifecycle for each marketed product and employs a robust, routine, proactive process for identifying safety signals with four main components described below. For newly marketed products including mepolizumab, intense and frequent review of data is required to detect emerging safety signals and to manage risks as the safety profile evolves thus an 'enhanced surveillance' is embedded in GSK's signal detection process. This routine approach will be applied for all approved indications and patient populations globally; no additional activities to the ones outlined below are planned.</p> <ol style="list-style-type: none"> <li>1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.</li> <li>2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.</li> <li>3. Systematic, regular review of the literature.</li> <li>4. Regular review of aggregate observational data.</li> </ol> <p>Sources screened for signals, both as part of GSK's routine pharmacovigilance and in the preparation of a Periodic Benefit Risk Evaluation Report (PBRER), include the GSK safety database, the GSK disproportionality analysis tool for Signal Management, global scientific literature, clinical study data, epidemiology study data, observational databases, and pre-clinical information.</p> <p>Monthly reviews of aggregate data via Signal Management tools are the primary mode of routine post-marketing signal detection for newly marketed products. Included in this regular review is a mandatory review of events reported from the paediatric population (&lt; 18 years of age). Quantitative analysis is the primary method for detecting signals in the paediatric population. The</p>	<p>The evaluator has noted the sponsor's justification.</p>



Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p>method identifies events reported with increased relative frequency for the population of interest (that is children &lt; 18 years of age) compared with: i) all patients within the population of interest for all drugs, and ii) the adult population (where age is between 18 and 64 years) for the drug of interest (that is mepolizumab).</p> <p>Newly identified safety signals meeting criteria for expedited reporting are communicated promptly to Regulatory Authorities, and all signals are prioritised for evaluation. Evaluation results are referred through the GSK medical governance process (that is the appropriate Safety Board and/or Labelling Committee) to consider any impact on the benefit-risk profile of the product, the need to amend the global data sheet and labels and the Risk Management Plan.</p> <p>See response to RMP Question 5 for additional related information.</p>	
<p>5. The indication difference between the EU and Australia means that patients aged 12 to 17 years are considered off-label use in the EU but not so in Australia. According to the EU-RMP, only 19 patients in this age group were enrolled in the severe asthma program in clinical trials. Monitoring and reporting of adverse events in this patient group is still necessary to collect further evidence. It is recommended that the sponsor undertakes to give specific consideration of all reported adverse events in patients below the age of 18 years in the Periodic Safety Update Reports (PSURs).</p>	<p>The sponsor's Summary of Clinical Safety provides a review of adverse events by age group from the severe asthma placebo controlled studies. The data show that the System Organ Class (SOC) adverse event profile for adolescent subjects aged 12 to 17 years followed a similar trend to the overall population in the severe asthma placebo controlled studies (Integrated Summary of Safety [ISS], Table 23 and Table 38- not included in this summary), despite the varying sample sizes. GSK recognises that the limited number of subjects 12 to 17 years of age (n = 28 across placebo and mepolizumab treatment groups) enrolled in these studies makes it challenging to interpret the results, nonetheless, the adverse event profile of the adolescent subgroup is consistent with the intent to treat (ITT) experience. The Periodic Benefit Risk Evaluation Report (PBRER) is GSK's primary global periodic safety report post approval. GSK will include in the PBRER all available data collected in the adolescent population that is indicative of a new potential or identified safety signal. Based on the available data to date, the safety profile in adolescent patients is similar to the overall population; therefore, GSK believes that routine processes described below are sufficient to monitor and evaluate the long-term safety in patients 12 to 17 years old. The EU RMP will be updated with any relevant new data from clinical trials and/or the post-marketing setting regarding</p>	<p>The evaluator has noted the sponsor's response. Although small scale clinical studies may not identify rare events or long-term effects due to their limited statistical power and the study duration, reporting of such events in the patient group that has not been adequately studied is an important routine pharmacovigilance measure. The sponsor should give specific consideration of all reported adverse events in patients aged 12 to 17 years in the PBRER/PSURs</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	<p>mepolizumab use in adolescent patients as appropriate.</p> <p>The following is a description of GSK's methods of signal detection and sources screened. GSK employs a robust, routine, pro-active process for identifying safety signals with four main components:</p> <ol style="list-style-type: none"> <li>1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.</li> <li>2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.</li> <li>3. Systematic, regular review of the literature.</li> <li>4. Regular review of aggregate observational data.</li> </ol> <p>Sources screened for signals, both as part of GSK's routine pharmacovigilance and in the preparation of a PBRRER, include the GSK safety database, the GSK disproportionality analysis tool for Signal Management, global scientific literature, clinical study data, epidemiology study data, observational databases, and nonclinical information.</p> <p>See response to RMP Question 4 for additional related information.</p>	<p><sup>11</sup>.</p>

## VI. Overall conclusion and risk/benefit assessment

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

### Quality

All quality issues have been resolved except that there appear to be some GMP clearance certificates that are still under application.

### Nonclinical

The nonclinical evaluator did not have any objections to the registration of mepolizumab for the proposed indication. No safety concerns were identified from the nonclinical data.

<sup>11</sup> Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Reports

## Clinical

### Pharmacodynamics and pharmacokinetics

The mechanism of action is well-established: prevention of binding of IL-5 to the eosinophil cell surface, which inhibits IL-5 signalling and consequently promotion growth and survival of eosinophils in the blood sputum and other tissues.

Subcutaneous absorption of mepolizumab is slow; absolute bioavailability: 74 to 80%;  $T_{max}$ : 4 to 8 days; absorption and distribution half-lives: 1 to 2 days; volume of distribution approximates plasma and interstitial space: 55 to 85 ml/kg; catabolism is by ubiquitous proteolytic enzymes; terminal phase elimination half-life: 16 to 22 days.

A population PK analysis showed that exponent for weight on clearance was 0.75. This is not considered clinically relevant and no dosage adjustment for body weight is currently recommended; although a further PK/PD study is planned before the product could be registered for children.

Given the mechanism of elimination (ubiquitous proteolytic enzymes), no dosage adjustments are proposed for renal or hepatic insufficiency.

Mepolizumab has low immunogenicity, which does not influence pharmacokinetics or pharmacodynamics.

### Efficacy

The evidence base for registration relies on three pivotal trials: two 'exacerbation' trials and one 'steroid-sparing' trial. The first of the exacerbation trials was also a dose-finding (IIb/III) study.

It is not the intention of this overview to reproduce, in full detail, the design or results of the three pivotal trials. They have been published as:

- Lancet 2012; 380(9842):651-9.
- New England Journal of Medicine 2014; 371(13):1198-207.
- New England Journal of Medicine 2014; 371(13):1189-97.

They have been assessed in the Clinical Evaluation Report. The sponsor has also provided the TGA with EMA reports, which have assessed and summarised the clinical development program.

Briefly, the first exacerbation trial did not show a dose-response for 75 mg, 250 mg, or 750 mg IV, 4-weekly for 48 weeks. That is, the reduction in exacerbations, compared to placebo, was similar for all three doses. Therefore, the posology taken forward to the second exacerbation trial was 75 mg IV and 100 mg SC (equivalent exposure: IV/SC; absolute bioavailability of SC dose is 75%).

Pooled results from the two exacerbation trials showed that mepolizumab (100 mg SC or 75 mg IV, 4-weekly) reduced severe exacerbations (requiring systemic corticosteroids, hospitalisation, or ED visit) by about 50%; pooled RR (ITT population) 0.51 (95% CI: 0.42, 0.61). In absolute terms, this roughly represents a decrease in severe exacerbations from about 2 per year to about 1 per year.

The third pivotal trial showed that the percentage of patients with some reduction in oral corticosteroids was greater for mepolizumab (64%) versus placebo (44%). However, this trial was small (mepolizumab n = 69; placebo n = 66), of relatively short duration (24 weeks, with a 4 week maintenance), and had a high level of protocol deviations. Also, interpretation was complicated by baseline imbalances between the two groups. However, based largely on the open label extension of this study, the EMA (p121 of 123, CHMP

Assessment Report- not included in this summary), has concluded that: *'In corticosteroid dependent patients, a modest improvement in pre-bronchodilator FEV<sub>1</sub> was observed and for some patients a decrease of >50% of OCS was possible, which was shown to be sustainable for at least an additional 6 months.'*

Secondary endpoints (for example pre/post bronchodilator FEV<sub>1</sub>, asthma control, quality-of-life) were inconsistent across the three trials, but did not raise any specific concerns, given the convincing results for reduction in exacerbations, which is probably the most important outcome for patients with severe asthma.

From EMA Day-120 evaluation (p104 of 123- not included in this summary): *'Exacerbations are the most important outcome in asthma control, because they constitute the greatest risk to patients, they are a cause of anxiety for patients and their families....'*

## **Safety**

Based on the currently available data (that is pre-market data), the safety profile of mepolizumab is mainly characterised by minor adverse effects (for example headache, nasopharyngitis, and local reactions).

On review of adverse reactions of special interest, there was no apparent increased risk of malignancy, infections, infestations, or major cardiovascular events; with the obvious caveat that the pivotal trials were too small and too short to detect uncommon/rare adverse reactions or delayed adverse reactions.

Local site reactions were more common for SC administration (8%) versus IV (3%) and placebo (3%). This is typical of SC administration and the reactions were manageable.

There was one report of a serious delayed type IV hypersensitivity reaction that required treatment in ICU (from an extension study). This hypersensitivity reaction occurred 3 days after the 9<sup>th</sup> dose of mepolizumab. A warning about the possibility of acute or delayed hypersensitivity reactions will be included in the PI.

For mAbs, in general, hypersensitivity reactions tend to be identified (and more completely understood) in post-marketing, rather than pre-marketing data.

In the pre-market data, only one patient developed neutralising antibodies.

Based on the currently available data, there does not seem to be any evidence of 'rebound' severe asthma on stopping treatment with mepolizumab.

The main limitation, from a safety perspective, is that, in the pre-market clinical development program, only 442 patients received mepolizumab for more than 12 months; and none of these patients received mepolizumab for more than 24 months.

## **Risk management plan**

### ***Summary of safety concerns***

A summary of safety concerns are shown in Table 9.

### ***Pharmacovigilance plan***

On-going studies, due to report following registration, are:

- MEA115666: This is an open label extension of the first exacerbation study (MEA112997). There was a treatment interruption of 12 to 28 months (median: 18 months) during which the exacerbation rate increased. The aim is to report long term safety data. Due date for final report is 2018.
- MEA201312: This is an open label extension of MEA115661, which enrolled patients from the two other Phase III trials (exacerbation MEA115588, steroid sparing

MEA115575) without treatment interruption for an additional 52 weeks. It showed sustained reductions in exacerbation rates. The further long term follow-up will primarily assess safety. It is due to report in 2018.

- **Pregnancy Surveillance Study:** This will evaluate outcome for mothers who become pregnant while taking mepolizumab (and outcomes for their babies). It is due to report in 2022.

### ***Risk minimisation measures***

The sponsor's plan is to mitigate the important safety concerns using routine risk minimisation measures (RMMs) (for example statements in PI). No additional RMMs are proposed.

### ***Advisory Committee on the Safety of Medicines (ACSOM)***

The Pharmacovigilance and Special Access Branch have requested advice from ACSOM about whether, any additional pharmacovigilance or risk minimisation measures are needed; should the product be registered for adolescents aged 12 to 17 years.

The current RMP is based on the EU RMP. In the EU, the application is only for registration in adults.

### **Risk-benefit analysis**

#### ***Delegate's considerations***

During the evaluation, the TGA sought advice from an independent external clinical expert on two issues:

- Definition/diagnosis of severe eosinophilia asthma.
- Inclusion of adolescents.

The background information outlining the TGA's current understanding of the evidence underpinning these two issues was provided. The independent external expert's advice provided to TGA was attached for the ACPM members to consider.

Also attached was the advice from the sponsor's two clinical experts in response to the same TGA questions. The sponsor states that neither of these experts was involved in the mepolizumab clinical trials conducted in Australia and are not representatives of advisory boards relating to mepolizumab.

The TGA has also sought advice on the same issues from the National Asthma Council. This advice will be provided when it is received.

In brief, on the issue of registration for adolescents, the external independent expert advised that the product could be registered for this age group. Refer to the attached advice for the reasoning (document not included in this summary).

### **Conditions of registration**

Biological chemistry has stipulated a condition of registration.

Standard conditions will apply about implementing the RMP.

### **Product information**

Negotiations with the sponsor will be finalised when the TGA has seen the final EMA SmPC and the FDA PI.

## Response from sponsor

GSK welcomes the TGA Delegate's assessment that there are no reasons that Nucala (mepolizumab) should not be approved. This is consistent with the positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 25 September 2015, which recommended registration for '*add-on treatment for severe refractory eosinophilic asthma in adult patients*' and the US Food and Drug Administration (FDA) decision on 4 November 2015 to register Nucala '*for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype*'.

The proposed indication for Australia is:

*Nucala is indicated as an add-on treatment for severe asthma with eosinophilic inflammation in patients aged 12 years and over with a history of exacerbations and/or dependency on systemic corticosteroids. Patients should have a blood eosinophil count  $\geq 150$  cells/ $\mu$ L at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu$ L in the prior 12 months.*

The indication is supported by:

- a comprehensive clinical trial program which included 2 pivotal clinical trials (112997 and 115588) which measured the frequency of clinically significant exacerbations as the primary outcome and 1 pivotal trial (115575) which was a steroid-sparing study in which OCS dose-reduction was the primary endpoint.
- the pooled results from the 2 pivotal exacerbation studies which demonstrated a 49% reduction in the likelihood of experiencing a clinically significant exacerbation [RR 0.51 (95% CI: 0.42, 0.61)] based on the inclusion criteria as defined in the indication.
- the pivotal steroid sparing study which demonstrated that mepolizumab allows patients to significantly reduce OCS usage, whilst maintaining asthma control, compared with subjects treated with standard of care (SOC)[OR 2.39, (p = 0.008)]. This clinically meaningful result in a 24 week study was confirmed for subjects who transferred to the open label extension study (115661) where the reduction in maintenance OCS was sustained over the duration of the trial (up to 76 weeks).
- data in adolescents which confirms that the PD and PK response is similar to adults and which has been accepted by the US FDA and reflected in the US approved indication.
- safety data that demonstrates that mepolizumab is safe and well tolerated with a safety profile comparable to standard of care (SOC). The clinical evaluator concluded that '*with the exception of injection site reactions, the safety profile of mepolizumab is comparable to placebo*'
- the incidence of hypersensitivity reactions and injection site reactions are comparable to other therapeutic proteins and when administered under the supervision of a healthcare professional are easily managed.

### ***Issues raised in the body of the delegate's request for ACPM's advice***

*Inclusion of adolescents in the indicated patient population*

*International regulatory status*

An indication for use in patients 12 and above was requested in the US and Australian applications. On the basis of discussions with the EU paediatric committee and agreement to conduct a further PK/PD and safety study in a paediatric population aged 6 to 11 and utilising the adolescent data from the pivotal severe asthma clinical studies to support a paediatric indication for 6 to 17 years, the initial application submitted to the European

Medicine Agency (EMA) did not request the inclusion of the adolescent population in the indication. The European SmPC includes all available adolescent data with a qualifying statement that the data and therefore conclusions from this data are limited. Similarly following pre submission feedback from Health Canada, the indication was restricted to adult patients ( $\geq 18$  years of age).

Questions relating to use in adolescents were also raised by the US FDA. A detailed subgroup analysis in adolescents was submitted to both the US FDA and TGA post FDA Advisory Committee outcomes and formed the basis of the decision by the US FDA to include adolescents in the registered indication.

#### *Unmet need*

Severe eosinophilic asthma is uncommon in paediatric patients; however, the unmet medical need is high. A paediatric respiratory physician in a signed expert statement to the TGA stated that '*Severe asthma is uncommon, however for affected patients, there are few alternatives to daily OCS which are associated with severe side effects, especially in children and adolescents. The only currently available alternative for patients not controlled on inhaled therapies and systemic corticosteroids is omalizumab (Xolair), which is not effective in all patients*'. He also confirmed that '*there is a definite clinical need for mepolizumab in adolescents with severe eosinophilic asthma in Australia*'.

The independent expert advising the TGA and the expert statements from the sponsor all support that the biology and pathophysiology of severe eosinophilic asthma in adults and adolescents is similar.

#### ***Clinical data in severe asthma***

##### *Efficacy*

Because severe asthma is uncommon in paediatric patients, the number of subjects recruited to the mepolizumab Phase III programme was relatively low. A total of 28 adolescents were randomised to studies MEA112997 (1 subject), MEA115588 (25 subjects), and MEA115575 (2 patients).

Despite having a mean age of 14.8 years, subjects had long duration of asthma considering their young age with a mean duration of 9.6 years. The majority (72%) of these subjects were atopic, consistent with the phenotype in this age group. The geometric mean baseline blood eosinophil count was 243 cells/ $\mu$ L, which is relatively similar to the overall population of 290 cells/ $\mu$ L.

Adolescent subjects had a history of poor control and frequent exacerbations similar to the overall population (mean of 3.7 versus 3.6 per year). In adolescents 40% required an emergency department (ED) visit or hospitalisation due to an exacerbation in the previous year compared with 33% of the overall population. Importantly, 32% were hospitalised due to an asthma exacerbation in contrast to 19% in the overall population, confirming the high unmet need in this population. The adolescent subgroup showed a similar reduction in the rate of exacerbations per year compared with the overall population (44% versus 47%). During the open-label extension study (OLE) MEA115661, the rates of exacerbations per year and the use of OCS remained low in the subjects who were previously treated with mepolizumab, indicating that the effect of mepolizumab on the reduction of exacerbations and OCS use is durable and stable over time.

A Respiratory Physician with clinical and research expertise in airway disease, provided the following comment on efficacy '*Additional effective treatment is urgently needed and the data in adolescents, although limited, suggests that this may be provided by mepolizumab*' as well as '*not aware of any biological reason for the efficacy of mepolizumab to be different in adults versus adolescents*'.

## *Safety*

All 28 adolescents were exposed to mepolizumab either in the pivotal placebo-controlled studies and/or in the OLE study MEA115661. The majority of adolescents (75%) had received at least a year of treatment with mepolizumab (75 mg IV and/or 100 mg SC) at this time. The incidence and profile of specific adverse events (AEs) experienced by adolescents was generally similar to the overall population in the placebo controlled studies. The most common AEs were headache and nasopharyngitis. There were no withdrawals due to AEs in the adolescent subgroup. Although the adolescent subgroup was small, there did not appear to be treatment- or dose-related effects on the incidence of AEs. The overall incidence and profile of serious adverse events (SAEs) in adolescents was also similar to the overall population in the placebo-controlled studies (14% versus 12%). Four adolescents (14%) experienced SAEs: 3 patients (11%) had serious asthma exacerbations (2 patients treated with placebo and 1 patient treated with 250 mg IV) and 1 patient (100 mg SC) had dyshidrotic eczema which resolved with continuing treatment. None of these events was considered related to study treatment by the investigators and all 4 patients continued in the study. In the OLE study MEA115661, the AE profile for adolescents remained generally similar to the overall population over the longer duration of mepolizumab treatment. Nasopharyngitis, asthma and sinusitis were reported most often. The incidence of SAEs with long term treatment also remained fairly consistent in the adolescents and overall population (19% versus 14 %). Five adolescents (19%) experienced SAEs during MEAE115661. All 5 patients had serious asthma exacerbations; in addition, two of these patients also experienced SAEs of influenza and gastroenteritis, respectively. None of these events was considered related to study treatment by the investigators and all 5 patients continued in the study. Three of these 5 patients had also had SAEs during the placebo-controlled studies.

### ***Pharmacodynamic (PD) response and pharmacokinetics (PK)***

In Study MEA115588, the PD response (eosinophil reduction) with mepolizumab was similar across adolescents and the overall population. For adolescent subjects treated with mepolizumab, the geometric mean eosinophil level was reduced to 40 cells/ $\mu$ L, a similar level to that observed in adults. Available data do not indicate that reduction of eosinophils has any untoward effects on normal health<sup>12</sup> thus, similar to adults, no negative effects are expected in adolescents treated with mepolizumab. Of note, the human immune system is fully functional by adolescence<sup>13</sup> therefore there should be no impact on response to infections, infestations, or malignancy risk.

In addition, population PK analysis showed that after adjusting for bodyweight there was no indication of an effect of age on the PK of mepolizumab. Adolescents displayed plasma concentrations consistent with adults and predicted individual clearance was within the range of the rest of the study population, irrespective of administration route.

### ***Proposed plan for monitoring safety in adolescent patients***

There is no evidence to suggest that safety profile of adolescents receiving mepolizumab will be meaningfully different from adults. The existing evidence supports similarity of disease in adolescents and adults and data with mepolizumab supports similar PK and PD responses in adolescents and adults. Furthermore, clinical data shows similar safety and efficacy outcome profiles in adolescent and adult patients receiving mepolizumab. Therefore it is GSK's position that our post-marketing surveillance and signal evaluation processes described below are sufficient to monitor and evaluate the long-term safety in patients 12 to 17 years old.

<sup>12</sup> Gleich Gjm Klion AD, Lee JJ, Weller PF: The consequences of not having eosinophils. *Allergy*. 2013;68.

<sup>13</sup> Jaspan HB, Lawn SD, Safrit JT, Bekker LG: The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents. *AIDS*. 2006;20



The Periodic Benefit Risk Evaluation Report (PBRER) is GSK's primary global periodic safety report post approval. GSK will include in the PBRER all available data collected in the adolescent population that is indicative of a new potential or identified safety signal. The EU Risk Management Plan (RMP) will be updated with any relevant new data from clinical trials and/or the post-marketing setting regarding mepolizumab use in adolescent patients as appropriate.

GSK conducts signal detection throughout the product lifecycle for each marketed product and employs a robust, routine, pro-active process for identifying safety signals<sup>14</sup> with the main components described below. For newly marketed products including mepolizumab, intense and frequent review of data is required to detect emerging safety signals and to manage risks as the safety profile evolves thus an enhanced surveillance is embedded in GSK's signal detection process. This approach will be applied for all approved indications and patient populations globally.

1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
3. Systematic, regular review of the literature.

Sources screened for signals, both as part of GSK's routine pharmacovigilance and in the preparation of a PBRER, include the GSK safety database, the GSK disproportionality analysis tool for Signal Management), global scientific literature, clinical study data, epidemiology study data and nonclinical information.

Monthly reviews of aggregate data the Signal Management tools are the primary mode of routine post-marketing signal detection for newly marketed products. Included in this regular review is a mandatory review of events reported from the paediatric population (< 18 years of age). Quantitative analysis is the primary method for detecting signals in the paediatric population in OSM. This method identifies events reported with increased relative frequency for the population of interest (that is children < 18 years of age) compared with: i) all patients within the population of interest for all drugs, and ii) the adult population (where age is between 18 and 64 years) for the drug of interest (that is mepolizumab).

Newly identified safety signals meeting criteria for expedited reporting are communicated promptly to regulatory authorities, and all signals are prioritised for evaluation. Evaluation results are referred through the GSK medical governance process (that is the appropriate Safety Board and/or Labeling Committee) to consider any impact on the benefit-risk profile of the product, the need to amend the global data sheet and labels and the RMP.

Of note is the recent approval by the FDA for mepolizumab in severe eosinophilic asthma on 4 November 2015 which includes adult and adolescent subjects 12 to 17 years). No restrictions specific to adolescents or additional surveillance measures were required as part of the approval.

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<sup>14</sup> A safety signal is defined as a report or reports of an event with an unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance (CIOMS VI).

## ***Indication and diagnosis of severe eosinophilic asthma***

### ***Indication***

The revised indication as proposed by GSK and considered acceptable for approval by the clinical evaluator is:

*'Nucala is indicated as an add-on treatment for severe asthma with eosinophilic inflammation in patients aged 12 years and over with a history of exacerbations and/or dependency on systemic corticosteroids. Patients should have a blood eosinophil count  $\geq 150$  cells/ $\mu$ L at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu$ L in the prior 12 months.'*

The proposed indication clearly outlines the condition and the patient population that would benefit from the treatment.

The clinical data supports this indication as confirmed by the clinical evaluator in the second round evaluation comments. The pooled results from the 2 pivotal exacerbation studies (112997 and 115588) demonstrated an approximately 50% reduction in the likelihood of experiencing a clinically significant exacerbation [RR 0.51 (95% CI: 0.42, 0.61)]. In addition to significant reductions in exacerbation, treatment with mepolizumab allows patients to significantly reduce OCS usage, whilst maintaining asthma control, compared with subjects treated with SOC [OR 2.39, (p = 0.008)]. The benefit of mepolizumab is further exemplified by the 94% voluntary continuation rate of subjects from both the mepolizumab and SOC arms in the pivotal Study 115588 to the long term open label Study 115661.

The indication statement together with the Clinical Trials section provides the prescriber with the necessary information in order to make the appropriate prescribing decision for their patient.

During the review of both the US and EU submissions the regulators chose to further simplify the indication statement to reflect the severe eosinophilic asthma phenotype only whilst utilising the prescribing information as a whole to define the specific population and study outcomes. This was their preferred approach to ensure that the full prescribing information is considered in its entirety by the prescriber to inform the appropriate prescribing decision for their patient. The sponsor believes that the indication statement proposed in the Australian Nucala application also achieves this objective.

### ***Definition and diagnosis of severe eosinophilic asthma***

The definition and diagnosis of severe eosinophilic asthma should be separated into:

- firstly, a diagnosis of severe asthma in accordance with the guidelines based on the requirement for intensive asthma medications (high dose ICS plus additional controllers), and
- secondly, a determination of the severe asthma phenotype of which eosinophilic inflammation is one type. Within the severe eosinophilic phenotype, increasing levels of sputum or blood eosinophils are associated with a higher frequency of clinically significant asthma exacerbations.

Therefore, the definition of a patient with severe eosinophilic asthma who will benefit from treatment with mepolizumab is a severe asthmatic with eosinophilic levels as defined in the pivotal clinical trials and shown to have a clinically and statistically significant benefit.

### ***Risk benefit assessment***

Extensive safety data was presented in the submission for approximately 1,300 patients, including data across the 3 pivotal studies (Study 112997, 115588 and 115575) and the final and interim analyses from two long term open label studies (Study 661 and 666

respectively). Across the three pivotal studies, the overall incidence of AEs and serious adverse events (SAE) was similar between placebo and mepolizumab groups.

The long term safety profile of mepolizumab in the open label studies was consistent with findings in the comparative studies. Additionally, the safety profile in adolescents is similar to adults.

Appropriate risk management measures are proposed for monitoring possible safety concerns.

Overall there was no evidence of increased risk compared with SOC and it can be concluded that the benefit risk assessment is positive for Nucala. This conclusion is supported by clinical evaluator and independent experts consulted on this application.

### **Conclusion**

GSK welcomes the Delegate's position that there are no reasons that Nucala (mepolizumab) should not be approved and the clinical evaluator's recommendation to register Nucala *'as an add-on treatment for severe asthma with eosinophilic inflammation in patients aged 12 years and over with a history of exacerbations and/or dependency on systemic corticosteroids. Patients should have a blood eosinophil count  $\geq 150$  cells/ $\mu\text{L}$  at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu\text{L}$  in the prior 12 months.'*

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Nucala powder for injection containing 100 mg of mepolizumab to have an overall positive benefit-risk profile for the proposed indication;

*... an add-on treatment for severe eosinophilic asthma in patients aged 12 years and over identified by either a blood eosinophil count  $\geq 150$  cells/ $\mu\text{L}$  at initiation of treatment or a blood eosinophil count  $\geq 300$  cells/ $\mu\text{L}$  in the prior 12 months, with a history of exacerbations and/or dependency on systemic corticosteroids.*

In making this recommendation the ACPM

- was of the view that the indication should include reference to 'severe eosinophilic asthma' and include patients over 12 years of age.
- was also of the view that inclusion of eosinophilic counts was appropriate.

### **Proposed conditions of registration**

The ACPM agreed with the Delegate on the proposed conditions of registration.

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

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Information regarding a possible rebound effect after cessation of mepolizumab pending further information from the sponsor.
- Inclusion of a weight restriction of greater than 45 kg under Dosage and Administration.
- Under Clinical Trials the following information be included regarding eosinophil count: *'In a subgroup analysis by baseline peripheral blood eosinophil count, pooled data from two exacerbation trials (MEA112997 and MEA115588) showed significant reduction in exacerbation frequency only in subjects with baseline eosinophil count equal to or greater than 300/ $\mu\text{L}$ .'*

### ***Specific advice***

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

1. *The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.*
- The ACPM noted advice from external experts regarding the role of mepolizumab in eosinophilic asthma and the treatment of adolescents. The ACPM was of the view that there was a role for mepolizumab in a rare subgroup of patients and that it provided a further treatment option with some efficacy. The ACPM advised that the underlying pathology for severe eosinophilic asthma is similar for adults and adolescents and that there is no biological reason for efficacy to be any different in these two populations.
  - The ACPM advised that the frequency of hypersensitivity reactions would also be expected to be similar in adults and adolescents. The ACPM was of the view that there should be a weight restriction for adolescents that is greater than 45 kg, but that this could be included in the dosing instructions in the PI rather than the indication.
  - The ACPM noted that a recent report suggested a possible rebound effect after cessation of mepolizumab, and questioned whether it might be necessary to include mention of this in the PI. The ACPM requested that the sponsor be asked to comment on this matter.
  - The ACPM noted that experience in children less than 12 years old had not been reported. The ACPM queried if there were plans for developing a paediatric indication. In addition, the ACPM noted a 'delayed hypersensitivity reaction' that was treated with adrenaline and was interested to know if there was more information regarding this case.
  - The ACPM 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.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Nucala mepolizumab (rch) 100 mg powder for SC injection indicated for:

*Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over (see Clinical Trials).*

### **Specific conditions of registration applying to these goods**

- The mepolizumab EU Risk Management Plan (RMP), (version 01.3, dated 12 August 2015 [data lock point 10 July 2014]), revised as specified by the Australian Specific Annex (version 2.0, dated August 2015), included with submission PM-2014-03872-1-5) and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The PI approved for Nucala at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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