EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nucala

International non-proprietary name: mepolizumab

Procedure No. EMEA/H/C/003860/0000

Note

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

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List of abbreviations

ACQ-5	Asthma Control Questionnaire-5
ACQ-6	Asthma Control Questionnaire-6
ACT	Asthma Control Test
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
ALUS	Automated Loading And Unloading System
AQLQ	Asthma Quality Of Life Questionnaire
ATS	American Thoracic Society
AUC(0-tau)	Area Under The Concentration-Time Curve Over The Dosing Interval
BL	Baseline
BLA	Biologics License Application
BMI	Body Mass Index
bpm	Beats Per Minute
CDRs	Complementarity Determining Regions
CEC	Clinical Endpoint Committee
CEX	Cation Exchange Chromatography
CGE	Capillary Gel Electrophoresis
CHMP	Committee For Medicinal Products For Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
cIEF	Capillary Isoelectric Focusing
CL	Clearance
CL/F	Apparent Clearance
Cmax	Maximum Plasma Concentration
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee For Proprietary Medicinal Products
CPPs	Critical Process Parameters
CQAs	Critical Quality Attributes
CSR	Clinical Study Report
CV	Cardiovascular
CVT	Cardiac, Vascular, And Thromboembolic
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DoE	Design Of Experiment
DP	Drug Product
DSC	Differential Scanning Calorimetry
EC50	Half Maximal Effective Concentration
ECG	Electrocardiogram
ED	Emergency Department
ED	Emergency Department
EGPA	Eosinophilic Granulomatosis With Polyangiitis
ENFUMOSA	European Network For Understanding Mechanisms Of Severe Asthma
EoE	Eosinophilic Esophagitis
EOPCB	End-Of-Production Cell Bank

EOSL	End-Of-Shelf-Life
ERS	European Respiratory Society
EU	European Union
FAAN	Food Allergy And Anaphylaxis Network
FDA	Food And Drug Administration
FEV1	Forced Expiratory Volume In 1 Second
FTIR	Fourier Transform Infrared
GCP	Good Clinical Practice
GINA	Global Initiative For Asthma
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GSK	Glaxosmithkline
HAP	Hamster Antibody Production Assay
HCP	Host Cell Proteins
HES	Hypereosinophilic Syndrome
hIL-5	Human Interleukin 5
HPLC	High Performance Liquid Chromatography
IC50	Half Maximal Inhibitory Concentration
ICS	Inhaled Corticosteroid(S)
ICU	Intensive Care Unit
ID50	Dose Associated With 50% Of The Maximal Inhibition Effect
ID90	Dose Associated With 90% Of The Maximal Inhibition Effect
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-4, IL-5, IL-13, IL -3	Interleukin-4, Interleukin-5, Interleukin-13, Interleukin-3
IM	Intramuscular
Imax	Maximum Inhibitory Effect
IND	Investigational New Drug Application
ITT	Intent-To-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
LABA	Long-Acting Beta Agonists
MAA	Marketing Authorisation Application
mAb	Monoclonal Antibody
MAP	Mouse Antibody Production Assay
MCB	Master Cell Bank
MCID	Minimally Clinically Important Difference
MDP1	Mepolizumab Drug Product 1 (250 Mg/Vial)
MDP2	Mepolizumab Drug Product 2 (100 Mg/Vial)
MDS1	Mepolizumab Active Substance 1
MDS2	Mepolizumab Active Substance 2
MedDRA	Medical Dictionary For Regulatory Activities
NANA	N-Acetylneuraminic Acid
NGNA	N-Glycolylneuraminic Acid
NIAID	National Institute Of Allergy And Infectious Disease
NICE	National Institute For Health And Care Excellence
NIH	National Institutes Of Health

NK	Natural Killer
NOAEL	No Observed Adverse Effect Level
NORs	Normal Operating Ranges
OCS	Oral Corticosteroid(S)
OLE	Open-Label Extension
PARs	Proven Acceptable Ranges
PD	Pharmacodynamic
PD	Pharmacodynamics
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PEF	Peak Exploratory Flow
PK	Pharmacokinetic
PK	Pharmacokinetics
PK	Pharmacokinetics
PMDA	Pharmaceuticals And Medical Devices Agency
PopPK	Population Pharmacokinetics
ppb	Parts Per Billion
PPV	Porcine Parvovirus
PRS	Primary Reference Standard
Q	Inter-Compartmental Clearance
QTc	Corrected QT Interval
QTc(F)	Corrected QT Interval Using Fridericia's Formula
QTPP	Quality Target Product Profile
rhIL-5	Recombinant Human IL-5
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SDS-PAGE	Sodium Dodecylsulfate Polyacrylamide Gel
SEC	Size Exclusion Chromatography
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary Of Product Characteristics
SMQ	Standard Meddra Query
SOC	System Organ Class
SPR	Surface Plasmon Resonance
TFUF	Tangential Flow Ultrafiltration
Th1, Th2	T Helper 1, T Helper 2
Tmax	Time To Maximum Concentration
URTI	Upper Respiratory Tract Infection
V1	Central Volume Of Distribution
V2	Peripheral Volume Of Distribution
WCB	Working Cell Banks

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services submitted on 3 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nucala, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No. 726/2004.

Mepolizumab, was designated as an orphan medicinal product EU/3/13/1116 on 6 February 2013 for the treatment of Churg-Strauss Syndrome and as orphan medicinal product EU/3/04/213 on 4 July 2004 for the treatment of hypereosinophilic syndrome (HES). Orphan designation was not in place for the applied indication.

The applicant applied for the following indication "as an add-on treatment for severe eosinophilic asthma in adult patients identified by either a blood eosinophil count ≥150 cells/µl at initiation of treatment or a blood eosinophil count ≥300 cells/µl in the prior 12 months, with a history of exacerbations and/or dependency on systemic corticosteroids."

The legal basis for this application refers to:

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

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

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-C2-000069-PIP02-10-M04 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0234/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active substance status

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

Scientific advice/Protocol assistance

The applicant received Scientific Advice from the CHMP on 17 February 2000, 29 May 2009, 20 October 2011 and 13 December 2012. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Greg Markey Co-Rapporteur: David Lyons

- The application was received by the EMA on 3 November 2014.
- The procedure started on 26 November 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 February 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 12 March 2015.
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 March 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2015.
- The PRAC Rapporteur Risk management Plan (RMP) assessment report was adopted by PRAC on 9 July 2015.
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 August 2015.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nucala.

2. Scientific discussion

2.1. Introduction

Asthma is a chronic heterogeneous lung disease characterised by inflammation, narrowing of the airways, and reversible airway obstruction. The majority of patients with asthma can be adequately controlled by following step-wise treatment recommendations of both the American Thoracic Society [ATS, 2014] and Global Initiative for Asthma [GINA, 2014]. However, a small minority of patients experience uncontrolled asthma despite attempts to control their disease following these recommendations (e.g., high dose inhaled corticosteroids plus additional controller medications). This group of high-risk patients suffers from frequent exacerbations, limited control of symptoms, and compromised quality of life. Exacerbations are particularly disabling for the patient and typically require treatment with high doses of systemic corticosteroids and may require hospital admission. Although patients with uncontrolled severe asthma represent less than 5% of the total asthma population [Barnes, 1996], these patients experience considerable morbidity [Polosa, 2008] and are responsible for approximately 50% of total health care costs associated with asthma [Cisternas, 2003].

Evidence shows that patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes, including a severe eosinophilic asthma phenotype [Chung, 2014]. Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic airway inflammation despite corticosteroid therapy [Wenzel, 2005]. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma [Cohn, 2004]. Immunoglobulin E (IgE) production and eosinophilic inflammation are promoted by T helper 2 (Th2) cytokines such as IL-5, and to a lesser extent IL-4, and IL-13.

Corticosteroids are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force [Chung, 2014] for severe asthma recommends that control should first be attempted through the use of high-dose ICS before adding daily oral corticosteroids (OCS) or omalizumab (for the subgroup of patients with elevated IgE and who are allergic to a perennial allergen).

Use of OCS on a regular basis has well-documented side effects. Short-term effects of OCS therapy include increased risk of glaucoma, fluid retention, increased blood pressure, mood swings, and weight gain. With long-term use of OCS, there is increased risk of cataracts, diabetes, infections, osteoporosis, fractures, menstrual irregularities, suppressed adrenal gland hormone production, and skin thinning [Manson, 2009]. For these reasons, physicians and patients are reluctant to use OCS on a regular basis to control their asthma and even short-term to treat exacerbations.

Omalizumab, a recombinant humanised mAb (IgG1) is recommended for use in GINA Step 5 (add-on treatment for allergic asthma), but only a small proportion of patients with severe asthma are appropriate candidates for its use based on specific weight and IgE levels in addition to a positive test for a perennial allergen. When the omalizumab label criteria are applied to the severe eosinophilic asthma population, there is a 30% overlap with the mepolizumab target population.

Studies using existing steroid-sparing treatments such as methotrexate, cyclosporine, and oral gold have demonstrated variable and marginal effects on OCS reduction and significant toxicity. Use of these agents is not recommended in the current guidelines because of their high risk/benefit ratio [GINA, 2013]. In addition, due to the undesirable safety profile of OCS and the limited application of omalizumab in severe asthma [Normansell, 2014], there are few treatment options to reduce the frequency of exacerbations and the dependence on systemic corticosteroids for patients with severe

eosinophilic asthma. Thus, there remains a high unmet need to provide better treatment options, without the side effects associated with systemic corticosteroids, for this small segment of the asthma population.

Mepolizumab is a recombinant humanised monoclonal IgG (IgG1 kappa) antibody which binds with high specificity and affinity to human interleukin 5 (hIL-5), preventing it from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting IL-5 signalling. IL-5 has been identified as the key cytokine responsible for regulation of blood and tissue eosinophils (the growth and differentiation, recruitment, activation and survival of eosinophils). . The overproduction of IL-5 in the airways has been specifically reported in patients with eosinophil-associated asthma [Robinson, 1992; Sur, 1995]. By targeting IL-5, mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signalling and the overexpression of peripheral blood and tissue eosinophils. However, complete blood eosinopenia is not possible due to redundant signalling by IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF) through a common β-sub-unit [Asquith, 2008]. In addition, available data do not indicate that reduction of eosinophils has any untoward effects on normal health [Gleich, 2013]; patients lacking eosinophils in association with immunodeficiency or as a consequence of IgG-mediated eosinophil precursor destruction do not display any distinguishing abnormalities related to the eosinophil reduction.

The current Marketing Authorisation Application (MAA) is a re-submission which had a different proposed indication (hyperesoniphphilic syndrome (HES)) and it was withdrawn by the same applicant during the assessment procedure

(http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500060631.pdf). The development of mepolizumab has targeted a number of indications associated with hypereosinophilia. This application is the first mepolizumab submission for severe eosinophilic asthma

The CHMP gave scientific advice on the development of mepolizumab for asthma three times regarding various aspects of the clinical trials design of the placebo-controlled phase IIb/III (e.g. eligibility of subjects, safety database, strategy to recruit patients, proposed statistical plan, target patient population, immunogenicity assessment, etc.). The scientific advice was largely followed.

2.2. Quality aspects

2.2.1. Introduction

Mepolizumab is a humanised monoclonal IgG (IgG_1 kappa) antibody, which is produced in Chinese hamster ovary cells by recombinant DNA technology (SmPC section 2) and binds with high specificity and affinity to soluble human interleukin 5 (IL-5), the key cytokine responsible for regulation of blood and tissue eosinophils. This IL-5 binding results in the inhibition of IL-5 signalling.

The product is presented as a sterile lyophilised white powder for solution for injection in Type I clear glass vials. Each vial contains 100 mg mepolizumab formulated with sodium phosphate dibasic heptahydrate, sucrose and polysorbate 80. After reconstitution with 1.2 mL of sterile water for injections, each mL of solution contains 100 mg mepolizumab (SmPC section 6). The vials are sealed with rubber stoppers and secured with aluminium overseals that have plastic flip-off caps.

2.2.2. Active substance

General information

Mepolizumab is an IgG_1 kappa monoclonal antibody consisting of two heavy and two light chains containing 449 aminoacids (49 kDa) and 220 amino acids (24 kDa) each, respectively. The heavy and light chains are covalently linked by a single disulfide bond and the heavy chains are linked to each other by two disulfide bonds resulting in a typical IgG molecule. Both heavy chains are glycosylated at asparagine 299 with complex biantennary oligosaccharides. The carbohydrate molecular mass is approximately 3 kDa resulting in a total estimated molecular mass of 149 kDa for mepolizumab.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The commercial manufacturing process, designated as MDS2, is a standard antibody production process consisting of upstream cell fermentation in CHO cells and downstream purification; altogether 12 production stages have been identified for the active substance manufacture. Mepolizumab active substance is manufactured at GlaxoSmithkline LLC, 893 River Road, Conshohocken, PA 19428, USA.

The fermentation 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 stepsand virus filtration. The resultant filtrate is formulated by concentration and diafiltration using tangential flow ultrafiltration (TFUF). Mepolizumab bulk undergoes filtration and is dispensed into containers, frozen and stored until transported to the finished product manufacturing site under validated shipment conditions.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given.

Development genetics and cell banking system

The cloning of the plasmids and generation of the cell lines has been described. The complementarity determining regions (CDRs) were grafted from the murine antibody, which was generated through the immunisation of mice with recombinant human IL-5. The sequence was humanised at several residues and the heavy and light chain vectors were fully sequenced. The plasmids were transfected in a Chinese hamster ovary (CHO) cell line which was adapted for serum-free growth.

Single colonies were selected and a master cell bank (MCB) was generated. Two working cell banks (WCB), prepared from the MCB, are currently in use and the applicant has stated that once the older WCB is depleted, the new WCB will be used for commercial supply. Comparability of both WCBs has been demonstrated and a protocol is in place for qualification of future WCBs. Comprehensive testing of both the MCB and WCB has been carried out in accordance with ICH guidelines and the cell lines have been shown to be free of viral contamination. Genetic stability has been demonstrated on cells at the limit of *in vitro* cell age and the stability of the production cell line from MCB to harvest has been demonstrated.

Process validation

The applicant has followed a three stage approach to process validation in support of the commercial manufacturing process for mepolizumab active substance.

Additional studies were also conducted to support validation of the commercial manufacturing process. These studies included resin and membrane lifetime and reuse, in-process product hold times, reprocessing, characterisation of the freezing process for the active substance and qualification of the active substance shipping procedure.

Manufacturing process development

Mepolizumab active substance was initially manufactured using a pilot scale bioreactor. This material was used for pre-clinical and Phase I/II clinical studies. The process was then scaled-up to a larger production bioreactor with a few minor changes and the material was used for clinical studies. Manufacture was subsequently moved to GSK LLC, Conshohocken and scaled up to a production bioreactor with a few minor changes. The active substance produced in GSK LLC, Conshohocken was used for clinical studies and to generate reference standard which has been designated as the Primary Reference Standard (PRS). Further modifications were made to the active substance manufacturing process resulting in the intended process for commercial registration.

Some of the changes introduced into the MDS2 manufacturing process are significant. Changes to the cell culture media and bioreactor equipment could impact on growth kinetics, viability and general metabolism of the CHO cells, which in turn could impact on the quality of the active substance produced. To address these issues the applicant demonstrated process comparability with regard to process attributes such as viability, doubling time, passage duration, CHO metabolism and yield. Replacement of the cell harvesting equipment is another change which could result in difference in active substance purity. Investigations were undertaken to examine if this occurs. The process comparability studies were based on results from multiple batches from both process versions and the outcome is considered satisfactory.

Development of control strategy

The control strategy for mepolizumab active substance manufacture includes control of raw materials and excipients, procedural controls, process parameter controls, process monitoring, in-process testing, release testing and characterisation testing. It was developed using a risk-based approach applied with product, process and facility knowledge. The resulting combination of process controls and product testing is in place to ensure product quality and patient safety.

Characterisation

a) Elucidation of structure and other characteristics

Full characterisation of mepolizumab PRS was performed using a range of biochemical, biophysical, biological and immunoassays to confirm the identity, purity and potency of the molecule.

- Physicochemical characterisation

The following tests were performed:

Primary sequence: Peptides mapping mass spectroscopy, free sulfhydryls content, disulfide mapping liquid chromatography tandem mass spectrometry (LC-MS/MS), intact and reduced mass were performed. The molecular mass, as well as the heavy and light chain sequences, matched the expected sequences based on the cDNA. Low levels of post-translational modifications were detected in mepolizumab. The location of the 16 disulfide bonds was confirmed, as well as the lack of free sulfhydryls.

Secondary and tertiary sequence: circular dichroism (near and far UV), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC).

Charge isoforms: capillary isoelectric focusing (cIEF), cation exchange chromatography (CEX).

Glycosylation: oligosaccharide profiling by high performance liquid chromatography (HPLC), capillary gel electrophoresis (CGE) and mass spectrometry, total carbohydrate content and monosaccharide composition by reverse phase HPLC, non-glycosylated heavy chain analysis by CGE.

Purity: CGE (reduced and non-reduced conditions), sodium dodecylsulfate polyacrylamide gel (SDS-PAGE) (reduced and non-reduced conditions), Western blot, size exclusion chromatography (SEC) and analytical ultracentrifugation (AUC).

- Biological characterisation

Testing was performed for specific binding analysis, kinetic analysis and neonatal Fc receptor (FcRn) binding analysis.

An *in vitro* method, neutralisation of IL-5-dependent cell proliferation, was used to determine the biological activity of mepolizumab.

b) Impurities

Low levels of process-related impurities were observed in the bulk active substance.

Low levels of product-related impurities and substances are present in mepolizumab bulk active substance. The applicant provided detailed information of the critical quality attributes (CQAs) of mepolizumab and control strategy used to monitor these attributes.

Specification

The proposed commercial specification for the active substance was established in consideration of the CQAs of mepolizumab, the cumulative batch release and stability data derived from the MDS1/MDP1 and MDS2/MDP2 processes, and prior clinical experience.

The specification for mepolizumab active substance includes controls of identity, purity and impurity, potency, quantity, safety and other general tests. The analytical methods used have been adequately described and appropriately validated.

The same product-specific reference standard is used for release and stability testing of mepolizumab active substance and finished product.

Stability

A shelf life of is applied to mepolizumab bulk active substance when stored under recommended conditions in specified containers. Stability data is provided to cover the intended storage period.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

Mepolizumab finished product, 100 mg/vial, is a white lyophilised cake, manufactured from a bulk active substance solution containing 75 mg/mL mepolizumab, sodium phosphate dibasic heptahydrate, sucrose, and polysorbate 80, at pH 7.0. Mepolizumab finished product is presented in 10 mL Type 1 clear glass vials, sealed with grey bromobutyl rubber single vent stoppers and aluminium overseals with red flip-off caps. After reconstitution with 1.2 mL of sterile water for injections, it forms a clear-to-opalescent, colourless-to-pale-yellow or pale-brown solution (SmPC section 6).

The components of the finished product were selected to deliver the quality target product profile (QTPP) to ensure product quality and safety.

During development of mepolizumab finished product, three different presentations were used for early clinical phase studies, for Phase 2 and for late phase clinical studies, and for Phase 3 clinical studies and proposed commercialisation.

The qualitative composition of the bulk active substance has not changed throughout clinical development. The formulation was optimised to create the formulation used for mepolizumab for injection, 100 mg/vial.

Manufacture of the product and process controls

The finished product is manufactured at a cGMP manufacturing facility. The finished product manufacturing process intended for commercial supply begins with thawing the bulk active substance followed by mixing, filtration, and filling into washed and depyrogenated 10 mL Type I glass vials. After filling, the vials are partially stoppered and transferred into a lyophiliser. After lyophilisation aluminium overseals are applied to the vials and the finished product is stored protected from light before labelling and packaging.

The manufacturing process development of mepolizumab 100 mg/vial finished product was based on experience gained during the development of the earlier finished product. A technical risk assessment was conducted to focus on potential areas that may require change during the manufacturing process development of the 100 mg/ vial finished product and where necessary a number of Design of Experiment (DoE) studies, engineering studies and proven acceptable ranges (PAR) studies were conducted to support these changes.

Minimal changes were made during development to optimise the process. Commercial process validation was conducted to confirm process robustness and reproducibility. The suitability of process parameters were tested. The adequacy of the in-process controls was evaluated in order to provide assurance that the manufacturing process is designed, controlled and monitored to reliably meet mepolizumab for injection, 100 mg/vial finished product quality attributes and specifications.

Product specification

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The specification for mepolizumab finished product includes controls of identity, purity, potency, quantity, safety and a number other general tests including European Pharmacopoeia (Ph. Eur.) tests. The approach for setting the specification of the finished product is similar to the one applied for the active substance.

Stability of the product

A 24 month shelf life at storage conditions ≤25°C, do not freeze (SmPC section 6), is applied on the basis of stability data generated from stability studies.

Adventitious agents

The adventitious agents control strategy includes raw material sourcing and testing, cell bank testing, manufacturing process controls (in-process testing adherence to purification protocols and establishment of viral clearance) and facility and equipment design and controls.

A thorough risk assessment of the MCB and WCBs, active substance and finished product was performed. This evaluation included a review of the sourcing and certification of ruminant or human-derived raw materials used in the manufacturing process and the materials that come into direct contact with equipment used during manufacture. Media used in facility and equipment validation studies were also included in this evaluation.

Overall, the TSE contamination risk from the cell banks or the raw materials is considered negligible.

Viral testing of the MCB, WCBs and end-of-production cell bank (EOPCB) was performed. Taken together, viral testing has been carried out in accordance with ICH Q5A.

Viral clearance studies were carried out. The small-scale models were described and the relationship of the model process parameters to the full scale process parameters was also outlined. Qualification of small-scale models was discussed in the dossier. The overall level of viral reduction provides assurance of viral safety.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The derivation of the coding sequence and construction of the light and heavy chain expression vectors were satisfactorily described. Both plasmids were fully sequenced.

The preparation of the MCB and WCB is described in detail and the two-tiered cell banking system was generated in accordance with ICH Q5 guidelines. The MCB and WCB were sufficiently characterised. An EOPCB was created and analysed, confirming absence of adventitious agents and genetic stability. Stability (viability) of the MCB and the first WCB were determined.

The manufacturing process is a standard antibody production process; it was adequately described, including reprocessing conditions.

The applicant gave a full list of raw materials used for the production of mepolizumab.

The process validation strategy was sufficiently explained. The process was run consistently and met acceptance specifications. Impurities clearance was sufficiently demonstrated.

Hold time validation consisted of microbial safety and biochemical stability.

The history of process development was given. A satisfactory history for the development changes to the purification process was provided. This includes an outline of significant changes between the processes.

Comparability between the processes is considered demonstrated. The approach to analytical comparability is accepted and includes data from all different development stages. The applicant has shown good process consistency throughout development.

For the control strategy, the applicant presented a list of CQAs and a gap analysis to determine potential risks to product quality. CQAs were identified using product and process knowledge and in the context of treatment of severe asthma, the mechanism of action, the molecular properties and the manufacturing process. The rationale for the assignment of criticality to quality attributes was provided.

The applicant also presented an overview of the approach to determining the critical process parameters (CPPs). Qualified small-scale models and DoEs as well as single parameter experiments were used to establish PARs and Normal Operating Ranges (NORs) for all stages of the manufacturing

process. Qualification of the small-scale models was satisfactory and where statistically significant differences were observed, these have been sufficiently explained.

Relevant aspects of the structure of mepolizumab were extensively analysed, using orthogonal methods where appropriate.

Monosaccharide and oligosaccharide profiling was carried out. Product-related impurities were isolated and analysed and a suitable control strategy is in place for any manufacturing changes.

In relation to process-related impurities, batch data and clearance studies support the removal of most tests from the specification. The analytical methods were set out with sufficient detail. Over the course of mepolizumab development the applicant made changes to a number of analytical procedures. These are justified and appropriate bridging studies were carried out. Where differences were observed due to transition of methods, these have been adequately explained and taken into account. This is acceptable.

The specifications are based on a statistical analysis of a suitable number of batches and supported by clinical qualification.

Reference standards were sufficiently characterised and the current working reference standard was demonstrated as comparable to the primary reference standard. Qualification of new working standards was described.

The description of the container closure system for the active substance includes acceptance controls of material and is adequate.

The proposed shelf life when stored at recommended conditions is considered acceptable.

Finished product

The rationale for the selection of excipients in the finished product formulation was given. The applicant has given sufficient background information on the formulation development. Justifications and supporting data were provided both at the level of the bulk active substance and the lyophilised finished product. The history of formulation development for the different concentrations was adequately captured.

The applicant set out details of the manufacturing process development history. The manufacturing process consists of filling and lyophilisation without a formulation step (the bulk active substance is already formulated). The main change for the development of the 100 mg/mL from the earlier formulation was the adjustment of the fill and lyophilisation process. In addition to batch analysis, an extended comparability study was undertaken on commercial scale batches. The data demonstrate that the finished product from the two processes is consistent and comparable.

For the manufacturing process control strategy, the applicant employed an analogous approach to that outlined for the active substance.

The rationale and development of the container closure system was adequately set out. A spectrum of potential process leachables was considered and tested for. Where compounds were detected their permissible levels were adequately justified.

Microbiological attributes were sufficiently considered.

As part of the compatibility studies an in-use stability of up to 8 hours at up to 30°C was established. Compatibility with polypropylene syringes for the duration and temperature ranges was also demonstrated, as well as suitability of different gauge needles.

For process validation, data that was submitted suggest the process is consistent.

Extensive information on the validation of various sterilisation processes was submitted, demonstrating that sterility of the process is assured.

Full shipping validation and analysis was undertaken on the finished fully packaged finished product.

Information on the transport of the bulk active substance to the finished product manufacturing site was also provided.

All excipients used in the manufacture of the finished product are Ph. Eur or US Pharmacopoeia grade and are adequately controlled.

The analytical procedures were set out and the methods were sufficiently validated.

Batch analytical data are all within specifications and demonstrate a consistent manufacturing process.

The approach for setting specifications is analogous to that employed for the active substance and based on clinical justification they are considered acceptable.

The release specifications listed are in accordance with the Ph. Eur. Monograph on Monoclonal Antibodies for Human Use (2031).

A 24 month shelf life is proposed for MDP2 at storage conditions $\leq 25^0$C on the basis of stability data generated. The claimed shelf life is considered acceptable.

Adventitious agents

The applicant set out the approach to the adventitious agents control strategy satisfactorily and in accordance with ICH guidelines. Adequate information was provided to support the conclusion that the TSE contamination risk is considered negligible.

Viral clearance studies were undertaken on relevant manufacturing steps. An appropriate panel of model viruses was chosen for the clearance studies. Small-scale models were appropriately qualified. Results in the summary report indicate sufficient clearance for the process.

An estimate of the worst case scenario dose risk for the product was given.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Nucala is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Nucala is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendations for future quality development

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

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development programme was designed in accordance with the guidance provided in ICH S6 R1) "Pre-clinical safety evaluation of biotechnology – derived pharmaceuticals" (CPMP/ICH/302/95, March 1998).

Most of the non-clinical studies were performed using mepolizumab, with the definitive *in vivo* studies conducted in cynomolgus monkeys as this is the only species commonly used for non-clinical toxicology studies in which mepolizumab has been shown to be pharmacologically active. However, assessments of male and female fertility and embryofoetal development, and an immunotoxicity study were conducted in mice using SB-264091, a rat homologous anti-human IL-5 monoclonal antibody (IgG2b) that is pharmacologically active in this species.

GLP

Safety pharmacology and pharmacokinetic studies were conducted in compliance with Good Laboratory Practice (GLP) regulations. All pivotal toxicity studies were performed in accordance with GLP. Other studies were performed in accordance with accepted scientific practice and in general agreement with the principles of GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacology of mepolizumab was characterised using predominantly *in vitro* studies investigating binding affinities, species specificity and effects on cell proliferation. The ability of mepolizumab to reduce levels of circulating eosinophils has also been examined in a range of *in vivo* pharmacodynamic and toxicity studies and in animal models of asthma and parasitic infection. Binding to human tissues (immunohistology) was investigated in a panel of thirty-one tissues.

A high resolution crystal structure for mepolizumab Fab fragments bound to recombinant IL-5 was determined in an *in-vitro* study. The steric hindrance by the full mepolizumab antibody was reported to inhibit the binding of hIL-5 to the IL-5 receptor alpha chain. In another *in- vitro* study, mepolizumab inhibited the proliferation of monkey and human bone marrow cells equipotently when stimulated by rhIL-5 (IC_{50} was 70 to 116 pM).

Mepolizumab was observed to inhibit three forms of rhIL-5 (derived from Drosophila, HEK293 and CHO cells) with similar half maximal inhibitory concentration (IC_{50}) in each cell line in a study using the erythroleukaemic human cell line TF-12.8. These results suggested that the level and type of glycosylation on rhIL-5 was not important for the pharmacologic activity of mepolizumab.

Mepolizumab had high affinity and high specificity for human IL-5 (hIL-5), but also recognised monkey IL-5. Biacore analysis showed that mepolizumab bound to IL-5 with a Kd of $\leq$ 100 pM, and with an estimated *off*-rate of $1.7x10^{-5}\ s^{-1}$ and an *on*-rate of $1.6x10^{5}M^{-1}s^{-1}$. A subsequent, more sensitive Biacore assay suggested an even higher affinity (Kd of 4.2 pM). In another study, the affinity for human IL-5 was shown to be very high, ranging from 110 to 258 pM at 25°C.

Stoichiometric analysis using titration microcalorimetry showed a 1:1 ratio of IL-5 to antibody and high affinity of mepolizumab for IL-5 (<130 pM at 25°C). Analytical ultracentrifugation, which measured IL-5 in its native homodimer format, showed a ratio of two mepolizumab antibodies bound to two IL-5 homodimers.

Mepolizumab was shown to neutralise up to 90% of IL-5 mediated cell proliferation in a human erythroleukaemic cell line (TF1.28) and in murine pre-B-cells (B13) with IC_{50} values of 100 to 150 pM respectively.

In vivo pharmacological activity of mepolizumab was assessed in the toxicology studies and was measured as a reduction in circulating eosinophils, with a decrease greater than 89-94% in basal eosinophil counts observed following the first dose of mepolizumab in monkeys receiving mepolizumab doses of ≥ 5 mg/kg.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed by the applicant, which the CHMP considered acceptable given the nature of mepolizumab.

Safety pharmacology programme

In monkeys, no acute effects of mepolizumab were observed on cardiovascular, respiratory and renal functions or on body temperature after single intravenous doses of up to 100 mg/kg in a single safety pharmacology study.

Mepolizumab binding was demonstrated using immunohistochemistry to be restricted to human lymphoid tissues, suggesting little likelihood for non-pharmacological effects.

Pharmacodynamic drug interactions

No secondary pharmacodynamic studies were performed by the applicant, which the CHMP considered acceptable given the nature mepolizumab. .

2.3.3. Pharmacokinetics

The non-clinical pharmacokinetic properties of mepolizumab were investigated in the cynomolgus monkey as part of the single and repeat dose toxicity studies at doses up to 304 mg/kg using the same dose route (intravenous).

Conventional studies of distribution, metabolism and excretion were not conducted by the applicant because mepolizumab is a monoclonal antibody.

Following a single intravenous administration of mepolizumab to monkeys, plasma concentrations declined in a bi-exponential manner with a long terminal half-life of approximately 2 weeks. The plasma clearance and volume of distribution were low (0.157 mL/h/kg and 65.6 mL/kg, respectively). The intravenous pharmacokinetic profile was similar for monkeys and humans. There were no marked differences in the pharmacokinetics of mepolizumab between male and female monkeys. Plasma concentrations were observed to increase with subsequent doses of mepolizumab, reaching a plateau after the fourth dose.

Bioavailability of mepolizumab was essentially 100% following subcutaneous administration at either 1 or 10 mg/kg. The terminal half-life (~15 days) was similar to that observed following intravenous administration. No notable accumulation (i.e. ≥2-fold) of mepolizumab was observed following once-

monthly repeat subcutaneous administration for 6 months in the chronic toxicity study and no sex differences were observed.

Following intravenous administration, mepolizumab crossed the monkey placenta and was generally quantifiable in infant plasma samples between the first post-partum sampling time on Day 14 and the Day 91 post-partum sample. Infant plasma concentrations of mepolizumab were on average 2.4-fold higher than maternal plasma concentrations. Mepolizumab was not quantifiable in maternal milk samples obtained from monkeys given doses of 10 mg/kg but was quantifiable on Day 14 in 6 of 7 females given doses of 100 mg/kg.

In a metabolism study using cultured human hepatocytes, exposure to mepolizumab for 48 hours produced no notable changes in the mRNA levels of cytochrome P450 3A4 (CYP3A4). At concentrations ≥1000 pg/mL, IL-5 and IL-6 decreased CYP3A4 mRNA levels by ≥69 and 77%, respectively.

In general, pharmacokinetic analyses indicated that mepolizumab exposure was not limited by development of immune antibody responses and that formation of anti-mepolizumab antibodies was accompanied by a faster clearance of mepolizumab from systemic circulation and also by a lower decrease in eosinophil counts.

In a study in mice using SB-264091, plasma concentrations of SB-264091increased with increasing dose from 5 to 50 mg/kg and were quantifiable over the 29 day sampling period. Considerable inter-animal variability was observed and the majority of these differences could be attributed to the presence of anti-SB-264091 antibodies.

2.3.4. Toxicology

The applicant conducted an abbreviated toxicity programme with mepolizumab, in only one species, the cynomolgus monkey, and at two doses in the pivotal studies. The choice of the cynomolgus monkey was justified on the basis of cross-reactivity with monkey IL-5. The CHMP accepted that other standard laboratory species would not have been suitable and that the doses chosen for the pivotal toxicity studies were adequate. Developmental and reproductive toxicity studies were conducted with mepolizumab in the cynomolgus monkey and in mice using SB 264091.

The toxicology programme consisted of single and repeat dose toxicity studies of up to 6 months' duration in cynomolgus monkeys, reproductive toxicology studies in mice and monkeys (a fertility and embryofetal development and a pre- and post-natal development study, respectively), and studies investigating antigenicity, immunotoxicity and local tolerance.

Single dose toxicity

In a single-dose toxicity study in cynomolgus monkeys, mepolizumab was administered in intravenous dose of 0, 3.0 or 304 mg/kg mepolizumab and monitored for one month. Mepolizumab was observed to be well tolerated with only an expected decrease in circulating eosinophil counts and there were no drug-related pathologic findings.

Repeat dose toxicity

In intravenous repeat dose studies of up to 6 months' duration, mepolizumab was well tolerated with no toxicity being found and no target organs identified. There was no delayed toxicity and acceptable local tolerance was demonstrated. The principal effect observed in toxicology studies of up to 6 months duration was related to the pharmacology of mepolizumab and was reversible following the cessation of treatment.

Intravenous and subcutaneous administration of mepolizumab to monkeys significantly decreased basal levels of circulating eosinophils and blocked blood eosinophilia resulting from rhIL-2 administration. The magnitude of the observed decreases was generally similar across the effective doses (≥ 5 mg/kg), with the major difference being in the duration of the decreases in eosinophil counts. Following clearance of mepolizumab from the circulation, eosinophil counts returned to pre-study levels.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were conducted by the applicant. The CHMP considered it acceptable as mepolizumab is a recombinant protein.

Reproduction Toxicity

Fertility and embryo-foetal development were investigated using SB-264091 (0.5 or 50 mg/kg) administered once weekly to male and female CD-1 mice. There was no investigation of littering or functional post-natal development. There was no effect observed on mating, fertility, gonadal function, or early embryonic or embryo-foetal development. The study despite not providing direct information for the risk assessment of mepolizumab did provide supporting evidence that blockade of IL-5 does not appear to have any effects on fertility and foetal morphology in mice.

Pre- and postnatal developments were investigated in cynomolgus monkeys. There were no effects on pregnancy, embryo-foetal development or immune development in offspring however no examinations to detect visceral or skeletal malformations were conducted.

Toxicokinetic analysis of the pre-and postnatal study confirmed exposure of the monkeys to sustained serum concentrations of mepolizumab. Exposures higher than that in humans were obtained with safety margins of 4.72 and 30.9 in the 10 and 100 mg/kg dose groups, respectively. The no observed adverse effect levels (NOAELs) for adults and offspring were both >100 mg/kg with a mean C_{max} of 1.159 mg/ml and an AUC of 254.1 mg.h/ml in the adults.

Mepolizumab was observed to cross the placental barrier in monkeys but the teratogenic potential of mepolizumab was not studied in the pre and post-natal study in monkeys and remains unknown. This was reflected in section 4.6 of the SmPC: Mepolizumab crosses the placental barrier in monkey. Animal studies do not indicate reproductive toxicity. The potential for harm to a human foetus is unknown.

A precautionary statement was also included in section 4.6 of the SmPC: As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy. Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Additional a pregnancy surveillance study (category 3) was included in the pharmacovigilance plan of the RMP to evaluate to evaluate pregnancy outcomes and birth defects.

Toxicokinetic data

The NOAEL for monkeys in the 6 month study was >100 mg/kg with a mean C_{max} of 2.4 mg/mL and AUC of 809 mg.h/mL at the end of the study. This exposure in monkeys represented a 70-fold multiple of the human mepolizumab 100 mg subcutaneous exposure. The CHMP considered this acceptable.

Local Tolerance

In repeated dose toxicity studies in monkeys, mepolizumab was generally well tolerated following intravenous and subcutaneous administrations. Therefore, no special local tolerance studies with mepolizumab were required.

Immunogenicity

Mepolizumab was only weakly immunogenic in the range of toxicology studies conducted in monkeys. Mepolizumab was demonstrated to bind to human lymphoid tissues. In the intravenous studies, only 3% of the animals generated anti-drug antibodies, which resulted in an enhanced systemic clearance of mepolizumab and in no adverse reactions.

2.3.5. Ecotoxicity / environmental risk assessment

The guidance on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00) specifically exempts amino acids, peptides and proteins from the need for a detailed environmental assessment.

Therefore, in compliance with this guidance, an environmental risk assessment for mepolizumab (a recombinant protein) was not considered necessary by the CHMP.

2.3.6. Discussion on non-clinical aspects

The non-clinical development programme for mepolizumab consisted of a range of pharmacodynamic, pharmacokinetic and toxicology studies, in which the activity of mepolizumab was investigated *in vitro* and *in vivo*. Mepolizumab recognised human IL-5 with high affinity and specificity, and inhibited binding of IL-5 to its receptor (IL-5 receptor α) with an IC_{50} of <1.0 nM.

No secondary pharmacodynamic studies or pharmacodynamic drug interactions studies were conducted by the applicant. This was considered acceptable by the CHMP.

The safety pharmacology of mepolizumab was addressed in a single study on the CNS, renal and respiratory function. Cardiovascular function was monitored in a 6 month toxicity study in monkeys.

Pharmacokinetic studies detailed the absorption, distribution and metabolism profile of mepolizumab. In the toxicity studies, mepolizumab was given intravenously and subcutaneously (the same route of administration used clinically). The non-clinical PK profile of mepolizumab has been studied in rats, rabbits and monkeys. Mepolizumab exhibited a low volume of distribution in monkeys and humans. Low concentrations of mepolizumab were detected in bronchalveolar lavage samples.

In a reproduction and development study, high levels of mepolizumab were shown to cross the placenta and low levels were detected in milk. In a metabolism study using cultured hepatocytes, at concentrations of ≥1000 pg/ml, IL-5 and IL-6 reduced CYP3A4 mRNA levels by ≥69 and 77%, respectively.

The maximum duration of treatment in toxicity studies was 6 months, which is in compliance with ICH S6 and thus supported the intended chronic, monthly administration to patients. Studies of a longer duration would not be expected to provide additional information to that predicted from the pharmacology of IL-5, either through inhibition with a monoclonal antibody antagonist or through genetic disruption (IL-5 knockout models), and there was no evidence to suggest a risk for long-term suppression of IL-5 in patients receiving mepolizumab. This was considered acceptable by the CHMP.

In monkeys, single or monthly repeated intravenous doses of up to 304 or 100 mg/kg mepolizumab, respectively, resulted in decreased peripheral blood eosinophil with no evidence of toxicological effects.

No genotoxicity or carcinogenicity studies were conducted by the applicant. This was considered acceptable by the CHMP.

The antagonism of IL-5 had no effect on reproductive function, pregnancy or development of the offspring in a fertility and early embryonic/embryofoetal development assessment of SB-264091 (≤50 mg/kg) in mice and a pre- and postnatal development study with mepolizumab (≤100 mg/kg) in monkeys. However, mepolizumab crosses the placental barrier and the teratogenic potential of mepolizumab was not studied in the monkey pre and post-natal study.

An embryofoetal development study was conducted in mice and not in monkeys. Although anti-SB-264091 antibodies were evident in mice, exposure was not directly quantified in the mouse embryofetal development study. The potential for masking of embryo-foetal toxicity due to insufficient drug exposure was considered unlikely. This was considered acceptable by the CHMP.

The effect of mepolizumab on human pregnancy is unknown; hence, mepolizumab should only be administered if the potential benefit to the mother outweighs the potential risks to the foetus. This was reflected appropriately in section 4.6 of the SmPC.

In local tolerance evaluations, intravenous or subcutaneous administration of mepolizumab was well tolerated. In an immunohistochemistry study, mepolizumab binding was restricted to human lymphoid tissues, indicating little likelihood of non-pharmacologically mediated effects. Administration of mepolizumab to monkeys resulted in a very low incidence of immunogenicity. The weight of evidence for mepolizumab suggests that the risk for potential immunotoxicity is low.

Overall, the non-clinical data has been adequately reflected in section 5.3 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The review of non-clinical data available for mepolizumab has provided adequate characterisation of primary pharmacological and toxicological properties of the compound. The *in vitro* and *in vivo* pharmacodynamic studies indicated that mepolizumab had an inhibitory effect on IL-5.

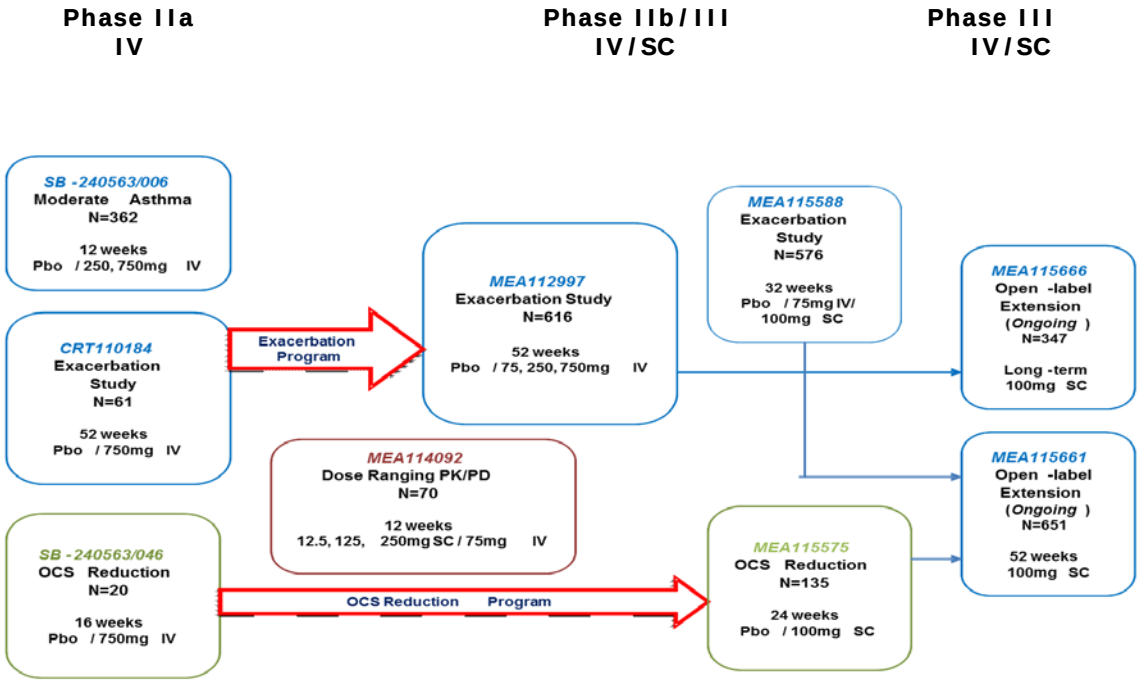
The applicant conducted a satisfactory programme of pharmacology studies and the CHMP considered that further studies were not required.

2.4. Clinical aspects

2.4.1. Introduction

The Phase II-III clinical development programme for mepolizumab in severe eosinophilic asthma is comprised of 9 studies as shown in figure 5.

Figure 5: Phase II – III clinical development programme for mepolizumab in severe eosinophilic asthma



GCP

The Clinical trials were performed in accordance with GCP.

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

- Tabular overview of the main clinical studies in severe eosinophilic asthma (table 9):

Table 9 – Overview of the main clinical studies in severe eosinophilic asthma

Study Identifier (Identifier of Study Report)	Type of Study	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total Subjects per Group (Entered / Completed)
Efficacy and Safety Studies – Controlled Clinical Studies						
MEA112997	Efficacy	Efficacy, safety, and PD	R, DB, PC, PG	Severe eosinophilic asthma	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo IV One infusion every 4 weeks for 52 weeks	153/129 152/131 156/133 155/127

MEA115588	Efficacy	Efficacy and safety	R, DB, PC, PG	Severe eosinophilic asthma	Mepolizumab 75 mg IV + Placebo SC Mepolizumab 100 mg SC + Placebo IV Placebo IV + Placebo SC One dose every 4 weeks for 32 weeks	191/175 194/185 191/179
MEA115575	Efficacy	Reduction of OCS use, efficacy, and safety	R, DB, PC, PG	Severe eosinophilic asthma	Mepolizumab 100 mg SC Placebo SC One dose every 4 weeks for 24 weeks	69/66 66/62
Open label extension studies						
MEA115666		Long-term safety and efficacy (subjects from MEA 112997)	OL	Severe eosinophilic asthma	Mepolizumab 100 mg SC Once dose every 4 weeks for 3.5 years	347/0
MEA115661		Long-term safety and efficacy (extension of MEA115588 and MEA115575)	OL	Severe eosinophilic asthma	Mepolizumab 100 mg SC Once dose every 4 weeks for 52 weeks	651/0

Note: Study MEA115661 was completed and the CSR submitted during the procedure.

2.4.2. Pharmacokinetics

Introduction

The pharmacokinetics of mepolizumab were previously characterised as part of the evaluation of Bosatria, which was proposed to be indicated for hypereosinophilic syndrome (HES) (http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500060631.pdf). For the current submission two new clinical pharmacology studies, one in healthy subjects (MEA 115705) and one in asthmatic subjects with elevated blood eosinophil levels (MEA 114092) were submitted. In addition, three clinical Phase IIb/III efficacy studies in severe eosinophilic asthma patients (MEA 112997, MEA 115588 and MEA 115575) were submitted, contributing to the pharmacokinetics and pharmacodynamic data to characterise the PK profile of mepolizumab in this target population. Sparse PK samples were collected and analysed using population PK methods.

A previous PopPK model was resubmitted and an updated model including the data of the new studies submitted in the application for severe eosinophilic asthma was presented during the procedure.

The measurement of mepolizumab plasma concentrations in support of clinical studies was carried out by validated bioanalytical immunoassay methods with a Lower limit of quantification (LLOQ) of 50 ng/mL and a range of 50 – 5000 ng/mL.

The relevant studies submitted in this application for the PK/PD evaluation are displayed in Table 10 (which provides an overview of the new clinical pharmacology studies) and Table 9 which includes an overview of the new clinical efficacy and safety studies contributing to the pharmacokinetic and pharmacodynamic data (MEA 112997, MEA115588 and MEA115575).

Table 10 New studies relevant for the PK/PD evaluation

Study Identifier (Identifier of Study Report)	Type of Study	Study Objective (s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total Subjects per Group (Entered/ Completed)
New Clinical Pharmacology Studies						
MEA115705	FTIH (Japanese)	Safety, PK and PD	R, SB, PC, PG	Healthy Japanese subjects (males only)	Mepolizumab 10mg IV;SD Mepolizumab 75mg IV; SD Mepolizumab 250mg IV; SD Mepolizumab 750mg IV; SD Placebo IV; SD	6/6 6/6 7/6 7/7 9/8
MEA114092	Dose-ranging, PKPD, Repeat dose	PD, PK, and safety	R, OL, DR, PG	Asthma	Mepolizumab 12.5 mg SC Mepolizumab 125 mg SC Mepolizumab 250 mg SC Mepolizumab 75 mg IV One dose every 4 weeks for 12 weeks	 21/20 15/14 23/21 11/11

Population PK model

The analyses of PK data from the Phase II and III studies in moderate/severe eosinophilic asthma were based on an initial population PK meta-analysis of IV mepolizumab developed using data from multiple studies in healthy subjects and in a range of diseases (asthma, HES, eosinophilic oesophagitis). This initial population PK meta-analysis of IV mepolizumab was previously part of the evaluation of Bosatria.

This initial Population PK (PopPK) meta-analysis of IV mepolizumab included a total of 327 subjects, 45% female, 55% male with average age of 37 years (range 18–74) and average weight of 76.1 kg. Ethnicity breakdown was 86% Caucasian, 10% Black, 2.7% other, and less than 1% East and South East Asian and South Asian.

The analysis was performed using the non-linear mixed effects modelling program NONMEM system. Estimates for population mean, Standard Errors (SE) and relative SE (%) of parameters, inter-individual variability and residual variability were obtained. A structural PK model was developed based on review of the known plausible pharmacology of mepolizumab. The covariate model was then developed using forward addition, followed by backward elimination.

The pharmacokinetics of IV mepolizumab was well-described by a two-compartment model with first-order elimination. The final structural model included the following pharmacokinetic parameters: Clearance (CL), central volume of distribution (V1), inter-compartmental clearance (Q), and peripheral volume of distribution (V2).

Twelve covariates (weight, height, age, sex, race, country of study site, disease state, creatinine clearance, and liver function [alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin]) were investigated. Bodyweight was the only statistically significant covariate for clearance and volume, although the magnitude of effect was not considered to be clinically relevant. Renal function (creatinine clearance) and hepatic function had no effect. However, the majority of values were within normal range and extrapolation was therefore limited.

Within this submission a new analysis of the PK data from the Phase II and III studies in moderate/severe eosinophilic asthma was submitted. One, study MEA112997, used the parameter values from the meta-analysis without updating. The other analyses (studies MEA114092, MEA115588

and MEA115575) included SC drug administration (+/- IV dosing). For these analyses, SC data were modelled independently, IV parameter values were updated and a different parameterisation of the impact of body weight on clearance and volume of distribution was used (fixed rather than fitted allometric exponents). Uncertainty in parameter estimates was assessed by standard error estimates.

During the procedure the CHMP requested an updated POPPKPD model that integrated both intravenous and subcutaneous data. Typical goodness of fit graphics and visual predictive check were used for model evaluation. Nonlinear mixed-effect modelling was used with the aid of NONMEM and other packages (WinBUGS, Monolix, SAS) where appropriate.

The analyses were conducted mainly to allow calculation of individual subject exposure parameters to be used in exposure-response analyses or individual concentration-time profiles to be used in PKPD analysis. The analyses were also used to identify important patient characteristics that might require dosage adjustment.

The covariate model selection procedure involved graphical evaluation, regression analysis, followed by forward addition ($p \leq 0.05$) and backward elimination ($p \leq 0.01$). The covariates tested varied across the analyses and included demographics, baseline clinical and disease status.

The main results of these analyses are summarised in Table 11 and the final population PK parameter estimates in Table 12. The diagnostics plots and visual predictive checks were considered appropriate by the CHMP.

In all the analyses bodyweight was identified as a statistically significant covariate of interest using allometric methods. The magnitude of effect on exposure in both moderate and severe eosinophilic asthma subjects and other populations was comparable, but was not considered of clinical importance (ranging from a 52% increase to a decrease of 47% for a bodyweight range of 40–162 kg and allometric scaling power of 0.75 for clearance: AUC ratio = $(40/70)^{-0.75} = 1.52$.

Albumin and creatinine clearance were identified as additional plausible physiological covariates for severe eosinophilic asthma subjects (from study MEA115588), however, like bodyweight, neither were deemed clinically significant and thus dose adjustment was not deemed necessary.

Table 11 Summary of selected population PK parameter estimates from multiple Phase II/III asthma studies

	MEA114092	Meta-analysis/ MEA112997	MEA115588	MEA115575
Number of subjects	69	327/443	377	69
Number of samples	1037	2359/1193	1226	202
Average number of samples per subject	15	7.2/2.7	3.3	2.9
Dosing routes	IV and SC	IV IV	IV and SC	SC
		Parameter Values		
CL (L/day)	0.21 (0.19-0.23)	0.23 (0.23-0.24)	0.22 (0.21-0.23)	NA
CL (ml/day/kg)	3.0	3.3	3.1	
BSV (%)	23%	26%	21%	
Allometric exponent	0.75 (fixed)	0.69 (0.57-0.80)	0.75 (fixed)	
CL/F (L/day)	0.31 (0.28-0.35)	NA	0.28 (0.27-0.30)	0.33 (0.27-0.40)
CL/F (ml/day/kg)	4.4		4.0	4.7
BSV (%)	58%		29%	33%
Allometric exponent	0.75 (fixed)		0.75 (fixed)	0.75 (fixed)
Vc (L)	3.6 (3.2-4.1)	3.2 (3.1-3.3)	4.9 (4.1-5.7)	NA
Vc (ml/kg)	51	46	69	
BSV (%)	17%	29%	NA	
Allometric exponent	1 (fixed)	0.63 (0.49-0.76)	1 (fixed)	
Vc/F (L)	4.6 (4.0-5.2)	NA	4.4 (4.1-4.8)	5.8 (4.9-6.8)
Vc/F (ml/kg)	65		63	82
BSV (%)	59%		NA	NA
Allometric exponent	1 (fixed)		1 (fixed)	1 (fixed)
F(%) (arm)	74% (54-102)	NA	80% (76–84)	NA

Values presented are mean (95% CI). CL/F and V/F are for SC route. BSV = between-subject variability, NA means not applicable. Weight-normalized values for clearance and volume are standardized to 70 kg. All estimates assume standardized values for other covariates, where included. F was calculated using post-hoc individual CL and CL/F values.

Table 12 Final mepolizumab population PK parameter estimates

PK parameter (unit)	THETA	S.E.	% RSE	PK parameter estimate	Lower 95% CI	Upper 95% CI
CL (L/day)	-4.73	0.0118	-0.249	0.212	0.207	0.217
V2 (L)	1.24	0.0173	1.40	3.46	3.34	3.57
Q (L/day)	-4.08	0.0961	-2.36	0.406	0.336	0.490
V3 (L)	0.779	0.0403	5.17	2.18	2.01	2.36
KA (/day)	-4.64	0.0629	-1.36	0.232	0.205	0.262
F (RO)	1.13	0.110	9.74	0.76	0.71	0.79
CL(ALB)	-0.496	0.0829	-16.7	-0.496	-0.658	-0.334
CL(CrCL)	0.123	0.0512	41.6	0.123	0.0226	0.223
BSV(CL) %	0.108	0.0140	13.0	34	29	38
BSC(CL-V2) %	0.0952	0.0172	18.1	32	25	37
BSV(V2) %	0.156	0.0268	17.2	41	33	48
BSV (V3) %	0.124	0.0265	21.4	36	27	44
BSV (KA) %	0.306	0.0737	24.1	60	42	75

Pharmacokinetic parameter estimation

$CLi = 24*EXP(\theta_{CL} + 0.75*LOG(BWT/70) + \theta_{ALB}*LOG(ALB/44)) + \theta_{CrCL}*LOG(CRCL/112) + \eta_1)$

$V2i = EXP(\theta_{V2} + LOG(BWT/70) + \eta_2)$

$Qi = 24*EXP(\theta_Q + \eta_3)$ [η_3 set to zero]

$V3i = EXP(\theta_{V3} + LOG(BWT/70) + \eta_4)$

$KAi = 24*EXP(\theta_{KA} + \eta_5)$

$Fi = EXP(\theta_{RO} + \eta_6)/(1 + EXP(\theta_{RO} + \eta_6))$ [η_6 set to zero]

Between-subject variability

$BSV(\eta_i) = SQRT(exp(\eta_i) - 1)$

Residual error

ε_1=0.0645 (3%) $SE(\varepsilon_1) = 0.0071$ $Y = IPRED*exp(\varepsilon_1)$

Parameters are expressed as Mean (95%CI). CL = clearance, V2 = central volume of distribution, Q = inter-compartmental clearance, V3 = peripheral volume of distribution, KA = absorption rate constant, F = bioavailability; BWT = bodyweight, ALB=Albumin, CRCL=Creatinine clearance; %RSE: percent relative standard error of the estimate = SE/parameter estimate *100; 95% CI= 95% confidence interval on the parameter; SE=Standard error of the estimate, CI = confidence interval, BSV= Between-subject variability; BSC = Between-subject covariance; ε= residual variability, i = individual subject parameter

Absorption

In healthy volunteers, absolute bioavailability results were the following: maximum observed concentration (C_{max}) for SC and IM were approximately 30% and 40% of IV, respectively; area under the concentration-time curves extrapolated to infinity ($AUC_{0-\infty}$), and hence absolute bioavailability, was 64–75% (SC) and 81% (IM) of those for IV infusion.

In patients with moderate/severe asthma, bioavailability was 74% (SC) compared with the IV treatment arm in Study MEA114092 model. In Study MEA115588, additional samples at approximate C_{max} were described using the same model. Absorption rate and bioavailability were comparable (0.29/day and 80%), whilst in Study MEA115575 absorption rate was 0.12/day, although only trough samples were collected.

Absorption of mepolizumab SC in subjects with moderate/severe asthma was described in Study MEA114092 using a two compartment population PK model with first-order absorption without time-lag, distribution and elimination. After fixing distribution parameters to IV values, the absorption rate was 0.19/day; implying absorption is complete after 18 days (five absorption half-lives). The estimated T_{max} in subjects with moderate/severe asthma was 6–8 days.

Distribution

Following IV infusion, mepolizumab distributed into central plasma volume and declined in a bi-exponential manner reflecting distribution into interstitial space and subsequent elimination. Analysis of Phase IIb/III study MEA112997 using a previous meta-analysis of early IV data estimated the central volume to be 3.2 L (46 ml/kg) (Table 11), without further model refinement. In the PopPK model meta-analysis the distribution half-life was 1–2 days, implying that following SC injection, absorption and distribution occur during the same time frame and that antibody tissue distribution is complete after approximately 5–10 days.

Metabolism

Mepolizumab is a humanized IgG1 monoclonal antibody that is catabolized by ubiquitous proteolytic enzymes, not restricted to hepatic tissue. Since the target for mepolizumab is a soluble cytokine (not a membrane-bound receptor), mepolizumab does not undergo target-mediated degradation.

Elimination

In healthy volunteers, the mean terminal-phase elimination half-life was 18–20 days for all administration routes.

The mean systemic clearance of mepolizumab in patients with moderate to severe eosinophilic asthma ranged from 0.21–0.23 L/day (3.0–3.3 ml/day/kg). The model-derived terminal-phase elimination half-life was 18–28 days independent of the route. The terminal-phase elimination half-life was consistent across studies and independent of dose, administration site, and route.

Dose proportionality and time dependencies

- Dose proportionality

Across all studies and all doses, mepolizumab systemic clearance was slow, linear and independent of dose, indicating linear pharmacokinetics over the entire dose range tested (12.5–750 mg).

- Time dependency

Mepolizumab showed time-independent pharmacokinetics, based on simulation of the third dose mean concentrations using superposition of a one-compartment PK model of the first dose data.

- Intra- and inter-individual variability

Intra-individual variability assessed as residual variability was low 24 -29% and inter-individual variability following adjustment for body weight was 29- 33%.

Special populations

- **Impaired renal function**

Mepolizumab is a humanized 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 were not anticipated to impact the elimination of mepolizumab and a renal impairment study was not, therefore, conducted.

From the PopPK analysis of Phase III severe asthma data there was no evidence of reduced mepolizumab clearance in patients with creatinine clearance values between 50–80 ml/min compared with patients with creatinine clearance values >80 ml/min. However, the data in patients with creatinine clearance values ≤ 50 ml/min are currently limited.

No dose adjustment in patients with renal impairment is recommended. This was endorsed by the CHMP and was appropriately reflected in the SmPC (section 4.2).

- **Impaired hepatic function**

A hepatic impairment study was not conducted because mepolizumab is catabolized by ubiquitous proteolytic enzymes that are not restricted to hepatic tissue. Consequently, hepatic function is not expected to impact the elimination of mepolizumab.

From the PopPK analysis of Phase IIb/III severe asthma data there was no evidence of any influence on clearance of markers of liver inflammation such as bilirubin (0–40 µmol/L), alkaline phosphatase (25–358 IU/L), alanine aminotransferase (4–228 IU/L), and aspartate aminotransferase (9–129 IU/L). Across the different studies and indications, the range for these variables were 0–60 µmol/L, 25–358 IU/L, 4–228 IU/L, and 9–175 IU/L for bilirubin, alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, respectively. The majority of values were within the normal range.

No dose adjustment in patients with hepatic impairment was recommended. This was endorsed by the CHMP and was appropriately reflected in the SmPC (section 4.2).

- **Gender**

Mepolizumab showed no apparent differences with gender.

- **Race**

A specific single ascending mepolizumab IV dose (10, 75, 250 and 750 mg) study was conducted in healthy male Japanese subjects (Study MEA115705). The results showed no apparent ethnic differences in mepolizumab pharmacokinetics when compared with historic data in Caucasian subjects.

A population PK analysis of the pivotal Phase III study MEA115588 conducted in severe eosinophilic asthma patients (including Japanese adult and adolescent subjects) did not identify race, ethnicity or country as covariates of exposure. Mepolizumab concentrations, clearance and apparent clearance (CL/F) in Japanese subjects were consistent with non-Japanese subjects.

- **Weight**

Although bodyweight was found to be a statistically significant covariate for clearance and volume in the population PK analysis for mepolizumab, the magnitude of effect was not considered to be clinically relevant and no dosage adjustment for body weight was recommended in the SmPC. The CHMP considered this acceptable.

- **Elderly**

Although specific studies were not conducted in the elderly, mepolizumab has been administered to subjects aged up to 82 years (including 90 subjects ≥ 65 years). Age was not identified as a covariate neither in the population PK meta-analysis of mepolizumab IV (which explored the age range between 18-74 years) nor in the three Phase IIb/III population PK analyses of mepolizumab IV and SC in severe eosinophilic asthma patients (which explored the age range between 12–82 years).

No dose adjustment was required for elderly patients. This was endorsed by the CHMP and is reflected in the SmPC (section 4.2).

- **Children**

Mepolizumab IV pharmacokinetics were evaluated in a paediatric study previous submitted and assessed as part of the evaluation of Bosatria, which involved subjects aged 2–17 years with eosinophilic oesophagitis. Three doses of 0.55, 2.5 and 10 mg/kg were studied in ~20 subjects each and sparse samples were taken for PK. After adjusting for bodyweight via weight-based dosing, it was concluded that age was not a determinant of exposure. A population PK analysis of the data using the previous adult meta-analysis model was performed and the exponent for weight on clearance was fixed at 0.75, not 1.

In the pivotal Phase IIb/III severe eosinophilic asthma studies, mepolizumab SC and IV pharmacokinetics were evaluated in nineteen adolescents aged 12–17 years. Population PK analysis of the Phase IIb/III data did not identify age as a covariate of exposure, and concentrations in adolescents were consistent with adults. Predicted clearance in adolescent subjects was within the rest of the study population range, irrespective of administration route.

However, the CHMP considered that the current available PK data in children were too limited to allow a robust model to be developed and no dose recommendation could be made. This was accordingly reflected in the SmPC (section 4.2): The safety and efficacy of Nucala in children and adolescents under 18 years of age has not yet been established. Very limited data are currently available in children 12 to 18 years old (therefore no recommendations can be made.

2.4.2.1. Pharmacokinetic interaction studies

- **In vitro**

No *in-vitro* PK interaction studies were submitted. This was considered acceptable by the CHMP based on the nature of mepolizumab.

- **In vivo**

The subcutaneous administration route is unaffected by food and therefore no food-effect studies were conducted. This was considered acceptable by the CHMP.

The potential for drug-drug interactions with mepolizumab was classified as low in consideration of mepolizumab's target, elimination mechanism, favourable safety profile at doses up to 750 mg IV and the lack of mechanism of action rationale for a potential interaction. No drug interaction studies have therefore been conducted. This was considered acceptable by the CHMP.

The target for mepolizumab is the cytokine IL-5, a soluble target, which promotes growth, differentiation and survival of eosinophils. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters. However, in the literature review conducted by

the applicant, elevation of systemic pro-inflammatory markers was found to be minimal in severe asthma and no evidence of IL-5 receptor alpha expression on hepatocytes was found. This has been adequately reflected in the SmPC (section 4.5).

Mepolizumab is a monoclonal antibody with a large molecular weight (149.2 kDa) precluding renal elimination, which is catabolized by ubiquitous proteolytic enzymes not restricted to hepatic tissue. Mepolizumab does not undergo target-mediated clearance and changes in target concentration do not influence exposure. The clearance mechanism is non-specific, with large capacity and no overlapping clearance mechanism with small molecule drugs.

In the population pharmacokinetics analyses of the Phase III studies, there was no evidence of an effect of commonly co-administered small molecule drugs on mepolizumab exposure. Likewise, there was no evidence of dose adjustments being required for the small molecule drugs commonly co-administered in the intended target population (e.g., inhaled and oral corticosteroids). These data supported the absence of a disease or mepolizumab –related effect on the CYP450 or drug transporter expression.

2.4.3. Pharmacodynamics

Mechanism of action

Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5), the key cytokine responsible for regulation of blood and tissue eosinophils. IL-5 is the most potent and specific cytokine for the eosinophil lineage and is responsible for cellular expansion, release from the bone marrow into the peripheral blood, and survival following a variety of triggers, typically TH2 stimuli.

By targeting IL-5, mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signalling and the over-expression of peripheral blood and tissue eosinophils. Neutralizing IL-5 reduces the promotion, growth and survival of eosinophils in blood, sputum and other tissues, although complete blood eosinopenia is not possible due to redundant signalling by IL-3 and GM-CSF through a common β-sub-unit [Asquith, 2008].

The rationale for targeting IL-5 with mepolizumab was based upon the role of the eosinophil as an important inflammatory cell in the pathogenesis of asthma. Asthma is a complex disorder characterised by intermittent, reversible airway obstruction and airway hyper-responsiveness. In response to allergen, some allergic asthmatics exhibit a biphasic bronchoconstrictor response with an early and late phase reaction. The early response is initiated by bronchospastic mediator release and the late phase response by recruitment and activation of inflammatory cells with concomitant mediator/cytokine release. It is this latter inflammatory response, mediated through recruitment of eosinophils to the lung, that is believed to be the major cause of the smooth muscle hypertrophy and chronic mucosal damage that leads to airway hyper-reactivity and deterioration in lung function over time. There is evidence that eosinophils are important in cough, airway remodelling and asthma exacerbations. Specifically, the role of eosinophils in exacerbations may be particularly important because an asthma management strategy directed at normalising the sputum eosinophil count reduced the number of severe exacerbations compared to standard management.

Primary pharmacology

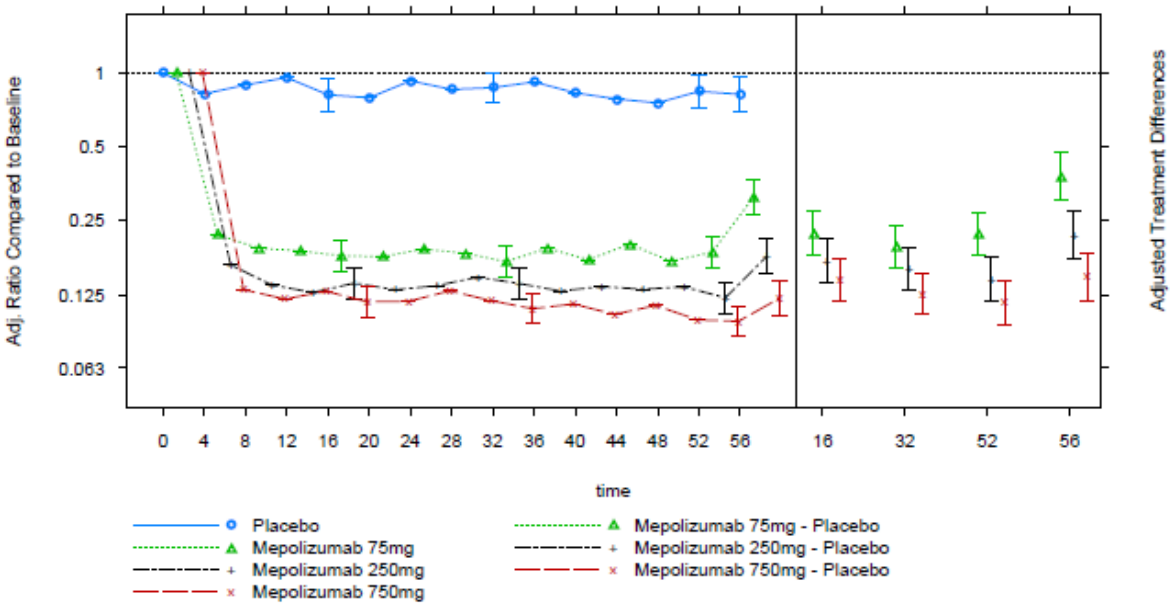
The effects of mepolizumab on eosinophils were studied in blood and sputum of patients with asthma. Serum free and total IL-5 were also measured to supplement the pharmacology of mepolizumab.

- **Blood eosinophils**

In single dose studies in healthy volunteers, mepolizumab IV produced reductions from baseline of at least 50%; their magnitude and duration was dose-dependent.

In repeat dose studies in mild to severe eosinophilic asthma, mepolizumab produced a sustained dose-dependent reduction in blood eosinophils from 57-88% with a dose-dependent time to repletion after treatment. Disease severity did not appear to be determinant of eosinophil response (figure 6).

Figure 6: Blood eosinophils ratio to BL (95% CI) - Study MEA112997 (severe asthma)



Administration route did not change the eosinophil response. After adjusting for absolute bioavailability the two asthma studies, MEA114092 and MEA115588, showed comparable blood eosinophil reductions of 80-86% for SC and IV doses.

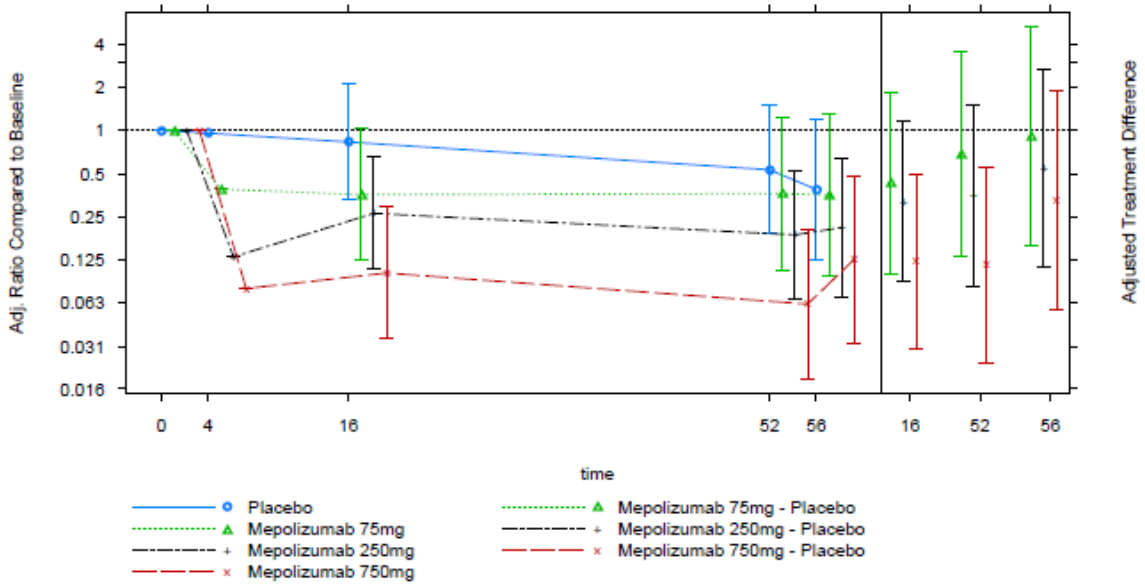
Likewise, concomitant steroid reduction did not influence the effects of mepolizumab on blood eosinophil reduction. Mepolizumab SC 100 mg produced reductions in blood eosinophil count of 84% with and without reductions in steroids (studies MEA115575 and MEA115588).

The consistent incomplete maximum blood eosinophil reductions of 80–90% are postulated to be due to redundancy in IL-5 signalling with GM-CSF and Interleukin-3 (IL-3) through a common β-sub-unit.

- **Sputum eosinophils**

In the moderate/severe and severe eosinophilic asthma studies, mepolizumab IV and SC both produced dose-dependent reductions in sputum eosinophils. In the Phase IIb/III study MEA112997, mepolizumab IV 75–750 mg produced reductions of 32–88% at Week 52 (Figure 7).

Figure 7 Sputum eosinophils ratio to BL (95% CI) - Study MEA112997 (severe asthma)



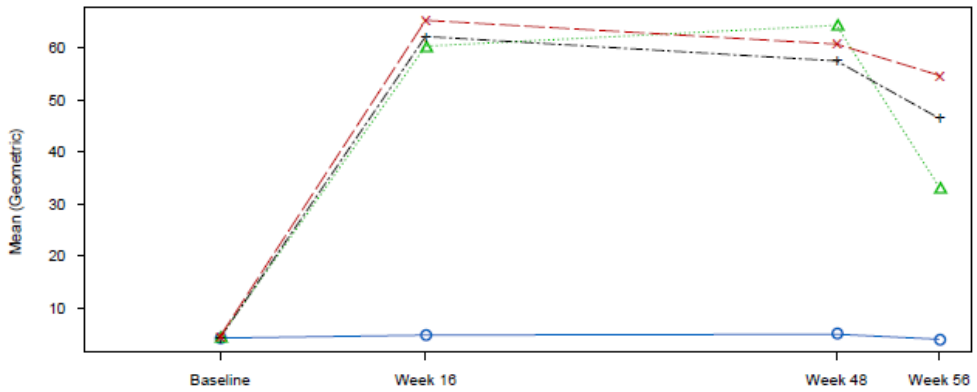
- **Interleukin 5**

Serum free IL-5 was undetectable at baseline in most subjects, whether healthy or asthmatic. Single IV doses of mepolizumab produced a dose-dependent increase in serum total IL-5.

In Study MEA114092, total IL-5 increased with no evidence of dose-response over the range 12.5 - 250 mg (3 SC doses at Day 1, 28, 56). At later time points post-treatment, a faster decline in total IL-5 was observed at the lower dose. There was no relationship between serum total IL-5 and blood eosinophils based on exploratory plots and correlation analyses.

In subjects with severe eosinophilic asthma (Study MEA112997), free IL-5 remained undetectable at all doses; however, total IL-5 increased to saturation, with no evidence of dose-response over the ranges 75–750 mg IV (Figure 8).

Figure 8 Mean total serum IL-5 (pg/mL) - Study MEA112997 (severe asthma)



No of Subjects				
Placebo (N=155)	154	146	133	5
Mepolizumab 75mg (N=153)	150	151	133	6
Mepolizumab 250mg (N=152)	144	147	136	4
Mepolizumab 750mg (N=156)	156	152	140	5

N.B. Values below the Lower Limit of Quantification (LLQ) were imputed using LLQ(7.8 pg/ml)/2.

Secondary pharmacology

Mepolizumab being a large molecule is unlikely to directly inhibit hERG channel. Furthermore, it has a highly specific target and does not bind to cardiac tissue. In an immunohistochemistry tissue cross-reactivity study, mepolizumab binding was restricted to human lymphoid tissues. Therefore, it has a low risk for QT-mediated proarrhythmia and a thorough QTc study was not conducted. However, thorough ECG monitoring was conducted in Phase III studies (see 2.6 safety section).

Relationship between plasma concentration and effect

Several PK/PD analyses were conducted to estimate mepolizumab exposure-response. Analysis of a previously submitted and assessed (as part of the evaluation of Bosatria) single ascending dose study in subjects with mild asthma showed that the PK/PD of mepolizumab was well-described by an indirect response model with 85% maximum reduction in eosinophil synthesis and a plasma concentration for half-maximal achievable effect (IC_{50}) of 0.45 mcg/ml. The PK/PD relationship was refined using analyses of studies MEA112997 and MEA114092. The estimated maximal effects (94% and 93%) and IC50's (0.23 and 1.3 mcg/ml) were both broadly consistent with the earlier values.

Study MEA114092 was conducted with the objective to show that the exposure-response relationship (AUCeos(0–Day 84) versus cumulative plasma mepolizumab AUC(0–Day 84) did not differ between the SC and IV administration.

This study "A multicentre, open-label, dose ranging study to determine the pharmacokinetics and pharmacodynamics of mepolizumab administered intravenously or subcutaneously to adult asthmatic subjects with elevated blood eosinophil levels"

The primary objective was to demonstrate that the PK/PD relationship between the exposure of subcutaneously (SC) administered mepolizumab and a marker of response, blood eosinophil, (AUC_{eos} (0–Day 84) did not differ from that observed following intravenous (IV) administration. Other objectives included an assessment of the immunogenicity, safety and tolerability of repeat doses of mepolizumab when administered SC and IV to asthmatic adult subjects with elevated blood eosinophil levels.

This was a multi-centre, randomised, open-label, parallel-group, repeat dose, dose-ranging study in adult subjects with moderate/severe asthma and blood eosinophil levels >300 cells/µL. Subjects were randomised 4:3:4:2 to mepolizumab SC 12.5, 125, 250 mg, and mepolizumab IV 75 mg.

They received three doses of mepolizumab every 28 days. The IV infusion was given over 30–60 minutes and the SC injection was given in the upper arm. Subjects were followed to Day 140. Blood samples were collected for pharmacokinetics (sparse sampling), eosinophil count and serum free and total IL-5, along with induced sputum for eosinophil count.

Seventy subjects were enrolled into the study. A dose-response to blood eosinophil count was observed, with the mepolizumab SC 12.5 mg showing notably higher eosinophil count compared with other doses.

A non-linear inhibitory dose-response model was used to describe Day 84 data. The maximum inhibitory effect (I_{max}) was 89% and the SC doses associated with half-maximal (ID_{50}) and 90% maximal (ID_{90}) response achievable by the drug were 11 mg and 99 mg, respectively, corresponding to an IV dose of 75 mg. The estimated SC absolute bioavailability was 74% and the terminal-phase elimination half-life was 22 days.

Independent data from the Phase IIb/III dose-ranging study MEA112997 were used to validate the dose-response by superimposing mepolizumab IV 75, 250 and 750 mg blood eosinophil count data over the model predictions and adjusting for absolute bioavailability.

Sputum eosinophil count also decreased in a dose-dependent manner, with larger decreases observed in the mepolizumab SC 125 mg and 250 mg treatment groups compared with 12.5 mg. Serum total IL-5 levels (i.e., free IL-5 plus complex) increased from baseline at all doses.

Sparse pharmacokinetic samples were collected and analysed using population PK methods. T_{max} was reached 6–8 days post-dosing in the SC dose groups and apparent clearance and volume, CL/F and V/F, were dose-independent implying linear-time-independent pharmacokinetics, with 1.7-fold accumulation for area under the concentration-time curve over the dosing interval ($AUC_{(0\text{-}tau)}$) and C_{max}.

The relationship between blood eosinophil count and mepolizumab plasma concentration was described using a population PK/PD analysis. The estimated maximum inhibition was 93% and the IC_{50} was 1.26 mcg/ml.

Administration route did not affect the mepolizumab exposure-response relationship for blood eosinophil count. Over the range 12.5–250 mg, mepolizumab SC pharmacokinetics were approximately dose proportional, linear and time-independent with accumulation predicted from the elimination half-life.

Overall, because of the limited range of data from the IV cohort it was not possible to test if the two half maximal effective concentration (EC_{50}) were different. Visual inspection showed however, that there was no obvious difference between the 75 mg IV and 125 mg SC arms.

Table 13 summarises the results of the PKPD modelling in studies MEA 114092 and MEA 112997.

Table 13 Summary of parameter estimates and 95% confidence interval for PKPD model of plasma eosinophil concentration as a function of mepolizumab plasma concentration

	MEA114092	**MEA112997**	**"Original model" (as listed in Study MEA112997)**
Number of subjects	69	611	
Number of PD data points	596	8171	
Average number of PD data points per subject	8.6	13.4	
Dosing routes	IV and SC	IV	
	Parameter Values		
KIN (GI/L/day)	**NA**	0.208 (fixed)	0.208 (0.177 -0.244)
KRO (GI/L)	0.710 (0.642, 0.784)	0.682 (fixed)	0.682 (0.612, 0.761)
KOUT (/day)	0.414 (0.297, 0.578)	NA	
IC_{50} (µg/mL)	1.26 (0.878, 1.81)	0.226 (fixed)	0.226 (0.100, 0.508)
IMAX	0.928 (0.875, 0.959)	0.94 (0.93, 0.95)	0.74 (0.70, 0.78)
BL covariate on KIN	NA	0.704 (fixed)	0.704 (0.457, 0.951)
BL covariate on KRO	0.701 (0.544, 0.858)	0.759 (fixed)	0.759 (0.672, 0.846)
BL on IMAX	NA	0.969 (0.842, 1.1)	NA

KRO=blood eosinophils baseline (KIN/KOUT); KIN=blood eosinophils rate of production; KOUT=blood eosinophils rate of elimination; IC_{50}=concentration inducing 50% of the maximum inhibitory effect; IMAX=maximum inhibitory effect; BL=baseline

An updated POPPKPD model based on blood eosinophil count was requested by the CHMP during the procedure which appeared consistent with previous analysis with a plasma concentration for half maximal effect of 0.9 µg/ml and a maximal effect of 83%.

A meta-analysis of annualised exacerbation rate dose-response using individualized weight-based doses from Phase IIb/III and Phase III studies MEA112997 and MEA115588 failed to estimate any parametric dose-response accurately.

A Bayesian analysis with informative log-normal for the half-maximal inhibitory efficacious dose confirmed that the ID_{50} for efficacy is consistent with the pharmacological value of 11 mg SC (or 0.16 mg/kg), nine-fold lower than the mepolizumab SC 100 mg clinical dose. Data from the combined Phase IIb/III studies shifted the prior from an initial mean of 20 mg SC to the pharmacological value, with a reduction in the width of the credibility interval, whilst retaining an approximate log-normal distribution.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Mepolizumab is an IgG1 monoclonal antibody, the pharmacokinetics of which are consistent with other monoclonal antibodies targeting soluble ligands. The pharmacokinetics are linear, dose-proportional and time-independent after both IV and SC administration.

Comparison of results of the four studies in moderate/severe eosinophilic asthma with earlier studies indicated that mepolizumab pharmacokinetics are unchanged in the population of interest of this application, severe eosinophilic asthma.

Mepolizumab subcutaneous absorption is slow, with an absolute bioavailability of 74– 80% following injection in the arm, a T_{max} of 4–8 days and an absorption and distribution half-lives of 1–2 days. Mepolizumab distributes into a volume that approximates plasma and interstitial space (55–85 ml/kg) and is catabolized by ubiquitous proteolytic enzymes.

Mepolizumab does not undergo target-mediated clearance. Mepolizumab is eliminated with a systemic clearance of 0.22 L/day (for 70 kg subject; or 3.1 ml/day/kg) and has a terminal-phase elimination half-life of 16–22 days, with two-fold accumulation following repeat dosing every four weeks, consistent with the long half-life. The pharmacokinetics of mepolizumab is consistent across studies, diseases and in Caucasian and Japanese subjects. Age does not affect the pharmacokinetics of mepolizumab however within this application there were no data in those over 82 years. As described in the relevant subsection of section 2.4.2, there are limited data in children; however, a population PK analysis studying the effect of weight on PK suggested that the exponent for weight on clearance is 0.75. Therefore weight-based dosing would result in slightly lower exposures in children than in adults. However the magnitude of effect was not considered to be clinically relevant and no dosage adjustment for body weight was recommended in the SmPC. The CHMP considered this acceptable.

Mepolizumab has low immunogenicity (≤ 6%), which does not influence either pharmacokinetics or pharmacodynamics discernibly in ADA-positive subjects.

The CHMP considered that no dosage adjustment for mepolizumab was necessary based on the population pharmacokinetic analyses submitted within application. This was reflected in the SmPC (section 4.2).

Pharmacodynamics

The CHMP considered that the mechanism of action of mepolizumab was well established. Mepolizumab prevents IL-5 binding to the eosinophil cell surface and thus inhibits IL-5 signalling and its downstream effects, i.e. the promotion, growth and survival of eosinophils in blood, sputum and other tissues, although complete blood eosinopenia is not possible due to compensatory signalling by IL-3 and GM-CSF.

The ligand interaction has been explored *in vitro* in the pre-clinical development and *in vivo* in human pharmacology studies of blood and sputum levels in patients with severe eosinophilic asthma. Mepolizumab was shown to have a potent and prolonged effect in reducing blood and sputum eosinophil levels over a wide range of doses. At the proposed recommended dose, a reduction of about 80% in blood eosinophils was consistently observed and this effect was slowly reversible, as blood eosinophil count remained reduced by about 60% eight weeks after discontinuation of treatment. A reduction in sputum eosinophils was also observed although more modest at this dose (about 30%).

No relationship was evident between serum IL-5 and blood eosinophils and no direct relationship between blood eosinophil levels and clinical effects, especially on the frequency of asthma exacerbations, were observed.

Serum IL-5 was not detectable in asthmatic patients and total IL-5 concentrations were observed to increase during treatment with mepolizumab as a result of the formation of mepolizumab-IL-5 complexes, which decreased IL-5 clearance. However, as there was no increase in free bioactive IL-5, no clinical consequence was expected. This was considered acceptable by the CHMP.

The applicant did no conduct conventional special clinical pharmacology studies due to the nature of the molecule, its mechanism of action and elimination pathways. No *in vitro* interaction studies were conducted by the applicant because the potential for drug-drug interaction (DDI) was deemed low. The applicant conducted a review of the scientific literature and did not find reports of IL-5 receptor alpha (IL-5Rα) expression on hepatocytes. In experiments with other interleukins that have minimal surface receptor expression, a low level of CYP3A4 suppression was generated. Together with negligible cell surface receptor expression and minimal stimulation of pro-inflammatory cytokine release, it was argued that cytokines with such characteristics (like IL-5) may pose less DDI risk with small-molecule drugs. Furthermore, clinical evidence shows that elevation of systemic pro-inflammatory markers is minimal in severe asthma compared to other inflammatory diseases. This was endorsed by the CHMP and appropriately reflected SmPC (section 4.5).

The applicant investigated potential associations between genetic polymorphisms, gender, race or ethnicity and mepolizumab treatment response (exacerbation rate and blood eosinophil count) in the two main studies. No apparent influence of genetic factors on the PD response to mepolizumab was observed.

The secondary pharmacology of mepolizumab was not explored in the clinical development of mepolizumab as the applicant claimed that there are no secondary pharmacology actions. However, in mice, IL-5 stimulates B-lymphocyte function and production of immunoglobulins, and eosinophils have a role in defence against some endoparasites.

Finally, as mepolizumab is unlikely to produce QTc prolongation, no specific study was performed but ECG monitoring and thorough evaluation of the data were conducted in the Phase III trials (see 2.6 safety section).

2.4.5. Conclusions on clinical pharmacology

Extensive PK and PD data were submitted. The PK profile of mepolizumab was well characterised and was adequately described in section 5.2 of the SmPC.

There was no need for dose adjustment in the elderly and patients with liver or renal impairment. However, data are currently limited in the paediatric population and do not allow a robust PK model to be developed. All this was endorsed by the CHMP and adequately reflected in section 5.2 of the SmPC.

2.5. Clinical efficacy

Three main studies are considered the primary efficacy studies for mepolizumab in severe eosinophilic asthma: one Phase IIb/IIIa exacerbation dose-ranging study (MEA112997) and two Phase IIIa studies an exacerbation study (MEA115588) and an OCS reduction study (MEA115575). Table 9 summarises these three main studies.

2.5.1. Dose response study

The dose-ranging study (MEA112997) was actually one of the three pivotal placebo-controlled trials in severe refractory asthma and is described in detail in section 2.5.2.

The aim was to investigate the dose-response relationship on PD and efficacy outcomes and it studied three intravenous doses (75 mg, 250 mg and 750 mg) of mepolizumab administered monthly. However no relationship between mepolizumab dose (75–750 mg IV) and clinical response (annualised exacerbation rate) in patients with severe eosinophilic asthma was observed. There was however evidence of increasing blood eosinophil reduction (78–88%) with increasing dose, albeit from already high inhibition.

The lowest dose was selected for further development based on PKPD modelling (see sections 2.4.2 and 2.4.3) .Based on the pharmacological correspondence showed in study MEA114092, mepolizumab SC 100 mg was selected for Phase III studies to provide the same pharmacological response as mepolizumab IV 75 mg (i.e., the ID_{90} for maximum achievable pharmacological effect).

2.5.2. Main studies

Study MEA112997 (DREAM study): A multicentre, randomised, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma

Methods

Study Participants

The inclusion criteria were the following: male or female non-smoking subjects aged ≥ 12 years and weighing ≥ 45 kg with severe refractory asthma [ATS workshop, 2000], with a requirement for regular treatment with high dose ICS (i.e., ≥880 µg/day fluticasone propionate or equivalent daily), plus

additional controller medication (e.g., long-acting beta-2 receptor agonist, leukotriene receptor antagonist or theophylline) and with or without maintenance OCS in the 12 previous months.

Subjects were also required to have persistent airflow obstruction as indicated by a pre-bronchodilator Forced Expiratory Volume in 1 second (FEV1) <80% predicted; a history of ≥ 2 asthma exacerbations requiring treatment with oral or systemic CS in the 12 previous months and evidence of asthma documented by one of the following measures: *(a)* airway reversibility (FEV1≥12% and 200 mL), *(b)* airway hyper-responsiveness (methacholine, histamine mannitol test), *(c)* airflow variability indicated by in clinic FEV1 ≥20% between two visits or >20% diurnal variability in Peak Exploratory Flow (PEF) observed on 3 or more days.

Finally subjects were also required to have airway inflammation likely to be eosinophilic in nature as indicated by one of the following characteristics demonstrated at the entry visit or documented in the previous 12 months: *(a)* peripheral blood eosinophil level ≥ 300/µL, *(b)* sputum eosinophils ≥3%, *(c)* exhaled nitric oxide ≥ 50 ppb or *(d)* prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≤ 25% reduction in regular maintenance dose of ICS or OCS in the previous 12 months.

The main exclusion criteria were: current smokers or smoking history of ≥10 pack/year, other lung condition, malignancy, unstable liver disease, Churg-Strauss syndrome, history of immunosuppressant therapies, omalizumab, or other anti-inflammatory biological treatment within a defined period before screening, regular systemic use of corticosteroids for diseases other than asthma, intramuscular corticosteroids within 1 month and long-acting depot corticosteroids within 3 months.

Treatments

Subjects were randomised to receive mepolizumab at doses of 75 mg, 250 mg or 750 mg or placebo IV once every 4 weeks for 48 weeks. The solution was administered as an infusion over approximately 30 minutes given by a designated, blinded member of the site staff.

Prior and concomitant medications

Additional asthma medications such as theophyllines or anti-leukotrienes were permitted provided they had been taken regularly in the 12 months prior to randomisation. Maintenance OCS were also permitted provided at least one of the exacerbations in the previous 12 months had occurred while the subject was receiving OCS and had been treated with a two-fold or greater increase in the dose of OCS for at least 3 days.

Prohibited medications included: investigational drugs, intra-articular corticosteroids, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, omalizumab or other biologicals for the treatment of inflammatory conditions, chemotherapy/radiotherapy and regular oral or systemic corticosteroids for the treatment of conditions other than asthma.

Objectives

Primary objective

To evaluate the dose response, based on efficacy and safety of three doses of mepolizumab (75 mg, 250 mg and 750 mg) over a 52 week treatment period in adult and adolescent subjects with severe uncontrolled refractory asthma.

Secondary objective

To assess the pharmacodynamic effect of mepolizumab on the number of eosinophils in blood, serum IL-5 and number of eosinophils in induced sputum.

Outcomes/endpoints

Primary efficacy endpoint

Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma which in the investigator's opinion required use of oral/systemic corticosteroids for at least 3 days and/or hospitalisation and/or emergency department (ED) visits. For subjects on maintenance OCS, an exacerbation requiring OCS was defined as the use of oral/systemic corticosteroids at least double the existing maintenance dose for at least 3 days.

In order to provide an objective assessment of the circumstances linked to the clinical decision that defined asthma exacerbations, the Investigator was to take into account changes from baseline on one or more of the following parameters recorded in the subject's e-diary: *(a)* a decrease in morning peak flow, *(b)* an increase in the use of rescue medication, *(c)* increases in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use and *(d)* an increase in overall asthma symptom score.

Secondary efficacy endpoints

- Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits
- Frequency of exacerbations and time to first exacerbation requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits
- Frequency and time to Investigator-defined exacerbations
- Mean change from baseline in clinic pre and post -bronchodilator FEV1 over the 52 week treatment period
- Mean change from baseline in Asthma Control Questionnaire (ACQ) score

Definitions of exacerbations

Clinically significant exacerbations, as previously defined, were recorded in the eCRF by the Investigator and verified using data from the patient eDiary. If an event described as an exacerbation had not been associated with deterioration in eDiary parameters, the Investigator was to provide an explanation to support the decision for defining the event as an exacerbation.

All exacerbations: These are the exacerbations that at a minimum met the requirement for worsening of asthma symptoms that required either treatment with systemic costicosteroids for at least 3 days and/or hospitalisation and/or ED visits. This term comprises both 'clinically significant exacerbations' and 'investigator-defined exacerbations'.

Investigator-defined exacerbation: These exacerbations are the subset of 'all exacerbations' that did not have objective data from either the eDiary or the Investigator to support the exacerbation.

Sample size

A total of 128 subjects per arm completing the study was estimated to give 90% power to detect a decrease in the exacerbation rate with increasing dose of mepolizumab 4-weekly, from 1.5 p.a. on placebo to 0.9 p.a. on mepolizumab 750 mg 4-weekly (a 40% decrease) at a two-sided 5%

significance level. Based on an assumed withdrawal rate of 15%, the planned number of randomised subjects was increased to 151 subjects per arm. The calculation assumed that the number of exacerbations per year would follow a negative binomial distribution with a dispersion parameter k=0.7.

Randomisation

After a screening visit (Visit 1), the study included a run-in period of 2 weeks during which maintenance asthma therapy had to be unchanged. At visit 2, patients underwent pulmonary functional testing and were randomised.

The randomisation schedule was generated based on randomly permuted blocks with a block size of eight using the validated randomisation software RandAll. Subjects were randomised centrally with equal numbers of subjects allocated to each treatment. The study was randomised separately for each country and subjects were stratified according to regular use, or not, of maintenance OCS.

Blinding (masking)

Mepolizumab and placebo were identical in appearance and were administered by a designated blinded member of the site staff. An unblinded pharmacist/designated site staff prepared the appropriate strength according to the medication assigned to the subject from a telephone interactive voice response system (IVRS). The study was blinded to those involved in the evaluation of the study (i.e. physician/nurse and subject) and this was maintained at all times.

Statistical methods

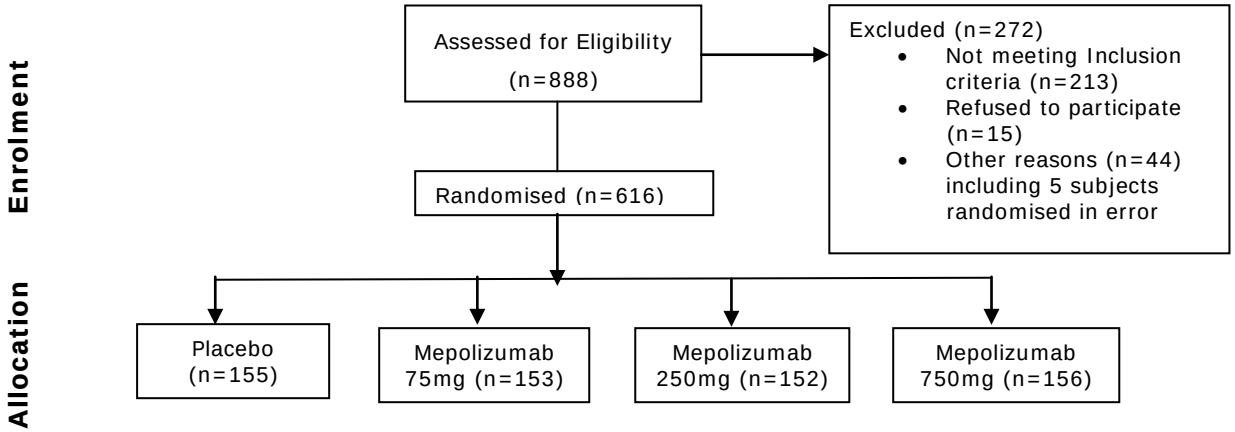
The primary comparison was the linear test for trend of a decrease in exacerbation rate with increasing dose of mepolizumab, with placebo being assigned as a dose of zero. Each of the three doses of mepolizumab had then to be compared to placebo. Multiplicity across these comparisons was controlled using a closed testing procedure followed by a one-sided Hochberg testing procedure.

Results

Participant flow

Overall, 888 subjects were screened, 272 subjects were excluded (including 5 patients randomised in error). The ITT Population consisted of all subjects randomised to treatment who received at least one dose of trial medication. This was the primary population for the analysis of all efficacy and safety endpoints. A diagram of the participant flow is presented in Figure 9.

Figure 9: Participant flow



Recruitment

The study was conducted in 81 centres in 13 countries. The highest recruitment was in Germany, US, Russia, Ukraine and in Romania.

Conduct of the study

Four minor protocol amendments were implemented during the study. None had a major impact.

Baseline characteristics

Subjects in the four arms were well matched in terms of demographic characteristics (Table 14).

Table 14 Summary of demographic characteristics

		Placebo N=155 n (%)	Mepolizumab 75 mg N=153 n (%)	Mepolizumab 250 mg N=152 n (%)	Mepolizumab 750 mg N=156 n (%)	Total N=616 n (%)
Age (years)	Mean (range)	46.4 (20–68)	50.2 (23–69)	49.4 (15–74)	48.6 (19–69)	48.6 (15–74)
Sex (n [%])	Female	97 (63)	104 (68)	93 (61)	93 (60)	387 (63)
	Male	58 (37)	49 (32)	59 (39)	63 (40)	229 (37)
Ethnicity (n [%])	Hispanic or Latino	16 (10)	15 (10)	14 (9)	16 (10)	61 (10)
	Not Hispanic or Latino	139 (90)	138 (90)	138 (91)	140 (90)	555 (90)
Height (cm)	Mean (range)	166.7 (145–193)	165.3 (138–191)	166.6 (147–190)	167.7 (147–191)	166.6 (138–193)
Weight (kg)	Mean (range)	78.4 (48–134)	77.8 (45–162)	78.6 (47–143)	81.4 (45–149)	79.0 (45–162)
BMI (kg/m²)	Mean (range)	28.3 (19–52)	28.4 (18–48)	28.3 (18–47)	28.9 (17–50)	28.5 (17–52)
Race (n [%])	White	140 (90)	139 (91)	135 (89)	140 (90)	554 (90)
	Asian	8 (5)	9 (6)	7 (5)	10 (6)	34 (6)
	African American/African Heritage	6 (4)	5 (3)	8 (5)	5 (3)	24 (4)
	American Indian or Alaskan Native	0	0	0	1 (<1)	1 (<1)
	Native Hawaiian or Other Pacific Islander	1 (<1)	0	0	0	1 (<1)
	African American/African Heritage and White	0	0	1 (<1)	0	1 (<1)
	Asian and White	0	0	1 (<1)	0	1 (<1)
Asthma duration (n [%])	<1 year	0	0	0	0	0
	≥1 year to <5 years	21 (14)	20 (13)	11 (7)	27 (17)	79 (13)
	≥5 years to <10 years	30 (19)	23 (15)	27 (18)	28 (18)	108 (18)
	≥10 years to <15 years	31 (20)	24 (16)	30 (20)	21 (13)	106 (17)
	≥15 years to <20 years	9 (6)	20 (13)	12 (8)	15 (10)	56 (9)
	≥20 years to <25 years	21 (14)	22 (14)	21 (14)	16 (10)	80 (13)
	≥25 years	43 (28)	44 (29)	51 (34)	49 (31)	187 (30)
Smoking status (n [%])	Never smoked	121 (78)	122 (80)	121 (80)	119 (76)	483 (78)
	Former smoker	34 (22)	31 (20)	31 (20)	37 (24)	133 (22)

Overall, during the previous 12 months, 33% had continuous OCS use (median dose = 10 mg/day) and 48% OCS bursts, 87% SABA usage, 63% urgent care visits, 30% prompt deterioration and 11% near fatal events. The baseline mean predicted FEV1 was 58% pre-salbutamol and 71% post-salbutamol. Overall, 54% of the subjects experienced more than 2 exacerbations within the 12 months prior to screening and 24% of the subjects required hospitalisation.

Numbers analysed

Overall, 616 subjects were included in the ITT Population and 591 in the PP Population (Table 15).

Table 15 Summary of analysis sets

	Placebo	Mepolizumab 75 mg	Mepolizumab 250 mg	Mepolizumab 750 mg	Total
All Subjects Enrolled					888
Intent-to-Treat Population	155	153	152	156	616
As Treated	155	153	152	156	616
Per Protocol Population[a]	151 (97%)	147 (96%)	142 (93%)	151 (97%)	591 (96%)

Source Data: Table 5.01

a) Percentages are based on the number of subjects in the Intent-to-Treat population.

Outcomes and estimation

The main efficacy results are presented in the section 'Analysis performed across trials' and in Table 20 (summary of efficacy for trial MEA 112997).

Ancillary analyses

The main subgroup analysis results are presented in the section 'Analysis performed across trials'.

Study MEA115588 (MENSA): A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma

Methods

Study Participants

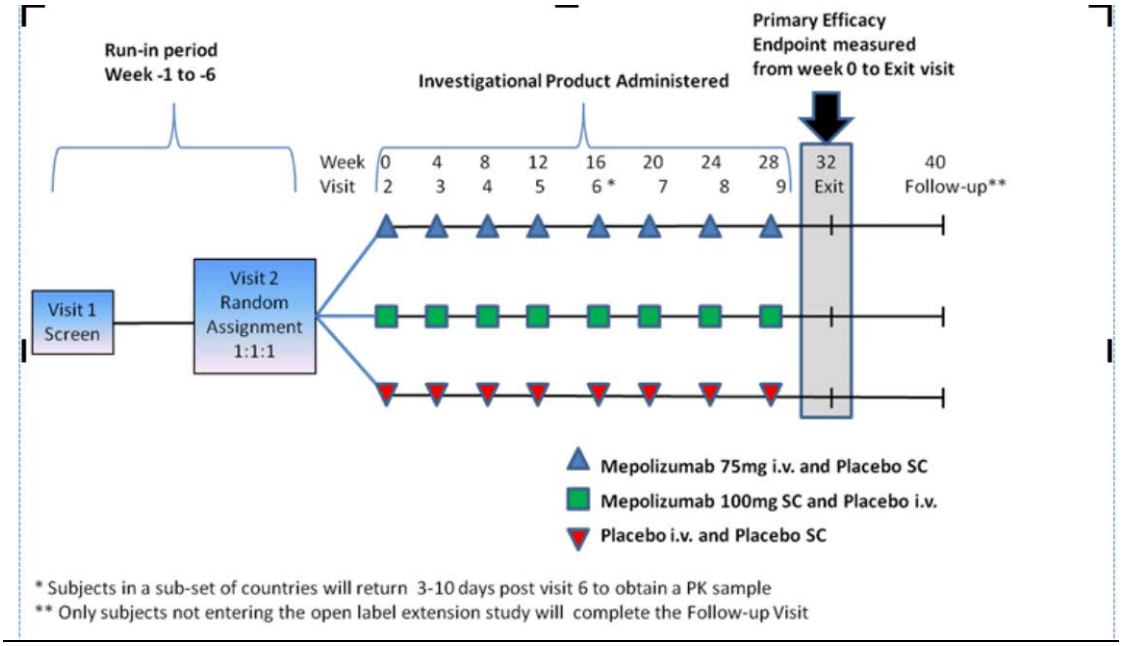
The selection criteria were the same as in Study MEA112997 except for:

- subjects aged 12-17 years for whom high ICS doses was defined as ≥440 µg/day Fluticasone Propionate (FP) (ex-actuator) or equivalent daily and pre-bronchodilator FEV1 <90% predicted; and
- the eosinophilic phenotype definition which for this study was defined as an elevated peripheral blood eosinophil count of ≥300/µL that is related to asthma demonstrated in the past 12 months prior to Visit 1 or an elevated peripheral blood eosinophil count of ≥150/µL at Visit 1.

Treatments

Subjects were randomised to receive mepolizumab at doses of 75 mg IV, 100 mg SC or placebo IV/SC once every 4 weeks for 28 weeks, (i.e. 8 doses). Due to the double dummy design, the subject had to receive 2 injections, one IV and one SC into separate arms. Prior and concomitant medications were the same as in Study MEA112997. The study schematic is shown in figure 10.

Figure 10: Study MEA115588 study design scheme



Objectives

Primary objective

The primary objective of the study was to evaluate the efficacy of mepolizumab 75 mg IV or 100 mg SC every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent subjects with severe, uncontrolled, refractory asthma.

Secondary objectives

Secondary objectives were to compare the safety and tolerability of mepolizumab with placebo in subjects with severe refractory asthma, and to evaluate the effects of mepolizumab compared with placebo on a range of clinical markers of asthma control, including pulmonary function (FEV1) and St. George's Respiratory Questionnaire (SGRQ).

Outcomes/endpoints

These were the same as for Study MEA112997 except for the use of the SGRQ instead of the AQLQ.

Sample size

The study, with 180 subjects randomised to each treatment arm, was designed to have over 90% power to detect a 40% decrease in exacerbation rate from 2.4 per annum (p.a.) on placebo to 1.44 p.a. on each of the mepolizumab treatment arms using a two-sided 5% significance level. The calculation assumed that the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter k=0.8.

Randomisation

Subjects were assigned to study treatment in accordance with the randomisation schedule which was generated using a validated randomisation software RandAll. Subjects were randomised in a 1:1:1 ratio.

Blinding (masking)

See Study MEA112997

Statistical methods

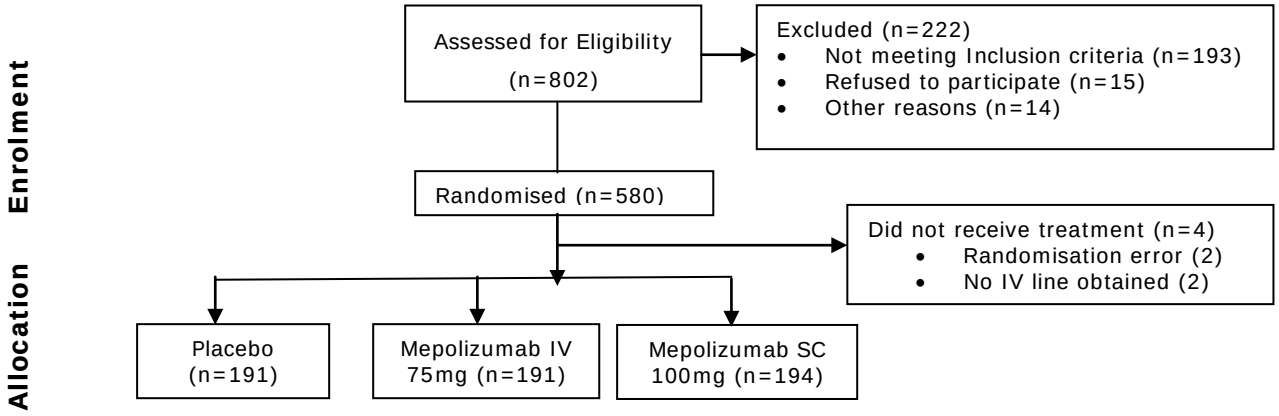
This study was designed to test the superiority of mepolizumab 75 mg IV vs. placebo and the superiority of mepolizumab 100 mg SC vs. placebo. Multiplicity across treatment comparisons and primary and secondary endpoints was controlled using a closed testing procedure: a one-sided Hochberg testing procedure was used for multiple treatment comparisons (75mg IV vs. placebo; 100mg SC vs. placebo) and a hierarchical 'gatekeeping' approach to control multiplicity across endpoints.

Results

Participant flow

Overall, 802 subjects were screened, 222 subjects were excluded, 580 were randomised but 576 received at least one dose of study drug (ITT Population); two subjects were randomised in error and 2 subjects were withdrawn due to issues in obtaining an IV line. A diagram of the participant flow is presented in Figure 11.

Figure 11 Participant flow



Recruitment

The study was conducted in 119 centres in 16 countries. The highest recruitment was in the EU and US.

Conduct of the study

No protocol amendment was implemented during the study.

Baseline characteristics

The study population was primarily white (78%) and more than half were female (57%); the mean age was 50 years. Twenty-five adolescent subjects (9 in each of the placebo and mepolizumab 75 mg IV groups and 7 in the mepolizumab 100 mg SC group) and 80 elderly subjects (26 in the placebo group, 24 in the mepolizumab 75 mg IV group and 30 in the mepolizumab 100 mg SC group) participated in the study.

Asthma history was similar between the treatment groups. The median duration of asthma was 17 years. The majority of subjects (76%) had asthma for ≥10 years; 31% of subjects had asthma for ≥25 years. The majority of subjects (69%) had ≥300 eosinophils/µL within 12 months prior to the Screening visit, and 83% of subjects had ≥150 eosinophils/µL at the Screening visit. Twenty-one subjects (4%) had been intubated due to asthma prior to the study. All subjects were treated with high-dose ICS for 12 months prior to screening and 24% were taking continuous OCS with a mean prednisone-equivalent dose of 13.2 mg/day, with doses ranging from 1 to 80 mg. Few subjects in each treatment group had a history of omalizumab use: 21 subjects (11%) in the placebo group, 29 subjects (15%) in the mepolizumab 75 mg IV and 25 subjects (13%) in the mepolizumab 100 mg SC group.

Overall, 57% of the subjects had >2 exacerbations in the previous 12 months and 19% had at least one hospitalisation.

Lung function tests at screening showed a mean pre-bronchodilator FEV1 of 1.69 L and percent predicted FEV1 of 57%. Mean post-bronchodilator lung function tests showed an FEV1 of 2.11 L, percent predicted FEV1 of 71%, FEV1/FVC ratio of 66%, and FEV1 reversibility of 28%.

Numbers analysed

Overall, 576 subjects were included in the mITT Population and 546 in the PP Population (Table 16).

Table 16 Summary of analysis sets

Population	Number (%) of Subjects			
	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	Total
Randomised[1]	193	193	194	580
Modified ITT	191	191	194	576
Per Protocol[2]	181 (95)	185 (97)	180 (93)	546 (95)

Outcomes and estimation

The main efficacy results are presented in the section "analysis performed across trials" and in Table 21 (Summary of efficacy for trial MEA115588).

Ancillary analyses

The main subgroup analysis results are presented in the section "Analysis performed across trials".

Study MEA115575 (SIRIUS): A randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma

Methods

Study Participants

The selection criteria were the same as in Study MEA115588 except that the requirement for frequent exacerbations was replaced by the requirement for regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisone or equivalent).

Treatments

Subjects were randomised to receive mepolizumab 100 mg SC or placebo every 4 weeks for 20 weeks (i.e. 6 doses). All subjects remained on their existing maintenance asthma therapy throughout this study, in addition to the study treatment, while reducing OCS (prednisone or prednisolone provided by the study site).

Study phases

The study consisted of four phases: 1) OCS Optimization; 2) Induction; 3) OCS Reduction; and 4) Maintenance phase. Figure 12 displays a schematic overview of the study design.

- OCS optimization phase

This phase was intended to assure that subjects entered the double-blind treatment phase on the lowest dose of OCS that would manage their symptoms. Its duration ranged from a minimum of 3 weeks to a maximum of 8 weeks (or 10 weeks if an exacerbation occurred).

The lowest effective OCS dose was defined during this phase by the emergence of asthma symptoms or the occurrence of an exacerbation. The emergence of asthma symptoms was determined by an increase in the ACQ-5 score of at least +0.5 from the Visit 1 score (collected via e-diary). The lowest effective OCS dose was identified as the OCS dose that the subject was taking just prior to the dose they were on when the symptoms emerged or the exacerbation occurred. Once the optimised dose was determined, the subject had to be able to remain on the optimized prednisone/prednisolone dose for 2 consecutive weeks prior to randomisation. Prednisone/prednisolone adjustments during this phase were made based on a predefined titration schedule.

- Induction phase

After randomisation and their first injection, subjects remained on their optimized dose of OCS, along with their baseline asthma medications. This phase (4-week duration) was designed to allow for sufficient time for those subjects randomised to the mepolizumab arm to achieve a decrease in the eosinophilic inflammation prior to the reduction in OCS.

- OCS reduction phase

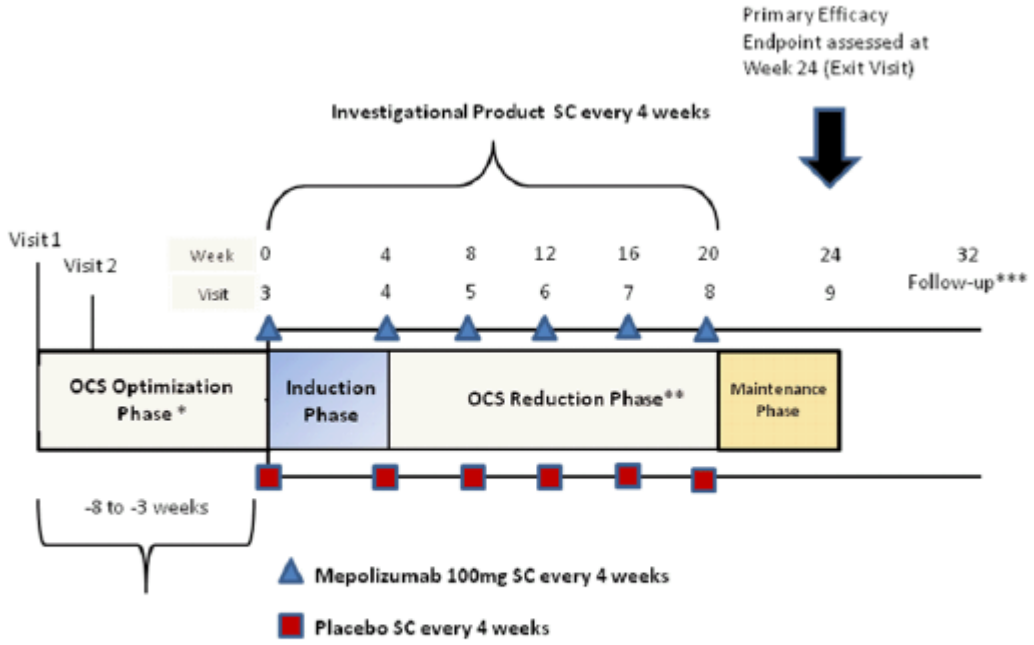
Subjects received five additional doses of double-blind study treatment (i.e., a dose every 4 weeks). The prednisone/prednisolone dose was titrated following a pre-defined schedule described. Subjects were assessed for OCS dose reduction every 4 weeks. Dose steps were greater and of longer duration (i.e., 4 weeks) compared with the schedule of the Optimization Phase. The 4-week timeframe allowed for carryover effects from the prior dose to be minimized and also minimized the risk for adrenal insufficiency complications. Subjects on lower doses of OCS at baseline could be completely weaned from OCS, while subjects on relativity higher doses of OCS at baseline (≥25 mg/day) would not be weaned completely.

OCS dose reduction was to occur per the schedule unless the subject met protocol defined criteria indicating that it was not acceptable to reduce OCS.

- Maintenance phase

Subjects were maintained during the last 4 weeks of the study (Weeks 20 through 24) without any further OCS dose adjustment.

Figure 12: Schematic overview of the study design of MEA115575:



*The OCS Optimization Phase could be extended to 10 weeks if a subject experienced an exacerbation during this phase.
** OCS dose titration occurred throughout the Optimization and Reduction Phases of the study. OCS titration did not necessarily coincide with the Visits scheduled for investigational product administration as indicated above.
*** Only subjects who did not enter the open label extension (OLE) study completed the Follow-up Visit at 12 weeks post last dose

Objectives

Primary objective

The primary objective of the study was to compare the effects of mepolizumab 100mg SC as an adjunctive therapy with placebo on reducing the use of maintenance OCS in systemic corticosteroid-dependent subjects with severe asthma with elevated eosinophils.

Secondary objectives

Secondary objectives were to compare the efficacy, safety, and tolerability of mepolizumab compared with placebo, in subjects with severe asthma with elevated eosinophils including an evaluation of the effects of mepolizumab on markers of asthma impairment and risk including, asthma symptoms, pulmonary function, exacerbation rate, and quality of life as assessed by the St. George's Respiratory Questionnaire (SGRQ).

Outcomes/endpoints

Primary efficacy endpoint

Percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose, while maintaining asthma control, categorized as follows: 90% to 100%; 75% to <90%; 50% to <75%; >0% to <50%; No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment.

Secondary efficacy endpoints

- Proportion of subjects who achieved a reduction of ≥50% in their daily OCS dose, compared with baseline dose
- Proportion of subjects who achieved a reduction of OCS dose to ≤5.0 mg
- Proportion of subjects who achieved a total reduction of OCS dose
- Median percentage reduction from baseline in daily OCS dose

Sample size

This study was designed to detect an increase of 25% in the proportion of subjects achieving ≥50% reduction in OCS dose. Based on a placebo proportion of 48%, this implied a mepolizumab proportion of 73% and an odds ratio (OR) of 2.9. For a proportional odds model, the sample size estimate was dependent on assumptions about the proportion of subjects in each reduction category, not just those that achieved a 50% reduction. Using the assumptions for each reduction category based on an OR of 2.9, a study with 60 subjects per group was estimated to have 90% power to detect an OR of 2.9 of a better category on mepolizumab compared with placebo.

Randomisation

Subjects were assigned to study treatment in accordance with the randomisation schedule which was generated using a validated randomisation software RandAll. The study was randomised separately for each country and the randomisation was stratified by duration of prior OCS use (<5 years vs. ≥5 years).

Blinding (masking)

See study MEA 112997 and MEA 115588.

Statistical methods

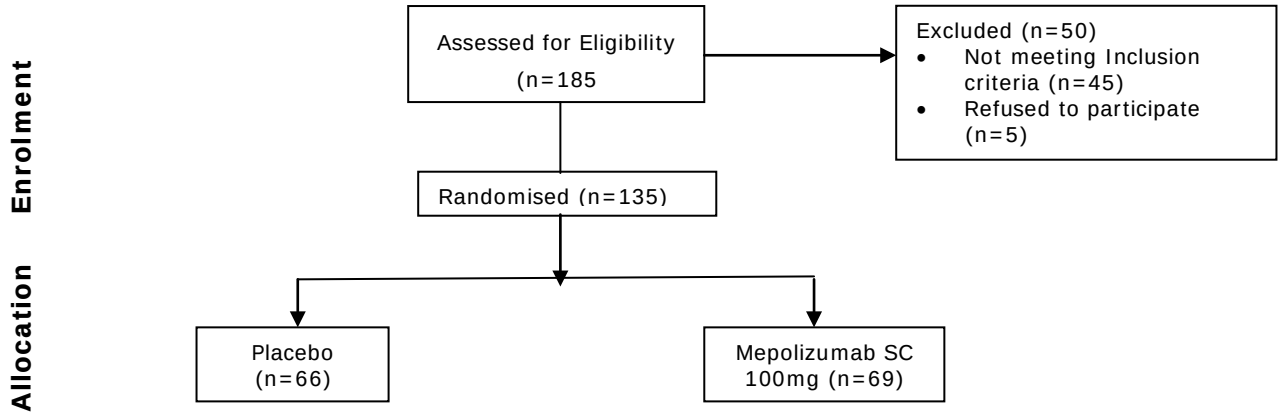
The number of subjects in each category for percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose was analysed using a proportional odds model (ordered logistic regression analysis) with covariates of treatment, region, duration of OCS use at baseline (<5 years vs. ≥5 years), and dose of OCS at baseline. All corticosteroids administered via oral, IV and IM routes were considered when calculating a subject's daily prednisone/prednisolone dose regardless of reason for administration. The OR was the model estimate of the ratio of the odds (mepolizumab/placebo) of a subject's outcome being in a better (greater reduction) category.

Results

Participant flow

Overall, 185 subjects were screened, 50 subjects were excluded and 135 were randomised (ITT Population). A diagram of the participant flow is presented in Figure 13.

Figure 13: Participant flow



The most frequent reasons for failures during the Optimization phase were that subjects did not achieve an optimized dose (27) or did not meet the eosinophilic phenotype as defined (10).

Recruitment

The study was conducted in 38 centres in 10 countries. The majority of subjects (73%) were recruited in the EU.

Conduct of the study

An early amendment was implemented, which contained clarifications and minor changes to the protocol.

Baseline data

The study population was essentially white (95%) with more than half being female (55%); the mean age was 50 years. Two adolescents and 14 elderly subjects were enrolled.

Asthma history was generally similar between the treatment groups. The mean duration of asthma was 19 years. The majority of subjects (69%) had asthma for ≥10 years; 30% of subjects had asthma for ≥25 years. Most subjects (90%) had ≥150 eosinophils/µL between visit 1 and visit 3 whereas this proportion at visit 3 (baseline) was only 76% (102/135); 68% had a history of blood count ≥300 eosinophils/µL within the previous 12 months.

One third of the subjects in each treatment arm (33%) had a history of omalizumab use. The majority of subjects in both treatment arms (85% placebo, 83% mepolizumab) had at least one exacerbation in the 12 months prior to the screening visit. The mean number of exacerbations experienced during this time period was slightly higher in the mepolizumab arm (3.3/year) compared with the placebo arm (2.9/year). Likewise, a larger proportion of subjects in the mepolizumab arm required hospitalization or an ED visit (33% vs. 17%) or required hospitalization (20% vs. 14%) for exacerbations.

In contrast, the median daily dose of OCS at baseline (optimized dose) was higher in the placebo arm (12.5 mg) than in the mepolizumab arm (10 mg). A larger percentage of subjects in the placebo arm were taking OCS doses ≥15 mg/day (41%) compared with the mepolizumab arm (28%); conversely, 9% vs. 17% of the subjects were taking the lowest dose (5mg/day).

Lung function tests at screening showed a mean pre- and post-bronchodilator percent predicted FEV1 of 56% and 68%, respectively, in the placebo arm vs. 58% and 72%, respectively, in the mepolizumab arm.

Numbers analysed

Overall, 135 subjects were included in the ITT Population and 122 in the PP Population (Table 17).

Table 17 Summary of analysis sets

	Number (%) of Subjects		
Population	Placebo	Mepolizumab 100 mg SC	Total
Randomized	66	69	135
ITT	66 (100)	69 (100)	135 (100)
PP[1]	61 (92)	61 (88)	122 (90)

Outcomes estimation and subgroup analysis

- *OCS dose reduction*

Subjects treated with mepolizumab were able to achieve a category of greater OCS reduction, while maintaining asthma control, compared with subjects treated with placebo; the OR was statistically significant in the ITT analysis (2.39; 95% CI: 1.25, 4.56; p=0.008) and in the Per-Protocol analysis (2.13; 95%CI: 1.07, 4.22, p=0.03).

Table 18 Percent OCS reduction from baseline during Week 20-24 (ITT population)

	Number (%) of Subjects	
Percent Reduction from Baseline	Placebo N=66	Mepolizumab 100 mg SC N=69
n	66	69
90% to 100%	7 (11)	16 (23)
75% to <90%	5 (8)	12 (17)
50% to <75%	10 (15)	9 (13)
>0% to <50%	7 (11)	7 (10)
No decrease in OCS, lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)
Odds ratio to placebo	---	2.39
95% CI	---	(1.25, 4.56)
p-value	---	0.008

During Weeks 20-24, more than half of subjects treated with mepolizumab (54%) achieved ≥50% reduction from baseline in daily OCS dose compared with 33% of subjects treated with placebo (p=0.027). More than half of subjects treated with mepolizumab (54%) also achieved a reduction in daily OCS dose to ≤5 mg compared with 32% of subjects treated with placebo (p=0.025). Although more subjects treated with mepolizumab achieved a total (100%) reduction in OCS dose (10 subjects, 14%) compared with those treated with placebo (5 subjects, 8%), the sample size was small and the OR was not statistically significant. The median percentage reduction from baseline in daily OCS dose was 50% in the mepolizumab group compared with 0% in the placebo group; this difference was statistically significant (p=0.007).

When the primary analysis was analysed by different subgroups based on baseline OCS dose, larger effects with mepolizumab were seen for the subgroups with the lowest level of baseline OCS dose (5 to <10 mg/day; OR=3.56; 95%CI: 0.97, 13.11) but mostly with the highest level of baseline OCS use (≥15 mg/day; OR=6.25; 95%CI: 1.67, 23.38) compared with the middle category (10 to <15 mg/day; OR=1.07).

In the subgroup analysis of the primary endpoint by baseline eosinophils, larger effects with mepolizumab were seen for the subgroup of patients with baseline blood eosinophils <150 cells/µL compared with those with higher levels (Table 21). In contrast, in the subgroup of patients who met the eosinophil inclusion criteria category of ≥300 cells/µL in the prior 12 months, the OR of 4.35 (95%CI: 1.86, 10.17) was statistically in favour of mepolizumab whereas it was only 1.16 (95%CI: 0.37, 3.64) in the subgroup of patients who did not meet this criterion.

Table 19 Percent OCS reduction from baseline by baseline blood eosinophils (ITT pop)

Subgroup – Baseline Eosinophil Level	Number (%) of Subjects	
	Placebo N=66	Mepolizumab 100 mg SC N=69
<150 cells/µL		
n	18	15
90% to 100%	1 (6)	6 (40)
75% to <90%	0	3 (20)
50% to <75%	3 (17)	2 (13)
>0% to <50%	3 (17)	1 (7)
No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	11 (61)	3 (20)
Odds ratio to placebo	---	6.87
95% CI	---	(1.53, 30.88)
150 to <300 cells/µL		
n	20	18
90% to 100%	3 (15)	4 (22)
75% to <90%	2 (10)	2 (11)
50% to <75%	2 (10)	2 (11)
>0% to <50%	1 (5)	1 (6)
No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	12 (60)	9 (50)
Odds ratio to placebo	---	2.03
95% CI	---	(0.53, 7.75)
300 to <500 cells/µL		
n	9	16
90% to 100%	1 (11)	3 (19)
75% to <90%	1 (11)	4 (25)
50% to <75%	1 (11)	3 (19)
>0% to <50%	1 (11)	1 (6)
No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	5 (56)	5 (31)
Odds ratio to placebo	---	3.64
95% CI	---	(0.69, 19.24)
≥500 cells/µL		
n	19	20
90% to 100%	2 (11)	3 (15)
75% to <90%	2 (11)	3 (15)
50% to <75%	4 (21)	2 (10)
>0% to <50%	2 (11)	4 (20)
No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	9 (47)	8 (40)
Odds ratio to placebo	---	1.01
95% CI	---	(0.31, 3.31)

Exacerbations

Compared with subjects treated with placebo, fewer subjects treated with mepolizumab experienced clinically significant exacerbations (42% vs. 68%), exacerbations requiring hospitalization or an ED visit (4% vs. 11%), and exacerbations requiring hospitalization (0% vs. 11%). Subjects treated with

mepolizumab had a 32% reduction in rate of clinically significant exacerbations (1.44/year) compared with subjects receiving placebo (2.12/year) (Rate ratio: 0.68, 95% CI: 0.47 to 0.99; p=0.042).

FEV1

At baseline, mean pre-bronchodilator FEV1 was higher in the placebo group (2.01 L) compared with the mepolizumab group (1.90 L). Beginning at Week 4 and continuing through Week 24, subjects treated with mepolizumab showed greater mean increases from baseline in pre-bronchodilator FEV1 compared with the placebo group at each 4-week assessment; the differences between the treatments were statistically significant at Weeks 4, 8, and 16 ($p<0.05$).

Mean post-bronchodilator FEV1 was also higher in the placebo group (2.38 L) compared with the mepolizumab group (2.24 L) at baseline. At the end of the treatment period (Week 24), the difference in the adjusted mean changes from baseline between mepolizumab and placebo groups was 114 mL for pre-bronchodilator FEV1 (95% CI: -42 to 271 mL; p=0.151) and 128 mL for post-bronchodilator FEV1 (95% CI: -8 to 264 mL; p=0.064).

Asthma Control Questionnaire-5 (ACQ-5)

At baseline, subjects in the mepolizumab arm had a higher mean ACQ-5 score (2.15) than subjects in the placebo arm (1.99); both scores were ≥1.5 indicating not well controlled asthma. Beginning at Week 2 and continuing through Week 24, subjects treated with mepolizumab showed greater decreases (improvement) from baseline in ACQ-5 compared with the placebo arm; the treatment differences were statistically significant at most weeks ($p\leq0.05$), except for Weeks 1, 12, and 17. At Week 24, subjects treated with mepolizumab had a statistically significant (decrease) improvement (mean=-0.61) compared to placebo (mean=-0.09); the difference was statistically significant (-0.52; 95% CI: -0.87, -0.17; p=0.004) and the improvement was also clinically relevant (≥≥ 0.5, minimal clinically importantly difference (MCID) for this instrument). The improvement in daily asthma symptom score up to 12 weeks was associated with less albuterol/salbutamol use and fewer night time awakenings requiring rescue medication. However, these improvements were not sustained to week 24, where no difference from placebo was observed.

Examination of ACQ-5 by score category at each visit showed that a larger proportion of subjects in the mepolizumab group compared with the placebo group were in the lowest score category (≤0.75), with the exception of Week 6, indicating well-controlled asthma status. Additionally, a larger proportion of subjects in the placebo group compared with the mepolizumab group were in the highest score category (≥1.5), with the exception of Weeks 1 and 12, indicating not well-controlled asthma status.

St. George's Respiratory Questionnaire (SGRQ)

At baseline, the mean total SGRQ score was slightly higher in the mepolizumab group (49.6) compared with the placebo group (45.0). At the end of the treatment period (Week 24), a larger mean decline (improvement) from baseline in SGRQ scores was observed in the mepolizumab arm (-8.8 points) compared with the placebo arm (-3.1 points); the treatment difference (-5.8; 95% CI: -10.6, -1.0; p = 0.019) was greater than the MCID (4-point improvement).

The cumulative proportion of subjects with ≥4-point improvement in SGRQ at week 24 was also greater in the mepolizumab arm (58%) compared with the placebo arm (41%). Furthermore, 45% of subjects treated with mepolizumab achieved a ≥10-point improvement in SGRQ compared with 24% treated with placebo.

When the SGRQ was examined by domain, larger declines (improvement) from baseline in the Activity, Impacts, and Symptoms domain scores were observed with mepolizumab compared with placebo at week 24. The Symptoms domain showed the most improvement with mepolizumab treatment.

Summary of main efficacy studies

The following tables 20, 21 and 22 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20 Summary of efficacy for trial MEA112997

Title: *A multicentre, randomised, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma*					
Study identifier	**Study MEA112997**				
Design	Double-blind, randomised, parallel group, placebo-controlled, multicentre multinational with central randomisation (IVRS) stratified by country and regular oral corticosteroid use Active and placebo of identical appearance prepared by unblinded pharmacist				
	Duration of main phase:	52 weeks			
	Duration of Run-in phase:	2 weeks			
	Duration of Extension phase:	Ongoing (after drug interruption)			
Hypothesis	Superiority – Evaluation of the dose-response Exploratory: definition of target population for subsequent pivotal trials				
Treatments groups	PLACEBO	One IV infusion every 4 weeks for 48 weeks; N=155			
	MEPO75	One IV infusion of 75mg every 4 weeks for 48 weeks; N=153			
	MEPO250	One IV infusion of 250mg every 4 weeks for 48 weeks; N=152			
	MEPO750	One IV infusion of 750mg every 4 weeks for 48 weeks; N=156			
Endpoints and definitions	Primary endpoint	EXACERB	Clinically significant exacerbations defined as requiring systemic CS and/or hospitalisation and/or emergency department visit (ED)		
	Secondary	HOSPIT/ED	Exacerbations requiring hospitalisation/ED		
	Secondary	HOSPIT	Exacerbations requiring hospitalisation		
	Secondary	FEV1 pre/post	FEV1 pre-/post-bronchodilator Change from BL		
	Secondary	ACQ	Asthma Control Questionnaire score Change from BL		
	Secondary	AQLQ	Asthma Quality of Life Questionnaire score Change from BL		
Database lock	25/06/2012				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (all subjects having received at least one dose) 52 weeks				
Descriptive statistics and estimate variability	Treatment group	PLACEBO	MEPO75	MEPO250	MEPO750
	Number of subject	155	153	152	156

	Primary EXACERB Rate/year	2.40	1.24	1.46	1.15
	Secondary HOSPIT/ED Rate/year	0.43	0.17	0.25	0.22
	Secondary HOSPIT Rate/year	0.18	0.11	0.12	0.07
	FEV1 pre LS mean change SE (mL)	 60 38	 121 38	 140 37	 115 37
	FEV1 post LS mean change SE (mL)	 -9 37	 36 36	 80 36	 69 36
	ACQ score LS mean change SE	 -0.59 0.09	 -0.75 0.09	 -0.87 0.09	 -0.80 0.09
	AQLQ score LS mean change SE	 0.71 0.09	 0.80 0.09	 0.77 0.09	 0.93 0.09
Effect estimate per comparison	Treatment group	PLACEBO	MEPO75	MEPO250	MEPO750
	Primary: EXACERB Rate ratio 95%CI p-value	MEPO/PLA	0.52 0.39, 0.69 <0.001	0.61 0.46, 0.81 <0.001	0.48 0.36, 0.64 <0.001
	Secondary HOSPIT/ED Rate ratio 95%CI p-value	MEPO/PLA	0.40 0.19, 0.81 0.011	0.58 0.30, 1.12 0.106	0.52 0.27, 1.02 0.056
	Secondary HOSPIT Rate ratio 95%CI p-value	MEPO/PLA	0.61 0.28, 1.33 0.214	0.65 0.31, 1.39 0.268	0.37 0.16, 0.88 0.025
	FEV1 pre Diff 95%CI (mL) p-value	MEPO-PLA	61 -39, 161 0.229	81 -19, 180 0.114	56 -43, 155 0.269
	FEV1 post Diff 95%CI (mL) p-value	MEPO-PLA	45 -50, 139 0.356	89 -6, 184 0.066	78 -16, 172 0.105
	ACQ score Diff 95%CI p-value	MEPO-PLA	-0.16 -0.39, 0.07 0.183	-0.27 -0.51, -0.04 0.020	-0.20 -0.43, 0.03 0.085
	AQLQ score Diff 95%CI p-value	MEPO-PLA	0.08 -0.16, 0.32 0.501	0.05 -0.19, 0.29 0.664	0.22 -0.02, 0.46 0.069
Notes	The study failed to show any dose-response relationship; the decrease in exacerbation rate was similar at the three doses. The trial investigated predictive markers of efficacy that were used in the two other trials. The two following criteria were selected: a blood eosinophil count ≥150 cells/µl at initiation of treatment or a blood eosinophil count ≥300 cells/µl in the prior 12 months.				

Table 21 Summary of efficacy for trial MEA115588

Title: *A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma*				
Study identifier	**Study MEA115588**			
Design	Double-blind, double dummy, randomised, parallel group, placebo-controlled, multicentre multinational with central randomisation Active and placebo of identical appearance prepared by unblinded pharmacist; patients received an IV infusion and a SC injection at each administration			
	Duration of main phase:	32 weeks		
	Duration of Run-in phase:	1 - 6 weeks		
	Duration of Extension phase:	Ongoing		
Hypothesis	Superiority			
Treatments groups	PLACEBO		One SC/IV injection every 4 weeks for 28 weeks; N=191	
	MEPO75		One IV infusion of 75mg every 4 weeks for 28 weeks; N=191	
	MEPO100		One SC injection of 100mg every 4 weeks for 28 weeks; N=194	
Endpoints and definitions	Primary endpoint	EXACERB	Clinically significant exacerbations defined as requiring systemic CS and/or hospitalisation and/or emergency department visit (ED)	
	Secondary	HOSPIT/ED	Exacerbations requiring hospitalisation/ED	
	Secondary	HOSPIT	Exacerbations requiring hospitalisation	
	Secondary	FEV1 pre	FEV1 pre-bronchodilator Change from BL	
	Secondary	SGRQ	St. George's Respiratory Questionnaire score Change from BL	
	Other	ACQ	Asthma Control Questionnaire score Change from BL	
	Other	FEV1 post	FEV1 post-bronchodilator Change from BL	
Database lock	03/03/2015			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified Intent to treat (all subjects having received at least one dose) 32 weeks			
Descriptive statistics and estimate variability	Treatment group	PLACEBO	MEPO75	MEPO100
	Number of subject	191	191	194
	Primary EXACERB Rate/year	1.74	0.93	0.83
	Secondary HOSPIT/ED Rate/year	0.20	0.14	0.08
	HOSPIT Rate/year	0.10	0.06	0.03

	FEV1 pre LS mean change SE (mL)	 86 31	 186 32	 183 31
	FEV1 post LS mean change SE (mL)	 30 34	 176 34	 167 33
	SGRQ score LS mean change SE	 -9.0 1.2	 -15.4 1.2	 -16.0 1.1
	ACQ score LS mean change SE	 -0.50 0.07	 -0.92 0.07	 -0.94 0.07
Effect estimate per comparison	Treatment group	PLACEBO	MEPO75	MEPO100
	Primary: EXACERB Rate ratio 95%CI p-value	 MEPO/PLA	 0.53 0.40, 0.72 <0.001	 0.47 0.35, 0.64 <0.001
	Secondary HOSPIT/ED Rate ratio 95%CI p-value	 MEPO/PLA	 0.68 0.33, 1.41 0.299	 0.39 0.18, 0.83 0.015
	HOSPIT Rate ratio 95%CI p-value	MEPO/PLA	0.61 0.23, 1.66 0.334	0.31 0.11, 0.91 0.034
	FEV1 pre Diff 95%CI (mL) p-value	MEPO-PLA	100 13, 187 0.025	98 11, 184 0.028
	FEV1 post Diff 95%CI (mL) p-value	MEPO-PLA	146 50, 242 0.003	138 43, 232 0.004
	SGRQ score Diff 95%CI p-value	MEPO-PLA	-6.4 -9.7, -3.2 <0.001	-7.0 -10.2, -3.8 <0.001
	ACQ score Diff 95%CI p-value	MEPO-PLA	-0.42 -0.61, -0.23 <0.001	-0.44 -0.63, -0.25 <0.001

Table 22 Summary of efficacy for trial MEA115575

Title: *A randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma*		
Study identifier	**Study MEA115575**	
Design	Double-blind, randomised, parallel group, placebo-controlled, multicentre multinational with separate randomisation for each country and stratified by duration of oral corticosteroid use Active and placebo of identical appearance prepared by unblinded pharmacist	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 3 - 10 weeks Ongoing
Hypothesis	Superiority	
Treatments groups	PLACEBO	One SC injection every 4 weeks for 20 weeks; N=66
	MEPO100	One SC injection of 100mg every 4 weeks for 20 weeks; N=69

Endpoints and definitions	Primary endpoint	% REDUC	Percent reduction of OCS dose during Weeks 20-24 compared to BL
	Secondary	≥50%	% subjects with reduction ≥50% from BL
	Secondary	≤5mg	% subjects achieving dose ≤5mg daily
	Secondary	Total	% subjects achieving total reduction
	Other	EXACERB	Clinically significant exacerbations
	Other	SGRQ	St. George's Respiratory Questionnaire score Change from BL
	Other	ACQ	Asthma Control Questionnaire score Change from BL
	Other	FEV1 pre/post	FEV1 pre-/post-bronchodilator Change from BL
Database lock	14/02/14		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (all subjects having received at least one dose) 24 weeks		
Descriptive statistics and estimate variability	Treatment group	PLACEBO	MEPO100
	Number of subject	66	69
	Primary % REDUC N (%) 90 – 100 75 - <90 50 - <75 >0 - <50 None / lack of control / withdrawal	 7 (11) 5 (8) 10 (15) 7 (11) 37 (56)	 16 (23) 12 (17) 9 (13) 7 (10) 25 (36)
	Secondary ≥50% N (%) ≤5mg N (%) Total N (%)	 22 (33) 21 (32) 5 (8)	 37 (54) 37 (54) 10 (14)
	EXACERB Rate/year	 2.12	 1.44
	FEV1 pre LS mean change SE (mL)	 -4 57	 111 55
	FEV1 post LS mean change SE (mL)	 -32 49	 96 48
	SGRQ score LS mean change SE	 -3.1 1.7	 -8.8 1.7
	ACQ score LS mean change SE	 -0.09 0.13	 -0.61 0.13
Effect estimate per comparison	Treatment group	PLACEBO	MEPO100
	Primary: % REDUC Odds ratio 95%CI p-value	MEPO/PLA	 2.39 1.25, 4.56 0.008
	Secondary EXACERB Rate ratio 95%CI p-value	MEPO/PLA	 0.68 0.47, 0.99 0.042

	FEV1 pre Diff 95%CI (mL) p-value	MEPO-PLA	114 -42, 271 0.151
	FEV1 post Diff 95%CI (mL) p-value	MEPO-PLA	128 -8, 264 0.064
	SGRQ score Diff 95%CI p-value	MEPO-PLA	-5.8 -10.6, -1.0 0.019
	ACQ score Diff 95%CI p-value	MEPO-PLA	-0.52 -0.87, -0.17 0.004
Notes	The treatment arms were not well balanced at BL regarding gender, past exacerbations, lung function, ACQ, blood eosinophils, prednisone dose.		

Analysis performed across trials (pooled analyses and meta-analysis)

A combined analysis (meta-analysis using individual patient data) was conducted on the results of the two placebo-controlled exacerbation studies of similar design (MEA112997 and MEA115588). The objective was to inform on a more precise effect size and to examine effects across subgroups. It used the Intent-to-Treat (ITT) Population consisting of all randomised subjects who received at least one dose of study medication and the following treatment comparisons were studied:

- 75 mg IV vs. Placebo
- 75 mg IV+100 mg SC vs. Placebo
- All mepolizumab doses combined vs. Placebo

The demographics of the study population in the combined analysis (1192 subjects in total) are presented in Table 8. Of note, the number of adolescents was small (26) but there were a total of 105 elderly patients (9%).

Table 23 Demographics of the combined analysis population

	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[1] N=538	Mepolizumab All Doses[2] N=846	Total N=1192
MEA112997+MEA115588						
N	346		344	538	846	1192
Gender, n(%)						
Female	204 (59)		209 (61)	325 (60)	511 (60)	715 (60)
Male	142 (41)		135 (39)	213 (40)	335 (40)	477 (40)
Age (yr)						
Mean (SD)	47.9 (13.08)		50.1 (12.70)	50.5 (13.39)	49.9 (12.70)	49.3 (12.83)
Min, Max	12, 76		13, 82	12, 82	12, 82	12, 82
Age Group, n(%)						
12-17 years old	9 (3)		9 (3)	16 (3)	17 (2)	26 (2)
18-64 years old	306 (88)		302 (88)	459 (85)	755 (89)	1061 (89)
≥65 years old	31 (9)		33 (10)	63 (12)	74 (9)	105 (9)
65-74 years old	28 (8)		29 (8)	51 (9)	62 (7)	90 (8)
75-84 years old	3 (<1)		4 (1)	12 (2)	12 (1)	15 (1)

Results of the combined analysis showed similar reductions in the rate of clinically significant exacerbations (49% for mepolizumab 75 mg IV+100 mg SC and 48% for mepolizumab 75 mg IV; $p<0.001$ for each) to the mepolizumab 100 mg SC dose in MEA115588 (53%, $p<0.001$) (Table 24).

Similar reductions in the rate of exacerbations requiring hospitalisation/ED visits were observed in the combined analysis (47% for mepolizumab 75 mg IV+100 mg SC and 42% for mepolizumab 75 mg IV; $p=0.007$ and $p=0.037$, respectively) compared with the mepolizumab 100 mg SC dose in MEA115588 (61%, $p=0.015$) (Table 25).

The combined analysis also showed significant reductions of 50% in the rate of exacerbations requiring hospitalisation for mepolizumab 75 mg IV+100 mg SC compared with placebo ($p=0.018$). There was a 43% reduction for mepolizumab 75 mg IV compared with placebo ($p=0.076$). Given the low number of events, the combined analysis provided a more robust assessment of the rate of exacerbations requiring hospitalisation than the individual studies (Table 26).

Table 24 Clinically significant exacerbations (individual studies and combined analysis, ITT Population)

Rate of Clinically Significant Exacerbations	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[4] N=538	Mepolizumab All Doses[5] N=846
MEA112997					
n	155		153		461
Exacerbation rate/year	2.40		1.24		1.28
Comparison vs. placebo[1]					
Rate ratio (mepolizumab/placebo)	---		0.52		0.53
(95% CI)	---		(0.39, 0.69)		(0.43, 0.67)
p-value	---		<0.001		<0.001
MEA115588					
n	191	194	191	385	385
Exacerbation rate/year	1.74	0.83	0.93	0.88	0.88
Comparison vs. placebo[2]					
Rate ratio (mepolizumab/placebo)	---	0.47	0.53	0.50	0.50
(95% CI)	---	(0.35, 0.64)	(0.40, 0.72)	(0.39, 0.65)	(0.39, 0.65)
p-value	---	<0.001	<0.001	<0.001	<0.001
MEA112997+MEA115588					
n	346		344	538	846
Exacerbation rate/year	1.91		1.00	0.98	1.01
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	---		0.52	0.51	0.53
(95% CI)	---		(0.42, 0.64)	(0.42, 0.62)	(0.44, 0.62)
p-value	---		<0.001	<0.001	<0.001

Source Data: Table 3.016, Table 3.017

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable.
2. Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions.
3. Analysis model as in footnote [2] where region is as defined for the Efficacy Summary and with an additional covariate of study.
4. For MEA112997, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since MEA112997 does not include a 100 mg SC dose.
5. MEA112997 includes 75, 250, and 750 mg IV. MEA115588 includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. MEA112997+MEA115588 includes 75, 250, and 750 mg IV and 100 mg SC.

Table 25 Exacerbations requiring hospitalisation/ED visit (combined analysis, ITT Population)

Rate of Exacerbations Requiring Hospitalization/ED Visits	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[4] N=538	Mepolizumab All Doses[5] N=846
MEA112997+MEA115588					
n	346		344	538	846
Exacerbation rate/year	0.26		0.15	0.14	0.16
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	---		0.58	0.53	0.60
(95% CI)	---		(0.35, 0.97)	(0.33, 0.84)	(0.40, 0.89)
p-value	---		0.037	0.007	0.012

Table 26: Exacerbations requiring hospitalisation (combined, ITT Population)

MEA112997+MEA115588					
n	346		344	538	846
Exacerbation rate/year	0.14		0.08	0.07	0.07
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	---		0.57	0.50	0.49
(95% CI)	---		(0.31, 1.06)	(0.28, 0.89)	(0.30, 0.81)
p-value	---		0.076	0.018	0.005

Treatment with mepolizumab showed greater increases over placebo in pre-bronchodilator FEV1 from baseline to Week 32 (difference of 63 mL for mepolizumab 75 mg IV+100 mg SC and 56 mL for mepolizumab 75 mg IV; p=0.040 and p=0.094, respectively) (Table 27).

Table 27 Change from baseline in pre-bronchodilator FEV1 (mL) (combined analysis, ITT Population)

	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
MEA112997+MEA115588					
Week 32					
n [1] at Week 32	343		340	532	839
n [2] at Week 32	313		312	497	773
LS Mean	1967		2023	2029	2001
LS Mean change	107		163	169	141
(SE for mean and mean change)	(23.8)		(23.9)	(19.8)	(15.1)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo)	---		56	63	37
(95% CI)	---		(-10, 122)	(3, 123)	(-18, 92)
p-value	---		0.094	0.040	0.189

Treatment with mepolizumab showed greater increases over placebo in post-bronchodilator FEV1 from baseline to Week 32 (difference of 89 mL for mepolizumab 75 mg IV+100 mg SC and 80 mL for mepolizumab 75 mg IV; p=0.005 and p=0.022, respectively) (Table 28).

Table 28 Change from baseline in post-bronchodilator FEV1 (mL) (combined analysis, ITT Population)

	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
MEA112997+MEA115588					
Week 32					
n [1] at Week 32	303		305	477	767
n [2] at Week 32	291		293	465	730
LS Mean	2221		2300	2313	2298
LS Mean change (SE for mean and mean change)	14 (25.2)		93 (25.1)	106 (21.2)	91 (15.6)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo)	---		80	89	76
(95% CI)	---		(11, 148)	(26, 152)	(18, 133)
p-value	---		0.022	0.005	0.010

Statistically significant improvements in ACQ score from baseline to Week 32 were observed in comparison to placebo: -0.34 points for mepolizumab 75 mg IV+100 mg SC and -0.29 points for mepolizumab 75 mg IV ($p<0.001$) (Table 29).

Table 29 Change from baseline in ACQ score

	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
MEA112997+MEA115588					
n [1] at Week 32	336		328	517	818
n [2] at Week 32	298		292	465	732
LS Mean	1.77		1.47	1.43	1.48
LS Mean Change (SE for Mean and Mean Change)	-0.55 (0.054)		-0.84 (0.055)	-0.88 (0.045)	-0.84 (0.035)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo)	---		-0.29	-0.34	-0.29
(95% CI)	---		(-0.45, -0.14)	(-0.48, -0.20)	(-0.42, -0.17)
p-value	---		<0.001	<0.001	<0.001

Source Data: ISE Table 3.057, ISE Table 3.058

1. Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, exacerbations in the year prior to the study (as an ordinal variable), treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. Estimates for MEA115588 and MEA112997+MEA115588 are based on weighting applied to each level of class variable determined from observed proportions. For the individual studies, region is as defined in the study. For the MEA112997+MEA115588 meta-analysis, region is as defined for the meta-analysis and study is included as a covariate.
2. For MEA112997, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since MEA112997 does not include a 100 mg SC dose.
3. MEA112997 includes 75, 250, and 750 mg IV. MEA115588 includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. MEA112997+MEA115588 includes 75, 250, and 750 mg IV and 100 mg SC.

Note: The ACQ-6 was used in MEA112997. The ACQ-5 was used in MEA115588. For the meta-analysis, only questions regarding symptoms collected in both studies were used to calculate a symptom score.

Note: n [1]=number of subjects with analyzable data for one or more time points; n [2]=number of subjects with analyzable data at the given time point

Subgroup analyses

The main subgroup analyses performed are presented for the combined analysis of studies MEA112997 and MEA115588. These are the rate of clinically significant exacerbations based on subgroups of gender, age, bodyweight, region and baseline eosinophils.

Gender

It was observed that male subjects tended to have a greater reduction in the rate of clinically significant exacerbations over placebo (58% for the mepolizumab 75 mg IV/100 mg SC group; from 1.76 to 0.74/year) compared with female subjects (45%; from 1.99 to 1.10/year).

Age

The effect of mepolizumab appeared more pronounced in subjects ≥65 years old (76% for the mepolizumab 75 mg IV/100 mg SC group; from 2.14 to 0.52/year) than in younger subjects (46%; from 1.87 to 1.02/year).

Bodyweight

Regardless of weight at screening, subjects treated with mepolizumab 100 mg SC or 75 mg IV achieved a greater reduction in the rate of clinically significant exacerbations than those treated with placebo (Table 30). There were no notable differences in the rate of clinically significant exacerbations across weight categories.

Table 30 Clinically significant exacerbations by bodyweight

	Placebo N=346	Mepolizumab 75 mg IV/100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
MEA112997+MEA115588			
≤60 kg			
n	57	106	149
Exacerbation rate/year	2.07	1.14	1.00
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.55	0.48
(95% CI)	---	(0.35, 0.86)	(0.31, 0.72)
>60 to ≤75 kg			
n	119	164	249
Exacerbation rate/year	1.73	0.76	1.00
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.44	0.57
(95% CI)	---	(0.31, 0.62)	(0.42, 0.78)
>75 to ≤90 kg			
n	97	170	261
Exacerbation rate/year	1.68	1.00	0.90
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.60	0.54
(95% CI)	---	(0.42, 0.84)	(0.39, 0.73)
>90 kg			
n	73	98	187
Exacerbation rate/year	2.15	0.94	1.11
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.44	0.51
(95% CI)	---	(0.29, 0.68)	(0.36, 0.73)

Source Data: ISE Table 3.064

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV_1, and study, with logarithm of time on treatment as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions. Region was as defined for the meta-analysis.
2. Only MEA115588 includes 100 mg SC dose.
3. Includes 75, 250, and 750 mg IV and 100 mg SC

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV_1, and study, with logarithm of time on treatment as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions. Region was as defined for the Efficacy Summary.
2. Only MEA115588 includes 100 mg SC dose.
3. Includes 75, 250, and 750 mg IV and 100 mg SC

Region

Regardless of geographic region, subjects treated with mepolizumab 100 mg SC or 75 mg IV achieved a greater reduction in the rate of clinically significant exacerbations than those treated with placebo (Table 31).

Table 31 Clinically significant exacerbations by region

	Placebo N=346	Mepolizumab 75 mg IV/100 mg SC[4] N=538	Mepolizumab All Doses[5] N=846
MEA112997+MEA115588			
United States			
n	43	63	102
Exacerbation rate/year	2.54	0.78	1.16
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.31	0.46
(95% CI)	---	(0.18, 0.51)	(0.30, 0.69)
European Union[2]			
n	162	249	388
Exacerbation rate/year	1.77	1.02	0.93
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.57	0.52
(95% CI)	---	(0.43, 0.76)	(0.41, 0.67)
Rest of World[3]			
n	141	226	356
Exacerbation rate/year	1.86	0.95	1.05
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.51	0.55
(95% CI)	---	(0.38, 0.69)	(0.42, 0.73)

Blood eosinophils

The greatest effect was observed in patients with baseline blood eosinophils ≥500/µL, who had the highest exacerbation rate (2.49/year) whereas the reduction was not or marginally significant in patients with baseline blood eosinophils <300/µL, i.e. normal eosinophil levels.

Table 32 Clinically significant exacerbations by baseline blood eosinophil levels

	Placebo N=346	Mepolizumab 75 mg IV/100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
MEA112997+MEA115588			
<150 cells/μL			
n	66	123	199
Exacerbation rate/year	1.73	1.16	1.28
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.67	0.74
(95% CI)	---	(0.46, 0.98)	(0.52, 1.04)
150 to <300 cells/μL			
n	86	139	224
Exacerbation rate/year	1.41	1.01	0.95
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.72	0.67
(95% CI)	---	(0.47, 1.10)	(0.45, 1.01)
300 to <500 cells/μL			
n	76	109	180
Exacerbation rate/year	1.64	1.02	1.06
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.62	0.64
(95% CI)	---	(0.41, 0.93)	(0.45, 0.92)
≥500 cells/μL			
n	116	162	238
Exacerbation rate/year	2.49	0.67	0.75
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.27	0.30
(95% CI)	---	(0.19, 0.37)	(0.23, 0.40)

Source Data: ISE Table 3.029

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV_1, and study, with logarithm of time on treatment as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions. Region was as defined for the meta-analysis.
2. Only MEA115588 includes 100 mg SC dose.
3. Includes 75, 250, and 750 mg IV and 100 mg SC

Supportive studies

The primary objective of the OLE studies was to describe the safety profile of mepolizumab in subjects receiving long-term treatment. The secondary objective of this study was to evaluate the effects of long-term dosing of mepolizumab on a range of clinical markers of asthma control.

Subjects who completed MEA112997 were offered the opportunity to consent for Study MEA 115666. All subjects had experienced a gap of at least 12 months since receiving their last double-blind study medication. Subjects who completed either MEA115588 or MEA115575 were offered the opportunity to consent for Study MEA115661. The last visit in MEA115588 or MEA115575 served as the baseline visit for this study.

Subjects received 100 mg of mepolizumab administered subcutaneously into the upper arm or upper thigh approximately every 4 weeks. During these studies, the commercial product (MDP2) was introduced.

Study MEA115666 is still ongoing and the cut-off date for the interim report is 28 February 2014. Study MEA115661 has been completed (13 March 2015) and the final report submitted during the procedure.

Study MEA115666

A total of 347 subjects were enrolled, received at least one dose of study drug, and were included in the As Treated (AT) Population. The majority of subjects (325 subjects; 94%) are continuing treatment as of the cut-off date. The proportion of subjects withdrawn prematurely was 6%. The most common reasons for withdrawal were adverse events (AEs; 8 subjects; 2%) and withdrawal by subject (8 subjects; 2%). No subjects were withdrawn due to lack of efficacy.

Subjects have been in the treatment phase for about one year on average and have received a median number of 14 injections. All received at least one dose of MDP1 and to date 313 subjects (90%) have received at least one dose of MDP2. The length of exposure to MDP1 is about twice that of MDP2

The mean time since completion of MEA112997 was 18.1 months (SD: 2.70) and the median time was 17.8 months (range: 12 to 28). During this interim time period, the mean number of self-reported exacerbations was 2.7 exacerbations per subject, i.e. an annualised rate of 1.74 exacerbations. A total of 280 subjects (81%) experienced at least one exacerbation with 75 subjects (22%) requiring either an emergency department (ED) visit or hospitalisation to treat the exacerbation. There were 55 subjects (16%) that were hospitalised for an asthma exacerbation.

A total of 151 subjects (44%) experienced 301 on-treatment exacerbations, with an estimated annual rate of 0.67 (95% CI: 0.57 to 0.79), i.e. a 61% reduction. There were 25 subjects (7%) who experienced 34 exacerbations requiring hospitalisation or an ED visit and 16 subjects (5%) that experienced 16 exacerbations requiring hospitalisation after treatment initiation.

The annualized rate of exacerbations was also calculated by screening blood eosinophil levels. For the 94 subjects with eosinophils <150 cells/µL, it was higher at 0.82/year (95% CI: 0.61 to 1.11) compared to the 243 subjects with eosinophils ≥ 150 cells/µL at 0.59/year (95% CI: 0.48 to 0.72).

Study MEA115661

A total of 651 subjects were enrolled, received at least one dose of study drug, and were included in the AT Population; 126 subjects had previously participated in Study MEA115575 and 525 subjects had previously participated in Study MEA115588. A total of 339 subjects (52%) entered Study 201312, a further extension study. Overall, 66 patients (10%) withdrew from the trial; the most common reasons for withdrawal were lack of efficacy (19 subjects; 3%), adverse events (11 subjects; 2%) and protocol deviation (8 subjects; 1%) including 4 pregnancies.

Overall, 540 subjects received MDP1 and 635 subjects received MDP2; 111 subjects (17%) received MDP2 from Visit 1. The median number of mepolizumab injections was 13, 3 with MDP1 (range 1-9) and 10 with MDP2 (range 1–14).

A total of 311 subjects (48%) experienced 654 on-treatment exacerbations and the estimated exacerbation rate per year was 0.93 (95% CI: 0.83 to 1.04); it was similar in patients previously treated with mepolizumab (0.90; 95% CI: 0.78, 1.04) and placebo (0.99; 95% CI: 0.83, 1.18). Fifty-nine subjects (9%) experienced 95 exacerbations requiring hospitalisation or an ED visit and 39 subjects (6%) experienced 65 exacerbations requiring hospitalisation.

Overall, 121 patients from study MEA115575 had OCS data up to week 52. At the end of the double-blind period, the median OCS dose was 10 mg/day in the placebo arm and 2.5 mg/day in the mepolizumab arm; during the open label period, it fluctuated between 2.5 and 4 mg/day in patients

previously treated with mepolizumab whereas it gradually decreased to 5 mg/day in patients having previously received placebo.

Finally, improvements in lung function and ACQ-5 score were sustained.

Combined analysis

A combined analysis of blood eosinophil data collected prior to 28 February 2014 (data cut-off) was performed for the ongoing MEA115666 and MEA115661 studies. The purpose of this analysis was to investigate whether there was any change in effect on blood eosinophils following introduction of the commercial product (MDP2) into these studies. There was no change in the geometric mean blood eosinophil level between the last measurement with MDP1 and the first measurement with MDP2 (geometric mean ratio for MEA115566+MEA115661=1.01) (Table 33), indicating that the two drug products were comparable in their pharmacodynamic effect.

Table 33 Summary of blood eosinophils (GI/L) at last MDP1 measurement and at first MDP2 measurement (As Treated Population)

	MEA115666 N=347	MEA115661 N=651	MEA115666+ MEA115661 N=998
Last MDP1 Measurement			
n	241	290	531
Geometric Mean	0.05	0.06	0.05
SD logs for mean	0.954	0.867	0.909
First MDP2 Measurement			
n	241	290	531
Geometric Mean	0.05	0.06	0.05
SD logs for mean	0.981	0.922	0.952
Ratio First MDP2/Last MDP1 Measurement			
n	241	290	531
Geometric Mean	0.99	1.02	1.01
SD logs for mean	0.893	0.979	0.941

Source Data: ISE Table 3.054

Abbreviations: MDP1=Mepolizumab Drug Product 1 (reconstituted from the 250 mg/vial strength); MDP2=Mepolizumab Drug Product 2 (reconstituted from the 100 mg/vial strength)

Note: Only those subjects that had a blood eosinophil sample collected from both drug product periods were summarized. MDP1 period ended and MDP2 period began when the subject received their first administration of MDP2.

Note: Data were log transformed prior to analysis. Where a result of zero was recorded, a small value (i.e., minimum all nonmissing result/2) was added prior to log transformation.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on three pivotal placebo-controlled trials in severe refractory asthma, for which the applicant received CHMP scientific advice. Two trials investigated the effect of mepolizumab on exacerbations (exacerbation trials, MEA 112997 and MEA 115588) and a third trial investigated its potential corticosteroid sparing effect (MEA 115575). The study population of these three trials had severe uncontrolled refractory asthma defined in accordance with current guidelines: International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma (ATS, 2014) and Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA, 2014). These patients required treatment with high dose inhaled corticosteroids plus a second controller (plus systemic corticosteroids in the third trial), and in spite of this treatment, had persistent airflow obstruction and, in the first two trials, a history of frequent (at least two per year) exacerbations requiring systemic corticosteroid treatment and/or hospitalisation or emergency department visit (i.e. 'severe exacerbations').

Based on published literature, it is known that only patients with an eosinophilic asthma phenotype would be likely to benefit from therapy with an anti-IL-5 antibody such as mepolizumab. The first exacerbation trial (MEA 112997) included a range of criteria susceptible to define this particular phenotype and, based on the results of this trial, two criteria were selected for the enrolment of subjects in the two subsequent trials (exacerbation (MEA 115588) and OCS sparing studies (MEA 115575)). This criteria were either an elevated peripheral blood eosinophil count of ≥300/µL in the previous 12 months or an elevated peripheral blood eosinophil count of ≥ 150/µL at study entry, if they were considered related to asthma.

The duration of the exacerbation trials was initially planned to be 12 months, in line with current CHMP guideline (Guideline on the clinical investigation of medicinal products for the treatment of asthma; CHMP/EWP/2922/01 Rev.1), but was shortened to 8 months in the second trial. Based on a post-hoc analysis of the data from the first trial (MEA 112997) the applicant showed that the treatment response to mepolizumab was marginally affected by seasonal changes in exacerbation frequency, and therefore, it was accepted that the duration of the second trial (MEA 11115588) was shortened. 8 months was considered adequate period of time to demonstrate a reduction in the rate of clinically significant exacerbations for patients receiving mepolizumab.

The main efficacy endpoints were the same in both trials. The primary endpoint of 'clinically significant exacerbations' corresponded to 'severe exacerbations' as defined in ATS guideline (2014) and CHMP guideline (Guideline on the clinical investigation of medicinal products for the treatment of Asthma (CHMP/EWP/2922/01 Rev.1). This definition included an objective verification of the deterioration of asthma symptoms as reflected in the patient eDiary data, but in the absence of deterioration criteria as defined in the protocol, the investigator provided information to the Sponsor's Medical Monitor as to why the exacerbation was to be considered clinically significant; this only occurred in 2-8% of the exacerbations depending on the trial. The CHMP agreed that this was the most important outcome in this patient population because severe exacerbations constitute the greatest risk to patients.

The main secondary endpoints were lung function tests (FEV1), asthma symptoms measured in the Asthma Control Questionnaire (ACQ) and quality of life assessed with the standardised Asthma Quality of Life Questionnaire (AQLQ(S) in MEA 112997 and the St. George's Respiratory Questionnaire (SGRQ) in MEA 115588. These were all validated questionnaires and the CHMP considered appropriate all the secondary endpoints.

The trials were randomised and blinded to the patient and personnel involved in the study drug administration and patient assessment; only the pharmacist preparing the study drug was unblinded. This blinding method had a limitation that could not be overcome as it would not be impossible for investigators to distinguish between placebo and active based on blood eosinophil counts. Of note, blood eosinophil counts were performed centrally and the investigators were not communicated the results after randomisation.

The first exacerbation trial, MEA 112997, studied three intravenous doses (75 mg, 250 mg and 750 mg) of mepolizumab administered monthly. These doses were selected on the basis of previous trials that had shown some clinical effect at the two highest doses. The aim was to investigate the dose-response relationship on PD and efficacy outcomes. This study was considered critical by the CHMP to allow for the development of a mechanistic model for the binding of mepolizumab to IL-5, its impact on blood or sputum eosinophil count and, most importantly, on clinical outcome, with the aim of establishing a target absolute or relative blood eosinophil value that could be used to support dose selection. However, these objectives were not achieved and no difference in clinical effects was observed between the three doses. Therefore, the lowest dose was selected for further development based on PKPD modelling (see sections 2.4.2 and 2.4.3).

The second exacerbation trial, MEA 115588, tested monthly doses of 75 mg IV and 100 mg SC using a double-dummy design. These two doses were expected to produce a similar exposure as the absolute bioavailability of the SC route had been shown to be approximately 75% in the PK/PD study MEA 114092 (see section 2.4.2). Furthermore, this study had indicated that these doses provided the same pharmacological response (i.e., the ID_{90} for maximum achievable pharmacological effect).

The third trial, study MEA 115575, was designed to investigate the corticosteroid sparing effect of mepolizumab in patients requiring at least 5 mg/day of oral prednisone or equivalent. The trial included before randomisation, an OCS optimization phase of 3-10 weeks to establish the lowest OCS dose needed to control the patient's symptoms. After randomisation, this dose had to be maintained for 4 weeks before the OCS reduction phase was started following a pre-defined algorithm. This phase lasted 16 weeks and was followed by a maintenance phase of 4 weeks without any dose adjustment, during which the evaluation of outcomes was conducted.

This was considered a short period to evaluate the durability of the effect; however data from the open label extension study (MEA 115661) were subsequently submitted during the procedure.

The primary endpoint in this trial was the relative reduction in OCS dose compared with the baseline dose provided no severe exacerbation occurred during these 4 weeks, which is not considered a stringent definition of asthma control. While the CHMP endorsed the study design, it also advised that the absolute decrease in OCS would be a key secondary endpoint and that this should be clinically meaningful and evaluated in relation to the baseline dose. These data were submitted by the applicant in response to CHMP request during the procedure.

The three trials were multinational but the EU was the largest contributor in terms of recruitment. Open label extension of the three studies is ongoing.

Efficacy data and additional analyses

Population

The two exacerbation trials (MEA 112997 and MEA 115588) included 1192 patients, mostly female (60%), white (84%), and overweight (mean BMI=28.1 kg/m^2). The mean age was 49 years (range: 12-82 years); the number of adolescents was small (n=26) but elderly patients (n=105) contributed 9% of the study population. Overall, 54% of the patients had suffered from asthma for more than 15

years and 55% had ≥3 exacerbations in the 12 months prior to screening (mean 3.6). About one third of the patients were taking continuous OCS with a median prednisone-equivalent dose of 10 mg/day.

Although the criteria defining the eosinophilic phenotype were different between the two exacerbation studies (MEA 112997 and MEA 115588), asthma severity as reflected by the proportion of patients with ≥3 severe exacerbations (54% vs. 57%), at least one hospitalisation (24% vs 19%) during the previous 12 months, mean FEV1 (60% vs 61%) and mean ACQ-score (2.4 vs. 2.2) was comparable between the two studies .Only concomitant OCS use was slightly more frequent in study MEA 112997 than study MEA 115588 (31% vs 24%).

Most patients were receiving the combination ICS/LABA (57% and 40%, respectively) or the combination plus an additional non-LABA controller (38% and 57%, respectively); the mean dose of equivalent fluticasone propionate was 1122 and 1085 mcg ex-valve, respectively. Treatment arms were well balanced with regard to demographics and asthma exacerbation history.

Most patients completed the studies: 84% in Study MEA112997 and 94% in Study 115588. The main reasons for discontinuation were withdrawal of consent and adverse event, which were balanced across treatment arms. The proportion of patients excluded from the PP analysis set for major deviations was low (4-5%); these were mainly related to the eligibility criteria (insufficient documentation of exacerbations or high ICS doses during the previous year, FEV1 or blood eosinophil count not meeting the inclusion criteria). The primary analysis was performed in a modified ITT population (all patients having received at least one dose of study drug), which the CHMP considered acceptable.

Primary endpoint

The primary endpoint was met in both studies (MEA 112997 and MEA 115588) and the relative reduction in the frequency of severe exacerbations was consistent across the studies at approximately 50% although in absolute terms the annual rate decreased from 2.40 on placebo to 1.24 (75 mg IV) in the study MEA 112997 but from only 1.74 (lower than the expected ≥ 2/year) to 0.88 in the study MEA115588 (75 mg IV/100 mg SC).

Importantly, the results were comparable in patients treated with 75 mg IV and 100 mg SC. In the combined analysis (ITT population) of these two trials, the rate ratio (mepolizumab/placebo) was 0.51 (95%CI: 0.42, 0.62; p<0.001) in the pooled 75 mg IV/100 mg SC arm and a similar ratio (0.53; 95%CI: 0.33, 0.84; p=0.007) was estimated for the exacerbations requiring hospitalisation/ED visit. Analyses in the PP population and other sensitivity analyses resulted in the same statistical inferences on the primary endpoint, and therefore, the CHMP considered this result to be robust.

The first trial (MEA112997) failed to show any dose-response relationship of the primary outcome across the doses investigated and the exposure achieved. However there was evidence of an increased reduction in blood eosinophils (from 78% to 88% compared to placebo) with increasing dose of mepolizumab, albeit from already high inhibition. Eight weeks after the last dose, blood eosinophil reduction was still 62% at the 75 mg dose, implying maintenance of the effect in the event of a missed dose. The results of this trial indicated a flat dose-response curve over the tested range (75 – 750 mg). The probability of a first clinically significant exacerbation by Weeks 16, 32 and 52 was lower in the three mepolizumab arms than in the placebo arm, suggesting that the reduction in exacerbation was evident early in the study.

The 100 mg SC dose, which was selected to be comparable to 75 mg IV based on the estimated SC absolute bioavailability, was found in the study MEA 114092 to provide approximately 90% of maximal pharmacology, and by implication efficacy; for antagonistic mechanisms (including IL-5 neutralisation) this is a desirable target for therapeutic benefit [Grimwood, 2009] (see section 2.4.3). In the first trial

(MEA112997), the exploratory multivariable modelling analysis of baseline factors that could predict the effect of mepolizumab on exacerbations found two significant factors: baseline blood eosinophil count and number of exacerbations in the year prior to study. Among those with a history of exactly two exacerbations in the previous year, there appeared to be a benefit in subjects with a baseline level of blood eosinophils above 150 cells/µL. The addition of the criterion of blood eosinophils ≥ 300 cells/µL during the previous year allowed to select additional patients that showed some benefit, although much smaller. These two criteria were used in the two subsequent pivotal trials (MEA115588 and MEA115575).

Secondary endpoints

The secondary endpoints did not provide consistent results between the two exacerbation trials (MEA112997 and MEA 115588). In the first trial (MEA112997), similar improvements were observed throughout the study in the placebo and mepolizumab arms for FEV1, ACQ-6 score and AQLQ score. Of note, the improvement in ACQ and AQLQ was clinically relevant (>0.5) in all arms including placebo. This finding was in line with those of earlier trials, which had not shown significant benefit on lung function and asthma symptoms. Although mepolizumab reduces sputum and blood eosinophil counts, it has little benefit in terms of airways function as conventionally measured. However it is acknowledged to have a demonstrable benefit on the frequency of acute asthma exacerbations. The disconnection between the two is counterintuitive but the CHMP acknowledged that the relationship between airway inflammation, lung function and symptoms is weak [Crimi, 1998; Rosi, 2000; Ronchi 1997].

In the second exacerbation trial (MEA115588), the improvement in pre-bronchodilator FEV1 was numerically greater on mepolizumab than placebo but the difference was not consistent throughout the study. Nevertheless, at week 32 (last visit) the mean increase in the placebo arm was 86 mL vs. 183 mL in the mepolizumab 100 mg SC arm ($p = 0.028$). The difference was more important for the post-bronchodilator FEV1 as the improvement on placebo was marginal (30 mL) compared to 167 mL in the mepolizumab 100 mg SC arm ($p = 0.004$).

While the ACQ score improvement was similar in the placebo arm to that observed in the first trial, it appeared significantly greater in the mepolizumab arms from week 4 to week 32 of this trial. At the last visit, the mean improvement from baseline was 0.50 in the placebo arm and 0.94 in the mepolizumab 100 mg SC ($p<0.001$) although the difference (0.44) did not exceed the MCID (0.5).

The quality of life questionnaire used in the second trial (SGRQ) was different from the AQLQ used in the first trial. According to the applicant, it was selected for its emphasis on disease impact in patients with exacerbating severe asthma. At the last visit, the improvement was significantly greater in patients treated with mepolizumab compared to those on placebo ($p < 0.001$). A clinically relevant improvement (≥4-point) was reported by 71% of patients in the mepolizumab 100 mg SC arm vs 55% in the placebo arm.

The differences between the two trials regarding improvement in lung function, asthma control and quality of life could not be explained by the applicant although it was speculated that this could be due to “better defined specific hematologic and clinical markers targeted to select mepolizumab treatment responders” in the second trial. Also, SGRQ may be more suitable for measuring impacted quality of life domains in severe asthma.

Nevertheless, the two exacerbation trials showed robust evidence of reduction in the frequency of severe exacerbations, a key outcome in the control of severe asthma, which was considered clinically meaningful by the CHMP. However, in the second trial (MEA115588) an annual rate of less than 2 severe exacerbations per year was observed on the placebo arm (not consistent with the target population). Explanatory factors to this could be a difference in the prevalence of circulating

respiratory-related viruses between the study years or the different definition of the eosinophilic phenotype.

Subgroup analyses

Subgroup analyses of the primary endpoint were conducted in the combined analysis. The effect of mepolizumab appeared broadly similar in both genders (although it tended to be lower in females than in males) and was not influenced by bodyweight. Importantly, the effect was notably greater in elderly subjects, who appeared to suffer from more frequent exacerbations (2.14/year) on placebo compared to younger subjects (1.87/year). In addition, in study MEA115588, the percent reduction was 56% - 70% in patients with at least 3 exacerbations in the previous year vs. 47% in patients with only 2 exacerbations in the previous year.

The literature suggests that airway eosinophilia is more prevalent in severe adult-onset asthma. Indeed, the number of adolescents was too small (n=26) to allow for proper evaluation of mepolizumab in this age group (12-17 years), and therefore, the proposed indication is currently restricted to adults. In study MEA115588, 25 adolescents, 13 girls and 12 boys, 9 aged 12 -14 years and 16 aged 15 – 17 years were enrolled. Of note, the inclusion criterion regarding the definition of high doses of ICS (i.e., half the doses of adults) did not correspond to current treatment guidelines in this age group: ATS (2014) and GINA (2014) guidelines. Of the total 25 subjects, 9 received placebo, 9 received mepolizumab 75mg IV, and 7 100 mg SC. The same proportion of subjects (3/9) receiving placebo and mepolizumab IV reported clinically significant exacerbations but none in those receiving mepolizumab SC.

The greatest effect (73% reduction) was observed in patients with baseline blood eosinophils ≥500/µL, who had the highest exacerbation rate (2.49/year) in the placebo arm (vs. 0.67/year in the treated patients)whereas the reduction was much smaller (~ 30%) in patients with baseline blood eosinophils <300/µL, i.e. normal eosinophil levels. Furthermore, in Study MEA115588, the effect of mepolizumab was marginal (exacerbations reduced by 18% in the SC arm and no effect at all in the IV arm) in the small subgroup of patients with only a history of elevated blood eosinophils during the previous 12 months (but screening blood eosinophil levels <150/µL); this result did not confirm the small effect observed in the first trial (MEA112997) in a similar subgroup where the exacerbation rate was reduced by 26%.

Definition of the target population

The definition of eosinophilic asthma is based on the pattern of inflammatory cellular infiltrate in the airway and induced sputum cell count is the gold standard for identifying eosinophilic inflammation. In spite of being associated to sputum eosinophils, blood eosinophil counts are generally considered poor predictors of sputum eosinophilic inflammation. However, in patients with severe asthma receiving very high doses of inhaled or systemic corticosteroids, a blood eosinophil count of greater than 450 cells/µL has recently been shown to correctly predict sputum eosinophilia in 9 of 10 cases [Fowler S ; 2015]. Furthermore, as blood eosinophil counts are easily available, they constitute a more actionable marker of the target population in clinical practice. Finally, systemic inflammation may play an independent role in these patients. Therefore, the use of blood eosinophil counts to define the target population for mepolizumab was considered acceptable by the CHMP.

However, the applicant's proposal of a dual blood eosinophil count threshold (either a blood eosinophil count ≥150 cells/µL at initiation of treatment or a blood eosinophil count ≥300 cells/µL in the prior 12 months) was not considered sufficiently supported by the data submitted.

Evidence from large studies has recently been emerging that suggests high blood eosinophil count (higher than 300 – 400 cells/ µL) is associated with more frequent asthma attacks. Indeed, a similar trend for severe exacerbations was observed in the mepolizumab placebo controlled studies where in the placebo arms, a rate of ≥ 2 exacerbations/year was consistently reported only in patients with baseline blood eosinophil levels ≥ 300 cells/µL. Importantly, subgroup analyses by baseline eosinophil count showed that the response to mepolizumab improved as the baseline blood eosinophil count increased (table 32). These data was reflected in detail in section 5.1 of the SmPC. However, the CHMP considered that these were not sufficient to define a definitive threshold for the selection of the patient population susceptible to respond to mepolizumab.

Mepolizumab is indicated for adult patients with severe refractory asthma characterised by an eosinophilic phenotype. The diagnosis of the phenotype is left to health care professionals specialised in the treatment of severe asthma based on sputum or blood eosinophilia. The magnitude of mepolizumab effect on severe exacerbations in relation to blood eosinophil levels is described in section 5.1 of the SmPC to further inform their therapeutic decision.

Corticosteroid sparing trial (MEA 115575)

Population

This was a small trial which included only 135 subjects, who had similar characteristics to those in the exacerbation trials. The two treatment arms did not appear well matched for a number of screening and baseline characteristics. The gender ratio was atypical in the placebo arm with more males than females. In the previous year, asthma seemed more severe in the mepolizumab arm with patients having more exacerbations, urgent care visits and oral steroid bursts. However, lung function at screening appeared slightly better in this arm. Furthermore, the median daily OCS dose after optimization was lower in the mepolizumab arm (10 mg) than in the placebo arm (12.5 mg) and 12 vs 6 patients, respectively, were on the lowest dose of 5 mg. The baseline ACQ score and blood eosinophils were higher in the mepolizumab arm.

Most patients (95%) completed the trial but there was a high level of protocol deviations, in particular regarding the OCS dosing algorithm (25%). In particular, 10 patients entered the trial on non-optimal OCS dose (6 (9%) in the mepolizumab arm and 4 (6%) in the placebo arm) and were excluded from the PP analysis. A further 13 patients had their OCS dose not stepped up post-exacerbation, which may have overestimated the dose reduction; these were not excluded from the PP analysis but occurred equally in both treatment arms.

OCS reduction

The primary endpoint, i.e. the relative (%) OCS reduction, was significantly greater in the mepolizumab arm compared to placebo in the ITT population with an odds ratio of 2.39 (95%CI: 1.25, 4.56; p = 0.008); 64% of the patients treated with mepolizumab experienced some level of reduction vs. 44% in the placebo arm. However, the results were far less compelling when the patients entered the trial with an appropriate OCS dose (PP population) as the lower limit of the CI was barely over 1.

The secondary endpoints did not show compelling reduction of the OCS dose either. In the mepolizumab arm, 37/69 (54%) subjects achieved a daily dose ≤5 mg (vs. 21/66 (32%) on placebo) but already 12 (17%) were receiving 5 mg/day at baseline. The proportion of subjects weaned off was low and not substantially different (around 10%) in the two treatment arms, especially considering the number of patients with a baseline daily dose of 5 mg in the mepolizumab arm. The fact that a number of patients on placebo were able to successfully withdraw from OCS questioned their CS dependence

but similar proportions on placebo (~ 10%) have been reported in other OCS sparing trials (e.g. Bateman E, 2006).

The median daily OCS dose decreased from 10 mg to 3 mg in the mepolizumab arm (12.5 mg to 10 mg in the placebo arm); a median reduction of 5 mg/day was reported in the mepolizumab arm while in the placebo arm, it was 0. The median reduction was the same whatever the level of the baseline OCS dose. Overall, ~40% of the mepolizumab-treated patients had a reduction > 5 mg/day (twice as many as in the placebo arm), and this is considered clinically relevant.

Other endpoints

During the 6-month treatment period, the frequency of clinically significant exacerbations was reduced on mepolizumab (1.44/year) compared to placebo (2.12/year) although the difference was barely significant (rate ratio = 0.68; 95% CI: 0.47, 0.99; p = 0.042). Furthermore, the median duration and dose of systemic CS associated with these exacerbations tended to be greater in the mepolizumab arm (8.5 days and 260 mg, respectively) than in the placebo arm (8 days and 237.5 mg, respectively). This was in contrast with the number of hospitalisations (7 on placebo vs. none on mepolizumab) but the numbers were too small to draw a definite conclusion.

In the placebo arm, there was no change in pre-bronchodilator FEV1 but post-bronchodilator FEV1 deteriorated whereas both parameters increased by approximately 100 mL on average in the mepolizumab arm at 24 weeks. At this time point, the difference vs. placebo was not statistically significant although between Weeks 4 to 16 differences in pre-bronchodilator FEV1 were observed to be significant between the mepolizumab and placebo arms.

Similarly, no change in asthma control in the placebo arm was observed while a significant and clinically meaningful improvement in the ACQ score was reported with mepolizumab compared to placebo (-0.52; 95% CI: -0.17, -0.87; p=0.004). However, the proportion of patients with poor asthma control (ACQ score ≥1.5) was still around 40% in the mepolizumab arm at the last two visits (week 20 and 24). In addition, and similar to pre-bronchodilator FEV1, the reduction in albuterol/salbutamol use and night time awakenings requiring rescue medication was not sustained after Week 12 as no difference from placebo was observed at Week 24; longer term data from the extension study will be provided post-authorisation to clearly demonstrate that there is maintenance of efficacy beyond 24 weeks.

The quality of life evaluation (SGRQ) showed a significant and clinically meaningful improvement with mepolizumab compared to placebo (-5.8; 95% CI: -1.0, -10.6; p = 0.019).

Subgroup analyses

Given the small size of the subgroups, the results of these analyses should be interpreted with caution. Nevertheless, the effect of mepolizumab in female patients, who are generally more affected with severe asthma than males, was marginal and not statistically significant. In the combined analysis of the exacerbation studies, a 12% difference was noted between the reduction rates reported for female and male patients in favour of the latter. However, there is no biological PK or PD rationale to explain this finding.

The effect of mepolizumab was mainly observed in subjects with shorter OCS use (<5 years) and high OCS doses (≥ 15mg/day). In the largest subgroup of patients with mid baseline OCS dose (10 - <15 mg), mepolizumab did not show any effect (OR = 1.07) but this is likely a chance finding.

The CHMP acknowledged that blood eosinophil levels are difficult to interpret in patients taking OCS as they are generally very low. However, 29% of the patients had baseline levels ≥ 500/µL after dose

optimization. These levels questioned either non-adherence (very common in these patients) or another diagnosis (e.g. Churg Strauss syndrome). However, in the other mepolizumab studies (studies MEA 112997 and MEA 115588), a similar proportion (28-33%) of patients on maintenance OCS exhibited high levels of blood eosinophils. Furthermore, this observation was corroborated by published literature [Taille, 2013].

Regarding the magnitude of treatment effect by baseline blood eosinophils and by inclusion criterion, results did not appear consistent with those observed in the exacerbation studies and given the small size of the subgroups are likely to be chance findings.

During the procedure the CHMP requested further data and justification on the OCS sparing effect in this trial (study MEA 115575). The applicant submitted the requested data. Overall, the CHMP considered that although the results were not compelling, the OCS sparing effect was statistically significant and could be considered clinically meaningful.

Extension studies

The interim data submitted for the two ongoing OLE studies provided additional efficacy information.

The first study (MEA115666) enrolled patients from the first exacerbation trial (MEA112997) after a treatment interruption of 12 to 28 months (median 18 months) during which the exacerbation rate increased. Mepolizumab at the recommended posology was able to reduce the exacerbation rate again. The mean exposure at the cut-off date of the interim report was approximately one year.

The second study (MEA115661), which enrolled patients from the two Phase III trials (MEA115588 and MEA115575) without treatment interruption for an additional 52 weeks of therapy, was completed during the procedure. It showed sustained effects on exacerbation rates, lung function and ACQ score. In addition, during the open label period, the median OCS dose in corticosteroid-dependent patients previously treated with mepolizumab was more or less stable within a range of 2.5 to 4 mg/day during the six months following the double-blind study.

Finally, as the commercial product was introduced during these studies, blood eosinophil determination before and after the switch was described to confirm that the PD effect of the commercial product was comparable to that of the product used during the pivotal trials.

2.5.4. Conclusions on the clinical efficacy

Based on the three pivotal efficacy trials submitted, the CHMP considered that mepolizumab has demonstrated a clinically relevant effect on the frequency of exacerbations in patients with severe refractory asthma and frequent exacerbations (at least 2 per year). However, the applicant's criterion regarding specific levels of the blood eosinophil count to define the target population was not endorsed by the CHMP.

The CHMP considered that the data provided were not sufficient to define a definitive threshold for the selection of the patient population susceptible to respond to mepolizumab. The wording of the indication agreed by the CHMP and reflected in section 4.2 of the SmPC is as follows:

Nucala is indicated in adult patients as an add-on treatment for severe refractory eosinophilic asthma (see section 5.1)

Based on additional data during the procedure provided by the applicant, the CHMP considered that mepolizumab treatment exerts some degree of corticosteroid sparing effect as it achieved a median reduction of 5 mg/day (prednisone equivalent) regardless of the baseline OCS level (up to 30 mg/day) taken by These patients.

2.6. Clinical safety

Safety data of mepolizumab administered to subjects across a range of diseases was submitted for this Application but the primary analysis was the safety data from the severe eosinophilic asthma development program where integrated safety data was presented in two sets of studies : Placebo-controlled severe asthma studies (MEA112997, MEA115588 and MEA 115575) and Open-label Extension (OLE) studies (MEA115661 and MEA115666). The safety population was defined as all subjects who received at least one dose of mepolizumab.

Patient exposure

A total of 2022 subjects have received at least one dose of mepolizumab in the applicant-sponsored studies and 661 subjects have received placebo. Overall, 1229 subjects with severe eosinophilic asthma received at least one dose of mepolizumab and 1018 of these 1229 subjects received mepolizumab 100 mg SC, either as part of a randomised placebo-controlled study or in an open-label extension to these studies.

Total treatment exposure for the 1018 subjects who received mepolizumab 100 mg SC was 1131 subject years. A total of 138 subjects (14%) were treated with mepolizumab 100 mg SC up to 12 months and 880 subjects (86%) were treated for 12 months to less than 24 months.

Table 34 displays the number and percentage of subjects treated with mepolizumab by indication and dose.

Table 34: Subjects treated by Indication and Dose (All studies combined, safety population)

	Number (%) of Subjects						
		Mepolizumab					
Indication	Placebo	100 SC	75 IV	250 IV	750 IV	All Doses[1]	Total[2]
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)[3]	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)

Source: Table 1.001

1. In addition to the 100 mg SC dose and the 75 mg, 250 mg, and 750 mg IV doses, this includes IV doses of 10 mg, 750/1500 mg, 0.05, 0.5, 0.55, 2.5 and 10 mg/kg and SC doses of 12.5, 125 and 250 mg, and IM dose: 250 mg
2. Total number of subjects treated across mepolizumab programs; a subject who participated in more than one study and received both placebo and mepolizumab or different doses of mepolizumab is counted once in each treatment and dose, but only once overall.
3. In the Compassionate Use Program, subjects received mepolizumab 750 mg IV as a starting dose. This dose was adjusted throughout the study based on clinical status of the subject.

Adverse events

Common AEs were defined as those which occurred in ≥3% of subjects in a given treatment group. The incidence of common AEs in the placebo controlled severe asthma studies was similar for the placebo group (82%) compared with the mepolizumab 100 mg SC group (79%), and the mepolizumab 75 mg IV group (83%). Headache and nasopharyngitis were the most frequently reported AEs in the placebo controlled severe asthma studies. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. The common symptoms reported with these events included pain, erythema, swelling, itching, and burning sensation (Table 35).

The overall incidence of subjects reporting the onset of an AE declined as time on treatment increased, but the pattern of AEs remained similar.

When adjusted for study difference as well as exposure, relative risks of more than 2 for mepolizumab compared with placebo were observed for three events: eczema, nasal congestion, and dyspnoea. All other relative risks were less than 2.

The SOC AE profile for both males and females was similar to the overall population. The number of adolescent subjects (n=0 to 9 across treatment groups; total receiving mepolizumab, n= 19) and elderly subjects (n=3 to 38 across treatment groups; total receiving mepolizumab, n=82) enrolled in the severe asthma studies was too limited to characterise the safety profile of mepolizumab in this population. The incidence of AEs in all SOCs was similar for subjects 18 to 64 years of age (total subjects receiving mepolizumab, n= 814) compared with the overall population.

The incidence of AEs in all SOCs was similar for white subjects (total 783 subjects receiving mepolizumab) compared with the overall population.

The total number of subjects receiving mepolizumab in the EU was 438, in the ROW 371 and in the US 106. The proportion of US subjects reporting AEs was higher than the overall population.

Table 35: Common on-treatment adverse events in the placebo-controlled severe asthma studies

Adverse Event (Preferred Term)	Number (%) of Subjects					
		Mepolizumab				
	Placebo N=412	100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Any Event	338 (82)	209 (79)	287 (83)	124 (82)	122 (78)	742 (81)
Headache	74 (18)	53 (20)	78 (23)	32 (21)	32 (21)	195 (21)
Nasopharyngitis	80 (19)	43 (16)	79 (23)	33 (22)	29 (19)	184 (20)
Asthma	61 (15)	15 (6)	32 (9)	26 (17)	16 (10)	89 (10)
URTI[1]	47 (11)	27 (10)	32 (9)	18 (12)	19 (12)	96 (10)
Bronchitis	39 (9)	16 (6)	31 (9)	13 (9)	13 (8)	73 (8)
Sinusitis	40 (10)	25 (10)	21 (6)	10 (7)	12 (8)	68 (7)
Back pain	20 (5)	16 (6)	22 (6)	7 (5)	15 (10)	60 (7)
Arthralgia	23 (6)	16 (6)	16 (5)	9 (6)	9 (6)	50 (5)
Oropharyngeal pain	27 (7)	11 (4)	16 (5)	12 (8)	6 (4)	45 (5)
Cough	21 (5)	5 (2)	16 (5)	11 (7)	9 (6)	41 (4)
Fatigue	17 (4)	12 (5)	14 (4)	7 (5)	2 (1)	35 (4)
Influenza	15 (4)	7 (3)	16 (5)	5 (3)	9 (6)	37 (4)
Infusion-related reaction	11 (3)	1 (<1)	8 (2)	12 (8)	19 (12)	40 (4)
Pain in extremity	16 (4)	12 (5)	8 (2)	4 (3)	8 (5)	32 (3)
Injection site reaction	13 (3)	21 (8)	10 (3)	0	0	31 (3)
Nausea	17 (4)	9 (3)	8 (2)	5 (3)	4 (3)	26 (3)
Urinary tract infection	9 (2)	10 (4)	13 (4)	8 (5)	1 (<1)	32 (3)
Diarrhoea	19 (5)	5 (2)	6 (2)	2 (1)	8 (5)	21 (2)
Hypertension	12 (3)	4 (2)	13 (4)	6 (4)	5 (3)	28 (3)
Dizziness	13 (3)	8 (3)	8 (2)	3 (2)	6 (4)	25 (3)
Rhinitis	12 (3)	6 (2)	11 (3)	5 (3)	3 (2)	25 (3)
Lower respiratory tract infection	10 (2)	7 (3)	10 (3)	4 (3)	4 (3)	25 (3)
Rhinitis allergic	7 (2)	3 (1)	12 (3)	6 (4)	6 (4)	27 (3)
Gastroenteritis	9 (2)	6 (2)	14 (4)	0	4 (3)	24 (3)
Pharyngitis	8 (2)	7 (3)	13 (4)	2 (1)	3 (2)	25 (3)
Abdominal pain upper	8 (2)	7 (3)	10 (3)	3 (2)	4 (3)	24 (3)
Myalgia	12 (3)	5 (2)	5 (1)	4 (3)	5 (3)	19 (2)
Pyrexia	9 (2)	8 (3)	8 (2)	4 (3)	2 (1)	22 (2)
Hypersensitivity	11 (3)	4 (2)	8 (2)	3 (2)	3 (2)	18 (2)
Nasal congestion	4 (<1)	7 (3)	10 (3)	1 (1)	6 (4)	24 (3)
Vomiting	7 (2)	3 (1)	8 (2)	7 (5)	3 (2)	21 (2)
Dyspnoea	4 (<1)	3 (1)	6 (2)	7 (5)	7 (4)	23 (3)
Edema peripheral	13 (3)	4 (2)	6 (2)	3 (2)	1 (<1)	14 (2)
Chest pain	6 (1)	5 (2)	4 (1)	7 (5)	3 (2)	19 (2)
Eczema	2 (<1)	11 (4)	5 (1)	4 (3)	3 (2)	23 (3)
Respiratory tract infection	7 (2)	1 (<1)	5 (1)	6 (4)	6 (4)	18 (2)
Toothache	6 (1)	7 (3)	5 (1)	2 (1)	5 (3)	19 (2)
Pruritus	5 (1)	7 (3)	6 (2)	5 (3)	1 (<1)	19 (2)
Viral infection	5 (1)	4 (2)	6 (2)	3 (2)	6 (4)	19 (2)
Gastroesophageal reflux disease	8 (2)	8 (3)	2 (<1)	3 (2)	2 (1)	15 (2)
Muscle spasms	4 (<1)	7 (3)	7 (2)	3 (2)	2 (1)	19 (2)

Adverse Event (Preferred Term)	Number (%) of Subjects					
		Mepolizumab				
	Placebo N=412	100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Insomnia	5 (1)	7 (3)	5 (1)	2 (1)	3 (2)	17 (2)
Ear infection	6 (1)	2 (<1)	9 (3)	2 (1)	2 (1)	15 (2)
Migraine	8 (2)	6 (2)	1 (<1)	2 (1)	4 (3)	13 (1)
Rash	4 (<1)	4 (2)	6 (2)	4 (3)	3 (2)	17 (2)
Pneumonia	5 (1)	7 (3)	1 (<1)	2 (1)	4 (3)	14 (2)
Respiratory tract infection viral	4 (< 1)	1 (<1)	6 (2)	4 (3)	4 (3)	15 (2)
Dyspepsia	6 (1)	1 (<1)	4 (1)	1 (<1)	5 (3)	11 (1)
Viral upper respiratory tract infection	7 (2)	1 (<1)	3 (<1)	4 (3)	1 (<1)	9 (<1)
Tendonitis	0	3 (1)	6 (2)	4 (3)	2 (1)	15 (2)
Blood creatine phosphokinase increased	3 (<1)	3 (1)	2 (<1)	0	5 (3)	10 (1)
Tooth infection	4 (<1)	1 (<1)	4 (1)	0	4 (3)	9 (<1)
Sinus congestion	1 (<1)	0	3 (<1)	0	5 (3)	8 (<1)

Note: Studies included: MEA112997, MEA115588 and MEA115575

[1] URTI = upper respiratory tract infection

Note: AEs that are shaded occurred either (i) at an incidence of <3% in the mepolizumab 100 mg SC and 75 mg IV groups or (ii) 3% or more in the mepolizumab 100 mg SC or 75 mg IV groups, but less than or equal to the incidence in the placebo group.

The ADRs included in section 4.8 of the SmPC were determined via a two-step process: Firstly, AEs that occurred at an incidence of ≥3% in the mepolizumab 100 mg SC group and were more common than placebo were identified. Secondly, common (≥3%) AEs in all doses of the randomised placebo-controlled studies (n=915) were cross-referenced.

Common adverse events that were also elevated in the more extensive exposure population (relative risks) were considered adverse reactions and were considered for inclusion in the SmPC.

Long-term safety

The overall incidence of subjects reporting the onset of an AE declined as time on treatment increased, but the pattern of AEs remained similar.

During the procedure the final clinical study report for the open-label extension study MEA115661 was submitted. The incidence and type of adverse events seen in study MEA115661 were similar to those seen in the placebo-controlled severe asthma studies. No new safety signals of concern were identified.

'Limited data in long-term safety of 100mg SC dose' was included in the RMP as missing information. Two ongoing long-term OLE studies (MEA115666 and 201312) are ongoing with the intent to further characterise the long-term safety of mepolizumab treatment in severe eosinophilic asthma.

Deaths

Data was provided during the procedure and the latest cut-off date was 6 May 2015. A total of 8 deaths have been reported in the placebo controlled severe asthma studies (n=5) and in OLE studies (n=3).

Two deaths were in subjects receiving placebo. None of the deaths were considered to be related to mepolizumab by the investigator. Of the 6 deaths in subjects receiving mepolizumab both in the placebo controlled severe asthma studies and in the OLE studies:

- One subject had undergone treatment for uterine carcinosarcoma and died of severe acute pancreatitis and septic shock;
- One subject committed suicide;
- One subject died following a severe respiratory arrest 244 days after the first dose of treatment and 21 days after the last dose which was assessed as due to his underlying asthma;
- One subject with a history of severe uncontrolled asthma experienced a fatal SAE of severe acute asthma exacerbation approximately 11 hours after receiving the second infusion (250mg IV) of mepolizumab. The subject was assessed as well (including asthma parameters) on the day of the last infusion;
- One subject experienced complications due to morbid obesity and died approximately 2.3 years since the first dose of mepolizumab and 15 days after the most recent dose;
- One subject died of acute heart failure subsequent to coronary heart disease approximately 19 months after the first dose of mepolizumab and 8 days after the most recent dose.

A total of 33 deaths have been reported in the mepolizumab clinical development program (which includes patients in the severe asthma and HES programmes). Eight deaths were in the severe asthma studies described above. From the remaining 25 deaths, 20 were patients who participated in the HES compassionate use program who have life-threatening disease, and have failed other available therapies. The compassionate use program was initiated in 2001 and is currently ongoing.

Other serious adverse events

Table 36 shows the on-treatment SAEs occurring in more than one subject in the placebo-controlled severe asthma studies. The incidence of serious adverse events in the placebo-controlled severe asthma studies was lower in the 100mg SC and 75mg IV mepolizumab groups than in the placebo group.

Table 36 On-treatment SAEs occurring in more than one subject in the placebo-controlled severe asthma studies

Serious Adverse Event (Preferred Term)	Number (%) of Subjects					
		Mepolizumab				
	Placebo N=412	100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Any SAE	63 (15)	17 (6)	34 (10)	23 (15)	18 (12)	92 (10)
Asthma	38 (9)	5 (2)	20 (6)	15 (10)	9 (6)	49 (5)
Pneumonia	3 (<1)	1 (<1)	1 (<1)	0	2 (1)	4 (<1)
Nephrolithiasis	3 (<1)	1 (<1)	0	0	0	1 (<1)
Bronchitis	2 (<1)	0	1 (<1)	0	0	1 (<1)
Lobar pneumonia	1 (<1)	0	2 (<1)	0	0	2 (<1)
Tendon rupture	1 (<1)	0	1 (<1)	0	1 (<1)	2 (<1)
Atrial flutter	1 (<1)	1 (<1)	0	0	0	1 (<1)
Cerebrovascular accident	2 (<1)	0	0	0	0	0
Herpes zoster	0	2 (<1)	0	0	0	2 (<1)
Hypersensitivity	1 (<1)	1 (<1)	0	0	0	1 (<1)
Hypertension	0	0	1 (<1)	0	1 (<1)	2 (<1)
Myocardial ischemia	0	0	1 (<1)	0	1 (<1)	2 (<1)
Viral upper respiratory tract infection	1 (<1)	0	1 (<1)	0	0	1 (<1)

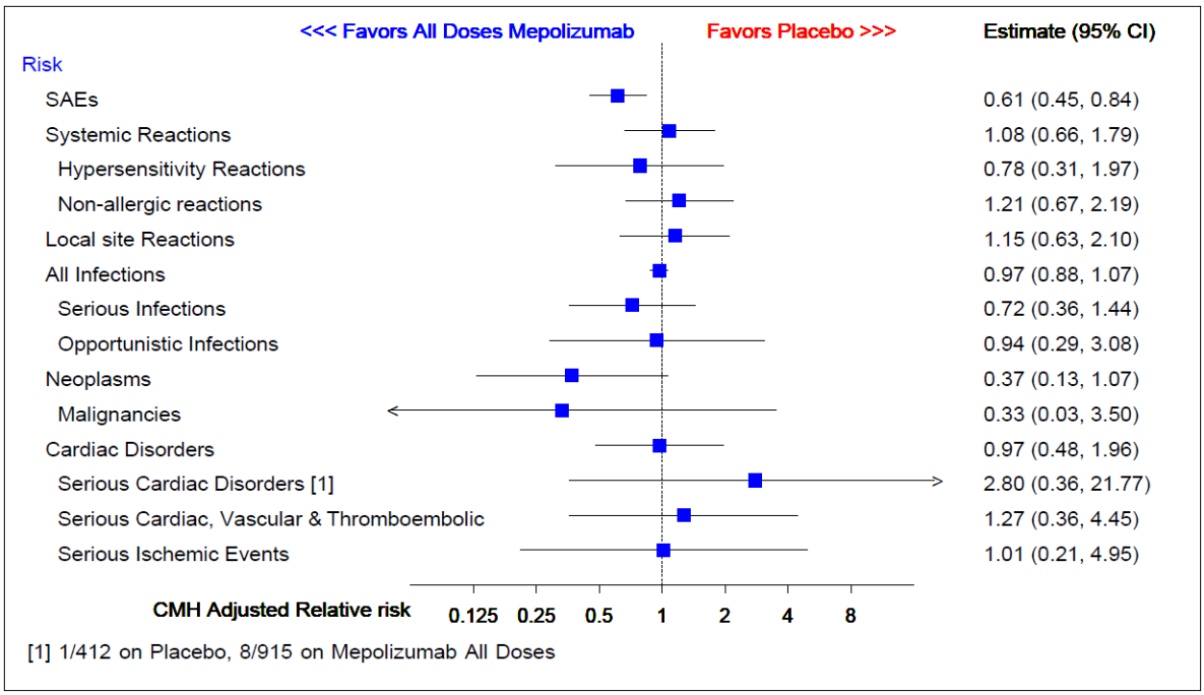
Serious Adverse Event (Preferred Term)	Exposure Adjusted[1]					
		Mepolizumab				
	Placebo Subj Yrs = 284	100 SC Subj Yrs = 147	75 IV Subj Yrs = 254	250 IV Subj Yrs = 142	750 IV Subj Yrs = 144	All Doses Subj Yrs = 687
Any SAE	348.6	189.9	204.5	232.1	188.1	203.7
Asthma	193.7	61.0	94.4	112.5	76.7	87.3
Pneumonia	10.6	6.8	3.9	0	13.9	5.8
Nephrolithiasis	10.6	6.8	0	0	0	1.5
Bronchitis	7.0	0	3.9	0	0	1.5
Lobar pneumonia	3.5	0	7.9	0	0	2.9
Tendon rupture	3.5	0	3.9	0	7.0	2.9
Atrial flutter	3.5	6.8	0	0	0	1.5
Cerebrovascular accident	7.0	0	0	0	0	0
Herpes zoster	0	13.6	0	0	0	2.9
Hypersensitivity	3.5	6.8	0	0	0	1.5
Hypertension	0	0	3.9	0	7.0	2.9
Myocardial ischemia	0	0	3.9	0	7.0	2.9
Viral upper respiratory tract infection	3.5	0	3.9	0	0	1.5

Source: Table 2.056, Table 2.057
Note: Studies included: MEA112997, MEA115588, and MEA115575
1. Numbers represent the frequency of an event per 1000 subject-years of exposure

Adverse events of special interest

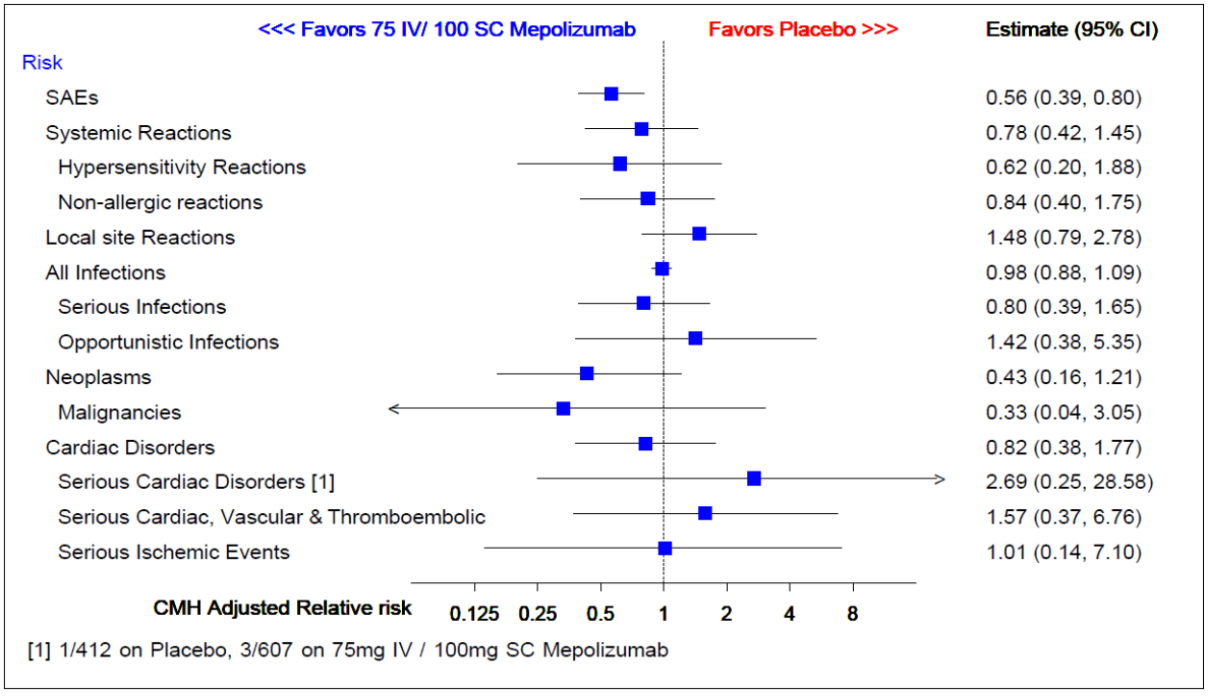
They were selected by on the results of the Cochran-Mantel-Haenszel (CMH) -adjusted relative risks of on treatment SAEs and AEs for all doses of mepolizumab combined compared with placebo and mepolizumab 100mg SC and 75 IV compared with placebo in placebo controlled severe asthma studies (Figures 14 and 15). The SAEs and AEs of special interest within mepolizumab program for subjects with severe eosinophilic asthma are described below. Clinical impact of immunogenicity was also of special interest.

Figure 14: On treatment SAEs and AEs of special interest: CHM-adjusted relative risk (All doses; placebo controlled severe asthma studies)



Note: Horizontal bars represent 95% confidence intervals

Figure 15: On treatment SAEs and AEs of special interest: CHM-adjusted relative risk (Mepolizumab 100mg SC/75mg IV; placebo controlled severe asthma studies)



Note: Horizontal bars represent 95% confidence intervals

- Systemic (allergic/hypersensitivity and non-allergic) and local site reactions

The overall risk of systemic allergic and non-allergic reactions with mepolizumab appeared to be low. In the OLE studies one serious type IV delayed hypersensitivity reaction with an onset of reaction 3 days after the 9th dose of mepolizumab was reported that required treatment in intensive care unit (ICU).

In placebo-controlled severe asthma studies, local site reactions were reported for more subjects in the mepolizumab 100 mg SC group (21 subjects, 8%) compared with the mepolizumab 75 mg IV group (11 subjects 3%) and the placebo group (14 subjects, 3%).

- Infections

The occurrence of AEs in the 'Infections and Infestations' SOC was 58% in the placebo group, 52% in the mepolizumab 100 mg SC group, and 61% in the mepolizumab 75 mg IV group. Thirty-seven subjects reported non-fatal SAEs in the 'Infections and Infestations' SOC, with an incidence of 3% each in the placebo and mepolizumab 100 mg SC groups and 2% in the mepolizumab 75 mg IV group.

Opportunistic infections were infrequent and were reported for 4 subjects (<1%) in the placebo group, 3 subjects (1%) in the mepolizumab 100 mg SC group and 4 subjects (1%) in the mepolizumab 75 mg IV group. The only opportunistic infection that occurred in more than one subject was herpes zoster, occurring in 4 subjects (1%) in the mepolizumab 75 mg IV group and 2 subjects each (<1%) in the placebo and mepolizumab 100 mg SC groups.

Eosinophils may be involved in the immunological host response to some helminth infections; however, the clinical studies of this application were not designed to study the effect of mepolizumab on risk for or response to treatment for helminth infections; as subjects with known parasitic infections were excluded from participation in the clinical studies. The helminth infection rate in the overall clinical program was less than 1 in 1000 subjects. The one report of 'parasitic gastroenteritis' treated with albendazole was in a subject in the mepolizumab 100 mg SC group in the study MEA115588, although no testing was done to confirm the diagnosis. The event was reported as non-serious and treatment with mepolizumab was continued.

- Malignancies

In the placebo controlled studies, neoplasms were reported by 2% of subjects in the placebo group, <1% of subjects in the mepolizumab 100 mg SC group, and 1% of subjects in the mepolizumab 75 mg IV group. Malignancies were reported by 3 subjects (<1%) in the placebo group and 1 subject (<1%) in the mepolizumab 75 mg IV group. The types of malignancies reported were those that are common in the general population. None of the types of malignancies were reported in more than one subject.

In the OLE Studies, neoplasms (both benign and malignant) were reported by 20 subjects (2%). Malignancies were reported by 9 subjects (<1%). The types of malignancies reported were basal cell carcinoma, bladder cancer, endometrial cancer, breast cancer, basosquamous carcinoma, gastric cancer, prostate cancer and squamous cell carcinoma. Basal cell carcinoma and breast cancer was the only malignancy that was reported in more than one subject (n=2).

- Serious Cardiac, Vascular, Thromboembolic (CVT) and ischaemic events

In study MEA112997, a numeric imbalance in the number of subjects with serious cardiac events was observed for mepolizumab (7/461) compared with placebo (1/155). These events were predominantly ischemic in nature. With the exception of one subject, these events were reported in subjects with CV risk factors at baseline. Further review of all CVT and ischemic SAEs showed that similar numbers of subjects experienced events from these SOCs across all treatment groups when events from other SOCs were considered.

Due to the imbalance in serious cardiac events observed in this study a CV monitoring strategy was implemented during the subsequent Phase III program (i.e. in the studies MEA115588, MEA115575, MEA115661, and MEA115666). The overall CV events reported from the two double blind studies (MEA 115588 and MEA 115575) were not sufficient to provide an assessment and it is continued to be monitored in the ongoing OLE studies. Table 37 provides and overview of the CVT and ischaemic SAEs in placebo-controlled severe asthma studies.

Table 37: Overview of cardiac, vascular, thromboembolic and Ischaemic SAEs (placebo-controlled severe asthma studies)

	Number (%) of Subjects					
		Mepolizumab				
Events Identified by Retrospective GSK Review	Placebo N=412	100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Any Cardiac, Vascular, and Thromboembolic event	3 (<1)	1 (<1)	4 (1)	2 (1)	4 (3)	11 (1)
Ischemic events	2 (<1)	0	2 (<1)	2 (1)	2 (1)	6 (<1)

The only ischemic SAEs that were reported by more than one subject were cerebrovascular accident (reported by 2 subjects in the placebo group) and myocardial ischemia (reported by 1 subject in the mepolizumab 75 mg IV group and 1 subject in the mepolizumab 750 mg IV group).

When serious CVT events were analysed by CV history or risk, 84% (11/14) of events occurred in subjects with a prior CV history or risk. The types of events reported were similar regardless of CV history although the numbers are small. The occurrence of a Serious CVT event was spread over time.

In the OLE Studies, CVT events were reported by 12 subjects (1%) in the mepolizumab 100 mg SC group. The only event that was reported by more than one subject was atrial fibrillation. When serious CVT events were analysed by CV history or risk, the incidence of events was greater for subjects who had a CV history/risk (8 subjects, 2%) compared with those who did not (4 subjects, <1%). Atrial fibrillation occurred in both subgroups of subjects.

Laboratory findings

No apparent treatment effects on clinical chemistry, liver function tests or haematology values were seen in the placebo-controlled or open-label severe asthma studies with the exception of the intended therapeutic effect on eosinophil levels.

- **Electrocardiograms**

An analysis of all ECG data related to QT/QTc interval data from the different studies conducted up to 2008 concluded that mepolizumab does not adversely affect the QT/QTc interval and the cardiovascular AE profile does not suggest an effect on conduction (e.g., torsade de pointes, sudden death). From then monitoring of QT/QTc continued during the mepolizumab severe asthma clinical programme.

During the procedure the CHMP requested additional ECG data. The data from the placebo-controlled asthma studies (MEA112997, MEA115588, and MEA115575) showed similar numbers of subjects across treatment groups experiencing an ‘abnormal’ or ‘abnormal-clinically significant’ result at any time post-baseline. In the OLE studies there was a small increase in the number of subjects with an ‘abnormal-clinically significant’ ECG at any time post-baseline compared to baseline. However, the percentage observed in the OLE studies was lower comparable to the percentage of patients in the

placebo group in the placebo-controlled asthma studies with an 'abnormal-clinically significant' ECG at any time post-baseline.

Safety in special populations

- **Use in Pregnancy and Lactation**

During the conduct of the mepolizumab clinical development program, female subjects were required to commit to consistent and correct use of an acceptable method of birth control (defined as failure rate of <1%) from the time of consent, for the duration of the trial, and for 4 months after the last dose of study drug administration.

As of 10 July 2014, 18 pregnancies were reported in female subjects receiving treatment in the completed and ongoing mepolizumab studies (all indications). At that time, the outcomes of 6 pregnancies were ongoing (all in mepolizumab treated subjects). Of the 12 known outcomes, 7 pregnancies resulted in live births (1 in the placebo group, 2 in the mepolizumab 75 mg IV group and 4 in the mepolizumab 750 mg IV group), 3 were spontaneous abortions (1 each in the placebo and mepolizumab 75 mg IV and 750 mg IV groups), and 2 were electively terminated (both in mepolizumab 750 mg IV group).

Since 10 July 2014 and at the completion of study MEA115661, 3 of the 6 subjects with ongoing pregnancies (referenced in the previous paragraph) had delivered normal live births. All three subjects received mepolizumab 100 mg SC.

Since there are limited pregnancy data from the mepolizumab asthma clinical trials, 'Limited data in pregnant and lactating females' was included as missing information in the RMP. A pregnancy surveillance study (category 3) was included in the pharmacovigilance plan of the RMP and it is planned to evaluate pregnancy outcomes and birth defects.

Withdrawal and Rebound

The AE data available did not support a return of symptoms or acute exacerbations in greater severity than seen at baseline in the follow-up or post follow-up periods after cessation of treatment.

In a 12-month investigator supported follow-up study [Haldar, 2014], the frequency of severe exacerbations increased after discontinuing mepolizumab; however, at 12 months post-treatment, the exacerbation frequency was not significantly different compared with subjects previously treated with placebo. Although symptoms increased after mepolizumab cessation, they were not considered indicative of rebound since there was no association with changes in other clinical measures or worsening of eosinophilic airway inflammation.

Immunological events

The applicant developed assays for binding antibodies and neutralising antibodies (non-cell-based ligand binding assay). The testing strategy and methods adopted for assessment were in agreement with the relevant CHMP guidelines (Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006) and Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010)).

Based on the currently available data from the severe asthma studies the applicant's conclusion that mepolizumab had low immunogenic potential, and that there was no apparent difference in antibody titres or antibody characteristics between drug products MDP1 or MDP2 was agreed by the CHMP.

In the placebo-controlled Phase III studies using the SC route, the incidence of emergent antibodies was 6%. In the totality of the safety database, 63/1160 subjects (5%) developed antibodies. Most

antibodies had low titres as only a few patients (16) developed antibodies at titres >32. The antibodies appeared mostly transient although the sampling frequency is not considered optimal; nevertheless, only 13 subjects (1%) had at least 3 positive blood samples spanning over a period of up to 44 weeks.

Overall, these antibodies did not seem to have an impact on PK, PD and safety, although, this cannot be totally ruled out. Only one subject was found to have neutralising antibodies and this was a treatment failure with regard to OCS reduction; in addition the treatment was stopped in this subject after two injections due to injection site reactions.

Immunogenicity was included as an 'Important potential risk' in the RMP.

Discontinuation due to adverse events

The number of subjects experiencing AEs leading to withdrawal in both the placebo-controlled and OLE severe asthma studies was low (35 and 19 subjects respectively).In the placebo-controlled studies the incidence of withdrawals due to adverse events was higher in the placebo group (3%), than the 100 SC and 75mg IV groups (1% in each group).

2.6.1. Discussion on clinical safety

A total of 2022 clinical trial subjects have received at least one dose of mepolizumab across a range of diseases including asthma, HES, eosinophilic oesophagitis and atopic dermatitis. Overall, 1229 subjects with severe eosinophilic asthma have received at least one dose of mepolizumab and 1018 of these 1229 subjects received mepolizumab 100 mg SC, either as part of a randomised placebo-controlled study or in an open-label extension to these studies. Of those treated with mepolizumab 100mg SC, 138 have been treated up to 12 months and 880 for 12 months to less than 24 months.

The CHMP considered sufficient the size of the safety database and degree of patient exposure for mepolizumab to support this application. There are two on-going open-label extension studies (MEA115666 and 201312) that will provide further data on long-term safety. The final report of the ongoing extension studies will be submitted when available. This applicant's commitment was included as category 3 studies in the pharmacovigilance plan of the RMP.

There were limited pregnancy data from the mepolizumab severe asthma clinical trials. Thus, 'Limited data in pregnant and lactating females' was included as missing information in the RMP. A pregnancy surveillance study (category 3) was included in the in the pharmacovigilance plan of the RMP. It is planned to evaluate pregnancy outcomes and birth defects. This was endorsed by the CHMP.

Generally treatment with mepolizumab appeared well-tolerated. Twelve ADRs were identified and included in Section 4.8 of the SmPC.
The overall incidence of subjects reporting the onset of an AE declined as time on treatment increased, but the pattern of AEs remained similar. Long-term safety will be assessed through the ongoing OLE studies.

The incidence of SAEs was lower for mepolizumab 100mg SC (6%) and 75mg IV (10%) than for placebo (15%). The number of patients that withdrew from the studies due to adverse events was low and as with SAEs, the number was lower for mepolizumab 100mg SC (1%) and 75mg IV (1%) than for the placebo group (3%).

On review of adverse events of special interest, there was no apparent increased risk of malignancy, infections, malignancies or serious cardiac, vascular, thromboembolic and ischaemic events.

During the procedure the CHMP requested further data on type IV hypersensitivity reactions cases and its potential association with mepolizumab. No reports of anaphylaxis considered possibly related to mepolizumab treatment have been reported. There was one report in the OLE studies of a serious delayed type IV hypersensitivity reaction that required treatment in ICU. After the assessment of the data provided, hypersensitivity reactions (systemic allergic) was added as an ADR in the SmPC in addition to the warning in section 4.4 as well as a warning regarding acute and delayed administration reactions (including hypersensitivity).

Local site reactions were reported for more subjects with a subcutaneous route of administration (8%) than in the IV (3%) and placebo (3%) groups. This can be expected for the SC route and the levels seen and severity of reactions do not raise a concern.

There were 8 deaths in the severe asthma studies, 2 of which occurred in the placebo group, 5 were considered unrelated to mepolizumab and in 1 case the association with mepolizumab could not be completely excluded due to the close temporal relationship with the administration of the dose. In this final case the subject experienced a severe acute asthma exacerbation approximately 11 hours after receiving the second infusion of mepolizumab.

With the exception of the intended therapeutic effect on eosinophil levels, no apparent treatment effects on clinical chemistry, liver function tests, haematology values or ECGs were seen in the placebo-controlled or open-label severe asthma studies.

Based on the currently available data there does not appear to evidence of 'rebound' of disease on cessation of treatment with mepolizumab.

The immunogenic potential of mepolizumab appeared to be low. In the placebo-controlled severe asthma studies, 15/263 (6%) of subjects treated with 100 mg SC and 13/652 (2%) of subjects treated with IV mepolizumab had anti-mepolizumab antibodies after having received at least one dose. As expected, immunogenicity is higher when using the SC route rather than the IV route, but the proportion of patients developing anti-mepolizumab antibodies with the recommended dosing was considered low. Furthermore, most antibodies had low titres and were transient. The majority of antibody positive subjects developed antibodies during the first 4 months of treatment.

In the severe asthma studies only one patient developed neutralising antibodies. The adverse event profiles for antibody positive and negative subjects appeared similar and treatment interruption and re-start did not seem to have a significant effect on immunogenicity. Overall, the development of antibodies did not appear to impact on the PK and PD profiles of mepolizumab although in rare individual cases, some effect on blood drug concentration and eosinophils cannot be ruled out. Data on immunogenicity will continue to be collected in the on-going OLE studies.

On comparison of the data available from the OLE studies for the new drug product (MDP2 – introduced in the OLE studies and planned for commercial use), no apparent difference in the adverse event or immunogenicity profiles was observed compared to that of the previous drug product (MDP1).

During the procedure the applicant submitted the final clinical study report for the open-label extension study MEA115661. The incidence and type of adverse events seen in this study were similar to those seen in the placebo-controlled severe asthma studies. No new safety signals of concern were identified. On review of adverse events of special interest, overall the rates of systemic (allergic and non-allergic) reactions were lower (2%) than those seen in the placebo-controlled severe asthma studies. For the 13 subjects that experienced investigator-defined systemic reactions, the binding ADA assay was negative in all cases except for one subject. This subject experienced a single injection-related reaction of pruritis and no further systemic reactions were reported with later injections.

2.6.2. Conclusions on the clinical safety

The CHMP agreed that overall the safety profile of mepolizumab does not currently give rise to any major concerns. Treatment with mepolizumab in the severe asthma placebo-controlled studies and the open label extension studies was generally well tolerated and exhibited a low immunogenic potential.

The CHMP considered sufficient the overall size of the safety database for mepolizumab to support the indication in adult patients with severe asthma. . One open-label study MEA115661 completed during the procedure providing long-term safety data up to 84 weeks of treatment. Two on-going open label extension studies (MEA115666 and 201312) are being undertaken that will provide further data on long-term safety.

The applicant will have to submit the final study reports when available. These were included in the pharmacovigilance plan of the RMP as category 3 studies.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: the PRAC considered that the risk management plan version 01.5 is acceptable.

The CHMP endorsed the Risk Management Plan version 01.5 with the following content:

Safety concerns

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
Missing information	Limited data in pregnant and lactating patients Limited data in patients <18 years of age Limited data in elderly patients Limited information in patients with parasites or at high risk of parasitic infection Limited data in long-term safety of 100 mg SC dose

Pharmacovigilance plan

Study / activity Type, title and category (1-4)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Pregnancy Surveillance Study (Category 3)	To evaluate outcomes for pregnant women with asthma and their infants exposed to mepolizumab	Use in patients who become pregnant while taking mepolizumab.	Planned	Final report 2Q 2022
MEA115666: A multi-centre, open-label, long-term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997 trial (Category 3)	To describe the long-term safety profile of mepolizumab	Long-term safety	Ongoing	Final report 2018
201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial (Category 3)	To provide extended treatment with mepolizumab to subjects from study MEA115661 and to further describe long-term dafety in these subjects.	Long-term safety	Ongoing	Final report 2018

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Systemic allergic/hypersensitivity and non-allergic reactions	SmPC Section 4.4- Special Warnings and Precautions for Use states: Hypersensitivity and Administration-related Reactions Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., typically within several days). These	No additional risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactions may occur for the first time after a long duration of treatment. SmPC Section 4.8- Undesirable effects lists “Hypersensitivity reactions (systemic allergic)” and “Administration-related reactions (systemic non-allergic)” as common (≥1/100 to <1/10) adverse reactions.	
Local injections site reactions	SmPC section 4.8, Undesirable effects, lists injection site reactions as a common (≥1/100 to <1/10) adverse reaction and states the most common symptoms associated with subcutaneous injections included: pain, erythema, swelling, itching, and burning sensation. Section 4.8 also states that injection site reactions occurred more frequently in the mepolizumab 100 mg SC group (8%) compared with placebo (3%). These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections.	No additional risk minimization measures
Immunogenicity	SmPC section 5.1 Pharmacodynamic Properties states: Immunogenicity Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of subjects treated with 100 mg dose subcutaneously developed anti-mepolizumab antibodies after having received at least one dose of mepolizumab. Neutralising antibodies were detected in one subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.	No additional risk minimization measures
Alterations in Immune Response (Infections)	SmPC section 4.8 Undesirable Effects lists pharyngitis, lower respiratory tract infection, and urinary tract infection as common (≥1/100 to <1/10) adverse reactions. SmPC section 4.4 Special Warnings and Precautions for Use states: Parasitic Infections Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with NUCALA and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.	No additional risk minimization measures
Alterations in Immune Response (Malignancies)	None proposed, this will be managed through routine proactive pharmacovigilance	No additional risk minimization measures
Alterations in cardiovascular safety	None proposed, this will be managed through routine proactive pharmacovigilance.	No additional risk minimization

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		measures
Exaggerated Response of Symptoms upon Cessation of Treatment	None proposed, this will be managed through routine proactive pharmacovigilance	No additional risk minimization measures
Limited data in pregnant and lactating patients	SmPC section 4.6 Fertility, pregnancy and lactation states Pregnancy There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women. Mepolizumab crosses the placental barrier in monkeys; animal studies do not indicate reproductive toxicity with anti-IL5 treatment. The potential for harm to the foetus is unknown. As a precautionary measure, it is preferable to avoid the use of NUCALA during pregnancy. Administration of NUCALA to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. Breast-feeding There are no data regarding the excretion of mepolizumab in human milk. However, mepolizumab was excreted into the milk of cynomolgous monkeys at concentrations of less than 0.5% of those detected in plasma. A decision must be made whether to discontinue breast-feeding or to discontinue NUCALA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Fertility There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL-5 treatment on fertility.	No additional risk minimization measures
Limited data in patients < 18 years of age	SmPC section 4.2 Posology and method of administration states: Paediatric population The safety and efficacy of NUCALA in children and adolescents under 18 years of age has not yet been established. Very limited data are currently available in children 12-18 year old (see sections 4.8, 5.1 and 5.2), therefore, no recommendations can be made. SmPC section 5.1 Pharmacodynamic properties states: The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. There were 25 adolescents, 13 girls and 12 boys, 9 aged 12-14 years and 16 aged 15-17 years, enrolled in study MEA115588. Of the total 25 subjects: 9 received placebo, 9 received 75mg IV, and 7 received 100 mg SC. The same proportion of subjects (3/9) receiving placebo and mepolizumab IV reported clinically significant exacerbations; but no exacerbations were reported in those receiving mepolizumab SC.	No additional risk minimization measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC section 5.2 Pharmacokinetic properties states: There are limited data available in the paediatric population (59 subjects with eosinophilic esophagitis, 19 subjects with severe asthma). Intravenous mepolizumab pharmacokinetics was evaluated by population PK analysis in a paediatric study conducted in subjects aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was predictable from adults, after taking into account bodyweight. Mepolizumab pharmacokinetics in adolescent subjects with severe eosinophilic asthma included in the phase 3 studies was consistent with adults.	
Limited data in elderly patients	SmPC section 4.2 Posology and method of administration states: No dose adjustment is required for elderly patients SmPC section 5.2 Pharmacokinetic properties states: There are limited pharmacokinetic data in elderly patients (≥65 years old), across all clinical studies (N=90). However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12-82 years.	No additional risk minimization measures
Patients with parasites or at a high risk of parasitic infections	SmPC section 4.4 Special Warnings and Precautions for Use states: Parasitic Infections Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with NUCALA and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.	No additional risk minimization measures
Limited data in long-term safety of 100 mg SC dose	SmPC section 4.8 Undesirable effects states: A total of 915 subjects with severe refractory eosinophilic asthma have received either a subcutaneous or an intravenous dose of mepolizumab during clinical studies of 24 to 52 weeks duration.	No additional risk minimization measures

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

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

the readability of the label and package leaflet of medicinal products for human use.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nucala (MEPOLIZUMAB) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

Benefits

Beneficial effects

Two pivotal placebo-controlled exacerbation trials (studies MEA112997 and MEA 115588) were conducted in a population of patients with severe refractory asthma not controlled despite high doses of inhaled corticosteroids and a second asthma controller; only the criteria used to define the eosinophilic phenotype differed. The two trials showed consistent evidence of reduction in the frequency of severe exacerbations by about 50%. In a combined analysis (ITT population) of the two trials, the rate ratio for clinically significantly exacerbation (mepolizumab/placebo) was 0.51 (95%CI: 0.42, 0.62; p<0.001) in the pooled 75 mg IV/100 mg SC arm and a similar ratio (0.50; 95%CI: 0.28, 0.89; p=0.018) was obtained for the exacerbations requiring hospitalisation.

In the second trial (study MEA 115588), which evaluated the recommended posology of 100 mg SC every 4 weeks, a decrease from 1.74 to 0.83 severe exacerbations per year and from 0.10 to 0.03 hospitalisations per year were observed in active treatment arm of the trial.

A third pivotal placebo–controlled trial (MEA 115575) investigated mepolizumab's potential sparing corticosteroid sparing effect. In this study, a statistically significant greater relative (%) reduction in OCS dose was observed in the mepolizumab arm compared to placebo in the ITT population with an odds ratio of 2.39 (95%CI: 1.25, 4.56; p = 0.008), with 64% of the patients treated with mepolizumab showing some level of reduction vs. 44% in the placebo arm; 54% of the patients treated with mepolizumab achieved a reduction to a dose ≤ 5 mg/day of prednisone vs. 32% in the placebo arm (p = 0.025). The median reduction was 5 mg/day regardless of the baseline OCS dose (up to 30 mg/d), which was considered clinically meaningful.by the CHMP.

Uncertainty in the knowledge about the beneficial effects

The results of the secondary endpoints were inconsistent across the trials. In the first exacerbation trial (Study MEA 112997) no significant difference was observed versus placebo over 12 months with respect to lung function, asthma control assessed with the ACQ questionnaire, and quality of life using the Asthma Quality of Life Questionnaire. It is known that the relationship between airway inflammation, lung function and symptoms is weak [Crimi, 1998; Rosi, 2000; Ronchi 1997]. In contrast, in the two other trials (studies MEA 115588 and MEA 115575), some level of improvement in lung function (FEV1) was observed; moreover, improvement in asthma control and patient quality of life using the St. George's Respiratory Questionnaire was clinically relevant and statistically significant compared with placebo.

In the corticoid-sparing trial (MEA 115575), the short duration of the evaluation period (4 weeks) was not considered sufficient to assess the durability of the response. However, information up to 52 weeks was provided as part of the extension study during the procedure showing that the treatment effect was sustained.

There were insufficient data in adolescents, and therefore, the current indication is restricted to adults.

No formal pharmacokinetic studies were conducted in subjects with renal or hepatic impairment but the CHMP considered this acceptable given that mepolizumab is a humanised monoclonal antibody. This was further addressed in the POPPK analyses and no dose adjustment in these patients was included in the SmPC.

Risks

Unfavourable effects

Generally treatment with mepolizumab appeared to be well-tolerated and the safety profile based on the data submitted did not raise major concerns.

Headache and nasopharyngitis were the most frequently reported adverse events in the severe asthma studies. The incidence of injection site reactions with mepolizumab 100mg SC and placebo was 8% and 3%, respectively. These adverse events were all non-serious, mild to moderate in intensity and the majority resolved within a few days.

There were 8 deaths in the severe asthma studies. Of the 6 deaths in mepolizumab-treated patients, 4 were unrelated to treatment and 2 were due to the patients underlying asthma. In one of the asthma related deaths, due to the close temporal relationship between the onset of symptoms and administration of the infusion a relationship to mepolizumab could not be completely excluded.

In the three placebo-controlled studies, the number of serious adverse events and of subject withdrawals due to adverse events was lower in the 100mg SC/75mg IV mepolizumab treatment groups (1% of withdrawals in each group) than in the placebo group (3% withdrawals).

The overall risk of systemic allergic and non-allergic reactions with mepolizumab appeared to be low. No reports of anaphylaxis considered possibly related to mepolizumab treatment were reported. One serious type IV delayed hypersensitivity reaction with an onset of reaction 3 days after the 9^{th} dose of mepolizumab was reported that required treatment in ICU.

The immunogenic potential of mepolizumab also appeared to be low. In the placebo-controlled severe asthma studies, 15/263 (6%) of subjects treated with 100 mg SC and 13/652 (2%) of subjects treated with IV mepolizumab developed anti-mepolizumab antibodies after having received at least one dose. Most antibodies had low titres and were transient.

Uncertainty in the knowledge about the unfavourable effects

Long-term safety of treatment, especially with the SC route, is limited and will be further assessed and characterise with the applicant's post-authorisation submission of results from the two on-going open label extension studies (Study MEA 115666 and Study 201312). This was included in the RMP.

Based on the currently available data, on review of adverse events of special interest, there was no apparent increased risk of malignancy, infections, malignancies or serious cardiac, vascular, thromboembolic and ischaemic events. The overall risk of systemic allergic and non-allergic reactions with mepolizumab and the immunogenic potential of mepolizumab appeared to be low.

During the procedure the final clinical study report for the open-label extension study MEA115661 was submitted. The incidence and type of adverse events seen in study MEA115661 were similar to those seen in the placebo-controlled severe asthma studies. No new safety signals of concern were identified.

Currently there was only a limited amount of the safety data for the elderly was limited; 82 subjects across all doses in the severe asthma studies were older than 65 years. Thus, it was difficult to draw any conclusion on whether the safety profile was similar to that of younger adults. Further data should be collected in the post-marketing setting.

Animal studies did not indicate reproductive toxicity. However, there was limited data from the use of mepolizumab in pregnant women to draw any conclusions. A pregnancy surveillance study (category 3) was included in the RMP to evaluate pregnancy outcomes and birth defects.

Benefit-risk balance

Importance of favourable and unfavourable effects

Asthma is a complex disorder characterised by intermittent, reversible airway obstruction and airway hyper-responsiveness. Recruitment of eosinophils to the lung, that is believed to be the major cause of the smooth muscle hypertrophy and chronic mucosal damage, leads to airway hyper-reactivity and deterioration in lung function over time. *In vivo*, targeting IL-5 with a neutralising monoclonal antibody such as mepolizumab, reduces the development and differentiation of eosinophils and leads to a direct reduction in the number of blood eosinophils. The rationale for targeting IL-5 with mepolizumab was based upon the role of the eosinophil as an important inflammatory cell in the pathogenesis of asthma.

Exacerbations are the most important outcome in asthma control, because they constitute the greatest risk to patients. The reduction in the frequency of severe exacerbations observed in the placebo-controlled exacerbation trials with mepolizumab (i.e. from approximately two to one per year) was considered clinically meaningful by the CHMP.

There is a recognised medical need in developing steroid sparing strategies due to the large number of complications of prolonged corticosteroid administration. The applicant conducted a small trial (MEA 115575, the results of which did not appear to be compelling; nevertheless, a reduction of 5 mg OCS/day regardless of the baseline OCS was obtained and was considered clinically relevant by the CHMP.

Similar effects on blood eosinophil levels and similar efficacy in terms of exacerbations and asthma control were observed with an IV formulation and an SC formulation of mepolizumab. The 100 mg SC formulation was considered more convenient for patients and healthcare professionals and in time it may result in self-administration. The burden of monthly subcutaneous injections was considered to be low by the patient.

There were few treatment discontinuations and both exacerbation studies (MEA112997 and MEA 115588) had high retention rates in both mepolizumab and placebo arms.

The overall safety profile of mepolizumab is mainly characterised by non-serious adverse reactions (headache, nasopharyngitis, and local reactions). Its immunogenicity and allergic potential is low although a risk of type IV hypersensitivity reactions is possible.

Benefit-risk balance

The CHMP considered that since the level of risk associated with mepolizumab use is low, even a moderate reduction in severe exacerbations and hospitalisations could outweigh these risks. Likewise,

a reduction of 5 mg/day prednisone in corticosteroid-dependent patient is considered clinically relevant and to exceed the risks. Therefore, the overall benefit/risk of mepolizumab is considered positive.

Discussion on the benefit-risk balance

The impact of mepolizumab on asthma exacerbations tended to increase as pre-treatment blood eosinophil levels and frequency of exacerbations increased. In the placebo-controlled trials, the patients who benefited the most were those who experienced the highest frequency of exacerbations and had the highest levels of blood eosinophils at study entry, which is fully consistent with the mechanism of action of mepolizumab.

Mepolizumab is indicated for adult patients with severe refractory asthma characterised by an eosinophilic phenotype. The diagnosis of the phenotype is left to health care professionals specialised in the treatment of severe asthma based on sputum or blood eosinophilia while the magnitude of mepolizumab effect is described in the SmPC (section 5.1) to further inform their therapeutic decision.

Although mepolizumab reduces sputum and blood eosinophil counts and asthma exacerbations it has little benefit on airways function.

In corticosteroid dependent patients, a modest improvement in pre-bronchodilator FEV1 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.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Nucala as an add-on treatment for severe refractory eosinophilic asthma in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

updates of the RMP.

An updated RMP should be submitted:

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

New Active Substance Status

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