16 September 2021
EMA/560938/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Nucala

International non-proprietary name: mepolizumab

Procedure No. EMEA/H/C/003860/II/0037

## Note

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

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# List of abbreviations

ADA Anti-drug antibody
AE(s) Adverse event(s)
AESI(s) Adverse event(s) of special interest
AI Autoinjector
BFI Brief Fatigue Inventory
BLA Biologics License Application
CHMP Committee for Medicinal Products for Human Use
CI(s) Confidence interval(s)
CMH Cochran-Mantel-Haenszel
COPD Chronic Obstructive Pulmonary Disease
CPRD Clinical Practice Research Datalink
CRL Complete response letter
CRO Contract research organization
CRSwNP Chronic rhinosinusitis with nasal polyps
CSR Clinical Study Report
CVT Cardiac, vascular, thromboembolic
EAP Expanded access program
ECG Electrocardiogram
eCRF(s) electronic Case Report Form(s)
EGPA Eosinophilic granulomatosis with polyangiitis
ELISA Enzyme-linked immunosorbent assay
EMA/EMEA European Medicines Agency
EoE Eosinophilic esophagitis
EU European Union
F/P Fip1-like1-Platelet Derived Growth Factor Receptor □
(FIP1L1-PDGFRa)
GCP Good Clinical Practice
GM-CSF Granulocyte macrophage colony-stimulating factor
GSK GlaxoSmithKline
HES Hypereosinophilic syndrome
HLT High level term
HRP Horseradish peroxidase
ICH International Conference on Harmonisation
ICOG-EO International Cooperative Working Group on Eosinophil
Disorders
IgG Immunoglobulin-G
IgG1 Immunoglobulin-G1
IL-3 Interleukin-3
IL-5 Interleukin-5
IND Investigational New Drug
INF□ Interferon alpha
ISE Integrated summary of efficacy
ISI Integrated summary of immunogenicity
ISS Integrated summary of safety
ITT Intent-to-treat
IV Intravenously
L-HES Lymphocytic hypereosinophilic syndrome

MAA Marketing authorization application
Mepo Mepolizumab
M-HES Myeloproliferative hypereosinophilic syndrome
NAb(s) Neutralizing antibody(ies)
NPS Named Patient Supply
OCS(s) Oral corticosteroid(s)
ODA Orphan Drug Act
OLE Open label extension
PBRER Periodic Benefit Risk Evaluation Report
PBO Placebo
PD Pharmacodynamic(s)
PK Pharmacokinetic(s)
PRO(s) Patient reported outcome(s)
PT(s) Preferred term(s)
QoL Quality of life
RAP Reporting and analysis plan
SAE(s) Serious adverse event(s)
SC Subcutaneous(ly)
SoC Standard of care
SOC System organ class
SSD Safety syringe device
TGA Therapeutic Goods Administration
Th1 T helper type 1
Th2 T helper type 2
Tmax Time to maximum concentration
UK United Kingdom
URTI Upper respiratory tract infection
USA United States of America
USPI United States Prescribing Information

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Trading Services Limited submitted to the European Medicines Agency on 10 October 2020 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include hypereosinophilic syndrome (HES) for Nucala (mepolizumab); as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 (in addition 6.6 for the powder for solution for injection only) of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7 of the RMP has also been submitted.
In addition, the Marketing authorisation holder took the opportunity to update the local representative in the PL.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMEA-P/0384/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0384/2020 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

Mepolizumab was granted an Orphan Drug designation for HES (EU/3/04/213) on 29 July 2004. On 24 September 2020, the MAH submitted a request to withdraw the Orphan Drug designation ahead of the submission of this type II variation. The removal of the designation was anticipated to allow the indication to be added on to the Nucala Marketing Authorisation indicated currently for severe eosinophilic asthma.

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Marketing Authorisation Holder (MAH) 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.

### *Scientific advice*

The MAH obtained two SAs from the CHMP in relation to the use of mepolizumab in patients with HES i.e. EMEA/H/SA/436/2/FU/2/2014/PA/II and EMEA/H/SA/436/2/FU/3/2016/PA/II

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Peter Kiely Co-Rapporteur: Ondřej Slanař

| Timetable | Actual dates |
|---|---|
| Start of procedure | 31 Oct 2020 |
| CHMP Co-Rapporteur Assessment Report | 21 Dec 2020 |
| CHMP Rapporteur Assessment Report | 22 Dec 2020 |
| PRAC Rapporteur Assessment Report | 04 Jan 2021 |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | n/a |
| PRAC endorsed relevant sections of the assessment report[3] | 14 Jan 2021 |
| CHMP members comments | 18 Jan 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 21 Jan 2021 |
| Request for supplementary information | 28 Jan 2021 |
| MAH submission of responses | 21 Apr 2021 |
| Re-Start of procedure | 26 Apr 2021 |
| CHMP Rapporteur Assessment Report | 31 May 2021 |
| CHMP Co-Rapporteur Assessment Report | 31 May 2021 |
| CHMP members comments | 14 June 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 17 June 2021 |
| 2nd Request for supplementary information/Opinion | 24 June 2021 |
| Submission | 13 July 2021 |
| Re-start | 19 July 2021 |
| CHMP Rapporteur Assessment Report | 17 August 2021 |
| PRAC Rapporteur Assessment Report | 20 August 2021 |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | n/a |
| PRAC endorsed relevant sections of the assessment report[3] | 02 September 2021 |
| CHMP members comments | 30 August 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 10 September 2021 |

| Timetable | Actual dates |
|---|---|
| Opinion | 16 September 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

HES is a group of rare hematologic disorders without a known cause in which eosinophils are overproduced in the bone marrow for prolonged periods of time. The sustained overproduction of eosinophils in the bone marrow results in high blood eosinophil levels (eosinophilia). When activated eosinophils from the bloodstream infiltrate various tissues, they cause inflammatory tissue damage and dysfunction.

Inadequate HES treatment can lead to profound end-organ damage and increased mortality.

The International Cooperative Working Group on Eosinophil Disorders (ICOG-EO) uses the following definition for HES: (1) blood eosinophilia of >1500 eosinophils/µL on 2 examinations (at an interval ≥1 month, except in case of life-threatening organ-damage when diagnosis can be made immediately) and/or tissue eosinophilia; (2) organ damage and/or dysfunction attributable to tissue eosinophilia; and (3) exclusion of other disorders or conditions as the major reason for organ damage [Valent, 2012b; Kahn, 2017]. HES is only diagnosed when organ damage and/or dysfunction are present.

### *State the claimed the therapeutic indication*

The proposed indication is related to Hypereosinophilic syndrome (HES) as follows:

*Nucala is indicated for the treatment of adult patients with hypereosinophilic syndrome.*

Posology:

Adults: The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

Children aged less than 18 years old: The safety and efficacy of mepolizumab in adolescents and children aged less than 18 years old have not yet been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

### *Epidemiology*

HES is considered a rare disease under EU legislation (defined as those affecting fewer than 5 in 10,000 people in the EU). Mepolizumab has been granted Orphan Drug Designation in the USA and in the EU on 29 July 2004 (EU/3/04/213); however, the MAH withdrew the Orphan Drug Designation in the EU.

HES is a rare and under-diagnosed disorder, making it difficult to estimate overall prevalence. Reliable estimates of the prevalence and/or incidence of HES are not readily available in the literature, and calculation of a meaningful prevalence estimate is difficult, as most publications are case reports or case series which lack a population denominator.

Using the MAH database in the United Kingdom (UK), the estimated prevalence of patients diagnosed with HES in 2018 was estimated to 0.8 cases per 100,000 persons and the estimated incidence rate was 0.14 per 100,000 person-years.

## *Biologic features*

The natural history and prognosis of HES depends on the HES variant. The ability to distinguish these different variants is critical for optimal patient management because the clinical manifestations and response to treatment vary considerably depending on the aetiology of eosinophilia. Clinically, the most frequent classifications are myeloproliferative (M-HES); lymphocytic (L-HES), and idiopathic HES.

M-HES is a clinically defined variant characterized by an extreme male predominance, pathologic evidence of eosinophil-related tissue damage and tissue fibrosis, elevated serum tryptase levels, and myeloproliferative features, including splenomegaly, anaemia, thrombocytopenia, bone marrow hypercellularity with reticulin fibrosis, and increased numbers of atypical mast cells.

The identification of the FIP1L1-PDGFRα (F/P) fusion tyrosine kinase genetic translocation in the majority of patients with M-HES led to a dramatic improvement in prognosis for these patients due to response to imatinib (a tyrosine kinase inhibitor) treatment. The prevalence of the F/P mutation in the total HES patient population was found to be between 11% and 18% [Ogbogu, 2009; Helbig, 2010]. Therefore, for the majority of HES patients that are F/P negative, no definitive genetic basis underlying their disease has been identified.

Identification of L-HES rests upon recognition of distinct helper T cell subsets (Th1 and Th2) and clonal overgrowth of specific cytokine-producing cells, particularly production of IL-5 by Th2 cell clones. The most prevalent T cell clone associated with L-HES appears to be the CD3-CD4+ clone. Although patients with L-HES typically do not show the same high incidence of life-threatening end-organ damage compared with M-HES, L-HES patients are at higher risk for developing peripheral T-cell lymphomas. Reported estimated incidence rates vary widely due to the small sample population from "rare", to 5% up to 14 to 25%. In a study of F/P negative HES patients, 21% were diagnosed with L-HES. In a retrospective study of 21 French patients with CD3- CD4+ L-HES and negative for the F/P mutation, 1 lymphoma occurred (5%) during the mean follow-up duration after HES diagnosis of 6.9□5.1 years.

Idiopathic HES describes cases of unknown cause that does not meet criteria for any of the other variants. It is estimated that more than 60% of patients with HES fall into this category.

## *Clinical presentation, diagnosis and stage/prognosis*

HES is a chronic disease that has been found to be associated with a high degree of morbidity and mortality [Schwartz, 2010]. As a heterogeneous disease, signs and symptoms of HES vary widely depending on specific organ involvement. Symptoms may range from non-specific to organ- or life-threatening. Many patients have 2 or more organ systems affected [Ogbogu, 2009; Helbig, 2010]. The most common reported clinical manifestations of HES are:

- Constitutional: fever, night sweats, weakness, malaise, weight loss, myalgia

- Dermatologic: pruritus, dermatitis, angioedema
- Pulmonary: asthma, persistent non-productive cough, dyspnea
- Gastrointestinal: abdominal pain, vomiting, diarrhea
- Cardiac/thromboembolic: congestive heart failure, mitral regurgitation, intracardiac thrombus, myocardial ischemia, arrhythmias

## *Management*

Important goals of HES therapy are to decrease symptoms and blood eosinophil levels in order to achieve disease control. The current approach is based on reduction of blood eosinophilia, reduction of active inflammation, suppression of the immune response, and treatment of disease-specific and/or treatment-related complications.

Standard of care (SoC) therapy for patients with HES includes corticosteroids (for F/P negative or F/P positive with cardiac involvement at diagnosis) or imatinib (for F/P positive) as first-line therapy and cytotoxics (e.g., hydroxyurea, cyclophosphamide) or immunomodulators (interferon alpha, cyclosporine, immunoglobulin) as second-line agents . Clinical responses to these therapies, however, are incomplete or inadequate in over 80% of HES patients (among those negative for F/P mutation).

The discovery of the F/P mutation in patients with M-HES and its response to imatinib has improved survival and QoL in this subpopulation. For most patients however, the only currently available treatment options are limited to chronic high doses of corticosteroids, and cytotoxic agents such as hydroxyurea and cyclophosphamide. The efficacy of these agents, even in combination, is not always adequate and side effects from long-term use are significant. Additional agents with increased efficacy and decreased toxicity are therefore greatly needed.

Although not approved for use in HES, corticosteroids are used in clinical practice as first-line treatment for most patients with HES due to lack of available options. The therapeutic strategy is to start with a moderate to high dose (≥40 mg/day prednisone or equivalent) and taper very slowly while monitoring the blood eosinophil count closely. Using this approach, most patients (85%, N=141) will respond initially to steroid therapy based on a decrease of blood eosinophil count to normal range and symptomatic improvement. However, many HES patients (72%, N=179) will need to be maintained on low steroid doses (median 10 mg/day) for long periods of up to 20 years since discontinuation of corticosteroids leads to eosinophilia and symptomatic recurrence in most patients.

Although the initial response to corticosteroid treatment is often positive, long-term use of oral corticosteroids (OCS) is associated with significant and commonly reported side effects, including truncal obesity, moon facies, buffalo hump, increased blood pressure, water retention, decreased bone density, weight gain, muscle atrophy, hyperglycemia, delayed wound healing, cataracts and glaucoma, peptic ulcers, and increased risk of infection. Therefore, with chronic use, the toxicities of steroid therapy become more significant, patient adherence diminishes, and additional or alternative corticosteroid-sparing therapies must be used. The chronic use of corticosteroids is often discontinued (42%, N=179) or used in combination therapy (33%, N=179) due to toxicity or failure in the majority of HES patients.

Discontinuation or inadequate treatment with HES therapies increases the risk of worsening symptoms and/or increased blood eosinophils.

In the absence of approved targeted therapies for HES, several of the second-line agents (chemotherapeutic agents such as hydroxyurea, IFNα, and other cytotoxics [e.g., cyclosporine, vincristine, methotrexate, and busulfan]) have been used based on empirical observational evidence of

benefit. These second-line agents are effective (defined as a decrease of eosinophil count and symptomatic improvement) only in a small number of HES patients, are associated with significant toxicities, have a slow onset of therapeutic effect, and confer an increased risk of patients developing malignancy. For example, the most commonly used second-line agent, hydroxyurea, is rarely useful as a single agent and its side effects and lack of efficacy result in discontinuation in the majority of patients (77%, N=64).

Despite significant advances in the understanding and management of HES, there remains the need for effective, well-tolerated treatments to control the disease and minimize the toxicities from chronic use of corticosteroids and second-line agents. This unmet medical need persists in particular for F/P negative HES, which comprises the majority (85%) of the HES patient population, due to the absence of a highly effective, well-tolerated therapy suitable for long-term use.

### 2.1.2. About the product

Mepolizumab is a humanized IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. The functional protein is a disulfide-linked tetramer consisting of two light (kappa) and two heavy (IgG1) chains. There is a single glycosylation site on each heavy chain. The complementary determining regions (CDRs) were grated from the murine antibody, 2B6, by molecular genetics techniques.

Mepolizumab is a fully humanized monoclonal antibody which binds to IL-5 with high affinity (Kd=185 pM) and specificity, thus preventing IL-5 from associating with the receptor α-chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting IL-5 signalling.

Neutralization of IL 5 leads to a reduction in the production and survival of eosinophils but does not appear to affect other immune cells including T cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B cells, NK cells or T cells.

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program to support an indication for the use of mepolizumab in adult patients with HES was based on a single pivotal Phase III study, 200622. This study was a randomized, double-blind, placebo-controlled study which investigated the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects. The study comprised a 32-week treatment period in which subjects received 300 mg mepolizumab subcutaneously (SC) every 4 weeks and an 8-week follow-up period.

Subjects who completed study 200622 were eligible for a 20-week open-label extension (OLE) study, 205203. During the extension treatment period, all subjects received 300 mg mepolizumab SC every 4 weeks, and their standard HES therapy could be adjusted per SoC.

The MAH had previously conducted a Phase III study, MHE100185 (completed in 2006), and its OLE study, MHE100901 (completed in 2010), in subjects with HES. Study MHE100185 compared the efficacy and safety of 750 mg mepolizumab administered intravenously (IV) every 4 weeks for 36 weeks with placebo in terms of the reduction in OCS dose (to 10 mg or less per day for 8 or more consecutive weeks) and the reduction in blood eosinophilia (to <600 eosinophils/μL for 8 or more consecutive weeks). The initial marketing authorization application (MAA) for mepolizumab in HES was submitted in September 2008 and was based on study MHE100185. While this study showed greater reductions in OCS dose for mepolizumab compared with placebo, the application was withdrawn in July

2009 as the Committee for Medicinal Products for Human Use (CHMP) did not consider the data available at that point in time conclusive of a positive risk/benefit balance for mepolizumab in HES.

Based on studies MHE100185 and MHE100901 as well as a mepolizumab dose-response (blood eosinophils) meta-analysis across multiple eosinophilic indications, a 300 mg SC dose was selected for investigation in patients with HES. With this information, study 200622 was designed to investigate mepolizumab 300 mg SC in a representative population of HES subjects with a clear definition of HES flares for efficacy assessment. HES flares were considered to be a clinically meaningful endpoint to assess the treatment effect of mepolizumab in this population.

The MAH also has an ongoing mepolizumab HES EAP which comprises the Initial Compassionate Use Program, MHE104317, a Named Patient Supply (NPS) Guidance Program, and treatment protocol MHE112562. The ongoing HES EAP offers mepolizumab to previous HES study participants as well as patients with life-threatening HES who demonstrated failure to standard therapy. As of the most recent clinical data cut-off date of 01 March 2019 for the interim HES EAP clinical study report (CSR), 359 patients have received mepolizumab in the HES EAP. Understanding the limitations of an open-label, uncontrolled EAP (non-placebo/active), the available data offers supporting evidence of long-term safety with mepolizumab for patients with severe HES (non-responsive or intolerant to alternative therapies).

The MAH obtained two SAs from the CHMP in relation to the use of mepolizumab in patients with HES i.e. EMEA/H/SA/436/2/FU/2/2014/PA/II and EMEA/H/SA/436/2/FU/3/2016/PA/II.

## 2.1.4. General comments on compliance with GCP

The following studies were inspected:

**Table 1: GCP inspection- study 200622**

| Site (Full address) | Country | Date of inspection | Regulatory Agency |
|---|---|---|---|
| Hôpital Erasme, Route de Lennik, 808, Brussels, 1070, Belgium | Belgium | 07 August 2018 | GSK CQA UK |
| Universitätsmedizin Mannheim, III. Medizinische Klinik, Theodor-Kutzer-Ufer 1-3, Mannheim, Baden-Wuerttemberg, 68167, Germany | Germany | 14-15 March 2019 | GSK CQA Pakistan |
| Samodzielny Publiczny Zaklad Opieki Zdrowotnej, Uniwersytecki Szpital Kliniczny nr 1 im. Norberta Barlickiego UM W Łodzi, Oddzial Kliniczny Chorób Wewnetrznych, Astmy i Alergii z Odcinkiem dla Dzieci, Ul. Kopcinskiego 22, Łódź, Łódzkie, 90-153, Poland | Poland | 16-18 April 2019 | GSK CQA UK |

**Table 2: GCP inspection- study 205203**

| Site (Full address) | Country | Date of inspection | Regulatory Agency |
|---|---|---|---|
| Almazov National Medical Research Center, Ministry of Health of Russian federation, 2, Akkuratova street, Saint Petersburg, 197341, Russian Federation | Russia | 14-16 May 2019 | GSK-CQA-UK |
| Institute for lung health, Department of Allergy and Respiratory Medicine, Glenfield Hospital, Respiratory Biomedical Research Unit, Groby Road, Leicester, LE3 9QP, United Kingdom | UK | 12-13 Feb 2019 | GSK-CQA-UK |

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Pharmacology

No new studies have been performed. An overview has been provided discussing the mechanism of action of mepolizumab to inhibit IL-5 signalling, reducing the production and survival of eosinophils and thereby a scientific rationale for potential efficacy in the proposed indication. This is adequate.

### 2.2.2. Toxicology

No new studies have been submitted and juvenile toxicity studies have not been conducted with mepolizumab. The available non-clinical data support administration of mepolizumab to paediatric patients from birth. A juvenile toxicity study would not provide additional relevant safety data.

### 2.2.3. Ecotoxicity/environmental risk assessment

Being natural proteins, therapeutic antibodies such as mepolizumab, are not excreted unchanged and do not give rise to metabolites with potential biological activity. In view of this, 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 complete environmental assessment and, therefore, no further assessment of mepolizumab drug substance has been undertaken.

### 2.2.4. Discussion on non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of mepolizumab.

Considering the above data, mepolizumab is not expected to pose a risk to the environment.

### 2.2.5. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of mepolizumab.

Considering the above data, mepolizumab is not expected to pose a risk to the environment.

No concerns are raised from non-clinical point of view for new indications in proposed dosing regimen and aimed patient population.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

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

The MAH 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.

**Table 3: Tabular overview of clinical studies**

| Study Identifier (Identifier of Study Report) | Study Objective(s) | Study Design | Healthy Subjects or Diagnosis of Patients | Treatment Details (Test Product(s); Dosage Regimen; Route; Duration) | Total No. of Subjects by Group (Entered[a]/Completed) | Study Reporting Status (Type of Report) |
|---|---|---|---|---|---|---|
| **Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication** | | | | | | |
| 200622 (2019N406842_01) | Efficacy, safety, PD, PK, and population PKPD | R, DB, PC, PG | HES (aged ≥12 years inclusive) | Mepolizumab 300 mg SC<br>Placebo SC<br><br>Three 100 mL injections Q4W for 32 weeks | 54/52<br>54/52 | Completed (Full CSR) |
| MHE100185 (UM2004/00091/01) | Efficacy, safety, and PK | R, DB, PC, PG | HES (aged 18-85 years inclusive) | Mepolizumab 750 mg IV<br>Placebo IV<br><br>One infusion Q4W for 36 weeks | 43/36<br>42/15 | Completed (Full CSR) |
| **Efficacy and Safety Studies: Uncontrolled Clinical Studies** | | | | | | |
| 205203 (2020N430011_00) | OLE of 200622 | OL | HES; participants who completed 32-week assessments in study 200622 | Mepolizumab 300 mg SC<br><br>Three 100 mL injections Q4W for 20 weeks | 102/98 | Completed (Full CSR) |
| MHE100901 (2010N104202_00) | OLE of MHE100185 | OL | HES; participated and received at least 2 doses of study medication in study MHE100185 | Stage I: Mepolizumab 750 mg IV Q4W<br><br>Stage II: Mepolizumab 750 mg IV; timing of dosing dependent on blood eosinophil count and clinical presentation<br><br>Stage III: Mepolizumab 750 mg IV per individual dosing schedule established at end of Stage II | 78/0[b] | Completed (Full CSR) |

### 2.3.2. Pharmacokinetics

Two placebo-controlled clinical studies in the rare disease HES were conducted during mepolizumab clinical development program: i) an initial Phase III adult study (MHE100185) completed in 2008 that investigated mepolizumab at a dose of 750 mg administered intravenously and ii) a single pivotal Phase III adolescent and adult efficacy study (200622), investigating a 300 mg SC dose of mepolizumab, which was conducted to support this indication submission. The sparse PK samples

collected in the initial Phase III HES study following IV administration (MHE100185) were included in the population PK meta-analysis of adult IV data from early studies in multiple diseases and again in the more recent population PK meta-analysis across studies, routes of administration and eosinophilic diseases, that were submitted previously.

### *Absorption*

Mepolizumab subcutaneous absorption is slow, with an absolute bioavailability of 74 to 80% following injection in the arm in adults or in adults/adolescents, a Tmax of 4 to 8 days, and an absorption half-life of 1 to 2 days.

### *Distribution*

Mepolizumab distributes into a volume of approximately plasma and interstitial space (55 to 85 mL/kg).

### *Elimination*

Mepolizumab is catabolized by ubiquitous proteolytic enzymes and 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 SC terminal-phase elimination half-life of 16 to 22 days, with two-fold accumulation following repeat dosing every four weeks, consistent with the long half-life.

## *Dose proportionality and time dependencies*

The pharmacokinetics of mepolizumab are linear, dose-proportional, and time-independent after both intravenous (IV) and subcutaneous (SC) administration.

## *Pharmacokinetics in the target population*

Sparse PK samples were collected throughout study 200622. A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome. Three blood samples per subject for the PK analysis of mepolizumab concentrations were taken pre-dose at Week 4, Week 16, and Week 32 visits. A PK sample was also taken at the early withdrawal visits and at the additional follow-up visit, when applicable. Fifty-four subjects were randomized to the mepolizumab group and all contributed to the 159 concentrations included into the analysis.

Thirty of the 54 mepolizumab-treated subjects were female. The median age was 48 years (range: 12 to 82 years). The median bodyweight at Screening was 75 kg (range: 35 to 171 kg). The median baseline creatinine clearance (CRCL) was 111 mL/min (range: 46.4 to 196 mL/min). The majority of the subjects had normal renal function. No mepolizumab-treated subjects had severe (CRCL <10 mL/min) renal impairment, one subject had moderate (CRCL <50 mL/min) renal impairment and 6 subjects had mild (CRCL >50 to <80 mL/min) renal impairment.

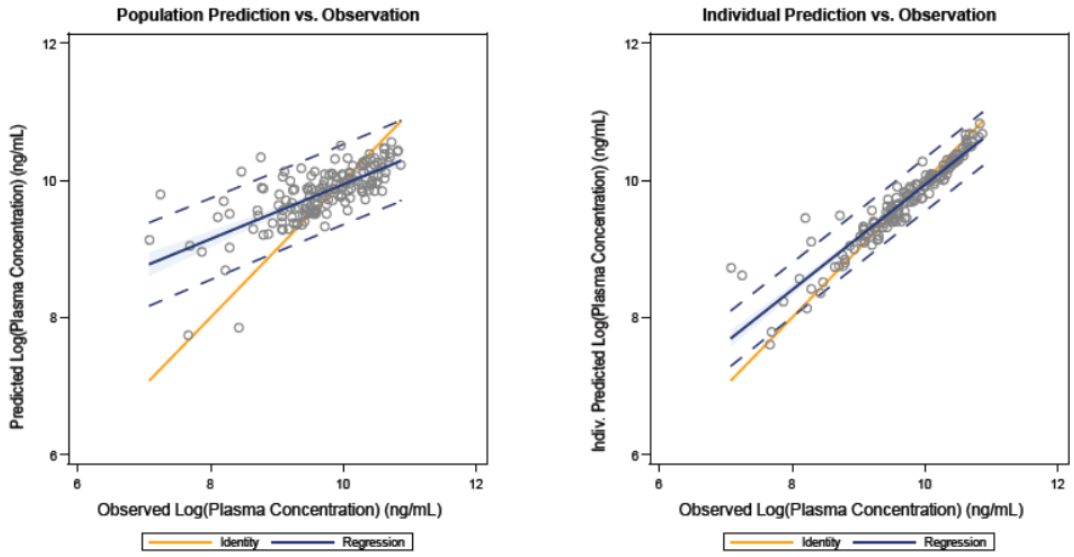
Population Pharmacokinetic Analysis

The impact of continuous and categorical covariates on individual parameter estimates was examined by visual inspection. Considering the small sample size of mepolizumab-treated subjects in the study (54 subjects) and the narrow range of values for some covariates, the covariate investigation is overall considered of limited value. The apparent trend observed for bodyweight, CRCL, and albumin, was already accounted for into the model. After considering co-linearity and plausibility, there was no

apparent obvious trend in any other covariates. No refinement of the model was therefore deemed necessary.

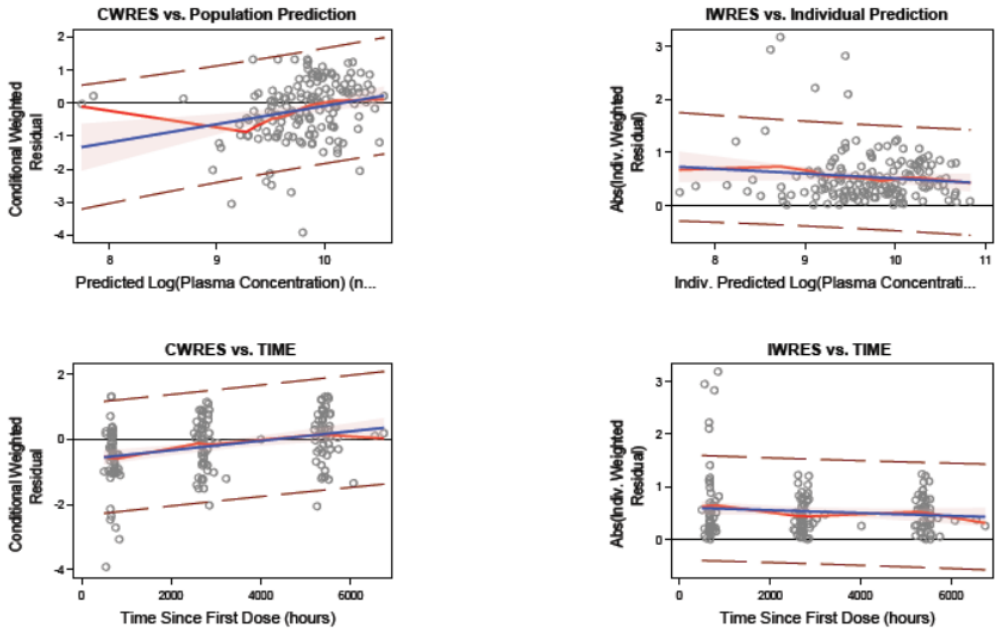
Model goodness of fit, as demonstrated by conventional plots and Normal Prediction Distribution Error (NPDE), are shown below:

**Figure 1: Goodness of Fit Plots (Regression)**



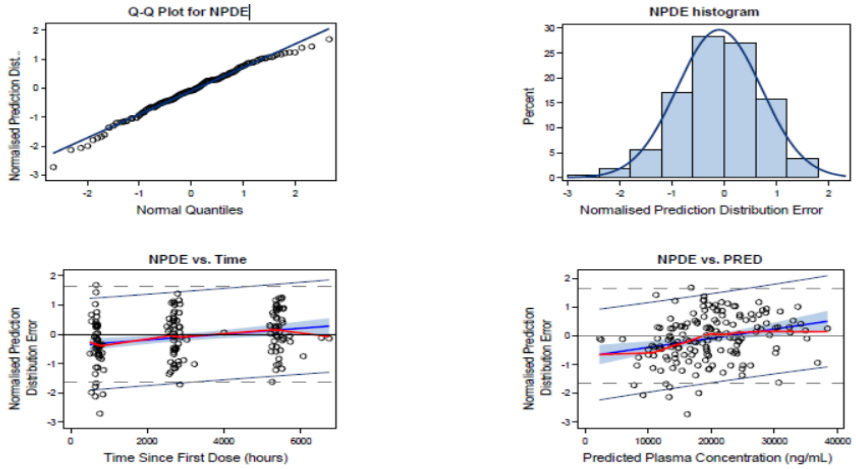

Plots show linear regression with 95% prediction interval (dashed lines)

**Figure 2: Goodness of Fit Regression (Summary Plots)**




CWRES = Conditional weighted residuals, IWRES = Individual weighted residuals

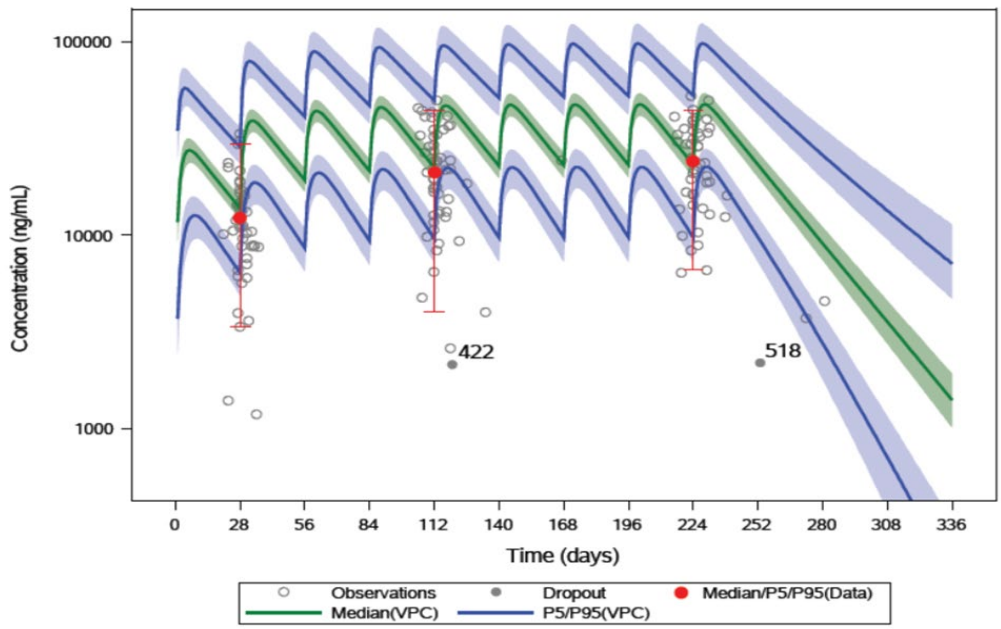
**Figure 3: Normalised Prediction Distribution Error**




Plots show linear regression (blue) with 95% prediction interval (dashed lines) and loess regression (red)

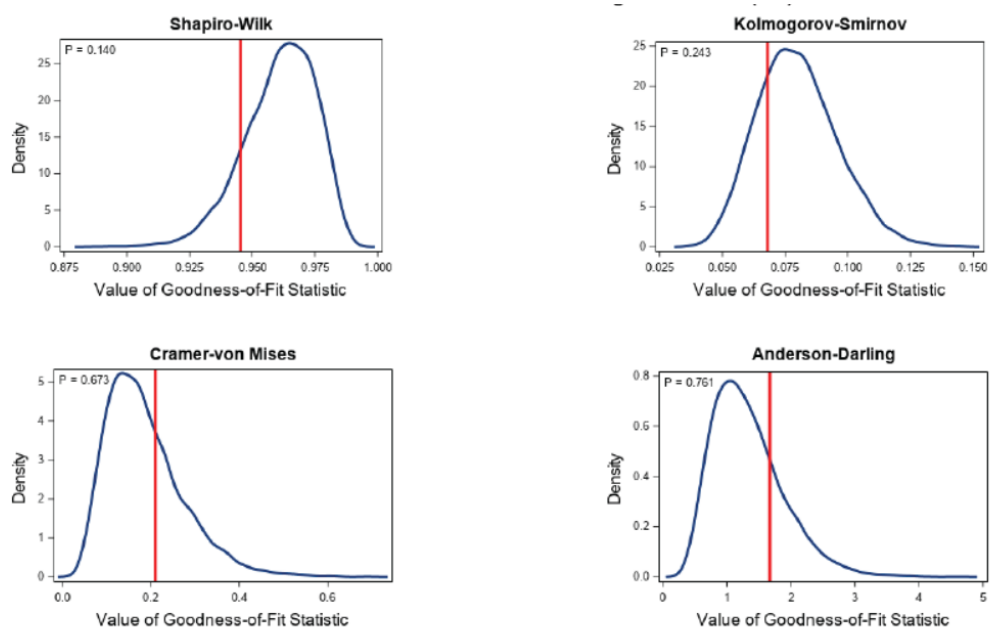
Final model performance was also assessed using VPC (see model visual predictive check below), with incorporation of parameter uncertainty and bootstrap resampling of subject covariates.

**Figure 4: Model Visual Predictive Check (Semi-log plot)**




In order to evaluate the concordance between the predicted and observed plasma concentrations in the study, individual plasma concentration predictions were generated against which the model was validated prospectively, using goodness of fit tests. Based on the following tests: Shapiro-Wilk, Kolmogorov-Smirnov, Cramér–von Mises and Anderson-Darling, there was no evidence at the 5% significance level to suggest that the observations and predictions were drawn from different distributions.

**Figure 5: PK Model Goodness of fit Statistics Showing Observation (red)**




It was therefore concluded that the recent meta-analysis population PK model was able to accurately predict mepolizumab plasma concentrations in an HES population following SC administration.

The range of the predicted individual clearance (CL) values in the study, obtained by post-hoc Bayesian approach, was 0.11 to 0.69 L/day (note: population CL estimate for a 70 kg subject is 0.21 L/day). A slight increase in CL was seen with increasing body weight, as anticipated, which is not considered clinically significant. The box plots of CL versus age, CRCL and ADAs (absence or presence) showed no major difference by visual inspection.

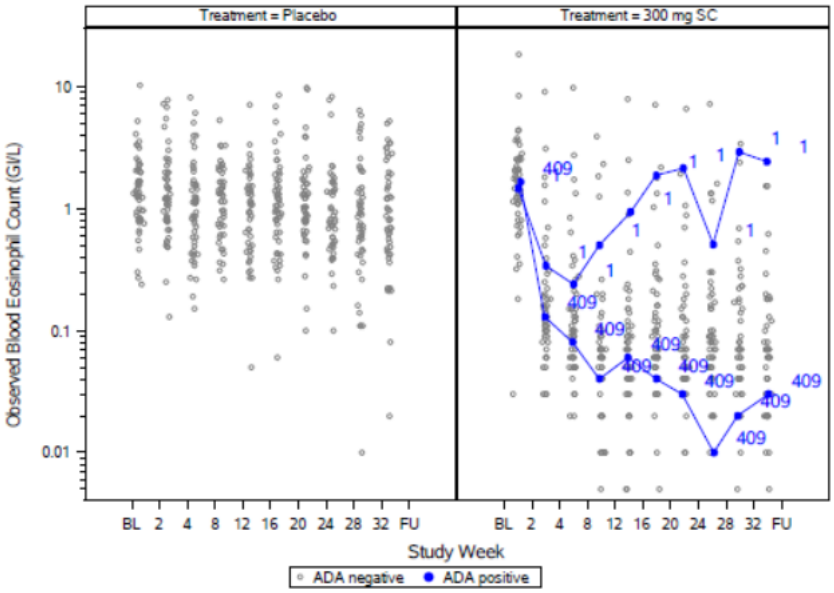
Accumulation ratios for repeat dosing were calculated using individual observed Ctrough values at Week 16 and Week 32 compared with Week 4. Approximately 2-fold accumulation is observed from Week 4 to Week 16, with only a further marginal increase at Week 32. Steady-state was therefore achieved around Week 16, as evidenced by the ratio of approximately unity for the comparison of Week 16 with Week 32.

Immunogenicity

None of the subjects in the placebo group tested positive for ADAs at any time. One subject in the mepolizumab group tested positive for ADAs at any time post Baseline (2%, 1/53). Another subject in the mepolizumab group tested positive for ADAs at Baseline only (2%, 1/54). None of the subjects were positive for NAbs. The presence of anti-mepolizumab antibodies did not influence mepolizumab PK discernibly.

The impact of the presence of ADAs on the blood eosinophil count profiles was assessed by visual inspection (see below). Out of the 2 subjects ADA positive in the study, one subject initially displayed a marked decrease in blood eosinophil counts up to Week 4, after which counts gradually increased to return to baseline levels during the remainder of the study treatment period.

**Figure 6: Observed Blood Eosinophil Count-Time Profiles (ADA Positive versus ADA Negative Subjects)**




## *Special populations*

No conventional special Clinical Pharmacology studies were conducted due to the nature of the molecule, its mechanism of action and elimination pathways.

Age, race, gender and disease are not covariates of mepolizumab exposure. Dose adjustments in special populations other than children (i.e., elderly, renal- and hepatic-impaired subjects) are not required.

Based on the population PK analysis (Study 200622), a slight increase in CL was seen with increasing body weight in patients with HES, which was not considered clinically significant. Of the four adolescents enrolled into the study, one adolescent was randomised to mepolizumab treatment (300 mg SC). The exposure in this 12-year old adolescent of 35 kg was at the upper range of the exposure observed in the study.

## *Pharmacokinetic interaction studies*

No interaction studies have been performed. The potential for drug-drug interaction is deemed low because IL-5 does not signal via hepatocytes.

## *Bioanalytical methods*

Two placebo-controlled studies and 3 open-label uncontrolled studies are included in this Hypereosinophillic syndrome (HES) indication submission. These studies were conducted at different time periods of the mepolizumab clinical development program. Blood samples for evaluation of mepolizumab and serum IL-5 were only collected in studies 200622 and MHE100185, while immunogenicity was assessed in studies 200622, 205203, MHE100185 and MHE100901.

The history of the assays life cycle, in particular the bridging between the PK assays, can be found in initial severe asthma MAA and is briefly summarised in the below respective sections of the assessment report.

*Analytical methods for the evaluation of Mepolizumab Plasma Concentrations.*

For the first phase III HES study MHE100185, the PK assay utilized a sandwich ELISA with a recombinant human IL-5 capture and protein G fluorescent detection. This assay was also initially used in the open-label study MHE100901, which later used an assay validated with a drug specific anti-immunoglobulin G HRP detection conjugate. Both validated assays had similar quantitation ranges (50 – 5000 ng/ml vs 50 – 2500 ng/ml, respectively). For clinical studies supporting the initial severe asthma application, the PK assay was validated at a clinical research organisation (CRO) and utilised a neutralising idiotypic antibody specific for the drug as the capture reagent (50 – 5000 ng/ml). This was the same PK assay used to support HES studies 200622 and 204203. Although different PK assays were used across the HES studies, the PK assays were bridged to allow for concentrations comparison across studies.

**Clinical studies 205203 and 200622**

The measurement of mepolizumab plasma concentrations for clinical studies 205203 and 200622 was carried out using method 111202M01 (version 6). This method is the same as the method used during the initial MAA procedures for the lyophilised and liquid formulations. The full validation report including addenda for method 111202M01 was included in the original MAA.

For assay runs to be acceptable, no more than one-third of the QC samples could deviate from the nominal concentration by more than 20% with %CV ≤ 20% In addition, at least 50% of the results from each QC concentration had to meet the aforementioned criteria for accuracy and precision. There are also additional assay acceptance criteria in place for the calibration curve accuracy and precision.

Analytical method for IL-5

Biomarker analysis for IL-5 concentration was performed by Quest to support HES study MHE100185. Since then, the assay for IL-5 concentration determinations was developed and validated to support clinical studies in the initial severe asthma application. This IL-5 biomarker was assay used during HES study 200622.

Method validation parameters include specificity (interference from mepolizumab), matrix effect/selectivity, prozone effect, dilutional integrity, precision (inter- and intra-), accuracy, stability in matrix and upper/lower limit of quantitation. A summary of the method validation is presented below in **Table 4**.

**Table 4 : Summary of method validation for total IL-5 method (M160527V01)**

| | |
|---|---|
| **Study Title:** | Validation of an Electrochemiluminescence-Based Method for the Quantification of Total Interleukin-5 in Human Serum |
| **Analyte:** | Total interleukin-5 (IL-5) |
| **Matrix:** | Human serum |
| **Type of assay:** | Electrochemiluminescence (ECL) immunoassay |
| **Regression method:** | Unweighted 4-parameter logistic regression |
| **Lower limit of quantitation:** | 7.81 pg/mL |
| **Upper limit of quantitation:** | 500 pg/mL |
| **Minimum required dilution:** | 2-fold |
| **Capture reagent:** | Rat antibody against human IL-5 |
| **Detection reagent:** | Biotinylated mouse antibody against human IL-5 |
| **Precision and accuracy (PA) for standards of 6 PA runs:** | Precision (%CV) = 0.3%–5.5%<br>Accuracy = 99.8%–105.3% |
| **Inter-assay precision and accuracy for standards of all runs:** | Precision (%CV) = 0.5%–6.3%<br>Accuracy = 97.7%–104.2% |
| **Validation samples (6 PA runs):** | Validation samples were prepared at 7.81, 25, 80, 375, and 500 pg/mL in human serum. |
| **Intra-assay precision and accuracy (bias) for validation samples:** | Precision (%CV) = 2.8%–13.8%<br>Bias (%RE) = −35.3%–26.2% |
| **Inter-assay precision and overall accuracy (bias) for validation samples:** | Precision (%CV) = 3.6%–24.0%<br>Bias (%RE) = −7.4%–14.4% |
| **Quality controls (QCs) in non-PA runs** | QCs were prepared at 25, 80, and 375 pg/mL in human serum. |
| **Overall precision and accuracy for QCs of all non-PA runs:** | Precision (%CV) = 8.2%–10.4%<br>Accuracy = 99.2%–105.2% |
| **Dilution integrity:** | Up to 1200-fold dilution:<br>Precision (%CV) = 3.2%–8.7%,<br>Accuracy = 109.8%–112.7% |
| **Prozone effect:** | Prozone effect was not observed at 150,000 pg/mL of IL-5 in human serum. |
| **Selectivity:** | Selectivity was confirmed in individual lots of normal human serum and asthma human serum. |
| **Matrix effect:** | No significant matrix effect was observed in normal human serum and asthma human serum. |
| **Stability in matrix:** | Benchtop stability at room temperature: 5 hours.<br>Freeze-thaw (−80°C/room temperature) stability: 4 cycles<br>Long-term storage stability at −80°C: 1 week |
| **Specificity:** | No significant interference effects were observed for SB-240563 on the quantification of IL-5 in human serum. |
| **Experimental start date:** | 26 July 2016 |
| **Experimental end date:** | 04 August 2016 |
| **Validated test method:** | Alliance Pharma Bioanalytical Method 160527M.02V **(Appendix 1)** |

For assay runs to be acceptable, no more than one-third of the QC samples could deviate from the nominal concentration by more than 20% with %CV ≤ 20% In addition, at least 50% of the results from each QC concentration had to meet the aforementioned criteria for accuracy and precision. There are also additional assay acceptance criteria in place for the calibration curve accuracy and precision.

*Analytical methods for the evaluation of anti-drug antibodies (ADA)*

The initial HES study MHE100185 was supported with the 3rd generation binding ADA assay and 2nd generation NAb assay. The open-label study MHE100901 was supported with the 4th generation binding ADA assay and the 3rd generation NAb assay. The validated 3rd generation NAb assay was also used to support the clinical studies in the initial severe asthma application and the liquid mepolizumab application, before being validated. The 6th generation binding ADA assay included an anti IL 5 blocking antibody and was validated at GSK to support the clinical studies in the initial severe asthma application.

The 6th generation binding ADA assay and 3rd generation NAb assay were used to support HES studies 200622 and 205203. While studies 200622 and 205203 used the same binding ADA and NAb assays that supported the initial severe asthma application, the earlier assay formats were never bridged to allow for comparison of immunogenicity incidences between studies.

Clinical study MHE100185

The 3rd generation binding ADA assay was used which is a bridging immunoassay that employed 50 μl of human serum sample and equimolar amounts of biotinylated SB240563 and BV-TAG Plus labelled mepolizumab as bridging reagents. Immune complexes are bound to streptavidin-coated parametric particles and ECL is measured.

The method validation addressed the following parameters: precision (inter- and intra-), specificity, stability, drug tolerance and sensitivity. Assay precision was determined across low (80.0 ng/ml), mid (800 ng/ml) and high (8000 ng/ml) quality controls. Intra- assay precision (% CV) was ≤ 13.3% and inter-assay precision was ≤ 16.4%. Human serum samples containing low and high levels of anti-mepolizumab antibodies were stable (within 20% of untreated controls) following exposure of the samples to either 4 hours at room temperature or 1-5 freeze-thaw cycles. Drug tolerance curves indicate that the assay can measure positive antibody responses in the presence of approx. an 8-fold excess of mepolizumab. Antibody at 625 ng/ml was measurable in the presence of up to 5 μg/ml of drug and 2500 ng/ml antibody could be detected in the presence of up to 20 μg/ml of drug. The sensitivity of the method was approx. 100 ng/ml.

The assay cut point was determined using 60 human serum samples. The (signal to background) S:B ratios of the samples related to the negative control pool were statistically evaluated for estimation of the positive/negative cut-off. Five samples were excluded as outliers, based on their values exceeding the mean + 3 SD value for the assay. The remaining samples were used to define the cut-point as the highest S:B ratio that would achieve the desired 5% false positive rate. The assay cut point was defined as 1.97, which is very close to the theoretical mean + 1.65SD (95th percentile statistic). The confirmation cut point is defined as ≥ 40% inhibition in the presence of excess drug. Titer was defined as the reciprocal of the last dilution at which the sample measured above the 1.97 cut-point.

Clinical study MHE100901

The 4th generation binding ADA assay (TLIAM-0084) was used to screen samples from study MHE100901. According to this method, diluted samples are incubated with biotinylated mepolizumab and ruthenylated ("sulfo tag") mepolizumab. Bridging immune complexes are formed if ADA is present. The incubated sample is transferred to a streptavidin coated MSD plate and read buffer is added which causes the sulfo tag to produce a chemiluminescence signal when voltage is applied. Samples are

considered negative if the response is less than or equal to the assay cut point. Positive samples are tittered and/or confirmed by a drug inhibition assay.

**Table 5 : Method validation summary for ADA assay TLIAM-0084**

| **Anti mepolizumab antibodies VALIDATION SUMMARY** | |
|---|---|
| Species/Matrix: | Human Serum |
| Analysis Method: | ECL on Meso-Scale Discovery platform |
| Data Management: | |
| Data Capture of ECL | Meso-Scale Discovery Workbench 3.0 |
| Additional Data Analysis and Calculations: | Microsoft® Office Excel 2003 |
| Cut point Analysis | 90 individual sera analyzed three times |
| Screening Cutoff | 1.204 for healthy individual human serum samples<br>1.221 for HES patient sera |
| The % Inhibition Confirmation Cutoff | 70.7849 |
| Minimum Required Dilution | 1:10 |
| Precision of Antibody of PTC (1 µg/mL) – Titration (Sensitivity) | |
| Intra- Assay Positive Screen Control – Precision – | Hi = 0.40-12.41%; Mid = 0.02 – 11.29 %; Low = 0.00 – 9.74 %; Negative = 0.00–49.19 % |
| Inter- Assay Positive Screen Control – Precision – | Hi = 2.68 %; Mid = 2.85 %; Low = 2.15 % ; Negative = 8.54 % |
| Method Sensitivity | Absolute = 1 ng/mL; Relative = 2 ng/mL |
| Drug Interference: | |
| Antibody Concentration ng/mL | Drug Concentration µg/mL |
| 312.5 | 182 |
| 156.3 | 104 |
| 78.13 | 88 |

| **Anti mepolizumab antibodies VALIDATION SUMMARY** | |
|---|---|
| Method Selectivity (Matrix Effect): | |
| (10 individual human serum samples) | |
| Selectivity Blanks (Unspiked Serum Samples): | 90 % of the samples classified as negative. |
| Selectivity Samples (Spiked at final concentration of 10 ng/mL): | 100 % of the samples classified as positive. |
| Specificity: | |
| Three Samples in presence of 0, 500 and 2000 ng/mL of anti-GSK315234A. | Little to no cross reactivity to anti-GSK315234A |
| Storage Stability in Matrix: | |
| Bench Top Stability | 22 hrs |
| 2 to 8 °C Stability | 7 Days |
| Freeze/Thaw Stability | 6 cycles |
| 30 Day stability | 30 Day stability demonstrated |

The screening cut point was determined using serum from 60 healthy donors and 30 HES subjects. Relative ECL data was provided, as the ratio of ECL/NC. Outliers were excluded using boxplots and Q-Q plots. The relative ECL data was log transformed and analysed using variance components analysis. The normality assumption is reasonably satisfied and the cut off was then derived at the 5% false positive rate (95$^{th}$ percentile around normal distribution). The confirmation cut point was calculated using the parametric approach to determine the upper 99% limit. To accomplish this, 20 randomly selected healthy individual human serum samples were spiked with PC antibodies at the relative sensitivity level with and without drug.

Clinical studies 205203 and 200622

The ADA method used is the same as the method used during the line extension for the liquid formulation although minor revisions have been made throughout the method. The sample analysis reports for studies 200622 and 205203 are provided in documents 2019N407648-00 and 2019N407651-00, respectively.

*Analytical methods for evaluation of neutralising antibodies (NAbs)*

Clinical study MHE 100185

The 2nd generation NAb was used to evaluate samples during clinical study MHE100185. This is a competitive ligand-binding neutralising antibody assay. According to the method, test samples (and controls) are incubated with a ruthenium-labelled mepolizumab. After incubation, samples are mixed with biotinylated recombinant human IL-5. Subsequently, streptavidin coated magnetic beads are added to the wells of the plate. The plate was read on a Bioveris M384 analyser and ECL units were measured.

The method was validated for the following parameters: precision (intra- and inter-), linearity (156 ng/ml – 10,000 ng/ml), range, sensitivity and drug interference. Two independently prepared PC-spiked samples (HQC 12.0 μg/ml and LQC 2.4 μg/ml) were titrated and run in an assay on 3 different days by 2 analysts. An intra-assay precision of < 20% CV was obtained for PC concentrations ranging from 750- 37.5 ng/ml (final assay concentration). An inter-assay precision of <20% CV was obtained with PC concentrations ranging from 1500 – 37.5 ng/ml (final assay concentration). The lowest PC standard (156 ng/ml final assay concentration) was set as the sensitivity value. At a PC concentration of 4 μg/ml, the presence of 2 μg/ml unlabelled drug interfered with the detection of the PC. At a PC concentration of 20 μg/ml, no false negatives were generated at any of the tested drug concentrations (3.9 - 125 μg/ml). However, drug concentrations greater than 15.6μg/ml generated a false positive signal of the negative control. Clinical samples containing drug levels greater than 15.6 mg/ml must be diluted prior to testing in the assay.

During screening cut point determination, 44 sera from normal human donors were analysed on 3 different days by at least 2 analysts. The distribution of the data was analysed and determined to be normal. A parametric cut point of 79.6% was determined using the 95th percentile.

**Clinical study MHE100901**

The validated 3rd generation NAb assay was used. This is the same assay that was used to support the clinical studies in the initial severe asthma application and the liquid mepolizumab application.

**Clinical study 200622**

The validated 3rd generation NAb assay was used. A summary of the method validation is presented below in **Table 6**.

**Table 6 : Summary of method validation for method M1707047 (version 3)**

| | |
|---|---|
| **Study Title:** | Validation of an Electrochemiluminescence-Based Method for the Detection of Anti-SB-240563 Neutralizing Antibodies in Human Serum |
| **Analyte:** | Anti-SB-240563 Neutralizing Antibodies |
| **Matrix:** | Human serum |
| **Type of assay:** | Electrochemiluminescence (ECL) immunoassay |
| **Minimum required dilution:** | 1:8 |
| **Intra-assay precision (%CV) for quality control samples:** | Negative control (NC, 0 µg/mL): 0.28% to 5.99%<br>Low quality control (LQC, 1.016 µg/mL): 2.29% to 5.75%<br>High quality control (HQC, 10.164 µg/mL): 2.67% to 8.33%<br>Background control (BC, 0 µg/mL, no drug): 4.55% to 13.04% |
| **Inter-assay precision (%CV) of quality controls (6 batches):** | NC (0 µg/mL): 10.14%<br>LQC (1.016 µg/mL): 14.64%<br>HQC (10.164 µg/mL): 12.94%<br>BC (0 µg/mL): 16.00% |
| **Neutralizing cutpoint:** | 85.75% |
| **Sensitivity:** | 0.494 µg/mL |
| **Acceptance criteria for negative control and quality controls:** | NC: ECL >10448.28<br>LQC: %Response <71.12%<br>HQC: %Response <1.06%<br>BC: %Response <0.33% |
| **Acceptable drug tolerance levels:** | Tolerated free drug concentration sensitivity limits:<br>≤1 µg/mL of drug at an assay sensitivity of 1.289 µg/mL of the positive control (PC)<br>≤2 µg/mL of drug at an assay sensitivity of 1.564 µg/mL of PC<br>≤4 µg/mL of drug at an assay sensitivity of 3.217 µg/mL of PC |
| **Acceptable IL-5 interference levels:** | No significant IL-5 interference was observed up to 2000 pg/mL of IL-5 |
| **Stability in matrix:** | Benchtop stability at room temperature: 26 hours<br>Freeze-thaw (−70°C/room temperature) stability: 6 cycles<br>Short-term storage stability at 4°C: 75 hours<br>Long-term storage stability at −70°C: 91 days<br>Long-term storage stability at −20°C: 48 days |
| **Experimental start date:** | 26 April 2018 |
| **Experimental end date:** | 25 July 2018 |
| **Validated test method:** | Alliance Pharma Bioanalytical Method 1707047M.02V (Appendix 1) |

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor

complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

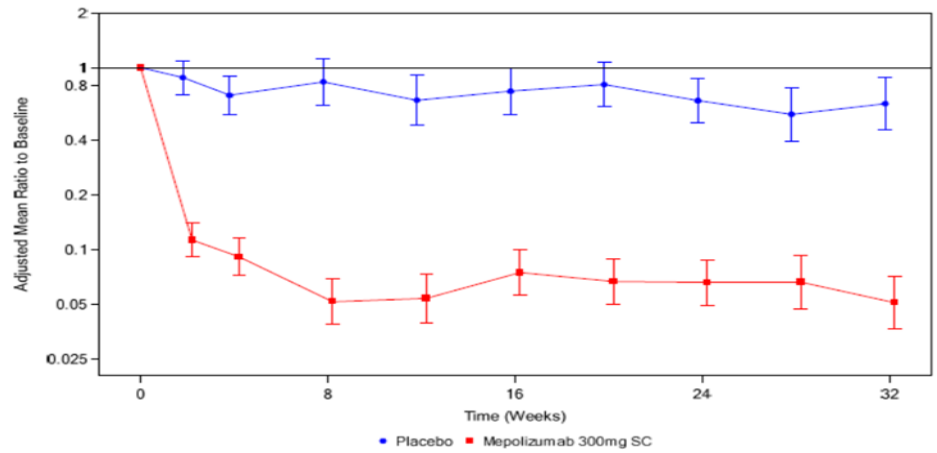
## *Primary pharmacology*

Mepolizumab produces a sustained, consistent, dose-dependent reduction in blood eosinophil count, irrespective of disease, age, baseline blood eosinophil count, or administration route, with maximum eosinopenia of approximately 90% due to IL-3 and granulocyte macrophage colony-stimulating factor (GM-CSF) redundancy. The blood eosinophil dose-response is well-characterised, validated by independent data, and supported the rationale for dose selection in pivotal Phase III studies across various eosinophilic conditions, including Study 200622.

***Study 200622:*** *A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome*

At baseline, geometric mean blood eosinophil levels were similar in the mepolizumab (1460 cells/µL) and placebo (1350 cells/µL) treatment groups. At the first post-dose assessment (Week 2), the geometric mean in the mepolizumab group showed a marked decline from baseline to 170 cells/µL compared with a slight initial decline in the placebo group (1260 cells/µL). The reduction in blood eosinophils observed at Week 8 in the mepolizumab group was maintained overall through Week 3 (see below):

**Figure 7: Ratio Compared to Baseline in Blood Eosinophil Count (Study 200622, While on Treatment Estimand, PD Population)**




At Week 32, subjects treated with mepolizumab had a 92% reduction in blood eosinophils compared with subjects receiving placebo (see below), with a geometric mean absolute count of 70 cells/µL. At the end of the 32-week Treatment Period, blood eosinophil levels remained slightly decreased from baseline in the placebo group.

| Blood Eosinophil Level at Week 32 | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
|---|---|---|
| n[a] | 54 | 54 |
| n[b] | 49 | 47 |
| LS mean (SE logs) | 0.90 (0.169) | 0.07 (0.170) |
| LS mean ratio to Baseline (SE logs) | 0.63 (0.169) | 0.05 (0.170) |
| Comparison mepolizumab 300 mg vs. placebo | | |
| Ratio | | 0.08 |
| 95% CI | | (0.05, 0.13) |
| p-value | | <0.001 |

a. Number of subjects with analyzable data for one or more time points
b. Number of subjects with analyzable data at the given time point.

Notes:

- Analysis performed using mixed model repeated measures with covariates of baseline eosinophil count (log scale), baseline OCS dose, region, treatment and visit, plus interaction terms for visit-by-baseline eosinophil count and visit-by-treatment group. LS mean estimates are weighted according to the observed proportion of each categorical covariate in the study data.
- Data were log transformed prior to analysis. Where a result of zero was recorded, a small value (0.005) was added prior to log transformation.

Abbreviations: CI=confidence interval; LS=least square; SE=standard error.

*Total Serum Interleukin-5 (IL-5)*

At baseline, geometric mean total serum IL-5 levels were similar in the mepolizumab (5.51 ng/L) and placebo (7.72 ng/L) treatment groups. At Week 32, the geometric mean in the mepolizumab group showed a marked increase to 166.07 ng/L and total serum IL-5 showed little change from baseline in the placebo group (6.38 ng/L). The increase in the mepolizumab group was anticipated considering the assay was measuring both free IL-5 and IL-5 bound to mepolizumab.

Results of the Wilcoxon Rank Sum test (median total IL-5) demonstrated a statistically significant difference between the mepolizumab and placebo treatment groups in the ratio to baseline of serum total IL-5 at Week 32 (median ratio 29.71).

### *Secondary pharmacology*

Mepolizumab does not bind to the hERG channel and QT-mediated pro-arrhythmia due to blockade is not a concern with mAbs due to their very high molecular weight. In clinical studies there were no adverse effects on cardiac conduction or repolarisation at doses in excess of the proposed marketed dose in the various indications. Furthermore, a concentration-response analysis did not show any effects of mepolizumab on QT interval corrected for heart rate (QTc). A thorough QTc study has not therefore been conducted.

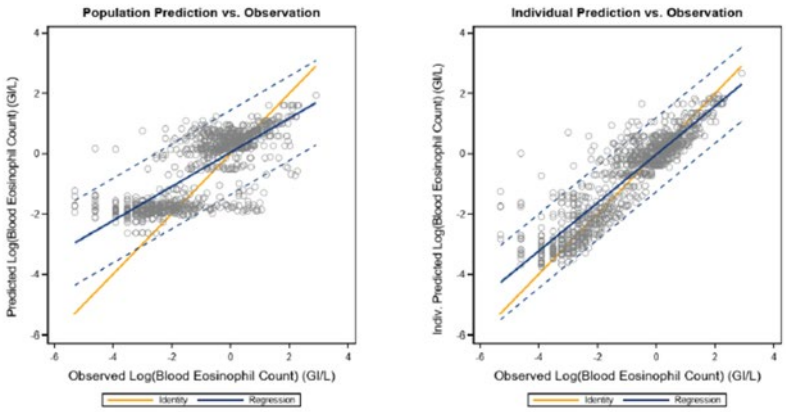
## 2.3.4. PK/PD modelling

A PK/PD analysis was conducted to investigate whether the blood eosinophil response to mepolizumab treatment in patients with HES was consistent with the response observed in patients with other eosinophilic conditions. 108 patients with HES from the pivotal Phase III study 200622 were included in the PKPD dataset. Post-hoc individual predicted mepolizumab concentrations were merged with blood eosinophil count data before model fitting.

Considering the small sample size of each treatment group in the study (54 subjects/treatment group) and the narrow range of values for some covariates, the covariate investigation is overall considered of limited value. With the exception of the baseline blood eosinophil count effect, which was already included as a covariate in the model, on baseline blood eosinophil count (KRO) and maximum effect (Imax), there was no apparent obvious trend in any other covariates. No refinement of the model was therefore deemed necessary.

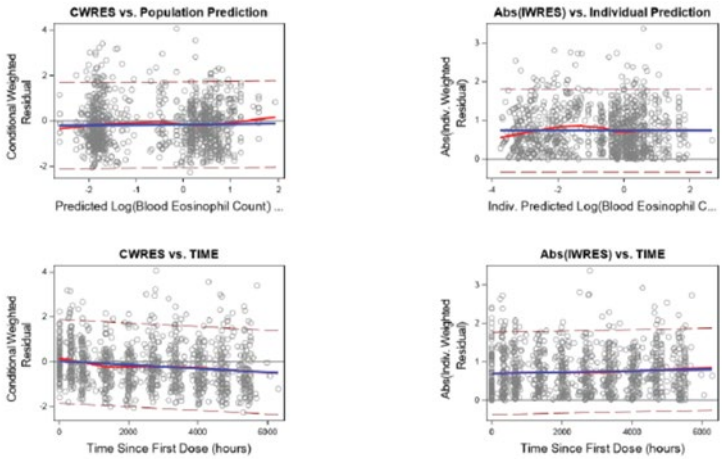
Goodness of fit for the model, as demonstrated by conventional plots and NPDE, are shown below:

**Figure 8: Goodness of Fit Regression**



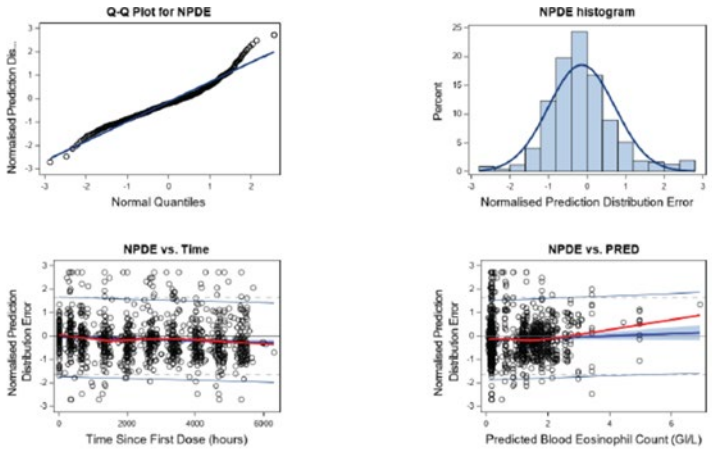

Plots show linear regression with 95% prediction interval (dashed lines)

**Figure 9: Goodness of Fit Regression (Summary Plots)**




CWRES = Conditional weighted residuals, IWRES = Individual weighted residuals

**Figure 10: Normalised Prediction Distribution Error**



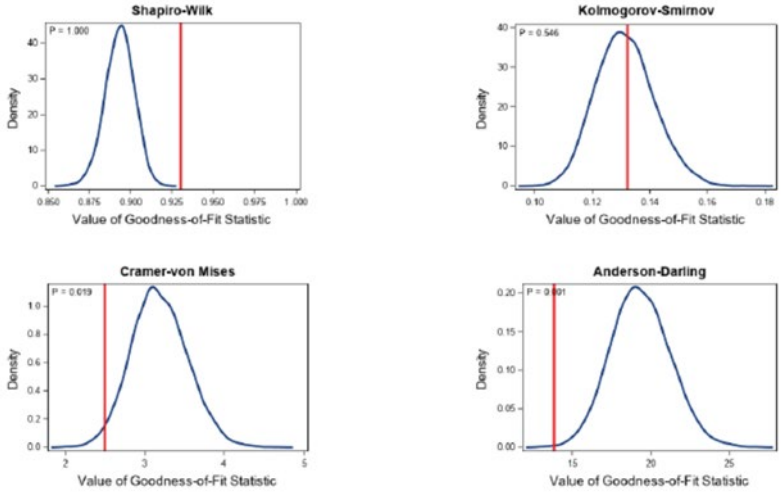

Plots show linear regression (blue) with 95% prediction interval (dashed lines) and loess regression (red)

In order to further evaluate the concordance between the predicted and observed blood eosinophil counts in the study, individual blood eosinophil count predictions were generated against which the model was validated prospectively using the following more stringent goodness of fit tests: Shapiro-Wilk, Kolmogorov-Smirnov, Cramér–von Mises and Anderson-Darling. The tests were applied to placebo and mepolizumab datasets separately.

Based on the Shapiro-Wilk (location) test for the placebo data and the Kolmogorov- Smirnov (location) test for the mepolizumab data, there was no evidence to suggest that the observations and predictions were drawn from different distributions at the 5% significance level.

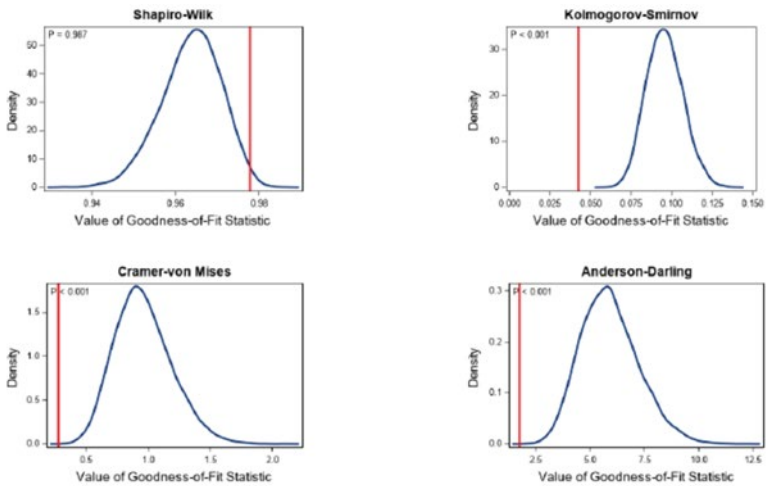
By contrast, based on the Cramér–von Mises and Anderson-Darling tests (which are tests sensitive to distribution tails), Shapiro-Wilk test (mepolizumab data only), and Kolmogorov-Smirnov test (placebo data only) it was not possible to reject (at the 5% +significance level) the null hypothesis that the observations and predictions are drawn from different distributions. Inclusion of imputed data (0.005 in place of 0), digit bias (values recorded to two decimal places), spikes in observed blood eosinophil count, and effects of blinded OCS treatment on eosinophil production during the study, most likely contributed to these results.

**Figure 11: Mepolizumab PKPD Model Goodness of fit Statistics Showing Observation (red)**




Distributions derived from 10000 bootstrap simulations of the model predictions

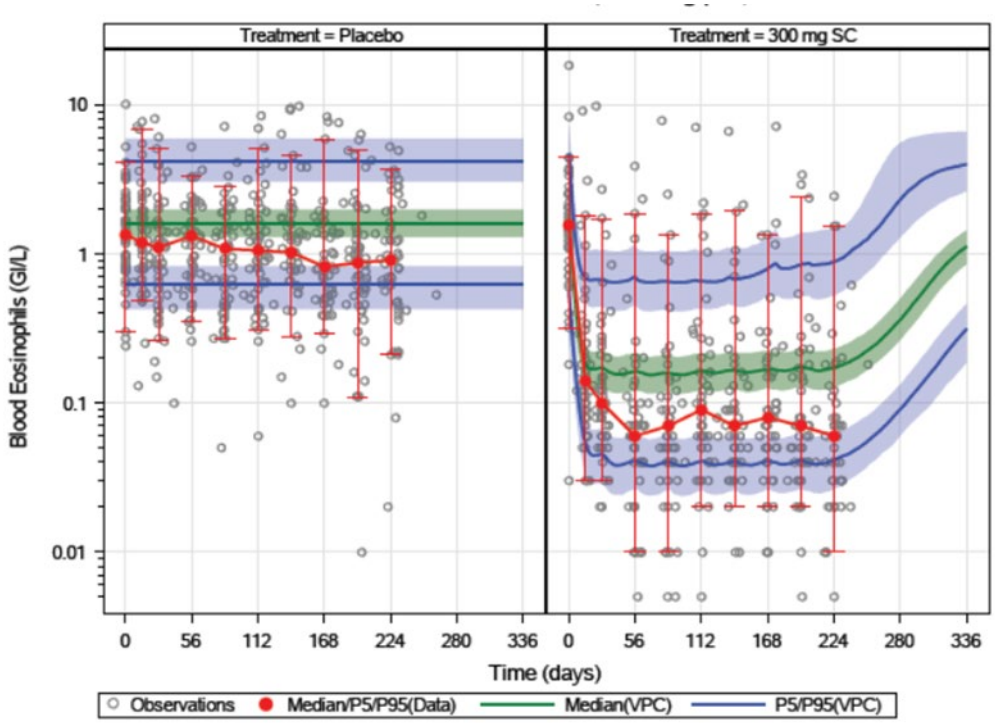
**Figure 12: Placebo PKPD Model Goodness of fit Statistics Showing Observation (red)**




Distributions derived from 10000 bootstrap simulations of the model predictions

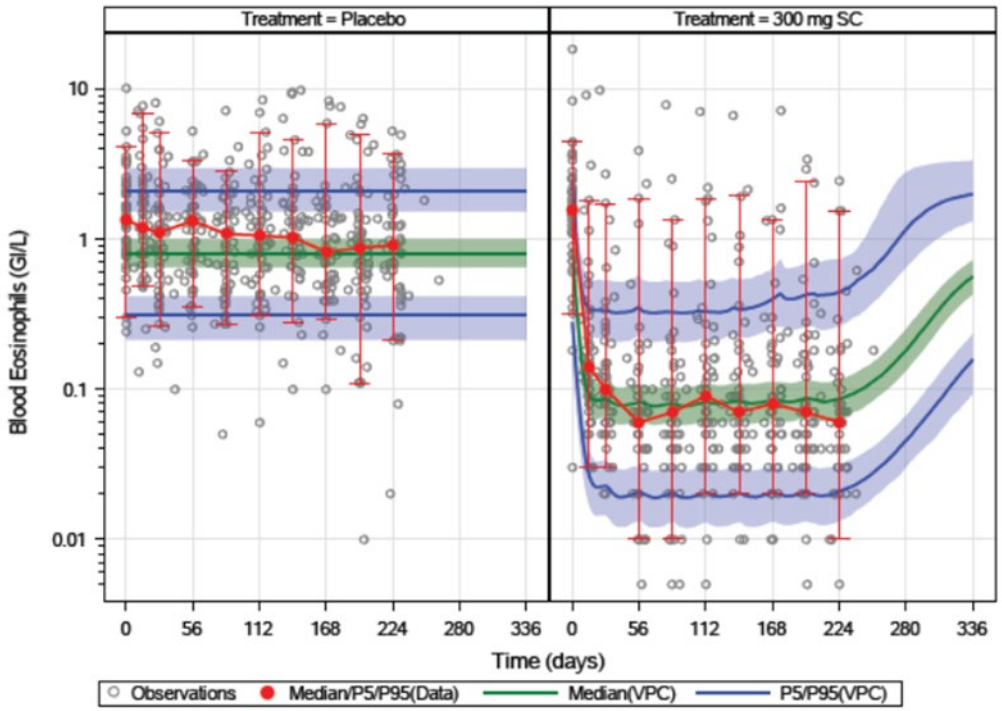
Final model performance was also assessed using VPC (see below), with incorporation of parameter uncertainty and bootstrap resampling of subject covariates.

**Figure 13: Model Visual Predictive Check (Semi-log plot)**




In order to reflect the baseline blood eosinophil count of the HES population enrolled into the study (much higher than in any other studies conducted with mepolizumab across indications) a factor of 2 for baseline count was applied (see below).

**Figure 14: Model Visual Predictive Check (Semi-log plot) – adjusted baseline**




Statistical tests only consider the statistical significance of the effect, which might, however, be too small to be of clinical significance. It is therefore recommended to interpret those results in conjunction with for example a Q-Q plot. Based on the totality of evidence, including visual predictive checks and

goodness of fit plots (including Q-Q plot), and in the context of a PD endpoint subject to considerable variability, it was concluded that the model was able to appropriately predict blood eosinophil counts in an HES population with high baseline blood eosinophil count following SC administration.

## 2.3.5. Discussion on clinical pharmacology

A single pivotal study (Study 200622) was conducted to support the proposed posology of 300 mg SC administered every 4 weeks in hypereosinophilic syndrome (HES) in which sparse PK sampling was taken. Mepolizumab PK data was analysed using the most recent population PK model, which it should be noted includes data from a HES IV administration study, Study MHE100185). It is accepted, based on the statistical tests employed, that at the 5% significance threshold there was no evidence that predicted and observed plasma concentrations were drawn from different distributions.

However, based on a visual inspection the GOF plots, the meta-analysis model does not appear to fit the HES data particularly well, especially at the population level. The VPC also suggests that the meta-analysis model does not predict the observed concentrations in HES patients particularly well. However, it is accepted that the clinical relevance of the apparent variability and poor model is likely to be low, and as such this issue has not been pursued further.

Although age was not considered a clinically relevant covariate in the population PK model, only one adolescent subject in study 200622 was dosed with mepolizumab. The single adolescent subject included in the mepolizumab arm in study 200622 exhibited exposures in the upper end of the range observed in the study and exhibited a marked reduction in eosinophils at week 4. The limited data available do not indicate an age-related difference in PK in the HES population.

Following treatment with 300 mg mepolizumab SC blood eosinophils were markedly reduced, this was maintained for the duration of the trial.

The MAH provided supportive evidence that subcutaneous administration of mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. This is added in section 5.2 of the SmPC.

The most recent meta-analysis PKPD mode) was applied to the PK/PD data collected from patients with HES in study 200622, without adjustment. No new relevant covariates were identified. The GOF plots indicated that the PKPD model did not fit the HES data particularly well. This was confirmed by several statistical goodness of fit tests, which were not able to reject the null at the 5% significance threshold that predicted and observed plasma concentrations were from different distributions. This suggests that the PD response to mepolizumab in subjects with HES may not be similar to other eosinophilic conditions. The VPCs also suggested that the meta-analysis model, without adjustment, does not predict well the reduction in eosinophil count with mepolizumab treatment in patients with HES but the data appear to fit better when an adjustment factor based on the higher blood eosinophil count of the HES population is applied.

The MAH argues the totality of the data, when taking into consideration the high variability of the PD endpoint is sufficient to conclude that the model could adequately predict blood eosinophil levels. They have submitted acceptable justification for the correction factor of 2 which was applied to baseline eosinophil counts which did improve the model fit. Additional data on additional goodness of fit statistical tests does not alter the previous assessment. It is accepted that as the model is not being used for extrapolation in this indication, that efficacy has been assessed in the target population and that the model fit is unlikely to have clinical implications. This issue can thus be considered resolved.

### 2.3.1. Conclusions on clinical pharmacology

The clinical pharmacology has been sufficiently characterised in the proposed indication.

## *2.4. Clinical efficacy*

### 2.4.1. Introduction

The original marketing authorization procedure for the treatment of patients with HES (EMEA/H/C/001069/00) was submitted in September 2008. This application was withdrawn in July 2009 as it was considered that the submitted data was insufficient to grant the marketing authorization. Although studies MHE100185 and MHE100901 were assessed during the original procedure (EMEA/H/C/001069/00), for completeness the results of this assessment is presented in the supportive studies section of this assessment report

The MAH submitted a single pivotal placebo-controlled Phase III study, 200622 in support of this marketing authorization application. This study is supplemented with efficacy data from the OLE study 205203. Studies MHE100185 and MHE100901 were also provided by the MAH however, due to differences in patient population, endpoints, eosinophil blinding, and mepolizumab doses the role of these studies in support of this application is limited.

### 2.4.2. Dose response study(ies)

A dose of mepolizumab 300 mg administered SC every 4 weeks was selected for investigation in this study. The dose selected was lower than the 750 mg intravenous (IV) dose administered every 4 weeks previously investigated in a HES study (MHE100185). The dose selection was guided by information observed during the uncontrolled phase of an open-label extension HES study MHE100901 during which dosing interval was tailored (4 to 12 weeks) according to individual patient disease and response, including blood eosinophil count assessment.

In support of the dose selection, a dose-response meta-analysis for blood eosinophil reduction (a proxy marker of pharmacology), including data from 16 studies and various eosinophilic conditions, albeit dominated by asthma, was carried out. Results highlighted differences between severe asthma and HES populations and confirmed the effects of OCS on blood eosinophil suppression in both diseases. Dose- response models confirmed that baseline blood eosinophil count is an important determinant of overall response, with both location and maximum achievable drug inhibition being baseline-dependent. Inversion of the dose response showed that to achieve clinically meaningful target absolute blood eosinophil counts in patients with HES, doses higher than the therapeutic severe asthma dose of 100 mg SC were required. Although HES experts recognized that there is no universal blood eosinophil level or degree of suppression cut-off at which clinical benefit would be expected in all HES patients, considering that the current therapeutic option aims to maintain blood eosinophils as low as possible, it was not unreasonable to target a level within a normal range, i.e., <500 cells/µL and ideally between 200-300 cells/µL in the majority of HES patients. Acknowledging the limitations of extrapolation outside the range of data included in the dose-response model (to adjust for the effects of concomitant OCS treatment), it was predicted that patients with a baseline blood eosinophil count between 1000 (minimal level required at baseline in the proposed study) and 8000 cells/µL would achieve a blood eosinophil count between 100-500 cells/µL following a SC dose of mepolizumab 300 mg every 4 weeks

## 2.4.3. Main study

**Title of Study : Study 200622**

**A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome.**

### *Methods*

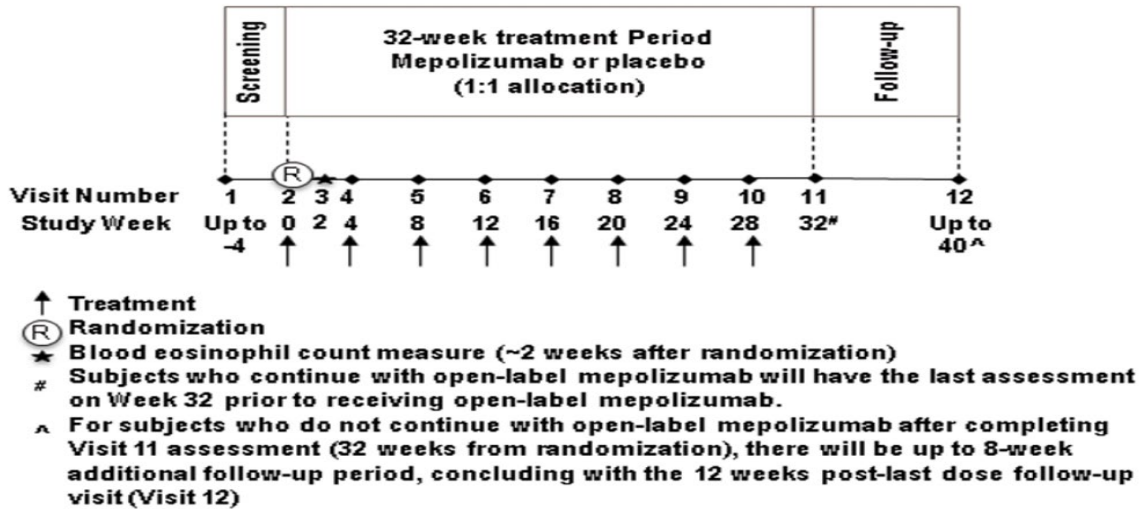
This was a 32-week, randomised, double-blind, placebo-controlled, parallel group, multi- centre study. Subjects were randomized 1:1 to receive either placebo or mepolizumab 300 mg subcutaneous (SC) every 4 weeks in addition to their maintenance HES treatment.

This study consisted of 3 periods:

- Screening: approximately 4 weeks
- Double-blind Treatment Period: 32 weeks
- Follow-up: 8 weeks (subjects that enrolled into the open label extension did not require a follow-up visit).

Subjects that completed the 32-week treatment period were eligible to screen for a 20- week open label extension (study 205203) where all subjects received mepolizumab 300 mg SC every 4 weeks.

**Figure 15: Study Schematic**




## Study participants

**Inclusion criteria**

- Male or female subjects ≥12 years of age diagnosed with HES for at least 6 months at randomization (Visit 2). HES diagnosis was based on signs or symptoms of organ system involvement and/or dysfunction that could be directly related to:
  - blood eosinophilia of >1500 eosinophils/µL on at least 2 occasions, and/or

- tissue eosinophilia documented prior to Visit 2 without a discernible secondary cause (e.g., drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus [HIV] infection, non-hematologic malignancy.

Tissue eosinophilia was defined as a history of one or more of the following:

- The percentage of eosinophils exceeded 20% of all nucleated cells in bone marrow sections.
- In the opinion of a pathologist, tissue infiltration by eosinophils was extensive (massive) when compared with the normal physiologic range, compared with other inflammatory cells, or both.
- A specific stain directed against an established eosinophil granule protein (e.g., major basic protein) revealed extensive extracellular deposition of eosinophil-derived proteins indicative of local eosinophil activation

- A history of 2 or more HES flares within the past 12 months prior to Screening (Visit 1). Historical HES flares were defined as documented HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. At least one HES flare within the past 12 months must not have been related to a decrease in HES therapy during the 4 weeks prior to the flare.
- Subjects must have had blood eosinophil count ≥1000 cells/μL present in the sample collected during Screening (within 4 weeks prior to randomization).
- Subjects must have been on a stable dose of HES therapy for the 4 weeks prior to randomization (Visit 2). HES therapy included but was not limited to OCS, immunosuppressive, and cytotoxic therapy.

**Exclusion criteria**

- Life-threatening HES or life-threatening HES co-morbidities: Imminently life-threatening HES disease severity such that the likelihood of death was high unless the course of the disease was interrupted within 12 weeks prior to randomization (Visit 2).
- Eosinophilia of unknown clinical significance.
    - 12-lead ECG finding:
    - QTc > 450 msec or QTc > 480 msec in subjects with bundle branch block
    - An abnormal ECG finding from the 12-lead ECG conducted at Visit 1 if considered to be clinically significant and would impact the subject's participation during the study based on the evaluation of the investigator.
- Documented history of any clinically significant cardiac damage prior to Screening (Visit 1) that, in the opinion of the investigator, would impact the subject's participation during the study.
- Malignancy:
    - history of or current lymphoma
    - current malignancy or previous history of cancer in remission for less than 12 months prior to randomization (Visit 2); localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure was not excluded
- FIP1L1-PDGFRα(F/P) Status: Positive for the F/P fusion tyrosine kinase gene translocation.
- Infection:

- chronic or ongoing active infections requiring systemic treatment, as well as clinically significant infections due to viruses, bacteria, and fungi within 4 weeks prior to randomization (Visit 2)
- pre-existing helminthes infestation within 6 months prior to randomization (Visit 2)

- Previous mepolizumab treatment in the 4 months prior to randomization (Visit 2).
- IV or SC corticosteroids in the 4-week period prior to randomization (Visit 2).
- Any other mAbs within 30 days or 5 half-lives, whichever was longer, of randomization (Visit 2).
- Liver abnormality/disease:
- ALT >2.5xULN or ALT>5xULN if documented HES with liver manifestations
- Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
- Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

NOTE: Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria.

## Treatments

In the study patients received either placebo or mepolizumab 300 mg subcutaneous (SC) every 4 weeks in addition to their maintenance HES treatment.

**Table 7: Mepolizumab Study Treatment**

| | **Mepolizumab Study Treatment** |
|---|---|
| **Product name:** | SB240563 (mepolizumab) |
| **Formulation description:** | Mepolizumab 100 mg vial for injection delivers 100 mg mepolizumab and approximately 7.14 mg sodium phosphate dibasic heptahydrate, 0.67 mg polysorbate 80 and 160 mg sucrose. |
| **Dosage form:** | Lyophilized powder for injection reconstituted with Sterile Water for Injection, just prior to use. |
| **Unit dose strength(s)/Dosage level(s):** | 3 vials (100mg/vial) per administration |

| | **Mepolizumab Study Treatment** |
|---|---|
| **Batch number(s):** | • 5503<br>• 6502 |
| **Route of Administration** | 3 SC injections per administration |
| **Dosing instructions:** | Subjects were dosed with three 100 mg SC injections every 4 weeks in accordance with the randomization schedule.<br><br>Injections were administered into the abdomen, upper arm, or thigh. |

**Placebo**

The placebo in this study was 0.9% sodium chloride (saline) solution and was provided by the investigational site. Three SC injections were administered every 4 weeks into the abdomen, upper arm, or thigh in accordance with the randomization schedule.

**Blinded OCS**

GSK provided blinded OCS for this study. Each bottle had a unique identifier number and contained either 5 mg OCS (prednisolone capsules) or matching placebo capsules.

**Prior and Concomitant Medications and Non-Drug Therapies**

**Permitted Medications and Non-Drug Therapies**

**Standard HES Therapy**

Use of standard HES therapy including OCS, immunosuppressive or cytotoxic therapy (e.g., hydroxyurea, IFNα, cyclosporine, imatinib, methotrexate, azathioprine) was permitted during the study. Subjects must have been on a stable dose of HES therapy for the 4 weeks prior to randomization (Visit 2). The same regimen of HES therapy must have been maintained throughout the 32-week Treatment Period unless there was worsening of symptom(s) that required an increase in therapy. If a subject had worsening

of symptom(s) and required an increase in therapy after randomization, the subject was considered to be experiencing a flare. Once the subject regained disease control, the investigator was encouraged, as medically appropriate, to adjust the dose of HES therapy back to the level prior to the disease worsening.

A reduction in standard HES therapy dose for safety reasons, with return to the original dosing regimen when possible, was permitted in consultation with the GSK Medical Monitor.

**Non-HES Related Medical Conditions**

Additional therapies required to treat non-HES related medical conditions during the study were permitted in consultation with the GSK Medical Monitor and must have been prospectively captured in the eCRF.

**Prohibited Medications and Non-Drug Therapies**

Initiation of new medications or herbal remedies which may alter the course of HES or interact with the study treatment was prohibited within their specified timeframe and throughout the study (Visit 0 to Visit 11 inclusive) with the exception of HES therapy to treat a HES flare.

In addition, the following medications were prohibited:

- any investigational agents (biologic or non-biologic) within the 30 days or 5 drug half-lives whichever was longer, prior to Screening (Visit 1), and until Visit 11
- any other biologic agents (except for IFNα): within 30 days or 5 half-lives, whichever was longer, of Screening (Visit 1), and until Visit 11.

## Objectives

### Primary objective

The primary objective of the study was to evaluate the efficacy and safety of mepolizumab for the treatment of subjects 12 years and older with HES receiving standard of care therapy.

### Secondary objective

The secondary objective was to demonstrate supportive evidence of the benefit of mepolizumab compared with placebo based on other measures of efficacy.

## Outcomes/endpoints

### Primary Efficacy Endpoint

The primary endpoint was the proportion of subjects who experienced a HES flare during the 32-week Treatment Period.

### Secondary Efficacy Endpoints

- time to first HES flare
- proportion of subjects who experienced a HES flare during Week 20 through Week 32
- rate of HES flares
- change from baseline in fatigue severity (Brief Fatigue Inventory [BFI]) item 3 (worst level of fatigue during past 24 hours) at Week 32

### Exploratory Efficacy Endpoints

- proportion of subjects who had an elevated blood eosinophil level that met the pre-defined threshold during the 32-week Treatment Period
- lung function tests
  - ✓ change from baseline forced expiratory volume in 1 second (FEV1) at each visit
  - ✓ change from baseline forced vital capacity (FVC) at each visit
  - ✓ FEV1/FVC at each visit
- echocardiogram scans at Screening and Week 32
- change from baseline in HES symptom severity based on HES Daily Symptoms (HES-DS) at Week 32
- change from baseline in BFI total and domain scores at Week 32
- clinician- and subject-rated overall response to therapy score (RTS) at Week 32
- change from baseline in Subject-Rated Symptom Severity (SSR) at Week 32

Definitions

### HES flare

In this study, disease flare (HES flare) was defined as (1) a HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms resulting in the need for therapy adjustment (increase in OCS dose of at least 10 mg/day or any increase in or addition of any cytotoxic/immunosuppressive HES therapy) or (2) receipt of 2 or more courses of blinded active OCS during the treatment period.

An increase in blood eosinophils above the pre-defined threshold level (2 x baseline value or baseline value + 2500 cells/μL) without any other clinical manifestations during the study led to administration of blinded active OCS treatment. If a subject received a 2nd course of blinded active OCS during the

32-week Treatment Period, the subject was considered to be experiencing a flare. The container list for the blinded OCS treatment (indicating which container numbers contained active OCS and which contained placebo OCS) was used to define HES flares meeting endpoint definition b). Subsequently, the date of the first blood draw at which blood eosinophil count was below the threshold to trigger blinded active OCS was considered the resolution date. Each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare was considered as an additional flare (e.g., 3 courses of blinded active OCS were considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

**HES Core Assessments to Monitor Disease Activities and Identify HES Flares during the Study:**

The clinical presentation of HES covers a wide variety of end-organ manifestations. In an effort to assess the clinical manifestations in the most commonly affected organ systems in patients with HES, the HES Core Assessments was utilized by the investigators to characterize the disease at Baseline and also to monitor the changes during the treatment period. This core assessment is the product of collective input from a panel of experts in the field and provided the consistent framework for the investigators to assess a HES flare. The HES Core Assessments tool was used to record the subject's clinical manifestations, but ultimately investigators used their clinical judgment to determine if a subject was experiencing a HES flare.

**Table 8: HES Core Assessments**

| Symptoms | Assessment |
|---|---|
| **Constitutional** | |
| Fatigue<br>Pain (including but not limited to muscle, joint, general pain)<br>Angioedema (swelling under the skin) | Each symptom rated using a 0-3 scale |
| **Dermatologic** | |
| Rash<br>Itch<br>Hives<br>Others (specify) | Each symptom rated using a 0-3 scale |
| **Gastrointestinal** | |
| Average number of vomiting a day in the past week<br>Average number of diarrhea a day in the past week<br>Average number of stools a day in the past week<br><br>Abdominal pain<br>Difficulty in swallowing food | <br><br><br><br>Each symptom rated using a 0-3 scale |
| **Respiratory** | |
| Breathing symptoms such as shortness of breath and wheezing | 0-3 scale |
| Dyspnea (shortness of breath) | 0-3 scale |
| Cough | 0-3 scale |

| Symptoms | Assessment |
|---|---|
| *Sinus-related symptoms:*<br>Nasal congestion<br>Sinus headache/facial pain/pressure<br>Postnasal drip (drainage down the back of the throat)<br>Purulent rhinorrhea (discolored & thick nasal discharge)<br>Ear fullness | Each symptom rated using a 0-3 scale |
| **Cardiovascular** | |
| Heart failure classification for functional capacity | Classes I-IV |
| Heart failure classification for objective assessment | Classes: A-D |
| **Neurologic** | |
| Sensory<br>Motor<br>Cognitive and Mental status change | Each symptom rated using a 0-3 scale |
| **Others** | |
| Vascular, venous, arterial, loss of pulse, splinter hemorrhage, renal failure, splenomegaly, other (specify) | Each identified symptom rated using a 0-3 scale |

Source: Protocol 20622 Section 7.3.2, Table 3
Note: 0-3 scale symptom score: 0 for not present or no impact, 1 for present but minimal impact, 2 for significant impact on daily activities, 3 for incapacitating

**Brief Fatigue Inventory (BFI)**

The BFI is a tool developed for the rapid assessment of fatigue severity for use in both clinical screening and clinical trials. The BFI has 9 items. The subject rated their average and worst fatigue levels over the previous 24 hours using a numeri rating scale anchored with 0 (no fatigue/interference) and 10 (as bad as you can imagine/completely interferes) numeric rating scales. The subject completed one item of the BFI daily and the full BFI every 7 days at home on the eDiary.

**HES Daily Symptoms (HES-DS)**

The HES-DS includes 6 constitutional and organ system-specific symptoms commonly reported by patients with HES. Each item has a 11-point numeric rating scale with 0 indicating that the symptom was not present and 10 indicating symptom was worst imaginable. At the Randomization Visit (Visit 2), the subject identified up to 3 symptoms that were most bothersome and the results were recorded in the eCRF. At home, each of the 6 symptoms were rated daily on the eDiary; the symptoms were rated by the subject each evening recalling the worst symptom experience over the previous 24 hours.

## Sample size

An initial sample size of 80 subjects was estimated dependent on a pre-planned blinded sample size re-estimation. The pre-planned blinded sample size re-estimation was planned to be performed after at least 60 subjects had been randomized, to assess the overall proportion of subjects that had a HES flare during the 32-week Treatment Period. If, based on the pre-planned blinded analysis, the overall flare rate was predicted to be <30%, the sample size could be increased up to a maximum of 120 subjects in total. When 60 subjects had been randomized, the estimated blinded overall proportion who would have a flare by the end of the 32-week Treatment Period was between 25 and 27.5% and therefore the decision was made to increase the sample size to 50 subjects per am (100 in total).

## Randomisation

The randomization was stratified by region due to potential differences in SoC between regions.

An unblinded site staff member was assigned to the study to prepare the appropriate study medication according to the subject's treatment assignment. Subjects eligible to enter the study were assigned to treatment randomly through an interactive response technology (IRT), the Registration and Medication Ordering System Next Generation (RAMOS NG).

## Blinding (masking)

The effect of mepolizumab on blood eosinophil counts is rapid, readily observable, and may lead to inadvertent unblinding of the treatment assignment. Therefore, in this study, investigators, participating subjects, and MAH study personnel were blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from randomization (Visit 2) to the end of the study. Since initiating treatment based on an increase in eosinophil levels alone (without clinical symptoms) is part of SoC for HES patients, blood eosinophil-unblinded MAH personnel/delegates not involved with other aspects of study conduct monitored the absolute eosinophil count results and triggered blinded OCS treatment to treat an eosinophilia flare. This was to ensure that subjects were not be placed at undue risk during the study, while maintaining the treatment blind.

### Treatment Blinding

Mepolizumab and placebo were identical in appearance (blinded syringes) and were administered by a blinded member of the site staff. The blinded site staff administered 3 blinded syringes SC, each containing 100 mg/1 ml of investigational product (mepolizumab or placebo).

Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management or welfare of the subject. The MAH Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind treatment codes in the event of an SAE.

### Blood Eosinophil Blinding

Investigators, MAH personnel involved in the study, and subjects were blinded to the results of absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%). Subjects that had an increase in blood eosinophils above the pre-determined threshold (2 x Baseline value [randomization] or Baseline value + 2500 cells/ µL) were instructed to take OCS capsules. In order to maintain the blind, this treatment was with blinded OCS capsules.

All subjects were provided 2 bottles of blinded OCS capsules, one containing 5 mg OCS capsules (active OCS treatment) and a second one containing matching placebo capsules (placebo OCS treatment). These were dispensed to each subject at each scheduled clinic visit and as needed.

Blood eosinophil-unblinded MAH personnel/delegates not involved with other aspects of study conduct reviewed the results from the central laboratory for absolute blood eosinophil count. If the pre-specified threshold blood eosinophil level (i.e., 2 x Baseline value [randomization] or Baseline value + 2500 cells/ µL) was reached (eosinophilia flare), blood eosinophil-unblinded MAH personnel/delegates communicated with the investigator to initiate blinded OCS treatment from one of the bottles provided (active treatment) unless the subject's HES therapy (OCS, cytotoxic agent, or immunosuppressive agent) had already been increased due to a symptom flare within the past 2 weeks.

The subject administered the blinded OCS from the assigned bottle for approximately 2 weeks. A subject who did not reach the pre-specified blood eosinophil threshold with a similar blood draw date was selected to initiate a placebo treatment in a blinded manner, to maintain study blood eosinophil blinding.

Approximately 2 weeks after the scheduled clinic visit, the blood eosinophil count was assessed again for the subject who started blinded OCS (both active and placebo). The subject who was administered active blinded OCS was instructed to either continue with a new course of blinded OCS regimen from Day 1 (i.e., 40mg) until the next scheduled clinic visit if the blood eosinophil count was at or above the threshold (unless the subject's HES therapy [OCS, cytotoxic agent, or immunosuppressive agent] had been increased due to a symptom flare since the initiation of the current course of blinded OCS), or to discontinue blinded OCS if the blood eosinophil count was below the threshold.

For subjects taking placebo-blinded OCS, continuation/discontinuation of blinded OCS was determined depending on the continuation/discontinuation of their matched subject on active-blinded OCS.

From 11 January 2018 onwards, the process described above for continuation with new course or discontinuation of treatment was modified. When a subject's blood eosinophil count was assessed again after approximately 2 weeks and was still above/at the threshold, the investigational site was not instructed to initiate a new course but instead instructed to retain the subject on a dose of 5 mg.

## Statistical methods

### Changes to Planned Analyses

From the SAP, the following change is of particular interest as it appears to relate to the primary outcome:

- The following changes to the exploratory endpoints we made:

**Table 9:**

| Protocol Endpoint | Revision Endpoint | Rationale for Change |
|---|---|---|
| Proportion of subjects who receive blinded active OCS due to an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period | Proportion of subjects who have an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period | RAP endpoint considered to be more clinically meaningful as it included all subjects with blood eosinophil counts meeting the pre-defined threshold during the 32-week study treatment period rather than including only the subset of these subjects who receive blinded active OCS. Subjects did not receive blinded active OCS if their physician had already increased their HES therapy based on symptoms. |

**Analysis Populations**

**Primary endpoint**

The proportion of subjects who experienced a HES flare during the 32-week Treatment Period was analysed using a Cochran-Mantel-Haenszel test stratified by the covariates of region and baseline OCS dose (0-≤20 mg/day and >20 mg/day prednisolone/prednisone or equivalent).

The analysis was supplemented with a logistic regression analysis adjusting for covariates of region, baseline OCS dose, and treatment. The model was used to estimate the odds ratio for the treatment difference and associated p-value and 95% confidence interval (CI).

**Secondary endpoints**

Time to first HES flare was analysed using a log-rank test stratified by the covariates of region and baseline OCS dose. This analysis was supplemented by a Cox proportional hazards regression model allowing for the covariates of region and baseline OCS dose. The hazard ratio was derived along with 95% confidence limits. Cumulative event rates were calculated using the Kaplan-Meier method.

The proportion of subjects who experienced a HES flare during Week 20 through Week 32 was analysed in the same way as the primary endpoint, using a Cochran-Mantel-Haenszel test stratified by covariates of region and baseline OCS dose.

The rate of HES flares was calculated for each subject as the number of observed HES flares divided by the time (expressed in years) between the first dose of study treatment and Week 32

The number of observed HES flares was calculated for each subject as the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the onset date of a HES flare must be at least 14 days apart from the resolution date of the preceding HES flare. The rate of HES flares was compared between the treatment groups using a stratified Wilcoxon Rank Sum test, stratified by covariates of region and baseline OCS dose.

The change from baseline in fatigue severity at Week 32 was calculated using the mean of the 7 daily assessments up to and including the date of the Week 32 visit as the Week 32 assessment, and the mean of the 7 daily assessments up to but not including the date of first dose of study treatment as the baseline assessment. The change from baseline in fatigue severity at Week 32 was compared between the treatment groups using a stratified Wilcoxon Rank Sum test, stratified by baseline fatigue severity, baseline OCS dose, and region.

**Estimands**

The primary estimand strategy was defined to be a 'treatment policy' approach with intercurrent events considered to a) discontinuation of study medication and b) receipt of alternative HES medications.

The study was designed to continue to collect data on HES flares for subjects who prematurely discontinue from their randomised study treatment. All data on HES flares collected for these subjects were to be included in the primary analysis. Subjects who withdrew from the study prior to Week 32 (Visit 11) and therefore had missing data on HES flares were included in the primary analysis as treatment failures, i.e. for the primary comparison, a subject was classed as not experiencing a HES flare only if they had no flares reported and completed Week 32 (Visit 11).

Sensitivity analyses was performed on the ITT population to examine the potential impact of the missing data:

- Subjects withdrawing from the study prematurely prior to reporting a HES flare, with the primary reason for treatment withdrawal reported as AE or Lack of Efficacy, was classed as experiencing a HES flare in the analysis. Subjects withdrawing from the study prematurely with any other reason for treatment withdrawal will be included as having a flare if one is recorded prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal.
- Subjects withdrawing from the study prematurely will be included as having a flare if one is recorded prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal.

A supplementary estimand using the 'while on treatment 'strategy was also defined for the intercurrent event of discontinuation of study medication. Subjects discontinuing from study treatment prematurely will be included as having a HES flare if a flare is recorded with an onset date equal or prior to 28 days after the last dose of study treatment, and not having a flare otherwise.

**Statistical Analysis of the Primary endpoint**

The ITT population was the primary population for all efficacy analyses.

For all efficacy analyses, the primary treatment effect to be estimated (estimand) was the treatment policy effect' of initial randomized treatment. A treatment policy strategy was used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. The study was designed to continue to collect data on HES flares for subjects who prematurely discontinued from their randomized treatment. All data on HES flares collected for these subjects were included in analysis of the primary estimand.

Primary Estimand: The proportion of subjects who experience a HES flare during the 32-week Treatment Period was analyzed using a Cochran-Mantel-Haenszel test stratified by the covariates of region and baseline OCS dose (0-≤20mg/day and >20mg/day prednisolone/prednisone or equivalent).

The analysis was supplemented with a logistic regression analysis adjusting for covariates of region, baseline OCS dose, and treatment. The model was used to estimate the odds ratio for the treatment difference and associated p-value and 95% confidence interval (CI). For subjects who withdrew prematurely from study treatment and for whom collection of data on HES flares was not possible, it was assumed for the primary endpoint that they were treatment failures, i.e., that they experienced a flare following study withdrawal.

Sensitivity analyses of the primary estimand were performed to examine the potential impact of the missing data.

The primary analysis was repeated using the Per Protocol population.

Supplementary Estimand: A supplementary estimand using the 'while on treatment' strategy was assessed for the intercurrent event of discontinuation of study medication. Subjects discontinuing from study treatment prematurely were included as having a HES flare if a flare was recorded with an onset date equal or prior to 28 days after the last dose of study treatment, and not having a flare otherwise.

**Statistical Analyses of key secondary endpoint**

**Time to first HES flare:** Time to first HES flare was analyzed using a log-rank test stratified by the covariates of region and baseline OCS dose. This analysis was supplemented by a Cox proportional

hazards regression model allowing for the covariates of region and baseline OCS dose. The hazard ratio was derived along with 95% confidence limits. Cumulative event rates were calculated using the Kaplan-Meier method. If a subject withdrew prematurely from the study prior to experiencing a HES flare, the event time was censored at the time point at which the subject withdrew from the study. Sensitivity analyses were performed to examine the potential impact of the missing data.

**Proportion of Subjects Who Experience a HES Flare during Week 20 through Week 32**

The proportion of subjects who experienced a HES flare during Week 20 through Week 32 was analyzed in the same way as the primary endpoint, using a Cochran-Mantel-Haenszel test stratified by covariates of region and baseline OCS dose. The analysis was supplemented with a logistic regression analysis adjusting for covariates of region, baseline OCS dose, and treatment.

Subjects who withdrew prematurely from the study prior to Week 32 (Visit 11) and therefore have missing data on HES flares during Week 20 through Week 32 were included in the analysis as treatment failures i.e., that they experience a flare during Week 20 through Week 32. Sensitivity analyses were performed to examine the potential impact of the missing data.

**Rate of HES Flares:** The rate of HES flares was calculated for each subject as the number of observed HES flares divided by the time (expressed in years) between the first dose of study treatment and either the Week 32 visit date if available, or otherwise the study withdrawal date.

The number of observed HES flares was calculated for each subject as the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the onset date of a HES flare must be at least 14 days apart from the resolution date of the preceding HES flare.

The rate of HES flares was compared between the treatment groups using a stratified Wilcoxon Rank Sum test, stratified by covariates of region and baseline OCS dose. This analysis was supplemented by an analysis using a negative binomial generalized linear model with a log link-function and included terms for treatment group, region, baseline OCS dose, and included the log of the observed time as an offset variable.

For subjects withdrawing prematurely from the study during the 32-week Treatment Period, all data up to the time of study withdrawal was used to calculate the rate of HES flares. A sensitivity analyses using a negative binomial generalized linear model was performed, in which missing data for subjects withdrawing from the study prematurely was imputed for the period between withdrawal from the study and Week 32. For subjects in the mepolizumab treatment group, the missing time period was imputed assuming that the subject's expected flare rate is shifted to that of the placebo arm (Jump to Reference [J2R]). For subjects in the placebo group, missing data was assumed to the missing at random (MAR).

**Change from Baseline in Fatigue Severity BFI Item 3 (Worst Level of Fatigue in Past 24 Hours) at Week 32.**

The change from baseline in fatigue severity at Week 32 was compared between the treatment groups using a stratified Wilcoxon Rank Sum test, stratified by baseline fatigue severity.

Subjects with missing change from baseline BFI item 3 at Week 32 were included in the analysis with the largest (i.e. worst) value observed for any subject. A supportive repeated measures analysis including assessments at Weeks 4, 8, 12, 16, 20, 24, 28, and 32, in which missing data was assumed to be MAR and was not imputed with the largest (i.e. worst) value was also performed.

**Multiplicity**

In order to provide strong control of type I error when making inferences for the pre-defined secondary endpoints, multiplicity was controlled using a hierarchical, closed testing procedure. The hierarchy of endpoints was defined as follows:

1. proportion of subjects who experienced a HES flare during the 32-week Treatment Period (primary endpoint)

2. time to first HES flare

3. proportion of subjects who experienced a HES flare during Week 20 through Week 32

4. rate of HES flares

5. change from baseline in fatigue severity based on BFI item 3 (worst level of fatigue during past 24 hours) at Week 32

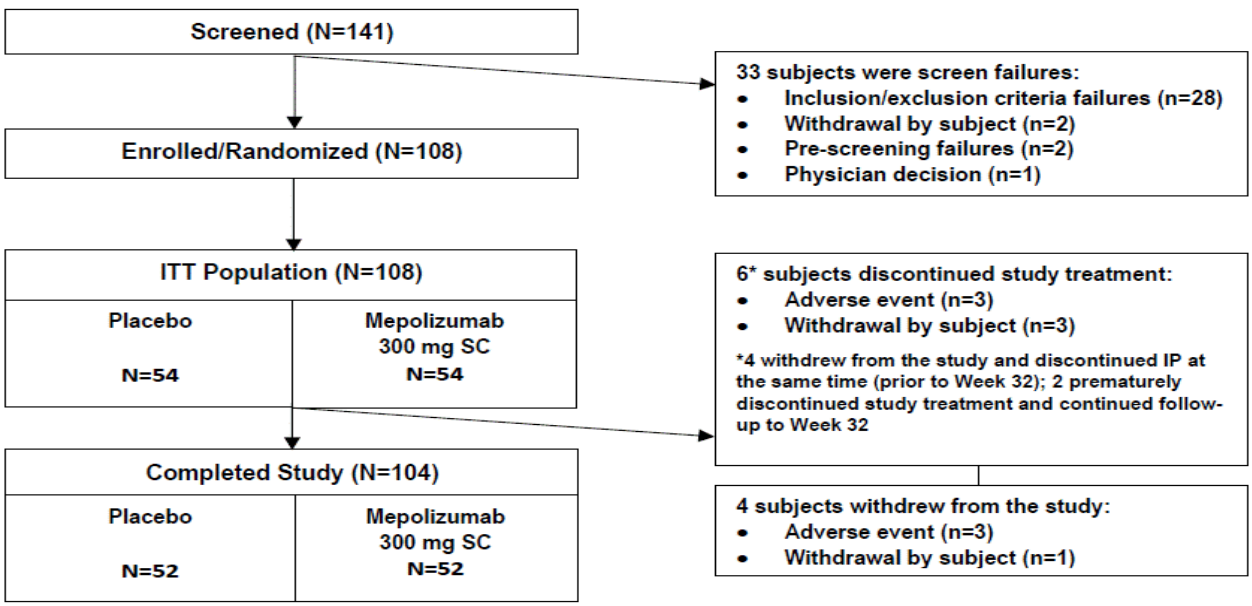
When strong control of type I error was implemented, each endpoint in the hierarchy was formally tested for confirmatory evidence of statistical significance only if all preceding tests were statistically significant.

## *Results*

## Participant flow

In total, 108 subjects were randomized and received at least one dose of study treatment (54 to placebo and 54 to mepolizumab). The study population included 4 adolescent (12-17 years) subjects. Of the 4 adolescents, 1 was randomized to mepolizumab and 3 were randomized to placebo.

**Figure 16: participants flow**




The majority of subjects in the ITT Population completed the study (104, 96%) and 102 subjects continued treatment in the OLE study 205203 (94%). Of the 6 (6%) subjects who prematurely discontinued study treatment, 4 subjects also withdrew from the study and 2 continued participation in

the study until Week 32 and Follow-up. The primary reasons for premature discontinuation of study treatment or withdrawal from the study were AE and voluntary withdrawal by the subject; one subject (in the mepolizumab group) had a fatal AE.

**Table 10: Subject Disposition (Study 200622, ITT Population)**

| | Number (%) of Subjects | |
|---|---|---|
| Status | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
| Subject status | | |
| Completed | 52 (96) | 52 (96) |
| Completed Week 32 and entered 205203 | 52 (96) | 50 (93) |
| Completed Week 32 and Follow-Up, did not enter 205203 | 0 | 2 (4) |
| Withdrawn | 2 (4) | 2 (4) |
| Withdrawn prior to Week 32 | 2 (4) | 2 (4) |
| Primary[a]/subreason[b] for study withdrawal | | |
| Adverse event | 2 (4) | 1 (2) |
| Protocol deviation | 0 | 0 |
| Study terminated by sponsor | 0 | 0 |
| Lost to follow-up | 0 | 0 |
| Physician decision | 0 | 0 |
| Withdrawal by subject | 0 | 1 (2) |
| Patient referred personal reason | 0 | 1 (2) |
| Outcome of adverse events which led to study withdrawal | | |
| Non-fatal | 2 (4) | 0 |
| Fatal | 0 | 1 (2) |

## Recruitment

This was a global study sponsored by GSK; 39 investigational sites randomized subjects to study treatment: 15 subjects in the United States of America (USA), 70 in Europe (11 in Belgium, 14 in Germany, 18 in France, 5 in Italy, 6 in the United Kingdom (UK), 3 in Spain, 10 in Poland, and 3 in Romania), 7 in Argentina, 5 in Mexico, 4 in Brazil, and 7 in Russia.

This study was initiated on 07 March 2017 (first subject, first visit) and completed on 08 August 2019 (last subject, last visit).

## Conduct of the study

Important protocol deviations were cited for 63% and 70% of subjects in the mepolizumab and placebo groups, respectively. The most frequent deviation was study procedures, which occurred with an incidence of 26% in each treatment group.

**Table 11: Important Protocol Deviations (Study 200622, ITT Population)**

| Category/Coded Term | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Any Important Deviation | | | Led to Exclusion from PP Population | |
| | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=108) | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
| **Any Important Protocol Deviations** | **38 (70)** | **34 (63)** | **72 (67)** | **2 (4)** | **3 (6)** |
| Informed Consent | 15 (28) | 8 (15) | 23 (21) | 0 | 0 |
| Wrong informed consent/assent version signed | 3 (6) | 3 (6) | 6 (6) | 0 | 0 |
| Informed consent/assent not signed and/or dated by subject (parent/legal representative, if applicable) | 1 (2) | 0 | 1 (<1) | 0 | 0 |
| Informed consent/assent not signed and/or dated by appropriate site staff | 0 | 1 (2) | 1 (<1) | 0 | 0 |
| Informed consent/assent not signed prior to any study procedure | 1 (2) | 0 | 1 (<1) | 0 | 0 |
| Other informed consent/assent deviations | 12 (22) | 5 (9) | 17 (16) | 0 | 0 |
| Eligibility criteria not met | 0 | 4 (7) | 4 (4) | 0 | 3(6) |
| Visit completion | 6 (11) | 8 (15) | 14 (13) | 0 | 0 |
| Missed visit/phone contact | 6 (11) | 8 (15) | 14 (13) | 0 | 0 |
| Assessment or time point completion | 5 (9) | 5 (9) | 10 (9) | 0 | 0 |
| Missed assessment | 5 (9) | 5 (9) | 10 (9) | 0 | 0 |

| Category/Coded Term | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Any Important Deviation | | | Led to Exclusion from PP Population | |
| | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=108) | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
| Wrong study treatment/ administration/ dose | 4 (7) | 0 | 4 (4) | 2 (4) | 0 |
| Wrong study treatment or assignment administered | 2 (4) | 0 | 2 (2) | 2 (4) | 0 |
| Use of study treatment impacted by temperature excursion - not reported/approved/disapproved for further use | 1 (2) | 0 | 1 (<1) | 0 | 0 |
| Other deviations related to wrong study treatment/administration/dose | 1 (2) | 0 | 1 (<1) | 0 | 0 |
| Study procedures | 14 (26) | 14 (26) | 28 (26) | 0 | 0 |
| Randomization procedure (e.g. subject assigned to wrong stratum, subject randomized out of order) | 5 (9) | 2 (4) | 7 (6) | 0 | 0 |
| Diary procedures | 4 (7) | 2 (4) | 6 (6) | 0 | 0 |
| Post study treatment observation not done | 4 (7) | 0 | 4 (4) | 0 | 0 |
| Biological sample specimen procedures | 0 | 2 (4) | 2 (2) | 0 | 0 |
| Other deviation from study procedures | 3 (6) | 7 (13) | 10 (9) | 0 | 0 |
| Study blinding/unblinding procedures | 0 | 3 (6) | 3 (3) | 0 | 0 |
| Failure to report safety events within the protocol-defined window | 6 (11) | 7 (13) | 13 (12) | 0 | 0 |
| Serious adverse events | 6 (11) | 7 (13) | 13 (12) | 0 | 0 |

**PP Population**

Protocol deviations were tracked by the study team throughout the study. The data was reviewed prior to source data lock to identify all deviations that could significantly impact the primary endpoint and lead to exclusion from the PP population prior to unblinding. Incorrect study treatment deviations were identified after source data lock. Based on these reviews, a total of 5 subjects were excluded from the PP population due to protocol deviations that could potentially impact the efficacy analyses: **3** (6%) subjects in the mepolizumab group did not meet eligibility criteria and **2** (4%) subjects in the placebo group received incorrect study treatment. Details are provided below.

Eligibility Criteria Deviations:

- One subject (mepolizumab 300 mg SC) was not on a stable dose of HES therapy for the 4 weeks prior to randomization
- One subject (mepolizumab 300 mg SC) was not on a stable dose of HES therapy for the 4 weeks prior to randomization
- One subject (mepolizumab 300 mg SC) did not have a reported history of 2 or more HES flares within the past 12 months prior to Screening; a history of 1 flare was reported before Screening

Wrong Treatment/Administration/Dose:

- One subject (placebo) was randomized to placebo, but inadvertently received active treatment at Visit 4.
- One subject (placebo) was randomized to placebo, but inadvertently received active treatment at Visit 6.

One additional subject in the mepolizumab group had an eligibility criteria deviation related to an ECG finding of QTc >450 msec or >480 msec with bundle branch block; however, this deviation was not considered to affect the study analyses and the subject remained in the PP population.

**MAH Investigation at Site 229946**

An investigation at Site 229946 in Mexico was conducted by the MAH following anomalies in pulmonary function test (PFT) data generated by this site for another MAH sponsored study with a different investigational product. The report concluded that "there was diminished confidence and trust in the integrity of the data generated at this site and this loss of trust extended to other aspects of study conduct at this site." Although there were no data findings for this site in study 200622, a sensitivity analysis of the primary estimand excluding the 2 randomized subjects from investigational site 229946 was performed and no impact on the primary analysis was observed.

**Baseline data**

**Demographics**

The demographic characteristics of the ITT population were generally similar across the treatment groups. Overall, the majority of the subjects were White (93%) and more than half were female (53%). The mean age was 46.0 years, and approximately 83% of the subjects were between 19 and 64 years of age. Four (4%) adolescent subjects (12-17 years of age) participated in this study.

**Table 12: Demographics and Baseline Measurements (Study 200622, ITT Population)**

| Demographic | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=108) |
|---|---|---|---|
| Sex, n (%) | | | |
| Female | 27 (50) | 30 (56) | 57 (53) |
| Male | 27 (50) | 24 (44) | 51 (47) |
| Age (years)[a] | | | |
| Mean (SD) | 45.4 (18.25) | 46.6 (12.99) | 46.0 (15.78) |
| Median | 44.5 | 48.0 | 47.0 |
| Min | 15 | 12 | 12 |
| Max | 80 | 82 | 82 |
| Age Group[a], n (%) | | | |
| ≤18 years | 3 (6) | 1 (2) | 4 (4) |
| 19-64 years | 41 (76) | 49 (91) | 90 (83) |
| ≥65 years | 10 (19) | 4 (7) | 14 (13) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 8 (15) | 9 (17) | 17 (16) |
| Not Hispanic or Latino | 46 (85) | 45 (83) | 91 (84) |
| Race, n (%) | | | |
| American Indian or Alaskan Native | 2 (4) | 1 (2) | 3 (3) |
| Asian | 2 (4) | 1 (2) | 3 (3) |
| Black or African American | 2 (4) | 0 | 2 (2) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 48 (89) | 52 (96) | 100 (93) |
| Height (cm) | | | |
| Mean (SD) | 168.2 (9.95) | 169.2 (9.99) | 168.7 (9.93) |
| Median | 167.5 | 169.5 | 168.0 |
| Min | 150 | 146 | 146 |
| Max | 192 | 191 | 192 |
| Weight (kg) | | | |
| Mean (SD) | 73.94 (16.465) | 75.75 (18.893) | 74.85 (17.661) |
| Median | 70.45 | 75.00 | 72.10 |
| Min | 41.0 | 35.0 | 35.0 |
| Max | 120.6 | 171.0 | 171.0 |
| Body Mass Index (kg/m$^2$) | | | |
| Mean (SD) | 26.20 (5.934) | 26.38 (5.885) | 26.29 (5.883) |
| Median | 25.07 | 24.94 | 25.07 |
| Min | 16.4 | 16.0 | 16.0 |
| Max | 41.9 | 57.8 | 57.8 |

**HES History and Disease-Related Symptoms**

HES history was similar between the treatment groups. The mean HES disease duration was 5.45 years and 5.66 years for mepolizumab and placebo, respectively. The Median duration was higher in the placebo arm versus Mepolizumab (8.035 vs 5.079 respectively).

At Baseline, the most bothersome HES-related symptoms were varied across subjects; breathing symptoms were the most common symptoms and were reported by 56% of subjects in both treatment groups

**Table 13: Summary of Most Bothersome HES Related Symptoms (Study 200622, ITT Population)**

| Most Bothersome HES Related Symptoms | Number (%) of Subjects | | |
|---|---|---|---|
| | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=108) |
| Abdominal pain or bloating | 24 (44) | 16 (30) | 40 (37) |
| Breathing symptoms | 30 (56) | 30 (56) | 60 (56) |
| Chills or sweats | 5 (9) | 10 (19) | 15 (14) |
| Muscle or joint pain | 20 (37) | 24 (44) | 44 (41) |
| Nasal or sinus symptoms | 19 (35) | 22 (41) | 41 (38) |
| Skin symptoms | 28 (52) | 25 (46) | 53 (49) |

**Medical Conditions**

Sixty four percent of subjects reported past medical conditions other than HES-related conditions. Past conditions with the highest incidence included pneumonia (23%), bone fractures (19%), and sinusitis (14%).

In addition to HES, most subjects had other current medical conditions. The most common co-morbid conditions were allergic rhinitis or hay fever (25%), hypertension (22%), and gastroesophageal reflux (21%).

**Baseline HES Treatment**

At baseline, almost all subjects (92%) had received regular maintenance medications for HES. The most frequently reported HES therapy at baseline was OCS (72%) and the incidence of use was similar between the treatment groups. The majority of subjects in both treatment groups were taking ≤20 mg prednisone or equivalent daily with a median dose of 5.6 mg/day and maximum dose of 50 mg/day. More subjects in the mepolizumab group (26%) were receiving cytotoxic/immunosuppressive therapy at baseline compared with the placebo group (17%).

Overall, 23% of subjects were not taking chronic OCS or cytotoxic/immunosuppressive therapy at baseline. All subjects had been treated with either OCS or cytotoxic/immunosuppressive therapy for historic flares prior to study entry.

**Table 14: Baseline HES Therapy (Study 200622, ITT Population)**

| Baseline HES Therapy | Number (%) of Subjects | | |
|---|---|---|---|
| | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=108) |
| Any baseline HES therapy | 49 (91) | 50 (93) | 99 (92) |
| Oral corticosteroids | 38 (70) | 40 (74) | 78 (72) |
| ≤20mg/day prednisone or equivalent | 37 (69) | 35 (65) | 72 (67) |
| >20mg/day prednisone or equivalent | 1 (2) | 5 (9) | 6 (6) |
| Cytotoxic/immunosuppressive therapy[a] | 9 (17) | 14 (26) | 23 (21) |
| Other HES therapy[b] | 19 (35) | 22 (41) | 41 (38) |
| Subjects not taking oral corticosteroids or cytotoxic immunosuppressive therapy | 14 (26%) | 11 (20%) | 25 (23) |

**Table 15: Baseline Prednisone Equivalent Dose (Study 200622,ITT Population)**

| Baseline Prednisone Dose | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=108) |
|---|---|---|---|
| Prednisone equivalent daily dose (mg) | | | |
| n | 54 | 54 | 108 |
| Mean (SD) | 6.8 (6.10) | 9.2 (11.38) | 8.0 (9.17) |
| Median | 5.6 | 5.6 | 5.6 |
| Min | 0 | 0 | 0 |
| Max | 25 | 50 | 50 |
| 0 | 16 (30) | 14 (26) | 30 (28) |
| 1 - ≤5 | 11 (20) | 13 (24) | 24 (22) |
| >5 - ≤10 | 18 (33) | 16 (30) | 34 (31) |
| >10 - ≤15 | 5 (9) | 2 (4) | 7 (6) |
| >15 - ≤20 | 3 (6) | 4 (7) | 7 (6) |
| >20 - ≤25 | 1 (2) | 1 (2) | 2 (2) |
| >25 - ≤30 | 0 | 1 (2) | 1 (<1) |
| >30 | 0 | 3 (6) | 3 (3) |

## Numbers analysed

**Table 16: Study Populations (Study 200622, Screened Subjects)**

| Population | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | No Treatment (N=33) | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Total (N=141) |
| Screened | 33 | 54 | 54 | 141 |
| Enrolled | 0 | 54 | 54 | 108 |
| Intent-to-treat (ITT) | 0 | 54 (100) | 54 (100) | 108 (100) |
| Safety | 0 | 54 (100) | 54 (100) | 108 (100) |
| Per-protocol (PP) | 0 | 52 (96) | 51 (94) | 103 (95) |
| Pharmacokinetic (PK) | 0 | 0 | 54 (100) | 54 (50) |
| Pharmacodynamic (PD) | 0 | 54 (100) | 54 (100) | 108 (100) |

## Outcomes and estimation

### Overview of HES Flares

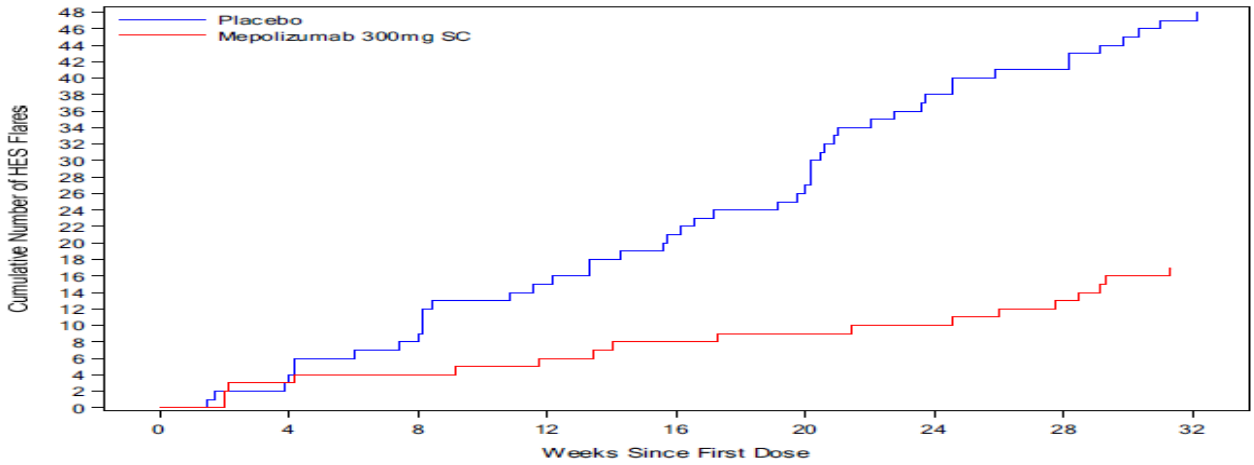
In this study, disease flare (HES flare) was defined as (1) a HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms resulting in the need for therapy adjustment (increase in OCS dose of at least 10 mg/day or any increase in or addition of any cytotoxic/immunosuppressive HES therapy) or (2) receipt of 2 or more courses of blinded active OCS during the treatment period.

In total, there were 48 flares in 28 (52%) subjects in the placebo group compared to 17 flares in 14 (26%) subjects randomized to mepolizumab. Of the 65 flares, 50 (77%) met HES flare definition a and 19 (29%) met HES flare definition b; 13 flares in the placebo group and 2 flares in the mepolizumab group met only HES flare definition b.

**Table 17: Overview of HES Flares (Study 200622, ITT Population)**

| Randomization to Week 32 | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
|---|---|---|
| n | 54 | 54 |
| All HES flare<br>Number of subjects, n (%)<br>Number of events | <br>28 (52)<br>48 | <br>14 (26)<br>17 |
| HES flare definition a only)[a]<br>Number of subjects, n (%)<br>Number of events | <br>22 (41)<br>31 | <br>12 (22)<br>15 |
| HES flare definition b only)[b]<br>Number of subjects, n (%)<br>Number of events | <br>6 (11)<br>13 | <br>2 (4)<br>2 |
| HES flare definition a) and b)[c]<br>Number of subjects<br>Number of events | <br>3 (6)<br>4 | <br>0<br>0 |

**Figure 17: Cumulative Number of HES Flares (Study 200622, ITT Population)**




**Proportion of Subjects who Experience a HES Flare during the 32-Week Treatment Period (Primary Endpoint)**

Primary Analysis

The primary analysis compared subjects who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week Treatment Period, 50% fewer subjects experienced a HES flare or withdrew from the study when treated with mepolizumab compared with placebo (p=0.002).

A parametric logistic regression analysis that adjusted for the covariates of region and baseline OCS dose was consistent with the primary analysis, demonstrating a statistically significant odds ratio in favor of mepolizumab (p=0.003).

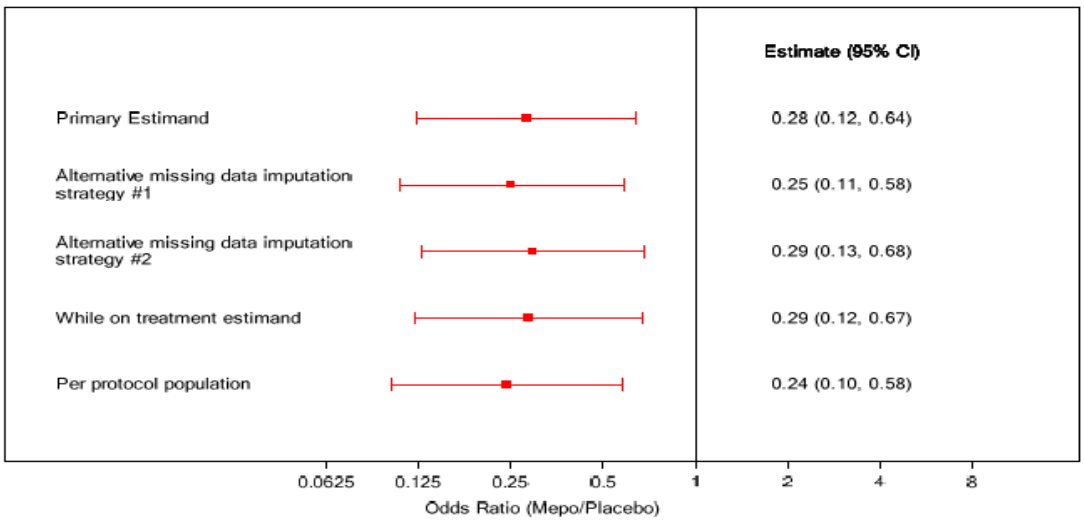
**Table 18: Analysis of Proportion of Subjects Who Experienced a HES Flare during the 32-Week Treatment Period (Study 200622, Treatment Policy Estimand, ITT Population)**

| HES Flare during the 32-Week Treatment Period | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
|---|---|---|
| n | 54 | 54 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 30 (56) | 15 (28) |
| Subjects with ≥1 HES flare, n (%) | 28 (52) | 14 (26) |
| Subjects with no HES flare who withdraw from study, n (%) | 2 (4) | 1 (2) |
| Subjects with no HES flare who complete study, n (%) | 24 (44) | 39 (72) |
| Comparison mepolizumab 300 mg vs placebo[a] | | |
| CMH p-value[b] | | 0.002 |
| Logistic regression[c] | | |
| Odds ratio | | 0.28 |
| 95% CI for odds ratio | | (0.12, 0.64) |
| p-value | | 0.003 |

**Sensitivity Analysis of the Primary Estimand**

Two sensitivity analyses of the primary estimand were performed to examine the impact of missing data (subjects withdrawing from the study prior to Week 32). The results were consistent with the primary estimand. Results of the supplementary 'while on treatment' estimand and the analysis of the PP population were also consistent with the primary estimand.

**Figure 18: Analysis of Proportion of Subjects Who Experienced a HES Flare during the 32-Week Treatment Period (Study 200622)**

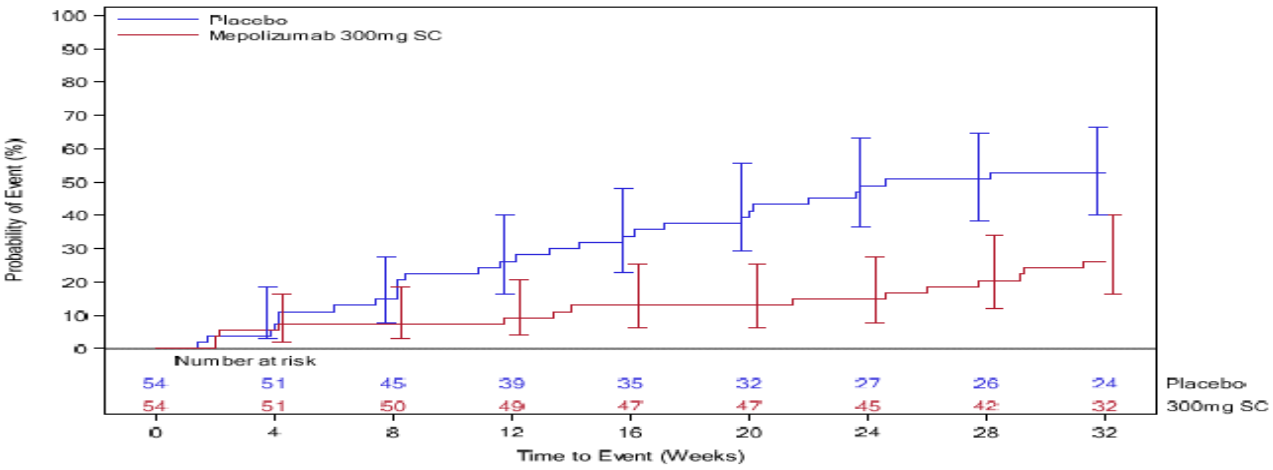



**Secondary endpoints**

**Time to First HES Flare**

Over the 32-week Treatment Period, a statistically significant increase in the time to first HES flare was observed for subjects treated with mepolizumab compared with placebo (p=0.002). The risk of first HES flare over the treatment period was 66% lower for subjects treated with mepolizumab compared with placebo (hazard ratio: 0.34; 95% CI 0.18, 0.67).

**Figure 19: Kaplan Meier Cumulative Incidence Curve for Time to HES Flare (Study 200622, Treatment Policy Estimand, ITT Population)**




Two sensitivity analyses were performed to assess the impact of missing data on time to first HES flare. These analyses were consistent with the primary estimand.

**Proportion of Subjects who Experience a HES Flare during Week 20 through Week 32 (Secondary Endpoint)**

From Week 20 through Week 32, fewer subjects experienced a HES flare or withdrew from the study when treated with mepolizumab compared with placebo (17% vs. 35% respectively, p=0.020).

A parametric logistic regression analysis that adjusted for the covariates of region and baseline OCS dose was consistent with the primary analysis, demonstrating a statistically significant odds ratio in favor of mepolizumab (p=0.022).

**Table 19: Analysis of Proportion of Subjects Who Experienced a HES Flare during Week 20 through Week 32 (Study 200622, Treatment Policy Estimand, ITT Population)**

| HES Flare during Week 20 through Week 32 | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
|---|---|---|
| n | 54 | 54 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 19 (35) | 9 (17) |
| Subjects with ≥1 HES flare, n (%) | 17 (31) | 7 (13) |
| Subjects with no HES flare who withdraw from study, n (%) | 2 (4) | 2 (4) |
| Subjects with no HES flare who complete study, n (%) | 35 (65) | 45 (83) |
| Comparison mepolizumab 300 mg vs placebo[a] | | |
| CMH p-value[b] | | 0.020 |
| Logistic regression[c] | | |
| Odds ratio | | 0.33 |
| 95% CI for odds ratio | | (0.13,0.85) |
| p-value | | 0.022 |

**Rate of HES Flares (Secondary Endpoint)**

Overall, subjects in the mepolizumab group experienced fewer HES flares during the 32-week Treatment Period compared with the placebo group.

Treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of HES flares (calculated for each subject as number of HES flares divided by time in the study) compared with placebo (unadjusted p=0.002; adjusted p=0.020).

A parametric analysis using a negative binomial model adjusted for the covariates of region and baseline OCS dose estimated that subjects treated with mepolizumab had a 66% reduction in annualized rate of HES flares compared with subjects receiving placebo (p<0.001)

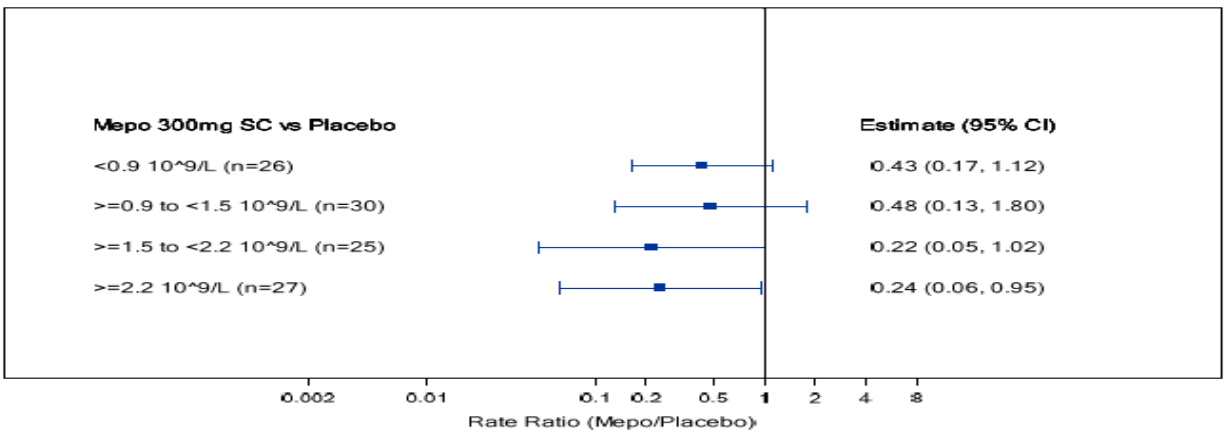
**Table 20: Analysis Rate of HES Flares (Study 200622, Treatment Policy Estimand, ITT Population)**

| Rate of HES Flares | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
|---|---|---|
| Adjusted mean rate/year[a] | 1.46 | 0.50 |
| Comparison mepolizumab 300 mg vs placebo | | |
| Wilcoxon rank sum test p-value[b] | | 0.002 |
| Negative binomial model[a] | | |
| Rate ratio | | 0.34 |
| 95% CI for rate ratio | | (0.19, 0.63) |
| p-value | | <0.001 |

**Analysis by Baseline Blood Eosinophils – Rate of Flares**

The rate of HES flares was lower in the mepolizumab group compared with placebo for each category of baseline blood eosinophils. An exploratory analysis including baseline blood eosinophil count as a continuous variable did not show any evidence that the rate ratio differed by baseline blood eosinophil count (treatment-by baseline blood eosinophil count interaction p=0.897).

**Figure 20: Analysis of Rate of HES Flares During the 32-Week Treatment Period by Baseline Eosinophil Categories (Study 200622, Treatment Policy Estimand, ITT Population)**




**Change from Baseline in Fatigue Severity BFI Item 3 (Worst Level of Fatigue during the Past 24 hours) at Week 32 (Secondary Endpoint)**

BFI item 3 asks subjects to record their fatigue severity by having them rate their worst Level of fatigue during the past 24 hours. Subjects recorded a score every day. Fatigue severity scores for each subject at each timepoint were calculated as a mean of up to 7 available daily scores prior to the visit.

At Baseline, mean BFI item 3 scores were similar between the treatment groups (4.74 for mepolizumab and 4.39 for placebo). At Week 32, a larger reduction in the mean change from baseline BFI item 3 score was observed in the mepolizumab group (-1.12) compared with the placebo group (-0.30).

The primary analysis compared the change from baseline in BFI item 3 score at Week 32 in the mepolizumab and placebo treatment groups. Seven subjects in the placebo group and 4 subjects in the

mepolizumab group had missing data for the change from baseline at Week 32; these subjects were included in the analysis with the largest (i.e. worst) change from baseline value observed for any subject.

Results of the Wilcoxon Rank Sum test demonstrated a statistically significant reduction in fatigue severity BFI item 3 at Week 32 for subjects treated with mepolizumab compared with placebo (unadjusted p=0.036; adjusted p=0.036).

**Exploratory endpoints**

**Proportion of Subjects who have an Elevated Blood Eosinophil Level that Meets the Pre-Defined Threshold during the 32-Week Study Treatment Period**

A significantly lower proportion of subjects treated with mepolizumab (9%) had an elevated blood eosinophil count that met the pre-defined threshold level (2 x Baseline value or Baseline value + 2500 cells/uL) or withdrew from the study during the 32-week Treatment Period compared with those subjects treated with placebo (35%) (p<0.001).

**Spirometry**

At Baseline, mean baseline pre-bronchodilator FEV1 (269.8 mL and 272.9 mL) and FVC (374.1 mL and 372.6 mL) were similar between the mepolizumab and placebo groups, respectively

At Week 32, subjects treated with mepolizumab had numerical improvement from Baseline in FEV1 and FVC compared with placebo  pre-bronchodilator FEV1 and FVC at Week 32 increased by 116 mL (95% CI: -3.5, 26.8; p=0.131) and 58 mL (95% CI: -12.1, 23.7; p=0.521) over placebo. Neither of these changes were statistically significant.

The FEV1/FVC ratio was also similar between the treatment groups at Baseline (0.714 and 0.727 for mepolizumab and placebo, respectively), and there was numerical improvement with mepolizumab from Week 8 and continuing to Week 32.

**Echocardiogram**

At Screening, mean left ventricular ejection fractions (LVEFs) were similar between the treatment groups (61.6 % for the mepolizumab group and 62.4% for the placebo group). LVEFs remained stable at the end of the treatment period; no changes were observed at Week 32 compared with Screening in either treatment group (61.9% for mepolizumab and 62.6% for placebo).

No trends supportive of deterioration or improvement in association with either mepolizumab or placebo treatment were apparent. No subjects had abnormal, clinically significant scan results at Week 32.

**Most Bothersome HES Symptom Severity Score**

At Baseline, the mean and median most bothersome HES-DS scores were similar between the mepolizumab group (4.61 and 4.18, respectively) and placebo group (4.26 and 4.37, respectively). At Week 32, a larger reduction in the observed mean change from baseline in the most bothersome HES-DS score was seen with the mepolizumab group (-1.80) compared with placebo group (-0.88). There was a statistically significant reduction (improvement) in the most bothersome symptom score at Week 32 for subjects treated with mepolizumab compared with placebo.

**HES Symptom Severity Score by Symptom**

At Week 32, a larger reduction in the observed mean change from baseline HESDS score was seen for each of the 6 symptoms.

**Non-Parametric Analysis**

Hypothesis tests using the Wilcoxon Rank Sum test ranked the 7 subjects in the placebo group and 4 subjects in the mepolizumab group, with missing change from baseline in HES-DS score at Week 32 as having the largest (i.e. worst) change from baseline observed for any subject. These tests compare the whole distribution of scores, not the median value.

Reductions (improvement) in the symptom score at Week 32 for subjects treated with mepolizumab compared with placebo were statistically significant at $p<0.05$ for all symptoms except the worst level of chills or sweats where results were suggestive of improvement ($p=0.051$).

## Ancillary analyses

### Subgroup Analyses

Exploratory analyses of the primary endpoint were also examined by the subgroup factors of age, sex, race, geographic region, weight, baseline OCS, and baseline blood eosinophils.

Generally, in these subgroups, the proportion of subjects who experienced ≥1 HES flare or who withdrew from the study during the 32-week Treatment Period was lower in the mepolizumab group compared with placebo.

**Table 21: Summary of Proportion of Subjects who Experienced a HES Flare During the 32-Week Treatment Period by Subgroup (Study 200622, Treatment Policy Estimand, ITT Population)**

| Subgroups | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
|---|---|---|
| **Age:** | | |
| **12 <18 years (n)** | 3 | 1 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 2 (67) | 0 |
| **18-64 years (n)** | 41 | 49 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 23 (56) | 13 (27) |
| **≥65 years (n)** | 10 | 4 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 5 (50) | 2 (50) |
| **Sex:** | | |
| **Female (n)** | 27 | 30 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 17 (63) | 6 (20) |
| **Male (n)** | 27 | 24 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 13 (48) | 9 (38) |
| **Race:** | | |
| **Black or African American (n)** | 2 | 0 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 2 (100) | 0 |
| **White (n)** | 48 | 52 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 27 (56) | 15 (29) |
| **Asian (n)** | 2 | 1 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 0 | 0 |
| **Other (n)** | 2 | 1 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 1 (50) | 0 |
| **Region:** | | |
| **USA (n)** | 8 | 7 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 5 (63) | 2 (29) |
| **Argentina, Mexico and Brazil (n)** | 8 | 8 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 3 (38) | 3 (38) |
| **Rest of World[a] (n)** | 38 | 39 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 22 (58) | 10 (26) |

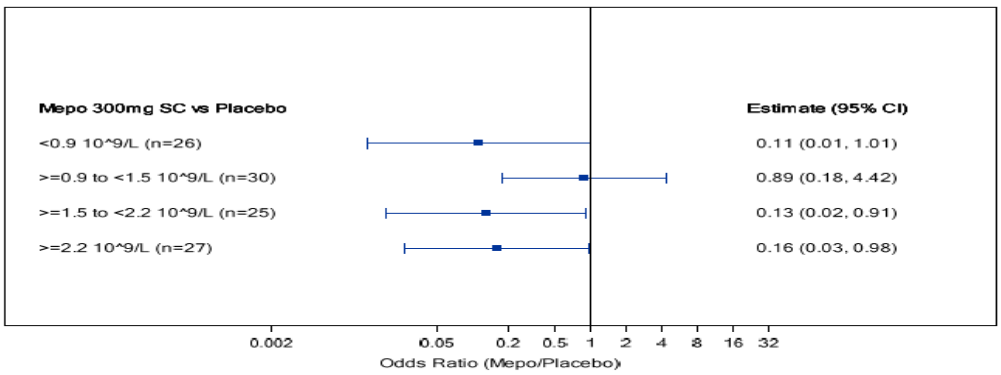
| | | |
|---|---|---|
| **Weight:** | | |
| **≤70 kg (n)** | 27 | 22 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 16 (59) | 6 (27) |
| **>70 kg to ≤85 kg (n)** | 16 | 20 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 9 (56) | 6 (30) |
| **>85 kg (n)** | 11 | 12 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 5 (45) | 3 (25) |
| **Baseline OCS Use:** | | |
| **0 to ≤20 mg/day Prednisone or Equivalent (n)** | 53 | 49 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 29 (55) | 13 (27) |
| **>20mg/day Prednisone or Equivalent (n)** | 1 | 5 |
| Subjects with ≥1 HES flare or who withdraw from study, n (%) | 1 (100) | 2 (40) |

**Analysis by Baseline Blood Eosinophils - Primary Endpoint**

The proportion of subjects who experienced ≥1 HES flare or who withdrew from the study during the 32-week Treatment Period was lower in the mepolizumab group compared with placebo for each category of baseline blood eosinophils.

An exploratory analysis including baseline blood eosinophil count as a continuous variable did not show any evidence that the odds ratio for the proportion of subjects with HES flare during the 32-week Treatment Period in the mepolizumab group compared with the placebo group differed by baseline blood eosinophil count (treatment by baseline blood eosinophil interaction p=0.762).

**Figure 21: Analysis of Proportion of Subjects who Experienced a HES Flare during the 32-Week Treatment Period by Baseline Eosinophil Categories (Study 200622, Treatment Policy Estimand, ITT Population)**




## *Summary of main study*

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

**Table 22: Summary of efficacy for Trial 200622**

| | | | |
|---|---|---|---|
| **Title:** A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome | | | |
| Study identifier | 200622<br>EudraCT number: 2014-001232-11 | | |
| Design | This was an international, Phase III, randomized, double-blind, placebo-controlled,parallel group, multicenter study of mepolizumab in adolescent and adult subjects with severe HES receiving standard of care (SoC) therapy that investigated the efficacy and safety of mepolizumab 300 mg subcutaneously (SC) every 4 weeks compared with placebo. | | |
| | Duration of main phase:<br>Duration of Screening phase:<br>Duration of Follow-up phase:<br><br>Duration of Run-in phase:<br>Duration of Extension phase: | | 32 weeks<br>4 weeks<br>Up to 8 weeks (for subjects who did not continuein the open-label extension study 205203)<br>Not applicable<br>20 weeks (open-label extension study 205203) |
| Hypothesis | Superiority | | |
| Treatment groups | Mepolizumab 300 mg SC | | Mepolizumab 300 mg SC, every 4 weeks for 32 weeks, n (number randomized) = 54 |
| | Placebo | | Placebo SC, every 4 weeks for 32 weeks, n(number randomized) = 54 |
| Endpoints and definitions | Primary endpoint | Proportion ofsubjects withHES flare during Weeks 0-32 | Proportion of subjects who experienced an HES flare or withdrew from the study over the 32-weektreatment period. |
| | Secondary endpoints | Time to firstHES flare | Time to first HES flare calculated from the first dose of study treatment to the onset date of firstHES flare. |
| | | Proportion ofsubjects withHES flare during Weeks 20-32 | Proportion of subjects who experienced an HESflare or withdrew from the study during Week 20through Week 32. |
| | | Rate of HES flares | Annualized rate of HES flares between the first dose of study treatment and either the Week 32visit, or the study withdrawal date. |
| | | Change in fatigue severity(BFI item 3) at Week 32 | Change from baseline in fatigue severity (Brief Fatigue Inventory [BFI]) item 3 (worst level of fatigue during past 24 hours) at Week 32. |
| Database lock | 10-Oct-2019 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis – Proportion of subjects with HES flare during Weeks 0-32** | | |

| | | | |
|---|---|---|---|
| Analysis population andtime point description | Intent to treat Population: All randomized subjects; based on the treatment to whichthe subject was randomized.<br>Timepoint: Week 0 to Week 32 | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Mepolizumab 300 mg SC |
| | Number of subjects | 54 | 54 |
| | Proportion of subjects with HES flare during Weeks 0-32(n, [%]) | 30 (56%) | 15 (28%) |
| Effect estimate percomparison | Proportion of subjects with HES flare during Weeks 0-32 | Comparison groups | Mepolizumab 300 mg SCvs. Placebo |
| | | Cochran-Mantel-Haenszel p-value | 0.002 |
| | | Odds ratio (95% CI) | 0.28 (0.12, 0.64) |
| Notes | Analysis compares the number of subjects who experience ³1 HES flare and/or withdraw from the study prematurely. | | |
| **Analysis description** | **Secondary Analysis – Time to first HES flare** | | |
| Analysis population andtime point description | Intent to treat Population: All randomized subjects; based on the treatment to whichthe subject was randomized.<br>Timepoint: Week 0 to Week 32. | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Mepolizumab 300 mg SC |
| | Number of subjects | 54 | 54 |
| | Time to first HES flareHES flare (n, %)<br>Withdrawn - censored, n (%)Completed - censored, n (%) | 28 (52%)<br>2 (4)<br>24 (44) | 14 (26%)<br>1 (2)<br>39 (72) |
| Effect estimate percomparison | Time to first HES flare | Comparison groups | Mepolizumab 300 mg SCvs. Placebo |
| | | Stratified log-rank p-value | 0.002 |
| | | Hazard ratio (95% CI) | 0.34 (0.18, 0.67) |
| Notes | Not applicable. | | |
| **Analysis description** | **Secondary Analysis – Proportion of subjects with HES flare during Weeks 20-32** | | |
| Analysis population andtime point description | Intent to treat Population: All randomized subjects; based on the treatment to whichthe subject was randomized.<br>Timepoint: Week 20 to Week 32 | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Mepolizumab 300 mg SC |
| | Number of subjects | 54 | 54 |
| | Proportion of subjects withHES flare during Weeks 20-32(n, [%]) | 19 (35%) | 9 (17%) |
| Effect estimate percomparison | Proportion of subjects withHES flare during Weeks 20-32 | Comparison groups | Mepolizumab 300 mg SCvs. Placebo |
| | | Cochran-Mantel-Haenszel p-value | 0.020 |

| | | | |
|---|---|---|---|
| | | Odds ratio (95% CI) | 0.33 (0.13, 0.85) |
| Notes | Analysis compares the number of subjects who experience ³1 HES flare and/or withdraw from the study prematurely. | | |
| **Analysis description** | **Secondary Analysis – Rate of HES flares** | | |
| Analysis population andtime point description | Intent to treat Population: All randomized subjects; based on the treatment to whichthe subject was randomized.<br>Timepoint: Week 0 to either Week 32 or study withdrawal | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Mepolizumab 300 mg SC |
| | Number of subjects | 54 | 54 |
| | Rate of HES flares (adjusted mean rate/year) | 1.46 | 0.50 |
| Effect estimate percomparison | Rate of HES flares | Comparison groups | Mepolizumab 300 mg SC vs. Placebo |
| | | Wilcoxon Rank Sum testp-value | 0.002 (unadjusted) |
| | | Rate ratio (95% CI) | 0.34 (0.19, 0.63) |
| Notes | The p-value presented is unadjusted for multiple comparisons. | | |
| **Analysis description** | **Secondary Analysis – Change in fatigue severity (BFI item 3) at Week 32** | | |
| Analysis population and time point description | Intent to treat Population: All randomized subjects; based on the treatment to which the subject was randomized.<br>Timepoint: Week 32 | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Mepolizumab 300 mg SC |
| | Number of subjects | 54 | 54 |
| | Change in fatigue severity (BFI Item 3) at Week 32 (median change) | 0.32 | -0.66 |
| Effect estimate per comparison | Change in BFI item 3 at Week 32 | Comparison groups | Mepolizumab 300 mg SC vs. Placebo |
| | | Wilcoxon Rank Sum test p-value | 0.036 (unadjusted) |
| Notes | The p-value presented is unadjusted for multiple comparisons.<br>Subjects with missing change from baseline BFI at Week 32 are included with the worst change observed for any subject.<br>BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine. | | |

## *Supportive study(ies)*

### a) Study 205203

A multi-centre, open-label extension, safety study to describe the long-term clinical experience of mepolizumab in participants with hypereosinophilic syndrome (HES) from Study 200622

***Objectives***

**Primary Objective**

The primary objective was to describe the long-term safety profile of mepolizumab in subjects with HES who took part in Study 200622.

**Exploratory Objectives**

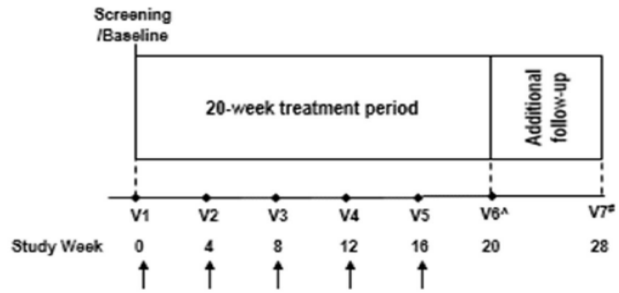
Exploratory objectives were:

To assess the effect of long-term use of mepolizumab on multiple clinical outcomes.
To assess the effect of long-term use of mepolizumab on a pharmacodynamics (PD) marker.

***Study design***

This was a multi-center, OLE, 20-week treatment period, safety study of mepolizumab in adolescent and adult subjects with HES who took part in the Phase III Study 200622

**Figure 22: Trial design**




↑: Mepolizumab treatment (300mg SC per administration)
V: Visit
^: Participants who continue with mepolizumab treatment via mepolizumab HES expanded access after Study 205203 will have the last assessment on Week 20 (Visit 6).
#: Participants who do not continue with mepolizumab via MHE104317/MHE112562 after Study 205203 will have additional follow-up 12 weeks after the last dose (Visit 7).

Subjects in Study 200622 who met one of the following criteria were screened to continue with participation in Study 205203:

1. Completion of the 32-week treatment period in Study 200622, or
2. If the subject was withdrawn from study treatment prematurely during Study 200622 but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

Re-screening of subjects was permitted upon approval by the MAH Medical Monitor.

Eligible subjects received **300 mg SC mepolizumab every 4 weeks** for a duration of 20 weeks starting approximately 32 weeks after the first dose of study treatment in Study 200622. In this OLE Study 205203, the final dose of mepolizumab was administered at Visit 5 (Week 16). Assessments during Visit 6 (20 weeks after the first dose and 4 weeks after the last dose) completed the study treatment period. Subjects who completed assessments at Visit 6 (Week 20) could continue with mepolizumab treatment via mepolizumab HES expanded access (e.g., MHE104317, MHE112562), where permitted by local regulations. Subjects in Study 205203 who did not continue with

mepolizumab HES expanded access had an additional follow-up assessment at Visit 7 (28 weeks after the first dose and 12 weeks after the last dose of mepolizumab).

During Study 205203, investigators were blinded to the blood eosinophil count for the sample collected at Visit 1 (first dosing visit), after which blood eosinophil counts were unblinded starting at Visit 2. Investigators were permitted to adjust the subjects' background HES therapy per SoC starting at Visit 2 (approximately 4 weeks after the first dose).

During Study 205203, subjects' HES SoC therapy could have been adjusted starting 4 weeks after the first dose (Visit 2) of mepolizumab, when investigators were unblended to blood eosinophil levels. In contrast, in Study 200622, the same regimen of background HES SoC therapy was maintained throughout the 32-week study treatment period unless there was a worsening of symptom(s) that required an increase in therapy.

***Study population /Sample size***

**Main inclusion criteria:**

Male and female subjects aged 12 years and older who were enrolled in Study 200622.

- To be considered for Study 205203, subjects in Study 200622 must have completed 32-week assessments since randomization:
    - Completion of the 32-week treatment period in Study 200622,
    - If the subject was withdrawn from study treatment prematurely during Study 200622 but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

**Main exclusion criteria**

- Subjects with current malignancy or malignancy that developed during Study 200622. Subjects who had localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure were not excluded.
- Subjects with QT interval corrected (QTc) >450 msec or QTc > 480 msec in subjects with bundle branch block based on local EGC reading.
- Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

NOTE: Stable chronic liver disease was generally defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis.

- Subjects who had received treatment with an investigational agent (biologic or non-biologic) within the past 30 days, or 5 drug half-lives, whichever was longer, prior to the first dose, other than Study 200622 study treatment.
- Subject had an adverse event (AE) (serious or non-serious) considered related to study treatment while participating in Study 200622 which resulted in permanent withdrawal of study treatment.

***Treatments***

All subjects were to receive 300 mg SC mepolizumab every 4 weeks for a duration of 20 weeks, starting approximately 32 weeks after the first dose of study treatment in Study 200622.

**Prior and Concomitant Medications and Non-Drug Therapies**

Use of SoC HES therapy, including OCS, immunosuppressive, or cytotoxic therapy (e.g., hydroxyurea, interferon alpha, cyclosporine, imatinib, methotrexate, azathioprine), was permitted during the study.

During Study 205203, subjects' HES SoC therapy was permitted to be adjusted starting 4 weeks after the first dose of mepolizumab.

Additional therapies required to treat non-HES-related medical conditions (e.g., mAbs or IV immunoglobulin therapy) during the study were permitted in consultation with the MAH Medical Monitor and must have been prospectively captured in the eCRF. If allowed, therapy should not have been administered at the same time as the mepolizumab injection(s) and physicians were to have taken measures to separate administration of another biological therapy as long as possible from administration of mepolizumab.

**Outcomes/endpoints**

The primary safety endpoints were:

- AEs: serious AEs (SAEs) and non-serious
- anti-drug antibodies (ADAs)

Other safety endpoints included:

- vital signs
- 12-lead electrocardiograms (ECGs)
- hematological and clinical laboratory tests

**Efficacy Endpoints**

Efficacy assessments were considered exploratory endpoints in this study. The following endpoints were assessed:

- rate of HES flare
- change in the mean daily OCS (prednisone or equivalent) dose from Week 0 to 4 to Week 16 to 20
- proportion of subjects who achieved a mean daily OCS (prednisone or equivalent) dose of ≤ 7.5 mg during Week 16 to 20
- proportion of subjects who achieved a mean daily OCS dose reduction of ≥ 50% from Week 0 to 4 to Week 16 to 20 for subjects with a mean OCS dose >0 mg/day during Week 0 to 4.

***Statistical Methods***

There was no sample size calculation for this study. The sample size was determined by the number of available subjects who were randomized in Study 200622 and were eligible for the current study based on the inclusion and exclusion criteria.

**Table 23: Summary of Analysis Populations**

| Population | Description | Analysis |
|---|---|---|
| All Subjects Enrolled | All subjects who signed the informed consent form and for whom a record existed in the database. | Screen failures |
| Safety | All subjects who received at least 1 dose of open-label mepolizumab. | Safety<br>Efficacy |
| PD | All screened subjects who had a Baseline blood eosinophil measurement and at least 1 post-treatment blood eosinophil measurement. | Blood eosinophils |

**Final Analyses**

The final planned primary analyses were performed after the completion of the following sequential steps:

- All subjects had completed the study as defined in the protocol.
- All required database cleaning activities were completed and final DBR and DBF were declared by Data Management.

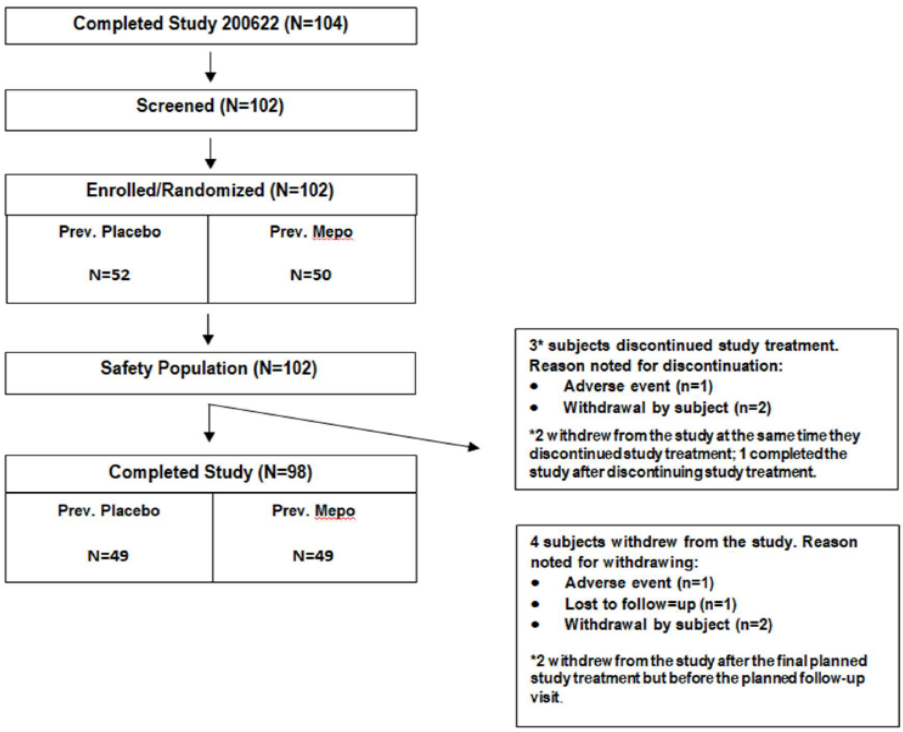
**Efficacy Analyses**

Efficacy analyses were considered exploratory in the study.

**Results**

A total of 102 subjects were enrolled from Study 200622 and received treatment in Study 205203; 52 subjects previously received placebo and 50 subjects previously received mepolizumab in Study 200622 (note: 6 subjects in Study 200622 did not enrol in Study 205203. There were no screen failures in Study 205203. Nine subjects who were re-screened in Study 200622 enrolled in Study 205203 after completing Study 200622.

**Figure 23: Subject Disposition**




The majority of subjects completed Study 205203 (98/102, 96%). Three (3%) subjects prematurely discontinued study treatment of these, 2 withdrew from the study at the same time they discontinued study treatment (1 due to an AE and 1 due to withdrawal by subject) and 1 completed the study. Two additional subjects withdrew from the study after receiving their final planned dose of study treatment: 1 due to withdrawal by subject (subject refused to participate after receiving the results of histology) and 1 lost to follow-up.

**Table 24: Subject Disposition (Study 205203, Safety Population)**

| Status | Number (%) of Subjects | | |
|---|---|---|---|
| | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
| Subject status | | | |
| Completed | 49 (94) | 49 (98) | 98 (96) |
| Withdrawn | 3 (6) | 1 (2) | 4 (4) |
| Primary reason[a]/subreason[b] for study withdrawal | | | |
| Adverse event | 1 (2) | 0 | 1 (<1) |
| Protocol deviation | 0 | 0 | 0 |
| Study terminated by sponsor | 0 | 0 | 0 |
| Lost to follow-up | 0 | 1 (2) | 1 (<1) |
| Investigator site closed | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 |
| Withdrawal by subject | 2 (4) | 0 | 2 (2) |
| Burden of studies visits | 1 (2) | 0 | 1 (<1) |
| The patient refused to participate in the study after receiving the results of histolotology | 1 (2) | 0 | 1 (<1) |
| Outcome of adverse events which led to study withdrawal | | | |
| Non-fatal | 1 (2) | 0 | 1 (<1) |
| Fatal | 0 | 0 | 0 |

**Table 25: Treatment Status and Reasons for Discontinuation of Study Treatment (Study 205203, Safety Population)**

| Status | Number (%) of Subjects | | |
|---|---|---|---|
| | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
| Treatment status | | | |
| Completed | 50 (96) | 49 (98) | 99 (97) |
| Withdrawn | 2 (4) | 1 (2) | 3 (3) |
| Primary reason[a]/subreason[b] for treatment discontinuation | | | |
| Adverse event | 1 (2) | 0 | 1 (<1) |
| Lack of efficacy | 0 | 0 | 0 |
| Protocol deviation | 0 | 0 | 0 |
| Subject reached protocol-defined stopping criteria | 0 | 0 | 0 |
| Study terminated by sponsor | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 |
| Site terminated by sponsor | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 |
| Withdrawal by subject | 1 (2) | 1 (2) | 2 (2) |
| Subject was hospitalized when Visit 5 was due and unable to come the long distance for appointment once dismissed. Visit 5 missed entirely. | 0 | 1 (2) | 1 (<1) |

Source: Table 1.2

**Table 26: Study Populations (Study 2052032, Screened Subjects)**

| Population | Number (%) of Subjects | | |
|---|---|---|---|
| | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
| Screened | 52 (100) | 50 (100) | 102 (100) |
| Enrolled | 52 (100) | 50 (100) | 102 (100) |
| Safety | 52 (100) | 50 (100) | 102 (100) |
| Pharmacodynamic | 51 (98) | 48 (96) | 99 (97) |

***Baseline data***

Overall, the majority of the subjects were White (93% [note: race information for France was not collected due to local restrictions]) and more than half were female (54%). The mean age was 46.0 years, and approximately 83% of the subjects were between 19 and 64 years of age. Four (4%) adolescent subjects (12-17 years of age) participated in this extension study.

**Table 27: Summary of Demographic Characteristics (Study 205203, Safety Population)**

| Demographic | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
|---|---|---|---|
| Sex, n (%) | | | |
| N | 52 | 50 | 102 |
| Female | 26 (50) | 29 (58) | 55 (54) |
| Male | 26 (50) | 21 (42) | 47 (46) |
| Age (years)[a] | | | |
| N | 52 | 50 | 102 |
| Mean (SD) | 45.5 (18.43) | 46.5 (11.99) | 46.0 (15.54) |
| Median | 44.0 | 48.0 | 48.0 |
| Min | 15 | 13 | 13 |
| Max | 81 | 71 | 81 |

| Demographic | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
|---|---|---|---|
| Age Group[a], n (%) | | | |
| ≤18 years | 3 (6) | 1 (2) | 4 (4) |
| 19-64 years | 39 (75) | 46 (92) | 85 (83) |
| ≥65 years | 10 (19) | 3 (6) | 13 (13) |
| Ethnicity[b], n (%) | | | |
| n | 43 | 42 | 85 |
| Hispanic or Latino | 9 (21) | 7 (17) | 16 (19) |
| Not Hispanic or Latino | 34 (79) | 35 (83) | 69 (81) |
| Race[b], n (%) | | | |
| n | 43 | 42 | 85 |
| American Indian or Alaskan Native | 2 (5) | 1 (2) | 3 (4) |
| Asian | 0 | 1 (2) | 1 (2) |
| Black or African American | 2 (5) | 0 | 2 (2) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 39 (91) | 40 (95) | 79 (93) |
| Height (cm) | | | |
| n | 52 | 50 | 102 |
| Mean (SD) | 168.5 (10.17) | 169.3 (10.21) | 168.9 (10.15) |
| Median | 167.5 | 169.5 | 168.0 |
| Min | 150 | 146 | 146 |
| Max | 192 | 191 | 192 |
| Weight (kg) | | | |
| n | 52 | 50 | 102 |
| Mean (SD) | 75.01 (17.087) | 76.27 (19.801) | 75.63 (18.386) |
| Median | 70.65 | 75.00 | 72.50 |
| Min | 44.0 | 38.0 | 38.0 |
| Max | 122.0 | 176.7 | 176.7 |
| Body Mass Index (kg/m$^2$) | | | |
| n | 52 | 50 | 102 |
| Mean (SD) | 26.45 (5.935) | 26.55 (6.261) | 26.50 (6.066) |
| Median | 24.78 | 25.49 | 25.12 |
| Min | 17.6 | 16.7 | 16.7 |
| Max | 41.0 | 59.7 | 59.7 |

**Prior and Concomitant Medications**

Prior and concomitant medications for the subjects participating in Study 205203 were similar to that of Study 200622. Almost all subjects (>99%) reported using concomitant medications during this extension study. The most frequently reported medications categories were alimentary tract and metabolism (87%), systemic hormonal preparations, excluding sex hormones and insulins (87%), and respiratory system (84%).

***Efficacy results***

Subjects remained on their SoC HES therapy while receiving mepolizumab. Investigators were permitted to adjust the subjects' background HES therapy per SoC starting at Visit 2 (approximately 4 weeks after the 1st dose).

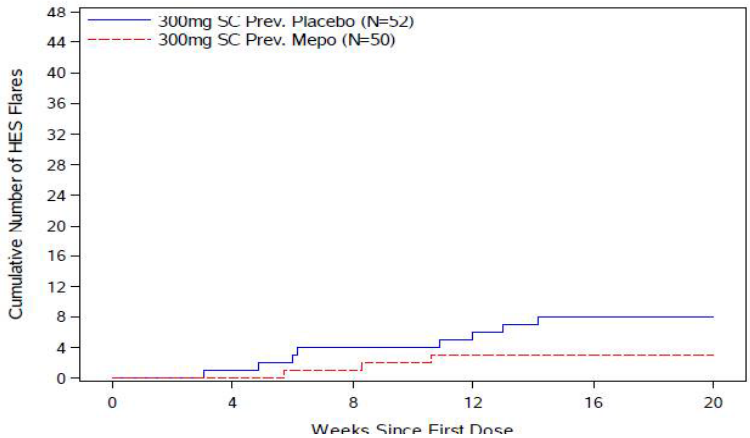
**Overview of HES Flares**

In total, there were 8 flares in 6 (12%) subjects previously treated with placebo and 3 flares in 3 (6%) subjects (1 flare each) previously treated with mepolizumab.

**Table 28: Overview of HES Flares (Study 205203, Safety Population)**

| Randomization to Week 20 | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
|---|---|---|---|
| n | 52 | 50 | 102 |
| All HES flares | | | |
| Number of subjects, n (%) | 6 (12) | 3 (6) | 9 (9) |
| Number of events | 8 | 3 | 11 |

**Figure 24: Cumulative Number of HES Flares (Study 205203, Safety Population)**




**Rate of HES Flares**

Overall, the estimated annualized rate of HES flares based on the 20-week treatment period was 0.26/year (95% CI 0.13, 0.52).

Subjects in Study 205203 who were previously treated with mepolizumab in Study 200622 had the lowest annualized rate of HES flares (adjusted mean rate/year: 0.14; 95% CI 0.04, 0.49). Subjects in Study 205203 who were previously treated with placebo in Study 200622 showed a similar annualized rate of HES flares to that observed in Study 200622 for subjects treated with mepolizumab (adjusted mean rate/year: 0.37 for both groups).

**Table 29: Summary of the Rate of HES Flares by Study (Study 200622 and Study 205203, Treatment Policy Estimand, Safety Population)**

| Rate of HES Flares | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
|---|---|---|---|
| Study 205203 (Week 32-52, open-label) | | | |
| n | 52 | 50 | 102 |
| 0, n (%) | 46 (88) | 47 (94) | 93 (91) |
| 1, n (%) | 4 (8) | 3 (6) | 7 (7) |
| 2, n (%) | 2 (4) | 0 | 2 (2) |
| 3, n (%) | 0 | 0 | 0 |
| 4, n (%) | 0 | 0 | 0 |
| Adjusted mean rate/year[a] | 0.37 | 0.14 | 0.26 |
| 95% CI | (0.16,0.86) | (0.04,0.49) | (0.13,0.52) |
| Study 200622 (Week 0-32, double-blind)[b] | | | |
| n | 52 | 50 | |
| 0, n (%) | 24 (46) | 39 (78) | |
| 1, n (%) | 15 (29) | 10 (20) | |
| 2, n (%) | 7 (13) | 1 (2) | |
| 3, n (%) | 5 (10) | 0 | |
| 4, n (%) | 1 (2) | 0 | |
| Adjusted mean rate/year[a] | 1.49 | 0.37 | |
| 95% CI | (1.09,2.05) | (0.21,0.68) | |

[redacted]

a. Negative binomial generalized linear model including terms for Baseline OCS dose from Study 200622, region and observed time (as an offset variable). A separate model is fitted to data from Study 200622 (Week 0 to 32) and Study 205203 (Week 32 to 52).

b. Study 200622 subjects presented in this table only include those subjects who continued into Study 205203.

Notes:

- For subjects withdrawing prematurely from the study, all data up to the time of study withdrawal were used to calculate the rate of HES flare.
- Definition of flares for Study 205203 (Week 32 to 52) differs from that for Study 200622 (Week 0 to 32) due to the requirements in Study 200622 to avoid decreases in background HES therapy that may confound a blinded subject's clinical status as well as the requirement during Study 200622 to blind blood eosinophil levels.

**Change in Mean Daily OCS Dose from Week 0 to 4 to Week 16 to 20**

As not all subjects were treated with OCS at Baseline, a separate analysis was performed including only those subjects with an OCS dose >0 mg during Week 0 to 4 to evaluate the effect of mepolizumab on OCS treatment. In the 73 subjects with a mean Week 0 to 4 OCS dose >0 mg/day (prednisone or equivalent), the mean dose of OCS (prednisone or equivalent) in Week 0 to 4 was 11.2 mg/day. The mean dose in these subjects decreased over time, with a mean dose of 10.6 mg/day at Week 4 to 8 and Week 8 to 12, 9.5 mg/day at Week 12 to 16, and 8.9 mg/day at Week 16 to 20. The mean change from Baseline OCS dose during Week 16 to 20 was -2.3 mg/day (prednisone or equivalent); a greater mean reduction was observed in subjects previously treated with placebo (-3.1 mg/day) compared with subjects previously treated with mepolizumab (-1.5 mg/day).

**Proportion of Subjects Who Achieved a Mean Daily OCS Dose ≤7.5mg during Week 16 to 20**

The proportion of all subjects who achieved a mean OCS dose ≤7.5mg/day (prednisone or equivalent) was 75% during Week 16 to 20 compared with 61% during Week 0 to 4.

**Proportion of Subjects Who Achieved a Mean Daily OCS Dose Reduction of ≥50% during Week 16 to 20**

During Week 16 to 20, 28% of all subjects with a mean Week 0 to 4 OCS dose >0 mg/day (prednisone or equivalent) had achieved a mean daily OCS dose reduction of 50%; a larger proportion of subjects previously treated with placebo achieved this reduction (37%) compared with subjects previously treated with mepolizumab (18%).

**b) MHE100185 study:**

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Phase III Study to Evaluate Corticosteroid reduction and -sparing Effects of Mepolizumab 750mg Intravenously in Subjects with Hypereosinophilic Syndrome (HES), and to Evaluate the Efficacy and Safety of Mepolizumab in Controlling the Clinical Signs and Symptoms of HES over Nine Months.

- **Study Participants**

This was a randomised placebo-controlled study comparing the addition of mepolizumab or placebo to prednisone therapy in patients whose clinical symptoms were stabilised with the use of prednisone monotherapy (20 to 60 mg/day). It was conducted from March 2004 to March 2006 in 26 centres: 11 in the USA (46% of the patients), 9 in the EU (3 in Belgium, 3 in Germany, 2 in France and one in Italy), 4 in Canada, and 2 in Australia.

Eligible subjects were:

- males and females, 18 to 85 years of age
- with a documented history of HES: peripheral blood eosinophils >1500 cells/μL for at least 6 months and signs/symptoms of organ system involvement or dysfunction directly related to eosinophilia and no evidence of parasitic, allergic, or other recognised causes of eosinophilia after comprehensive evaluation
- with a negative test for the presence of the FIP1-PGFRAα fusion gene
- with a stable prednisone monotherapy status prior to randomization, as reflected by a blood eosinophil count <1000 cells/μL with no new or worsening HES signs/symptoms on ≥20 mg to ≤60 mg once daily for at least 1 week.

Subjects that tested positive for FIP1L1-PDGFRα fusion gene were excluded from the study population, since they usually have a more aggressive myeloproliferative disease and develop acute myelogenous eosinophilic leukaemia.

- **Treatments**

The study comprised a Screening Visit, a prednisone run-in and stabilization period, a baseline Visit, a Treatment Period of 36 weeks and a Safety Follow Up (FU) Visit. After the initial screening, subjects will washout all the other HES medications, switch to prednisone and/or adjust their prednisone dose in order to achieve a stable prednisone monotherapy status. The Treatment Period commenced at Day 1 after randomization and completes at Week 36. Central randomization was applied using randomly permuted blocks within two strata based upon subjects' stable entry prednisone daily doses of ≤ 30 mg or >30 mg. Subjects in each strata were randomized at 1:1 ratio to receive either 750 mg mepolizumab iv infusion, or saline (as placebo) iv infusion every 4 weeks beginning from Day 1 until the last infusion at Week 32. Weekly prednisone taper started one week after the first dose following the Prednisone Taper Schedule. The maximum total study duration for a participating subject was 51 weeks.

The infusion solution, either mepolizumab 750 mg or saline, was administered over approximately 30 minutes once every 4 weeks beginning at Day 1 after randomisation until the last dose at Week 32, i.e. a total of 9 infusions. Patients received their infusions in the clinic. No other treatment for HES was permitted than prednisone (or equivalent). After screening, patients entered a run-in period of up to 6 weeks, during which all other treatments had to be discontinued and prednisone monotherapy was administered to achieve a stable clinical status as previously defined. Starting one week after the first infusion of the tested drug, prednisone taper followed a predefined weekly schedule.

Unblinded blood eosinophil counts were provided to investigators throughout the study since this was essential to guide disease management and the steroid tapering schedule in accordance with predefined guidelines.

- **Objectives**

The primary endpoint was the proportion of subjects who achieved a total daily prednisone dose of ≤10mg for a period of 8 consecutive weeks.

The following secondary endpoints were analyzed in a hierarchical manner for statistical differences between the placebo and mepolizumab treatment groups:

1. Proportion of subjects who maintained a blood eosinophil count of <600/µL for a period of 8 consecutive weeks during the Treatment Period.
2. Time until treatment failure with treatment failure defined as clinical worsening requiring other HES based therapy or an increase of prednisone dose to >60mg/day per discretion of the investigator, or withdrawal from the study for any reason.
3. Proportion of subjects who achieved a total daily prednisone dose of ≤7.5mg (sub-adrenal threshold) during the Treatment Period.
4. Proportion of subjects who were corticosteroid-free during the Treatment Period.
5. Mean total daily dose of prednisone.
6. Component analysis of QoL and current health status: improvement to physical summary score analysis of the SF-12v2.
7. Component analysis of QoL and current health status: improvement to mental summary score analysis of the SF-12v2.
8. Proportion of subjects who achieved a total daily prednisone dose of ≤10mg within 20 weeks and who maintained a total daily prednisone dose of ≤10mg for a period of 8 consecutive weeks.
9. Proportion of subjects who achieved total prednisone daily doses 12 weeks after randomization in the following categories: 0mg, 2.5-7.5mg, 10mg and >10mg, respectively.
10. Pruritus visual analogue scale (pVAS).
11. Erythema/oedema score.

**Results**

**Patient disposition and baseline characteristics**

A total of 107 subjects with HES were screened and 85 were randomized to treatment (42 to placebo and 43 to mepolizumab. Of the 22 screen failures, most (77%) were due to not fulfilling eligibility criteria for randomization. Demographics were generally comparable between the treatment groups. The majority of subjects were White (85%), >45 years of age (59%) (mean age 48 years) and received ≤30mg prednisone/day at baseline (71%). Overall, the distribution of sex was balanced; however there was a greater proportion of males in the mepolizumab group (60%) compared with the placebo group (40%). Most subjects (73%) had HES ≤5 years; 39% of subjects had HES for ≤1 year. Mean duration of the disease was greater in the placebo group (6.5 years) compared with the mepolizumab group (4.3 years). The mean age at onset was 43 years. The most prominent current HES-related conditions included skin/subcutaneous tissue disorders (47%) and respiratory disorders (41%). The incidence of skin disorders was higher in the placebo group (57%) than in the

mepolizumab group (37%). While the mepolizumab groups were generally comparable across regions patients in the NA placebo group were likely to be more severe than those in the ROW placebo group as reflected by baseline prednisone dose, incidence of prior HES therapies and HES-related medical conditions.

The majority of subjects randomized to the mepolizumab group (84%) completed the study, whereas the majority of subjects in the placebo group (64%) withdrew, primarily due to lack of efficacy (50% of subjects).

The patient disposition by region is shown in the table below.

**Table 30: The patient disposition**

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | North America | | Rest of the World | |
| Subject Disposition | Placebo N=29 | Mepolizumab 750mg N=21 | Placebo N=13 | Mepolizumab 750mg N=22 |
| Status | | | | |
| Completed | 7 (24) | 17 (81) | 8 (62) | 19 (86) |
| Withdrawn | 22 (76) | 4 (19) | 5 (38) | 3 (14) |
| Reason for WD | | | | |
| Lack of Efficacy | 18 (62) | 2 (10) | 3 (23) | 3 (14) |
| Adverse event | 1 (3) | 1 (5) | 1 (8) | 0 |
| Consent WD | 1 (3) | 1 (5) | 0 | 0 |
| Disease Progess | 0 | 0 | 1 (8) | 0 |
| Other | 2 (7) | 0 | 0 | 0 |

**Primary endpoint**

The proportion of responders for the primary endpoint was almost two-fold greater in the mepolizumab group (84%) compared with the placebo group (43%) and this difference was statistically significant Statistically significant differences were also observed in the proportion of responders between mepolizumab and placebo in the two baseline prednisone dose subgroups, with the difference being greater in the >30mg subgroup. In the analysis of primary endpoint, the Breslow-Day test did not reveal a statistically significant treatment by baseline prednisone dose level interaction.

The difference between the primary response rate (84% vs. 43%) was essentially due to the differential withdrawal rate between placebo (23/24 non responders) and mepolizumab (4/7 non responders) because, in this analysis, all withdrawals before the primary endpoint was achieved were assumed to be non-responders. However, the trial cannot be considered fully blinded since the investigator had access to blood eosinophil counts in order to adjust the prednisone tapering and might have been keen to enrol patients into the open label extension of the trial after withdrawal from the controlled trial. Therefore, this 'missing as failure' analysis has the potential to be highly biased in favour of mepolizumab. The MAH has not provided any evidence that these withdrawals were actually due to lack of efficacy in compliance with the protocol guidelines on prednisone taper and rescue. In the absence of detailed and documented information on the reason for each individual withdrawal from the study, the results of the primary 'missing as failure' analysis cannot provide a reliable estimate of the efficacy of mepolizumab.

**Table 31 : Proportion of patients achieving a total daily prednisone dose of ≤10mg for a period of at least 8 consecutive weeks**

| Baseline Prednisone Dose Level Group | Placebo N=42 | Mepolizumab 750mg N=43 |
|---|---|---|
| All subjects (all prednisone doses) | | |
| Number analyzed[1,2] | 42 | 43 |
| Responders[3], n (%) | 18 (43) | 36 (84) |
| Odds ratio vs. placebo | --- | 8.01 |
| [95% CI] | --- | [2.69, 23.78] |
| p-value | --- | <0.001 |
| <=30mg prednisone | | |
| Number analyzed[1] | 30 | 30 |
| Responders[3], n (%) | 17 (57) | 26 (87) |
| Odds ratio vs. placebo | --- | 4.97 |
| [95% CI] | --- | [1.39, 17.82] |
| p-value | --- | 0.011 |
| >30mg prednisone | | |
| Number analyzed[1] | 12 | 13 |
| Responders[3], n (%) | 1 (8) | 10 (77) |
| Odds ratio vs. placebo | --- | 36.67 |
| [95% CI] | --- | [3.26, 412.26] |
| p-value | --- | <0.001 |
| Breslow Day Test[4] p-value | --- | 0.140 |

[redacted]

1. Cochran-Mantel-Haenszel analysis.
2. Adjusted for baseline prednisone (or equivalent) dose (<=30mg/>30mg).
3. Subjects who achieved a total daily prednisone dose of <=10mg for a period of at least 8 consecutive weeks.
4. Assesses homogeneity of the odds ratios across strata.

The taper or weaning off prednisone can be considered beneficial as long as the disease remains well-controlled, based not only on blood eosinophil counts but also on an evaluation of the disease progression and the incidence, type, severity of the clinical flares occurring throughout the study. Such information is lacking although it is clear from the safety analyses that numerous HES-related events occurred during the study.

Although agreed with the Regulatory Authorities, the primary endpoint, i.e. the proportion of patients achieving a daily prednisone dose ≤ 10 mg for at least 8 consecutive weeks, does not appear a hard endpoint, especially for subjects on 20 mg/day at baseline. This is illustrated by a response rate of 100% in the 14 placebo patients on baseline prednisone dose of 20 mg/day. Therefore, more weight is given to more stringent endpoints.

**Treatment-by-region interaction**

The Breslow-Day test shows statistically significant treatment by region interaction with a p-value=0.006. The treatment effect is evident in North America, with the response rates being 24% in placebo group and 86% in the mepolizumab group. On the other hand, no treatment effect can be seen in the Rest of the World region, with the response rates being 85% and 82% in placebo and active treatment groups, respectively.

**Table 32: Analysis of Proportion of Subjects who Achieved a Total Daily Prednisone dose of <=10mg for a Period of at Least 8 Consecutive Weeks Stratified by Region (ITT population)**

| Baseline Prednisone Dose Level Group | Placebo N=42 | Mepolizumab 750mg N=43 |
|---|---|---|
| **All subjects (both regions)** | | |
| Number analyzed[1,2] | 42 | 43 |
| Responders[3], n (%) | 18 (43) | 36 (84) |
| Odds ratio vs. placebo | --- | 5.34 |
| [95% CI] | --- | [1.98, 14.40] |
| p-value | --- | <0.001 |
| **North America** | | |
| Number analyzed[1] | 29 | 21 |
| Responders[3], n (%) | 7 (24) | 18 (86) |
| Odds ratio vs. placebo | --- | 18.86 |
| [95% CI] | --- | [4.25, 83.59] |
| p-value | --- | <0.001 |
| **Rest of the World** | | |
| Number analyzed[1] | 13 | 22 |
| Responders[3], n (%) | 11 (85) | 18 (82) |
| Odds ratio vs. placebo | --- | 0.82 |
| [95% CI] | --- | [0.13, 5.23] |
| p-value | --- | 0.834 |
| Breslow Day Test[4] p-value | --- | 0.006 |

1. Cochran-Mantel-Haenszel analysis.
2. Adjusted for baseline prednisone (or equivalent) dose (<=30mg/>30mg).
3. Subjects who achieved a total daily prednisone dose of <=10mg for a period of at least 8 consecutive weeks.
4. Assesses homogeneity of the odds ratios across strata.

It can be seen in the table below that the treatment wise proportions of baseline prednisone levels are different between the regions. This imbalance may, at least partially, explain the significant interaction, since, as noticed earlier the treatment effect seems to depend on the baseline prednisone level. Individual centers were not considered in the analyses because of the small number of subjects in each center.

However, since placebo patients in North America were likely to be more severe than those in the ROW, this could explain why they were more likely to drop out. Thus, the imbalance in severity across regions coupled with the imbalance in assignment to placebo, suggests that this interaction can be explained.

**Table 33: Baseline Prednisone Dose (mg) by Region (ITT)**

| Baseline Prednisone Dose Level Group | North America | | Rest of the World | |
|---|---|---|---|---|
| | Placebo N=29 | Mepolizumab 750mg N=21 | Placebo N=13 | Mepolizumab 750mg N=22 |
| **All subjects (all doses), n** | 27[1] | 21 | 13 | 22 |
| Mean (SD) | 32.1 (12.1) | 27.1 (9.4) | 26.5 (10.9) | 31.3 (11.5) |
| **<=30mg prednisone, n** | 17 | 16 | 11 | 14 |
| Mean (SD) | 24.1 (4.4) | 22.7 (4.6) | 22.3 (3.4) | 23.8 (5.3) |
| **>30mg prednisone, n** | 10 | 5 | 2 | 8 |
| Mean (SD) | 45.8 (7.6) | 41.5 (4.9) | 50.0 (0.0) | 44.4 (6.2) |

1. Baseline prednisone data missing for 2 subjects

**Secondary endpoints**.

In the pivotal study, secondary endpoints were met for steroid sparing effects and reduction of eosinophil counts. Skin manifestations and pruritus were not changed Quality of life results did not show a clear effect. Comparisons of following secondary endpoints showed statistically significant overall difference between the response rates of mepolizumab and placebo groups:

1. proportion of subjects who maintained blood eosinophil count <600/ul for a period of at least 8 consecutive weeks during treatment period,
2. proportion of subjects who achieved a total daily prednisone dose of ≤7.5mg during the treatment period
3. proportion of subjects who were corticosteroid-free during the treatment period.

However, the Breslow-Day test revealed a statistically significant treatment by baseline prednisone dose level interaction (endpoints 1. and 2.; nearly statistically significant P-value=0.075 in endpoint 3.). Further, it is well known that the power of B-D test to detect even rather large clinically meaningful differences between odds ratios across strata is rather poor. The reason for the observed interactions is that the response rates in the placebo group of ≤ 30 mg prednisone strata are constantly higher than in the placebo group of >30 mg prednisone, but the response rates in the mepolizumab group are very similar over baseline prednisone strata. The results give an evidence for the claim that the difference between mepolizumab and placebo treatments depends on the level of baseline prednisone dose.

**Control of end-organ damage**

The long-term clinical benefits for morbidity or mortality resulting from reduction of end-organ complications or corticosteroid sparing are not evident based on current studies. No improvement or deterioration was observed in Neurological Examinations, Pulmonary function tests, CT scans of the abdomen, sinuses, or chest at Week 36, Echocardiograms or skin (based on Skin photographs).

In spite of the protocol planning repeated skin and GI tissue biopsies in patients affected at baseline, data were only available for 3 patients, respectively. This might have permitted to collect useful supporting information on eosinophil infiltration in these tissues since the level of eosinophilia is not a true reflection of organ damage.

**c) Study MHE100901:**

An Open-label Extension Study to Study MHE100185, to Evaluate Long-term Safety, Efficacy and Optimal Dosing Frequency of 750 mg Intravenous Mepolizumab in Subjects with Hypereosinophilic Syndrome.

This open-label study is an extension to Study MHE100185. It was designed to investigate the long-term safety, efficacy, and optimal dosing frequency of mepolizumab 750 mg IV infusion in subjects with various clinical manifestations of HES. The planned duration of the study was approximately 39 months. This study however was terminated by the sponsor (29 September 2010). Subjects eligible to continue mepolizumab treatment were transferred into the compassionate use program (study MHE104317).

The primary objective of this study was to evaluate the long-term safety of mepolizumab 750 mg IV infusion at maximum dosing frequency of once every month in subjects with HES.

Of the 85 subjects who participated in Study MHE100185, 78 subjects enrolled and received treatment in MHE100901 (ITT Population).

A subject could be withdrawn from the study at any time at the investigator's discretion or at the request of the subject. The reason for withdrawal was documented for all subjects prematurely withdrawing from the study. The most common reasons for withdrawal were adverse events and lack of efficacy (6 subjects for each). All study subjects received mepolizumab 750mg IV in variable dosing schedules in 3 stages:

- Stage 1: HES Medication Taper and Stabilization Period
- Stage 2: Optimization of Dosing Frequency
- Stage 3: Assessment of Long-Term Safety and Efficacy

**Patient disposition**

A total of 78 subjects from 23 centers were enrolled and received treatment in MHE100901; 38 subjects previously received placebo and 40 subjects previously received mepolizumab in Study MHE100185. There were no screen failures. Randomized subjects from study MHE100185 continued into this extension study: 36 in the United States, 27 in Europe (7 in Belgium, 7 in Germany, 10 in France and 3 in Italy), 8 in Canada, and 7 in Australia. Seven subjects did not continue from study MHE100185 into the extension study MHE100901.

Fifty-four subjects (69%) withdrew due to study MHE100901 termination by the sponsor. Ten subjects (13%) withdrew due to an AE. No subjects were withdrawn due to disease progression.

**Results**

Almost all subjects (43/48, 90%) who entered in Stage 2 with a daily prednisone dose of ≤10 mg were able to maintain a daily prednisone dose of ≤10 mg (as sole background therapy) for a continuous period of at least 12 weeks. The majority of subjects (22/30, 73%) who entered in Stage 1 with a daily prednisone dose of >10 mg achieved a daily prednisone dose of ≤10 mg (as sole background therapy) for a continuous period of at least 12 weeks. Eight of 20 responders remained at a daily prednisone dose of ≤10 mg for a continuous period of ≥144 weeks.

The mean daily prednisone dose for all subjects over the course of the study (5 mg) was lower compared with the mean baseline prednisone dose (12 mg). At the end of the study, 53 (68%) were corticosteroid-free and 25 (32%) were receiving corticosteroids.

Median eosinophil counts remained below 300 cells/µL at most post-baseline assessments for subjects receiving mepolizumab monotherapy or mepolizumab in conjunction with prednisone. At the end of Stage 2, nearly half of the subjects (30/59,51%) had a dosing interval between infusions that was >12 weeks. Median pVAS scores and erythema/oedema scores were low at baseline and remained low during treatment.

Minimal changes from baseline in median pVAS and median total erythema/oedema scores were observed.

## 2.4.4. Discussion on clinical efficacy

The MAH submitted a single pivotal placebo-controlled Phase III study, 200622 in support of this marketing authorization application. This study was supplemented with efficacy data from the OLE study 205203. Studies MHE100185 and MHE100901 were also provided by the MAH however, due to differences in patient population, endpoints, eosinophil blinding, and mepolizumab doses the role of these studies in support of this application is limited.

The MAH submitted a marketing authorization procedure for the treatment in patients with HES (EMEA/H/C/001069/00) back in September 2008. This application was withdrawn in July 2009 as it was considered that the submitted data was insufficient to grant the marketing authorization.

A dose of mepolizumab 300 mg administered SC every 4 weeks was selected for investigation in the pivotal study supporting this marketing authorization application. This dose was lower as compared to the dose investigated previously (i.e. 750 mg every 4 weeks) in studies MHE100185 and MHE100901. This new dose was based on the results of meta-analysis of 16 previous clinical trials investigating mepolizumab in several indications and integrating PK/PD data. The analysis shows that the clinical benefit beyond the planned dose of 300 mg sc q4w would be limited. This dose selection strategy was discussed as a part of the CHMP scientific advice and the approach taken by the MAH was considered acceptable.

## Design and conduct of clinical studies

In the pivotal study (200622) subjects were randomized 1:1 to receive either placebo or mepolizumab 300 mg subcutaneous (SC) every 4 weeks in addition to their maintenance HES treatment. The study consisted of 3 periods: screening (4 weeks), double-blind treatment period (32 weeks) and follow-up (8 weeks).Subjects that completed the 32-week treatment period were eligible to screen for a 20-week open label extension (study 205203) where all subjects received mepolizumab 300 mg SC every 4 weeks.

### Study population

The study was enrolling adult patients with at least 6-month diagnosis of HES. The diagnosis of HES was based on signs or symptoms of organ system involvement or dysfunction that could be directly related to high blood (>1500 eosinophils/µL) or tissue eosinophilia without a discernible secondary cause. The diagnostic criteria used in the study were similar to those proposed by Valent, 2012 and therefore they are considered acceptable.

The 200622 study was aimed to enrol a more severe HES population with a greater likelihood of experiencing a flare while receiving stable maintenance HES treatment. Therefore, at screening all patients were required to have blood eosinophil count >1000 cells/uL despite receiving SoC therapy. In addition, a history of two or more HES flares within the past 12 months prior to screening were required for enrolment.

HES encompasses a heterogeneous group of rare hematologic disorders with widely variable end organ complications and prognosis. This has led to the concept of HES subtypes or variants that can be distinguished on the basis of clinical and laboratory characteristics. In the 200622 study, HES variants were not required to be specified for enrolment with exception to patients with F/P fusion tyrosine kinase gene translocation. These patients were excluded from the study. Although many HES patients do not meet diagnostic criteria for any of the defined subtypes, the MAH was requested to provide information on the percentage of patients for whom HES variant was identified prior to the enrolment. The MAH clarified that the information on subtypes were not collected at baseline.

Patients with clinically significant cardiac damage, current active liver or biliary disease liver (with ALT >2.5xULN or ALT>5xULN or Bilirubin >1.5xULN) or life-threatening HES were excluded from the study. The SmPC was therefore updated to state in section 4.4 of the SmPC that Nucala has not been studied in patients with life-threatening manifestations of HES.

### Study treatment

In the study, patients received either placebo or mepolizumab 300 mg subcutaneous (SC) every 4 weeks in addition to their maintenance HES treatment. A stable dose of OCS, immunosuppressive or

cytotoxic therapy (e.g., hydroxyurea, IFNα, cyclosporine, imatinib, methotrexate, azathioprine) was permitted in the study.

If a subject had worsening of symptoms and required an increase in therapy after randomization, the subject was considered to have experienced a flare.

In case of an asymptomatic increase in eosinophil levels, triggered blinded OCS treatment could be initiated. A second increase in eosinophil levels which required such treatment was classified as a flare. In addition, each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare was considered as an additional flare (e.g., 3 courses of blinded active OCS were considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

**Study endpoints**

Primary endpoint

The primary endpoint in this study was the proportion of subjects who experienced a HES flare during the 32-week Treatment Period. HES flares were defined as either: (a) a HES-related clinical manifestation based on a physician documented change in clinical signs or symptoms resulting in the need for therapy adjustment (increase in OCS dose of at least 10mg/day or any increase in or addition of any cytotoxic/ immunosuppressive HES therapy), or (b) receipt of two or more courses of blinded active OCS during the study treatment period.

This endpoint was discussed during the CHMP scientific advice. While this primary endpoint has never been tested in previous trials, in principle, it was considered acceptable and clinically relevant for the selected target population.

The clinical presentation of HES covers a wide variety of end-organ manifestations. It is acknowledged that challenges exist in establishing an objective definition of flare in this disease. To improve the objectivity of this assessment the HES Core Assessments were utilized by investigators to characterize the disease at baseline and also to monitor the changes during the treatment period and the flare. However, as stated in the study report investigators ultimately used their clinical judgment to determine if a subject was experiencing a HES flare.

The definitions used to identify flares was based on an increase in the maintenance OCS dose by greater than or equal to 10 mg/day. The MAH clarified that although some events of OCS dose increase were less than 10 mg/day or for fewer than 5 days and therefore not reported as a flare, the number of such events was small i.e. 3 patients in the mepolizumab treated group received an increase in OCS dose not fulfilling the definition of a HES flare as compared to 7 placebo treated patients. It is agreed with the MAH that this is unlikely to affect the study results.

It needs to be highlighted that the efficacy of mepolizumab in preventing of development of HES flares was investigated in patients for whom background medications were maintained. In clinical practice, however withdrawing background medications, especially oral corticosteroids would be an important treatment goal.

Three out of 4 secondary endpoints under multiplicity adjustment strategy were also investigated the effect of mepolizumab on flares. These endpoints were: time to first HES flare, proportion of subjects who experienced a HES flare during Week 20 through Week 32 and rate of HES flares.

A primary focus of the pivotal study was the assessment of efficacy of mepolizumab in reducing exacerbations (flares). On the other hand, the effects of mepolizumab on other aspects of the disease or symptoms were only briefly examined.

Various patient reported outcome questionnaires were used in the study to assess changes in symptoms in patients receiving mepolizumab as compared to those on placebo. However, only one endpoint investigating the effect on fatigue severity (Brief Fatigue Inventory [BFI]) score item 3) was under multiplicity adjustment strategy. The CHMP requested the MAH to justify the use of this endpoint for the assessment of patients with HES as detailed below. The clarification was considered acceptable.

The MAH clarified that prior to designing the pivotal HES study, they ran a dedicated PRO study with the HES team at the US National Institute of Health (NIH) in order to create a HES PRO as there is no validated PRO in HES available. Unfortunately, the results of the HES PRO study with NIH were too heterogeneous and a HES specific PRO was unable to be established [Kovacs, 2020]. In light of these results, the MAH discussed and agreed with a HES expert that it would be appropriate to use the BFI in HES to capture the patient perspective of fatigue, a key symptom of HES.

Exploratory assessments in respect to changes in symptoms scores included the use of the following scales: HES Daily Symptoms (HES-DS), Clinician- and Subject-Rated Overall Response to Therapy Score (RTS), Subject-Rated Symptom Severity (SSR) and Modified Memorial symptom Assessment Scale-Short Form (MSAS-SF).

Organ-specific disease activity was investigated through the use of the lung function test and echocardiogram scans.

## Efficacy data and additional analyses

In total, 108 subjects were randomized and received at least one dose of study treatment (54 to placebo and 54 to mepolizumab). The majority of subjects in the ITT Population completed the study (104, 96%) and 102 subjects continued treatment in the OLE study 205203 (94%). Of the 6 (6%) subjects who prematurely discontinued study treatment, 4 subjects also withdrew from the study and 2 continued participation in the study until Week 32 and Follow-up.

**Baseline characteristics**

Overall, the majority of the subjects enrolled to this pivotal study were white (93%) and more than half were female (53%). The mean age was 46.0 years and approximately 83% of the subjects were between 19 and 64 years of age. Only 14 subjects were over 65 years of age and only 4 adolescents were enrolled to this study.

People with HES may suffer from a wide variety of symptoms, depending upon which parts of the body are affected. The MAH presented HES related symptoms reported by patients at baseline which were varied across subjects; breathing symptoms were the most common and were reported by 56% of subjects in both treatment groups.

At baseline, almost all subjects (92%) had received regular maintenance medications for HES. OCS were used most frequently (72%). The median dose was 5.6 mg/day and maximum dose of 50 mg/day. More subjects in the mepolizumab group (26%) were receiving cytotoxic/immunosuppressive therapy at baseline compared with the placebo group (17%). In line with the trial protocol, the dose of the maintenance/ background medications for HES should not be changed during the study.

The information regarding the baseline characteristic of the study population provided by the MAH was insufficient. The following additional information was requested to be provided:

- The number of HES flares within the past 12 months prior to Screening and percentage of patients who reported two, three or more flares in the past 12 months. The primary endpoint results should be provided depending on the number of flares prior to screening

- blood eosinophil count at screening. The MAH should also clarify the percentage of patients for whom diagnosis of HES were made on the basis of tissue eosinophil as opposite to blood eosinophila

The MAH provided information on the number of HES flares within the past 12 months prior to Screening and percentage of patients who reported two, three or more flares in the past 12 months. It is noted that the distribution of the frequency of HES flares pre-study was similar across both treatment groups. Further, the efficacy was shown both in patients who reported two flares and in patients who reported three or more flares in the past 12 months. The mean Blood Eosinophil Count (10^9/L) at Screening was 1.69 in the placebo group and 1.50 in the treatment group.

**Primary endpoint results**

The proportion of subjects who experience a HES flare during the 32-week treatment period was investigated as a primary endpoint in this study.

This primary endpoint was met as significantly less flares were reported in patients treated with mepolizumab as compared to those on placebo i.e. there were 17 flares in 14 (26%) subjects randomized to mepolizumab compared to 48 flares in 28 (52%) subjects in the placebo group. The odd ratio for comparison of mepolizumab 300 mg vs placebo (primary analysis) was 0.28 (95%CI (0.12, 0.64, p value=0.003).

The primary outcome (HES flare) was defined as: an increase in the maintenance OCS dose by at least 10mg/day for 5 days, an increase in or addition of any cytotoxic and/or immunosuppressive HES therapy or receipt of two or more courses of blinded active OCS during the treatment period.

The results of sensitivity analysis of the primary estimand and the results of the supplementary 'while on treatment' estimand and the analysis of the PP population were also consistent with the primary estimand.

The MAH was requested to clarify the approach to patients who will be experiencing flares while on mepolizumab treatment in particular the MAH was requested to discuss in more detail what criteria should be used to declare the lack of efficacy in HES patients. In addition, the MAH was requested to discuss approach to patients for whom a long-term remission was achieved. The MAH clarified that there is no accepted definition of remission and/or its assessment criteria which could be used standardly in clinical practice to declare either lack of efficacy or achievement of long-term remission. The decision to stop or continue mepolizumab treatment of HES patients shall be based on the physician's clinical judgment, which is guided by the patient's overall clinical status and its background medication. Therefore ,the following text was included in the SmPC section 4.1.and agreed with CHMP, reflecting also that mepolizumab was not studied in patients with life-threatening HES condition.:

*Nucala is intended for long-term treatment. The need for continued therapy should be considered reviewed at least on an annual basis determined by physician assessment of the patient's disease severity and level of symptom control. Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population*

**Secondary and exploratory endpoints**

Three out of 4 secondary endpoints (under multiplicity adjustment strategy) were also based around flares. The results of these secondary endpoints were consistent with the primary endpoint results. The risk of a first HES flare over the treatment period was 66% lower for subjects treated with mepolizumab compared with placebo (hazard ratio: 0.34; 95% CI 0.18, 0.67). From Week 20 through Week 32, fewer subjects experienced a HES flare or withdrew from the study when treated with

mepolizumab compared with placebo (17% vs. 35% respectively, p=0.020). Finally, the treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of HES flares (calculated for each subject as number of HES flares divided by time in the study) compared with placebo (adjusted p=0.020).

Only one secondary endpoint was not investigating flares but assessed the effect on fatigue severity by using Brief Fatigue Inventory [BFI]) score. Using this score a statistically significant reduction in fatigue severity was reported at Week 32 for subjects treated with mepolizumab compared to those in the placebo group (unadjusted p=0.036; adjusted p=0.036).

Some exploratory endpoints also recorded improvements in symptoms. For HES Daily Symptoms (HES-DS) scale there was a significant reduction (improvement) in the most bothersome symptom score at Week 32 for subjects treated with mepolizumab compared with placebo.

Only limited organ-specific assessments were performed in the study i.e. lung function tests and echocardiogram scans. These tests showed no difference between the treatment groups. Other assessments such as neurological examinations, CT scans of the abdomen, sinuses, or chest, or skin assessments were not performed. The MAH clarified that while cardiac dysfunction is a progress event that can be monitored and associated with hypereosinophilia [Lefebvre 1989], others are episodic or no objective monitoring measures are available. Some of organ involvements are predominantly shown as symptoms without objective assessment, e.g., gastrointestinal involvement is assessed by presence of abdominal pain, nausea/vomiting, or diarrhea [Williams, 2016], the assessment of control of disease activity is the combination of subjective (symptoms) and objective (signs) measures. This justification was considered acceptable.

The primary endpoint results were also examined in the subgroup depending on age, sex, race, geographic region, weight, baseline OCS, and baseline blood eosinophils. The MAH claimed that in all these subgroups, the proportion of subjects who experienced ≥1 HES flare or who withdrew from the study during the 32-week Treatment Period was lower in the mepolizumab group compared with placebo.

**Long term efficacy**

The long-term efficacy was assessed in the open label extension (OLE) study 205203.

In this study, although subjects could remain on their SoC HES therapy while receiving mepolizumab, investigators were permitted to adjust the subjects' background HES therapy per SoC starting at Visit 2 (approximately 4 weeks after the 1st dose).

In the OLE study flares were reported infrequently with slightly better results reported in patients treated with mepolizumab in the parent study as compared to those who originally received placebo. In total, there were 8 flares in 6 (12%) subjects previously treated with placebo and 3 flares in 3 (6%) subjects previously treated with mepolizumab. Overall, the estimated annualized rate of HES flares based on the 20-week treatment period was 0.26/year (95% CI 0.13, 0.52) which was lower than the rate recorded in the pivotal study (0.5/year in the mepolizumab group and 1.46/year in the placebo group). In the extension study, some small reduction in the OCS dose was possible. The mean change from baseline OCS dose during Week 16 to 20 was -2.3 mg/day (prednisone or equivalent). The proportion of all subjects who achieved a mean OCS dose ≤7.5mg/day (prednisone or equivalent) was 75% during Week 16 to 20 compared with 61% during Week 0 to 4.

In general, the results of the OLE study are supportive although the limitation of the design (open label, lack of comparator) is noted.

**The comparison to the original authorization procedures for HES**

Some limitations identified during the original procedure (EMEA/H/C/001069/00) have been addressed with the current submission.

The primary endpoint in the originally submitted pivotal MHE100185 study was the proportion of subjects who achieved a total daily prednisone dose of ≤10mg for a period of 8 consecutive weeks.

This primary endpoint was met however, the difference between the primary response rate (84% vs. 43%) was essentially due to the differential withdrawal rate between placebo (23/24 non responders) and mepolizumab (4/7 non responders) because, in this analysis, all withdrawals before the primary endpoint was achieved were assumed to be non-responders. However, the trial cannot be considered fully blinded since the investigator had access to blood eosinophil counts in order to adjust the prednisone tapering and might have been keen to enrol patients into the open label extension of the trial after withdrawal from the controlled trial. Therefore, this 'missing as failure' analysis had the potential to be highly biased in favour of mepolizumab. Additionally, the MAH has not provided any evidence that these withdrawals were actually due to lack of efficacy in compliance with the protocol guidelines on prednisone taper and rescue.

In the current submission, the percentages of patients who withdrew from the pivotal study (200622) in both treatment groups was very small and investigators were blinded to blood eosinophil counts of their patients.

In the MHE100185 study, the disease control was not documented and information on all HES-related events (disease exacerbations and progression) was not provided. For this reason, it was not clear if patients for whom reduction in the corticosteroid dose was achieved remained stable.

In the pivotal study (200622) provided with this submission, the effects on disease exacerbations (flares) were assessed in the primary endpoint and a number of secondary endpoints.

**Additional aspects related to the indication**

Various patterns of disease courses are observed in hypereosinophilic syndromes (HES). Some patients are experiencing a single flare without subsequent relapse. For these patients a long-term therapy is unlikely to be needed. Others suffer from several relapses with intervals of complete remission. Last, a third set of patients have chronic persistent disease. It seems that the majority of patients enrolled to the pivotal study have relapsing or maybe also persistent disease.

The following indication was initially proposed by the MAH:

*Nucala is indicated for the treatment of adult patients with hypereosinophilic syndrome.*

It was considered that the proposed indication was very broad and did not reflect the population of patients investigated in the pivotal study.

The pivotal study was only enrolling the more severe patients, as all were required to have blood eosinophil count >1000 cells/uL despite receiving SoC therapy. In addition, a history of two or more HES flares within the past 12 months prior to screening were required for enrolment. In addition, patients with F/P fusion tyrosine kinase gene translocation were excluded. Finally, in the pivotal study mepolizumab was given as add on therapy to standard maintenance therapy of HES.

During the assessment of the application, the MAH was requested by CHMP to discuss and justify why the criteria which defined severity of the disease were not reflected in the text of the indication.

The applicant was requested to:

- update the indication reflecting that Nucala is to be given to patients with relapsing or persistent disease i.e. receiving a chronic therapy for the HES.
- highlight that patients with 'severe HES' were enrolled to the pivotal study. As there is no accepted definition for severe HES in the medical community the use the term "inadequately controlled" to appropriately qualify the study population was considered more meaningful to prescribers. Further details of inadequate control are described in the study eligibility criteria in section 5.1 of the SmPC.

Further the MAH agreed to the CHMP request to reflect the use of mepolizumab in patients without an identifiable non-haematologic secondary cause, based on the aetiologies of HES and the pharmacological activity of mepolizumab.

The wording of the updated indication reads:

*Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see Section 5.1)*

### 2.4.5. Conclusions on the clinical efficacy

All concerns in relation to the efficacy data is considered adequate to support the revised restricted indication as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause.

## *2.5. Clinical safety*

### Introduction

This Safety Summary focuses on the safety data from clinical studies in subjects with hypereosinophilic syndrome (HES) and also includes key safety data from the broader mepolizumab development program. Safety data from the 193 subjects (97 exposed to mepolizumab) participating in the 2 completed placebo-controlled Phase 3 HES studies, 200622 and MHE100185, have been integrated.

The 300 mg subcutaneous (SC) dose for mepolizumab, which is the dose intended for registration, was assessed in pivotal Phase 3 placebo-controlled study 200622 and supportive open-label extension (OLE) study 205203.

The 750 mg intravenous (IV) dose was assessed in completed supportive Phase 3 placebo-controlled study MHE100185 and completed supportive OLE study MHE100901. Additionally, doses up to 750 mg IV are utilized in the ongoing mepolizumab HES Expanded Access Program (EAP).

For the assessment of mepolizumab safety, the completed MAH-sponsored clinical studies and those ongoing MAH-sponsored studies with interim safety data are grouped into 2 sets.

HES Placebo Controlled Studies: HES studies 200622 and MHE100185 were integrated as these are the 2 completed placebo-controlled studies in the HES indication. The integrated HES studies, 200622 and MHE100185, comprise the study grouping referred to as 'HES Placebo Controlled Studies'; these data are the primary focus of this Safety Summary.

All Studies Combined: The study grouping referred to as 'All Studies Combined' comprises of completed MAH-sponsored studies and ongoing studies with an interim report across all indications. In this Safety Summary, integrated summaries of demographics, exposure, incidence of SAEs and deaths

will be presented. For the completed supportive HES OLE studies 205203 and MHE100901, and for the ongoing mepolizumab HES EAP with an interim report, demographics, exposure, and key safety information, such as adverse events (AEs), SAEs, and deaths are summarized.

## Patient exposure

A total of 97 subjects received at least 1 dose of mepolizumab in the HES Placebo Controlled Studies. Of these, 54 subjects were treated with mepolizumab 300 mg SC and 43 subjects were treated with mepolizumab 750 mg IV. Total treatment exposure in the HES Placebo Controlled Studies was 50.69 subject-years in the integrated placebo group and 59.78 subject-years in the mepolizumab all doses group (32.51 subject-years in the mepolizumab 300 mg SC group and 27.27 subject-years in the mepolizumab 750 mg IV group) (***Table 34***). Due to the design of Study MHE100185, and a larger number of subject withdrawals from the placebo group, the duration of exposure to mepolizumab in the HES Placebo Controlled Studies was approximately 17% longer than exposure to placebo.

The majority of subjects in the HES Placebo Controlled Studies who were treated with mepolizumab (82%), were exposed to study treatment for 6 to <9 months (94% for mepolizumab 300 mg SC and 67% for mepolizumab 750 mg IV). Similarly, 71% of subjects who received placebo were exposed to study treatment for 6 to <9 months. The mean number of treatment administrations in the HES Placebo Controlled Studies was 6.8 in the placebo group and 7.9 in the mepolizumab group.

**Table 34: Summary of Exposure to Study Treatment by Dose (HES Placebo Controlled Studies, Safety Population)**

| | 200622 | | MHE100185 | | Both studies | |
|---|---|---|---|---|---|---|
| Treatment Exposure | PBO N=54 | Mepo 300 mg SC N=54 | PBO N =42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 |
| **Exposure (therapeutic coverage)[1], (months), n** | | | | | | |
| Mean (SD) | 7.2 (1.15) | 7.2 (1.04) | 5.2 (2.64) | 7.6 (1.94) | 6.3 (2.17) | 7.4 (1.51) |
| Median | 7.4 | 7.4 | 4.2 | 8.3 | 7.4 | 7.6 |
| Min, Max | 2, 8 | 2, 8 | 1, 9 | 2, 10 | 1, 9 | 2, 10 |
| **Range of Exposure [1], n(%)** | | | | | | |
| 1 to <3 months | 2 (4) | 1 (2) | 6 (14) | 2 (5) | 8 (8) | 3 (3) |
| 3 to <6 months | 1 (2) | 2 (4) | 17 (40) | 4 (9) | 18 (19) | 6 (6) |
| 6 to <9 months | 51 (94) | 51 (94) | 17 (40) | 29 (67) | 68 (71) | 80 (82) |
| 9 to <12 months | 0 | 0 | 2 (5) | 8 (19) | 2 (2) | 8 (8) |
| **Subject-years Exposure [2]** | 32.45 | 32.51 | 18.23 | 27.27 | 50.69 | 59.78 |
| **Treatments Administered** | | | | | | |
| Mean (SD) | 7.7 (1.20) | 7.7 (1.14) | 5.5 (2.86) | 8.1 (2.05) | 6.8 (2.35) | 7.9 (1.61) |
| Median | 8.0 | 8.0 | 4.5 | 9.0 | 8.0 | 8.0 |
| Min, Max | 2, 8 | 2, 9 | 1, 9 | 2, 9 | 1, 9 | 2, 9 |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Max = maximum; Mepo = mepolizumab; Min = minimum; PBO = placebo; SC = subcutaneously; SD = standard deviation.

1. Exposure (Therapeutic Coverage) = Treatment stop date - Treatment start date + 29. For the categorical summary, exposure is rounded to the nearest whole month.
2. Sum across subjects of (treatment stop date - treatment start date + 29)/365.25.

Note: Studies included: 200622 and MHE100185.

**OLE HES Study 205203**

A total of 102 subjects received at least 1 dose of mepolizumab 300 mg SC in Study 205203, with a total exposure of 39.26 subject-years.

**OLE HES Study MHE100901**

A total of 78 subjects received at least 1 dose of mepolizumab 750 mg IV in Study MHE100901, with a total exposure of 286.96 subject-years.

**Exposure in Ongoing Mepolizumab HES EAP**

As of the mepolizumab HES EAP iCSR cut-off date, a total of 338 patients were recorded as receiving at least 1 dose of mepolizumab in MHE104317. In MHE104317, the mean SC dose of mepolizumab per patient was calculated, and the median of these values was 823.4 mg. In addition, as of the iCSR cut-off date, 15 patients were recorded as receiving at least 1 dose of mepolizumab in the Initial Compassionate Use Program and 18 patients were recorded as receiving at least 1 dose of mepolizumab in the NPS Guidance Program.

**Overall Exposure in HES**

Overall, 462 subjects with HES received at least 1 dose of mepolizumab (***Table 35***). There were 106 HES subjects who received at least 1 dose of mepolizumab as a fixed dose of 300 mg SC, 81 HES subjects who received at least 1 dose of mepolizumab as a fixed dose of 750 mg IV, and a total of 359 HES patients who received at least 1 dose of mepolizumab as a variable dose based on clinical need in the mepolizumab HES EAP (all patients receiving mepolizumab in the mepolizumab HES EAP are included in the 'other' dose group). Subjects participating in more than 1 study or program and receiving different doses of mepolizumab were counted only once in each dose category; the 750 mg IV dose group in the summary tables does not include those patients who received 750 mg IV in the mepolizumab HES EAP. Overall, 96 subjects with HES received at least 1 dose of placebo. Total treatment exposure of HES subjects to mepolizumab 300 mg SC was 71.41 subject-years, to 750 mg IV was 320.04 subject-years, and total treatment exposure in the mepolizumab HES EAP ('other' mepolizumab doses) was 1520.12 subject-years.

**Table 35: Summary of Exposure (Therapeutic Coverage) to Study Treatment in the HES Program (All Studies Combined, Safety Population)**

| | PBO | Mepolizumab | | | |
|---|---|---|---|---|---|
| | | 300 SC | 750 IV | Other[1, 4] | All doses[4] |
| **Subjects in the Safety Population (HES program), n** | 96 | 106 | 81 | 359 | 462 |
| **Range of Exposure[2], n (%)** | 96 | 106 | 81 | 353 | 456 |
| 1 - <3 months | 8 (8) | 2 (2) | 3 (4) | 30 (8) | 27 (6) |
| 3 - <6 months | 18 (19) | 53 (50) | 2 (2) | 48 (14) | 74 (16) |
| 6 - <9 months | 68 (71) | 1 (<1) | 6 (7) | 30 (8) | 32 (7) |
| 9 - <12 months | 2 (2) | 1 (<1) | 1 (1) | 12 (3) | 17 (4) |
| 12 - <24 months | 0 | 49 (46) | 9 (11) | 37 (10) | 97 (21) |
| 24 - <36 months | 0 | 0 | 1 (1) | 24 (7) | 25 (5) |
| 36 - <48 months | 0 | 0 | 1 (1) | 12 (3) | 12 (3) |
| 48 - <60 months | 0 | 0 | 21 (26) | 17 (5) | 18 (4) |
| ≥60 months | 0 | 0 | 37 (46) | 143 (41) | 154 (34) |
| **Exposure (Months)[2], n** | 96 | 106 | 81 | 353 | 456 |
| Mean (SD) | 6.3 (2.17) | 8.1 (3.80) | 47.4 (23.25) | 51.7 (48.83) | 50.3 (55.82) |
| Median | 7.4 | 5.1 | 58.3 | 33.8 | 17.8 |
| Min, Max | 1, 9 | 1, 13 | 1, 71 | 1, 201 | 1, 201 |
| **Total Subject-years Exposure[3]** | 50.69 | 71.41 | 320.04 | 1520.12 | 1910.44 |

[redacted]

Abbreviations: EAP = Expanded Access Program; HES = hypereosinophilic syndrome; IM = intramuscularly; ISS = Integrated Summary of Safety; IV = intravenously; Max = maximum; Min = minimum; PBO = placebo; SC = subcutaneously; SD = standard deviation.

1. Includes IV doses: 10 mg, 750 mg/1500 mg, 0.05, 0.5, 0.55, 2.5, and 10 mg/kg, SC doses: 12.5, 40, 40/100, 125, and 250 mg and IM dose: 250 mg. In addition includes all subjects enrolled in the mepolizumab HES EAP.
2. Exposure Duration (Months) = (Treatment stop date - Treatment start date + 29)/365.25.
3. Sum across subjects of (treatment stop date - treatment start date + 29)/365.25.
4. For 6 subjects in the HES EAP, exposure duration was not recorded.

Note: A subject who participated in more than 1 study and received different doses was counted once in each dose.
Note: Studies included: 200622, MHE100185, 205203, MHE100901, Mepolizumab HES EAP (MHE104317/ MHE112562/ 112000).

**Demographics**

In the HES Placebo Controlled Studies, the majority of subjects were White (90%), and 51% of subjects were female (***Table 36***). Subjects of African American/ African Heritage comprise 5% of the population, Asian subjects comprise 3% of the population, and American Indian or Alaskan Native subjects comprise 2% of the population. Subjects of Hispanic/Latino ethnicity comprised 16% of subjects where data is available (ethnicity was collected in Study 200622 only). The mean age of subjects in the HES Placebo Controlled Studies was 46.9 years. The majority of subjects (83%) were between 18 and 64 years of age and 4 subjects (2%) were ≤17 years of age. Demographics were balanced across the placebo and mepolizumab treatment groups.

**Table 36: Demographics (HES Placebo Controlled Studies, Safety Population)**

| | 200622 | | MHE100185 | | Both studies | | Total |
|---|---|---|---|---|---|---|---|
| Demographic | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 | N=193 |
| Gender (n[%]), n | 54 | 54 | 42 | 43 | 96 | 97 | 193 |
| Female | 27 (50) | 30 (56) | 25 (60) | 17 (40) | 52 (54) | 47 (48) | 99 (51) |
| Male | 27 (50) | 24 (44) | 17 (40) | 26 (60) | 44 (46) | 50 (52) | 94 (49) |
| Age (years), n | 54 | 54 | 42 | 43 | 96 | 97 | 193 |
| Mean (SD) | 45.4 (18.25) | 46.6 (12.99) | 49.1 (14.39) | 47.0 (16.22) | 47.0 (16.70) | 46.8 (14.43) | 46.9 (15.56) |
| Median | 44.5 | 48.0 | 50.5 | 47.0 | 48.0 | 48.0 | 48.0 |
| Min, Max | 15, 80 | 12, 82 | 19, 75 | 18, 74 | 15, 80 | 12, 82 | 12, 82 |
| Age Group (years), n(%) | | | | | | | |
| 12-17 | 3 (6) | 1 (2) | 0 | 0 | 3 (3) | 1 (1) | 4 (2) |
| 18-64 | 41 (76) | 49 (91) | 35 (83) | 35 (81) | 76 (79) | 84 (87) | 160 (83) |
| ≥65 | 10 (19) | 4 (7) | 7 (17) | 8 (19) | 17 (18) | 12 (12) | 29 (15) |
| Race (n[%]), n | 54 | 54 | 42 | 43 | 96 | 97 | 193 |
| White | 48 (89) | 52 (96) | 36 (86) | 38 (88) | 84 (88) | 90 (93) | 174 (90) |
| African American/ African Heritage | 2 (4) | 0 | 5 (12) | 3 (7) | 7 (7) | 3 (3) | 10 (5) |
| Asian | 2 (4) | 1 (2) | 1 (2) | 2 (5) | 3 (3) | 3 (3) | 6 (3) |
| American Indian or Alaskan Native | 2 (4) | 1 (2) | 0 | 0 | 2 (2) | 1 (1) | 3 (2) |
| Ethnicity [1] (n[%]), n | 54 | 54 | | | 54 | 54 | 108 |
| Not Hispanic/Latino | 46 (85) | 45 (83) | | | 46 (85) | 45 (83) | 91 (84) |
| Hispanic/Latino | 8 (15) | 9 (17) | | | 8 (15) | 9 (17) | 17 (16) |
| BMI (kg/m²), n | 54 | 54 | 42 | 43 | 96 | 97 | 193 |
| Mean (SD) | 26.20 (5.934) | 26.38 (5.885) | 27.81 (5.843) | 27.04 (6.424) | 26.91 (5.918) | 26.67 (6.106) | 26.79 (5.999) |
| Median | 25.07 | 24.94 | 26.09 | 25.67 | 25.41 | 25.26 | 25.32 |
| Min, Max | 16.4, 41.9 | 16.0, 57.8 | 21.5, 47.0 | 15.2, 43.4 | 16.4, 47.0 | 15.2, 57.8 | 15.2, 57.8 |

[redacted]

Abbreviations: BMI = body mass index; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Max = maximum; Mepo = mepolizumab; Min = minimum; PBO = placebo; SC = subcutaneously; SD = standard deviation.

1. Ethnicity not collected in Study MHE100185.

Note: Studies included: 200622 and MHE100185.

In the HES Placebo Controlled Studies, mean disease duration was 6.02 years in the placebo group and 4.94 years in the mepolizumab group. In both groups, the majority of subjects had HES for ≤5 years (73% in the placebo group and 64% in the mepolizumab group).

## Adverse events

**Table 37** shows the proportion of subjects reporting the most common on-treatment AEs (defined as AEs with an incidence of ≥3% in any treatment group) in the HES Placebo Controlled Studies and the corresponding event rates adjusted for exposure (frequency of events per 1000 subject-years of exposure). The incidences of on-treatment AEs was similar between the placebo (92%) and mepolizumab all doses group (91%). The most common on-treatment AEs in the HES Placebo Controlled Studies in both the placebo and mepolizumab all doses groups were headache, fatigue, and pruritus (**Table 37**). The AE that occurred with a higher incidence in the mepolizumab all doses group compared with the placebo group (>10% difference) was URTI. Cough was reported with a >10% higher incidence in the placebo group compared with the mepolizumab all doses group.

Relative risks using the CMH method were calculated for the most common on-treatment AEs for placebo and mepolizumab (all doses), together with the corresponding CMH-adjusted proportions (**Figure 25**). The relative risk for mepolizumab all doses vs placebo for URTI was 2.79 (95% confidence intervals [CI]: 1.16, 6.75). URTI and related events are described further under AESIs.

**Table 37: Most Frequent On-Treatment Adverse Events Occurring in ≥3% of Subjects in the Integrated Placebo or Mepolizumab All doses Group (HES Placebo Controlled Studies, Safety Population)**

| | 200622 | | | | MHE100185 | | | | Both studies | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PBO | | Mepo 300 mg SC | | PBO | | Mepo 750 mg IV | | PBO | | Mepo all doses | |
| | N=54 | | N=54 | | N=42 | | N=43 | | N=96 | | N=97 | |
| Preferred term | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] |
| **Any on-treatment AE** | 47 (87) | 8628.2 [280] | 48 (89) | 10180.0 [331] | 41 (98) | 17439.9 [318] | 40 (93) | 15843.8 [432] | 88 (92) | 11798.2 [598] | 88 (91) | 12763.3 [763] |
| Headache | 7 (13) | 462.2 [15] | 7 (13) | 338.3 [11] | 9 (21) | 603.3 [11] | 10 (23) | 623.5 [17] | 16 (17) | 513.0 [26] | 17 (18) | 468.4 [28] |
| Fatigue | 5 (9) | 277.3 [9] | 3 (6) | 92.3 [3] | 11 (26) | 822.6 [15] | 13 (30) | 623.5 [17] | 16 (17) | 473.5 [24] | 16 (16) | 334.6 [20] |
| Pruritus | 7 (13) | 246.5 [8] | 4 (7) | 123.0 [4] | 9 (21) | 493.6 [9] | 12 (28) | 586.8 [16] | 16 (17) | 335.4 [17] | 16 (16) | 334.6 [20] |
| Bronchitis | 10 (19) | 369.8 [12] | 8 (15) | 246.0 [8] | 1 (2) | 54.8 [1] | 6 (14) | 220.1 [6] | 11 (11) | 256.5 [13] | 14 (14) | 234.2 [14] |
| Diarrhea | 7 (13) | 215.7 [7] | 5 (9) | 215.3 [7] | 5 (12) | 383.9 [7] | 8 (19) | 476.8 [13] | 12 (13) | 276.2 [14] | 13 (13) | 334.6 [20] |
| Arthralgia | 4 (7) | 123.3 [4] | 4 (7) | 307.6 [10] | 7 (17) | 493.6 [9] | 9 (21) | 440.1 [12] | 11 (11) | 256.5 [13] | 13 (13) | 368.0 [22] |
| URTI | 2 (4) | 61.6 [2] | 8 (15) | 307.6 [10] | 4 (10) | 274.2 [5] | 9 (21) | 440.1 [12] | 6 (6) | 138.1 [7] | 17 (18) | 368.0 [22] |
| Nasopharyngitis | 7 (13) | 277.3 [9] | 7 (13) | 215.3 [7] | 4 (10) | 274.2 [5] | 4 (9) | 146.7 [4] | 11 (11) | 276.2 [14] | 11 (11) | 184.0 [11] |
| Nausea | 2 (4) | 92.4 [3] | 3 (6) | 123.0 [4] | 7 (17) | 383.9 [7] | 8 (19) | 330.1 [9] | 9 (9) | 197.3 [10] | 11 (11) | 217.5 [13] |
| Rhinitis | 6 (11) | 184.9 [6] | 5 (9) | 184.5 [6] | 2 (5) | 109.7 [2] | 6 (14) | 330.1 [9] | 8 (8) | 157.8 [8] | 11 (11) | 250.9 [15] |
| Dyspnea | 2 (4) | 92.4 [3] | 3 (6) | 153.8 [5] | 6 (14) | 383.9 [7] | 7 (16) | 440.1 [12] | 8 (8) | 197.3 [10] | 10 (10) | 284.4 [17] |
| Myalgia | 3 (6) | 92.4 [3] | 4 (7) | 215.3 [7] | 3 (7) | 274.2 [5] | 8 (19) | 403.4 [11] | 6 (6) | 157.8 [8] | 12 (12) | 301.1 [18] |
| Back pain | 3 (6) | 123.3 [4] | 3 (6) | 123.0 [4] | 6 (14) | 438.7 [8] | 5 (12) | 183.4 [5] | 9 (9) | 236.8 [12] | 8 (8) | 150.5 [9] |
| Cough | 4 (7) | 123.3 [4] | 0 | 0 [0] | 8 (19) | 658.1 [12] | 5 (12) | 183.4 [5] | 12 (13) | 315.7 [16] | 5 (5) | 83.6 [5] |
| Sinusitis | 4 (7) | 154.1 [5] | 2 (4) | 61.5 [2] | 6 (14) | 329.1 [6] | 5 (12) | 183.4 [5] | 10 (10) | 217.0 [11] | 7 (7) | 117.1 [7] |
| Vomiting | 3 (6) | 92.4 [3] | 4 (7) | 123.0 [4] | 4 (10) | 274.2 [5] | 5 (12) | 220.1 [6] | 7 (7) | 157.8 [8] | 9 (9) | 167.3 [10] |
| Asthma | 5 (9) | 215.7 [7] | 2 (4) | 61.5 [2] | 3 (7) | 219.4 [4] | 5 (12) | 220.1 [6] | 8 (8) | 217.0 [11] | 7 (7) | 133.8 [8] |
| Dizziness | 3 (6) | 92.4 [3] | 4 (7) | 123.0 [4] | 3 (7) | 164.5 [3] | 5 (12) | 220.1 [6] | 6 (6) | 118.4 [6] | 9 (9) | 167.3 [10] |
| Pyrexia | 2 (4) | 61.6 [2] | 4 (7) | 153.8 [5] | 6 (14) | 383.9 [7] | 3 (7) | 183.4 [5] | 8 (8) | 177.6 [9] | 7 (7) | 167.3 [10] |
| Pain in extremity | 2 (4) | 61.6 [2] | 6 (11) | 215.3 [7] | 5 (12) | 383.9 [7] | 1 (2) | 36.7 [1] | 7 (7) | 177.6 [9] | 7 (7) | 133.8 [8] |
| Rash | 2 (4) | 61.6 [2] | 2 (4) | 61.5 [2] | 6 (14) | 383.9 [7] | 4 (9) | 293.4 [8] | 8 (8) | 177.6 [9] | 6 (6) | 167.3 [10] |
| Abdominal pain | 3 (6) | 123.3 [4] | 1 (2) | 30.8 [1] | 5 (12) | 383.9 [7] | 4 (9) | 220.1 [6] | 8 (8) | 217.0 [11] | 5 (5) | 117.1 [7] |
| Urticaria | 5 (9) | 215.7 [7] | 0 | 0 [0] | 1 (2) | 54.8 [1] | 5 (12) | 183.4 [5] | 6 (6) | 157.8 [8] | 5 (5) | 83.6 [5] |

| | 200622 | | | | MHE100185 | | | | Both studies | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PBO | | Mepo 300 mg SC | | PBO | | Mepo 750 mg IV | | PBO | | Mepo all doses | |
| | N=54 | | N=54 | | N=42 | | N=43 | | N=96 | | N=97 | |
| Preferred term | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] |
| Contusion | 1 (2) | 61.6 [2] | 4 (7) | 123.0 [4] | 3 (7) | 164.5 [3] | 2 (5) | 73.4 [2] | 4 (4) | 98.6 [5] | 6 (6) | 100.4 [6] |
| Oropharyngeal pain | 2 (4) | 61.6 [2] | 1 (2) | 61.5 [2] | 6 (14) | 329.1 [6] | 1 (2) | 36.7 [1] | 8 (8) | 157.8 [8] | 2 (2) | 50.2 [3] |
| Paraesthesia | 0 | 0 [0] | 3 (6) | 92.3 [3] | 3 (7) | 219.4 [4] | 3 (7) | 110.0 [3] | 3 (3) | 78.9 [4] | 6 (6) | 100.4 [6] |
| Urinary tract infection | 0 | 0 [0] | 5 (9) | 184.5 [6] | 3 (7) | 219.4 [4] | 1 (2) | 36.7 [1] | 3 (3) | 78.9 [4] | 6 (6) | 117.1 [7] |
| Chest pain | 1 (2) | 30.8 [1] | 1 (2) | 30.8 [1] | 2 (5) | 109.7 [2] | 4 (9) | 146.7 [4] | 3 (3) | 59.2 [3] | 5 (5) | 83.6 [5] |
| HES | 1 (2) | 30.8 [1] | 1 (2) | 30.8 [1] | 4 (10) | 329.1 [6] | 2 (5) | 73.4 [2] | 5 (5) | 138.1 [7] | 3 (3) | 50.2 [3] |
| Oedema peripheral | 1 (2) | 30.8 [1] | 1 (2) | 30.8 [1] | 1 (2) | 54.8 [1] | 5 (12) | 256.7 [7] | 2 (2) | 39.5 [2] | 6 (6) | 133.8 [8] |
| Peripheral swelling | 2 (4) | 61.6 [2] | 1 (2) | 30.8 [1] | 3 (7) | 219.4 [4] | 2 (5) | 73.4 [2] | 5 (5) | 118.4 [6] | 3 (3) | 50.2 [3] |
| Abdominal pain upper | 2 (4) | 92.4 [3] | 1 (2) | 30.8 [1] | 2 (5) | 109.7 [2] | 2 (5) | 146.7 [4] | 4 (4) | 98.6 [5] | 3 (3) | 83.6 [5] |
| Alopecia | 0 | 0 [0] | 4 (7) | 123.0 [4] | 0 | 0 [0] | 3 (7) | 110.0 [3] | 0 | 0 [0] | 7 (7) | 117.1 [7] |
| Constipation | 1 (2) | 61.6 [2] | 3 (6) | 184.5 [6] | 1 (2) | 54.8 [1] | 2 (5) | 146.7 [4] | 2 (2) | 59.2 [3] | 5 (5) | 167.3 [10] |
| Erythema | 2 (4) | 61.6 [2] | 0 | 0 [0] | 2 (5) | 109.7 [2] | 3 (7) | 110.0 [3] | 4 (4) | 78.9 [4] | 3 (3) | 50.2 [3] |
| Muscle spasms | 1 (2) | 30.8 [1] | 1 (2) | 30.8 [1] | 2 (5) | 164.5 [3] | 3 (7) | 146.7 [4] | 3 (3) | 78.9 [4] | 4 (4) | 83.6 [5] |
| Rhinorrhea | 4 (7) | 123.3 [4] | 1 (2) | 30.8 [1] | 1 (2) | 54.8 [1] | 1 (2) | 36.7 [1] | 5 (5) | 98.6 [5] | 2 (2) | 33.5 [2] |
| Swelling face | 1 (2) | 61.6 [2] | 1 (2) | 30.8 [1] | 3 (7) | 274.2 [5] | 2 (5) | 73.4 [2] | 4 (4) | 138.1 [7] | 3 (3) | 50.2 [3] |
| Asthenia | 5 (9) | 184.9 [6] | 0 | 0 [0] | 0 | 0 [0] | 1 (2) | 36.7 [1] | 5 (5) | 118.4 [6] | 1 (1) | 16.7 [1] |
| Epistaxis | 2 (4) | 61.6 [2] | 1 (2) | 30.8 [1] | 0 | 0 [0] | 3 (7) | 110.0 [3] | 2 (2) | 39.5 [2] | 4 (4) | 66.9 [4] |
| Hypoaesthesia | 1 (2) | 30.8 [1] | 3 (6) | 92.3 [3] | 1 (2) | 54.8 [1] | 1 (2) | 36.7 [1] | 2 (2) | 39.5 [2] | 4 (4) | 66.9 [4] |
| Influenza | 1 (2) | 30.8 [1] | 3 (6) | 92.3 [3] | 2 (5) | 109.7 [2] | 0 | 0 [0] | 3 (3) | 59.2 [3] | 3 (3) | 50.2 [3] |
| Musculoskeletal chest pain | 0 | 0 [0] | 3 (6) | 92.3 [3] | 1 (2) | 54.8 [1] | 2 (5) | 73.4 [2] | 1 (1) | 19.7 [1] | 5 (5) | 83.6 [5] |
| Oral herpes | 2 (4) | 61.6 [2] | 2 (4) | 92.3 [3] | 0 | 0 [0] | 2 (5) | 73.4 [2] | 2 (2) | 39.5 [2] | 4 (4) | 83.6 [5] |
| Pneumonia | 0 | 0 [0] | 1 (2) | 30.8 [1] | 2 (5) | 109.7 [2] | 3 (7) | 146.7 [4] | 2 (2) | 39.5 [2] | 4 (4) | 83.6 [5] |
| Toothache | 1 (2) | 30.8 [1] | 2 (4) | 92.3 [3] | 1 (2) | 54.8 [1] | 2 (5) | 110.0 [3] | 2 (2) | 39.5 [2] | 4 (4) | 100.4 [6] |
| Acne | 0 | 0 [0] | 0 | 0 [0] | 2 (5) | 109.7 [2] | 3 (7) | 110.0 [3] | 2 (2) | 39.5 [2] | 3 (3) | 50.2 [3] |
| Influenza like illness | 2 (4) | 61.6 [2] | 3 (6) | 92.3 [3] | 0 | 0 [0] | 0 | 0 [0] | 2 (2) | 39.5 [2] | 3 (3) | 50.2 [3] |
| Injection site reaction | 2 (4) | 308.1 [10] | 3 (6) | 153.8 [5] | 0 | 0 [0] | 0 | 0 [0] | 2 (2) | 197.3 [10] | 3 (3) | 83.6 [5] |
| Nasal obstruction | 2 (4) | 61.6 [2] | 3 (6) | 92.3 [3] | 0 | 0 [0] | 0 | 0 [0] | 2 (2) | 39.5 [2] | 3 (3) | 50.2 [3] |

| | 200622 | | | | MHE100185 | | | | Both studies | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PBO | | Mepo 300 mg SC | | PBO | | Mepo 750 mg IV | | PBO | | Mepo all doses | |
| | N=54 | | N=54 | | N=42 | | N=43 | | N=96 | | N=97 | |
| Preferred term | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] |
| Neck pain | 0 | 0 [0] | 1 (2) | 30.8 [1] | 3 (7) | 164.5 [3] | 1 (2) | 36.7 [1] | 3 (3) | 59.2 [3] | 2 (2) | 33.5 [2] |
| Palpitations | 0 | 0 [0] | 2 (4) | 61.5 [2] | 1 (2) | 54.8 [1] | 2 (5) | 73.4 [2] | 1 (1) | 19.7 [1] | 4 (4) | 66.9 [4] |
| Pharyngitis | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 109.7 [2] | 2 (5) | 73.4 [2] | 3 (3) | 59.2 [3] | 2 (2) | 33.5 [2] |
| Rhinitis allergic | 0 | 0 [0] | 1 (2) | 30.8 [1] | 0 | 0 [0] | 4 (9) | 146.7 [4] | 0 | 0 [0] | 5 (5) | 83.6 [5] |
| Abdominal discomfort | 0 | 0 [0] | 1 (2) | 30.8 [1] | 3 (7) | 164.5 [3] | 0 | 0 [0] | 3 (3) | 59.2 [3] | 1 (1) | 16.7 [1] |
| Decreased appetite | 3 (6) | 92.4 [3] | 0 | 0 [0] | 0 | 0 [0] | 1 (2) | 36.7 [1] | 3 (3) | 59.2 [3] | 1 (1) | 16.7 [1] |
| Gastroenteritis viral | 2 (4) | 92.4 [3] | 0 | 0 [0] | 1 (2) | 54.8 [1] | 1 (2) | 36.7 [1] | 3 (3) | 78.9 [4] | 1 (1) | 16.7 [1] |
| Nasal congestion | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 274.2 [5] | 1 (2) | 36.7 [1] | 3 (3) | 118.4 [6] | 1 (1) | 16.7 [1] |
| Papule | 0 | 0 [0] | 0 | 0 [0] | 3 (7) | 219.4 [4] | 1 (2) | 36.7 [1] | 3 (3) | 78.9 [4] | 1 (1) | 16.7 [1] |
| Pruritus generalized | 1 (2) | 30.8 [1] | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 73.4 [2] | 1 (1) | 19.7 [1] | 3 (3) | 50.2 [3] |
| Tooth abscess | 0 | 0 [0] | 1 (2) | 61.5 [2] | 1 (2) | 54.8 [1] | 2 (5) | 73.4 [2] | 1 (1) | 19.7 [1] | 3 (3) | 66.9 [4] |
| Alanine aminotransferase increased | 0 | 0 [0] | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 110.0 [3] | 0 | 0 [0] | 3 (3) | 66.9 [4] |
| Chest discomfort | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 109.7 [2] | 0 | 0 [0] | 3 (3) | 59.2 [3] | 0 | 0 [0] |
| Malaise | 0 | 0 [0] | 2 (4) | 61.5 [2] | 0 | 0 [0] | 1 (2) | 36.7 [1] | 0 | 0 [0] | 3 (3) | 50.2 [3] |
| Musculoskeletal pain | 2 (4) | 61.6 [2] | 0 | 0 [0] | 1 (2) | 54.8 [1] | 0 | 0 [0] | 3 (3) | 59.2 [3] | 0 | 0 [0] |
| Oedema | 0 | 0 [0] | 0 | 0 [0] | 0 | 0 [0] | 3 (7) | 146.7 [4] | 0 | 0 [0] | 3 (3) | 66.9 [4] |
| Presyncope | 3 (6) | 92.4 [3] | 0 | 0 [0] | 0 | 0 [0] | 0 | 0 [0] | 3 (3) | 59.2 [3] | 0 | 0 [0] |
| Rash pruritic | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 164.5 [3] | 0 | 0 [0] | 3 (3) | 78.9 [4] | 0 | 0 [0] |
| Respiratory tract infection | 0 | 0 [0] | 2 (4) | 61.5 [2] | 0 | 0 [0] | 1 (2) | 36.7 [1] | 0 | 0 [0] | 3 (3) | 50.2 [3] |
| Seasonal allergy | 0 | 0 [0] | 1 (2) | 30.8 [1] | 0 | 0 [0] | 2 (5) | 146.7 [4] | 0 | 0 [0] | 3 (3) | 83.6 [5] |
| Somnolence | 2 (4) | 61.6 [2] | 0 | 0 [0] | 1 (2) | 54.8 [1] | 0 | 0 [0] | 3 (3) | 59.2 [3] | 0 | 0 [0] |
| Vaginal hemorrhage | 0 | 0 [0] | 3 (6) | 153.8 [5] | 0 | 0 [0] | 0 | 0 [0] | 0 | 0 [0] | 3 (3) | 83.6 [5] |

[redacted]

Abbreviations: AE = adverse event; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously; URTI = upper respiratory tract infection.

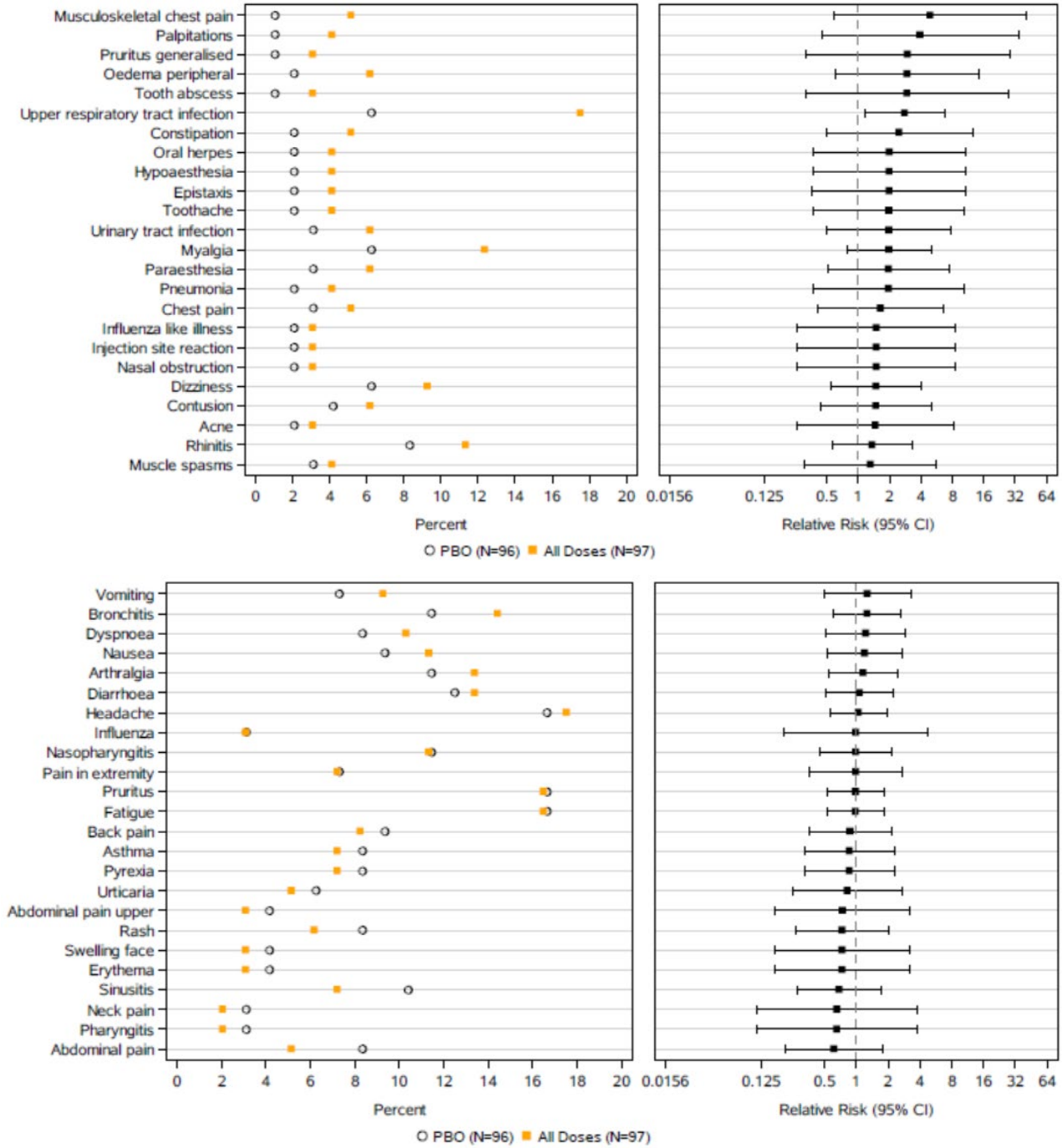
1. Represents the frequency of events per 1000 subject-years of exposure.

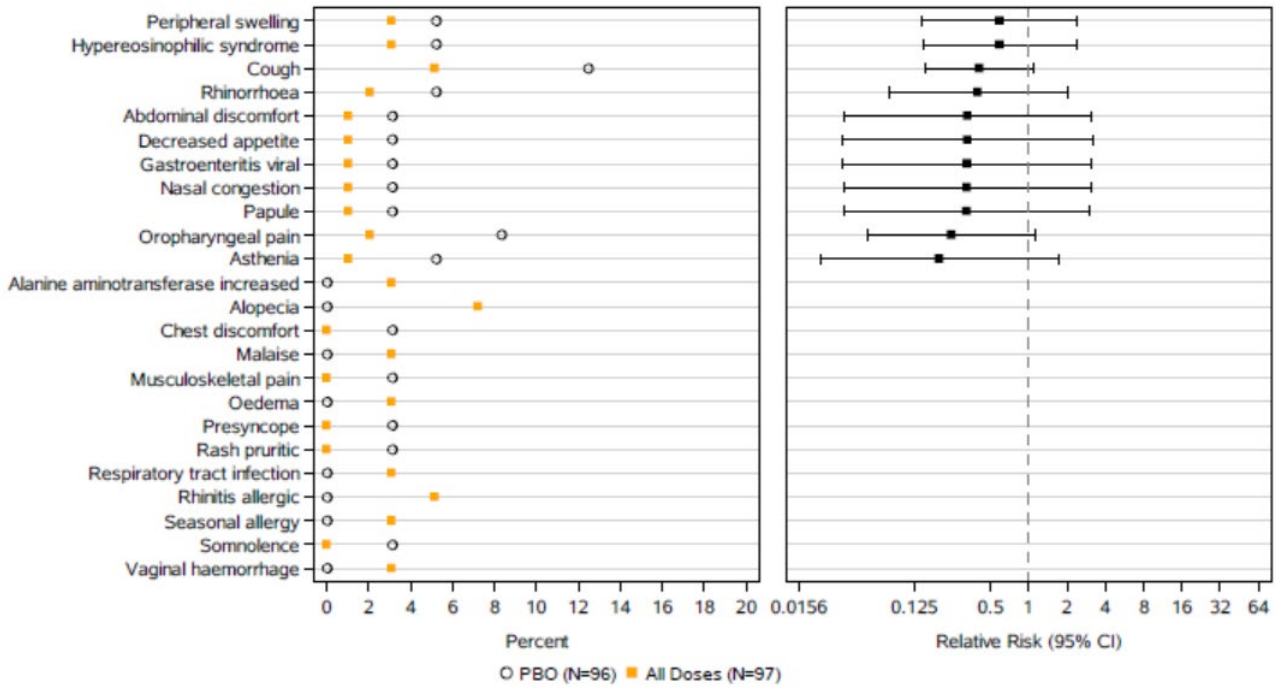
Note: Common AEs are defined as AEs with frequency ≥3% prior to rounding in either treatment group.

Note: Exposure-adjusted frequency is calculated as: (Total number of AEs/ Total Duration of Exposure in days)/ 365.25*100.

Note: Studies included: 200622 and MHE100185.

**Figure 25: Common On-Treatment Adverse Events (>=3% in Any Treatment Group) CMH Adjusted Relative Risk – Mepolizumab All Doses vs Placebo (HES Placebo Controlled Studies)**






In Study 200622, it was noted that a number of subjects in both treatment groups had AEs of bleeding (incidence in the Haemorrhages SMQ was 7% [4/54 subjects] in the placebo group and 19% [10/54 subjects] in the mepolizumab 300 mg SC group). A Haemorrhages SMQ was then utilized to further characterize these events in the integrated HES Placebo Controlled Studies; the incidence of on-treatment AEs in the Haemorrhages SMQ was 9% (9/96 subjects) for placebo and 16% (16/97 subjects) for mepolizumab all doses; no dose response was evident. In the HES Placebo Controlled Studies, 7 subjects on mepolizumab and 2 subjects on placebo reported more than one event. Except for one subject on mepolizumab who reported SAEs of vaginal haemorrhage and contusion (Study 200622), all AEs in the Haemorrhages SMQ were non-serious; no events led to discontinuation of study treatment.

The majority of AEs were mild or moderate in intensity, resolved, and were not considered to be drug-related by the investigators. Seven of 16 subjects on mepolizumab, and none on placebo, reported concomitant medications that could increase the risk of bleeding: 1 Subject (Study 200622) (haematochezia, haemorrhagic erosive gastritis) had concurrent rivaroxaban, and events were reported in the context of hospitalization for an HES flare, and septic shock; 1 Subject (Study 200622) (rectal haemorrhage) had concurrent ibuprofen; 1 Subject (Study 200622) (vaginal haemorrhage, contusion) had concurrent warfarin; 1 Subject (Study 200622) (vaginal haemorrhage, contusion) had concurrent medroxyprogesterone acetate; 1 Subject (Study 200622) (epistaxis, contusion) had concurrent naproxen; 1 Subject (Study MHE100185) (epistaxis, ecchymosis) had concurrent warfarin and aspirin; and 1 Subject (Study MHE100185) (epistaxis) had concurrent warfarin.

Eight subjects on mepolizumab and 2 subjects on placebo reported events after the 1st dose of study treatment. In Study 205203 (OLE to 200622), the incidence of AEs in the Haemorrhages SMQ was 4% (4/102 subjects). All events were non-serious and did not lead to study treatment discontinuation. For context, AEs in the Haemorrhage SMQs in the placebo-controlled studies across indications were reviewed. In the integrated placebo-controlled studies in severe asthma and the integrated placebo-controlled studies in COPD, the incidences of on-treatment AEs in the Haemorrhages SMQ were similar between the placebo and mepolizumab groups. In severe eosinophilic asthma, this was 6% (39/690 subjects) in the integrated placebo group vs 5% (59/1188 subjects) in the mepolizumab all doses group. In severe COPD, this was 6% (38/645 subjects) in the integrated placebo group vs 7% (58/865 subjects) in the mepolizumab all doses group mepolizumab doses in the severe asthma studies were

100 mg SC, 250 mg IV, and 750 mg IV. Mepolizumab doses in the COPD studies were 100 mg SC and 300 mg SC. In the integrated placebo-controlled studies in CRSwNP, the incidences of AEs in the Haemorrhages SMQ were 11% (29/253 subjects) in the integrated placebo group and 9% (24/259 subjects) in the mepolizumab all doses group. Mepolizumab doses in the CRSwNP studies were 100 mg SC and 750 mg IV. In the placebo-controlled study in EGPA, the incidences of AEs in the Haemorrhages SMQ were 13% (9/68 subjects) in the placebo group and 13% (9/68 subjects) in the mepolizumab 300 mg SC group. There was no evidence of dose response between mepolizumab doses ranging from 100 mg SC to 750 mg IV in any of the clinical programs. There is no known mechanism for anti-IL-5 effects on bleeding potential.

In summary, the incidences of events in the Haemorrhages SMQ in the HES Placebo Controlled Studies were 9% (9/96 subjects) in the placebo group and 16% (16/97 subjects) in the mepolizumab all doses group. Review of the events showed that the vast majority were non-serious, resolved, and none led to treatment discontinuation. Seven of 16 subjects on mepolizumab and none on placebo reported concomitant medications that could increase the risk of bleeding, including 4 subjects on anticoagulants. In Study 205203 (OLE to 200622), the incidences of AEs in the Haemorrhages SMQ were 4% (4/102 subjects). The incidences of events in the Haemorrhages SMQ were similar between placebo and mepolizumab treatment groups in the severe eosinophilic asthma, severe COPD, CRSwNP, and EGPA placebo-controlled studies. No dose response was evident in the HES Placebo Controlled Studies, nor in the integrated placebo-controlled studies in other indications. Given the totality of the clinical data and lack of biological plausibility, a causal association between mepolizumab and haemorrhagic events is unlikely.

**Adverse Events by Maximum Intensity**

The maximum intensity for the majority of on-treatment AEs in the HES Placebo Controlled Studies was mild or moderate intensity (72% in the placebo group and 63% in the mepolizumab group). The incidence of events of severe intensity was 20% in the placebo group and 28% in the mepolizumab group. The most frequently reported AEs of severe intensity (>1% of subjects in either treatment group) were pruritus, diarrhoea, abdominal pain, vomiting, oropharyngeal pain, arthralgia, headache, and HES in the placebo group, and fatigue, dyspnoea, vomiting, contusion, renal failure, and HES in the mepolizumab group.

**Drug-Related Adverse Events**

The incidence of on-treatment AEs considered to be drug-related by the investigators was 20% in the placebo group and 29% in the mepolizumab group (***Table 38***). The incidence of each drug-related AE PT was low, and the PTs reported for ≥3% of subjects in either treatment group were fatigue, injection site reaction, peripheral swelling, arthralgia, myalgia, headache, cough, and dyspnoea. None of the on-treatment drug-related AEs reported in the HES Placebo Controlled Studies was serious.

**Table 38: On-Treatment Drug-Related Adverse Events Occurring in >1 Subject in the Integrated Placebo or Mepolizumab All Doses Group (HES Placebo Controlled Studies, Safety Population)**

| | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | |
| Preferred term | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 |
| **Any on-treatment drug-related AE** | 7 (13) | 12 (22) | 12 (29) | 16 (37) | 19 (20) | 28 (29) |
| Fatigue | 1 (2) | 0 | 1 (2) | 4 (9) | 2 (2) | 4 (4) |
| Injection site reaction | 2 (4) | 3 (6) | 0 | 0 | 2 (2) | 3 (3) |
| Peripheral swelling | 0 | 0 | 3 (7) | 0 | 3 (3) | 0 |
| Oedema peripheral | 1 (2) | 0 | 1 (2) | 0 | 2 (2) | 0 |
| Pruritus | 0 | 0 | 2 (5) | 2 (5) | 2 (2) | 2 (2) |
| Rash | 0 | 1 (2) | 2 (5) | 1 (2) | 2 (2) | 2 (2) |
| Erythema | 0 | 0 | 2 (5) | 1 (2) | 2 (2) | 1 (1) |
| Urticaria | 1 (2) | 0 | 1 (2) | 1 (2) | 2 (2) | 1 (1) |
| Arthralgia | 0 | 0 | 2 (5) | 4 (9) | 2 (2) | 4 (4) |
| Myalgia | 1 (2) | 0 | 2 (5) | 2 (5) | 3 (3) | 2 (2) |
| Headache | 0 | 0 | 4 (10) | 2 (5) | 4 (4) | 2 (2) |
| Dizziness | 0 | 1 (2) | 0 | 1 (2) | 0 | 2 (2) |
| Diarrhea | 1 (2) | 0 | 1 (2) | 1 (2) | 2 (2) | 1 (1) |
| Cough | 0 | 0 | 3 (7) | 0 | 3 (3) | 0 |
| Dyspnea | 1 (2) | 0 | 2 (5) | 0 | 3 (3) | 0 |
| Gamma-glutamyltransferase increased | 0 | 0 | 0 | 2 (5) | 0 | 2 (2) |

[redacted]

Abbreviations: AE = adverse event; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.
Note: Studies included: 200622 and MHE100185.

Post-Treatment Adverse Events

Post-treatment AEs were defined as events with an onset of >28 days after the last dose of study treatment. The incidences of post-treatment AEs in the HES Placebo Controlled Studies were similar between the placebo group (8%) and the mepolizumab group (6%). The post-treatment AEs reported for >1 subject overall were nausea (2 subjects; 1 in each group) and dyspnea (2 subjects; both in the mepolizumab group). For 3 subjects (3%) (all in the mepolizumab group) the post-treatment event was an SAE; these subjects had 1 SAE each: gastroenteritis, rhinitis, and dehydration.

The most frequently reported SOC in both treatment groups was Infections and Infestations, and the incidence was higher in the mepolizumab group (68%) compared with the placebo group (53%) (***Table 39***); this imbalance is explained by increased incidence of URTI in the mepolizumab group (18%) vs the placebo group (6%) (**Table 37**). The other SOC with a ≥10% difference between treatment groups were Musculoskeletal and Connective Tissue Disorders (**Table 39**), which is likely explained by the results of the MHE100185 study where a significantly greater proportion of subjects in the mepolizumab group achieved a prednisone dose of ≤7.5 mg per day or became prednisone-free during the treatment period compared with placebo. Therefore, an increase in musculoskeletal events (e.g., myalgia in Study MHE100185 and in the integrated dataset, but not in Study 200622) in the mepolizumab group compared with placebo is likely due to secondary adrenal insufficiency subsequent to the tapering of steroids in the subjects who received mepolizumab.

**Table 39: System Organ Classes with ≥10% Incidence of On-Treatment Adverse Events in the Integrated Placebo or Mepolizumab All Doses Group (HES Placebo Controlled Studies, Safety Population)**

| | 200622 | | | | MHE100185 | | | | Both studies | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PBO | | Mepo 300 mg SC | | PBO | | Mepo 750 mg IV | | PBO | | Mepo all doses | |
| | N=54 | | N=54 | | N=42 | | N=43 | | N=96 | | N=97 | |
| System Organ Class | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] | n (%) | Rate [1] [# events] |
| Infections and Infestations | 28 (52) | 1848.9 [60] | 37 (69) | 2183.6 [71] | 23 (55) | 2029.2 [37] | 29 (67) | 2310.5 [63] | 51 (53) | 1913.7 [97] | 66 (68) | 2241.5 [134] |
| Skin and Subcutaneous Tissue Disorders | 16 (30) | 1171.0 [38] | 13 (24) | 615.1 [20] | 23 (55) | 2413.1 [44] | 25 (58) | 2163.8 [59] | 39 (41) | 1617.8 [82] | 38 (39) | 1321.5 [79] |
| General Disorders and Administration Site Conditions | 15 (28) | 1140.2 [37] | 18 (33) | 799.6 [26] | 20 (48) | 1974.3 [36] | 23 (53) | 1613.7 [44] | 35 (36) | 1440.2 [73] | 41 (42) | 1170.9 [70] |
| Musculoskeletal and Connective Tissue Disorders | 14 (26) | 554.7 [18] | 18 (33) | 1814.6 [59] | 17 (40) | 2413.1 [44] | 24 (56) | 1650.4 [45] | 31 (32) | 1223.2 [62] | 42 (43) | 1739.7 [104] |
| Respiratory, Thoracic and Mediastinal Disorders | 19 (35) | 1016.9 [33] | 13 (24) | 584.4 [19] | 19 (45) | 2138.9 [39] | 21 (49) | 1613.7 [44] | 38 (40) | 1420.5 [72] | 34 (35) | 1053.8 [63] |
| Gastrointestinal Disorders | 16 (30) | 1047.7 [34] | 17 (31) | 1291.7 [42] | 22 (52) | 2413.1 [44] | 16 (37) | 2127.2 [58] | 38 (40) | 1538.9 [78] | 33 (34) | 1672.8 [100] |
| Nervous System Disorders | 13 (24) | 801.2 [26] | 17 (31) | 891.9 [29] | 15 (36) | 1590.4 [29] | 18 (42) | 1430.3 [39] | 28 (29) | 1085.1 [55] | 35 (36) | 1137.5 [68] |
| Injury, Poisoning and Procedural Complications | 4 (7) | 154.1 [5] | 9 (17) | 338.3 [11] | 6 (14) | 383.9 [7] | 9 (21) | 440.1 [12] | 10 (10) | 236.8 [12] | 18 (19) | 384.7 [23] |
| Investigations | 1 (2) | 30.8 [1] | 5 (9) | 184.5 [6] | 3 (7) | 164.5 [3] | 7 (16) | 513.5 [14] | 4 (4) | 78.9 [4] | 12 (12) | 334.6 [20] |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.
1. Represents the frequency of events per 1000 subject-years of exposure.
Note: Exposure-adjusted frequency is calculated as (Total number of adverse events / Total Duration of Exposure in days)/365.25*1000.
Note: Studies included: 200622 and MHE100185.

**OLE HES Study 205203**

In Study 205203, the safety profile of mepolizumab 300 mg administered SC every 4 weeks for up to 20 weeks (39.26 subject-years of exposure to mepolizumab) was similar to that observed in Study 200622 (where mepolizumab 300 mg or placebo were administered SC every 4 weeks for up to 32 weeks [32.51 subject-years of mepolizumab exposure]). No new safety issues were identified overall or by previous treatment group (previous placebo or previous mepolizumab) (***Table 40***).

The overall incidence of AEs was 65%, and the SOC with the highest incidence of on-treatment AEs was Infections and Infestations (35%), followed by the Gastrointestinal Disorders SOC (22%). The most frequently reported on-treatment AE (occurring in >10% of subjects) was diarrhoea (12%) (***Table 41***). The maximum intensity of reported on-treatment AEs was mild for 18 (18%) subjects, moderate for 32 (31%) subjects, and severe for 12 (12%) subjects overall. The incidence of AEs considered to be drug-related by the investigator was 15%. One subject (Subject; previous placebo) reported a non-serious, drug-related AE of pain that was of severe intensity and led to withdrawal from the study.

On-treatment AEs in the Haemorrhages SMQ for Study 205203 were reported for 4 of 102 subjects (4%). All of these AEs were non-serious, the majority of the events were of mild intensity and considered to be unrelated to study treatment by the investigator, and none led to discontinuation of study treatment.

**Table 40: Adverse Event Overview (Study 205203, Safety Population)**

| Adverse Event Type | Number (%) of Subjects | | |
|---|---|---|---|
| | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
| **Any AE** | 40 (77) | 26 (52) | 66 (65) |
| AE related to study treatment | 11 (21) | 4 (8) | 15 (15) |
| AE leading to permanent discontinuation of study treatment | 1 (2) | 0 | 1 (<1) |
| AE leading to withdrawal from the study | 1 (2) | 0 | 1 (<1) |
| **Any SAE** | 6 (12) | 3 (6) | 9 (9) |
| SAE related to study treatment | 1 (2) | 0 | 1 (<1) |
| Fatal SAE | 0 | 0 | 0 |
| Fatal SAE related to study treatment | 0 | 0 | 0 |
| **Any On-Treatment AE** | 38 (73) | 24 (48) | 62 (61) |
| **Any On-Treatment SAE** | 6 (12) | 2 (4) | 8 (8) |

[redacted]

**Table 41: Most-Frequent On-Treatment Adverse Events Occurring in ≥3% of Subjects Overall (Study 205203, Safety Population)**

| Preferred Term | Number (%) of Subjects | | |
|---|---|---|---|
| | 300 mg SC Prev. Placebo (N=52) | 300 mg SC Prev. Mepo (N=50) | 300 mg SC Total (N=102) |
| **Any Event** | **38 (73)** | **24 (48)** | **62 (61)** |
| Diarrhea | 8 (15) | 4 (8) | 12 (12) |
| Pruritus | 4 (8) | 3 (6) | 7 (7) |
| Headache | 4 (8) | 2 (4) | 6 (6) |
| Vomiting | 6 (12) | 0 | 6 (6) |
| Arthralgia | 4 (8) | 1 (2) | 5 (5) |
| Constipation | 2 (4) | 3 (6) | 5 (5) |
| Nasopharyngitis | 2 (4) | 3 (6) | 5 (5) |
| Nausea | 3 (6) | 2 (4) | 5 (5) |
| Sinusitis | 2 (4) | 3 (6) | 5 (5) |
| Bronchitis | 2 (4) | 2 (4) | 4 (4) |
| Fatigue | 2 (4) | 2 (4) | 4 (4) |
| Injection site reaction | 1 (2) | 3 (6) | 4 (4) |
| Upper respiratory tract infection | 2 (4) | 2 (4) | 4 (4) |

[redacted]

**OLE HES Study MHE100901**

Overall, incidence and pattern of AEs reported in Study MHE100901 (mepolizumab 750 mg IV) was similar to that in the parent Study MHE100185 when considering the longer duration of exposure in Study MHE100901.

In Study MHE100901, the incidence of on-treatment AEs was 97%, and the most frequently reported PTs were cough (33%), fatigue (31%), headache (29%), URTI (29%), and sinusitis (28%). AEs in the Infections and Infestations SOC were the most frequently reported (76%). In Study MHE100901, the incidence of on-treatment drug-related AEs was 26%, and the PTs reported in >1% of subjects were fatigue (8%), nausea (4%), arthralgia, pain in extremity, pruritis, and headache (3% each).

**Mepolizumab HES EAP**

Mepolizumab HES EAP was ongoing at the time of the safety cut-off date for this submission (01 June 2020), with an iCSR cut-off date of 01 March 2019.

As of the mepolizumab HES EAP iCSR safety cut-off date, most of the patients in the program were enrolled in MHE104317 (339). Patients enrolled in the MHE104317 program provided the majority of the safety data.

In MHE104317, the incidence of on-treatment AEs was 91%, and the most frequently reported PTs were URTI (24%) and fatigue (22%). AEs in the Infections and Infestation SOC were the most frequently reported (71%). The incidence of on-treatment drug-related AEs in MHE104317 was 23%, and the most frequently reported (≥2% incidence) AEs were headache, fatigue, and nausea. One AE considered to be drug-related by the physician was fatal (multiple organ dysfunction syndrome).

**Adverse Events of Special Interest**

Within the mepolizumab clinical development program, the following are considered AESIs: systemic (allergic [Type I hypersensitivity] and other systemic) reactions, local injection site reactions, infections (including potentially opportunistic), malignancies, and cardiac disorders including serious cardiac, vascular, and thromboembolic (CVT) events and serious ischemic events.

The relative risk and risk difference for SAEs and AESIs for mepolizumab (all doses) compared with placebo in the HES Placebo Controlled Studies are shown in ***Table 42***. Systemic reaction and local injection site reaction AESIs were explicitly collected via a targeted eCRF only in Study 200622, and therefore in ***Table 42*** these events are summarized for Study 200622 only. For the AESIs of malignancies, serious CVT events and serious ischemic events, relevant PTs were identified based on MedDRA version 22.0.

Infections were the most frequently reported AESIs in both treatment groups (53% in the placebo group and 68% in the mepolizumab all doses group). The incidence of on-treatment serious infections was 1.0% in the placebo group and 9.3% in the mepolizumab all doses group (***Table 42*** and

**Figure 26**). Cardiac Disorders were the next most frequent category of AESI in both treatment groups and were reported with a similar incidence in the placebo and mepolizumab groups (5.2% and 7.2%, respectively). The relative risk of AESIs was greater with mepolizumab for all AESI categories other than Neoplasms and Malignancies (0.99 for both) (***Table 42***); the wide CIs for the relative risks reflect the small number of subjects with these events.

**Table 42: On-Treatment Serious Adverse Events and Adverse Events of Special Interest: Incidence, Relative Risk, and Risk Difference (HES Placebo Controlled Studies, Safety Population)**

| | Number (%) of Subjects | | | | | | Mepolizumab vs Placebo | |
|---|---|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | | | |
| SAE/AESI | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 | CMH-Adjusted Relative Risk (95% CI)[1] | % Risk Difference (Exact 95% CI) |
| **Any on-treatment SAE** | 8 (15) | 10 (19) | 5 (12) | 7 (16) | 13 (13.5) | 17 (17.5) | 1.30 (0.67, 2.52) | 4.0 (-9.9, 18.1) |
| **Systemic Reactions [2]** | 0 | 1 (2) | | | | | | 1.9 (-17.7, 21.3) |
| Anaphylaxis[3] | 0 | 0 | | | | | | |
| Allergic (Type I) Hypersensitivity[2] | 0 | 0 | | | | | | |
| Other Systemic [2] | 0 | 1 (2) | | | | | | 1.9 (-17.7, 21.3) |
| **Local Injection Site Reactions[2]** | 2 (4) | 4 (7) | | | | | 2.00 (0.38, 10.47) | 3.7 (-15.9, 23.1) |
| **All Infections [4]** | 28 (52) | 37 (69) | 23 (55) | 29 (67) | 51 (53.1) | 66 (68.0) | 1.28 (1.02, 1.62)) | 14.9 (0.4, 28.4) |
| Serious Infections | 0 | 7 (13) | 1 (2) | 2 (5) | 1 (1.0) | 9 (9.3) | 8.87 (1.15, 68.70) | 8.2 (-5.8, 22.1) |
| Potential Opportunistic Infections[5] | 4 (7) | 3 (6) | 0 | 3 (7) | 4 (4.2) | 6 (6.2) | 1.49 (0.43, 5.15) | 2.0 (-12.0, 16.1) |
| **Neoplasms [4]** | 2 (4) | 0 | 0 | 2 (5) | 2 (2.1) | 2 (2.1) | 0.99 (0.14, 7.10) | 0.0 (-14.0, 14.0) |
| **Malignancies [6]** | 1 (2) | 0 | 0 | 1 (2) | 1 (1.0) | 1 (1.0) | 0.99 (0.06, 16.06) | 0.0 (-14.0, 14.0) |
| **Cardiac Disorders [4]** | 2 (4) | 4 (7) | 3 (7) | 3 (7) | 5 (5.2) | 7 (7.2) | 1.38 (0.46, 4.20) | 2.0 (-12.0, 16.1) |
| Serious Cardiac Disorders | 1 (2) | 1 (2) | 0 | 1 (2) | 1 (1.0) | 2 (2.1) | 1.99 (0.18, 21.75) | 1.0 (-13.0, 15.0) |
| **Serious CVT Events [6]** | 2 (4) | 2 (4) | 0 | 1 (2) | 2 (2.1) | 3 (3.1) | 1.49 (0.26, 8.74) | 1.0 (-13.0, 15.0) |
| Serious Ischemic Events [7] | 0 | 0 | 0 | 0 | 0 | 0 | | |

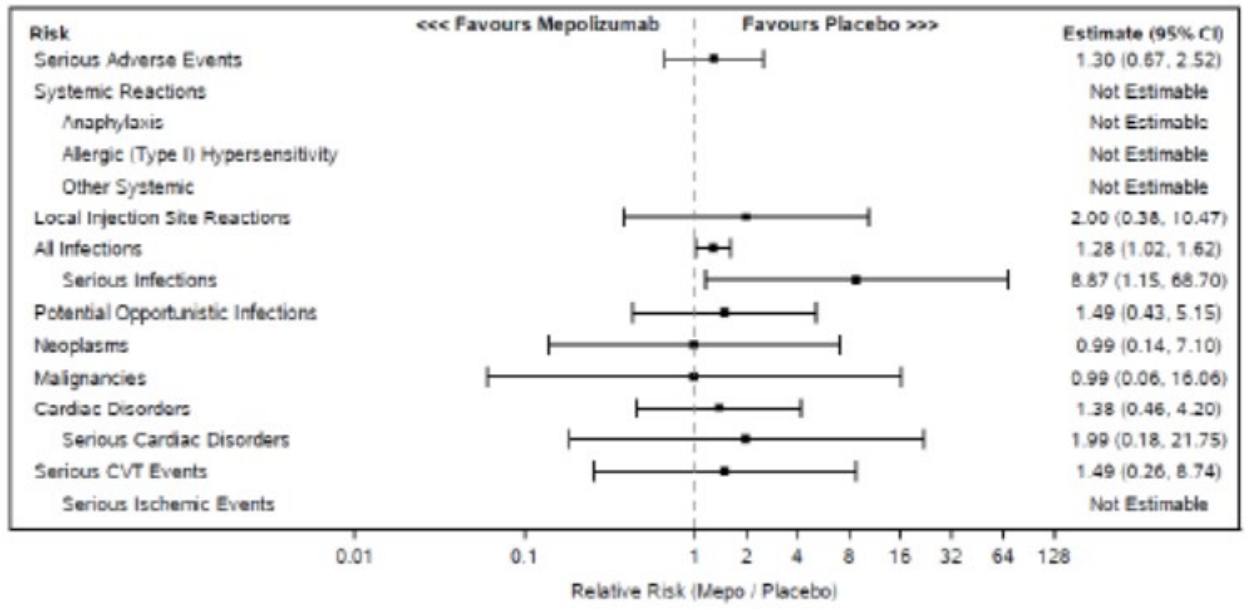
[redacted]

Abbreviations: AESI = adverse event of special interest; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CSR = Clinical Study Report; CVT = cardiac, vascular, and thromboembolic; eCRF = electronic Case Report Form; GSK = GlaxoSmithKline; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; MedDRA = Medical Dictionary for Regulatory Activities; Mepo = mepolizumab; PBO = placebo; SAE = serious adverse event; SC = subcutaneously; SMQ = standardized MedDRA query; SOC = System Organ Class.

1. Calculated using the CMH method.
2. Data from Study 200622 only (placebo N=54, mepolizumab all doses N=54). Identified by the investigator, and collected via eCRF designed for collecting data on systemic reactions and local injection site reactions.
3. Data from Study 200622 only (placebo N=54, mepolizumab all doses N=54). Considered by the investigator to represent systemic reactions meeting the Sampson's criteria for anaphylaxis [Sampson, 2006].
4. Infections from Infections and Infestations SOC; Neoplasms from Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) SOC; Cardiac Disorders from Cardiac Disorders SOC
5. Identified based on published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015].
6. Identified from SMQs prespecified by the GSK Safety Review Team.
7. Subset of serious CVT events identified through SMQs prespecified by the GSK Safety Review Team.

Note: Studies included: 200622 and MHE100185.

**Figure 26: On-Treatment Serious Adverse Events and Adverse Events of Special Interest CMH-Adjusted Relative Risk – Mepolizumab All Doses vs Placebo (HES Placebo Controlled Studies, Safety Population)**




[redacted]

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CVT = cardiac, vascular, and thromboembolic; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety.
Note: Systemic Reactions, Anaphylaxis, Allergic (Type I) Hypersensitivity, Other Systemic Reactions, and Local Injection Site Reactions contain data from Study 200622 only.
Note: Studies included: 200622 and MHE100185.

**Systemic Reactions**

**Study 200622**

Systemic (allergic [Type I Hypersensitivity] and other systemic) Reactions were collected via targeted eCRF in Study 200622 only. On-treatment events considered by the investigator to represent systemic reactions were reported for 1 subject (1.9%) (mepolizumab group) (***Table 42***), and this event was classified by the investigator as other systemic reaction. There were no systemic hypersensitivity reactions, and no events of anaphylaxis in the mepolizumab group in this study. In the placebo group, 2 SAEs of anaphylaxis were reported for a 15-year-old male subject with history of peanut allergy and anaphylaxis prior to enrolment. Both events were not considered to be drug-related by the investigator (considered possibly related to known peanut allergy), and both resolved.

Study treatment was continued unchanged.

**Study MHE100185**

There were 2 subjects in Study MHE100185 (both on mepolizumab 750 mg IV) with hypersensitivity reactions. One subject reported pruritus and rash one day after the 1st dose of mepolizumab, which resolved spontaneously; this subject completed remaining infusions with no recurrence of symptoms. The other subject with prior history of skin swelling, erythema, rash and itching, reported pruritus, rash, and swollen lips twice during the study, which led to interruption of the angiotensin-converting enzyme inhibitor; the events resolved. There were no events of anaphylaxis in the mepolizumab all doses group in the HES Placebo Controlled Studies.

**OLE HES Study 205203**

No events of anaphylaxis were reported. Three (3%) subjects reported events considered by the investigator to represent systemic reactions. Allergic (type I hypersensitivity) reactions were reported for 2 subjects (PTs: rash and urticaria) and other systemic reactions were reported for 2 subjects (PTs: fatigue and paresthesia). All events were non-serious and considered to be drug-related by the investigator; all but 1 event (PT: fatigue) resolved, and no events led to discontinuation of study treatment.

**Local Injection Site Reactions**

**Study 200622**

Local Injection Site Reactions were collected via targeted eCRF in Study 200622 only. In Study 200622, 2 subjects (4%) in the placebo group reported 10 events of local injection site reactions, and 4 subjects (7%) in the mepolizumab 300 mg SC group reported 6 events of local injection site reaction (***Table 43***). Event characteristics were similar between the treatment groups. All events for both the placebo and mepolizumab group were non-serious, of mild intensity, resolved, considered to be drug-related by the investigator, and did not lead to study treatment discontinuation.

**Table 43: On-Treatment Adverse Events Reported by the Investigator as Local Injection Site Reactions (Study 200622, Safety Population)**

| | Number (%) of Subjects | |
|---|---|---|
| Preferred term | Placebo N=54 | Mepolizumab 300 mg SC N=54 |
| Any on-treatment event | 2 (4) | 4 (7) |
| Injection site reaction | 2 (4) | 3 (6) |
| Injection site hematoma | 0 | 1 (2) |
| [redacted] | | |

Abbreviations: SC = subcutaneously.

**Study MHE100185**

In Study MHE100185, where mepolizumab 750 mg or placebo were administered via IV infusion there were no reports of on-treatment AEs of local injection site reaction or administration site reaction

**OLE HES Study 205203**

Six (6%) subjects reported a total of 15 events considered by the investigator to represent local injection site reactions. All events were non-serious, 14 were of mild intensity and 1 was of moderate intensity, all were considered to be drug-related by the investigator, all events resolved, and none of the events led to discontinuation of study treatment. Symptoms reported by >1 subject were erythema/redness, itching/pruritus, and warm to touch.

**Infections**

The incidence of on-treatment AEs in the Infections and Infestations SOC in the HES Placebo Controlled Studies was higher in the mepolizumab group (68.0%) than the placebo group (53.1%); this imbalance is largely explained by the incidence of URTI (6% on placebo and 18% on mepolizumab). The most frequently reported PTs within this SOC overall were bronchitis, URTI, nasopharyngitis, and rhinitis.

Since an SMQ for URTI is not available, URTI MedDRA HLT under High Level Group Term Infections-pathogen unspecified was utilized to identify PTs related to PT URTI. The incidence of on-treatment AEs within the URTI MedDRA HLT was similar in the placebo group (39%) and mepolizumab all doses group

(41%) (***Table 44***). Eight subjects on placebo and 13 subjects on the mepolizumab reported >1 event each. All AEs in the URTI HLT were non-serious, mild or moderate in intensity (except for 2 events of severe sinusitis, 1 in each treatment group; both in Study MHE100185), all but 3 AEs (reported for a single subject) were not considered to be drug-related by the investigator, and no event led to discontinuation of study treatment.

**Table 44: On-Treatment Adverse Events Within Upper Respiratory Tract Infection MedDRA High Level Term (HES Placebo Controlled Studies, Safety Population)**

| | Number (%) of Subjects | |
|---|---|---|
| Preferred term | PBO N=96 | Mepo all doses N=97 |
| **Any on-treatment event** | 37 (39) | 40 (41) |
| URTI | 6 (6) | 17 (18) |
| Nasopharyngitis | 11 (11) | 11 (11) |
| Rhinitis | 8 (8) | 11 (11) |
| Sinusitis | 10 (10) | 7 (7) |
| Pharyngitis | 3 (3) | 2 (2) |
| Acute sinusitis | 2 (2) | 1 (1) |
| Chronic sinusitis | 0 | 1 (1) |
| Pharyngotonsillitis | 0 | 1 (1) |
| Tracheitis | 1 (1) | 0 |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; Mepo = mepolizumab; PBO = placebo; URTI = upper respiratory tract infection.
Note: Studies included: 200622 and MHE100185.

**Serious Infections**

The incidence of on-treatment SAEs in the Infections and Infestations was 9.3% (9 subjects) in the mepolizumab all doses group and 1.0% (1 subject) in the placebo group. No dose response was evident for the mepolizumab 300 mg SC and 750 mg IV groups (***Table 42***).

No patterns with respect to the anatomical site of infection or the type of infection were observed in the mepolizumab all doses group; 7/9 subjects in the mepolizumab all doses group had a pre-existing condition or other factor which likely contributed to the development of infection. These were: HES flare (1 subject; fatal SAE of septic shock), known diverticulosis (1 subject; SAE of diverticulitis), history of Whipple procedure (1 subject; SAE of liver abscess), fall (2 subjects; SAE of erysipelas and bursitis infective), possible exposure to infectious source due to being a hospital worker (1 subject; SAE of pneumonia), and comorbid condition of asthma (1 subject, SAE of bronchitis). For the 2 remaining subjects in the mepolizumab all doses group with serious infections of bronchitis and tooth infection, recovery was reported within the expected timeframe. All but 1 event (fatal septic shock) resolved with continued mepolizumab treatment and all were not considered to be drug-related by the investigator.

The single subject with a serious infection of pneumonia in the placebo group also had a pre-existing condition that likely contributed to the development of infection (comorbid condition of asthma).

To place the results of the HES Placebo Controlled Studies with respect to serious infections in context of the existing clinical safety data for mepolizumab, the incidence of on-treatment AEs and SAEs in the Infections and Infestations SOC was reviewed in the placebo-controlled studies in severe asthma, COPD, CRSwNP, and EGPA.

In the severe asthma and COPD integrated placebo-controlled studies, the incidences of on-treatment AEs and SAEs in the Infections and Infestations SOC were similar between placebo and mepolizumab groups. In severe eosinophilic asthma the incidence of infections was 58% (239/412 subjects) in the integrated placebo group vs 57% (519/915 subjects) in the mepolizumab all doses group, and serious infections were reported for 3% of subjects in both the integrated placebo (14/412) and mepolizumab all doses (23/915). In severe COPD the incidence of infections was 53% (341/645 subjects) in the integrated placebo group and 51% (439/865 subjects) in the mepolizumab all doses group, and serious infections were reported for 9% of subjects in both the integrated placebo (60/645) and mepolizumab all doses (79/865) groups. In addition to lower doses, these studies used mepolizumab 300 mg SC (COPD), and mepolizumab 250 mg IV and 750 mg IV (severe asthma), with no dose response evident in the severe asthma or COPD integrated placebo-controlled studies.

In the integrated placebo-controlled studies in CRSwNP that evaluated mepolizumab 100mg SC dose and 750mg IV dose, the incidences of on-treatment AEs and SAEs in the Infections and Infestations SOC were similar between placebo and mepolizumab groups. The incidence of infections was 63% (160/253 subjects) in the integrated placebo group vs 54% (140/259 subjects) in the mepolizumab all doses group , and serious infections were reported for 2% (4/253 subjects) in the integrated placebo group and <1% (1/259 subjects) in the mepolizumab all doses group.

In the placebo-controlled EGPA study that evaluated mepolizumab 300mg SC dose, the incidences of on-treatment AEs and SAEs in the Infections and Infestations SOC were similar between placebo and mepolizumab groups. The incidence of infections was 78% (53/68 subjects) in the placebo group vs 84% (57/68 subjects) in the mepolizumab group, and serious infections were reported for 15% (10/68 subjects) in the placebo group and 6% (4/68 subjects) in the mepolizumab group.

From the biological plausibility perspective, mepolizumab has not produced immunosuppression in animals or patients. There are literature publications using in vitro and in vivo murine model systems that appear to demonstrate a potential role for eosinophils in host immune defense of viral and/or bacterial infections, but these nonclinical observations have not translated to human experience with anti-IL-5 or anti-IL-5 receptor α (IL-5Rα) monoclonal antibody therapy [Gleich, 2013; Roufosse, 2018].

In summary, considering the totality of the information, the imbalance in the serious infections in the HES Placebo Controlled Studies may be due to chance especially considering the small sample size relative to the larger sample sizes in severe asthma, COPD, and CRSwNP studies, and a causal relationship between mepolizumab and infections is unlikely.

**Potential Opportunistic Infections**

Since SMQs for opportunistic infections were not available at the time of the finalization of the reporting and analysis plan, expert opinion on what constitutes opportunistic infections in the setting of biological therapy [Winthrop, 2015] was considered as a reference for selecting PTs for events potentially representing opportunistic infections in Study 200622. This was also retrospectively applied to data from Study MHE100185. All PTs applicable to the list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy by Winthrop et al were selected [Winthrop, 2015]. For PTs that were not specific enough to definitively match to the list of pathogens and/or presentations in the expert publication, a conservative approach was used, and a term was included. For example, while only invasive and/or pharyngeal candidiasis is considered to represent an opportunistic infection, non-specific terms like 'candida infection' or 'candida test' were included. The incidence of on-treatment AEs identified as potentially representing opportunistic infections was 4% in the placebo group and 6% in the mepolizumab group (**Table 45**).

**Table 45: Summary of On-Treatment Potential Opportunistic Infections (HES Placebo Controlled Studies, Safety Population)**

| System Organ Class<br>Preferred term | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | |
| | PBO<br>N=54 | Mepo<br>300 mg SC<br>N=54 | PBO<br>N=42 | Mepo<br>750 mg IV<br>N=43 | PBO<br>N=96 | Mepo<br>all doses<br>N=97 |
| Infections and Infestations | 4 (7) | 3 (6) | 0 | 3 (7) | 4 (4) | 6 (6) |
| Oral herpes | 2 (4) | 2 (4) | 0 | 2 (5) | 2 (2) | 4 (4) |
| Herpes simplex | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Herpes virus infection | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Herpes zoster | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Oesophageal candidiasis | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.
Note: Events matching terms based on a published list considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015].
Note: Studies included: 200622 and MHE100185.

The reported events of oral herpes and herpes simplex are unlikely to represent an invasive disease based on being reported as non-serious, of mild intensity and verbatim terms suggestive of localized infection (e.g., cold sore).

Events of herpes zoster (placebo), herpes virus infection (mepolizumab), and oesophageal candidiasis (mepolizumab) are considered to meet the criteria of opportunistic infection by Winthrop et al [Winthrop, 2015].

**OLE HES Study 205203**

On-treatment AEs in the Infections and Infestations SOC were reported for 36 (35%) subjects, and SAEs in the Infections and Infestations SOC were reported for 5 (5%) subjects. The incidence of on-treatment AEs in the URTI MedDRA HLT was 19%. Two (2%) subjects reported 1 event each of potential opportunistic infections (PTs: oral herpes and mycobacterium abscess infection). The event of mycobacterium abscessus infection was considered to meet the criteria for opportunistic infection [Winthrop, 2015].

**Malignancies**

The incidence of on-treatment AEs categorized as malignancies was 1% (1 subject) in both treatment groups: 1 subject with T-cell lymphoma (SAE) in the placebo group and 1 subject with basal cell carcinoma in the mepolizumab group.

**T-Cell Lymphoma**

Lymphocytic variant of HES (L-HES) is characterized by clonal expansion of immunophenotypically-aberrant T-cells, and patients may develop or present concomitantly with T-cell lymphoma indicating that L-HES has malignant potential [Gleich, 2009; Shomali, 2019].

Given that both HES and T-cell lymphoma are rare, the risk of T-cell lymphoma in patients with L-HES is not quantified. One of the largest studies of patients with L-HES is by Lefevre et al who conducted a national multi-center retrospective study in the French Eosinophil network to describe characteristics and outcomes of L-HES patients. They identified 21 patients diagnosed with L-HES, one of whom developed T-cell lymphoma (angioimmunoblastic T-cell lymphoma [AITL]) 8 years after HES diagnosis. The mean (± standard deviation) follow-up duration after HES diagnosis was 6.9 ±5.1 years in this

study, which gives the incidence of T-cell lymphoma of 6.9 cases per 1000 patient-years [Lefevre, 2014].

Rates of reported cases of lymphoma in the HES clinical program are presented in ***Table 46***, and abbreviated narratives for the 19 cases (18 in the HES clinical program and 1 in the COPD clinical program) are provided in Section 8.1. As of 01 June 2020, 18 AEs of lymphoma were reported in the mepolizumab HES clinical program. One of these 18 cases was a non-serious event of lymphoma (verbatim: knee lymphoma) of mild intensity, reported in the mepolizumab HES EAP MHE104317 as resolved in 59 days; based on the verbatim term and resolution in 59 days this event is unlikely to represent lymphoma and therefore is not included in ***Table 46*** below.

Of the 17 remaining cases of lymphoma in the HES clinical program, 13 cases were reported in the mepolizumab HES EAP, 1 case was reported in Study 200622 (placebo group), 2 cases were reported in the completed OLE study MHE100901 , and 1 case was reported in the completed OLE study (***Table 46***). In the mepolizumab HES EAP, safety data for the Initial Compassionate Use Program and treatment protocol MHE112562 were not reported in the clinical database. Seven of the 13 cases reported in the mepolizumab HES EAP were also reported in the clinical database.

One additional event of lymphoma was reported in the placebo arm in the COPD study MEA117106. As of 01 June 2020, no events of lymphoma have been reported in the severe eosinophilic asthma, EGPA, nasal polyposis, atopic dermatitis, and EoE clinical programs. Some of these programs included mepolizumab doses of 300 mg and higher: 300 mg SC in the EGPA program, 750 mg IV in the severe asthma study MEA112997 and 300 mg SC in the COPD study MEA115113. Importantly, the incidence of malignancies was similar for placebo and mepolizumab in the integrated placebo-controlled studies in severe eosinophilic asthma (placebo: 3/412 [<1%]; mepolizumab all doses: 2/915 [<1%]) and severe COPD (placebo: 13/645 [2%]; mepolizumab all doses: 16/865 [2%]).

Of the 17 reports of lymphoma in the HES clinical program, duration of HES was reported for 14 cases, and ranged from less than a year to 15 years prior to enrolment into a clinical study or entering the HES EAP. Duration of HES was one year or less for 5 cases, between 1 and 5 years for 5 cases, and greater than 5 years for 4 cases. Five of the 17 cases of lymphoma in the HES program were diagnosed within the first 90 days of initiating mepolizumab/placebo, suggesting that in these 5 cases, it was likely a pre-existing condition. The remaining 12 subjects were diagnosed with lymphoma while receiving treatment with mepolizumab for longer than 90 days. Six of the 12 subjects were reported to have the L-HES variant, which increases the risk of T-cell lymphoma. One subject with unknown HES phenotype had concurrent immune deficiency and was diagnosed with Hodgkin's lymphoma. Another subject with unknown HES phenotype had suspected occult lymphoma since the time of HES diagnosis. One subject was considered by the treating physician to have secondary (reactive) HES due to long-lasting undiagnosed epidermotropic T-cell indolent lymphoma.

**Table 46: Incidence and Rate of Lymphoma in the Mepolizumab HES Clinical Program (Studies 200622, MHE100185, 205203, MHE100901, and the HES EAP), Safety Population**

| | Placebo | Mepolizumab all doses |
|---|---|---|
| **Integrated HES Placebo-Controlled Studies 200622 and MHE100185** | | |
| Number of subjects | 96 | 97 |
| Subject years of exposure | 50.69 | 59.78 |
| Number of reports of lymphoma | 1 | 0 |
| Rate (# events) of lymphoma per 1000 subject-years of exposure | 19.7 | 0 |
| **Open-Label Single-Arm Extension Study 205203** | | |
| Number of subjects | | 102 |
| Subject years of exposure | | 39.26 |
| Number of reports of lymphoma | | 1 |
| Rate (# events) of lymphoma per 1000 subject-years of exposure | | **25.5** |
| **Open-Label Single-Arm Extension Study MHE100901** | | |
| Number of subjects | | 78 |
| Subject years of exposure | | 286.96 |
| Number of reports of lymphoma | | 2 |
| Rate (# events) of lymphoma per 1000 subject-years of exposure | | **6.97** |
| **Mepolizumab HES EAP (Uncontrolled)** | | |
| Number of subjects | | 353 |
| Subject years of exposure[1] | | 1520.12 |
| Number of reports of lymphoma | | 13 |
| Rate (# events) of lymphoma per 1000 subject-years of exposure | | **8.6** |

[redacted]

Abbreviations: CSR = Clinical Study Report; EAP = Expanded Access Program; HES = hypereosinophilic syndrome; GSK = GlaxoSmithKline; ISS = Integrated Summary of Safety; OLE = open-label extension.

1. The clinical database, and therefore the exposure calculation, does not include exposure data for the Initial Compassionate Use Program and treatment protocol MHE112562 in the mepolizumab HES EAP; exposure as of 01 March 2019; cut-off date for safety database search is 01 June 2020.

In summary, L-HES is associated with an increased risk of T-cell lymphoma, and therefore the incidence and characteristics of T-cell lymphoma were evaluated in the mepolizumab HES clinical program.

The majority (13/17) of the cases of lymphoma in the HES clinical program were reported in the mepolizumab HES EAP, which also has the most subject-years of exposure compared with exposure in clinical studies. Exposure-adjusted incidences of lymphoma in the mepolizumab HES clinical program are similar to the estimate from the study by Lefevre et al [Lefevre, 2014].

As of 01 June 2020, there have been no reports of lymphoma in the mepolizumab clinical programs in severe eosinophilic asthma, COPD (except for 1 case on placebo), EGPA, nasal polyposis, atopic

dermatitis, and EoE. There is no known mechanism to link mepolizumab with potential for developing or accelerating malignancies. The incidence of malignancies was similar for mepolizumab and placebo in the integrated placebo-controlled studies in severe eosinophilic asthma and severe COPD.

**Serious Cardiac, Vascular, and Thromboembolic Events and Serious Ischemic Events**

The incidences of on-treatment AEs in the Cardiac Disorders SOC were similar for the placebo (5.2%) and mepolizumab all doses (7.2%) groups (***Table 47***). The incidences of on-treatment SAEs in the Cardiac Disorders SOC were also similar between the placebo group (1%) and the mepolizumab all doses group (2%). The incidence of AEs categorized as serious CVT events was 2% (2 subjects) in the placebo group and 3% (3 subjects) in the mepolizumab all doses group (**Table 46**).

One subject (mepolizumab group) had a fatal cardiac arrest, described in the next section. No serious ischemic events were reported in the HES Placebo Controlled Studies (**Table 47**).

**Table 47: Summary of On-Treatment Serious Cardiac, Vascular, and Thromboembolic Events (HES Placebo Controlled Studies, Safety Population)**

| | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | |
| Preferred term | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 |
| **Serious CVT events** | 2 (4) | 2 (4) | 0 | 1 (2) | 2 (2) | 3 (3) |
| Hypertension | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Peripheral artery occlusion | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Arrhythmia | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Cardiac arrest | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Restrictive cardiomyopathy | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |

[redacted]

Abbreviations: CVT = cardiac, vascular, and thromboembolic; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.
Note: Studies included: 200622 and MHE100185

**OLE HES Study 205203**

There were no serious CVT events reported.

## Serious adverse event/deaths/other significant events

The incidences of on-treatment SAEs in the HES Placebo Controlled Studies were similar between placebo (14%) and mepolizumab all doses (18%) groups (***Table 48***). The System Organ Class (SOC) with the highest incidence of on-treatment SAEs overall was Infections and Infestations: the incidences of SAEs in the Infections and Infestations SOC were 1% for the placebo group and 9% for mepolizumab all doses group. In the placebo group, the most frequently reported SOCs were Blood and Lymphatic System Disorders (3%), Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) (2%), and Gastrointestinal Disorders (2%) (***Table 48***). On-treatment SAE PTs reported for >1 subject overall were HES (1 fatal [mepolizumab group]), pneumonia (1 fatal [mepolizumab group]), asthma, bronchitis, and renal failure. No on-treatment SAEs were considered to be drug-related by the investigator.

**Table 48: On-Treatment Serious Adverse Events by System Organ Class (HES Placebo Controlled Studies, Safety Population)**

| System Organ Class<br>Preferred term | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | |
| | PBO<br>N=54 | Mepo<br>300 mg SC<br>N=54 | PBO<br>N=42 | Mepo<br>750 mg IV<br>N=43 | PBO<br>N=96 | Mepo<br>all doses<br>N=97 |
| **Any on-treatment SAE** | 8 (15) | 10 (19) | 5 (12) | 7 (16) | 13 (14) | 17 (18) |
| Infections and Infestations | 0 | 7 (13) | 1 (2) | 2 (5) | 1 (1) | 9 (9) |
| Pneumonia | 0 | 1 (2) | 1 (2) | 1 (2) | 1 (1) | 2 (2) |
| Bronchitis | 0 | 1 (2) | 0 | 1 (2) | 0 | 2 (2) |
| Bursitis infective | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Diverticulitis | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Erysipelas | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Liver abscess | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Septic shock | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Tooth infection | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Blood and Lymphatic System Disorders | 1 (2) | 1 (2) | 2 (5) | 1 (2) | 3 (3) | 2 (2) |
| HES | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 2 (2) | 2 (2) |
| Eosinophilia | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Gastrointestinal Disorders | 2 (4) | 2 (4) | 0 | 1 (2) | 2 (2) | 3 (3) |
| Abdominal pain | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Abdominal pain upper | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Fecaloma | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Pancreatitis | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Vomiting | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Cardiac Disorders | 1 (2) | 1 (2) | 0 | 1 (2) | 1 (1) | 2 (2) |
| Arrhythmia | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Cardiac arrest | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Restrictive cardiomyopathy | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Injury, Poisoning and Procedural Complications | 0 | 2 (4) | 0 | 1 (2) | 0 | 3 (3) |
| Contusion | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Foot fracture | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Spinal compression fracture | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Renal and urinary disorders | 0 | 0 | 1 (2) | 2 (5) | 1 (1) | 2 (2) |
| Renal failure | 0 | 0 | 0 | 2 (5) | 0 | 2 (2) |
| Nephrotic syndrome | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 1 (2) | 0 | 2 (5) | 0 | 3 (3) |
| Asthma | 0 | 0 | 0 | 2 (5) | 0 | 2 (2) |
| Respiratory failure | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Musculoskeletal and Connective Tissue Disorders | 0 | 1 (2) | 1 (2) | 0 | 1 (1) | 1 (1) |
| Costochondritis | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Osteonecrosis | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |

| System Organ Class<br>Preferred term | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | |
| | PBO<br>N=54 | Mepo<br>300 mg SC<br>N=54 | PBO<br>N=42 | Mepo<br>750 mg IV<br>N=43 | PBO<br>N=96 | Mepo<br>all doses<br>N=97 |
| Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) | 2 (4) | 0 | 0 | 0 | 2 (2) | 0 |
| T-cell lymphoma | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Uterine leiomyoma | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Vascular disorders | 1 (2) | 1 (2) | 0 | 0 | 1 (1) | 1 (1) |
| Hypertension | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Peripheral artery occlusion | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| General Disorders and Administration Site Conditions | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Pyrexia | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Hepatobiliary Disorders | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Hepatitis | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Immune System Disorders | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Anaphylactic reaction | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Metabolism and Nutrition Disorders | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Dehydration | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Nervous System Disorders | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Dysesthesia | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Polyneuropathy | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Reproductive System and Breast Disorders | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Vaginal hemorrhage | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SAE = serious adverse event; SC = subcutaneously.
Note: Studies included: 200622 and MHE100185.

**OLE HES Study 205203**

All SAEs reported in Study 205203 were non-fatal. The overall incidence of on-treatment SAEs was 8%; SAEs were most frequently reported within the SOC of Infections and Infestations (5%). None of the on-treatment SAEs was reported in more than 1 subject.

**OLE HES Study MHE100901**

The incidence of SAEs was 51%. Non-fatal SAEs reported for >1 subject were pneumonia (4 subjects [5%]), pyrexia (3 subjects [4%]), cardiac failure, cholecystitis acute, diarrhea, eosinophilia, dyspnea, and prostate cancer (each 2 subjects [3%]).

**All Serious Adverse Events (MHE104317)**

In MHE104317, the incidence of SAEs was 52%. The incidence of non-fatal SAEs was 47%, and the most frequently reported PTs were pneumonia and asthma (both 6%).

**Deaths**

There were 2 deaths in the HES Placebo Controlled Studies, both in the mepolizumab group (1 on 300 mg SC and 1 on 750 mg IV).

**One subject** (Study 200622), a 66-year-old male with a medical history of hypertension, hypercholesterolemia, congestive heart failure, and cardiomyopathy, on 09 January 2019, 1 day after receiving the 3rd dose of mepolizumab, had SAEs of HES flare, pneumonia, respiratory failure, and septic shock, all reported with fatal outcome. The investigator stated the HES flare did not respond to high doses of steroids. The subject was hospitalized on 13 January 2019 due to an HES flare and treated with high dose IV steroids and levofloxacin for intestinal infection. During hospitalization, the subject was diagnosed with oesophageal candidiasis, worsening of dyspnoea and oedema, and nosocomial pneumonia. The subject's condition progressed to respiratory failure, requiring intubation on 02 February 2019. The subject later died. An autopsy was not performed. The events were not considered to be drug-related by the investigator.

The second subject (Study MHE100185), an 18-year-old male, had a fatal SAE of cardiac arrest 110 days after the 1st dose (26 days since the last dose), which was not considered to be drug-related by the investigator. This subject had 2 other on-treatment SAEs (pyrexia and renal failure), of which the renal failure was ongoing at the time of the cardiac arrest. This subject had severe HES with multiple cardiovascular complications. The subject's past medical history included cardiovascular accident, deep vein thrombosis, cardiac arrest, defibrillator insertion, pulmonary embolism, myocardial infarctions, seizures, and vena cava filter insertion. Medical conditions ongoing at the time of death included cardiomyopathy, Loeffler's endocarditis, renal insufficiency, and systemic hypertension. Pre-treatment echocardiograms performed pre-treatment revealed a decline in left ventricular ejection fraction between Screening and Baseline. An external cardiologist assessed the on-treatment electrocardiogram (ECG) findings and indicated that there was a minimal change during the treatment period compared with

Baseline including a progressive widening of the QRS duration compatible with right bundle branch block. An autopsy was not performed. The cause of death on the discharge summary was cardiac arrest due to dysrhythmia and failure of the internal pacemaker/defibrillator.

**OLE HES Study 205203**

No deaths were reported in Study 205203

**OLE HES Study MHE100901**

There were 4 deaths in this study: one subject with cardiac failure, sepsis, and multi-organ failure, one subject with aspiration pneumonia and respiratory failure, one subject with sudden death, and one subject with AITL and cardiopulmonary failure. The AITL was considered to be drug-related by the investigator (T-cell lymphomas are described further above under AESI).

**Deaths (Mepolizumab HES EAP)**

The mepolizumab HES EAP was initiated to treat patients with severe HES that have organ- or life-threatening disease that have not responded to multiple standard of care therapies and were often too unstable to enter placebo-controlled clinical studies. Combined with the long duration of treatment (median 3.0 years, ranging from 1 month to 16.75 years), patients in the mepolizumab HES EAP had more time to experience SAEs and fatal events than subjects in a typical clinical study of 1-year duration. There were total of 33 deaths reported in mepolizumab HES EAP. Of these, 25 were reported in MHE104317, 14 on-treatment and 11 during the follow-up period. The fatal SAE PTs (on- and post-treatment) occurring in >1 patient were cardiac arrest (3 patients), respiratory failure (3 patients),

myocardial infarction (2 patients), multiple organ dysfunction (2 patients), cardio-respiratory arrest (2 patients), and sepsis (2 patients). One fatal SAE (multiple organ dysfunction syndrome; on-treatment) was considered to be drug-related by the physician.

The remaining 8 deaths were reported in the:

- Initial Compassionate Use Program (3 patients): 1 paediatric patient with a fatal SAE of respiratory insufficiency; 1 patient with a fatal SAE of unexplained nasal Haemorrhage, and 1 patient with a fatal SAE of suicide; none of the events were considered to be drug-related by the physician.
- NPS Guidance Program (3 patients): 1 patient with a fatal SAE of multiple organ dysfunction syndrome, 1 patient with a fatal SAE of pulmonary superinfection associated with septic shock (not drug-related), and 1 patient with a fatal SAE of T-cell lymphoma (relationship to mepolizumab treatment unknown). T-cell lymphomas are described further above under AESIs.
- Treatment protocol MHE112562 (2 patients): 1 patient with a fatal SAE of septic shock and 1 patient with a fatal SAEs of sudden death, respiratory failure, and mechanical ventilation; none of the events were considered to be drug-related by the physician.

All Studies Combined

Table **49** presents the incidence of deaths in the All Studies Combined by dose and indication. The exposure-adjusted rate of death for the integrated placebo group was 20.9 per 1000 subject-years of exposure and for the mepolizumab all doses group was 10.3 per 1000 subject years of exposure.

**Table 49: Summary of Deaths by Indication and Dose (All Studies Combined, Safety Population)**

| | PBO | Mepolizumab | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 100 mg SC | 300 mg SC | 75 mg IV | 250 mg IV | 750 mg IV | Other [1] | All doses |
| | N=2087 | N=2722 | N=458 | N=361 | N=294 | N=446 | N=607 | N=4363 |
| **All indications** | 30 (1) | 29 (1) | 11 (2) | 0 | 2 (<1) | 6 (1) | 26 (4) | 74 (2) |
| HES, n | 96 | 0 | 106 | 0 | 0 | 81 | 359 | 462 |
| Deaths, n(%) | 0 | 0 | 1 (<1) | 0 | 0 | 5 (6) | 26 (7) | 32 (7) |
| Asthma, n | 972 | 1613 | 0 | 355 | 275 | 285 | 130 | 2217 |
| Deaths, n(%) | 3 (<1) | 9 (<1) | 0 | 0 | 2 (<1) | 1 (<1) | 0 | 12 (<1) |
| Severe asthma, n | 803 | 1613 | 0 | 344 | 152 | 156 | 26 | 1850 |
| Deaths, n(%) | 3 (<1) | 9 (<1) | 0 | 0 | 2 (1) | 1 (<1) | 0 | 12 (<1) |
| Atopic dermatitis, n | 38 | 19 | 0 | 0 | 0 | 20 | 0 | 39 |
| Deaths, n(%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| COPD, n | 645 | 640 | 225 | 0 | 0 | 0 | 0 | 865 |
| Deaths, n(%) | 26 (4) | 20 (3) | 8 (4) | 0 | 0 | 0 | 0 | 28 (3) |
| EGPA, n | 68 | 0 | 127 | 0 | 0 | 0 | 0 | 127 |
| Deaths, n(%) | 0 | 0 | 2 (2) | 0 | 0 | 0 | 0 | 2 (2) |
| EoE, n | 6 | 0 | 0 | 0 | 0 | 0 | 64 | 64 |
| Deaths, n(%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CRSwNP, n | 253 | 206 | 0 | 0 | 0 | 53 | 0 | 259 |
| Deaths, n(%) | 1 (<1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Healthy volunteers, n | 9 | 244 | 0 | 6 | 19 | 7 | 54 | 330 |
| Deaths, n(%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

[redacted]

Abbreviations: COPD = chronic obstructive pulmonary disease; CRSwNP = chronic rhinosinusitis with nasal polyps; EAP = Expanded Access Program; EGPA = eosinophilic granulomatosis with polyangiitis; EoE = eosinophilic esophagitis; HES = hypereosinophilic syndrome; IM = intramuscularly; ISS = Integrated Summary of Safety; IV = intravenously; PBO = placebo; SC = subcutaneously.

1. Includes IV doses: 10 mg, 750 mg/1500 mg, 0.05, 0.5, 0.55, 2.5 and 10 mg/kg, SC doses: 12.5, 40, 40/100, 125, 250 mg, and IM dose: 250 mg, as well as all patients enrolled in the mepolizumab HES EAP.

Note: A subject who participated in more than 1 study and received different doses was counted once in each dose.
Note: Studies included: Asthma - MEA114092, SB240563/001, SB240563/006, SB240563/017, SB240563/035, SB240563/036; Severe Asthma - 200363, 200862, 201312, 204471, 204959, 205667, MEA112997, 201810, MEA115575, MEA115588, MEA115661, MEA115666; HES - 200622, MHE100185, MHE100901, MHE104317, 205203; EoE - MEE103219, MEE103226; Atopic Dermatitis - 205050, SB240563/045; Healthy Volunteers - 204958, MEA115705, SB240563/018; EGPA - MEA115921, MEA116841, 201607; CRSwNP - MPP111782, 205687; COPD - MEA117106, MEA117113.

## Laboratory findings

### Clinical Chemistry

There was no evidence of treatment effect on clinical chemistry parameters. For all post-Baseline clinical chemistry parameters in the HES Placebo Controlled Studies, the majority of subjects in each treatment group had values shift to the normal range or no change. The incidence of subjects with clinical chemistry parameter values outside the normal range at any time post-Baseline occurred with comparable incidence across the treatment groups (Table 50). The parameter with a ≥10% difference in incidence between placebo and mepolizumab groups was lactate dehydrogenase (to high in both treatment groups; higher in placebo).

**Table 50: Clinical Chemistry Changes from Baseline Relative to the Normal Range Any Time Post-Baseline (Incidence >10% in the Integrated Placebo or Mepolizumab All Doses Group) (HES Placebo Controlled Studies, Safety Population)**

| Clinical chemistry parameter | Change from Baseline | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|---|
| | | 200622 | | MHE100185 | | Both studies | |
| | | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 |
| Glucose, n | | 54 | 54 | 39 | 39 | 93 | 93 |
| | To low | 10 (19) | 4 (7) | 10 (26) | 7 (18) | 20 (22) | 11 (12) |
| | To high | 15 (28) | 15 (28) | 3 (8) | 6 (15) | 18 (19) | 21 (23) |
| Chloride, n | | 54 | 54 | 42 | 43 | 96 | 97 |
| | To high | 10 (19) | 5 (9) | 9 (21) | 14 (33) | 19 (20) | 19 (20) |
| Creatine kinase, n | | 54 | 54 | 42 | 43 | 96 | 97 |
| | To high | 8 (15) | 8 (15) | 2 (5) | 7 (16) | 10 (10) | 15 (15) |
| Protein, n | | 54 | 54 | 42 | 43 | 96 | 97 |
| | To low | 4 (7) | 3 (6) | 7 (17) | 5 (12) | 11 (11) | 8 (8) |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.
Note: Subjects were counted in the category that their value changes to (low, normal, or high), unless there is no change in their category. Subjects whose lab value category was unchanged (e.g., High to High), or whose value became normal, were recorded in the "To Normal or No Change" category. Subjects were counted twice if the subject has values that changed 'To Low' and 'To High', so the percentages may not add to 100%. Subjects with missing Baseline value were assumed to have normal Baseline value.
Note: Worst case post-Baseline includes scheduled and unscheduled assessments.
Note: Studies included: 200622 and MHE100185.

A small number of subjects had clinical chemistry changes from baseline that met pre-defined potential clinical concern values (≤2 subjects in both treatment groups in a specific clinical chemistry parameter).

In the HES Placebo Controlled Studies, there were no possible 'Hy's Law' events (i.e., drug-induced liver injury with hyperbilirubinemia, defined as alanine aminotransferase [ALT] ≥3x upper limit of normal [ULN] and bilirubin ≥2xULN [>35% direct] [or ALT ≥3xULN and international normalized ratio [INR] >1.5, if INR measured]). Two subjects in the mepolizumab group (1 in Study 200622 [met the protocol-defined liver monitoring criteria, but not liver stopping criteria] and 1 in Study MHE100185 [liver chemistry monitoring/ stopping criteria were not defined in this study]) had ALT ≥3x ULN.

**Hematology**

Laboratory parameters for haematology that were assessed in both Study 200622 and Study MHE100185 were integrated.

Blood eosinophil counts were considered a pharmacodynamics assessment in the HES Placebo Controlled Studies and are not described in this section. There was no evidence of treatment effect on haematology parameters (except for blood eosinophil counts). For most post-Baseline haematology parameters in the HES Placebo Controlled Studies, the majority of subjects in each treatment group had values shift to the normal range or no change. The incidence of subjects with haematology parameter values outside the normal range at any time post-baseline occurred with comparable incidence across the treatment groups (Table 51). Of the haematology parameters with subjects with worst case post-Baseline shifts outside the normal range, the parameters with a ≥10% higher in incidence in mepolizumab vs placebo were: lymphocytes ($10^9$/L) (to low), monocytes/leukocytes (%) (to high), segmented neutrophils/leukocytes (%) (to high), neutrophils/leukocytes (%) (to high); and parameters with a ≥10% higher in incidence in placebo vs mepolizumab were: leukocytes ($10^9$/L) (to high), monocytes ($10^9$/L) (to low), neutrophils ($10^9$/L) (to high), segmented neutrophils ($10^9$/L) (to high), neutrophils/leukocytes (%) (to low).

No subjects had haematology changes from Baseline that met pre-defined potential clinical concern values.

**Table 51: Hematology Changes from Baseline Relative to the Normal Range Any Time Post-Baseline (Incidence >10% in the Integrated Placebo or Mepolizumab All Doses Group) (HES Placebo Controlled Studies, Safety Population)**

| Hematology parameter | Change from Baseline | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|---|
| | | 200622 | | MHE100185 | | Both studies | |
| | | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 |
| Eosinophils/ leukocytes | To high | 4 (7) | 0 | 28 (67) | 6 (14) | 32 (33) | 6 (6) |
| Erythrocytes | To low | 9 (17) | 4 (7) | 3 (7) | 5 (12) | 12 (13) | 9 (9) |
| Hemoglobin | To low | 12 (22) | 4 (7) | 6 (14) | 10 (23) | 18 (19) | 14 (14) |
| Leukocytes | To high | 15 (28) | 6 (11) | 10 (24) | 8 (19) | 25 (26) | 14 (14) |
| Lymphocytes | To low | 7 (13) | 14 (26) | 5 (12) | 10 (23) | 12 (13) | 24 (25) |
| | To high | 6 (11) | 3 (6) | 5 (12) | 1 (2) | 11 (11) | 4 (4) |
| Lymphocytes/ leukocytes | To low | 17 (31) | 15 (28) | 12 (29) | 11 (26) | 29 (30) | 26 (27) |
| Monocytes | To low | 11 (20) | 12 (22) | 22 (52) | 9 (21) | 33 (34) | 21 (22) |
| Monocytes/ leukocytes | To high | 5 (9) | 13 (24) | 0 | 11 (26) | 5 (5) | 24 (25) |
| Neutrophils | To high | 15 (28) | 7 (13) | 12 (29) | 8 (19) | 27 (28) | 15 (15) |
| Neutrophils, segmented | To high | 15 (28) | 7 (13) | 12 (29) | 8 (19) | 27 (28) | 15 (15) |
| Neutrophils, segmented/ leukocytes | To low | 17 (31) | 1 (2) | 9 (21) | 4 (9) | 26 (27) | 5 (5) |
| | To high | 16 (30) | 28 (52) | 12 (29) | 13 (30) | 28 (29) | 41 (42) |
| Neutrophils/ leukocytes | To low | 17 (31) | 1 (2) | 9 (21) | 4 (9) | 26 (27) | 5 (5) |
| | To high | 16 (30) | 28 (52) | 12 (29) | 13 (30) | 28 (29) | 41 (42) |
| Platelets | To high | 5 (9) | 6 (11) | 4 (10) | 7 (16) | 9 (9) | 13 (13) |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.

Note: Subjects were counted in the category that their value changes to (low, normal or high), unless there was no change in their category. Subjects whose lab value category was unchanged (e.g., high to high), or whose value became normal, were recorded in the "to normal or no change" category. Subjects were counted twice if the subject has values that changed 'to low' and 'to high', so the percentages may not add to 100%. Subjects with missing Baseline value were assumed to have normal Baseline value.

Note: Worst case post Baseline includes scheduled and unscheduled assessments.

Note: Studies included: 200622 and MHE100185.

**Vital Signs**

Mean values for systolic blood pressure and diastolic blood pressure were similar between the placebo and mepolizumab all doses groups in the HES Placebo Controlled Studies. Mean values for pulse rate and temperature were also similar between the treatment groups.

**Electrocardiograms**

Different methods of ECG data collection were used in studies 200622 and MHE100185. No treatment related effects were noted for ECG parameters in both studies (Table 52).

**Table 52: Maximum Post-Baseline Values and Change from Baseline in QTc Interval (Study 200622, Safety Population)**

| Any Time Post Baseline | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | QTc(B) | | QTc(F) | |
| | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) | Placebo (N=54) | Mepolizumab 300 mg SC (N=54) |
| **Value (msec)** | | | | |
| n | 50 | 49 | 50 | 49 |
| No change or decrease to ≤450 | 49 (98) | 46 (94) | 50 (100) | 48 (98) |
| Increase To >450 to ≤480 | 1 (2) | 2 (4) | 0 | 0 |
| Increase To >480 to ≤500 | 0 | 1 (2) | 0 | 1 (2) |
| Increase To >500 | 0 | 0 | 0 | 0 |
| **Change from Baseline (msec)** | | | | |
| n | 50 | 49 | 50 | 49 |
| Increase of ≤30 msec | 50 (100) | 46 (94) | 50 (100) | 45 (92) |
| Increase of 31-60 msec | 0 | 3 (6) | 0 | 4 (8) |
| Increase of >60 msec | 0 | 0 | 0 | 0 |

[redacted]

Note: Includes scheduled and unscheduled assessments.

**Immunogenicity Results**

**Immunogenicity in HES Placebo Controlled Studies**

Serum samples were assessed for immunogenicity using a tiered analysis approach with validated assays: i) for binding anti-drug antibody (ADA): screening, confirmation, and titration analysis; and ii) for neutralizing antibody (NAb). Studies 200622 and MHE100185 used different methods to detect binding ADAs (6th and 3rd generation assay, respectively) and NAbs (3rd and 2nd generation assay, respectively). Given the assay differences, a comparison between studies is not appropriate. Note that Study 200622 used the same binding ADA and NAb assays as the mepolizumab severe asthma clinical program.

**Study 200622**

Two subjects in the mepolizumab 300 mg SC group tested positive for ADAs. One subject (2%, 1/54) was positive for ADAs at Baseline only, and one subject (2%, 1/53) was positive for ADAs at any time post-baseline (at Week 32). For both subjects, the titer values were low (titer values: 4). Neither of the subjects were positive for NAbs.

For the post-baseline ADA positive subject, there were 2 non-serious AEs of URTI on Days 45 and 132, neither of which were considered to be drug-related by the investigator. This subject's blood eosinophil count was high at both Screening (14,500 cells/μL) and Day 1 (1450 cells/μL), this decreased up to Week 4, after which counts gradually increased to return to Baseline levels during the remainder of the study treatment period (2430 cells/μL at the end of study [Week 32]). The post-baseline ADA assessment for this subject in Study 205203 was negative.

**Study MHE100185**

Post-baseline, 5 subjects tested positive for ADAs: 1 subject (1/41) in the placebo group (titer 4) and 4 subjects (4/43) in the mepolizumab 750 mg IV group (range: <2 to 64). No subjects tested positive for NAbs.

Of the 4 subjects in the mepolizumab group who had detectable ADAs post-baseline, 1 subject had a systemic reaction of hypersensitivity on Days 5, 35, and 78, and a fatal SAE of cardiac arrest (HES-related; not drug-related) on Day 110. This subject had a progressive increase in blood eosinophils in the visits prior to the fatal event: 200 cells/µL on Day 1 (pre-dose), this decreased and remained stable up to Day 64, after which counts increased progressively to 2840 cells/µL on Day 107. One other subject in the mepolizumab group with ADAs had an increase in blood eosinophil count: 70 cells/µL at Day 1 (pre-dose), this decreased up to Day 28 (10 cells/µL), after which counts increased to 980 cells/µL by Day 112, thereafter declining to 430 cells/µL at Day 224. The clinical significance of this finding remains unclear as the subject was noted to have an ADA titer of 32 at Day 168 but was simultaneously undergoing successful prednisone tapering. For the 2 other subjects on mepolizumab who tested positive for ADAs, there were small changes in blood eosinophil count for two Subjects and the reduction was maintained throughout the study.

**Immunogenicity in the Supportive HES Studies**

The incidence of immunogenicity following mepolizumab administration was low in Study 205203. One subject (previously receiving mepolizumab in Study 200622) who tested positive for ADA at baseline (which was also the Week 32 Visit of Study 200622) became negative at Week 20. No subjects had a confirmed positive ADA assay result at any time post-Baseline. This study used the same validated assays that also supported Study 200622.

Immunogenicity was assessed in the completed OLE study MHE100901. This study utilized different binding ADA (4th generation) and NAb (3rd generation) assays, and 57% of subjects (39/69) confirmed positive for ADAs (range of titre values: 5 to 1600). No subjects tested positive for NAbs.

The different immunogenicity incidences are most likely due to the various assay formats. The 3rd generation ADA assay (used with Study MHE100185 samples) utilized the Bioveris platform (reagents and plate reader); which became unavailable following its purchase. The 4th generation ADA assays (used with Study MHE100901 samples) utilized a platform from MesoScale Discovery (bridging assay with electro-chemiluminescent detection). This assay format was susceptible to false positive ADA responses due to the homodimer target (i.e., IL-5) binding the drug conjugates. The inclusion of an anti-IL-5 blocking antibody to mitigate target interference (6th generation ADA assay [used with study samples from 200622 and 205203, and in the severe asthma clinical program]) reduced the false positive assay responses from IL-5.

## Safety in special populations

**Adverse Events by Age**

Of the HES Placebo Controlled Studies, only Study 200622 enrolled adolescent subjects (ages 12 to 17 years). In Study 200622, there were 4 adolescent subjects (ages 12 to 17 years), 3 in the placebo group and 1 in the mepolizumab group. Two subjects in the placebo group had an on-treatment AE. No AE PTs in this age group were reported for >1 subject. One of the subjects in the placebo group had an ontreatment SAE of anaphylactic reaction. No on-treatment AEs were reported for the adolescent subject in the mepolizumab group.

In the HES Placebo Controlled Studies, the majority of subjects in both the placebo and mepolizumab groups were aged 18 to 64 years (**Table 36**). The incidence of on-treatment AEs in this age group was

similar to that observed in the Safety Population (92% in both treatment groups); the most frequently reported SOC and PTs reflected that of the Safety Population.

Given the low proportion of the Safety Population that was aged ≥65 years (18% [17/96 subjects] in the placebo group and 12% [12/97 subjects] in mepolizumab all doses group), there is a limited ability to compare the incidence and pattern of on-treatment AEs this subgroup to the Safety Population.

**Adverse Events by Gender**

The incidence of on-treatment AEs and the incidence of the most frequently reported SOC and PTs were similar in the female and male subgroups and reflected that observed in the Safety Population.

**Adverse Events by Race**

Most subjects in the Safety Population were White (90%) (**Table 36**). Amongst White subjects, the incidence of on-treatment AEs and the incidence of the most frequently reported SOC and PTs were similar to that observed in the Safety Population. Given the low proportion of subjects in the Safety Population who were of African American/African Heritage (5%) or Asian (3%) (**Table 36**), there is a limited ability to compare the incidence and pattern of on-treatment AEs these subgroups to the Safety Population.

**Extrinsic Factors**

Safety was not summarized by extrinsic factor.

**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 study, and for 4 months after the last dose of study drug administration. As of 23 September 2019 (cut-off date for current Investigator's Brochure), 33 pregnancies were reported for 31 female subjects receiving investigational product in the completed and ongoing mepolizumab studies (all indications) (***Table 53***). Of the 33 pregnancies, 2 were reported in subjects who received placebo. There was one report of congenital anomalies for the live births (see description below). Two additional pregnancies were reported for the female partners of study subjects: 1 on placebo which resulted in a spontaneous abortion (Study SB-240563/035), 1 on mepolizumab 100 mg SC which resulted in live birth with congenital anomaly (study 201312). These exposures via partner cases are not included in **Table 53**.

**Table 53: Reported Pregnancies in the Mepolizumab Clinical Development Program (Completed and Ongoing GSK-Sponsored Studies and Expanded Access Program; Status as of 23 September 2019)**

| Pregnancy outcome | Blinded | PBO | Mepolizumab | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 100 mg SC | 300 mg SC | 75 mg IV | 500 mg IV | 750 mg IV | All doses |
| Total | 3 | 2 | 12 | 1 | 4 | 2 | 9[1] | 33[2] |
| Ongoing | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Live birth | 2 | 1 | 7 | 1 | 3 | 1 | 5[3] | 20[2] |
| Elective termination | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 3 |
| Spontaneous abortion | 1 | 1 | 3 | 0 | 1 | 0 | 2 | 8 |

[redacted]

Abbreviations: EAP = Expanded Access Program; GSK = GlaxoSmithKline; HES = hypereosinophilic syndrome; IV = intravenously; PBO = placebo; SC = subcutaneously

1. One subject with HES who received mepolizumab 750 mg IV had 2 pregnancies; 1 electively terminated and 1 resulting in a live birth.
2. Two live births were reported from blinded studies 201810 and 205687; treatment is currently unknown.
3. One subject with HES (MHE104317; mepolizumab HES EAP) received mepolizumab dose of 700 mg IV.

Two studies, 201810 and 205687, have been completed and unblinded. The live birth of a healthy neonate in Study 201810 (***Table 53***) was reported for a female subject who was randomized to continued mepolizumab 100 mg SC in Part C of the study. The live birth with congenital anomalies of low haemoglobin, mild pulmonary valve stenosis, and heart murmur in Study 205687 (***Table 53***) was reported for a female subject who received mepolizumab 100 mg SC. The pregnancy was confirmed after the 4th dose of mepolizumab, and study treatment was discontinued. Another female subject in Study 205687 (***Table 53***), who was randomized to receive placebo, reported a missed abortion 41 days after her first dose of placebo and was withdrawn from the study.

**Overdose**

The dose of mepolizumab considered to be an overdose has not been defined. Single doses of up to 1500 mg have been administered IV without evidence of dose-related toxicities. There are no known antidotes and the MAH does not recommend a specific treatment in the event of a suspected overdose. Clinical judgment should be used in treating the symptoms of a suspected overdose.

**Drug Abuse**

There is no evidence for and no anticipation of patient abuse of mepolizumab.

**Withdrawal and Rebound**

In the HES Placebo Controlled Studies, the incidences of post-treatment AEs were similar between the mepolizumab and placebo groups. There were no verbatim reports of 'rebound' of disease.

Subjects completing Study MHE100185 were eligible to enroll in Study MHE100901. Subjects continuing mepolizumab treatment in Study MHE100901 had no treatment break, that is, subjects received the first dose of mepolizumab in Study MHE100901 within 28 days of receiving the last dose in Study MHE100185. Likewise, subjects completing Study 200622 were eligible to enroll in Study 205203, and those continuing mepolizumab treatment in Study 205203 were not to have a treatment break. Due to study design, it has not been possible to assess rebound in these studies. There was no evidence of rebound in the clinical program in severe asthma, EGPA, and CRSwNP.

**Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability**

There have been no studies to investigate the effect of mepolizumab on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology or adverse reaction profile of mepolizumab.

**Discontinuation or Withdrawal from study**

Of the 193 subjects in the Safety Population of the HES Placebo Controlled Studies, 155 (80%) were considered study completers (***Table 54***); fewer subjects in the placebo group completed the studies (70%) compared with the mepolizumab group (91%). This is explained by the higher proportion of subjects withdrawing from the placebo group (50%) due to lack of efficacy (12% in the mepolizumab group) in Study MHE100185. In Study MHE100185, blood eosinophil counts were not blinded, and investigators were permitted to withdraw subjects from the study if they did not respond to treatment, in order for them to commence treatment with mepolizumab in OLE study MHE100901. In Study MHE100185, subjects discontinuing study treatment were withdrawn from the study, whereas in Study 200622, subjects discontinuing study treatment were encouraged to continue in the study. In the HES Placebo Controlled Studies, there were 2 subjects who discontinued study treatment and did not withdraw from the study (1 on placebo and 1 on mepolizumab 300 mg SC, both in Study 200622, and the reason for withdrawal from treatment for both was 'withdrawal by subject').

Of the 108 subjects randomized into Study 200622, a total of 102 subjects were enrolled and received treatment in Study 205203; 52 subjects previously received placebo and 50 subjects previously received mepolizumab in Study 200622.

**Table 54: Summary of Subject Disposition by Dose (HES Placebo Controlled Studies, Safety Population)**

| | Number (%) of Subjects | | | | | | |
|---|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | | |
| | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 | Total N=193 |
| **Subject Status** | | | | | | | |
| Completed study treatment | 51 (94) | 51 (94) | 15 (36) | 36 (84) | 66 (69) | 87 (90) | 153 (79) |
| Completed study | 52 (96) | 52 (96) | 15 (36) | 36 (84) | 67 (70) | 88 (91) | 155 (80) |
| **Discontinued Study Treatment** | | | | | | | |
| Lack of efficacy | 0 | 0 | 21 (50) | 5 (12) | 21(22) | 5 (5) | 26 (13) |
| Adverse event | 2 (4) | 1 (2) | 2 (5) | 1 (2) | 4 (4) | 2 (2) | 6 (3) |
| Withdrawal by subject | 1 (2) | 2 (4) | 1 (2) | 1 (2) | 2 (2) | 3 (3) | 5 (3) |
| Other | 0 | 0 | 2 (5) | 0 | 2 (2) | 0 | 2 (1) |
| Disease progression [1] | | | 1 (1) | 0 | 1 (1) | 0 | 1 (<1) |
| **Withdrew from Study** | | | | | | | |
| Lack of efficacy [2] | | | 21 (50) | 5 (12) | 21 (22) | 5 (5) | 26 (13) |
| Adverse event | 2 (4) | 1 (2) | 2 (5) | 1 (2) | 4 (4) | 2 (2) | 6 (3) |
| Withdrawal by subject | 0 | 1 (2) | 1 (2) | 1 (2) | 1 (1) | 2 (2) | 3 (2) |
| Other | 0 | 0 | 2 (5) | 0 | 2 (2) | 0 | 2 (1) |
| Disease progression [2] | | | 1 (2) | 0 | 1 (1) | 0 | 1 (<1) |

[redacted]

Abbreviations: eCRF = electronic Case Report Form; HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.

1. Disease progression was an option for reasons for treatment discontinuation on MHE100185 eCRF only.
2. Lack of efficacy and disease progression were options for reasons for study withdrawal on MHE100185 eCRF only.

Note: In 200622, subjects discontinuing treatment continued in the study; separate reasons for study and treatment discontinuation are recorded in the eCRF. In MHE100185, subjects discontinuing treatment were withdrawn from the study.

Note: One reason for study/treatment discontinuation is recorded in the eCRF.

Note: Studies included: 200622 and MHE100185.

The incidence of AEs that led to permanent discontinuation of study treatment or withdrawal from the HES Placebo Controlled Studies was 6% in the placebo group and 2% in the mepolizumab group (***Table 54***). The PT occurring in >1 subject overall was HES. For 6 subjects, these events were SAEs: 2 subjects in the mepolizumab group (1 subject with fatal SAEs of HES, pneumonia, respiratory failure, and septic shock, and 1 subject with fatal SAE of cardiac arrest), and 4 in the placebo group (1 subject with T-cell lymphoma, 1 subject with lung neoplasm malignant, 1 subject with nephrotic syndrome, and 1 subject with eosinophilia and polyneuropathy). The lung neoplasm malignant event occurred pre-treatment. None of the AEs leading to treatment discontinuation or study withdrawal were considered to be drug-related by the investigator.

**Table 55: On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study (HES Placebo Controlled Studies, Safety Population)**

| | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | 200622 | | MHE100185 | | Both studies | |
| Preferred term | PBO N=54 | Mepo 300 mg SC N=54 | PBO N=42 | Mepo 750 mg IV N=43 | PBO N=96 | Mepo all doses N=97 |
| **Any on-treatment event** | 2 (4) | 1 (2) | 4 (10) | 1 (2) | 6 (6) | 2 (2) |
| Hypereosinophilic syndrome | 0 | 1 (2) | 1 (2) | 0 | 1 (1) | 1 (1) |
| Eosinophilia | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Lung neoplasm malignant | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| T-cell lymphoma | 1 (2) | 0 | 0 | 0 | 1 (1) | 0 |
| Asthma | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Respiratory failure | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Sinus disorder | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Cardiac arrest | 0 | 0 | 0 | 1 (2) | 0 | 1 (1) |
| Pneumonia | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Septic shock | 0 | 1 (2) | 0 | 0 | 0 | 1 (1) |
| Polyneuropathy | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |
| Nephrotic syndrome | 0 | 0 | 1 (2) | 0 | 1 (1) | 0 |

[redacted]

Abbreviations: HES = hypereosinophilic syndrome; ISS = Integrated Summary of Safety; IV = intravenously; Mepo = mepolizumab; PBO = placebo; SC = subcutaneously.
Note: Studies included: 200622 and MHE100185.

**OLE HES Study 205203**

The incidence of AEs leading to permanent discontinuation of study treatment and/or withdrawal from the study was <1%. One subject discontinued study treatment and withdrew from the study due to an AE (PT: pain). The event was of severe intensity, was considered to be drug-related by the investigator, and the event was recovered/resolved.

**OLE HES Study MHE100901**

There were 10 subjects who withdrew from the study due to an on-treatment AE (including 4 subjects due to a fatal event). No AE PTs were reported for >1 subject. For 7 subjects, the event was an SAE (4 fatal and 3 non-fatal [transverse myelitis, disease progression, and hypotension]). For 2 subjects, the AE that led to study withdrawal was considered to be drug-related by the investigator (1 subject with transverse myelitis [SAE] and 1 subject with urticaria).

**EAP (MHE104317)**

All patients who discontinued treatment with mepolizumab were to have phone call follow-up 12 weeks after the last dose and were withdrawn from the program. In MHE104317, 35 patients (11%) discontinued mepolizumab treatment/withdrew from the program due to an on-treatment AE, and the PTs reported for ≥2 patients were angioimmunoblastic T-cell lymphoma, central nervous system vasculitis, dyspnea, lymphoma, multiple organ dysfunction syndrome, nausea, and respiratory failure (2 patients each).

## Post marketing experience

A summary of safety data from post-marketing sources, together with results of a full review of the literature, is presented in the European Union (EU) Periodic Safety Update Reports (EU-PSUR) provided to regulatory agencies on a regular basis. The most recent /EU-PSUR has a cut-off date of 23 September 2019.

As of the cut-off date for the most recent EU-PSUR, NUCALA is approved in the United States of America (US), all EU Member States, Japan, and over 20 further countries for use in patients with severe eosinophilic asthma, and for the treatment of patients with EGPA in the US, Japan as well as other countries. The cumulative exposure to NUCALA in the post-marketing setting is estimated to be 76,383 patient-years.

The safety profile of mepolizumab from post-marketing sources remains generally similar to that known at initial market authorization. During the post-marketing period, following a review of spontaneous post marketing reports of anaphylaxis, the mepolizumab label was updated to include "anaphylaxis" in the existing Warning regarding hypersensitivity reactions and in the Adverse Reactions section.

## 2.5.1. Discussion on clinical safety

Duration of exposure in the main safety study 200622 was similar across treatment groups (mean 7.2 months). However, in study MHE100185, mepolizumab treated subjects received treatment for substantially longer than placebo patients (mean 7.6 months versus 5.2 months), largely due to an increased rate of withdrawals due to lack of efficacy in the placebo arm (placebo group 50%, mepolizumab group 12%).

As per the iCSR for the EAP programmes, the mean s.c. dose and duration of treatment for MHE104317 was 751.1mg and 53.5 months and for the NPS Guidance Program (MHE112562 and 112000) was 925.7mg and 16.6 months.

The demographics across treatment arms was generally well balanced except for the % of elderly (≥65 years) in study 200622 (placebo 19%, mepolizumab group 7%). Overall, the number of elderly patients treated with mepolizumab is low (n= 12) and no conclusion can be drawn in this population.

The overall incidence and % of HES patients that experienced any AE was similar across all main studies, 91% and 92% in mepolizumab and placebo treatment arms respectively. The most common AEs were headache, fatigue and pruritus which occurred at a similar frequency across both treatment arms. For the controlled HES studies, most of the AEs were mild to moderate in severity.

The SOC with the highest incidence of on-treatment AEs in both treatment groups was Infections and Infestations, the incidence was 53% in the placebo group and 68% in the mepolizumab all doses group, this imbalance was driven, in part, by an increased incidence of URTI (upper respiratory tract infection) in the mepolizumab group (18%) vs the placebo group (6%). The majority of URTI cases were non-serious, mild or moderate in intensity.

Across both studies, there were a number of individual AEs where the CMH adjusted relative risk was >2 in the mepolizumab all doses group compared with the placebo group. These were Musculoskeletal chest pain, 4.92, Palpitations, 3.93, Pruritus generalised, 2.98, Oedema peripheral, 2.95, Tooth abscess, 2.94, Upper respiratory tract infection (URTI) 2.79 and Constipation, 2.47. The MAHs rationale that while there were numerical differences in the incidences of AEs observed between mepolizumab all doses and placebo in the HES placebo-controlled studies, the sample size in the HES

studies was relatively small, and 95% confidence intervals for the CMH adjusted relative risks were wide and included 1.0 for all events except for the event of upper respiratory tract infection. For the event of upper respiratory tract infection, MedDRA HLT under High Level Group Term Infections-pathogen unspecified was utilized to identify terms related to upper respiratory tract infection in the integrated placebo-controlled HES studies and it can be accepted that when these wider terms are included, the incidence of AEs linked to upper respiratory tract infections were similar across both treatment groups.

In Study 200622, the number of Haemorrhages was increased for mepolizumab compared to the placebo treatment arm, 7 versus 19% (SMQ). In study 205203 (OLE to 200622), the incidences of AEs in the Haemorrhages SMQ were 4%. The MAH provided a discussion regarding this imbalance including that these events were mild or moderate in intensity, resolved, and were not considered to be drug-related by the investigators. Almost half of the cases in mepolizumab treated patients were confounded by concomitant medications that could increase the risk of bleeding. There was no evidence of an imbalance in other clinical trial indications and no known mechanism for anti-IL-5 effects on bleeding potential. The analysis of data from other indications did not point at divergency between the mepolizumab and placebo group or evidence of dose-response relationship.

Across both controlled studies, the level of adverse reactions was 20% in the placebo group and 29% in the mepolizumab group. Fatigue, injection site reaction, arthralgia, myalgia and headache were the most common adverse reactions to occur. Of these, headache and injection site reaction are expected as per the Nucala SmPC with a frequency of very common, while fatigue, arthralgia and myalgia did not occur in mepolizumab treated patients in the pivotal study with the proposed licenced HES posology. Therefore, no new safety concerns are raised for the adverse reactions.

Study 205203 which is an OLE extension of study 200622 demonstrated a comparable and more favourable safety profile to that observed in mepolizumab treated patients in study 200622. The overall percentage of AEs following 300mg s.c. mepolizumab in study 205203 was lower at 77% and 52% for patients previously on placebo and mepolizumab arms compared with 89% in study 200622.

Study MHE100901 which is an OLE extension of study MHE100185 demonstrated a comparable safety profile to that observed in mepolizumab treated patients in study MHE100185. The overall percentage of AEs following 750mg i.v. mepolizumab in study MHE100901 was 97% compared with 93% in study MHE100185.

Similar safety trends were observed for the EAP study for AEs, although the varying doses and route of administration limit the interpretation of this data

AESI include systemic reactions, local injection site reactions, infections, malignancies, and cardiovascular safety events.

Systemic reactions occurred in n=3 mepolizumab-treated participants and n=2 placebo patients in the across the main controlled studies (including n=1 mepolizumab-treated participant in pivotal study 200622). No cases of anaphylaxis occurred in mepolizumab treated patients. This is in line with hypersensitivity reactions being listed in section 4.8 of the SmPC with a frequency of common, while systemic reactions are considered an important identified risk in the RMP and subject to routine risk minimisation procedures. In addition, a targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis. The following text is proposed to be added to the SmPC and is accepted *"In the 32-week placebo-controlled study, no systemic allergic (type I hypersensitivity) reactions were reported. Other systemic reactions were reported by 1 subject (2%) in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group".*

Injection site reactions occurred with a higher frequency in mepolizumab-treated participants, with a RR of 2.0. This is in line with Injection site reactions being listed in section 4.8 of the SmPC with a frequency of common. All events were non-serious, of mild intensity and resolved and plausibly related to the method of administration. The following text is proposed to be added to the SmPC which is accepted *"In the placebo-controlled study, injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of mepolizumab compared with 4% in patients receiving placebo."*

Infections and serious infections occurred with a higher frequency in mepolizumab-treated participants, with a RR of 1.28 and 8.87 respectively across controlled studies. 9% of mepolizumab patients compared to 1% of placebo patients experienced an SAE in the SOC of Infections and Infestations. There was a small number of opportunistic infections, and a fatality. The frequency of serious infections in OLE 205203 was 5%. The increased relative risk for serious infections has not been observed in other indications and there is no pattern in the type of infections that occurred. While an increased risk of infections may be a plausible mechanism of action based on the immunosuppressive nature of the active, generally mepolizumab does not appear to have produced immunosuppression in animals or patients thus far. As a result, the MAH considers this result may be a chance result, which could be agreed.

Malignancies occurred at a similar frequency in both mepolizumab and placebo-treated participants in the main studies, with a RR of 0.99. However, across the HES development programme there were 18 cases of lymphoma, compared to a total of 19 cases of lymphoma across the whole development programme (1 case in COPD, placebo). Of these 18 HES lymphomas, 1 occurred in a placebo treated patient, of the 17 cases in mepolizumab treated HES patients: 1 case was non-serious, resolved within 2 months and was possibly not a lymphoma and 4 cases occurred within 90 days of initiating mepolizumab treatment and therefore were likely to be pre-existing. Of the remaining 12 HES lymphomas, half occurred in L-HES, this variant is known to be associated with an increased risk of developing lymphomas. 10 of these 18 lymphomas also occurred in patients receiving 700-750mg IV dose which is not the to be marketed posology.

Two of the cases in HES patients were fatal (AITL, related, OLE Study MHE100901, and T-cell lymphoma, unknown relatedness, NPS Guidance program). In addition, a further 4 cases were considered to be related, possibly related or had unknown relatedness (study MHE104317). The association between the reported lymphoma cases and mepolizumab cannot be clearly excluded based on available data showing the onset of number of lymphoma cases in HES EAS population treated with mepolizumab. While HES is associated with an increased risk of lymphomas, due to the rarity of HES it is hard to quantify or estimate the incidence of lymphomas in HES. Alterations in immune response (malignancies) is an important potential risk., This risk is subject to routine risk minimisation procedures only and not subject to any additional monitoring which is accepted.

Cardiac, Vascular, Thromboembolic and Ischemic Events occurred at a higher frequency in mepolizumab-treated participants than placebo patients. Alterations in cardiovascular safety is an important potential risk in the RMP, subject to routine risk minimisation procedures. In addition, targeted follow-up questionnaires are employed to collect data on MI/Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism. Therefore, no further action is anticipated.

The level of on-treatment SAEs in the Controlled Studies was higher in the mepolizumab treated patients than in the placebo treated patients (18% versus 14%). Much of this difference is accounted for based on the imbalance in the numbers of serious infections across the treatment arms as the SOC Infections and infestations accounts for the highest number of SAEs in both main studies. .In addition,

the increased incidence of SAEs in MHE100185 may partly be explained by the increased duration of treatment in the mepolizumab compared to the placebo arm (27.27 versus 18.23 subject-years).

The numbers of SAEs in other SOCs were low and comparable across both treatment arms. The level of SAEs was 8% in the OLE study 205203, 51% in the OLE study MHE100901, and was 52% in the OLE main EAP study MHE104317. The higher rate of SAEs in MHE100901 and EAP may be attributable to the increased duration of treatment compared to the controlled studies. For EAP MHE104317 the higher rate of SAEs may also be due to the EAP patients having a more severe and organ and life-threatening disease compared to the controlled and OLE studies.

Two fatalities occurred in the controlled HES studies, both of these occurred in the mepolizumab treatment arms, 1 occurred with the to be licenced HES posology. Neither was considered related to mepolizumab by the investigator. Both subjects had several cardiovascular comorbidities. There were four fatalities in the OLE studies, all of these occurred in study MHE100901, (4/78, 5%) with the higher dose of i.v. mepolizumab, 1 of these was considered drug related by the investigator (AITL, MHE100901). There were no fatalities in OLE study 205203. The low number of HES patients in the controlled studies with the to be marketed HES dose and route of administration limits the overall assessment of the risk of HES fatalities.

There was a substantial number of fatalities in the EAP studies (n=33). Patients in the EAP had severe HES and organ- or life-threatening disease that have not responded to multiple standard of care therapies and were often too unstable to enter placebo-controlled clinical studies. Patients were excluded from the clinical trials if they had life-threatening HES or HES co-morbidities. The EAP patients therefore represented a higher risk than HES patients recruited in the controlled and OLE clinical trials.

Of these 33 EAP fatalities, 1 was considered related to drug treatment (multiple organ dysfunction syndrome), one had unknown relatedness (T-cell lymphoma), while the others were not considered drug related by the investigator. The majority of these patients were treated with higher i.v. doses of mepolizumab than is proposed for the licenced posology in HES, and for a longer duration than in the controlled studies.

Of the 3 fatalities that were considered by investigators to be related, possibly related, or unknown relatedness, the lymphoma fatalities (n=2) are discussed and queried elsewhere. For the related fatality multiple organ dysfunction syndrome, the MAH has clarified the patient was treated with 750mg i.v. mepolizumab and not the to be marketed lower HES posology.

As HES is a rare disease, data on fatality rates are limited, the American Academy of Allergy, Asthma & Immunology suggest more than 80% of HES patients survive five years or more. Following queries, the MAH also provided estimated background incidence rates from literature reports for mortality in HES patients of 8 – 15%. This is compares favourably with the 7% fatality rate for the mepolizumab HES clinical programme.

For the majority of chemistry and haematological laboratory results, there was no evidence of treatment effect. Although there was evidence of differences in a number of laboratory results changing from baseline to low or high values between the different treatment arms, most of these changes were not considered clinically significant.

Mean values for vital signs were similar to baseline throughout the course of HES studies for both placebo and mepolizumab all doses groups, with the majority of patients having results in the normal ranges. Similarly, for ECG and QT measurements, mean values were comparable between treatment group and majority of results within normal ranges.

Immunogenicity with mepolizumab in HES patients was low at 2% in the pivotal 200622 study. This is in line with the low (although slightly higher) level of immunogenicity seen in severe asthma patients. No neutralising antibodies were detected in any patient that tested positive for ADAs. The SmPC has been updated accordingly.

Different assays were used for OLE study MHE100185 which resulted in a high false positive rate, however the immunogenicity results for this study are less relevant as it is a supportive study

Mepolizumab is not indicated for paediatric or adolescent HES patients. However, study 200622 enrolled 4 adolescent patients, only 1 of which received Mepolizumab, this patient did not experience any AEs.

It is noted that paediatric and adolescent patients (n = 24) were included in the EAP programme for HES, however this data is uncontrolled, the majority of these patients had higher doses than the proposed HES posology. In addition, there were 5 fatalities (21%) in this group.

There was a low number of elderly (≥65 years) (n= 12), African American/African Heritage (5%) or Asian (3%) HES patients treated with mepolizumab limiting safety analysis in these sub-groups. There are no restrictions for the elderly or based on race in the SmPC and this is accepted.

No formal studies have been performed on renal and hepatic impairment, however based on population pharmacokinetic analyses no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min, while changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab due to mepolizumab being degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue. Renal and hepatic impairment have not been discussed by the MAH in relation to HES patients, however no differences are anticipated in these patients.

The numbers of pregnancies in mepolizumab treated clinical trial subjects is low (n=33) and as per the SmPC use in pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

No concerns are raised regarding the potential for overdose, drug abuse, the ability to operate machinery or to drive. This is reflected in the current SmPC, no changes are warranted.

The levels of discontinuations, treatment interruptions and withdrawals due to AEs was low across both treatment groups for the pivotal study 200622. However as previously referred to, for study MHE100185 the rate of withdrawals for placebo patients was significantly higher than for mepolizumab patients, resulting in different levels of exposure between both treatment arms in this trial.

## 2.5.2. Conclusions on clinical safety

Overall, the safety profile of mepolizumab in HES patients is largely consistent with what is already known about mepolizumab in other indications.

## 2.5.3. PSUR cycle

Nucala is being approved for Eosinophilic Granulomatosis with Polyangiitis (EGPA), Hypereosinophilic Syndrome (HES) and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) indications concomitantly. As data in patients are limited, the safety profile in EGPA remains to be further characterised in the post marketing setting and will need to be closely monitored. Therefore, the PRAC/CHMP considers that an increase in PSUR frequency is warranted to monitor adequately the safety profile of mepolizumab in the new patients populations, mainly for the indication EPGA. The PSUR frequency is therefore

increased to 6 monthly basis. The MAH should plan at least a further 6-month DLP period after the next December 2021 submission.

Based on the above considerations, the CHMP is of the opinion that the already existing entry in the EURD list for mepolizumab needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 23 September 2021.

## *2.6. Risk management plan*

The MAH was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 7.2 with the following content:

### *Safety concerns*

| | |
|---|---|
| **Important identified risks** | • Systemic Reactions including anaphylaxis |
| **Important potential risks** | • Alterations in immune response (malignancies)<br>• Alterations in cardiovascular safety |
| **Missing information** | • Limited data in pregnant and lactating patients<br>• Safety of mepolizumab in children with EGPA<br>• Safety of mepolizumab in patients with organ- or life-threatening EGPA |

### *Pharmacovigilance plan*

| **Study**<br><br>**Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances | | | | |
| None | | | | |
| **Category 3**- Required additional pharmacovigilance activities | | | | |
| 200870<br>The Mepolizumab Pregnancy Exposure Study: a VAMPSS | To evaluate outcomes for pregnant women with asthma and their | Use in patients who become pregnant while taking mepolizumab. | Final Report | 2Q-2024 |

| Study<br><br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| post marketing surveillance study of Mepolizumab safety in pregnancy | infants exposed to mepolizumab | | | |
| A post-marketing study to evaluate the safety and efficacy of mepolizumab in children aged 6 – 17 years with EGPA (the protocol, with study number, will be developed and submitted to PRAC for review at a later date) | To evaluate the safety and efficacy of mepolizumab in children aged 6 – 17 years with EGPA | Use in children aged 6 – 17 years | Protocol submission<br><br>Final Report | 28 February 2022<br><br>Q1 2031 |

The post-marketing study to evaluate the safety and efficacy of mepolizumab in children aged 6-17 years with EGPA is added in the context of an extension of indication for EGPA (EMEA/H/C/003860/II/0036/G) running in parallel whose positive opinion is granted at September CHMP.

## *Risk minimisation measures*

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Safety concern 1<br><br>Systemic reactions including anaphylaxis | **Routine risk minimisation measures:**<br><br>The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions) and Section 4.8 (Undesirable effects).<br><br>Equivalent wording is included in the patient leaflet Section 2 and Section 4.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br><br>As standard across all GSK products, a targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis.<br><br>**Additional pharmacovigilance activities**:<br><br>None |
| Safety concern 2<br><br>Potential Risk of Alterations in immune response (malignancies) | **Routine risk minimisation measures:**<br><br>None proposed<br><br>**Additional risk minimisation measures**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Safety concern 3<br><br>Potential Risk of Alterations in cardiovascular safety | **Routine risk minimisation measures:**<br><br>None proposed<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>To further evaluate this potential risk targeted follow-up questionnaires to collect data on MI/Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism.<br><br>**Additional pharmacovigilance activities:**<br><br>None |
| Safety concern 4<br>Limited data in pregnant and lactating patients | **Routine risk minimisation measures:**<br><br>The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available on NUCALA.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>The Mepolizumab Pregnancy Exposure Study (200870): a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy |
| Safety concern 5<br><br>Safety of mepolizumab in children with EGPA | **Routine risk minimisation measures:**<br><br>SmPC Section 4.2, Posology and method of administration, advises prescribers on the dose of mepolizumab for children.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>A post-marketing study is proposed to evaluate the safety and efficacy of mepolizumab in children aged 6 – 17 years with EGPA. |
| Safety concern 6<br><br>Safety of mepolizumab in patients with organ- or life-threatening EGPA | **Routine risk minimisation measures:**<br><br>SmPC Section 4.4 Warnings and Precautions, and Section 5.1 Pharmacodynamic properties, advises prescribers on the exclusion of patients with organ-threatening or life-threatening EGPA from the study.<br><br>**Additional risk minimisation measures:** | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | None | |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Minor clarification is also introduced in section 6.6 of the SmPC.

### User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: limited changes introduced in the proposed PI.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

HES is a group of rare hematologic disorders without a known cause in which eosinophils are overproduced in the bone marrow for prolonged periods of time. The sustained overproduction of eosinophils in the bone marrow results in high blood eosinophil levels (eosinophilia). When activated eosinophils from the bloodstream infiltrate various tissues, they cause inflammatory tissue damage and dysfunction.

Inadequate HES treatment can lead to profound end-organ damage and increased mortality.

The International Cooperative Working Group on Eosinophil Disorders (ICOG-EO) uses the following definition for HES: (1) blood eosinophilia of >1500 eosinophils/µL on 2 examinations (at an interval ≥1 month, except in case of life-threatening organ-damage when diagnosis can be made immediately) and/or tissue eosinophilia; (2) organ damage and/or dysfunction attributable to tissue eosinophilia; and (3) exclusion of other disorders or conditions as the major reason for organ damage [Valent, 2012b; Kahn, 2017]. HES is only diagnosed when organ damage and/or dysfunction are present.

### 3.1.2. Available therapies and unmet medical need

Important goals of HES therapy are to decrease symptoms and blood eosinophil levels in order to achieve disease control. The current approach is based on reduction of blood eosinophilia, reduction of active inflammation, suppression of the immune response, and treatment of disease-specific and/or treatment-related complications.

Standard of care (SoC) therapy for patients with HES includes corticosteroids (for F/P negative or F/P positive with cardiac involvement at diagnosis) or imatinib (for F/P positive) as first-line therapy and cytotoxics (e.g., hydroxyurea, cyclophosphamide) or immunomodulators (interferon alpha [INF$\alpha$],

cyclosporine, immunoglobulin) as second-line agents [Roufosse, 2010]. Clinical responses to these therapies, however, are incomplete or inadequate in over 80% of HES patients (among those negative for F/P mutation).

The discovery of the F/P mutation in patients with M-HES and its response to imatinib has improved survival and QoL in this subpopulation [Klion, 2009; Wechsler, 2012]. For most patients however, the only currently available treatment options are limited to chronic high doses of corticosteroids, IFN, and cytotoxic agents such as hydroxyurea and cyclophosphamide. The efficacy of these agents, even in combination, is not always adequate and side effects from long-term use are significant.

Although not approved for use in HES, corticosteroids are used in clinical practice as first-line treatment for most patients with HES due to lack of available options [Ogbogu, 2009; Helbig, 2010]. The therapeutic strategy is to start with a moderate to high dose (≥40 mg/day prednisone or equivalent) and taper very slowly while monitoring the blood eosinophil count closely. Using this approach, most patients (85%, N=141) will respond initially to steroid therapy based on a decrease of blood eosinophil count to normal range and symptomatic improvement. However, many HES patients (72%, N=179) will need to be maintained on low steroid doses (median 10 mg/day) for long periods of up to 20 years since discontinuation of corticosteroids leads to eosinophilia and symptomatic recurrence in most patients [Klion, 2009; Ogbogu, 2009; Helbig, 2010].

Although the initial response to corticosteroid treatment is often positive, long-term use of oral corticosteroids (OCS) is associated with significant and commonly reported side effects, including truncal obesity, moon facies, buffalo hump, increased blood pressure, water retention, decreased bone density, weight gain, muscle atrophy, hyperglycemia, delayed wound healing, cataracts and glaucoma, peptic ulcers, and increased risk of infection [Poetker, 2010]. Therefore, with chronic use, the toxicities of steroid therapy become more significant, patient adherence diminishes, and additional or alternative corticosteroid-sparing therapies must be used [Roufosse, 2013]. The chronic use of corticosteroids is often discontinued (42%, N=179) or used in combination therapy (33%, N=179) due to toxicity or failure in the majority of HES patients [Ogbogu, 2009].

In the absence of approved targeted therapies for HES, several of the second-line agents (chemotherapeutic agents such as hydroxyurea, IFNα, and other cytotoxics [e.g., cyclosporine, vincristine, methotrexate, and busulfan]) have been used based on empirical observational evidence of benefit. These second-line agents are effective (defined as a decrease of eosinophil count and symptomatic improvement) only in a small number of HES patients, are associated with significant toxicities, have a slow onset of therapeutic effect, and confer an increased risk of patients developing malignancy. For example, the most commonly used second-line agent, hydroxyurea, is rarely useful as a single agent and its side effects and lack of efficacy result in discontinuation in the majority of patients (77%, N=64) [Ogbogu, 2009].

Despite significant advances in the understanding and management of HES, there remains the need for effective, well-tolerated treatments to control the disease and minimize the toxicities from chronic use of corticosteroids and second-line agents. This unmet medical need persists in particular for F/P negative HES, which comprises the majority (85%) of the HES patient population, due to the absence of a highly effective, well-tolerated therapy suitable for long-term use.

### 3.1.3. Main clinical studies

The applicant submitted a single pivotal placebo-controlled Phase III study, 200622 in support of this marketing authorization application. This study is supplemented with efficacy data from the OLE study 205203. Studies MHE100185 and MHE100901 were also provided by the applicant however, due to

differences in patient population, endpoints, eosinophil blinding, and mepolizumab doses the role of these studies in support of this application is limited.

The primary endpoint in this study was the proportion of subjects who experienced a HES flare during the 32-week Treatment Period. HES flares were defined as either: (a) a HES-related clinical manifestation based on a physician documented change in clinical signs or symptoms resulting in the need for therapy adjustment (increase in OCS dose of at least 10mg/day or any increase in or addition of any cytotoxic/ immunosuppressive HES therapy), or (b) receipt of two or more courses of blinded active OCS during the study treatment period.

This endpoint was discussed during the CHMP scientific advice. While this primary endpoint has never been tested in previous trials, in principle, it was considered acceptable and clinically relevant for the selected target population.

## *3.2. Favourable effects*

This primary endpoint was met as significantly less flares were reported in patients treated with mepolizumab as compared to those on placebo i.e. there were 17 flares in 14 (26%) subjects randomized to mepolizumab compared to 48 flares in 28 (52%) subjects in the placebo group. The odd ratio for comparison of mepolizumab 300 mg vs placebo (primary analysis) was 0.28 (95%CI (0.12, 0.64, p value=0.003).

Three out of 4 these secondary endpoints under multiplicity adjustment were also investigated the effect of Mepolizumab on flares. These endpoints were: time to first HES flare, proportion of subjects who experienced a HES flare during Week 20 through Week 32 and rate of HES flares. The results of these secondary endpoints were consistent with the primary endpoint results. The risk of a first HES flare over the treatment period was 66% lower for subjects treated with mepolizumab compared with placebo (hazard ratio: 0.34; 95% CI 0.18, 0.67). From Week 20 through Week 32, fewer subjects experienced a HES flare or withdrew from the study when treated with mepolizumab compared with placebo (17% vs. 35% respectively, p=0.020). Finally, the treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of HES flares (calculated for each subject as number of HES flares divided by time in the study) compared with placebo (unadjusted p=0.002; adjusted p=0.020).

Only one secondary endpoint was not investigating flares but assessed the effect on fatigue severity by using Brief Fatigue Inventory [BFI]) score. Using this score a statistically significant reduction in fatigue severity at Week 32 for subjects treated with mepolizumab compared with placebo were reported (unadjusted p=0.036; adjusted p=0.036).

Some exploratory endpoints (HES Daily Symptoms (HES-DS) scale) also recorded improvements in symptoms. For HES Daily Symptoms (HES-DS) scale there was a significant reduction (improvement) in the most bothersome symptom score at Week 32 for subjects treated with mepolizumab compared with Placebo as assessed through the use of HES-DS score. For some other exploratory endpoints no improvements were recorded.

The long-term efficacy was assessed in the open label extension (OLE) study 205203.

In the OLE flares were reported infrequently with slightly better results reported in patients treated with mepolizumab in the parent study as compared to those who originally received placebo. In total, there were 8 flares in 6 (12%) subjects previously treated with placebo and 3 flares in 3 (6%) subjects (1 flare each) previously treated with mepolizumab. Overall, the estimated annualized rate of HES flares based on the 20-week treatment period was 0.26/year (95% CI 0.13, 0.52) which was lower than the rate recorded in the pivotal study (0.5/year in the mepolizumab and 1.46 in the placebo

group). In the extension study, some small reduction in OCS dose was possible. The mean change from baseline OCS dose during Week 16 to 20 was -2.3 mg/day (prednisone or equivalent). The proportion of all subjects who achieved a mean OCS dose ≤7.5mg/day (prednisone or equivalent) was 75% during Week 16 to 20 compared with 61% during Week 0 to 4.

## *3.3. Uncertainties and limitations about favourable effects*

A primary focus of the pivotal study was the assessment of efficacy of Mepolizumab in reducing exacerbations (flares)The primary endpoint in this study was the proportion of subjects who experienced a HES flare during the 32-week Treatment Period. In addition, 3 out of 4 secondary endpoints under multiplicity adjustment strategy also investigated the effect of mepolizumab on flares.

On the other hand, the effects of mepolizumab on other aspects of the disease or symptoms were only briefly examined.

Various patient reported outcome questionnaires were used in the study to assess changes in symptoms in patients receiving mepolizumab as compared to those on placebo. However, only one endpoint investigating the effect on fatigue severity (Brief Fatigue Inventory [BFI]) score item 3) was under multiplicity adjustment strategy. The remaining assessments were only exploratory. BFI score was developed to rapidly assess the severity and impact of cancer-related fatigue. It is not validated in patients with HES although, according to the MAH recommended by one external HES expert as appropriate to capture the patient perspective of fatigue, a key symptom of HES.

Only limited organ-specific assessments were performed in the study i.e. lung function tests and echocardiogram scans. These tests showed no difference between the treatment groups. Other assessments such as neurological examinations, CT scans of the abdomen, sinuses, or chest, or skin assessments were not performed.

Patients with clinically significant cardiac damage, current active liver or biliary disease liver (with ALT >2.5xULN or ALT>5xULN or Bilirubin >1.5xULN) or life-threatening HES were excluded from the study. Cardiovascular complications of HES are a major source of morbidity and mortality in this disease, whereas liver involvement has been reported to be fairly common in HES. The SmPC was updated to state that Nucala has not been studied in patients with life-threatening manifestations of HES.

Various patterns of disease courses are observed in hypereosinophilic syndromes (HES). Some patients are experiencing a single flare without subsequent relapse. For these patients a long-term therapy is unlikely to be needed. Others suffer from several relapses with intervals of complete remission. Last, a third set of patients have chronic persistent disease. It seems that the majority of patients enrolled to the pivotal study have relapsing or persistent disease. 77% of patients were taking chronic OCS or cytotoxic/immunosuppressive therapy at Baseline. In addition, all patients were required to have blood eosinophil count >1000 cells/uL despite receiving SoC therapy. Further, a history of two or more HES flares within the past 12 months prior to screening were required for enrolment. Therefore, the agreed indication reflects the population of patients investigated in the pivotal study i.e. patients with relapsing and chronic persistent disease.

In addition, patients with F/P fusion tyrosine kinase gene translocation were excluded and this is reflected in section 5.1 of the SmPC.

## *3.4. Unfavourable effects*

From clinical trial data in patients with HES, mepolizumab treated patients experienced a similar level of AEs compared to placebo treated patients. Most AEs were mild to moderate in severity. Fatigue,

injection site reaction, arthralgia, myalgia and headache were the most common adverse reactions to occur across both controlled studies.

When comparing mepolizumab treated patients to placebo treated patients in the controlled studies: there were a number of preferred terms that had a relative risk of >2, there was an increased rate of severe AEs (28% versus 20%), adverse reactions (29% versus 20%), SAEs (18% versus 14%) and serious infections (9% and 1%) across both controlled studies. In addition, in the pivotal study with the to be licensed posology, there was an increased number of haemorrhage events when comparing mepolizumab treated patients to placebo treated patients (19% versus 7%).

AESI include systemic reactions, local injection site reactions, infections, malignancies, and cardiovascular safety events. Hypersensitivity reactions (systemic allergic) and local injection site reactions are listed in SmPC, while Alterations in immune response (malignancies) and cardiovascular events are listed in the RMP.

Malignancies occurred at a similar frequency in both mepolizumab and placebo-treated participants in the main controlled studies, however a total of 18 cases of lymphoma occurred in HES patients (out of 19 cases in the mepolizumab development programme). Many of these lymphomas occurred in the L-HES variant, known to be associated with an increased risk of developing lymphomas and some occurred within 90 days of starting mepolizumab treatment and likely to be pre-existing. However, there were a number of lymphoma cases that were considered related, possibly related, or had unknown relatedness to mepolizumab, while 2 cases were also fatal.

There was a 7% mortality rate in HES patients treated with mepolizumab. The majority of these fatalities occurred in the early access programme ( AP). Patients in the EAP had severe HES and organ- or life-threatening disease that had not responded to multiple standard of care therapies and were often too unstable to enter placebo-controlled clinical studies. Patients were excluded from the clinical trials if they had life-threatening HES or HES co-morbidities. The EAP patients therefore represented a higher risk than HES patients recruited in the controlled and OLE clinical trials and the 7% fatality rate for the mepolizumab HES clinical programme compares favourably to the estimated background incidence rates from literature reports of a 8 – 15% fatality rate.

## *3.5. Uncertainties and limitations about unfavourable effects*

The number of patients recruited to HES controlled studies is low, limiting interpretation of unfavourable effects. The long-term safety in adult patients with HES remains unknown.

In one of the two controlled studies, patients received mepolizumab by i.v. administration and at a dose of 750mg, the proposed licenced posology for HES is s.c. administration and at the lower dose of 300mg. The data in this study is therefore not reflective of the 300mg dose and route of administration to be approved and should be considered supportive safety data.

The majority of the EAP data is also at a higher dosing level with a longer duration of treatment than the controlled studies and thus are not reflective of the proposed 300mgHES dose and should be considered supportive safety data.

The majority of lymphomas and fatalities in HES patients occurred in uncontrolled OLE studies and the EAP programme. HES is known to be associated with an increased risk of developing lymphomas, however the rarity of HES makes its hard to determine the normal background incidence of lymphoma in HES. Similarly considering the rarity of HES it is not possible to confirm the estimated background incidence of fatalities in HES patients.

## 3.6. Effects Table

**Table 56: Effects Table for Mepolizumab for the treatment of adult patients with hypereosinophilic syndrome**

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| | Primary Analysis – Proportion of subjects with HES flare during Weeks 0-32 | | Mepolizumab 300 mg SC<br><br>15(28%) | Placebo<br><br>30 (56%) | Mepolizumab 300 mg SC vs. Placebo<br><br>Odds ratio (95% CI)<br>0.28 (0.12, 0.64)<br>P value 0.002 | |
| | Secondary Analysis – Time to first HES flare | | Mepolizumab 300 mg SC<br>14 (26%) | Placebo<br><br>28 (52%) | Mepolizumab 300 mg SC vs. Placebo<br><br>Hazard ratio (95% CI)<br>0.34 (0.18, 0.67)<br>P value 0.002 | |
| | – Proportion of subjects with HES flare during Weeks 20-32 | | Mepolizumab 300 mg SC<br><br>9 (17%) | Placebo<br><br>19 (35%) | Mepolizumab 300 mg SC vs. Placebo<br>Odds ratio (95% CI)<br>0.33 (0.13, 0.85)<br>P value 0.020 | |
| | Rate of HES flares | | Mepolizumab 300 mg SC<br><br>0.50 | Placebo<br><br>1.46 | Mepolizumab 300 mg SC vs. Placebo<br><br>Rate ratio (95% CI)<br>0.34 (0.19, 0.63) | |
| | Change in fatigue severity (BFI item 3) at Week 32 | | Mepolizumab 300 mg SC<br><br>-0.66 | Placebo<br><br>0.32 | Mepolizumab 300 mg SC vs. Placebo | |
| **Unfavourable Effects** | | | | | | |
| AEs | | No. of events n(%) | Mepolizumab<br>48/54(89)<br><br>41/43(95) | Placebo<br>47/54(87)<br><br>41/42(98) | | 200622<br><br>MHE100185 |
| SAEs | | No. of events n(%) | Mepolizumab<br>10/54(19)<br><br>7/43(16) | Placebo<br>9/54(17)<br><br>5/42(12) | | 200622<br><br>MHE100185 |
| Lymphoma | | No. of events n | Mepolizumab<br>0/97<br><br>1/102<br><br>2/78<br><br>13/353 | Placebo<br>1/96<br><br>-<br><br>-<br><br>- | | 200622+ MHE100185<br><br>OLE 205203<br><br>OLE MHE100901<br><br>EAP |
| Fatalities | | No. of events n(%) | Mepolizumab<br>1/106(1)<br><br>5/81(6)<br><br>*26/359(7) | Placebo<br>0(0)<br><br>0(0)<br><br>- | | 200622+ OLE 205203<br><br>MHE100185+OLE MHE100901<br><br>EAP<br>*Not all deaths included |

## 3.7. Benefit-risk assessment and discussion

### 3.7.1. Importance of favourable and unfavourable effects

The treatment with mepolizumab was associated with a significant reduction in the number of flares as compared to the placebo group in patients enrolled to this pivotal study.

The primary endpoint in the pivotal study was met. There were 17 flares in 14 (26%) subjects randomized to mepolizumab compared to 48 flares in 28 (52%) subjects in the placebo group. The odd

ratio for comparison of mepolizumab 300 mg vs placebo (primary analysis) was 0.28 (95%CI (0.12, 0.64, p value=0.003)

Three out of 4 these secondary endpoints under multiplicity adjustment were also investigated the effect of mepolizumab on flares. These endpoints were: time to first HES flare, proportion of subjects who experienced a HES flare during Week 20 through Week 32 and rate of HES flares. The results of these secondary endpoints were consistent with the primary endpoint results.

Further the Applicant agreed to the CHMP request to reflect the use of this medicine in patients without an identifiable non-haematologic secondary cause, based on the aetiologies of HES and the pharmacological activity of mepolizumab.

During the assessment of the application, the MAH was requested by CHMP to discuss and justify why the criteria which defined severity of the disease were not reflected in the text of the indication.

The applicant was requested to

- update the indication reflecting that Nucala is to be given to patients with relapsing or persistent disease i.e. receiving a chronic therapy for the HES.
- highlight that patients with 'severe HES' were enrolled to the pivotal study.

The CHMP finally agreed that the use the term "inadequately controlled" to appropriately qualify the study population was considered more meaningful to prescribers as there is no accepted definition for severe HES in the medical community. The CHMP considers that the indication as mentioned below is reflecting the population studied and does not expand to patients with milder disease. Further details of inadequate control are described in the study eligibility criteria in section 5.1 of the SmPC.

The wording of the agreed indication reads:

*Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see Section 5.1)."*

The MAH was requested to discuss approach to patients for whom a long-term remission was achieved. Since there is no accepted definition of remission and/or its assessment criteria which could be used standardly in clinical practice to declare either lack of efficacy or achievement of long-term remission, the decision to stop or continue mepolizumab treatment of HES patients shall be based on the physician's clinical judgment, which is guided by the patient's overall clinical status and its background medication. Therefore, the following text was included in the SmPC and agreed with CHMP, reflecting also that mepolizumab was not studied in patients with life-threatening HES condition.:

*Nucala is intended for long-term treatment. The need for continued therapy should be considered reviewed at least on an annual basis determined by physician assessment of the patient's disease severity and level of symptom control. Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population*

The most important and concerning unfavourable effects relate to malignancies (lymphomas) defined as a safety concern and the overall mortality rate (approx. 7%). The majority of the fatalities occurred in the EAP programme where patients in this programme had severe HES and organ- or life-threatening disease that had not responded to multiple standard of care therapies and were often too unstable to enter placebo-controlled clinical studies. Patients were excluded from the clinical trials if they had life-threatening HES or HES co-morbidities. The EAP patients therefore represented a higher risk than HES patients recruited in the controlled and OLE clinical trials. The majority of lymphomas and fatalities

occurred in the EAP programme where subjects were on average treated with higher i.v. doses than the proposed licenced posology. This safety concern will be followed as routine pharmacovigilance.

### 3.7.2. Balance of benefits and risks

The agreed indication is as follows adequately reflecting the studied population:

*Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see Section 5.1).*

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## *3.8. Conclusions*

The overall B/R of Nucala for the treatment of HES is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include hypereosinophilic syndrome (HES) for Nucala (mepolizumab); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2. In addition, section 6.6 of the SmPC (for the powder for solution for injection only) has been updated to introduce minor clarifications. The Package Leaflet is updated in accordance. Version 7.2. of the RMP has also been adopted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

## *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0384/2020 and the results of these studies are reflected in the

Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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

### Risk management plan (RMP)

The Marketing authorisation holder (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.

In addition, 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.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Nucala-H-C-3860-II-37'.

## Attachments

1. SmPC, Annex II Labelling Package Leaflet (changes highlighted), as a relevant example with changes highlighted as adopted by the CHMP on 16 September 2021.