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SCIENCE MEDICINES HEALTH

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Assessment report on extension(s) of marketing authorisation

Nucala

International non-proprietary name: mepolizumab

Procedure No. EMEA/H/C/003860/X/0018

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
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AI	AutoInjector
AUC	area under the concentration-time curve
AUC	Analytical ultracentrifugation
AUC(0-t)	area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-∞)	area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BDS	bulk drug substance
BET	Bacterial Endotoxins Test
BLA	Biologics License Application
BSE	Bovine spongiform encephalopathy
CCI	Container closure integrity
CD	Circular Dichroism
CDR	Complementarity Determining Region
CE	Conformité Européene
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
CGE	Capillary Electrophoresis
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	confidence interval
cIEF	Capillary Isoelectric Focusing
C _{max}	maximum observed plasma concentration
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
CPP	Critical Process Parameter

CPSR	clinical pharmacology study report
CQA	Critical Quality Attributes
CSR	clinical study report
Ctrough	trough concentration
CVT	cardiac, vascular, and thromboembolic
Da	Dalton
DP	Drug Product
DS	Drug Substance
DSC	Differential scanning calorimetry
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
EGPA	eosinophilic granulomatosis with polyangiitis
EMA/EMEA	European Medicines Agency
ESI-MS	Electro Spray Ionization Mass Spectra
EU	European Union
EU	Endotoxin Units
EU-PSUR	European Union Periodic Safety Update Report
FAAN	Food Allergy and Anaphylaxis Network
Fab	Fragment Antigen-binding
FcRn	Neonatal FC receptor
FDA	Food and Drug Administration
FTIR	Fourier transform infrared
Fuc	Fucose
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GSK	GlaxoSmithKline
HC	Heavy Chain
HCP	healthcare professional
HCP	Host Cell Protein
HES	hypereosinophilic syndrome

HF	Human Factors
HPLC	High performance liquid chromatography
IFU	Instructions for Use
IgG	Immunoglobulin
IgG1	immunoglobulin G1
IL-5	interleukin-5
IND	Investigational New Drug
IPC	In Process Control
ISS	integrated summary of safety
JNDA	Japanese New Drug Application
KD	Dissociation constant
Kg	kilogram(s)
L	liter(s)
LC	Light Chain
LER	Low endotoxin recovery
LOD	Limit of Detection
LOQ	Limit of Quantitation
LSM	Large scale manufacturing
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MALDI	Matrix-Assisted Laser Desorption/Ionization-
MCB	Master Cell Bank
MDS	Mepolizumab drug substance
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram(s)
mL	millilitre(s)
msec	millisecond
MuLV	Murine Leukemia Virus
MVD	Maximum valid dilution
MVM	Minute Virus of Mice
MWCC	Molecular weight cut off

NA or N/A	Not Applicable
NGHC	Non glycosylated heavy chain
NIAID	National Institute of Allergy and Infectious Disease
NLT	Not Less Than
NMR	Nuclear magnetic resonance
NMT	Not More Than
NVR	Non volatile residue
OOS	Out of specification
PAI	pre-approval inspection
PBRER	Period Benefit Risk Evaluation Report
PCI	potential clinical importance
PD	pharmacodynamic(s)
PDE	Permitted daily exposure
PFS	Prefilled Syringe
Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PMDA	Pharmaceutical and Medical Devices Agency
PPV	Porcine Parvovirus
PREA	Pediatric Research Equity Act
PS80	Polysorbate 80
PSP	Pediatric Study Plan
qPCR	Quantitative Polymerase Chain Reaction
QTc QT	interval corrected for heart rate
QTOF	Quadrupole-Time-of-Flight
S/N	Signal-to-Noise Ratio
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SEC	Size Exclusion Chromatography
SEC-MALLS	SEC- Multi-Angle Laser Light Scattering

SH	Sulphydryl group
SMQ	Standardised Medical Dictionary for Regulatory Activities Queries
SOC	System Organ Class
SPR	Surface Plasmon Resonance
SSD	Syringe safety device
SV-AUC	Sedimentation velocity- Analytical ultracentrifugation
TAMC	Total Aerobic Microbial Count
TEM	Transmission Electron Microscopy
TOCS	Time out of cold storage
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeast Microbial Count
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

GlaxoSmithKline Trading Services Limited submitted on 14 September 2018 an extension of the marketing authorisation as follows:

Extension application to introduce a new pharmaceutical form, solution for injection (in pre-filled syringe or in pre-filled pen).

The Marketing Authorisation Holder (MAH) applied for the following indication for the new pharmaceutical form:

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (d) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0239/2017 covering the application on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0239/2017 covering the application was completed.

In addition, the PIP P/0239/2017 eligible for the reward was completed.

The PDCO issued an opinion on compliance for the PIP P/0239/2017 eligible for the reward.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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 did seek Scientific advice at the CHMP. The scientific advice specific to the development of liquid formulations was provided by EMA/CHMP document references EMA/CHMP/SAWP/271080/2016.

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: N/A

The application was received by the EMA on	14 September 2018
The procedure started on	04 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	03 January 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	31 January 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	27 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 April 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	23 May 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nucala on	29 May 2019

2. Scientific discussion

2.1. Problem statement

Mepolizumab is already approved as a lyophilised powder in a vial.

This line extension is to introduce a liquid form of mepolizumab drug product in a pre-filled syringe or pre-filled pen/autoinjector. The currently marketed drug product is supplied as a 100 mg single-dose vial containing a sterile, preservative-free, lyophilized powder for reconstitution and subcutaneous injection. The MAH submitted this application to obtain marketing approval for a new drug form (mepolizumab injection, liquid drug product) of mepolizumab in the same and future indications currently registered for the Nucala lyophilised drug product (mepolizumab for injection).

2.1.1. Disease or condition

Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, acute and chronic bronchoconstriction, airway oedema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products.

The poor response of some patients with asthma to the standard regimen of controller and reliever therapies may reflect the number of cellular and molecular mechanisms operative in asthma. Recent therapeutic approaches in asthma have been focused on trying to control the Type 2/ T-helper cell-2 (Th2) response. Up-regulation of the Th2 cell-derived cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13) has been implicated as an important inflammatory component of asthma disease progression.

2.1.2. Epidemiology

Asthma is a chronic airway disease affecting approximately 334 million people worldwide and is responsible for approximately 250,000 premature deaths each year.

Asthma prevalence varies by geographical region. Accurate assessment of the prevalence of asthma has been hindered by varying definitions of asthma and methods of data collection, each combining to make data comparison across studies difficult.

Risk factors include sex (gender influence varies with age), airway hyper reactivity, atopy, allergens, infections, tobacco smoke, obesity, and perinatal factors.

Asthma is common in adolescents but is frequently undiagnosed because of under-reporting of symptoms.

2.1.3. Biologic features

The disease is characterized by airway inflammation with oedema, cellular infiltration and mucus plugging, bronchial smooth muscle hypertrophy which results in variable airway obstruction and bronchial hyper-responsiveness.

2.1.4. Clinical presentation, diagnosis

There is no single diagnostic test for asthma, the diagnosis is a clinical one. The absence of consistent gold-standard diagnostic criteria means that it is not possible to make unequivocal evidence-based recommendations on how to make a diagnosis of asthma. The diagnosis of asthma in children and adults is based on the recognition of a characteristic pattern of respiratory symptoms, signs and test results and the absence of any alternative explanation for these.

Typical symptoms of asthma include periodic wheezing, chest tightness, shortness of breath, and cough, all of which worsen at night. Patients with asthma experience exacerbations of these symptoms which acutely worsen in response to various triggers such as allergens, microbes, and pollutants, resulting in significant reductions in expiratory flow as measured by forced expiratory volume in 1second (FEV).

Symptoms and signs of asthma in adolescents are no different from those of other age groups.

2.1.5. Management

The goals of chronic asthma management may be divided into two domains: reduction in impairment and reduction of risk.

Complete control of asthma is defined as (British Thoracic Society/SIGN guideline):

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV1 and/or PEF >80% predicted or best)
- minimal side effects from medication.

In clinical practice patients may have different goals and may wish to balance the aims of asthma management against the potential side effects or inconvenience of taking medication necessary to achieve perfect control.

Effective asthma management requires a proactive, preventive approach, similar to the treatment of hypertension or diabetes. Routine follow-up visits for patients with active asthma are recommended, at a frequency of every one to six months, depending upon the severity of asthma. These visits should be used to assess multiple aspects of the patient's asthma and to discuss steps that patients can take to intervene early in asthma exacerbations (an asthma "action plan"). The aspects of the patient's asthma that should be assessed at each visit include the following: signs and symptoms, pulmonary function, quality of life, exacerbations, adherence with treatment, medication side effects, and patient satisfaction with care.

Pharmacologic treatment is the mainstay of management in most patients with asthma. The stepwise approach to pharmacotherapy is based on increasing medications until asthma is controlled, and decreasing medications when possible to minimize side effects. Adjustment of the patient's management should be considered at every visit.

The first step in determining appropriate therapy for patients who are not already on a controller medication is classifying the severity of the patient's asthma. For patients already taking one or more controller medications, treatment options are guided by an assessment of asthma control rather than asthma severity.

Specific evidence about the pharmacological management of adolescents with asthma is limited and is usually extrapolated from paediatric and adult studies.

Decreasing therapy once asthma is controlled is recommended, but often not implemented leaving some patients over-treated.

About the product

Mepolizumab (SB-240563) is a humanised monoclonal antibody (IgG1, kappa) directed against the human cytokine interleukin-5 (hIL-5), the major cytokine responsible for the growth and differentiation, recruitment, activation and survival, of eosinophils. Mepolizumab binds to human IL-5, preventing IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting signalling.

Neutralisation of IL-5 leads to a reduction in the production rate and survival of eosinophils which is expected to provide therapeutic benefit in hypereosinophilic conditions.

NUCALA (mepolizumab) 100 mg powder for solution for injection was approved on 2nd December 2015 for use as add-on treatment for severe refractory eosinophilic asthma in adult patients.

The currently marketed drug product is supplied as a 100 mg single-dose vial containing a sterile, preservative-free, lyophilized powder for reconstitution and subcutaneous injection. The MAH submitted this application to obtain marketing approval for a new drug form (mepolizumab injection, liquid drug product) of mepolizumab in the same and future indications currently registered for the Nucala lyophilised drug product (mepolizumab for injection).

The mepolizumab liquid clinical development program consisted of three clinical studies designed to demonstrate:

- Comparable pharmacokinetic systemic exposure between the liquid drug product and the approved lyophilized drug product (Study 204958)
- Real-world usability of the safety syringe and autoinjector devices, along with the IFU, to allow for patient self-administration or administration by a caregiver (Studies 205667 and 204959)
- Comparable safety profile between the liquid drug product and the approved lyophilized drug product (Studies 204958, 205667, and 204959)

In addition Mepolizumab is under development for the treatment of patients with chronic obstructive pulmonary disease (COPD), Eosinophilic Granulomatosis with Polyangiitis (EGPA; also known as Churg-Strauss Syndrome), and hypereosinophilic syndrome (HES). Additional development programs are under consideration based on the mechanism of action of mepolizumab and its effects on eosinophils.

Type of Application and aspects on development

This is a Centralised Marketing Authorisation Application (MAA) under Article 8(3) of Directive 2001/83/EC for NUCALA® 100 mg powder for solution for injection. The product is eligible for submission of an MAA under Article 3(1) – Indent 1 – Biotech medicinal product of Regulation (EC) No. 726/2004.

GlaxoSmithKline (GSK) submitted this application to obtain marketing approval for a new drug form (mepolizumab injection, liquid drug product) of mepolizumab in the same and future indications currently registered for the Nucala lyophilised drug product (mepolizumab for injection).

PRIME

N/A

2.2. Quality aspects

2.2.1. Introduction

Mepolizumab is currently approved as a 100 mg lyophilised powder for solution for injection in a vial. This line extension seeks to introduce a liquid formulation:

- 1 mL solution containing 100 mg mepolizumab in a Type 1 glass syringe with a fixed needle and passive safety needle guard (also referred to as safety syringe);
- 1 mL solution containing 100 mg mepolizumab in a Type 1 glass syringe with a fixed needle in a pre-filled pen (also referred to as auto-injector).

The liquid formulation will be marketed as one pre-filled syringe (PFS) or one pre-filled pen (PFP) and multipacks comprising 3 (3 packs of 1) PFS or PFP.

Mepolizumab is formulated with sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, EDTA disodium dihydrate and water for injections.

The manufacture of active substance for the liquid formulation duplicates the same process steps used for the previously authorised lyophilised formulation, from vial thaw and cell culture through harvest, purification and virus clearance (Stages 1 through 10). At the Tangential Flow Ultrafiltration step (Stage 11), the processes diverge to accommodate buffer exchange into separate formulations.

A substantial amount of active substance CMC information is therefore harmonised for the manufacturing processes for the lyophilised and liquid formulations due to their shared manufacturing steps. Where information supportive of the liquid formulation was previously provided in the application for the lyophilised product, the information is included in this application for the liquid product by cross-reference to the approved application. To assist with the cross-referencing strategy, a nomenclature has been developed to identify the processes at each facility:

- MDS2 is the historical code for the approved active substance process for the lyophilised formulation at GSK, Conshohocken.
- MDS2_LYO_RKV refers to the process for the lyophilised formulation at HGS, Rockville. This process was recently introduced by a Type 1B variation implementing a previously approved post approval change management protocol.
- MDS2_LIQ_RKV refers to the active substance process for the liquid formulation at HGS, Rockville

2.2.2. Active Substance

General Information

Mepolizumab is a recombinant humanised monoclonal antibody specific for human IL-5. The heavy chain contains 449 amino acids with an estimated molecular mass of approximately 49 kDa. The light chain contains 220 amino acids with an estimated molecular mass of approximately 24 kDa.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Mepolizumab is produced in CHO cells using a manufacturing process at the Human Genome Sciences, Inc, Large Scale Manufacturing (LSM) facility. The upstream manufacturing process includes vial thaw, seed expansion, growth of cells and harvest by centrifugation and depth filtration. Downstream processing includes a series of chromatography, ultrafiltration and viral inactivation and filtration steps.

The manufacturing process registered with this line extension is designated as MDS2 LIQ RKV (mepolizumab active substance process 2, liquid, Rockville). The Rockville active substance manufacturing process for the

currently approved lyophilised finished product is designated MDS2 LYO RKV. MDS2 LIQ RKV is primarily the same as MDS2 LYO RKV, with only minor changes to the purification processes. Minor changes have been made to the registered process parameters.

Control of materials

The cell banks and most of the raw materials are identical to those used in manufacture of the currently approved active substance. Details of the raw materials used for the revised Stages 11 and 12 are provided in the dossier along with reference to the relevant pharmacopoeias.

Control of critical steps and intermediates

Critical process parameters (CPPs), acceptable ranges, and associated critical quality attributes (CQAs) for stages 11 and 12 of the purification process are presented in the dossier. The controls include tests for concentration, bioburden, endotoxin, container closure torque and filter integrity test. The proposed controls are acceptable.

Process validation

Stages 1-10 have been validated as part of the currently approved process. Validation data is presented from process performance qualification (PPQ) batches for Stages 11 and 12 and includes relevant data from process parameters, CPPs, and in-process controls (IPCs). The results from all PPQ batches were within the relevant acceptance criteria for each control parameter. Impurity clearance data show sufficient clearance of relevant impurities. The data provided demonstrate that Stages 11 and 12 for the MDS2 LIQ RKV process have been successfully validated. A verification protocol has been provided. Hold times are registered throughout the manufacturing process and have been supported by relevant process validation data.

Manufacturing process development

A comparability study was presented to justify that the MDS2 LIQ RKV process can be considered comparable to the MDS2 / MDS2 LYO RKV process. The comparability studies included in-process data from MDS2 batches, MDS2 LIQ RKV batches and MDS2 LYO RKV batches. During the assessment of the Type 1B variation to introduce process MDS2 LYO RKV, it was concluded that MDS2 LYO RKV and MDS2 are comparable. Overall, considering the totality of the comparability data provided in this line extension application, comparability of Stages 1-10 is considered demonstrated.

Process data from Stages 11 and 12 along with impurity clearance data support the comparability claim. Comparability was also demonstrated using side-by-side testing of batches of MDS2 and batches of MDS2 LIQ RKV. The data from these tests support the claim of comparability. A comparison of batch release also supported the comparability claim.

The control strategy is essentially the same as for the approved active substance. Differences have been supported by small-scale studies.

Characterisation

The active substance has previously been characterised in the approved marketing authorisation. Process-related impurity clearance data has been provided from MDS2 LIQ RKV batches and shows an acceptable level of clearance, which is comparable to the approved active substance.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The proposed specifications include control of identity, purity, potency and other general tests. They are generally consistent with those seen for monoclonal antibodies; they are in accordance with ICH Q6B and are accepted. The majority of acceptance criteria are identical to those approved for the MDS2 LYO RKV active substance. The limit for host cell proteins (HCP) is wider than the available batch data; however as part of the ongoing process verification HCP levels in the bulk active substance are monitored to an interim control limit.

Analytical procedures

Analytical methods which are common to the previously authorised Nucala lyophilised powder formulation are cross-referenced to that dossier. This approach is acceptable as it is confirmed that the methods are identical for both products. Pharmacopoeial methods contain reference to their specific monograph which is acceptable, while non-pharmacopoeial methods are described in the dossier. In general, the level of description is acceptable. Overall, the applicant has provided detailed validation reports for new methods and supplementary validation reports for methods previously used for lyophilised active substance. All analytical procedures were validated in accordance with ICH Q2.

Batch analysis

The applicant has provided batch data for six PPQ batches manufactured according to the proposed commercial process as well as four clinical batches. Results are comparable between batches and meet all specification limits.

Reference standards

The approach to reference standards has not changed from the approved dossier. The current reference standards were assessed during the initial marketing authorisation and continue to be acceptable.

Container closure system

The primary container closure system was assessed during the initial marketing authorisation and is acceptable.

Stability

The real-time stability data generated for MDS2 LIQ RKV active substance indicate that the active substance is physically, chemically and biologically stable when stored at the recommended storage conditions. A comprehensive stability protocol has been provided, which tests the main quality attributes at all time-points. Stability reports demonstrate that all quality attributes remained within specification during shelf life. In addition accelerated studies support the stability of the active substance. Photo-stability studies indicate that the active substance is sensitive to degradation upon exposure to light, and therefore should be stored protected from light.

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

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The product is presented as a single-use, sterile liquid finished product in a clear glass pre-filled syringe (PFS) intended to deliver 100 mg of mepolizumab for subcutaneous use. It is referred to as MDP3 to differentiate it from the currently approved MDP2 finished product. The primary container and closure consists of a 1 mL long Type 1 glass siliconised barrel with a staked 29G thin wall x 12.7 mm stainless steel needle with a thermoplastic elastomer needle shield covered by rigid plastic shield sealed with a fluororesin coated bromobutyl rubber plunger stopper. The PFS is assembled into either an auto-injector or a safety syringe device. A minimum fill volume of 1.01 mL is provided in the PFS to ensure the required 1.0 mL volume is delivered. The finished product composition includes 100 mg of active substance, sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80 and EDTA disodium dihydrate.

Sufficient details of the formulation development have been provided. Several formulations were tested which included different buffers as well as different concentrations of sucrose and polysorbate 80. The differences between the liquid and currently registered lyophilised presentation include a lower amount of sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80, and the addition of citric acid monohydrate and EDTA.

Small scale process characterisation studies were carried out to identify the CPPs and define the proven acceptable ranged (PARs). A mixing study was performed at worst case conditions and confirmed that the shear stress does not negatively impact on quality. A filtration study showed no impact on quality. Sufficient data on compatibility has been presented.

The CQAs for the finished product have been listed and were defined based on regulatory requirements and risk assessment. Further details of this risk assessment have been requested. The panel of CQAs cover all relevant aspects of purity, potency and safety.

Comparability studies have been provided to support the comparability of MDP2 and MDP3 finished product. Batches of MDP2 were compared to Batches of MDP3. In addition, a comparison of MDP3 batch data to the historical range of MDP2 batches supported the comparability claim. Extensive forced degradation studies were also carried out which supported comparability.

The primary container closure is a PFS, which is assembled into an auto-injector or safety syringe. Details of design verification and design validation studies have been provided. The technical dossier was provided in 3.2.R. Details of functional performance testing have been provided and include cap removal force, injection actuation force, needle extension, delivered volume, and needle safe distance. In addition, the auto-injector was tested for injection time, audible click, and needle cover over-ride; and the safety syringe was tested for needle guard actuation force, needle guard over-ride force, and needle guard lockout. The testing is in accordance with relevant ISOs 11608 and 11404. Biocompatibility testing has been performed in accordance with ISO 10993-1. Formative and summative human factors studies and real-world use studies have also been performed. The device performance was also evaluated during the PK trial. Overall, the level of detail provided for the PFS, auto-injector and safety syringe is considered acceptable. Extractables and leachables have been sufficiently addressed and are concluded to pose no risk.

Container closure

The primary container closure system is a PFS, which is assembled into an auto-injector or a safety syringe device. The syringe glass conforms to Ph. Eur. requirements for glass and the proposed specifications are acceptable. They cover relevant tests for visual defects, quality of material, microbial testing and performance

testing. A specification for silicone is included for the PFS. It has been confirmed that the silicone oil used in the syringes is in conformance with Ph. Eur. 3.1.8 Silicone oil used as a lubricant. The rubber stoppers conform to Ph. Eur. 3.2.9 and the specifications cover visual defects, identity, sterility and dimensional requirements and are acceptable. The names of the PFS and rubber stopper manufacturers have been supplied including the address of the sites responsible for sterilisation. The syringes are sterilised by the supplier using ethylene oxide, and a specification for residual ethylene oxide is included.

Sufficient details and acceptable specifications have been provided for the safety syringe. The auto-injector is manufactured by Ypsomed and is a single-use disposable device, which is not exposed to the finished product. The specifications include visual tests performed by the MAH and functional tests performed by Ypsomed. Relevant functional tests are registered in the specifications (Table 4). A technical dossier for the auto-injector is provided which includes details of conformance with the General Safety and Performance Requirements of the Medical Device Directive. Human factors study reports are also provided. Overall, the level of detail registered for safety syringe and auto-injector is considered acceptable.

Manufacture of the product and process controls

Manufacture

The manufacturing process is standard for a monoclonal antibody finished product and has been sufficiently well described in the dossier. Frozen active substance is thawed, pooled and diluted to the target concentration. Formulation buffer and bulk active substance are mixed and then filtered into a holding bag, followed by sterile filtration and filling into PFSs. The PFSs are assembled into an auto-injector or safety syringe.

Process controls

IPCs are listed throughout the manufacturing. The level of control is considered appropriate for this type of manufacturing process.

Process validation

Data is provided for five PPQ batches. For manufacture of the formulation buffer and dilution/mixing of the bulk active substance, two samples were taken. For the filling process, six samples were taken. The acceptance criteria for the PPQ campaign were based on the finished product release specifications. Data are provided on relevant CQAs, CPPs and IPCs throughout the manufacturing process. The assembly into auto-injector or safety syringe was successfully validated and included a sufficient number of functional performance tests. Shipping validation data has also been provided and is acceptable.

Sterile filtration has been sufficiently validated. A microbial retention study was carried out at the maximum flow rate. Media fills have been performed under worst-case conditions and successfully passed. Routine environmental monitoring is also performed. Details of the filter extractable study were provided and the levels identified were below the reporting threshold of daily patient exposure.

Product specification, analytical procedures, batch analysis

Specifications

The panel of tests included in the finished product specifications are in accordance with ICH Q6B and cover the relevant aspects of identity, purity and impurities, potency and other general tests. The testing panel is generally consistent with the approved Nucala marketing authorisation. The proposed specifications for device functionality include tests for delivered volume, needle guard lock-out and container closure integrity. Stability

studies have confirmed acceptable break-loose force and extrusion force over the shelf life of the PFS. The applicant has justified the proposed acceptance criteria for the finished product on the basis that they are the same as the approved lyophilised product, are compendial, or are the same as the clinical acceptance criteria.

Analytical procedures

There are three finished product specific methods; bioassay, container closure integrity and post-use needle guard lock-out. The other analytical procedures are either compendial, or the same as for the active substance. The descriptions and validation of the analytical methods are acceptable.

Batch analysis

Batch data has been presented from MDP3 clinical and PPQ batches. The finished product batches were all manufactured from active substance batches. From these active substance batches, PFS batches were manufactured. These PFS batches were used to manufacture safety syringe batches and seven auto-injector batches, for which data is provided. All release data were well within specification and demonstrate that the process is capable of producing finished product batches of consistent quality. In addition to the release tests, the functional testing of the MDP3 PFS batches included maximum break loose force, maximum peak extrusion force and maximum average extrusion force. These tests are for information only and have not been included in the proposed commercial release specifications. This is acceptable.

Reference standard

The reference standard is described in the active substance section.

Stability

The proposed shelf life of the finished product is 24 months at 2-8°C, plus 1 week at room temperature (up to 30°C/35% residual humidity (RH)) is acceptable. The shelf life specifications are the same as for release, apart from SEC and cIEF. The stability data includes batches from the PFS, auto-injector and safety syringe which are the intended commercial container closure system. The data included storage in the horizontal, upright and vertical positions. The real time stability data show no significant changes in quality parameters. At the accelerated storage condition of 30°C/35%RH, the finished product was out of specification after 3 months. Photostability studies have shown that the finished product is sensitive to light and an appropriate warning is included in Section 6.4 of the SmPC. The product must be administered within 8 hours once the pack is opened.

Stability data from functional assays have been submitted to support the functionality of the PFS across the shelf life. Data are provided for maximum break-loose force, maximum peak extrusion force and maximum average extrusion force. To address the functional performance of the auto-injector during storage, stability data was provided for cap removal force, actuation force, needle cover lockout, needle extension, force to overcome lockout, delivery time, and needle safe distance.

Up to 24 months stability data has been provided which covers the claimed shelf life. The storage conditions also include the possibility of storage for 1 week at 30°C. Data has been provided where the finished product was stored for 2 weeks at 30°C/35%RH, followed by 12 months' storage at 2-8°C. This stability study is ongoing. In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Adventitious agents

None of the steps which impact viral clearance is changed compared with the approved process and no additional possible sources of viral contamination are introduced.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacturing process is identical to the currently approved mepolizumab active substance manufacturing process apart from the final two manufacturing steps. Comparability to the currently approved process has been shown. The finished product includes a new formulation and a new presentation in a PFS or PFP. Comparability to the currently approved finished product has been demonstrated. The manufacturing process is well under control and the batch data are consistent and the finished product manufacturing process has been validated. Sufficient details have been provided regarding the pre-filled syringe and pre-filled pen, which conform to current legislation and guidance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, CHMP considers that this line extension application is approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. *Non-clinical aspects*

No non clinical data have been submitted in this application. This is acceptable by CHMP.

2.4. *Clinical aspects*

- **Tabular overview of clinical studies**

Table 1 Tabular Listing of All Mepolizumab Liquid 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/ Completed	Study Reporting Status (Type of Report)
Pharmacokinetic/Pharmacodynamic Studies						
204958 (2017N342446_00)	PK/PD Safety and Tolerability Immunogenicity Safety syringe and autoinjector use	R, OL, PG	Healthy subjects	Mepolizumab 100 mg SC liquid drug product, single dose either in autoinjector or safety syringe Mepolizumab 100 mg SC lyophilised powder for solution for injection, single dose.	Autoinjector 79/79 Safety syringe 80/80 Lyophilised powder 85/84	Completed/ Reported (CPSR)
Efficacy and Safety Studies: Controlled Clinical Studies Using Liquid						
205687 (2018N371779_00)	Safety and Efficacy in the treatment of nasal polyposis	R, DB, PC, PG	Nasal polyposis	Mepolizumab 100 mg SC liquid drug product Q4W for 52 weeks Placebo SC Q4W for 52 weeks Administered by a healthcare professional via a prefilled safety syringe	245 (enrolment in progress)	Ongoing
Real World Use and Safety Studies: Uncontrolled Clinical Studies						
204959 (2017N349209_00)	Autoinjector use PK/PD Asthma exacerbations Safety and Tolerability Immunogenicity	OL, RWU	Severe eosinophilic asthma	Mepolizumab 100 mg SC liquid drug product Q4W for 12 weeks self-administered by the subject (or their caregiver) using an autoinjector.	159/157 ^a	Completed/ Reported (CSR)
205667 (2017N331753_00)	Safety syringe use PK/PD Asthma exacerbations Safety and Tolerability Immunogenicity	OL, RWU	Severe eosinophilic asthma	Mepolizumab 100 mg SC liquid drug product Q4W for 12 weeks self-administered by the subject (or their caregiver) using a safety syringe.	56/55	Completed/ Reported (CSR)

a. 19 subjects enrolled and received study medication in both 205667 and 204959. In all cases, subjects first participated and completed Study 205667 before enrolling in Study 204959.

Abbreviations: CPSR= Clinical Pharmacology Study Report; CSR=Clinical Study Report; DB = Double-blind; HCP = Healthcare Professional; mg = milligram(s); OL=Open Label; PC = Placebo-controlled; PD = Pharmacodynamic, PG = Parallel Group; PK = Pharmacokinetic; Q4W=once every 4 weeks; R = Randomised, RWU = Real-world Use, SC = Subcutaneous(ly).

2.4.1. Pharmacokinetics

• Introduction

The purpose of this application is to obtain marketing approval for mepolizumab liquid drug product, delivered via a prefilled safety syringe or an autoinjector device, in the same and future indications currently registered for Nucala lyophilised drug product.

Three clinical studies of mepolizumab liquid drug product support this application; a pharmacokinetic (PK) comparability study in healthy subjects (Study 204958), and two Real-World Use studies in subjects with severe eosinophilic asthma, one with the autoinjector (Study 204959) and one with the safety syringe (Study 205667).

• Methods

Analytical methods

The same bioanalytical methods used in support of the currently approved lyophilised presentation were used in support of the current submission to evaluate Mepolizumab plasma concentrations and presence of Mepolizumab ADA and NAbS. This approach is acceptable.

The applicant has provided data that shows the assay runs used to analyse samples from the clinical studies met pre-defined acceptance criteria. The data from these runs was therefore valid.

For evaluation of ADAs in the current submission, the method was transferred to a new laboratory. The validation status of the method has been summarised. This has been performed in accordance with current guidelines. The method remains in a valid state.

Updated sample stability data has also been provided.

Pharmacokinetic data analysis

Mepolizumab PK parameters were derived from the plasma concentration-time data for each subject by standard non-compartmental methods using Phoenix WinNonlin Version 6.3.

Statistical methods

In the PK comparability study (204958), the primary statistical analysis was to compare the primary PK parameters [C_{max}, AUC(0-t) and AUC(0-∞)] for each test treatment (liquid drug product in autoinjector or safety syringe) with the reference treatment (reconstituted lyophilised drug product from a vial). The primary PK parameters were log_e transformed and analysed separately using a fixed effects analysis of covariance (ANCOVA) model, including treatment group, injection site and baseline body weight as covariates. Point estimates and associated two-sided 90% CIs were constructed for the ratio of the geometric mean of each test treatment to the geometric mean of the reference treatment (obtained by back-transforming estimates and 90% CIs for the treatment differences from the statistical model on the log_e scale). The sample size for this study was based on the number of subjects needed to demonstrate a 2-sided 90% CI for the ratio of the geometric mean of each test treatment to the geometric mean of the reference treatment, within the guide range of 0.80-1.25, for primary PK parameters.

In the two real-world use studies (204959 and 205667), statistical analyses were descriptive only and no formal sample size calculations were performed.

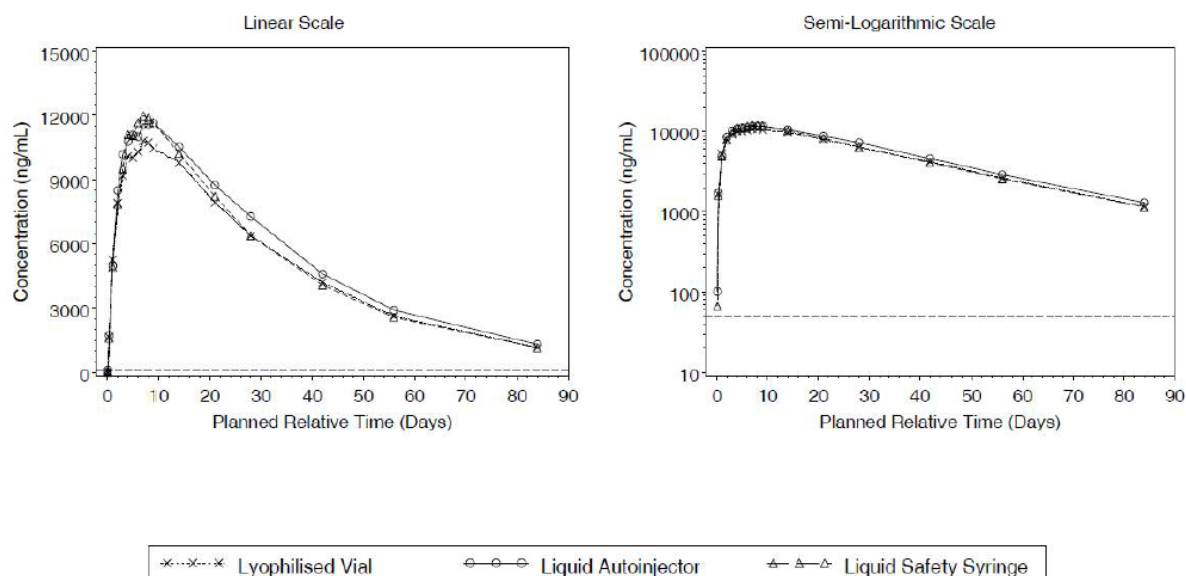
In all three studies, analyses were performed on all available data and no imputation was performed for missing data.

- **Bioequivalence**

Study 204958 was an open label, randomised, three arm, single dose, multicentre, parallel group study in healthy subjects to compare the pharmacokinetics of subcutaneous mepolizumab when delivered as a liquid drug product in a safety syringe or an autoinjector with a reconstituted lyophilised drug product from a vial.

244 healthy subjects received mepolizumab treatment and provided PK samples for analysis. The demographics and baseline characteristics were comparable across treatment arms. The plasma concentration-time profiles following a single SC dose of mepolizumab 100 mg from the lyophilised drug product or from the liquid drug product, delivered by an autoinjector or a safety syringe, were similar (Figure 3).

Figure 3 Median Plasma Mepolizumab Concentration-Time Plots by Treatment (Linear and Semi-Log) (Study 204958 PK Population)



Source Data: [Figure 7.4](#)

Note: Lower limit of quantification = 50 ng/mL

The pharmacokinetics of a single mepolizumab 100 mg SC dose, administered as liquid drug product using either autoinjector or safety syringe, was shown to be statistically comparable to the pharmacokinetics of the commercialized lyophilized drug product. All 90% CIs for the treatment ratios (liquid drug product in autoinjector vs. lyophilized drug product and liquid drug product in safety syringe vs. lyophilized drug product) of mepolizumab C_{max}, AUC(0-∞) and AUC(0-t) were contained within the conventional bioequivalence bounds of 0.80, 1.25 (Table 1).

The similarity of secondary PK parameters (t_{max}, apparent clearance, terminal phase half-life) across the 3 treatment arms provide further support for the comparability of the 2 test treatments and the reference (Table 10). The geometric mean extrapolated portion of AUC(0-∞) was 7 to 8% (range for individual values 0.5-19.9%). PK parameters were consistent with those observed in a previous study conducted in healthy subjects with the lyophilised drug product (Study SB-240563/018).

Table 1 **Adjusted Treatment Ratios between Mepolizumab Liquid Drug Product in a Safety Syringe (test) or an Autoinjector (test) and Mepolizumab Lyophilized Drug Product (reference) for AUC(0-∞), AUC(0-t), and Cmax (Study 204958, PK Population)**

	Mepolizumab 100 mg SC	
	Liquid in Safety Syringe vs. Lyophilized	Liquid in Autoinjector vs. Lyophilized
AUC(0-∞) day*µg/mL	1.02 (90% CI: 0.95, 1.09)	1.07 (90% CI: 1.00, 1.13)
AUC(0-t) day*µg/mL	1.04 (90% CI: 0.97, 1.12)	1.08 (90% CI: 1.01, 1.15)
Cmax µg/mL	1.06 (90% CI: 0.99, 1.12)	1.04 (90% CI: 0.98, 1.11)

Source: 204958 [CPSR Table 7.13](#)

Note: The estimates of the geometric mean are adjusted for injection site (arm, abdomen, thigh) and baseline weight (log_e scale).

Table 10 Summary of Derived Plasma Mepolizumab PK Parameters Following a Single SC 100 mg Dose by Treatment (Study 204958 PK Population)

Parameter	Mepolizumab 100 mg SC		
	Lyophilised Vial (N=85)	Liquid Drug Product In Autoinjector (N=79)	Liquid Drug Product In Safety Syringe (N=80)
Primary PK Parameters			
C _{max} (µg/mL) ¹	85 11.57 (10.92, 12.27)	79 11.98 (11.27, 12.74)	80 12.07 (11.32, 12.87)
AUC(0-∞) (day*µg/mL) ¹	84 450.83 (425.67, 477.47)	79 478.06 (450.47, 507.34)	80 454.11 (423.03, 487.48)
AUC(0-t) (day*µg/mL) ¹	85 403.84 (377.83, 431.63)	79 434.49 (411.34, 458.94)	80 415.15 (388.36, 443.78)
Secondary PK Parameters			
AUC(0-week4) (day*µg/mL) ¹	84 244.97 (232.64, 257.96)	79 254.56 (240.97, 268.93)	80 248.81 (233.82, 264.76)
%AUC _{Cex} (%) ¹	84 7.67 (6.88, 8.54)	79 7.64 (6.55, 8.90)	80 7.20 (6.19, 8.37)
CL/F (L/day) ^{1,2}	84 0.222 (0.209, 0.235)	79 0.209 (0.197, 0.222)	80 0.220 (0.205, 0.236)
V _Z /F (L) ¹	84 7.02 (6.69, 7.37)	79 6.74 (6.41, 7.08)	80 6.94 (6.53, 7.37)
t _{1/2} (days) ¹	84 21.95 (21.03, 22.92)	79 22.34 (21.21, 23.53)	80 21.83 (20.72, 23.01)
λ _Z (/day) ^{1,2}	84 0.0316 (0.0302, 0.0330)	79 0.0310 (0.0295, 0.0327)	80 0.0317 (0.0301, 0.0335)
t _{max} (days) ³	85 7.04 (0.9, 14.1)	79 7.05 (2.9, 21.0)	80 7.06 (1.9, 14.0)
t _{last} (days) ³	85 83.97 (14.0, 87.0)	79 83.98 (81.1, 87.1)	80 83.99 (55.9, 87.9)

Source Data: [Table 7.5](#) and [Table 7.6](#)

1. Number of subjects and geometric mean with 95% CI presented.

2. Source data unit converted from "per hour" to "per day" (i.e., × 24).

3. Number of subjects and median (minimum-maximum) presented.

AUC(0-week4) = area under the concentration-time curve from time zero (pre-dose) to Week 4

Overall, the site of injection (abdomen, thigh, or arm) did not markedly influence mepolizumab PK, irrespective of drug product or device used.

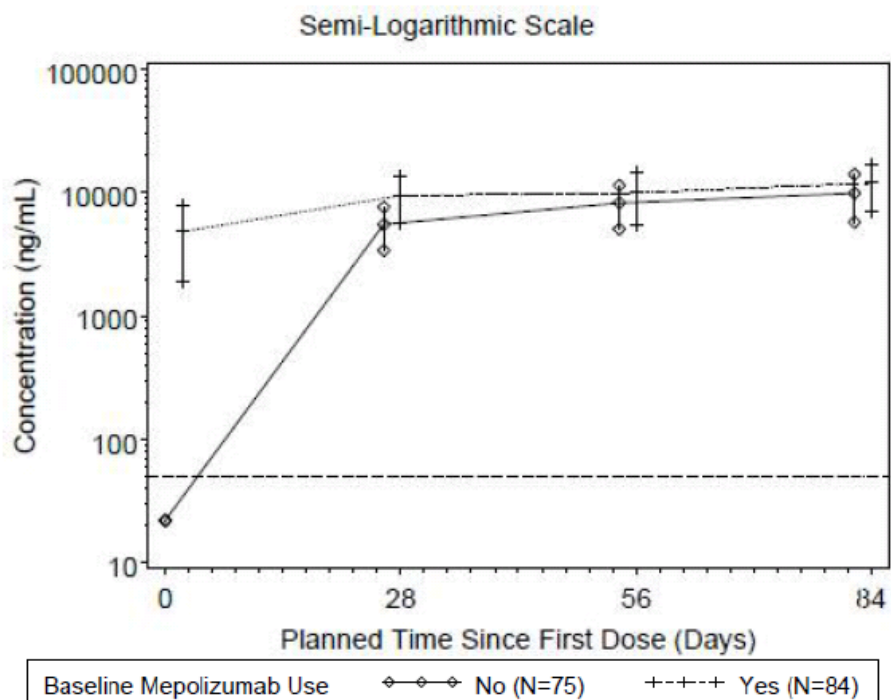
The post-baseline incidence of positive ADA results in this study was low and was similar across the treatment groups (4%, 6% and 4% for the lyophilised drug product, liquid drug product in autoinjector and liquid drug product in safety syringe, respectively). Titres were generally low, with a maximum titre of 320 (in 1 subject in the safety syringe group at Day 29), and decreasing or remaining stable over time. In the 11 subjects with positive post baseline ADA results, there was no evidence of mepolizumab plasma concentrations or blood eosinophil counts being affected by the presence of ADAs. There was no discernible impact of ADAs on mepolizumab plasma concentrations or blood eosinophils. No subjects tested positive for neutralising antibodies to mepolizumab.

- **Pharmacokinetics in the target population**

In subjects with severe eosinophilic asthma, two repeat dose Real-World Use studies of 100 mg SC every 4 weeks for 12 weeks using liquid drug product in autoinjector (**Study 204959**) or safety syringe (**Study 205667**) were conducted. Both studies were open-label, single arm, repeat dose, multi-centre studies, to evaluate the use of an autoinjector or a safety syringe for the subcutaneous administration of mepolizumab in subjects with severe eosinophilic asthma. In these studies, the PK of mepolizumab was assessed by measuring mepolizumab plasma trough concentrations.

159 subjects and 56 subjects had samples collected for PK assessment in Study 204959 and Study 205667, respectively. In each study, the mean mepolizumab plasma trough concentration increased following each self-administration, and at the End of Study Visit the mean mepolizumab plasma trough concentration was similar to that observed in subjects already receiving mepolizumab at Screening (Figure 3 [204959] and Figure 3 [205667]). Mepolizumab plasma trough concentrations were consistent between studies, and were indicative of correct self-administration by the subjects themselves (or their caregivers) using the autoinjector and safety syringe devices.

Figure 3 Mepolizumab Plasma Concentration-Time Plots by Baseline Mepolizumab Use (PK Population, Study 204959)



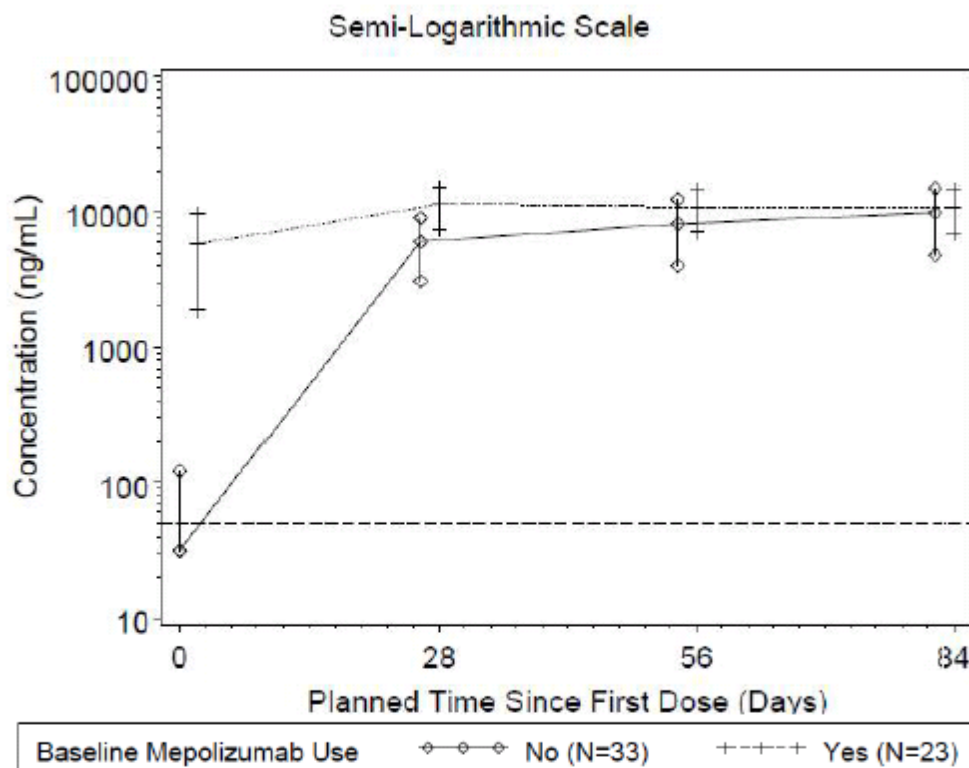
Source: Figure 8.4.

Note: Data presented as mean \pm SD.

Note: LLQ=50 ng/mL

LLQ = lower limit of quantification.

Figure 3 Mepolizumab Plasma Concentration-Time Plots by Baseline Mepolizumab Use (PK Population, Study 205667)



Source: Figure 8.4.

Note: Data presented as mean±SD.

Note: LLQ=50 ng/mL.

LLQ = lower limit of quantification, mL = millilitre(s), ng = nanogram(s).

When assessed by the site of injection (abdomen, thigh, or arm), the mean mepolizumab concentration-time plots were overall similar across the three sites, irrespective of the device used. However, there is insufficient evidence to conclude no difference in the upper arm site of injection compared to the abdomen or thigh, with only 5 subjects in Study 204959 and 4 subjects in Study 205667 using the upper arm as a site of injection.

Consistent with Study 204958, the post-Baseline incidence of mepolizumab antidrug antibodies in both studies was low and no subjects tested positive for neutralising antibodies to mepolizumab. There was no evidence of mepolizumab plasma trough concentrations and blood eosinophil counts being affected by the presence of ADAs.

- **Conclusion**

Overall, the PK of mepolizumab was studied and characterised sufficiently for this application. In healthy subjects, the PK of a single mepolizumab 100 mg SC dose, administered as liquid drug product using either autoinjector or safety syringe, was shown to be statistically comparable to the PK of the commercialised lyophilized drug product. In subjects with severe eosinophilic asthma, two repeat dose Real-World Use studies of 100 mg SC mepolizumab every 4 weeks for 12 weeks using liquid drug product in autoinjector or safety syringe, showed consistent mepolizumab plasma trough concentrations. In all studies, the post-Baseline

incidence of mepolizumab antidrug antibodies was low and no subjects tested positive for neutralising antibodies to mepolizumab.

2.4.2. Pharmacodynamics

- **Introduction**

The pharmacodynamics (PD) of mepolizumab were investigated in three clinical studies. Study 204958 was a comparative PK study conducted in healthy volunteers, which included an exploratory PD analysis. Studies 204959 and 205667 were real-world use studies of mepolizumab in subjects with severe eosinophilic asthma, which included assessments of the PD effect of mepolizumab via an autoinjector (Study 204959) and via a safety syringe (Study 205667).

- **Mechanism of action**

Mepolizumab is a humanised monoclonal antibody which interacts with interleukin-5 (IL-5) to inhibit its binding to and signalling via the cell-surface IL-5 receptor complex expressed on eosinophil cells. IL-5 promotes the proliferation of eosinophils, and the antagonistic action of mepolizumab results in reduced blood, sputum, and tissue eosinophils.

- **Primary pharmacology**

Mepolizumab produces a reduction of blood eosinophil levels and has shown clinical benefit in the treatment of severe eosinophilic asthma.

Study 204958 was a comparative PK study in healthy volunteers. This study included an exploratory PD analysis, to evaluate mepolizumab PD effects on blood eosinophil count following a single 100 mg SC dose of liquid drug product, in safety syringe or autoinjector, in comparison with the reconstituted lyophilised drug product.

In all treatment groups, a single dose of mepolizumab produced a decrease in eosinophil counts up to Day 29, which then started to return towards baseline. The reductions in blood eosinophil counts observed using the liquid drug product in autoinjector or safety syringe were comparable, and comparable with the lyophilized drug product.

Geometric mean ratios to baseline blood eosinophils over time (adjusted for baseline blood eosinophil count [loge scale], injection site [arm, abdomen, thigh] and baseline weight [loge scale]) were similar across the 3 treatment groups with a value of 0.335, 0.344 and 0.311 (a reduction from baseline of 67%, 66% and 69%) at Day 29 for the lyophilised drug product, liquid drug product in autoinjector and liquid drug product in safety syringe, respectively.

In the comparisons of the liquid drug product in autoinjector and the liquid drug product in safety syringe with the lyophilised drug product, the geometric mean ratios of blood eosinophil counts for both comparisons were approximately 1 (range 1.029 to 1.147 for the liquid drug product in autoinjector vs lyophilised drug product comparison and 0.929 to 1.123 for the liquid drug product in safety syringe vs lyophilised drug product comparison). This suggests that both test treatments (liquid drug product in autoinjector or safety syringe) had similar effects on blood eosinophils as the lyophilised drug product.

Studies 204959 and 205667 were real-world use studies of mepolizumab in subjects with severe eosinophilic asthma, which included assessments of the PD effect of mepolizumab. The PD profile of mepolizumab liquid drug

product in an autoinjector or safety syringe was assessed by measuring blood eosinophils. 158 subjects and 56 subjects had samples collected for PD assessment in studies 204959 and 205667, respectively.

In subjects with severe eosinophilic asthma, 100 mg SC every 4 weeks for 12 weeks using liquid drug product in autoinjector (Study 204959) or safety syringe (Study 205667), resulted in a sustained reduction in blood eosinophil counts. The reductions in blood eosinophil counts observed using the liquid drug product in autoinjector or safety syringe were comparable (Figure 4 Study 204959 and Figure 4 Study 205667). Blood eosinophil counts were indicative of correct self-administration by the subjects (or their caregivers) using the autoinjector and safety syringe devices.

Figure 4 Summary of Ratio to Baseline Blood Eosinophils by Visit and Baseline Mepolizumab Use (PD Population, Study 204959)

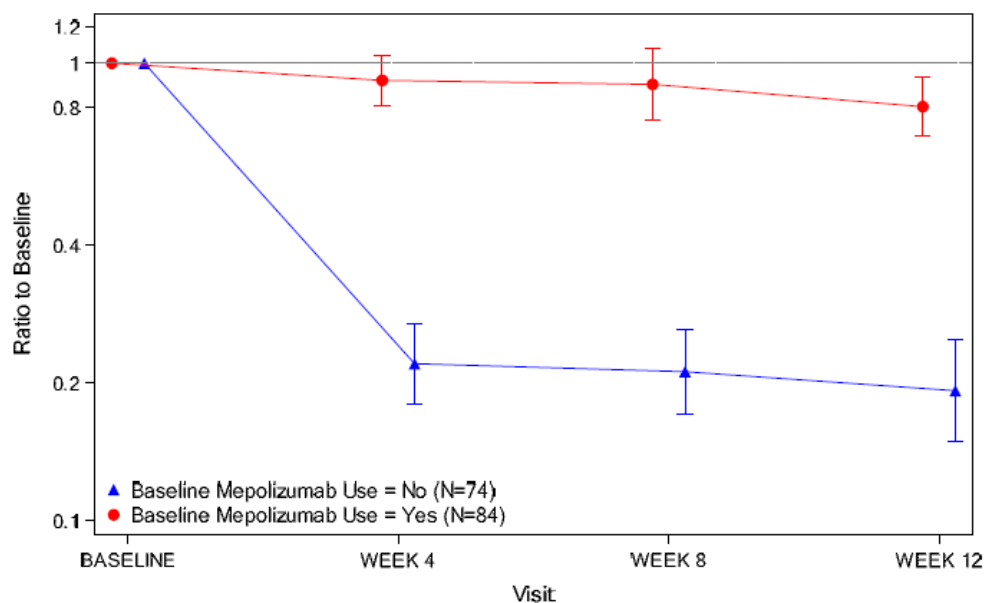
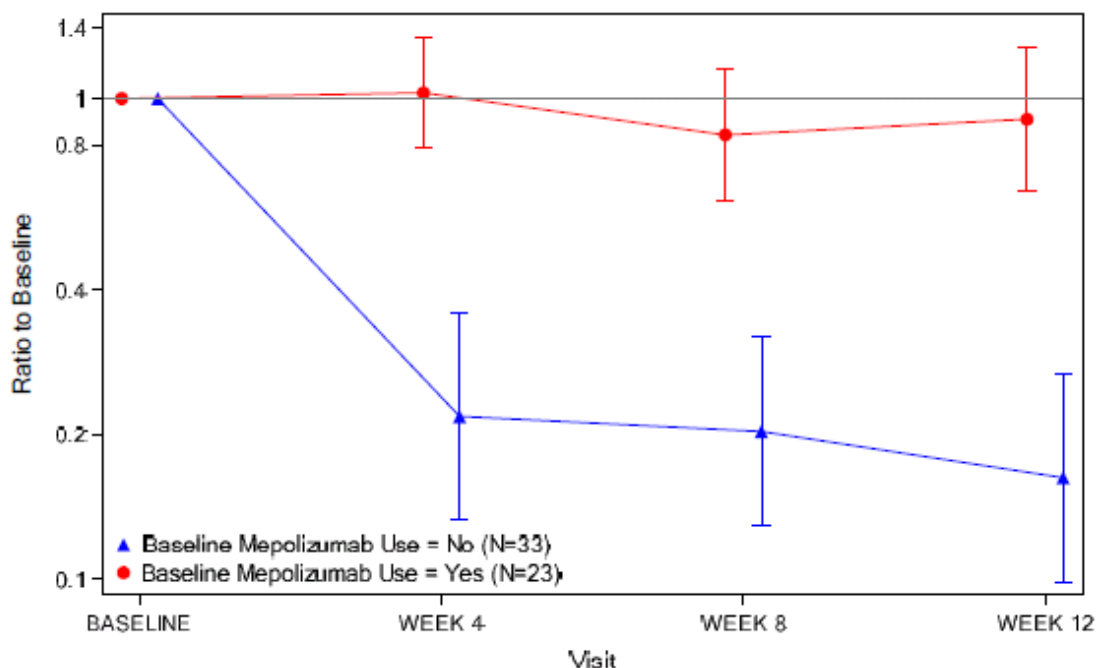


Figure 4 Summary of Ratio to Baseline Blood Eosinophils by Visit and Baseline Mepolizumab Use (PD Population, Study 205667)



Overall, in subjects with severe eosinophilic asthma, the site of injection (abdomen, thigh, or arm) did not appear to influence the effect of mepolizumab on blood eosinophils, irrespective of the device used, although there were too few subjects using the upper arm site in either study to be able to conclude no difference.

- **Conclusion**

The PD of mepolizumab was studied and characterised sufficiently for this application. In healthy subjects, a single 100 mg SC dose of mepolizumab produced a decrease in eosinophil counts up to Day 29. The reductions in blood eosinophil counts observed using the liquid drug product in autoinjector or safety syringe were comparable, and comparable with the lyophilized drug product.

In subjects with severe eosinophilic asthma, 100 mg mepolizumab SC every 4 weeks for 12 weeks, using liquid drug product in autoinjector or safety syringe, resulted in a sustained reduction in blood eosinophil counts. The reductions in blood eosinophil counts observed using the liquid drug product in autoinjector or safety syringe were comparable.

2.4.3. Discussion on clinical pharmacology

To support the development of the liquid formulation administered via a safety syringe or an autoinjector, three clinical studies were conducted; a PK comparability study in healthy subjects (204958), and two Real-World Use studies in subjects with severe eosinophilic asthma, one with the autoinjector (204958) and one with the safety syringe (205667).

Pharmacokinetics and pharmacodynamics in healthy subjects

In the PK comparability study (Study 204958), 244 healthy subjects were administered a single dose of mepolizumab 100 mg SC by a health care professional. The primary PK endpoints were C_{max}, AUC(0-∞), and AUC(0-t).

The design of this study is considered acceptable. The parallel group design was appropriate given the long half-life of mepolizumab and the potential influence of immunogenicity with a cross-over design. The demographics and baseline characteristics were well balanced between the 3 treatment arms. The sampling time points were adequate for characterisation of the whole mepolizumab PK profile, including the late elimination phase. The collection of samples up to Day 85 ensured that the extrapolated portion of AUC(0-∞) was less than 20% in all subjects.

The results provide evidence for statistical PK comparability between the liquid drug product, in a safety syringe or an autoinjector, and the lyophilised drug product. All 90% CIs of the geometric mean ratios of primary PK parameters were contained well within the predefined equivalence margin (0.80 to 1.25). The similarity of secondary PK parameters (t_{max}, apparent clearance, terminal phase half-life) across the 3 treatment arms further supports the comparability of the liquid drug product (autoinjector or safety syringe) and the lyophilized drug product.

In the exploratory PD component of this study, the geometric mean ratios of blood eosinophil counts for the comparisons of the liquid drug product in autoinjector and in safety syringe with the lyophilized drug product were approximately unity at the various time-points, with the 95% CIs for the ratios falling within bounds of 0.70, 1.43 (±30%). This suggests that both test treatments (liquid drug product in autoinjector or safety syringe) and lyophilized drug product had similar effects on blood eosinophils, although these wider confidence bounds were not defined or justified in the study protocol.

Overall, the site of injection (abdomen, thigh, or arm) did not appear to markedly influence mepolizumab PK, nor the effect of mepolizumab on blood eosinophils, irrespective of drug product or device used.

A number of other concerns were raised for this study, as follows:

1. At pre-dose, 11 subjects had measurable plasma mepolizumab concentrations, with 2 of these subjects having pre-dose concentrations >5% of their respective C_{max}. In line with the EMA bioequivalence guideline, subjects with non-zero baseline concentrations >5% of C_{max} should be excluded from bioequivalence calculations. The applicant was asked to justify the non-exclusion of these 2 subjects from the statistical analysis. The applicant was also asked to provide an explanation for subjects having measurable mepolizumab concentrations before receiving the first dose.

In response to this concern, the applicant conducted a sensitivity analysis excluding the 2 subjects with pre-dose concentration >5% of C_{max} and the results showed that the exclusion of these 2 subjects had no impact on the interpretation of the study results. The applicant also provided confirmation that the method used for sample analysis was validated for being accurate, precise, selective, sensitive and reproducible. This issue was concluded to be resolved.

2. The applicant reported performing a database unfreeze to allow for the reanalysis of PK samples with measurable concentrations prior to administration of mepolizumab as well as 2 unexpectedly high concentrations (post-dosing), and to investigate a potential swapping of samples. Derivation of PK parameters and statistical analysis had not been completed at that stage. This reanalysis of the PK samples resulted in final PK concentrations for 15 samples in 14 subjects being updated. However, reanalysis of samples did not appear to be addressed in the study protocol. Therefore, in terms of the reanalysed samples, the applicant was asked to: (i) identify and provide the initial value of the reanalysed samples; (ii) provide the reason for reanalysis; (iii) provide the values obtained in the

reanalysis; (iv) provide the finally accepted value; and (v) provide a justification for the acceptance of this value.

In response to this concern, the applicant identified the samples and provided the rationale for their re-analysis. The initial value of the reanalysed samples, the values obtained in the re-analysis and the final accepted values were provided. A justification for the acceptance of the final value was also provided. Given the low number of samples re-analysed, this was considered acceptable and the issue was concluded to be resolved.

3. The applicant was asked to clarify how data below the lower limit of quantification were handled.

In response to this concern, the applicant provided an adequate clarification of how data below the LLOQ was handled and the matter was concluded to be resolved.

4. Pharmacokinetic data source Table 7.1 (Summary of Plasma Mepolizumab Concentration-Time Data by Treatment) showed that data were imputed at pre-dose, 2 hours and 8 hours post-dose, and at follow-up time points. The study report stated that analyses were performed on all available data and that no imputation was performed for missing data. The applicant was asked to explain these imputations.

In response to this concern, the applicant explained that the imputation relates to BLQ data and confirmed that there was no imputation of missing data. The matter was concluded to be resolved.

5. The applicant was asked to provide the following (per EMA bioequivalence guideline): (i) individual concentration data and PK parameters listed by drug product; (ii) the number of points on the terminal log-linear phase used to estimate the terminal rate constant for each subject; and (iii) the analysis of covariance tables, including the appropriate statistical tests of all effects in the model.

In response to this concern, the applicant provided individual concentration data and PK parameters listed by drug product. In all subjects, the number of points on the terminal log-linear phase used to estimate the terminal rate constant for each subject was greater than three. The analysis of covariance tables, including the appropriate statistical tests of all effects in the model were provided and discussed. The matter was concluded to be resolved.

Pharmacokinetics and pharmacodynamics in severe eosinophilic asthma subjects

In subjects with severe eosinophilic asthma, two repeat-dose Real-World Use studies of 100 mg SC every 4 weeks for 12 weeks using liquid drug product in autoinjector (Study 204959) or safety syringe (Study 205667), showed consistent mepolizumab plasma trough concentrations and blood eosinophil counts.

159 subjects and 56 subjects had samples collected for PK and PD assessment in Study 204959 and Study 205667, respectively. In each study, the mean mepolizumab plasma trough concentration increased following each self-administration, and at the End of Study Visit the mean mepolizumab plasma trough concentration was similar to that observed in subjects already receiving mepolizumab at Screening. Mean mepolizumab plasma trough concentrations were comparable in subjects using the liquid product in autoinjector or safety syringe.

Mepolizumab 100 mg SC every 4 weeks for 12 weeks, using liquid drug product in autoinjector or safety syringe, resulted in a sustained reduction in blood eosinophil counts. The reductions observed in blood eosinophil counts using the liquid drug product in autoinjector or safety syringe were comparable.

Plasma trough concentrations and blood eosinophil counts observed in these studies were indicative of correct self-administration by the subjects themselves (or their caregivers) using the autoinjector and safety syringe devices.

Overall, the site of injection (abdomen, thigh or arm) did not appear to markedly influence mepolizumab PK, nor the effect of mepolizumab on blood eosinophils, irrespective of device used. However, there is insufficient evidence to conclude no difference in the upper arm site of injection compared to the abdomen or thigh, with only 5 subjects in Study 204959 and 4 subjects in Study 205667 using the upper arm as a site of injection. Further discussion to support the recommendation of the 3 injection sites (upper arm, thigh and abdomen as per the proposed SmPC) is requested to be provided.

In response to this concern, the applicant explained that the principal data supporting the similarity of mepolizumab between the three sites of injection (abdomen, thigh and upper arm) comes from the PK comparability study 204958, rather than from studies 204959 and 205667 which were real world use studies where the upper arm was only permitted as an injection site if the injection was administered by a caregiver. In the parallel group study 204958, injection site was randomised 1:1:1 to the abdomen, arm and thigh arm and 80, 80 and 84 subjects received injections, respectively. For each of the three PK parameters ($AUC(0-\infty)$, $AUC(0-t)$ and C_{max}) and three injection sites, the 90% confidence interval for eight out of the nine pairwise comparisons is contained within the 0.8, 1.25 bounds required to demonstrate PK comparability. The single exception; C_{max} for arm vs. thigh, has a lower 90% confidence interval bound of 0.78, which is sufficiently close to 0.8 to be unremarkable.

The explanation was considered adequate to support the conclusion of no difference in the upper arm site of injection compared to the abdomen or thigh. The matter was concluded to be resolved.

Impact of immunogenicity on PK and PD of mepolizumab

The post-baseline incidence of mepolizumab ADAs was consistently low across the three clinical studies, and there was no discernible impact of ADAs on mepolizumab plasma concentrations or blood eosinophil counts. No subjects tested positive for neutralising antibodies.

2.4.4. Conclusions on clinical pharmacology

Overall, the PK and PD of mepolizumab were studied and characterised sufficiently for this application. The applicant's conclusions are generally supported. In healthy subjects, the PK of a single mepolizumab 100 mg SC dose, administered as liquid drug product using either autoinjector or safety syringe, was shown to be statistically comparable to the PK of the commercialized lyophilized drug product. In subjects with severe eosinophilic asthma, two repeat dose Real-World Use studies of 100 mg SC mepolizumab every 4 weeks for 12 weeks using liquid drug product in autoinjector or safety syringe, showed consistent mepolizumab plasma trough concentrations. The reductions in blood eosinophil counts observed using the liquid drug product in autoinjector or safety syringe were comparable, and comparable with the lyophilized drug product.

No major objections were raised with the PK or PD analyses. Some other concerns were raised to which the applicant responded adequately. All of these issues were concluded to be resolved.

2.4.5. Clinical efficacy

GlaxoSmithKline (GSK) is submitting this application to obtain marketing approval for a new drug form (mepolizumab injection, liquid drug product) of mepolizumab in the same and future indications currently registered for the Nucala lyophilised drug product (mepolizumab for injection).

Only limited efficacy data were provided as part of this application.

The mepolizumab liquid drug product clinical development programme consisted of 3 studies which support this application: 1 pharmacokinetic (PK) comparability study in healthy volunteers and 2 Real-World-Use (RWU) studies in subjects with severe eosinophilic asthma. All 3 studies assessed the safety profile of the mepolizumab liquid drug product.

2 Real-World-Use (RWU) studies are discussed in the PK, efficacy and safety section of this assessment report.

The pharmacokinetic (PK) comparability study is discussed in the PK and safety section of this assessment report.

In addition the applicant performed Human Factors studies on the instructions for use in the Nucala leaflet. They are discussed in the efficacy section as well.

2.4.6. Dose response study

Not applicable.

2.4.7. Main study

There are no main studies in this application, only supportive studies described below.

Supportive studies

Real-world use studies 204959 and 205667

Two separate open-label, single-arm, multi-dose, multi-center, 12-week studies were conducted to investigate the real-world use of an autoinjector (204959) and a safety syringe (205667) in subjects ≥ 12 years of age with severe eosinophilic asthma. In study 204959, two autoinjector device labels were used: standard device label + pictogram and standard device label.

The objective of these studies was to assess the correct real-world use of the devices for the repeat self-administration (or caregiver administration) of mepolizumab 100 mg SC by determining the proportion of subjects who were successfully able to self-administer a dose. Three doses of mepolizumab were administered: the first and third injections (Week 0 and Week 8) were self-administered under observation in the clinic; the second injection (Week 4) was self-administered at home. Training on the study treatment, device handling and administration techniques, including a review of the instructions for use (IFU), was provided by the investigator or qualified site staff immediately prior to self-administration of the first dose at Week 0. Quantitative and qualitative subject feedback regarding the device use and the IFU were obtained at the end of each study. The primary endpoint for both studies was the proportion of subjects who were successfully able to self-administer their third observed dose at Week 8.

For each self-administration (or caregiver administration), injection success was determined by the investigator/site staff, by reviewing the steps required to successfully administer the injection against a checklist (i.e., Observer Checklist for in-clinic administrations or the At-Home Checklist for injections outside the clinic) alongside findings from the visual inspection of the device following the injection (in-clinic administrations) or when returned to the site.

At the end of the study, the individual who performed the injections (subject or caregiver) completed a Device Usability/Functionality Questionnaire which captured the individual's perception of the training provided by the investigator/site staff for use of the device, the IFU supplied, and the usability and convenience of the device.

Exit Interviews were conducted in a subset of subjects at selected sites within 6 weeks following the final visit to qualitatively assess their experience with mepolizumab liquid drug product in an autoinjector (with either device label) or safety syringe. Exit Interviews were conducted over the telephone in a semi-structured format by a trained interviewer and analysed by a third-party provider.

Results

159 subjects were enrolled in the autoinjector study (104 using the standard device label + pictogram and 55 using the standard device label) and 56 subjects were enrolled in the safety syringe study. The majority of subjects (73% in Study 204959 and 71% in Study 205667) had no prior self-injection experience.

Nearly all subjects ($\geq 98\%$) completed the studies. Three subjects discontinued prematurely. None of the withdrawals were considered related to study treatment by the investigator.

Autoinjector assessment (Study 204959)

Assessment of injection success

- Autoinjector with Standard Device Label + Pictogram

For the primary endpoint, all but one subject ($>99\%$) successfully self-administered the third dose of mepolizumab on the first attempt at Week 8 using the standard device label + pictogram autoinjector (Table 11). The one subject who had an unsuccessful injection made a per-protocol error of selecting an incorrect injection site (upper arm), but received the dose of study treatment.

Over the course of the study, injection success rate was high with 95% of subjects able to self-administer/caregivers administer all three doses of mepolizumab on the first attempt using the standard device label + pictogram autoinjector. Five subjects (5%) had an unsuccessful injection due to one or more user errors, 3 due to selecting the incorrect injection site per-protocol (upper arm intended for caregiver only), one due to pulling the autoinjector away before the end of the injection on the first dose, and one due to a reported device error (unsubstantiated following root-cause analysis) prior to the second dose. Four of the 5 subjects corrected their errors at subsequent injections; the 5th subject selected the incorrect injection site for the injection of two doses.

Table 11 Injection Success on First Attempt (Real World Use Study 204959, Autoinjector Standard Device Label + Pictogram, All Subjects)

Visit	Mepolizumab Liquid Autoinjector (Standard Device Label + Pictogram) N=104			
	Attempted Injection(s) n	Successful Injection ^{a,b} n (%) [95% CI]	Unsuccessful Injection ^b n (%)	Reason for Failure, n
Week 0, First dose (observed in clinic)	104	101 (97) [92, 99]	3 (3)	Incorrect injection site (upper arm)- 2 ^c Pen pulled away before end of injection, evidence of liquid leaking from injection site- 1 ^d
Week 4, Second dose (unobserved at home)	103	101 (98) [93, 100]	2 (2)	Incorrect injection site (upper arm)- 1 ^c Other user/reported device error- 1 ^e
Week 8, Third dose Primary endpoint (observed in clinic)	103	102 (99) [95, 100]	1 (<1)	Incorrect injection site (upper arm)- 1 ^c
Weeks 4 and 8	103	100 (97) [92, 99]		
Weeks 0, 4, and 8	103	98 (95) [89, 98]		

Source: 204959 CSR Table 7.1, Table 7.5, and Listing 16

- The denominator was the number of subjects/caregivers attempting an injection at that visit. Where multiple visits were assessed, the denominator was the number of subjects/caregivers attempting an injection at all the applicable visits.
- Investigator evaluation
- This error was classified as unsuccessful per-protocol. Despite this error, the subject received the dose of study treatment on initial attempt. One subject made this error at Weeks 0 and 4.
- Second attempt at the first dose also resulted in an unsuccessful injection ("pen was not pushed all the way down and held, evidence of liquid leaking from injection site"), thus investigator administered the first dose. Second and third doses were successfully self-administered by the subject on first attempt.
- Subject did not engage the device before the medication had left the autoinjector, the medication fully dispensed all over the counter; root-cause analysis concluded no device error occurred (204959 CSR Section 15.4). Second attempt with another autoinjector was successful.

- Autoinjector with Standard Device Label

For the primary endpoint, all but one subject (98%) successfully self-administered the third dose of mepolizumab on the first attempt at Week 8 using the standard device label autoinjector (Table 12). The one subject who had an unsuccessful injection made a per protocol error of selecting an incorrect injection site (upper arm), but received the dose of study treatment.

Over the course of the study, injection success rate was high with 89% of subjects able to self-administer (or caregivers administer) all three doses of mepolizumab (Weeks 0, 4 and 8) on the first attempt using the standard device label autoinjector. Six subjects (11%) had an unsuccessful injection each due to one or more user errors: 4 due to pulling the autoinjector away before the end of the injection (2 on the first dose and 2 on the second dose), one due to a reported device error on the first dose (leakage from injection site when removing the autoinjector), which was unsubstantiated following root-cause analysis, and one due to selecting the incorrect injection site (upper arm). All subjects corrected their errors at subsequent injections, as applicable.

Table 12 Injection on First Attempt (Real-World Use Study 204959, Autoinjector Standard Device Label, All Subjects)

Visit	Mepolizumab Liquid Autoinjector (Standard Device Label) N=55			
	Attempted Injections n	Successful Injection ^a n (%) [95% CI]	Unsuccessful Injection ^b n (%)	Reason for Failure, n
Week 0, First dose (observed in clinic)	55	52 (95) [85, 99]	3 (5)	Pen pulled away before end of injection, reported device failure- 1 ^{c,d}
				Pen pulled away before end of injection- 1 ^c
				Evidence of leaking from injection site when removing pen, reported device failure- 1 ^e
Week 4, Second dose (unobserved at home)	54	52 (96) [87, 100]	2 (4)	Pen pulled away before end of injection- 1
				Pen pulled away before end of injection, reported device failure- 1 ^d
Week 8, Third dose Primary endpoint (observed in clinic)	54	53 (98) [90, 100]	1 (2)	Incorrect injection site (upper arm)- 1 ^f
Weeks 4 and 8	54	51 (94) [85, 99]		
Weeks 0, 4, and 8	54	48 (89) [77, 96]		

Source: 204959 CSR Table 7.2, Table 7.6, and Listing 16

- The denominator was the number of subjects/caregivers attempting an injection at that visit. Where multiple visits were assessed, the denominator was the number of subjects/caregivers attempting an injection at all the applicable visits.
- Investigator evaluation
- Subject made a successful repeat attempt at injection
- The investigator/site staff entered explanatory text under the 'device failure' section on the eCRF describing the user error.
- Root-cause analysis concluded no device error occurred (204959 CSR Section 15.4).
- This error was classified as unsuccessful per-protocol. Despite incorrect injection site, subject received the dose of study treatment on initial attempt.

Table 12 Injection on First Attempt (Real-World Use Study 204959, Autoinjector Standard Device Label, All Subjects)

Visit	Mepolizumab Liquid Autoinjector (Standard Device Label) N=55			
	Attempted Injections n	Successful Injection ^a n (%) [95% CI]	Unsuccessful Injection ^b n (%)	Reason for Failure, n
Week 0, First dose (observed in clinic)	55	52 (95) [85, 99]	3 (5)	Pen pulled away before end of injection, reported device failure- 1 ^{c,d}
				Pen pulled away before end of injection- 1 ^c
				Evidence of leaking from injection site when removing pen, reported device failure- 1 ^e
Week 4, Second dose (unobserved at home)	54	52 (96) [87, 100]	2 (4)	Pen pulled away before end of injection- 1
				Pen pulled away before end of injection, reported device failure- 1 ^d
Week 8, Third dose Primary endpoint (observed in clinic)	54	53 (98) [90, 100]	1 (2)	Incorrect injection site (upper arm)- 1 ^f
Weeks 4 and 8	54	51 (94) [85, 99]		
Weeks 0, 4, and 8	54	48 (89) [77, 96]		

Source: 204959 CSR Table 7.2, Table 7.6, and Listing 16

- The denominator was the number of subjects/caregivers attempting an injection at that visit. Where multiple visits were assessed, the denominator was the number of subjects/caregivers attempting an injection at all the applicable visits.
- Investigator evaluation
- Subject made a successful repeat attempt at injection
- The investigator/site staff entered explanatory text under the 'device failure' section on the eCRF describing the user error.
- Root-cause analysis concluded no device error occurred (204959 CSR Section 15.4).
- This error was classified as unsuccessful per-protocol. Despite incorrect injection site, subject received the dose of study treatment on initial attempt.

Device usability and functionality

Responses from the usability/functionality questionnaire revealed an overall positive experience from subjects (or their caregivers) regarding the training provided by the investigator/site staff, clarity of the IFU, and the usability of the standard device label + pictogram autoinjector or the standard device label autoinjector (Table 13).

Subjects/caregivers felt comfortable with the in-clinic training provided on the autoinjector, and only a small percentage of subjects (11% to 12%) requested additional guidance (review of the IFU and/or answering questions related to the IFU) prior to the unobserved, at home injection. Most subjects/caregivers found the IFU steps to be clear and understandable.

Most subjects/caregivers felt confident using the autoinjector based on the IFU and their ability, and found it easy and convenient to use. Nearly all of the 153 subjects questioned (99%) expressed that they would recommend the mepolizumab liquid drug product in an autoinjector to other patients with asthma. Of the subjects previously receiving mepolizumab administered by a HCP (n=72), almost all (96%) expressed a preference for receiving mepolizumab using an autoinjector at home rather than an injection administered by a HCP.

Table 13 Device Usability and Functionality Questionnaire Summary (Real-World Use Study 204959, All Subjects)

Response to Question	Number (%) of Subjects	
	Mepolizumab Liquid Autoinjector	
	Standard device label + pictogram N=104	Standard device label N=55
n completing questionnaire	102	51
Very or extremely comfortable with in-clinic training provided	98 (96)	45 (88)
Requested additional guidance prior to at-home injection	12 (12)	6 (11)
IFU steps very or extremely clear and understandable ¹	94 (92) to 98 (96)	45 (88) to 47 (92)
Very or extremely confident using autoinjector on your own based on the IFU	97 (95)	46 (90)
At the end of the study, very or extremely confident in ability to use autoinjector correctly on your own	98 (97)	45 (88)
Autoinjector is very or extremely easy to use at home	94 (92)	44 (86)
Very or extremely convenient to receive mepolizumab using the autoinjector at home	97 (95)	47 (92)
Would recommend autoinjector to other patients with asthma	100 (98)	51 (100)
Prefer to use autoinjector at home rather than have administered by HCP ²	45/47 (96)	24/25 (96)

Source: 204959 CSR Table 7.9, Table 7.10, Table 7.11, and Table 7.12

1. Questions were asked on various individual steps in the IFU
2. Question only asked for subjects receiving mepolizumab at baseline

Exit interviews

Responses from the Exit Interviews conducted in a subset of 25 subjects at selected sites who used either the standard device label + pictogram autoinjector (n=11) or the standard device label autoinjector (n=14), were consistent with the positive findings from the device usability/functionality questionnaire. During the interviews, subjects generally expressed that feelings of anxiety or concern associated with autoinjector use decreased after the first administration. All subjects reported that the ease and convenience of self-administering mepolizumab using the autoinjector underpinned their positive impressions and all interviewed subjects saw no problems in incorporating the self-injection using the autoinjector into their lifestyles. Around half (48%) of subjects stated that they felt pain when using the autoinjector, but stated that it was mild and localised to the injection site.

Reliability

No substantiated device failures occurred with the autoinjector during the Real-World Use clinical study. Additionally, when 100 of the returned autoinjectors used by subjects/caregivers in Study 204959 were inspected as a representative sample of used autoinjectors, no undetected malfunctions were found.

Safety syringe assessment (Study 205667)

Assessment of injection success

In the Real-World Use study, a 100% injection success rate was reported across all injection endpoints with the safety syringe (Table 9). All subjects/caregivers were reported by the investigator/site staff to have successfully self-administered their first, second, and third dose of mepolizumab liquid drug product using the safety syringe.

Table 9 Proportion of Subjects Successfully Able to Self-Administer Mepolizumab by Visit (Real-World Use Study 205667, Safety Population)

Timepoint	Mepolizumab Liquid Safety Syringe N=56		
	Attempted Injection(s)	Successful Injections ^{1,2}	
	n	n (%)	95% CI
Week 0, First Dose (observed in the clinic)	56	56 (100)	94, 100
Week 4, Second Dose (unobserved at home)	56	56 (100)	94, 100
Week 8, Third Dose Primary endpoint (observed in the clinic)	55	55 (100)	94, 100
Weeks 4 and 8	55	55 (100)	94, 100
Weeks 0, 4 and 8	55	55 (100)	94, 100

Source: 205667 CSR Table 7.1.

1. The denominator was the number of subjects/caregivers attempting an injection at that visit. Where multiple visits were assessed, the denominator was the number of subjects/caregivers attempting an injection at all the applicable visits
2. Investigator evaluation.

Device usability and functionality

Responses from the usability/functionality questionnaire revealed an overall positive experience from subjects (or their caregivers) regarding the training provided by the investigator/site staff, the IFU, and the usability of the safety syringe (Table 10).

Most subjects/caregivers were comfortable with the training provided on the safety syringe and only a small number of subjects (6 subjects, 11%) requested additional guidance (review of the IFU and/or answering questions related to the IFU) prior to the unobserved, at home injection. Most subjects/caregivers found the IFU steps to be clear and understandable.

Most subjects/caregivers felt confident using the safety syringe based on the IFU and their ability, and found it easy and convenient to use. All but one of the 56 subjects questioned (98%) expressed that they would recommend the mepolizumab liquid drug product in a safety syringe to other patients with asthma. Of the subjects previously receiving mepolizumab administered by a HCP (n=23), all but one (96%) expressed a preference for receiving mepolizumab using a safety syringe at home rather than an injection administered by a HCP.

Table 10 Device Usability and Functionality Questionnaire Summary (Real-World Use Study 205667, All Subjects)

Response to Question	Number (%) of Subjects
	Mepolizumab Liquid Safety Syringe N=56
n completing questionnaire	56
Very or extremely comfortable with in-clinic training provided	48 (86)
Requested additional guidance prior to at-home injection	6 (11)
IFU steps very or extremely clear and understandable ¹	51 (91) to 55 (98)
Very or extremely confident using safety syringe on your own based on the IFU	50 (89)
At the end of the study, very or extremely confident in ability to use safety syringe correctly on your own	51 (91)
Safety syringe is very or extremely easy to use at home	46 (82)
Very or extremely convenient to receive mepolizumab using the safety syringe at home	46 (82)
Would recommend safety syringe to other patients with asthma	55 (98)
Prefer to use safety syringe at home rather than administered by HCP ²	22/23 (96)

Source: 205667 CSR Table 7.4 and Table 7.5

1. Questions were asked on various individual steps in the IFU
2. Question only asked for subjects receiving mepolizumab at baseline

Exit interviews

Responses from the Exit Interviews conducted in a subset of subjects at selected sites (n=7) were consistent with the positive findings from the device usability/functionality questionnaire. During the interviews, subjects expressed that the text and pictures on the IFU were detailed and easy to understand, that feelings of anxiety associated with safety syringe use decreased and their confidence increased as they became more familiar with the device, and minimal to no discomfort was associated with use of the safety syringe.

Reliability

No device failures were reported with the safety syringe device during the Real-World Use clinical study.

Overall conclusions

- The device assessment results have shown that:
- The autoinjector and safety syringe can be correctly used by a representative population to successfully perform a self-injection procedure.
- The representative patient population and their caregivers can comprehend, learn from, and utilize the IFU to successfully administer a dose of medication.
- The IFU are understood by HCPs and are sufficient to utilize for any training that is required for their patients.
- Patients are confident with self-administration outside of the clinical setting.
- The autoinjector and safety syringe are reliable; no device failures occurred.

Summary and evaluation of Human Factors studies on the instructions for use in the Nucala leaflet.

A product-line extension for Nucala 100 mg solution for subcutaneous injection in pre-filled pen or pre-filled syringe. This medicine is administered, by 4-weekly subcutaneous (SC) injection; it may be self-administered by the patient, or administered by a caregiver, if their healthcare professional determines that it is appropriate and the patient or caregiver is trained in injection techniques.

The package leaflet (PL) for Nucala 100 mg solution for injection is supplied in a multi-part assembly, with a separate, detachable leaflet for each language. Sections 1 to 6 of the PL are printed on one side of the leaflet; on the other side are the Instructions for Use (IFU) of the device used for injection—the pre-filled pen or pre-filled syringe.

Development and testing of the US IFU

The IFU were originally developed in the US, where—together with the relevant injection device — they were subject to usability testing, in the form of two comprehensive Human Factors Validation studies carried out and completed in April 2018. Testing was conducted in an environment designed to simulate that of a medical clinic or a home, as applicable to the participant group.

For the pre-filled pen, the study was conducted with a total of 75 participants (see below for an explanation of ‘trained’ and ‘untrained’):

- ◆15 adult asthma patients—‘untrained’
- ◆15 juvenile asthma patients—‘trained’
- ◆15 adult COPD patients—‘trained’
- ◆15 adult family caregivers—‘untrained’
- ◆15 healthcare providers (HCPs)—‘untrained’

For the pre-filled syringe, the study was conducted with a total of 90 participants:

- ◆15 adult asthma patients—‘untrained’
- ◆30 juvenile asthma patients—15 ‘trained’; 15 ‘untrained’
- ◆30 adult COPD patients — 15 ‘trained’; 15 ‘untrained’
- ◆15 adult caregivers—‘untrained’

No participant had prior experience of the IFU being tested. A minority had previously used a pre-filled pen or pre-filled syringe for injecting other products.

Participants were selected across a wide demographic range, in terms of age, education and other ability-affecting conditions such as visual, motor or neurological impairment.

The family caregivers were people with experience of caring for someone with any medical condition.

The HCPs were selected to represent those who might treat patients with asthma or COPD and might be responsible for training them to use the pre-filled pen or pre-filled syringe.

The study was designed to reflect as accurately as possible the circumstances in which Nucala will be used. All injections performed were simulated into an injection pad placed over the injection site assigned to the participant, or placed onto a manikin for caregivers and HCPs.

Caregivers and HCPs were all assigned the upper arm as injection site; other participants were assigned the abdomen or thigh, in equal numbers.

'Trained' participants (juvenile asthma patients and adult COPD patients) attended one training session, during which they reviewed the IFU and were given a verbal description of the injection procedure (but no actual demonstration). At the end of this first session, they performed one supervised injection. Approximately one week later, they attended a second session, when they performed one unaided injection, answered comprehension and knowledge probe questions, and gave feedback on the IFU.

All other participants ('untrained') attended a single session, at which they were given time to familiarise themselves with the IFU and device, then performed one unaided injection, answered comprehension and knowledge probe questions, and gave feedback on the IFU.

Performance

For the pre-filled pen, 73 of the 75 participants (97%) were successful in injecting to achieve a full dose of Nucala. Two participants lifted the pen from the skin early, which would have resulted in an incomplete dose—one 'trained' patient was not referring to the IFU when she carried out the injection, thinking she could do it from memory; one 'untrained' caregiver did not thoroughly read the IFU before injecting. Neither failure could therefore be attributed to inadequacies in the IFU.

For the pre-filled syringe, all 90 participants (100%) successfully carried out the full injection procedure to achieve a full dose of Nucala.

There was no significant difference in performance between 'trained' and 'untrained' participants.

Knowledge and comprehension

For the pre-filled pen, there was a 99.7% success rate for correctly answering specific knowledge probe questions, demonstrating that users could correctly identify and interpret information in the IFU regarding:

- ◆ storage of the pen before use
- ◆ leaving the pen for 30 minutes to come to room temperature before injecting
- ◆ how to dispose of a used pen (*US-specific*)

There was a 100% success rate for comprehension of information about all stages of the preinjection and injection procedure.

For the pre-filled syringe, there was a 99.7% success rate for correctly answering specific knowledge probe questions, demonstrating that users could correctly identify and interpret information in the IFU regarding:

- ◆ storage of the pen before use
- ◆ how to inspect the solution in the pen before use
- ◆ the need to wait 30 minutes for the solution to reach room temperature
- ◆ the allowable injection sites
- ◆ how to dispose of a used pen (US-specific)

There was a 99.8% success rate for comprehension of information about all stages of the preinjection and injection procedure.

Subjective feedback

Asked for general feedback on the quality of the IFU, all participants stated that they found it easy to read, understand and follow.

Modification of the IFU for EU markets

Some relatively minor amendments were made to the IFU for the EU PL, while preserving the essential elements of structure, design, layout and wording of the US version. This is acceptable for the CHMP.

Conclusions and recommendations

The MAH conducted two human factor studies for the prefilled syringe and the prefilled pen. The studies enrolled adult and juvenile patients, caregivers and healthcare professional and consisted of both trained and untrained cohorts.

For the pre-filled pen, enrolled 75 patients of which 73 participants (97%) were successful in injecting to achieve a full dose of Nucala. There was a 99.7% success rate for correctly answering specific knowledge probe questions, demonstrating that users could correctly identify and interpret information

For the pre-filled syringe, enrolled 90 patients, all 90 (100%) successfully carried out the full injection procedure to achieve a full dose of Nucala.

There was no significant difference in performance between 'trained' and 'untrained' participants.

There was a 99.8% success rate for comprehension of information about all stages of the preinjection and injection procedure.

To further reduce risk of incorrect administration the SPC currently states Nucala may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate and the patient or caregiver are trained in injection techniques.

2.4.8. Discussion on clinical efficacy

The methodology of the two real-world use studies (204959 and 205667) is acceptable. The applicant's conclusions are supported. These studies demonstrated the usability of the auto-injector and safety syringe, including self-administration outside of the clinic, in patients with severe eosinophilic asthma. The efficacy data are limited in this application however this is acceptable as it pertains to the approval of a new formulation. No major objections or other concerns are raised.

The two human factor studies were well designed and competently conducted. The results constitute sufficient validation that the Instructions For Use in the EU PL are readable, comprehensible and usable by the target user population.

2.4.9. Conclusions on clinical efficacy

The two real-world use studies (204959 and 205667) demonstrated the usability of the auto-injector and safety syringe, including self-administration outside of the clinic, in patients with severe eosinophilic asthma. The results of the two human factor studies can be taken to constitute sufficient validation that the IFU in the EU PL are readable, comprehensible and usable by the target user population. No further testing of the IFU for the EU PL is recommended.

2.5. Clinical safety

Patient exposure

Mepolizumab is currently authorized as a lyophilised powder (100 mg single-dose vial), reconstituted in 1 mL of sterile water for injection prior to subcutaneous (SC) injection. GlaxoSmithKline (GSK) has developed mepolizumab as a liquid drug product which will be provided as a solution (100 mg/mL) in a prefilled syringe assembled into either a safety syringe or an autoinjector device. In this section the safety data available for liquid formulations are being discussed. A total of 196 patients with severe eosinophilic asthma received ≥ 1 dose of mepolizumab 100 mg SC in real-world use (RWU) studies. The majority of subjects in the RWU Studies (71%) participated in only the autoinjector Study 204959 and represented a maximum of 3 months exposure. Nineteen subjects (10%) enrolled and received mepolizumab liquid drug product in both studies (Study 205667 followed by Study 204959) and represented a maximum of 6 months exposure. Demographic and baseline characteristics of patients enrolled to RWU studies was similar to those enrolled into the pivotal studies e.g. 60 % of subjects were females, the mean age was around 50, the majority of patients were white.

Table 1 - Subjects Treated with Mepolizumab 100 mg SC (RWU Studies, Safety Population)

Study	Number (%) of Subjects
RWU Studies, N	196
Study 205667 only	37 (19)
Study 204959 only	140 (71)
Study 205667 followed by Study 204959	19 (10)

Table 2 - Mepolizumab Exposure (RWU Studies, Safety Population)

	Mepolizumab Liquid 100 mg SC		
	205667 Safety Syringe N=56	204959 Autoinjector N=159	RWU Studies N=196 ¹
Treatment Exposure (months)			
Mean (SD)	2.80 (0.219)	2.78 (0.233)	3.06 (0.833)
Median	2.79	2.79	2.79
Min, Max	2.0, 3.3	1.0, 3.1	1.0, 5.9
Range of Exposure², n (%)			
1 month	0	2 (1)	2 (1)
2 months	5 (9)	1 (<1)	2 (1)
3 months	51 (91)	156 (98)	173 (88)
4 months	NA	NA	0
5 months	NA	NA	8 (4)
6 months	NA	NA	11 (6)
Total Subject-years^{3,4}	---	---	49.96

In addition 244 healthy adult subjects received a single dose of mepolizumab 100 mg SC in study 204958 e.g 85 subjects received lyophilised drug product, 80 subjects received liquid drug product in a safety syringe, and 79 subjects liquid drug product in an autoinjector.

Finally 245 subjects with nasal polyposis are being treated with Mepolizumab liquid drug product or placebo in ongoing phase III randomised, double-blind, placebo-controlled study.

The Applicant confirmed that there is no post-marketing data are available for liquid formulations.

Adverse events

1. 2 real-world use studies: 205667- safety syringe and 204959- autoinjector

A total of 71 subjects (36%), including 5/11 adolescents enrolled, reported on-treatment AEs, and 6 subjects (3%) reported events considered related to mepolizumab by the investigator.

Two subjects (1%) had events which led to treatment discontinuation and study withdrawal (1 subject due to an SAE of asthma and 1 subject due to 6 SAEs associated +with a road traffic accident). On-treatment SAEs were reported for 7 subjects (4%), none of which were fatal.

Table 3 - Adverse Event Summary (RWU Studies, Safety Population)

Adverse Event Type	Number (%) of Subjects		
	Mepolizumab Liquid 100 mg SC		
	205667 Safety Syringe N=56	204959 Autoinjector N=159	RWU Studies N=196 ¹
Adverse events			
All adverse events	NR	NR	75 (38)
On-treatment	17 (30)	56 (35)	71 (36)
Drug-related ²	2 (4)	5 (3)	6 (3)
Post-treatment	0	5 (3)	5 (3)
Led to treatment discontinuation/study withdrawal	1 (2)	1 (<1)	2 (1)
Serious adverse events			
All serious adverse events	NR	NR	8 (4)
Pre-treatment	0	1 (<1)	1 (<1)
On-treatment	3 (5)	4 (3)	7 (4)
Drug-related ²	0	0	0
Post-treatment	0	0	0
Fatal	0	0	0

AEs in the Infections and infestations SOC were the most commonly ($\geq 3\%$) reported during the treatment period in the RWU Studies (20% of subjects). AEs in the Respiratory, thoracic, and mediastinal disorders SOC were the next most frequently reported (8% of subjects).

Table 4 - On-treatment Adverse Events by System Organ Class ($\geq 3\%$ Incidence in the RWU Studies) (RWU Studies, Safety Population)

Adverse Event System Organ Class	Number (%) of Subjects		
	Mepolizumab Liquid 100 mg SC		
	205667 Safety Syringe N=56	204959 Autoinjector N=159	RWU Studies N=196 ¹
Any event	17 (30)	56 (35)	71 (36)
Infections and infestations	9 (16)	31 (19)	39 (20)
Respiratory, thoracic and mediastinal disorders	4 (7)	12 (8)	16 (8)
General disorders and administration site conditions	2 (4)	11 (7)	12 (6)
Injury, poisoning and procedural complications	0	12 (8)	12 (6)
Musculoskeletal and connective tissue disorders	1 (2)	9 (6)	10 (5)
Nervous system disorders	0	10 (6)	10 (5)
Gastrointestinal disorders	2 (4)	3 (2)	5 (3)
Investigations	0	5 (3)	5 (3)

Common Adverse Events

The most commonly ($\geq 3\%$) reported on-treatment AEs in the RWU Studies were nasopharyngitis (5%), headache (4%), upper respiratory tract infection (4%), and urinary tract infection (3%)

Table 5 - Common ($\geq 3\%$ Incidence in the RWU Studies) On-Treatment Adverse Events (RWU Studies, Safety Population)

Adverse Event Preferred Term	Number (%) of Subjects		
	Mepolizumab Liquid 100 mg SC		
	205667 Safety Syringe N=56	204959 Autoinjector N=159	RWU Studies N=196 ¹
Any event	17 (30)	56 (35)	71 (36)
Nasopharyngitis	0	9 (6)	9 (5)
Headache	0	8 (5)	8 (4)
Upper respiratory tract infection	1 (2)	6 (4)	7 (4)
Urinary tract infection	1 (2)	5 (3)	6 (3)

Safety in healthy subjects — study 204958

In total, 34% of subjects reported an on-treatment AE (29%, 34%, and 38% for the lyophilised drug product, liquid drug product in an autoinjector, and liquid drug product in a safety syringe, respectively). Headache (9%), viral upper respiratory tract infection (5%) and fatigue (3%) were the most frequently reported AEs across the treatment groups.

Twenty two percent of subjects had AEs that were considered related to mepolizumab by the investigator (20%, 22%, and 25% for the lyophilised drug product, liquid drug product in an autoinjector, and liquid drug product in a safety syringe, respectively) with headache (7%) and fatigue (4%) reported most frequently. No on-treatment SAEs or fatal SAEs were reported during the study.

Table 6 - Adverse Event Summary (Study 204958, Safety Population)

Adverse Event Type Preferred term ¹	Number (%) of Subjects				
	Mepolizumab 100 mg SC				
	Lyophilised N=85	Liquid- Safety Syringe N=80	Liquid- Autoinjector N=79	Total Liquid N=159	Total Mepo N=244
Any on-treatment event	25 (29)	30 (38)	27 (34)	57 (36)	82 (34)
Occurring in $\geq 3\%$ of subjects ²					
Headache	6 (7)	8 (10)	9 (11)	17 (11)	23 (9)
Viral upper respiratory tract infection	2 (2)	6 (8)	3 (4)	9 (6)	11 (5)
Fatigue	5 (6)	1 (1)	2 (3)	3 (2)	8 (3)
Any drug-related event³	17 (20)	20 (25)	17 (22)	37 (23)	54 (22)
Occurring in $\geq 1\%$ of subjects ²					
Headache	4 (5)	7 (9)	5 (6)	12 (8)	16 (7)
Fatigue	5 (6)	2 (3)	2 (3)	4 (3)	9 (4)
Back pain	1 (1)	2 (3)	0	2 (1)	3 (1)
Diarrhoea	1 (1)	1 (1)	1 (1)	2 (1)	3 (1)
Dizziness	1 (1)	2 (3)	0	2 (1)	3 (1)
Hypersensitivity	2 (2)	1 (1)	0	1 (<1)	3 (1)
AEs leading to study withdrawal	0	0	0	0	0
Any SAE	1 (1)	0	0	0	1 (<1)
On-treatment	0	0	0	0	0
Post-treatment ⁴	1 (1)	0	0	0	1 (<1)
Fatal	0	0	0	0	0

Serious adverse events and deaths

In the RWU Studies twelve on-treatment non-fatal SAEs were reported for 7 subjects however none of these SAEs were considered related to mepolizumab by the investigator. No deaths were reported.

No on-treatment SAEs or fatal SAEs were reported during study 204958 in healthy subjects.

Laboratory findings

There were no apparent treatment effects on clinical chemistry, liver function tests or haematology values were seen in the RWU Studies.

Safety in special populations

No apparent differences in the safety profile in special populations enrolled to the RWU studies were noted. Only 11 subjects in the 12-17-year subgroup participated in the RWU studies. 5 out 11 subjects reported any AE. The AEs (PTs) reported by the 12-17-year subgroup were similar to the other subgroups and to the overall population. The overall incidence of on-treatment AEs was 40% in females and 31% in males, and overall AE profiles were similar for males and females. The white racial group comprised most of the population (161/196

subjects) and the profile of AEs by SOC in this subgroup was similar to the overall population. All other racial groups had few subjects.

Immunological events

1. Real-world use studies: 205667- safety syringe and 204959- autoinjector

ADA assessments were conducted for all 196 subjects at Baseline and 192 subjects at Week 12/EW Visit (as applicable). Positive ADA results were reported for a total of 7 subjects (4%) at Baseline and 4 subjects (2%) at the Week 12/EW Visit. Of the subjects with a positive ADA result at Baseline all but 2 were receiving mepolizumab at Screening. Of the subjects with a positive ADA result at Week 12, 1 was receiving current treatment with mepolizumab at Screening. There were 2 subjects who had positive ADA results at both Baseline and Week 12. 1 was receiving mepolizumab at Screening and the other was not. No subject positive for ADAs tested positive for neutralising antibodies. None of the 19 subjects who participated in both studies tested positive for ADAs.

One subject who was not receiving mepolizumab at Screening, tested positive at both Baseline and at the Week 12 visit, and had an increase in titre value from 16 at Baseline to 5120 at Week 12. This 40 year old female had not participated in any other mepolizumab clinical trials prior to Study 204959.

The reported current medical conditions at baseline were eosinophilic asthma, nasal polyps, sinusitis, and hypercholesterolemia. The 1 AE reported for this subject was a non-serious event of injection site haemorrhage, of mild intensity that resolved within 10 days. This subject completed the study. For this subject, the mepolizumab plasma trough concentration values remained similar during the treatment period with no evidence of accumulation of drug despite repeat dosing following mepolizumab treatment initiation (204959 CSR Listing 20). There was no evidence of mepolizumab PD (blood eosinophil counts) being affected by the presence of ADAs (204959 CSR Listing 41).

Table 7 - Summary of Baseline and Post-Baseline Binding ADA Assay Results (RWU Studies, Safety Population)

	Mepolizumab Liquid 100 mg SC					
	205667 Safety Syringe N=56		204959 Autoinjector N=159		RWU Studies N=196 ¹	
Baseline Mepolizumab Use	No	Yes	No	Yes	No	Yes
Week 0 (Baseline), n	33	23	75	83	108	88
Negative, n (%)	32 (97)	21 (91)	74 (99)	80 (96)	106 (98)	83 (94)
Positive, n (%)	1 (3)	2 (9)	1 (1)	3 (4)	2 (2)	5 (6)
Titre value, median	80	20	16	8	48.0	8.0
Min, Max	80, 80	8, 32	16, 16	8, 8	16, 80	8, 32
Week 12/EW Visit, n	31	22	74	84	105	87
Negative, n (%)	30 (97)	21 (95)	72 (97)	84 (100)	102 (97)	86 (99)
Positive, n (%)	1 (3) ²	1 (5)	2 (3) ³	0	3 (3)	1 (1)
Titre value, median	128.0	32.0	2576.0	---	128.0	32.0
Min, Max	128, 128	32, 32	32, 5120	---	32, 5120	32, 32

Among the 4 subjects with positive ADA results at the Week 12, 2 subjects reported on-treatment AEs during the study. On subject a 44 year old female reported 4 AEs: dyspepsia, tachycardia, fatigue (all of moderate intensity), and wheezing (severe intensity); none considered related to mepolizumab by the investigator. All events occurred after the first dose, were non-serious, resolved with continued study treatment, and the subject completed the study.

2. Safety in healthy subjects — study 204958

ADA assessments were conducted at 5 visits during the study, Screening, Day 1 (Baseline), Day 29, Day 43, and Follow-up.

Positive ADA results were reported for 11 subjects (5%) post-Baseline: 4%, 4%, and 6% for the lyophilised drug product, liquid drug product in safety syringe, and liquid drug product in autoinjector respectively. None of whom tested positive for neutralising antibodies.

ADA measurements for 9 subjects were classified as persistent positive.

Titres were generally low, with a maximum titre of 320 observed at Study Day 29 in 1 subject treated with the liquid drug product in a safety syringe.

None of the 9 subjects with persistent positive post-Baseline ADA results reported on-treatment AEs. One of the 2 subjects who had a transient positive ADA result on Study Day 29 (titre value: 16), reported non-serious AEs of oropharyngeal discomfort at Study Day 2 and an event of systemic reaction (hypersensitivity) with symptom of pruritus at Study Day 13 categorised as other systemic reaction by the investigator.

Table 8 - Summary of ADA Confirmatory Assay Results at Baseline and at Any Post-Baseline Visit (Study 204958, Safety Population)

	Number (%) of Subjects				
	Mepolizumab 100 mg SC				
	Lyophilised N=85	Liquid- Safety Syringe N=80	Liquid- Autoinjector N=79	Total Liquid N=159	Total Mepo N=244
Day 1 (Baseline), n	85	80	79	159	244
Negative	83 (98)	80 (100)	79 (100)	159 (100)	242 (>99)
Positive	2 (2)	0	0	0	2 (<1)
Any post-Baseline visit, n	84	80	79	159	243
Negative	81 (96)	77 (96)	74 (94)	151 (95)	232 (95)
Positive ¹	3 (4)	3 (4)	5 (6)	8 (5)	11 (5)
Transient positive	1 (1)	0	1 (1)	1 (<1)	2 (<1)
Persistent positive	2 (2)	3 (4)	4 (5)	7 (4)	9 (4)
Titre value ² , median	16.0	256.0	32.0	32.0	32.0
Min, Max	16, 32	32, 320	8, 32	8, 320	8, 320

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted. No new data were provided.

Discontinuation due to AES

Two subjects (1%) were discontinued from treatment and withdrawn from the RWU Studies for the reason of AEs 1 subject due to an asthma exacerbation and 1 subject due to 6 SAEs associated with a road traffic accident.

No subject was withdrawn due to AES from study 204958 in healthy subjects.

Post marketing experience

There is no post-marketing data are available for liquid formulations.

2.5.1. Discussion on clinical safety

A total of 196 patients with severe eosinophilic asthma received ≥ 1 dose of mepolizumab 100 mg SC in real-world use (RWU) studies. The majority of subjects in the RWU Studies (71%) participated in only the autoinjector Study 204959 and represented a maximum of 3 months exposure. Nineteen subjects (10%) enrolled and received mepolizumab liquid drug product in both studies (Study 205667 followed by Study 204959) and represented a maximum of 6 months exposure. Demographic and baseline characteristics of patients enrolled to RWU studies was similar to those enrolled into the pivotal studies e.g. 60 % of subjects were females, the mean age was around 50, the majority of patients were white.

In addition 244 healthy adult subjects received a single dose of mepolizumab 100 mg SC in study 204958 e.g 85 subjects received lyophilised drug product, 80 subjects received liquid drug product in a safety syringe, and 79 subjects liquid drug product in an autoinjector.

Finally 245 subjects with nasal polyposis are being treated with Mepolizumab liquid drug product or placebo in ongoing phase III randomised, double-blind, placebo-controlled study.

In real-world use (RWU) studies a total of 71 subjects (36%), including 5/11 adolescents enrolled, reported on-treatment AEs, and 6 subjects (3%) reported events considered related to mepolizumab by the investigator. The types of common adverse events reported during the RWU Studies were similar to those reported in the pivotal studies. The most commonly ($\geq 3\%$) reported on-treatment AEs in the RWU Studies were nasopharyngitis (5%), headache (4%), upper respiratory tract infection (4%), and urinary tract infection (3%). However the data is very limited in duration and in terms of adolescents therefore longer term safety is not well documented and comparative safety to adults cannot be concluded however is not anticipated to be different.

In the RWU Studies twelve on-treatment non-fatal SAEs were reported for 7 subjects however none of these SAEs were considered related to mepolizumab by the investigator. No deaths were reported.

In a single dose study in healthy subjects on-treatment AEs were reported in 34% of subjects (29%, 34%, and 38% for the lyophilised drug product, liquid drug product in an autoinjector, and liquid drug product in a safety syringe, respectively). The type and frequency of reported AEs do not raise concern. No on-treatment SAEs or fatal SAEs were reported during this study.

Adverse events of special interest (AESI) that were prospectively identified in the severe asthma programme and remained AESIs throughout the mepolizumab clinical programme include:

- systemic (allergic [type I hypersensitivity] and other systemic) reactions,
- local injection site reactions,
- infections, including serious and opportunistic, malignancies,
- serious cardiac, vascular, and thromboembolic (CVT) events.

Anaphylaxis or allergic/Type I hypersensitivity was not reported in the RWU studies nor in healthy subject studies. Other type systemic reactions were reported for 12 subjects (1 in the RWU studies and 11 in healthy subject studies). All but 1 were of mild or moderate intensity. One subject who received mepolizumab liquid drug product reported the non-serious AE of drug hypersensitivity with an intensity of severe 6 days after dosing. Symptoms included fatigue, pharyngeal discomfort, swallowing difficulties, acute diarrhoea and submandibular swelling. The event had a duration of 4 days and was reported as recovered/resolved. The SmPC includes the following statement: Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of Nucala.

In the RWU studies 9 local injection site reactions were reported for 5 subjects (3%) including 2 adolescents. One subject, an adolescent who participated in both Study 205667 and Study 204959, reported 5 injection site reactions (3 injection site erythema and 2 injection site reaction), 2 of mild intensity and 3 of moderate.

In the healthy subjects study, events of local injection site reaction were reported for 4 subjects (2%): 1 subject in the lyophilised drug product group, 1 subject in the liquid drug product autoinjector and 2 subjects in the liquid drug product safety syringe group.

The following information is present in the SmPC for Nucala in relation to local injection site reactions: In 2 placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment

and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

No serious infections, malignancy, or serious CVT events were reported.

The currently available data from the severe asthma studies indicating that mepolizumab has low immunogenic potential. In the context of the current procedure the ADA responses were investigated in the two real-world use studies where patients were treated with new liquid formulations only (205667- safety syringe and 204959- autoinjector). In addition the ADA responses were investigated in study 204958 in healthy subjects where the currently approved lyophilised drug product as well as new liquid drug products were tested.

In the RWU studies the applicant investigated the antibody response at baseline and at week 12 (at end of trial visit). No assessment of ADA response at follow up was performed in the RWU studies.

In these studies the positive ADA results were reported for a total of 7 subjects (4%) at Baseline and 4 subjects (2%) at the Week 12/EW Visit. No subject positive for ADAs tested positive for neutralising antibodies. In general in the RWU studies the ADA response seems to be not greater than the ADA response observed in the originally submitted pivotal studies although the comparison between these studies is difficult e.g. a short duration of the RWU studies and the lack of the follow-up assessment is likely to underestimate the overall antibody occurrence.

One subject who was not receiving mepolizumab at Screening, tested positive at both Baseline and at the Week 12 visit, and had an increase in titre value from 16 at Baseline to 5120 at Week 12. 1 AE reported for this subject was a non-serious event of injection site haemorrhage, of mild intensity that resolved within 10 days. As indicated by the applicant no changes in PK profile of mepolizumab in this subject was reported. Such high titre value was not reported in any subject in three pivotal studies. One additional subject with the ADA positive response reported 4 AEs: dyspepsia, tachycardia, fatigue (all of moderate intensity), and wheezing (severe intensity).

In study healthy subjects (study 204958) ADA assessments were conducted at 5 visits during the study e.g. at Screening, Day 1 (Baseline), Day 29, Day 43, and Follow-up. In this study positive ADA results were reported for 11 subjects (5%) post-Baseline: 4%, 4%, and 6% for the lyophilised drug product, liquid drug product in safety syringe, and liquid drug product in autoinjector respectively. None of whom tested positive for neutralising antibodies. ADA measurements for 9 subjects were classified as persistent positive. One subject with the positive ADA response reported non-serious AEs of oropharyngeal discomfort at Study Day 2 and an event of systemic reaction (hypersensitivity) with symptom of pruritus at Study Day 13.

Based on the provided data, no apparent differences in the ADA response between lyophilised drug product and liquid drug products were noted.

AEs were reported in single patients with the positive ADA response e.g 2 subjects in the RWS and 1 subject in study 204958.

No apparent differences in the safety profile in special populations enrolled to the RWU studies were noted, although the data is quite limited. Only 11 subjects in the 12-17-year subgroup participated in the RWU studies. 5 out of 11 subjects reported any AE. The AEs (PTs) reported by the 12-17-year subgroup were similar to the other subgroups and to the overall population. The overall incidence of on-treatment AEs was 40% in females and 31% in males, and overall AE profiles were similar for males and females. The White racial group comprised most of the population (161/196 subjects) and the profile of AEs by SOC in this subgroup was similar to the overall population. All other racial groups had few subjects.

The above safety data collated in the PK comparability study 204958 and Real World Use studies 204959 and 205667 with the liquid drug product give reassurance regarding the safety profile of new liquid formulation .

Comparable in-vitro biochemical and biophysical properties, together with the same drug product specifications for the liquid and lyophilized products and comparable systemic exposure between the liquid and lyophilized drug products in the pharmacokinetic study (PK comparability study 204958) concur to provide bridge between the formulations. Overall no new safety findings were observed with the new formulation compared to the current approved lyophilized product.

2.5.2. Conclusions on clinical safety

No major safety issues were identified in the clinical data provided with the new formulation. The safety profile is considered comparable to the safety profile observed with the current formulation.

2.6. Risk Management Plan

Safety concerns

Important identified risks	Systemic Allergic and Non-Allergic Reactions
Important potential risks	Alterations in immune response (malignancies) Alterations in cardiovascular safety
Missing information	Limited data in pregnant and lactating patients

Pharmacovigilance plan

Study 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 The Mepolizumab Pregnancy Exposure Study: a VAMPSS post marketing surveillance study of Mepolizumab safety in	To evaluate outcomes for pregnant women with asthma and their infants exposed to mepolizumab	Use in patients who become pregnant while taking mepolizumab.	Final report	2Q 2024

pregnancy				
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Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety concern 1 Systemic allergic/hypersensitivity and non-allergic reactions	<p>Routine risk minimisation measures:</p> <p>The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions) and Section 4.8 (Undesirable effects). Equivalent wording is included in the patient leaflet Section 2 and Section 4.</p> <p>Additional risk minimisation measures:</p> <p>None</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>As standard across all GSK products, a targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis.</p> <p>Additional pharmacovigilance activities:</p> <p>None</p>
Safety concern 2 Potential Risk of Alterations in immune response (malignancies)	<p>Routine risk minimisation measures:</p> <p>None proposed</p> <p>Additional risk minimisation measures:</p> <p>None</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>None</p> <p>Additional pharmacovigilance activities:</p> <p>None</p>
Safety concern 3 Potential Risk of Alterations in cardiovascular safety	<p>Routine risk minimisation measures:</p> <p>None proposed</p> <p>Additional risk minimisation measures:</p> <p>None</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>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.</p> <p>Additional pharmacovigilance activities:</p> <p>None</p>
Safety concern 4 Limited data in pregnant and lactating patients	<p>Routine risk minimisation measures:</p> <p>The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available on NUCALA.</p> <p>Additional risk minimisation measures:</p> <p>None</p>	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <p>None</p> <p>Additional pharmacovigilance activities:</p> <p>The Mepolizumab Pregnancy Exposure Study (200870): a VAMPSS post marketing</p>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		surveillance study of Mepolizumab safety in pregnancy

Conclusion

The CHMP and PRAC considered that the risk management plan version 6 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. 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: There is no need to submit a user testing for the proposed changes.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nucala (mepolizumab) is already included in the additional monitoring list.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is a chronic airway disease affecting approximately 334 million people worldwide and is responsible for approximately 250,000 premature deaths each year.

Asthma prevalence varies by geographical region. Accurate assessment of the prevalence of asthma has been hindered by varying definitions of asthma and methods of data collection, each combining to make data comparison across studies difficult.

Risk factors include sex (gender influence varies with age), airway hyper reactivity, atopy, allergens, infections, tobacco smoke, obesity, and perinatal factors.

Asthma is common in adolescents but is frequently undiagnosed because of under-reporting of symptoms.

There is no single diagnostic test for asthma, the diagnosis is a clinical one. The absence of consistent gold-standard diagnostic criteria means that it is not possible to make unequivocal evidence-based recommendations on how to make a diagnosis of asthma. The diagnosis of asthma in children and adults is based on the recognition of a characteristic pattern of respiratory symptoms, signs and test results and the absence of any alternative explanation for these.

Typical symptoms of asthma include periodic wheezing, chest tightness, shortness of breath, and cough, all of which worsen at night. Patients with asthma experience exacerbations of these symptoms which acutely worsen in response to various triggers such as allergens, microbes, and pollutants, resulting in significant reductions in expiratory flow as measured by forced expiratory volume in 1second (FEV).

Symptoms and signs of asthma in adolescents are no different from those of other age groups.

3.1.2. Available therapies and unmet medical need

The goals of chronic asthma management may be divided into two domains: reduction in impairment and reduction of risk.

Complete control of asthma is defined as:

- no daytime symptoms
- no night-time awakening due to asthma
- no need for rescue medication
- no asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV₁ and/or PEF > 80% predicted or best)
- minimal side effects from medication.

In clinical practice patients may have different goals and may wish to balance the aims of asthma management against the potential side effects or inconvenience of taking medication necessary to achieve perfect control.

Effective asthma management requires a proactive, preventative approach, similar to the treatment of hypertension or diabetes. Routine follow-up visits for patients with active asthma are recommended, at a frequency of every one to six months, depending upon the severity of asthma. These visits should be used to assess multiple aspects of the patient's asthma and to discuss steps that patients can take to intervene early in asthma exacerbations (an asthma "action plan"). The aspects of the patient's asthma that should be assessed at each visit include the following: signs and symptoms, pulmonary function, quality of life, exacerbations, adherence with treatment, medication side effects, and patient satisfaction with care.

Pharmacologic treatment is the mainstay of management in most patients with asthma. The stepwise approach to pharmacotherapy is based on increasing medications until asthma is controlled, and decreasing medications when possible to minimize side effects. Adjustment of the patient's management should be considered at every visit.

The first step in determining appropriate therapy for patients who are not already on a controller medication is classifying the severity of the patient's asthma. For patients already taking one or more controller medications, treatment options are guided by an assessment of asthma control rather than asthma severity.

Specific evidence about the pharmacological management of adolescents with asthma is limited and is usually extrapolated from paediatric and adult studies.

Decreasing therapy once asthma is controlled is recommended, but often not implemented leaving some patients over-treated.

The purpose of this line extension related to a new formulation was to seek approval for the prefilled syringe and auto injector in order to improve administration of this medicinal product.

3.1.3. Main clinical studies

The MAH is submitting this application to obtain marketing approval for a new drug form of a prefilled pen or syringe (mepolizumab injection, liquid drug product) of mepolizumab. The indications currently registered for the Nucala lyophilised drug product (mepolizumab for injection) remain.

The main supportive data is obtained from the pharmacokinetic study which demonstrated bioequivalence of both new formulations to the already authorised powder for solution. Only limited efficacy data were provided as part of this application which is acceptable as it pertains to introduction of a new pharmaceutical form.

The mepolizumab liquid drug product clinical development programme consisted of 3 studies which support this application: 1 pharmacokinetic (PK) comparability study in healthy volunteers and 2 Real-World-Use (RWU) studies in subjects with severe eosinophilic asthma. All 3 studies assessed the safety profile of the mepolizumab liquid drug product.

3.2. Favourable effects

The PK of mepolizumab, administered subcutaneously as liquid drug product using either autoinjector or safety syringe, was shown to be statistically comparable to the PK of the commercially available lyophilized drug product.

The two real-world use studies demonstrated the usability of the auto-injector and safety syringe, including self-administration outside of the clinic, in patients with severe eosinophilic asthma.

The results of the two human factor studies can be taken to constitute sufficient validation that the Instructions For Use in the EU Package Leaflet are readable, comprehensible and usable by the target user population.

3.3. *Uncertainties and limitations about favourable effects*

There are no major uncertainties. Overall, the site of injection (abdomen, thigh or arm) did not appear to markedly influence mepolizumab PK, nor the effect of mepolizumab on blood eosinophils, irrespective of device used. However, there is insufficient evidence to conclude whether there is no difference in the upper arm site of injection compared to the abdomen or thigh, since only 5 subjects in Study 204959 and 4 subjects in Study 205667 using the upper arm as a site of injection.

3.4. *Unfavourable effects*

In real-world use (RWU) studies a total of 71 subjects (36%), including 5/11 adolescents enrolled, reported on-treatment AEs, and 6 subjects (3%) reported events considered related to mepolizumab by the investigator. The types of common adverse events reported during the RWU Studies were similar to those reported in the pivotal studies. The most commonly ($\geq 3\%$) reported on-treatment AEs in the RWU Studies were nasopharyngitis (5%), headache (4%), upper respiratory tract infection (4%), and urinary tract infection (3%).

In the RWU Studies twelve on-treatment non-fatal SAEs were reported for 7 subjects however none of these SAEs were considered related to mepolizumab by the investigator.

Asthma (verbatim text: asthma exacerbation) was the only SAE reported for >1 subject (including 1 adolescent subject).

Six SAEs were reported for 1 subject due to a road traffic accident. None of the SAEs were considered related to mepolizumab by the investigator.

In a single dose study in healthy subjects on-treatment AEs were reported in 34% of subjects (29%, 34%, and 38% for the lyophilised drug product, liquid drug product in an autoinjector, and liquid drug product in a safety syringe, respectively).

In the RWU Studies a positive ADA results were reported for a total of 7 subjects (4%) at Baseline and 4 subjects (2%) at the Week 12/EW Visit. No subject positive for ADAs tested positive for neutralising antibodies.

In this study positive ADA results were reported for 11 subjects (5%) post-Baseline: 4%, 4%, and 6% for the lyophilised drug product, liquid drug product in safety syringe, and liquid drug product in autoinjector respectively. None of whom tested positive for neutralising antibodies.

3.5. *Uncertainties and limitations about unfavourable effects*

The types of common adverse reactions reported during the RWU Studies (mepolizumab injection, liquid drug product) are similar to those reported in the pivotal studies. However as the safety data are limited with the new formulation no final conclusion can be made at present and this will be monitored in the post approval setting via routine pharmacovigilance. However no differences with the known safety profile of the existing pharmaceutical form would be expected.

There was no direct comparison between the new liquid formulations tested the RWU Studies and lyophilised formulation therefor only indirect comparisons could be made. This is acceptable by the CHMP.

3.6. Effects Table

An effect table is not appropriate in view of the clinical data submitted in this application.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The PK of mepolizumab, administered subcutaneously as liquid drug product using either prefilled pen or prefilled syringe was shown to be statistically comparable to the PK of the commercially available lyophilized drug product.

The two real-world use studies demonstrated the usability of both formulations, including self-administration outside of the clinic, in patients with severe eosinophilic asthma.

Based on the data available no major differences in relation to the safety profile between the approved lyophilised formulation and new liquid formulations formation were noted. The types of Treatment Emergent Adverse Events reported were similar to those reported in the pivotal studies.

3.7.2. Balance of benefits and risks

The balance of the benefit and risks is positive for this new pharmaceutical form. The liquid formulation will add a new option in comparison with the powder for injection currently available.

3.7.3. Additional considerations on the benefit-risk balance

3.8. NA.Conclusions

The overall Benefit/Risk of Nucala solution for injection in pre-filled pen and syringe is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nucala new pharmaceutical form is favourable in the following indication:

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Nucala subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2). *Conditions and requirements of the marketing authorisation*

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0239/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change:

Variation requested		Type	Annexes affected
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extension	I, IIIA, IIIB and A

Extension application to introduce a new pharmaceutical form, solution for injection in pre-filled syringe or in pre-filled pen). The indication approved for this new pharmaceutical form is the same indication as the one approved for the lyophilised powder for solution for injection.