9 November 2017
EMA/58724/2018
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nucala

mepolizumab

Procedure no: EMEA/H/C/003860/P46/006

Note

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

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1. Introduction

On 25 August 2017, the MAH submitted Part A (completed) of a paediatric study for Nucala (mepolizumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Part B of the study is on-going.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Currently in the EU, Nucala is centrally approved as a lyophilised powder for solution for injection as an add-on treatment for severe refractory eosinophilic asthma in adult patients (EU/1/1/1043/001-001).

The MAH stated that study 200363 'An open-label study to characterise the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma (Interim report; final Part A results only) is part of a clinical development program and that Part A of the Paediatric Study 200363 has been conducted in accordance with an agreed paediatric investigation plan (EMEA-PIP- 000069-02-10). Part B of this study is ongoing. The type II variation application supporting an indication in paediatric patients consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted in Q4 2017. A line listing of all the concerned studies is annexed (Annex 1).

2.2. Information on the pharmaceutical formulation used in the study

Mepolizumab was provided as a lyophilised cake in sterile vials for individual use. Prior to administration, the vial was reconstituted, with sterile Water for Injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an interim report; final Part A results only, for:

- Study number 200363: 'An open-label study to characterise the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma'.

2.3.2. Clinical study

Description

This was a multi-centre, open-label, repeat dose study of mepolizumab in subjects with severe eosinophilic asthma, aged 6 to 11 years.

This study consisted of 2 phases:

- Part A (pharmacokinetic/pharmacodynamic [PK/PD] phase) consisted of Pre-Screening/Screening/Run-in, 12-week treatment period and 8-week follow-up period;

- Part B (long-term safety/pharmacodynamic phase) consists of a 52-week long-term treatment period and 8-week follow-up period.

On completion of Part B, subjects were offered entry into the long-term access programme until mepolizumab becomes commercially available for this age group, within the subject's participating country. The Part B follow-up period was not required for subjects transitioning to the long-term access programme.

The MAH has stated that the study report submitted in this Article 46 procedure describes Part A only. Part B is ongoing and will be reported separately.

Methods

Objectives and Endpoints

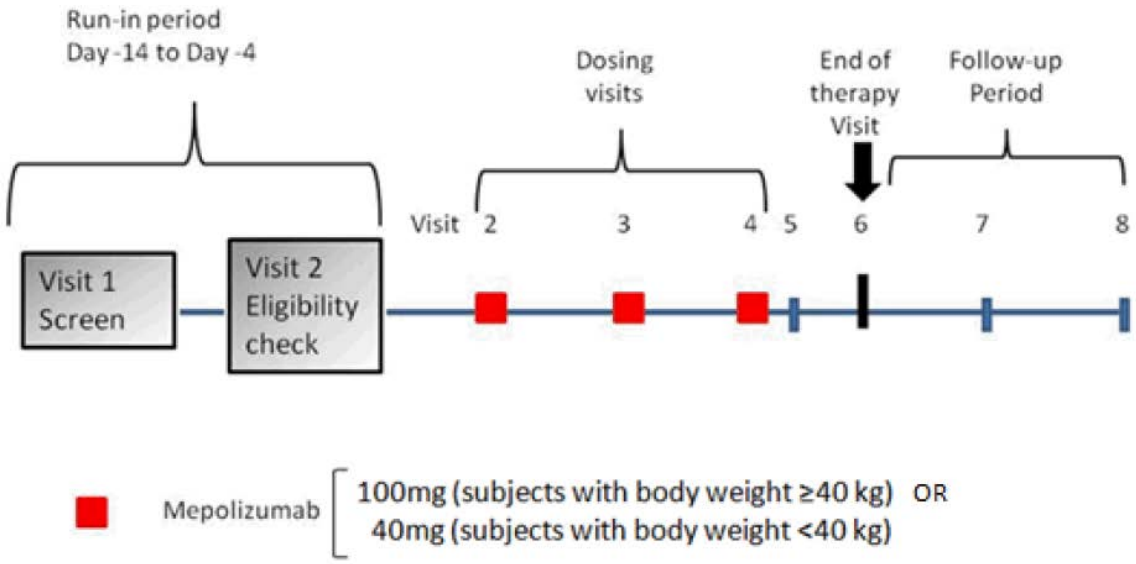
Objectives	Endpoints
Primary	
To characterise the PK of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	Population-PK model derived estimates of clearance, area under the plasma-concentration time curve to infinity ($AUC_{[0\text{-}inf]}$), maximum plasma concentration (C_{max}), and terminal phase elimination half-life ($t_{½}$) of mepolizumab
To characterise the PD of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	Change from baseline in absolute blood eosinophil count at Week 12
Secondary	
To compare the bodyweight-adjusted clearance between adults and subjects aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab is administered subcutaneously	Bodyweight-adjusted clearance estimates obtained by population-PK methods.
To characterise asthma control following SC administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	Change from Baseline in ACQ-7 measured at Week 12 Change from Baseline in ACQ-7 measured at Weeks 4, 8, 16 and 20 Change from Baseline in C-ACT measured at Week 12 Change from Baseline in C-ACT measured at Weeks 4, 8, 16 and 20

Objectives	Endpoints
To assess the safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	Incidence of adverse events (AEs) Incidence of clinically significant changes in clinical laboratory parameters Frequency of positive anti-mepolizumab binding antibodies and neutralising antibodies Incidence of clinically significant changes in vital sign measurements
Exploratory	
To assess the number of asthma exacerbations that occur during the study following SC administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	Number of asthma exacerbations that occur while on treatment (Week 0 to Week 12). Number of asthma exacerbations that occur on-treatment and post-treatment (Week 0 to Week 20)
To assess forced expiratory volume in 1 second (FEV1) following SC administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	Change from Baseline in FEV1 measured at Week 12

Study design

The PK and PD of either mepolizumab, 40 or 100 mg (depending on subject bodyweight), administered subcutaneously once every 4 weeks as an add-on to best standard of care, for a total duration of 12 weeks, to subjects aged 6 to 11 years with severe eosinophilic asthma, were assessed. The study also assessed safety, tolerability and immunogenicity of mepolizumab in this population along with clinical outcome measures, the ACQ-7 and the C-ACT.

*Study design schematic pharmacokinetic/pharmacodynamic phase**



Visit 2 (week 0), visit 3 (week 4), visit 4 (week 8), visit 5 (week 9), visit 6 (week 12), visit 7 (week 16), visit 8 (week 20).

*A time and events table that outlines all study assessments and the times that they were to be completed for Part A of the study can be found in Annex 2 at the end of this assessment report

Study population /Sample size

Number of subjects

Approximately 40 subjects were to be screened to achieve approximately 28 eligible subjects entering the treatment phase, to allow for availability of 20 evaluable subjects, with a minimum of 6 subjects enrolled in the <40 kg bodyweight group (mepolizumab 40 mg SC dose).

The sample size was determined by paediatric population PK trial simulation based on 1000 trial simulations per scenario. A sample size of 16 to 32 subjects was deemed sufficient to maintain precision in exposure estimation (and hence bodyweight-adjusted clearance) below 20%, (compared with the guideline 40% [FDA General Clinical Pharmacology Considerations for Pediatric Studies]), providing 5 PK samples (including 1 close to time of occurrence of C_{max} [T_{max}]) were collected and 4 model parameters were fixed to adult values in the population PK model.

For blood eosinophils, it was expected that this trial would have a similar residual variance to that observed in the Phase III exacerbation trial of mepolizumab in adults and adolescents (MEA115588). Based on this assumption, 20 subjects provided sufficient precision for the 95% confidence interval (CI) for the ratio to baseline to lie within 50% of the observed value.

Diagnosis and main criteria for inclusion

Males or females, between 6 and 11 years of age inclusive at screening with a diagnosis of severe asthma for at least 1 year, as defined by regional asthma guidelines, were eligible for inclusion. Subjects were required to have eosinophilic airway inflammation that was related to asthma; this was characterised as eosinophilic in nature as indicated by: a peripheral blood eosinophil count of ≥300 cells/μL demonstrated within 12 months of screening or a peripheral blood eosinophil count of ≥150 cells/μL at Visit 1. Subjects were also required to have a well-documented requirement for regular

treatment with an inhaled corticosteroid (ICS) (>200 µg/day fluticasone propionate dry powder inhaler [DPI] or equivalent daily) therapy, in the 12 months prior to Visit 1, with or without maintenance oral corticosteroids (OCS) and were to have been on current treatment with an additional controller medication for at least 3 months (or had a documented treatment failure in the past 12 months of an additional controller medication, for at least 3 successive months). Subjects were to have a persistent airflow obstruction at either Visit 1 or Visit 2 (a pre-bronchodilator forced expiratory volume in 1 second [FEV1] <110% predicted, or FEV1:forced vital capacity [FVC] ratio <0.8) and had a confirmed history of 2 or more exacerbations requiring treatment with systemic corticosteroids (CS), in the 12 months prior to Visit 1, despite the use of ICS. For subjects receiving maintenance OCS, the treatment for the exacerbations must have been a 2-fold or greater increase in the CS dose.

Statistical Methods

The primary population used for all analyses of study population and safety measures was the Safety Population, which comprised all subjects receiving at least 1 dose of mepolizumab, beginning at Visit 2. The following analysis populations were used:

- Safety - all subjects receiving at least 1 dose of mepolizumab, beginning at Visit 2.
- PK - subjects from the Safety Population with at least 1 blood sample taken at Visit 3 or thereafter with a measurable mepolizumab plasma concentration.
- PD Blood Eosinophils (PDe) - subjects from the Safety Population with at least 1 blood sample evaluable for blood eosinophil count.
- PD Outcome Assessments (PDo) - subjects from the Safety Population with at least 1 assessment of PD outcomes (ACQ-7, C-ACT, asthma exacerbation, FEV1, immunoglobulin [Ig]E or interleukin [IL]-5).
- PK/PD - subjects from the Safety Population with at least 1 blood sample taken at Visit 3 or thereafter with a measurable mepolizumab plasma concentration and with at least 1 blood sample evaluable for blood eosinophil count.

Primary analysis population PK: Mepolizumab plasma PK concentrations collected during Part A of the study were analysed using the NLMIXED procedure in SAS software (Version 9.2). The most recent population-PK model (two-compartment model with first order absorption and first order elimination) was applied, with a number of PK distribution parameters fixed to adult values. Appropriateness of the final model was assessed using goodness of fit plots, simulations and a set of statistical tests.

Primary analysis blood eosinophil counts: The ratio of blood eosinophil count to baseline (or change from baseline on the log scale) at Week 12 was summarised. The absolute blood eosinophil count and ratio to baseline was summarised, listed and graphically presented by visit for each mepolizumab dose and overall.

All analyses were performed as pre-defined within the Reporting and Analysis Plan

Results

Recruitment / Number analysed

Recruitment

This study was conducted at 13 centres; 3 in Japan, 2 in Poland, 6 in the United Kingdom and 2 in the United States. The first subject was enrolled into Part A on 25-Aug-2015 (first observation on the database) and the last subject completed Part A on 07-Dec-2016 (last observation on the database).

Subject disposition

Seven of the 44 subjects in the 'All subjects enrolled' population did not meet the inclusion/exclusion criteria, and 1 (2%) subject did not meet the continuation criteria, resulting in screening or run-in failures. A total of 36 subjects were enrolled to mepolizumab SC treatment (26 subjects to 40 mg [weight <40 kg] and 10 subjects to 100 mg [weight ≥40 kg]). Of these, 32 (89%) subjects completed Part A of the study.

Summary of subject populations

Population	Number (%) of Subjects		
	Mepo SC 40 mg (weight <40 kg)	Mepo SC 100 mg (weight ≥40 kg)	Mepo SC
ASE, N			44
Safety, N	26	10	36
PK, n (%)	26 (100)	10 (100)	36 (100)
PDe, n (%)	26 (100)	10 (100)	36 (100)
PDo, n (%)	26 (100)	10 (100)	36 (100)
PK/PD, n (%)	26 (100)	10 (100)	36 (100)

Source Data: Table 1.1 and Table 2.10
Note: Percentages are of the Safety Population.
ASE = All subjects enrolled; PDe = PD blood eosinophils; PDo = PD outcome assessments; PK = Pharmacokinetic; PK/PD = Pharmacokinetic/pharmacodynamic.

Baseline data

Demographics

A majority of the subjects in both groups were White. In the mepolizumab 40 mg group (weight <40 kg; N=26), there was a higher proportion of male subjects whereas the male/female ratio was balanced in the mepolizumab 100 mg group (weight ≥40 kg; N=10). The mean body mass index was 16.11 kg/m2 in the mepolizumab 40 mg group (weight <40 kg), 23.05 kg/m2 in the mepolizumab 100 mg group (weight ≥40 kg) and 18.04 kg/m2 overall.

Key baseline characteristics

	Mepo SC 40 mg (weight <40 kg) (N=26)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC (N=36)
Number of Exacerbations in 12 months Prior to Screening Requiring Oral/Systemic Corticosteroid Treatment, mean (SD)	4.1 (3.19)	3.7 (3.33)	4.0 (3.18)
Number of Subjects Experiencing an Exacerbation Requiring Hospitalisation in the 12 months Prior to Screening, n (%)	14 (54)	2 (20)	16 (44)
Blood Eosinophil Count, n (%)			
≥150 cells/µL at Visit 1	20 (77)	10 (100)	30 (83)
≥300 cells/µL in 12 months prior to Visit 1	21 (81)	9 (90)	30 (83)
≥150 cells/µL at Visit 1 and ≥300 cells/µL in 12 months prior to Screening	15 (58)	9 (90)	24 (67)
OCS Daily Dose (Prednisolone Equivalent), n (%)			
Any use	6 (23)	2 (20)	8 (22)
<7.5 mg/day	3 (12)	0	3 (8)
≥7.5 to <15 mg/day	1 (4)	0	1 (3)
≥15 to <30 mg/day	0	1 (10)	1 (3)
≥30 mg/day	2 (8)	1 (10)	3 (8)
Baseline Pre-bronchodilator Lung Function, mean (SD)			
FEV1 (mL)	1406.9 (364.69)	1940.0 (309.77)	1555.0 (422.27)
Predicted normal FEV1 (%)	88.70 (16.925)	92.34 (6.944)	89.71 (14.824)
FVC (mL)	1805.2 (372.05)	2436.0 (448.38)	1985.4 (484.27)
FEV1/FVC	0.784 (0.1134)	0.804 (0.0910)	0.789 (0.1066)

At Screening, of the 36 subjects enrolled to study treatment, 7 (19%) subjects were on medium dose ICS and 29 (81%) subjects were on high dose ICS. Overall, the median ICS dose was 500 µg/day fluticasone propionate (DPI) equivalent.

In addition, a wide range of concomitant non-asthma medications were being used across most subjects (83%); the most common of which was cetirizine (22%).

Efficacy results

Pharmacokinetics

Analysis dataset

For the PK analysis of mepolizumab plasma concentrations, 6 blood samples per subject were to be taken pre-dose at Week 4 and Week 8, at Week 9 for an approximate peak plasma concentration, at Week 12 and finally during the Follow-up phase at Weeks 16 and 20. A PK sample was also to be taken at the Early Withdrawal Visit (when applicable). The 36 subjects who received mepolizumab SC contributed a total of 202 blood samples to the analysis. No concentration data were excluded from the analysis.

Population PK Analysis Results

Mepolizumab population PK parameter estimates from the final model are presented in the table below. Parameters were normalised to 70 kg (typical adult bodyweight used for comparison with historic data) and mean bodyweights for the 2 weight groups: 50 kg (in the ≥40 kg group receiving 100 mg mepolizumab SC); and 27 kg (in the <40 kg group receiving 40 mg mepolizumab SC). Predicted AUC(0-inf) exposure normalised to 50 kg was within 1.5-fold of that normalised to 27 kg and both exposures were within 2-fold of the historical target adult value of 343 µg.day/mL from the Phase III exacerbation study MEA115588. Dose adjustment beyond that studied was therefore not deemed necessary in children age 6 to 11 years old.

PK parameter (unit)	PK parameter estimate	Standard error	Lower 95% CI	Upper 95% CI
$AUC_{(0\text{-}inf)}$ (µg.day/mL) 70 kg	508.23	41.8036	423.27	593.18
$AUC_{(0\text{-}inf)}$ (µg.day/mL) 50 kg	675.20	35.8980	602.24	748.15
$AUC_{(0\text{-}inf)}$ (µg.day/mL) 27 kg	454.39	15.8876	422.10	486.67
$C_{max\ SS}$ (µg/mL) 70 kg	22.3221	1.5577	19.1565	25.4878
$C_{max\ SS}$ (µg/mL) 50 kg	28.4559	1.6807	25.0402	31.8715
$C_{max\ SS}$ (µg/mL) 27 kg	17.7549	1.2040	15.3082	20.2016
CL/F (L/day) 70 kg	0.1968	0.01618	0.1639	0.2297
CL/F (L/day) 50 kg	0.1481	0.007874	0.1321	0.1641
CL/F (L/day) 27 kg	0.08803	0.003078	0.08178	0.09429
Half-life (days) 70 kg	20.9583	1.6520	17.6011	24.3155
Half-life (days) 50 kg	21.8420	1.0999	19.6068	24.0773
Half-life (days) 27 kg	23.5582	0.8406	21.8500	25.2664
BSV (CL)	0.02388	0.006253	0.01117	0.03658
Residual	0.02924	0.003204	0.02273	0.03575

AUC(0-inf) = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; BSV = Between-subject variability;BWT = Bodyweight; CI = Confidence interval; CL/F = Apparent plasma clearance after extravascular (e.g., subcutaneous) administration; Cmax ss = Maximum plasma concentration at steady state; PK = Pharmacokinetic(s).
Note: Parameters are normalised to 70 kg (BWT for a typical adult individual); 50 kg (mean in the ≥40 kg group receiving 100 mg mepolizumab SC) and 27 kg (mean in the <40 kg group receiving 40 mg mepolizumab SC).

The bodyweight-adjusted apparent clearance (i.e., CL/F at 70 kg) point estimate and 90% CI of 0.20 (90% CI: 0.17-0.22) L/day fell outside the 80% to 125% historical adult point estimate and range values of 0.29 (80%-125% interval: 0.23-0.36) L/day, implying a slightly lower CL/F in the 6 to 11 year old population.

An exploratory population PK analysis, using the most recent meta-analysis PK model, estimated that a slightly higher SC absolute bioavailability of 105% (95% CI: 55-155%), rather than a lower clearance, is the most likely explanation for the difference in apparent clearance in the 6 to 11 years old population. The analysis confirmed that adult PK data can predict observations in children 6 to 11 years old with severe eosinophilic asthma, after adjustment for bioavailability in this age group. Furthermore, after adjustment for bodyweight and bioavailability, age, gender and race were not covariates of mepolizumab exposure.

Pharmacodynamics

Blood eosinophil count

Geometric mean baseline absolute blood eosinophil counts were 386, 331 and 370 cells/µL in the mepolizumab 40 mg SC (weight <40 kg), 100 mg SC (weight ≥40 kg) groups and overall, respectively. Marked, sustained, and similar reductions in blood eosinophil counts were observed at both doses.

At Week 12, the geometric mean ratio of blood eosinophil count to baseline was 0.115 in the mepolizumab 40 mg SC group (weight <40 kg), 0.166 in the mepolizumab 100 mg SC group (weight ≥40 kg) and 0.129 overall, indicating an 88.5%, 83.4% and 87.1% reduction, respectively.

Total serum interleukin-5

The majority of subjects in this study had total serum IL-5 level at baseline below the limit of quantification of the assay (<7.81 ng/L). Following administration of mepolizumab, total serum IL-5 increased, as anticipated since the total serum IL-5 assay is measuring both free IL-5 and IL-5 bound to mepolizumab; thus, it was concluded that there was target engagement.

Clinical assessment results

Given the small sample size, short duration of treatment and uncontrolled design, the study was not designed to detect significant changes in the clinical assessments.

Asthma control was characterised in this study through the use of the ACQ and C-ACT questionnaires. Overall, an improvement in asthma control was observed for the ACQ-7 and ACQ-5 responses. At Week 12, a ≥0.5-point reduction from baseline (minimally clinically important change) was observed in 48% and 55% of subjects overall in the ACQ-7 and ACQ-5 questionnaires, respectively. For the C-ACT questionnaire, an increase in total score, suggesting an improvement in asthma control, was observed with a peak response at Visit 4 (Week 8) for the 2 treatment groups combined. No clear effect of mepolizumab was observed on FEV1 values.

Following mepolizumab administration, on-treatment asthma exacerbations were reported in 28% of subjects. Four subjects required an on-treatment hospitalisation or emergency room visit, of which 3 subjects were hospitalised; all subjects were in the mepolizumab 40 mg SC group (weight <40 kg).

Safety results

Overall, mepolizumab was well tolerated in the study, and no new safety concerns were identified for this age group. The overall incidence of subjects reporting any on-treatment AE was 67%. Headache and injection site reaction (14% in both cases) were the most frequent on-treatment events overall. The System Organ Class (SOC) with the highest frequency of AEs was Infections and Infestations (50%).

AE SOC	Number (%) of Subjects		
	Mepo SC 40 mg (weight <40 kg) (N=26)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC (N=36)
Any AE	**18 (69)**	**6 (60)**	**24 (67)**
Infections and infestations	14 (54)	4 (40)	18 (50)
Respiratory, thoracic and mediastinal disorders	8 (31)	2 (20)	10 (28)
Gastrointestinal disorders	6 (23)	1 (10)	7 (19)
General disorders and administration site conditions	6 (23)	0	6 (17)
Nervous system disorders	3 (12)	2 (20)	5 (14)
Skin and subcutaneous tissue disorders	2 (8)	3 (30)	5 (14)
Investigations	2 (8)	1 (10)	3 (8)
Musculoskeletal and connective tissue disorders	2 (8)	0	2 (6)
Immune system disorders	1 (4)	0	1 (3)
Injury, poisoning and procedural complications	1 (4)	0	1 (3)
Metabolism and nutrition disorders	0	1 (10)	1 (3)
Renal and urinary disorders	1 (4)	0	1 (3)

AE = Adverse event; SOC = System Organ Class; SC = Subcutaneous

Deaths and serious adverse events (SAEs)

No fatal SAEs were reported during this study. In total, 6 (17%) subjects reported on-treatment SAEs, the majority (5/6 subjects) of which were reported by subjects in the mepolizumab 40 mg SC group (weight <40 kg). Asthma and lower respiratory tract infection were the SAEs reported by more than 1 subject in either treatment group (asthma by 3 subjects in the mepolizumab 40 mg SC group and lower respiratory tract infection was reported for 1 subject in the mepolizumab 40 mg SC [weight <40 kg] and 1 subject in the mepolizumab 100 mg SC group [weight ≥40 kg]); all other SAEs were only reported for 1 subject overall. Two subjects had on-treatment non-fatal SAEs that were considered drug-related (SAEs of back pain, chest pain, dizziness, headache, nausea and pain were observed in 1 subject and an SAE of asthma (worsening) was reported in another subject), both subjects were in the 40 mg SC group (weight <40 kg).

Adverse events of special interest (AESIs)

AESIs in this study included systemic (non-allergic and allergic/hypersensitivity) reactions, local injection site reactions, cardiac disorders including cardiac, vascular, thromboembolic and serious ischemic events, infections, and malignancies. No on-treatment events of anaphylaxis, malignancies, or cardiac AESIs were reported. The most commonly reported on-treatment AESIs were local injection site reactions, reported by 5 (14%) subjects in the mepolizumab 40 mg SC group (weight <40 kg); all were non-serious and mild in intensity. In addition, 1 subject in the mepolizumab 40 mg SC group (weight <40 kg) had a non-serious event of mild intensity hypersensitivity with associated symptoms of pruritus. Three subjects had infections that were considered serious whilst on-treatment: 2 subjects had a serious on-treatment event of lower respiratory tract infection and 1 subject had a serious on-treatment event of cellulitis. All events resolved without any dose interruption or changes to mepolizumab treatment.

One subject had a post-treatment SAE of campylobacter infection of moderate intensity, and 1 subject had a non-serious post-treatment AE of mild mitral valve incompetence. Both events were in the 40 mg SC group (weight <40 kg) and were not resolved at the time of reporting.

Anti-drug antibody (ADA)

The frequency of positive ADA samples in the study was low (2/35 subjects, 1 subject in each dose group; 6% overall). The titres were low, and the presence of ADAs was transient in the 2 ADA positive subjects with negative results at all subsequent visits. No subjects tested positive for neutralising antibodies at any time point. The AE profiles were comparable between subjects who tested positive for ADA and those who were negative at all time points.

Other safety parameters

There were no apparent treatment related changes in clinical laboratory parameters, ECGs or vital signs.

In summary, there were no new safety concerns following treatment with mepolizumab (40 mg or 100 mg SC) compared with adults and adolescents with severe eosinophilic asthma following treatment with mepolizumab 100 mg SC.

3. Rapporteur's overall conclusion and recommendation

In the EU, currently Nucala (mepolizumab) is centrally approved as an add-on treatment for severe refractory eosinophilic asthma in adult patients.

The MAH has submitted Part A (completed) of the paediatric study 200363 'An open-label study to characterise the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma', in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This study is part of a clinical development program and Part A of study 200363 has been conducted in accordance with an agreed paediatric investigation plan. Part B of this study is ongoing. The MAH plans to submit a type II variation application supporting an indication in paediatric patients consisting of the full relevant data package, including several studies as listed in Annex 1, in Q4 2017. Therefore, no updates to the Nucala product information are proposed by the MAH as part of this Article 46 submission.

Whilst a description of Part A of study 200363 with a summary of the methods and results provided by the company have been described above, as only Part A of the study is complete and the results from this study are intended to be integrated with the other agreed PIP measures to support the planned type II extension of indication variation procedure in Q4 2017, a full assessment of study 200363 has not been undertaken at this time.

The sample size in this study was small (36) and it was an open-label uncontrolled study, therefore limiting the ability of the study to assess the secondary efficacy and safety objectives. However, no new safety signals were identified in Part A of the study.

☒ Fulfilled:

No regulatory action required.

Annex 1: Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Studies as agree in the PIP EMEA-000069 PIP02-10-M08

Product Name: Nucala Active substance: Mepolizumab

Study title	Study number	Date of completion (LSLV date)	Date of submission of final study report
Double-blind, double-dummy, randomised, multi-centre, placebo-controlled, parallel-group study to evaluate efficacy and safety of mepolizumab as add-on therapy in children from 12 to less than 18 years old with severe uncontrolled asthma (and in adults).	Study MEA115588 (PIP measure 2 – completed)	18 January 2014	PIP compliance checked 13 October 2014 Submitted as part of Nucala MAA 3860 3rd November 2014
Double-blind, randomised, multi-centre, placebo-controlled, parallel-group study to evaluate efficacy of mepolizumab on reduction of oral corticosteroid use as add-on therapy in children from 12 to less than 18 years old with severe asthma (and in adults).	Study MEA115575 (PIP measure 3 – completed)	12 December 2013	PIP compliance checked 13 October 2014 Submitted as part of Nucala MAA 3860 3rd November 2014
Double-blind, randomised, dose ranging, parallel group trial to evaluate PK/PD, safety and tolerability of mepolizumab in children from 2 to less than 18 years of age with eosinophilic esophagitis.	Study MEE103219 (PIP measure 6 – completed)	25 November 2008	PIP compliance checked 13 October 2014 Submitted as part of Nucala MAA 3860 3rd November 2014
An open-label study to characterize the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma	Study 200363 (PIP measure 7 – completed)	7 December 2016	Currently being compliance check against PIP EMEA-000069 PIP02-10-M08 Planned to be submitted Q4 2017 as part of a Type II variation

Clinical Pharmacology studies

Study title	Study number	Date of completion	Date of submission of final study report
Mepolizumab paediatric extrapolation report in the severe asthma indication	NA Report Number: 2017N323587_00	NA (report not finalised)	Currently being compliance check against PIP EMEA-000069 PIP02-10-M08 Planned to be submitted Q4 2017 as part of a Type II variation

Annex 2: Time and Events Table – Pharmacokinetic/Pharmacodynamic Phase (Part A)

Procedure	Pre-Screen[1]	Screening	Treatment Period				Exit Visit[3]	Follow-up		Early Withdrawal
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[8]**	
Week of Study (visit window ±3 days, ±1 day Visit 5)	Prior to or same day as Visit 1	Up to 14 days prior to Visit 2	0	4	8	9	12	16	20	
Subject Screen										
Informed consent	X									
Inclusion and exclusion criteria		X	X							
Demography	X									
Medical history, including bronchodilator reversibility history[4]		X								
Past and current medical conditions		X								
Asthma exacerbation history		X								
Safety Assessments										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Haematology (including eosinophils)		X	X	X	X	X	X	X	X	X
Clinical Chemistry		X		X	X		X		X	X
12-lead ECG		X		X			X			X
Vital signs		X	X	X	X	X	X	X	X	X
Bodyweight			X							
Brief physical examination		X								
Adverse events		X	X	X	X	X	X	X	X	X
Cardiovascular events		X	X	X	X	X	X	X	X	X
Liver events		X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Urinalysis		X							X	X
Pregnancy Test		U	U[5]	U[5]	U[5]		U	U	U	U
HBsAg and hepatitis C antibody		X[6]								
Serum IgE (total)			X[5]							
PK blood sample				X[5]	X[5]	X	X	X	X	X

Procedure	Pre-Screen[1]	Screening	Treatment Period				Exit Visit[3]	Follow-up		Early Withdrawal
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[8]**	
Week of Study (visit window ±3 days, ±1 day Visit 5)	Prior to or same day as Visit 1	Up to 14 days prior to Visit 2	0	4	8	9	12	16	20	
IL5 serum sample			X[5]				X			
Blood sample for immunogenicity[2,7]			X[5]					X	X[2]	X
Outcomes Assessments										
FEV1		X	X	X	X		X	X	X	X
ACQ-7			X	X	X		X	X	X	X
C-ACT			X	X	X		X	X	X	X
Assessment of exacerbation	X	X	X	X	X	X	X	X	X	X
Investigational Product										
Mepolizumab SC dose administered			X	X	X					
Study Administration										
Email to GSK Operational Lead	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X		

1. Pre-screen must be completed prior to or on the same day as Screen Visit.
2. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available) an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.
3. Exit Visit should be performed as close as possible to the planned Week 12 visit date.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
5. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
6. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary.
7. This immunogenicity sample must always be collected 12 weeks (±7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (±7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
8. Visit 8 to be performed 12 weeks post last dose. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the Visit 8 assessments have been completed. Assessments performed at Visit 8 that are also listed for Visit 9 should not be duplicated if Visit 8 and Visit 9 are performed on the same day.