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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/P46/010

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 July 2018, the MAH submitted a completed paediatric study, Study 200363 Part B, for Nucala in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of a post-authorisation measure, as a Post Approval Safety Study (PASS) in the Risk Management Plan (RMP).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Nucala is approved in the EU for use as an add-on treatment for severe refractory eosinophilic asthma in adult patients.

The MAH stated that Part A of the study completed on 7 December 2016 and the corresponding study report was submitted and assessed under Article 46 (EMA/H/C/003860/P46/006). Part A was also included in the Type II variation EMEA/H/C/003860/II/0013/G, submitted on 21 November 2017 and completed with the CHMP opinion on 26 July 2018; this was an extension of indication to adolescents and children from 6 years of age.

The final Clinical Study Report for 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 (Parts A and B), which achieved Last Subject Last Visit on 31 January 2018, is now submitted.

Once the European Commission Decision is received for the above procedure, the MAH plans to propose an update to the Nucala Product Information with the study 200363 Part B results and to fulfil the upcoming post approval commitment (from variation EMEA/H/C/380/II/0013_G) as part of a Type II variation. Therefore, no changes to the Nucala Product Information are proposed as part of this Article 46 procedure.

This study is part of a clinical development programme for which a line listing is attached. All documentation pertaining to the other studies have already been submitted.

2.2. Information on the pharmaceutical formulation used in the study

Nucala is currently marketed as a sterile, single-use, preservative-free, 100 mg lyophilised powder for solution for injection which requires aseptic reconstitution in sterile water for injection prior to subcutaneous (SC) injection by a healthcare professional (HCP). This is the formulation that was used in the trial.

2.3. Clinical aspects

2.3.1. Introduction

Only Part B of study 200363 is the subject of this evaluation; it has not been conducted in accordance with an agreed Paediatric Investigation Plan.

2.3.2. Clinical study

Description

The primary objective of Part B (52-week treatment period) was to assess the long-term safety and tolerability of mepolizumab when administered subcutaneously to asthmatic children from 6 to 11 years of age.

Methods

At the end of Part A, a benefit/risk assessment was performed by the Investigator and, if this assessment supported continued therapy with mepolizumab, the subject was offered to continue into Part B of the study.

- Patients received mepolizumab 40 or 100 mg SC, depending on subject bodyweight measured at Visit 9 (inclusion in Part B): 40 mg for subjects <40 kg and 100 mg for subjects ≥40 kg. Subjects were to be monitored post-SC administration according to standard practice at the site.
- From Visit 10 onwards, patients received mepolizumab at 4-weekly intervals for a total of 48 weeks. Patients with bodyweight <40 kg at Visit 9 were weighed at each subsequent visit and their dose adjusted to 100 mg once their bodyweight reached 40 kg. From this time onwards, the dose was not to be adjusted again.
- On completion of Visit 22, subjects not transitioning to the long-term access programme (Study 201956) entered into the Part B Follow-up phase, which consisted of one additional follow-up visit at Week 80 (Visit 23). Part B follow-up was not required for subjects transitioning to the long-term access programme (Study 201956) at the end of Part B.

The total duration of Part B was approximately 60 weeks (52 weeks for subjects transitioning to the long-term access programme).

Objectives

- To assess the long-term safety and tolerability of mepolizumab
- To characterise the long-term durability of PD response
- To characterise the long-term asthma control
- To assess the number of asthma exacerbations

Study design

Open-label single arm trial with 13 injections of mepolizumab

Study population

The main inclusion criteria for Part A were:

- subjects between 6 and 11 years of age inclusive, at the time of screening
- diagnosed with severe asthma, defined by regional asthma guidelines, for at least 1 year

- with eosinophilic airway inflammation, as indicated by: elevated peripheral blood eosinophil count of ≥ 300 cells/µL within 12 months of screening or elevated peripheral blood eosinophil count of ≥ 150 cells/µL at Visit 1
- with 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). The ICS dose should have represented a medium or high dose in children aged 6 to 11 years of age [GINA, 2015]
- on current treatment with an additional controller medication for at least 3 months, or documented failure in the past 12 months of an additional controller medication for at least 3 successive months (e.g., long-acting beta-2-agonist, leukotriene receptor antagonist, or theophylline)
- with a persistent airflow obstruction, as indicated by pre-bronchodilator forced expiratory volume in 1 second [FEV1] <110% predicted or FEV1:forced vital capacity (FVC) ratio <0.8
- with a previously confirmed history of 2 or more exacerbations requiring treatment with systemic corticosteroids (CS) (intramuscular, IV or oral), 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.

Outcomes/endpoints

Safety: incidence of AEs, incidence of clinically significant changes in vital sign measurements, incidence of clinically significant changes in clinical laboratory parameters

Immunogenicity: frequency of positive anti-mepolizumab binding antibodies and neutralising antibodies

Pharmacodynamics: change from Week 0 (Visit 2) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80

Clinical assessments: change from Week 0 (Visit 2) in C-ACT and ACQ-7 at weeks 32, 44, 56, 68, 72 and 80; incidence of asthma exacerbations

Time and events table

Procedure	Eligibility Check/First Dose	Treatment Period												Exit Visit	Follow-up[3]	Early Withdrawal
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	
Week of Study (visit window ±5 days)	20	24	28	32	36	40	44	48	52	56	60	64	68	72	80	
Subject Screen																
Informed consent	X[1]															
Inclusion and exclusion criteria	X[1]															
Safety Assessments																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology (including eosinophils)[2]	X			X			X			X			X	X	X	X
Clinical Chemistry[2]	X			X			X			X			X	X		X
12-lead ECG														X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bodyweight	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiovascular events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]																
Urinalysis	X[1]					X								X		X
Pregnancy Test	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Blood sample for immunogenicity[2]							X						X		X	X
Outcomes Assessments																
FEV1	X[1]			X			X			X			X	X	X	X
ACQ-7	X[1]			X			X			X			X	X	X	X
C-ACT	X[1]			X			X			X			X	X	X	X
Assessment of exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Statistical Methods

Descriptive statistics

Results

Recruitment / Number analysed

A total of 36 patients were enrolled in Part A and 30 patients continued onto the optional Part B of the study. Two subjects who completed Part A chose not to continue within Part B and the remaining 4 subjects did not complete Part A and were therefore not eligible for Part B.

There were 20 subjects with bodyweight <40 kg (enrolled to 40 mg treatment group) and 10 subjects with bodyweight ≥ 40 kg (enrolled to 100 mg treatment group). Within the <40 kg group (enrolled to 40 mg treatment group), 4 subjects transitioned to 100 mg during the Part B treatment period after they reached a bodyweight ≥ 40 kg.

A total of 29 (97%) patients completed Part B of the study as one subject in the 40 mg group was withdrawn following 2 administrations of mepolizumab due to a lack of adherence.

One subject reported repeated missed visits and completed the study after only receiving 6 of the 13 required doses of mepolizumab SC.

All 30 patients were included in the safety and PD datasets.

Baseline data

Demographics

	Number (%) of Subjects			
	Mepo SC 40 mg (weight <40 kg) (N=16)	**Mepo SC 100 mg (weight ≥40 kg) (N=10)**	**Mepo SC 40/100 mg[1] (N=4)**	**Mepo SC (N=30)**
Derived Age, Years[2]				
Mean (SD)	7.5 (1.63)	10.0 (1.33)	9.3 (1.50)	8.6 (1.89)
Median (Min – Max)	7.0 (6 – 11)	10.0 (7 – 12)	10.0 (7 – 10)	8.5 (6 – 12)
Sex, n (%)				
Female:	4 (25)	5 (50)	1 (25)	10 (33)
Male:	12 (75)	5 (50)	3 (75)	20 (67)
Body Mass Index at Visit 9, kg/m² Mean (SD)	16.11 (1.309)	23.46 (2.696)	16.78 (4.016)	18.49 (4.039)
Height at Visit 9, cm Mean (SD)	130.4 (7.69)	149.7 (6.36)	142.5 (5.92)	138.0 (11.26)
Weight at Visit 9, kg Mean (SD)	27.47 (3.918)	52.52 (6.602)	34.05 (7.755)	36.15 (12.529)
Ethnicity, n (%)				
Hispanic or Latino	1 (6)	0	0	1 (3)
Not Hispanic or Latino	15 (94)	10 (100)	4 (100)	29 (97)
Race, n (%)				
Asian - Japanese Heritage	5 (31)	1 (10)	1 (25)	7 (23)
Black or African American	2 (13)	3 (30)	2 (50)	7 (23)
White – White/Caucasian/European Heritage	8 (50)	6 (60)	1 (25)	15 (50)
Multiple – Black or African American and White	1 (6)	0	0	1 (3)

Source Data: Table 1.31, Table 1.32 and Table 1.33

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.
2. Only year of birth collected, with age derived using an imputed birth date of 30 June. Derived age may not represent the actual age of a subject at entry to the study.

Asthma exacerbations

	Mepo SC 40 mg (weight <40 kg) (N=16)	**Mepo SC 100 mg (weight ≥40 kg) (N=10)**	**Mepo SC 40/100 mg[1] (N=4)**	**Mepo SC (N=30)**
Number of Exacerbations Requiring Oral/Systemic Corticosteroid Treatment in the 12 months Prior to Screening, mean (SD)	2.9 (1.24)	3.7 (3.33)	5.0 (2.16)	3.5 (2.29)
Number of Subjects Experiencing an Exacerbation Requiring Hospitalisation in the 12 months Prior to Screening, n (%)	8 (50)	2 (20)	2 (50)	12 (40)

Source Data: Table 1.34

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.

All subjects were receiving ICS and short-acting beta-2 agonist asthma medication during and post-mepolizumab treatment. The most frequently used ICS medication was fluticasone propionate (in combination with salmeterol) and the most frequently used short-acting beta-2 agonist was salbutamol.

Exposure

Most patients (27; 90%) received all 13 treatments and spent an average of 355.3 days on-treatment. One patient withdrew following 2 doses, one received only 6 doses and the third only 12 doses. The total patient-years exposure was 29 years.

Safety results

Overview of adverse events

	Number (%) of Subjects			
	Mepo SC 40 mg (weight <40 kg) (N=16)	**Mepo SC 100 mg (weight ≥40 kg) (N=10)**	**Mepo SC 40/100 mg[1] (N=4)**	**Mepo SC (N=30)**
Any AE[2]	**15 (94)**	**8 (80)**	**4 (100)**	**27 (90)**
AEs related to study treatment	5 (31)	3 (30)	1 (25)	9 (30)
AEs leading to permanent discontinuation of study treatment or withdrawal from the study	0	0	0	0
Any SAE[2]	**4 (25)**	**2 (20)**	**1 (25)**	**7 (23)**
SAEs related to study treatment	0	0	0	0
Fatal SAEs	0	0	0	0
Any On-Treatment AE	15 (94)	8 (80)	4 (100)	27 (90)
Any On-Treatment SAE	4 (25)	2 (20)	1 (25)	7 (23)

Source Data: Table 3.55

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.
2. Includes all on-treatment and post-treatment events.

AE = Adverse event; SAE = Serious adverse event

On-treatment AEs were considered as any AE within 4 weeks of the last dose of mepolizumab. The overall incidence of patients reporting any on-treatment AE was 90%. Bronchitis (30%) was the most frequent on-treatment event overall. No AEs of injection site reaction were observed in Part B.

In the mepolizumab 40 mg SC group, the most frequently reported on-treatment AEs were bronchitis, headache and asthma (exacerbation). The following AEs were considered severe in intensity: asthma (exacerbation), headache, hypoglycaemia, anaphylactic shock and aggression (each in 1 subject). Of these, 2 events (asthma [exacerbation] and anaphylactic shock) were also SAEs.

In the mepolizumab 100 mg SC group, the most frequently reported on treatment AEs were bronchitis and headache. The following AEs were considered severe in intensity: asthma (exacerbation) (4 episodes in 2 subjects) and pneumonia (1 subject); all of these were also SAEs.

In the mepolizumab 40/100 mg SC group, nasopharyngitis was the only AE seen in more than 1 subject.

The majority of all AEs, across both groups, were moderate in intensity.

On-treatment AEs by SOC

AE SOC	Number (%) of Subjects			
	Mepo SC 40 mg (weight <40 kg) (N=16)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC 40/100 mg[1] (N=4)	Mepo SC (N=30)
Any AE	**15 (94)**	**8 (80)**	**4 (100)**	**27 (90)**
Infections and infestations	11 (69)	7 (70)	4 (100)	22 (73)
Respiratory, thoracic and mediastinal disorders	8 (50)	5 (50)	1 (25)	14 (47)
Skin and subcutaneous tissue disorders	6 (38)	3 (30)	0	9 (30)
Nervous system disorders	4 (25)	3 (30)	1 (25)	8 (27)
Gastrointestinal disorders	4 (25)	2 (20)	1 (25)	7 (23)
General disorders and administration site conditions	2 (13)	2 (20)	0	4 (13)
Injury, poisoning and procedural complications	2 (13)	2 (20)	0	4 (13)
Musculoskeletal and connective tissue disorders	2 (13)	2 (20)	0	4 (13)
Eye disorders	2 (13)	1 (10)	0	3 (10)
Metabolism and nutrition disorders	2 (13)	0	1 (25)	3 (10)
Psychiatric disorders	3 (19)	0	0	3 (10)
Immune system disorders	2 (13)	0	0	2 (7)
Blood and lymphatic system disorders	0	1 (10)	0	1 (3)
Endocrine disorders	0	0	1 (25)	1 (3)
Hepatobiliary disorders	1 (6)	0	0	1 (3)
Investigations	1 (6)	0	0	1 (3)
Vascular disorders	1 (6)	0	0	1 (3)

Source Data: Table 3.56 and Listing 62

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.

AE = Adverse event; SOC = System organ class

Drug-related AEs

The proportion of on-treatment AEs considered to be drug-related, in the opinion of the investigator, was 27%. The most common drug-related AEs in the mepolizumab 40 mg SC group were headache and upper abdominal pain, the most common drug-related AE in the mepolizumab 100 mg SC group was headache and the only drug-related AE in the 40/100 mg SC group was hyperglycaemia.

On-treatment drug-related AEs

AE PT	Number (%) of Subjects			
	Mepo SC 40 mg (weight <40 kg) (N=16)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC 40/100 mg[1] (N=4)	Mepo SC (N=30)
Any AE	**4 (25)**	**3 (30)**	**1 (25)**	**8 (27)**
Headache	2 (13)	2 (20)	0	4 (13)
Abdominal pain upper	2 (13)	1 (10)	0	3 (10)
Pyrexia	1 (6)	1 (10)	0	2 (7)
Aggression	1 (6)	0	0	1 (3)
Cough	0	1 (10)	0	1 (3)
Epistaxis	1 (6)	0	0	1 (3)
Haemorrhage subcutaneous	1 (6)	0	0	1 (3)
Hyperglycaemia	0	0	1 (25)	1 (3)
Hypoglycaemia	1 (6)	0	0	1 (3)
Neutrophil count decreased	1 (6)	0	0	1 (3)
Rash generalised	0	1 (10)	0	1 (3)
Rhinitis	0	1 (10)	0	1 (3)
Wheezing	0	1 (10)	0	1 (3)

Source Data: Table 3.61 and Table 3.62

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.

Death and SAEs

No fatal AE was reported; 9 non-fatal on-treatment SAEs were reported in 7 (23%) patients: asthma (6 AEs) in 5 patients, anaphylactic shock (peanut allergy), epistaxis and pneumonia in 1 patient each. None was considered drug-related.

AEs of special interest (AESIs)

AESIs for mepolizumab include: systemic (allergic/hypersensitivity and non-allergic) reactions, local injection site reactions, cardiac disorders including serious cardiac, vascular, thromboembolic and serious ischemic events, infections and malignancies.

In part B, AESIs included anaphylactic shock (peanut allergy; 1); generalised rash (1) considered drug-related 3 days after the last dose;

A total of 22 patients (73%) reported an infection, including one patient with 2 events of oral herpes. None was considered drug-related.

Immunogenicity

There were no positive ADA samples in any patient in Part B. Of the 2 patients who previously had positive ADA responses in Part A, only 1 subject continued into Part B and this subject was ADA negative throughout Part B.

Laboratory parameters

Clinical chemistry

The majority of subjects had values for clinical chemistry parameters within the normal range.

Two subjects reported AEs related to chemistry changes; one hypoglycaemia (single value of 1 mmol/L, no control value provided, for 9 days – all other values normal) and one hyperglycaemia (8.9 mmol/L, no control value provided, for 3 months, i.e. the interval until the next blood test in the study – all other values normal). They were considered drug-related, but no action was taken.

No elevations in ALT/AST above the upper limit of normal were reported.

Haematology

With the exception of an expected decline in blood eosinophils, which can be attributed to the mechanism of action of mepolizumab, there were few abnormalities of potential clinical concern in any haematology parameter.

One patient had an AE of decreased neutrophil count (0.52 x 10^9/L), which was considered to be related to study treatment. The event resolved after 37 days without a mepolizumab interruption or dose change. This subject had a neutrophil count below the lower limit of normal range at every Part A study visit, including screening and baseline prior to mepolizumab treatment (range 0.89 to 1.33 x 10^9/L). During Part B, neutrophil values remained below the lower limit of normal at almost every study visit.

ECG

For 9 subjects, the baseline ECG was classified as abnormal. At any visit post-baseline, the ECGs were classified as abnormal for 4 subjects: intraventricular conduction defect (2), sinus bradycardia (1), prolonged QTc (1; but this was pre-existing at baseline without any change). None of these ECG abnormalities were considered AEs.

All subjects with data had maximum post-baseline QTcF and QTcB values ≤ 450 msec except for one QTcB value between 450 and 480 msec. Most changes from baseline were between -30 and +30 msec; two patients had changes between +30 and +60 msec.

Vital signs

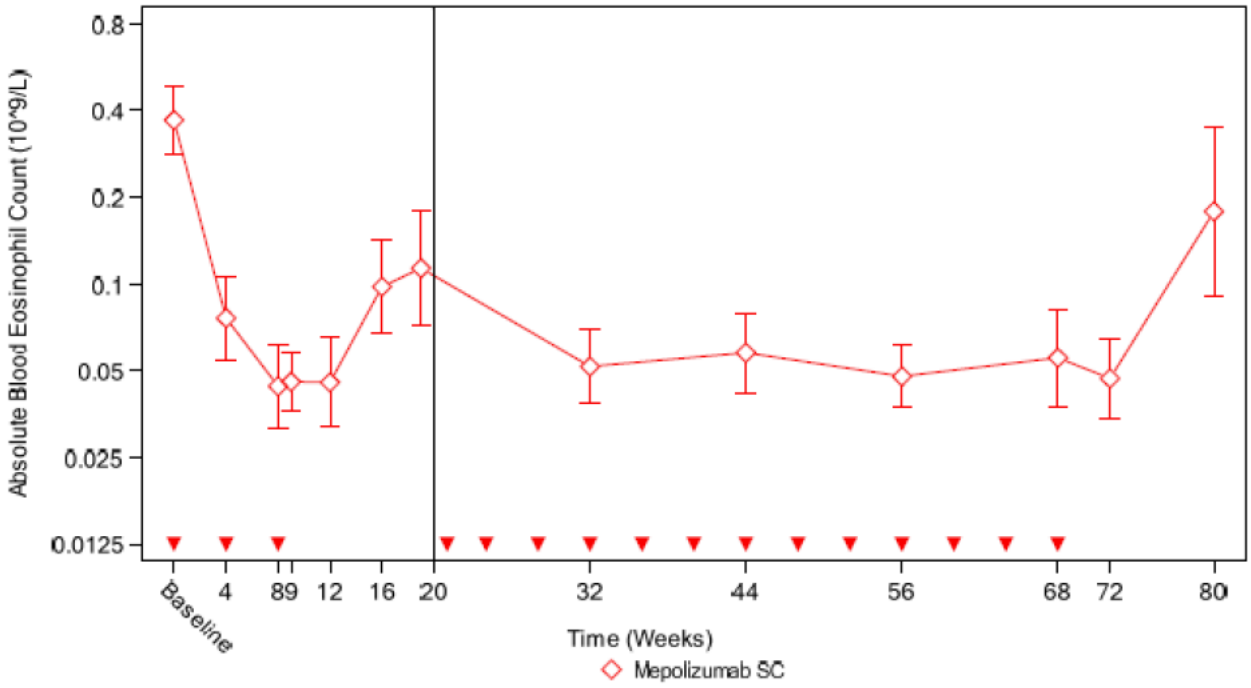
Overall, there was a trend in change from baseline towards higher values at week 52 for systolic (median = +3 mmHg) and diastolic BP (median = +1 mmHg) while there were obvious trends towards increased weight and height (median = +7 cm).

PD results

Blood eosinophil count

The geometric mean baseline absolute blood eosinophil count was 336 cells/µL overall. Marked and similar reductions in blood eosinophil counts were observed in all dose groups at Week 32 compared with baseline, with these reductions sustained through to Week 72 (4 weeks after the last dose of mepolizumab); the reduction from baseline was 86.5% at Week 72. At Week 80, blood eosinophil counts had started to return towards baseline values, but still not reached baseline values. In the 40/100 mg group, it appears that mepolizumab 40 mg and 100 mg SC both provided similar eosinophil suppression following the increase in mepolizumab dose.

Absolute Blood Eosinophil Count (Geometric Mean and 95% CI) in Part A through B



Clinical assessment

Asthma control questionnaire

Summary of 0.5 Point or More Reduction in ACQ-7 and ACQ-5 Score from Baseline

	Number (%) of Subjects			
	Mepo SC 40 mg (weight <40 kg) (N=16)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC 40/100 mg[1] (N=4)	Mepo SC (N=30)
ACQ-7				
Visit 12 (Week 32)	10/15 (67)	3/10 (30)	2/4 (50)	15/29 (52)
Visit 15 (Week 44)	7/15 (47)	4/10 (40)	2/3 (67)	13/28 (46)
Visit 18 (Week 56)	10/15 (67)	6/10 (60)	3/4 (75)	19/29 (66)
Visit 21 (Week 68)	11/15 (73)	4/10 (40)	3/4 (75)	18/29 (62)
Exit Visit (Week 72)	9/15 (60)	4/10 (40)	3/4 (75)	16/29 (55)
Follow-up (Week 80)	9/12 (75)	3/9 (33)	0/2	12/23 (52)
ACQ-5				
Visit 12 (Week 32)	11/15 (73)	4/10 (40)	2/4 (50)	17/29 (59)
Visit 15 (Week 44)	8/15 (53)	4/10 (40)	2/3 (67)	14/28 (50)
Visit 18 (Week 56)	11/15 (73)	6/10 (60)	3/4 (75)	20/29 (69)
Visit 21 (Week 68)	11/15 (73)	5/10 (50)	3/4 (75)	19/29 (66)
Exit Visit (Week 72)	9/15 (60)	4/10 (40)	4/4 (100)	17/29 (59)
Follow-up (Week 80)	8/12 (67)	3/9 (33)	0/2	11/23 (48)

Source Data: Table 2.27 and Table 2.29

Note: The baseline is defined as the latest value recorded prior to the first dose of mepolizumab in Part A.

Note: Time is displayed as Part B visit (cumulative week since first Part A dose).

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.

ACQ-5 = Asthma control questionnaire 5; ACQ-7 = Asthma control questionnaire 7

At Week 72 (Exit Visit), a ≥ 0.5-point reduction from baseline (minimally clinically important change) was observed in 55% and 59% of subjects overall in the ACQ-7 and ACQ-5 questionnaires, respectively.

FEV1

Overall, there was an increase in pre-bronchodilator FEV1 values over the Part B treatment period; the mean was 1594 mL at baseline and, at Week 72, the median increase from baseline was 320 mL.

Asthma exacerbations

A total of 14 children (47%) had an exacerbation during part B, with 5 children requiring hospitalisation.

The annualised rates of exacerbations were lower on-treatment than baseline values for each treatment group. Overall, 80% of subjects had a ≥ 50% reduction in the rate of exacerbations in Part B compared with the 12 months prior to screening.

Annualised Rate of On-Treatment Exacerbations

	Mepo SC 40 mg (weight <40 kg) (N=16)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC 40/100 mg[1] (N=4)	Mepo SC (N=30)
Exacerbation rate/year (95% CI)[2]	0.76 (0.34-1.68)	1.20 (0.51-2.83)	1.98 (0.58-6.79)	1.09 (0.63-1.89)
Exacerbations requiring hospitalisation rate/year (95% CI)[2]	0.14 (0.03-0.62)	0.30 (0.08-1.08)	0.25 (0.03-2.19)	0.21 (0.08-0.55)

Source Data: Table 2.45 and Table 2.47

1. Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.
2. For completers: exacerbations on-treatment between first Part B dose date and Week 52 visit date. For non-completers: exacerbations on-treatment between first Part B dose date and earliest date of withdrawal/last dose + 28 days.

2.3.3. Discussion on clinical aspects

Safety

The safety profile for mepolizumab in Part B was consistent with Part A of the study. Mepolizumab was well-tolerated over the 52-week treatment period, and no new safety concerns were identified for this age group compared with the known safety profile in adults and adolescents.

Bronchitis (30%) was the most frequent on-treatment event overall. There were no AEs leading to discontinuation of study treatment. No local injection site reactions, malignancies, or cardiac AESIs were reported. The most commonly reported AESIs were infections, reported by 73% of subjects overall (no invasive opportunistic infection). One allergic reaction of a generalised rash was attributed to mepolizumab.

No SAEs were considered drug-related; they were mostly asthma exacerbations.

The most frequent AEs considered drug-related were headache, upper abdominal pain and pyrexia, which are all listed ADRs of mepolizumab. Other AEs were reported in only one patient and some are

likely to be related to the underlying disease. The hypo- and hyper-glycaemic events are questionable on the basis of the data provided. Low neutrophil count (drug-related) was reported in one patient, who had low counts during the whole study including screening and baseline. There were no other clinically relevant laboratory abnormalities.

ECG and vital sign follow-up did not reveal significant abnormal findings.

Immunogenicity

Mepolizumab has low immunogenic potential. ADAs were not detected in any patient during Part B of the study.

Blood eosinophils

A marked blood eosinophil reduction was observed in all treatment groups, which was evident from Week 32, maintained throughout the 52-week treatment phase (4 weeks after the last dose of mepolizumab), and followed by a return towards baseline 8 weeks later. The overall observed reduction from baseline of 86.5% at Week 72 was similar to that observed in Part A of the study (Week 12; 87.1%) and comparable to the results in adult/adolescent studies.

Clinical assessments

Over the 52-week treatment period, all groups showed an overall improvement in asthma control, as indicated by the results of the ACQ-7 and ACQ-5 questionnaires; clinically significant improvement was reported in 50-60% of the patients. These results are consistent with those previously observed in Part A of the study and in adult/adolescent studies (52%). For the C-ACT questionnaire, an increase in total score, suggesting an improvement in asthma control was observed in all groups

As expected, with a longer duration, there was a higher incidence (47% of subjects overall) of on-treatment asthma exacerbations during Part B of this study compared with Part A, including exacerbations leading to hospital visits. However, the rates of annual on-treatment exacerbations were lower than baseline values for each treatment group.

Substantial improvement was seen in FEV1 values in Part B; however, as there was no control group, it is not possible to evaluate the contribution of subjects' growth and consequent increase in lung volume.

3. CHMP overall conclusion and recommendation

The objective for Part B of the 200363 study was to assess the long-term (52 weeks) safety and pharmacodynamic profiles of mepolizumab in subjects aged 6 to 11 years old with severe eosinophilic asthma. These results do not raise any concerns about the long-term safety of mepolizumab in this paediatric population.

Once the extension of indication of Nucala to children aged 6-17 years is approved, the MAH plans to propose an update to the Nucala Product Information with the study 200363 Part B results.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development programme

Clinical studies –

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	18 January 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	12 December 2013	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	25 November 2008	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, Part A	7 December 2016	25 August 2017 Additionally submitted as part of EMEA/H/C/3860_II/G 21 November 2017
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, Part B	31st January 2018	Submitted with this procedure.

Extrapolation Study

Study title	Study number	Date of completion	Date of submission of final study report
Mepolizumab paediatric extrapolation report in the severe asthma indication	Report Number: 2017N323587_00	24th October 2017	Submitted as part of EMEA/H/C/3860_II/G: 21 November 2017