22 August 2024
EMA/CHMP/216873/2024
Human Medicines 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/P46/018

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

On 19th March 2024, the MAH submitted a completed paediatric study (Study 204524) for mepolizumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Since no amendments to the product information are foreseen as a result of the conclusions from the study, this report is submitted as a Post Authorisation Measure.

Study 204524 is not part of any Paediatric Investigation Plan.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

2.1.1. The MAH stated that Study 204524 is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

This was a non-interventional study intended to collect and assess information regarding the safety and effectiveness of the long-term use of authorised presentations of Nucala in Japanese patients in routine clinical practice. The following was provided in relation to formulations used in the study:

Trade name	Nucala for s.c. injection 100 mg Nucala solution for s.c. injection 100 mg Syringe Nucala solution for s.c. injection 100 mg Pen
Active ingredient	Mepolizumab (genetical recombination)
Marketing Authorization Holder (MAH)	GlaxoSmithKline K.K.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report, dated 14th December 2023, for:

Study 204524, entitled Nucala Subcutaneous Injection Special Drug Use Investigation (Long-Term) (Study on Bronchial Asthma).

2.3.2. Clinical Study 204524

Description

Methods

Objectives

The primary objective of this non-interventional study was to collect and assess information regarding the safety and effectiveness of the long-term use of mepolizumab for subcutaneous injection in Japanese patients with bronchial asthma in routine clinical practice.

Study design/objectives

The target population for this study was patients who had received a diagnosis of bronchial asthma (a refractory asthma whose symptoms are inadequately controlled despite receiving standard asthma medications), and who had not previously been treated/prescribed with Nucala.

This study involved a "central enrollment method" with data entry into an electronic data capture (EDC) system and subject enrollment to be completed within 14 days from the initiation of Nucala treatment.

The observation period (Nucala treatment period) per subject was one year (52 weeks) from the initiation of Nucala treatment. In addition, the follow-up investigation was to be conducted for 2 years after the observation period (or after the discontinuation/termination of Nucala treatment in discontinued/terminated cases) to investigate for occurrences of malignant tumour.

As per the submitted Protocol Synopsis, the following details were to be ascertained at "observation times":

1) Information regarding medical institutions
2) Patient characteristics (at the initiation of Nucala treatment)
   Identification number, gender, year of birth, start date of Nucala administration, hospitalization status, reason for use, presence/absence and names of comorbidities (renal impairment, hepatic impairment, allergies, others), history of smoking, duration of asthma, pre-administration severity and type of asthma
3) Prior medications for bronchial asthma (during 4 weeks prior to the initiation of Nucala treatment)
4) Administration status of Nucala
5) Concomitant medications
6) Concomitant therapies for bronchial asthma (except for medications)
7) Blood test items
8) Exacerbation of asthma
9) Respiratory function test (peak expiratory flow: PEF)
10) Asthma control test (ACT)
11) Global assessment of effectiveness
12) Status (continuation/discontinuation) of Nucala treatment at the end of the observation period
13) Occurrence status of malignant tumor during 2 years after the observation period (follow-up investigation)
14) Pregnancy
15) Adverse events (AEs)

In this study, effectiveness was assessed by the investigators as either "effective" or "not effective" at Week 52 of Nucala treatment or at the time of treatment discontinuation/termination, based on the course of subjective symptoms, course of clinical symptoms, and other findings from the initiation of Nucala treatment to the end of the observation period. If effectiveness could not be determined for some reasons, it was assessed as "indeterminable."

The safety assessments were a collection of all adverse events (serious and non-serious) including deaths. In this study, "hypersensitivity reaction including anaphylaxis," "infections," and "malignant tumour" were classified as "safety specifications and priority investigation matters". Of note, as per the regulations of the PMDA, the Japanese competent authority, only adverse events which are considered to be related to study treatment are required to be reported in the clinical study report. Causality assessment between adverse events and the study drug was determined by treating physicians, and not the sponsor.

Study participants

The study included patients who had received a diagnosis of bronchial asthma (a refractory asthma whose symptoms were inadequately controlled despite receiving standard asthma medications), and who had not previously been treated/prescribed Nucala.

The study was open to adult and paediatric enrolment.

Treatments

This was a non-interventional study in routine clinical practice using authorised Nucala medicinal products:

Trade name	Nucala for s.c. injection 100 mg Nucala solution for s.c. injection 100 mg Syringe Nucala solution for s.c. injection 100 mg Pen
Active ingredient	Mepolizumab (genetical recombination)
Marketing Authorization Holder (MAH)	GlaxoSmithKline K.K.

Outcomes

Effectiveness

Assessment of effectiveness of treatment by investigators: As either "effective", "not effective" or "indeterminable" at Week 52 or at the time of treatment discontinuation/termination.

The final CSR (Section 2.5) provides results pertaining to the measurement of other effectiveness outcomes:

- "exacerbation of bronchial asthma": Changes from baseline ("during the 52 weeks before the initiation of Nucala treatment") in the frequency of exacerbations after Nucala treatment ("at Week 52 of treatment or at the time of treatment discontinuation"
- "respiratory function test/peak expiratory flow": The mean peak expiratory flow (PEF, L/min) "at the initiation of Nucala treatment," "at 12 weeks after the initiation of Nucala treatment (at Week 12 of treatment)," "at Week 24 of treatment," and "at Week 52 of treatment" or "at the time of treatment discontinuation/termination"]
- "asthma control test": The mean asthma control test (ACT) 10) score "at the initiation of Nucala treatment," "at 12 weeks after the initiation of Nucala treatment (at Week 12 of treatment)," "at Week 24 of treatment," and "at Week 52 of treatment"

Safety

Adverse events (their type, incidence, time to onset, relatedness to IP), including those of specific interest in the study ("hypersensitivity reaction including anaphylaxis," "infections," and "malignant tumor").

Blood eosinophil count at prespecified timepoints were recorded; "before treatment initiation (9 to 52 weeks before the initiation of Nucala treatment)," "at the time of treatment initiation (0 to 8 weeks before the initiation of Nucala treatment)," "at 12 weeks after the initiation of Nucala treatment (Week 12 of treatment)," "at Week 24 of treatment," and "at Week 52 of treatment or at the time of treatment discontinuation/termination".

Serum total IgE concentration (IU/mL) before Nucala treatment and the presence or absence of "a history of omalizumab use" was investigated in the 1,027 patients in the safety analysis set. In addition, Serum

total IgE levels were collected prior to omalizumab administration or at 1 year or later after discontinuation of omalizumab treatment if there was a history of omalizumab use.

Sample size

There was a target enrolment of 1000 patients.

Randomisation and blinding (masking)

This was a non-interventional study in routine clinical practice.

Statistical Methods

No statistical analysis plan or discussion of statistical methods was provided in the submission.

CHMP comments

Study 204524 was an open label, non-interventional study that was designed to collect and assess safety and efficacy data from the long-term use of Nucala in Japanese clinical practice. Due to enrolment of paediatric patients in the study, the MAH was obliged, under Article 46 of Regulation 1901/2006, to submit the final clinical study report (CSR) and critical expert overview within 6 months of the completion of the study. The study was not part of a PIP.

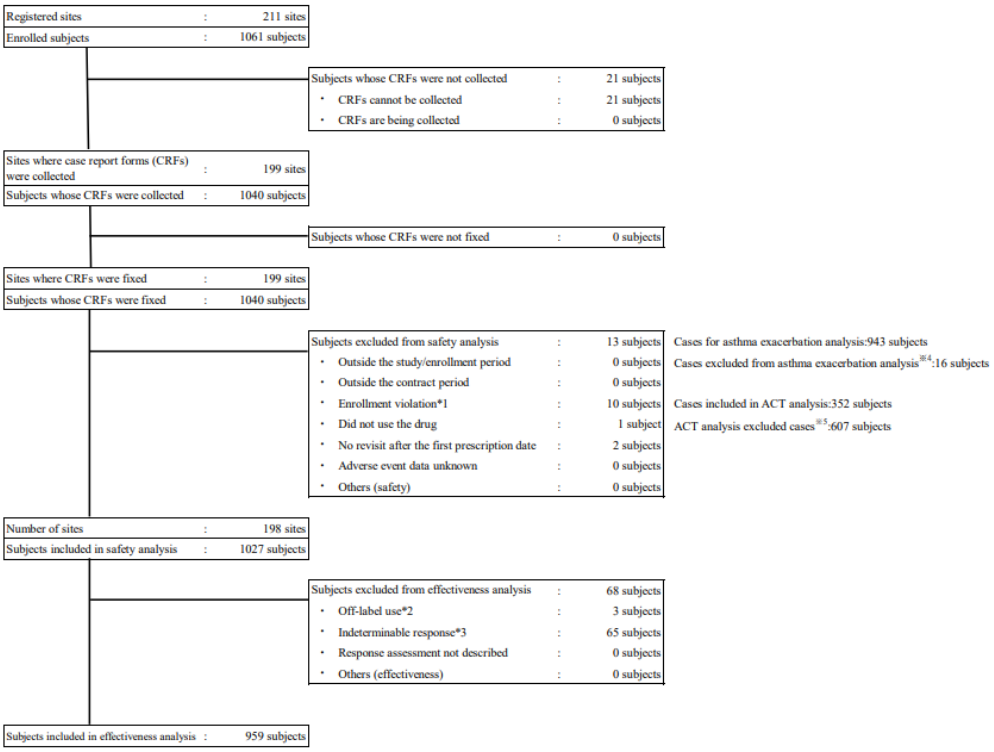
No study protocol was provided by the applicant, and the final CSR was not written in accordance with ICH E3 Clinical Study Reports guidelines, making it difficult to evaluate certain aspects of study design (inclusion/exclusion criteria, schedule of assessments, handling patient withdrawals/dropouts etc), study conduct and statistical methods (definition of safety and effectiveness analysis sets, ADRs, responders etc) employed. Lack of such detail presents challenges in the interpretation of the robustness of data. Comparing generated data to other studies in Nucala's clinical development is confounded by the differences in patient characteristics, study methods and study conditions between Study 204524 and previous studies.

That said, the applicant has provided this Article 46 paediatric study submission in line with EMA guidance, and sufficient detail is present to allow for evaluation of data in the context of this submission type. A request for further documentation will not be pursued.

Results

Recruitment/ Participant flow/ Number analysed

In total, 1061 subjects were enrolled in the study. 1027 subjects were included in the safety analysis set and 959 subjects in the effectiveness set. Subject disposition was as follows:



*1: Subjects who were found to have been enrolled in violation of the enrollment deadline specified in the implementation guideline (within 14 days after the start of administration of this drug (the start date of administration is defined as Day 1)) after collection of the CRF. No adverse drug reactions were observed in these subjects.

*2: Bronchiectasis (1 subject), bronchiolitis (1 subject), and eosinophilic granulomatosis with polyangiitis (1 subject)

*3: Subjects considered indeterminable by the investigator for the following reasons: "indeterminable because the drug was administered only once," "the subject did not visit the hospital after only one administration," "because the drug was administered only once," "because the drug was discontinued since EGPA occurred after the first administration and steroid pulse therapy was administered," "unable to evaluate because of the comorbidity of bronchial asthma attack after the first administration," "because the drug was discontinued for adverse events after the first administration," "because the drug was administered only twice," "the subject did not visit the hospital for three months," "the subject stopped visiting the hospital after the third administration," "because the drug was discontinued for aggravation of EGPA," "because the drug was discontinued too early," "because the patient was transferred too early (personal reason)," "because Fasenra was recommended by the primary care physician, and the drug was discontinued," "the subject stopped visiting the hospital due to coronavirus pandemic," "the subject said he/she had an effect for a few days although the data did not show that," "dropout," "request to discontinue the treatment only once due to high medical expenses," "because the treatment was discontinued after the subject had temporal effects but lost the effect," "because the subject did not visit the hospital," "because the drug was discontinued due to the subject's intention," "due to the subject's request," "because Nucala was discontinued and Fasenra was used at the subject's request," "smoking," "because the subject was dead of disease during the clinical course," "economic reason," "inability to continue the treatment due to economic reason," "discontinuation due to economic reason," "administration only once due to economic reason," "discontinuation after the third administration due to economic reason," "it was found that eosinophilic sinusitis was not improved and the subject had been diagnosed as atopic dermatitis", "changed to Dupixent because eosinophilic sinusitis did not improve", "because the number of times of use was small", "because the duration of use was short", "because the drug was discontinued for less than 2 months", "Unevaluable due to interruption of treatment", "no visit to the primary physician", "the subject did not visit to the hospital. Unable to contact the subject," "insufficient treatment duration," "due to early transfer to another hospital," "due to early discontinuation," "no change despite after-hours visit due to exacerbation," "discontinued in a short period," "discontinued in a short period of time at the subject's request," "interrupted," "the visit was irregular and the drug was administered only twice, and therefore the condition was not markedly changed," "unevaluable due to transfer to another hospital," "no visit due to transfer to another hospital," "discontinued at 1 year after the start of administration," "the administration duration was short," "the administration duration was too short," "the details of the statement were unclear due to dementia," "discontinued at the subject's request due to exacerbation of comorbidity," "oral steroid was required even after administration of this drug," "the subject's complaint was unclear," "treatment was discontinued after one dose due to the drug price," "adverse events," "early discontinuation due to adverse events," "the drug was effective but the subject wished to discontinue on February 12 due to malaise." and "no visits."

*4: Subjects included in effectiveness analysis for whom the number of asthma exacerbation before and after the start of administration of this drug was not described.

*5: Subjects included in effectiveness analysis for whom the ACT score before and after the start of administration of this drug was not measured.

Subject disposition in the 2-year follow-up period was as follows:

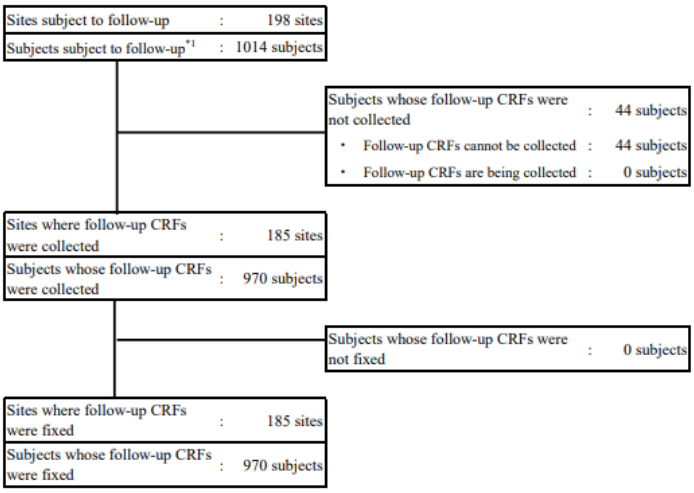


Figure 2 Subject disposition (follow-up)

*1: Among the subjects included in the safety analysis, those who completed the observation period and those who discontinued/completed the administration of this drug (excluding fatal cases) were followed up.

Baseline data

Of the 1027 patients included in the safety analysis set, 641 (62.4%) were female, including two pregnant women. The mean age was 62.7 ± 16.1 [(mean ± standard deviation (SD)] years, and 555 patients (54.0%) were "≥65" years of age. **There were 11 paediatric patients (<15 years) and 3 adolescents (15 to <18 years) included in the safety analysis set. 14 patients less than 18 years were included in the effectiveness set. No children under 12 years of age were treated**.

Nucala was administered for "bronchial asthma" in 1,024 patients (99.7%) and for "other conditions" in 3 patients (0.3%). The majority of patients, 995 (96.9%), had primary disease reported as "severe persistent" or "most severe persistent". 656 (63.9%) patients had baseline blood eosinophil counts ≥150 cells/μL. Baseline blood eosinophil counts were not reported for 208 (20.3%) patients.

A summary of patient demographics and baseline disease characteristics for patients in both the safety analysis and effectiveness analysis sets, which were generally similar, are as follows:

Subject characteristics		Subjects included in safety analysis		Subjects included in effectiveness analysis	
		Number of subjects studied	Composition ratio (%)	Number of subjects studied	Composition ratio (%)
Total		1027	100.0	959	100.0
Gender	Male	386	37.6	355	37.0
	Female	641	62.4	604	63.0
Pregnancy status "Female only"	No	623	97.2	589	97.5
	Yes	2	0.3	1	0.2
	Unknown	16	2.5	14	2.3
Age 1 [years] Mean ± SD: 62.7±16.1/62.6±16.1 Minimum: 12/12 Median: 66.0/66.0 Maximum: 93/93	<15	11	1.1	11	1.1
	15≤ to <65	461	44.9	431	44.9
	65≤ to <75	280	27.3	257	26.8
	75≤	275	26.8	260	27.1
Age 2 [years]	<65	472	46.0	442	46.1
	65≤	555	54.0	517	53.9
Age 3 [years]	<12	0	0.0	0	0.0
	12≤ to <18	14	1.4	14	1.5
	18≤	1013	98.6	945	98.5
Hospitalization status	Inpatient	59	5.7	50	5.2
	Outpatient	968	94.3	909	94.8
Reason for use of this drug	Bronchial asthma	1024	99.7	959	100.0
	Other	3	0.3	0	0.0
Breakdown of other reasons for use of this drug (name of disease)(multiple reasons)	Bronchiectasis	1	0.1	0	0.0
	Bronchiolitis	1	0.1	0	0.0
	Eosinophilic granulomatosis with polyangiitis	1	0.1	0	0.0
Comorbidity	No	290	28.2	280	29.2
	Yes	737	71.8	679	70.8
Comorbidity (renal impairment)	No	1002	97.6	938	97.8
	Yes	25	2.4	21	2.2
Comorbidity (hepatic impairment)	No	997	97.1	931	97.1
	Yes	30	2.9	28	2.9
Comorbidities (allergies)	No	625	60.9	592	61.7
	Yes	402	39.1	367	38.3
Comorbidities (other conditions)	No	411	40.0	392	40.9
	Yes	616	60.0	567	59.1
Smoking history	Never-smoker	702	68.4	668	69.7
	Ex-smoker	289	28.1	260	27.1
	Current-smoker	36	3.5	31	3.2
Primary disease (disease duration [years])	≤2	33	3.2	29	3.0
	2< to ≤5	68	6.6	60	6.3
	5< to ≤10	143	13.9	137	14.3
	10<	638	62.1	589	61.4
	Unknown	145	14.1	144	15.0
Primary disease (severity before administration)	Mild intermittent	0	0.0	0	0.0
	Mild persistent	2	0.2	2	0.2
	Moderate persistent	30	2.9	29	3.0
	Severe persistent	688	67.0	642	66.9
	Most severe persistent	307	29.9	286	29.8
Primary disease (disease type)	Atopic	532	51.8	485	50.6
	Non-atopic	382	37.2	364	38.0
	Unknown	113	11.0	110	11.5
Blood eosinophil count (9 to 52 weeks before start of administration of this drug)[/μL] Mean ± SD: 701.0±935.1/708.1±938.0 Minimum: 0/0 Median: 460.0/466.0 Maximum: 9999/9999	<150	110	10.7	97	10.1
	150≤ to <300	95	9.3	93	9.7
	300≤ to <500	143	13.9	134	14.0
	500≤	308	30.0	290	30.2
	Unknown	371	36.1	345	36.0
Blood eosinophil count (baseline)[/μL] Mean ± SD: 641.5±822.9/634.7±813.8 Minimum: 0/0 Median: 418.0/409.0 Maximum: 7500/7500	<150	163	15.9	150	15.6
	150≤ to <300	110	10.7	103	10.7
	300≤ to <500	196	19.1	182	19.0
	500≤	350	34.1	325	33.9
	Unknown	208	20.3	199	20.8
History of omalizumab use	No	871	84.8	813	84.8
	Yes	156	15.2	146	15.2
Prior medications for bronchial asthma	No	7	0.7	7	0.7
	Yes	1020	99.3	952	99.3
Concomitant medications	No	75	7.3	69	7.2
	Yes	952	92.7	890	92.8
Concomitant therapies for bronchial asthma (other than drug therapy)	No	1013	98.6	946	98.6
	Yes	14	1.4	13	1.4

The "mean ± SD," "minimum," "median," and "maximum" for each subject factor are presented in the order of "safety analysis set" / "effectiveness analysis set."

Of the 1027 patients included in the safety analysis set, 616 (60.0%) had reported comorbidities; the most common (in descending order) were "hypertension" (204; 19.9%), "gastroesophageal reflux disease" (102; 9.9%), "osteoporosis" 87 (87; 8.5%), "diabetes mellitus" (86; 8.4%), "insomnia" (86; 8.4%), and "chronic obstructive pulmonary disease" (73; 7.1%).

The most commonly used prior medications were "inhaled corticosteroid/long-acting β2-agonist combination products" in 922 (89.8%) patients. "Oral corticosteroids" had been used as prior medications in 353 (34.4%) patients. A summary of prior medications is given, by safety analysis and effectiveness analysis sets, is given below:

Item/Category		Subjects included in safety analysis								Subjects included in effectiveness analysis			
		Daily dose for 4 weeks prior to the start of administration of this drug*				Number of subjects	Usage ratio (%)	Number of subjects with adverse drug reactions	Incidence of adverse drug reactions (%)	Number of subjects	Usage ratio (%)	Number of responders	Rate of responders (%)
		Mean ± SD	Minimum	Median	Maximum								
Prior medications	Inhaled corticosteroid alone					126	12.3	4	3.2	118	12.3	101	85.6
	Flutide					14	1.4	0	0.0	13	1.4	11	84.6
	Qvar					22	2.1	0	0.0	22	2.3	21	95.5
	Alvesco					53	5.2	3	5.7	50	5.2	40	80.0
	Pulmicort					24	2.3	1	4.2	22	2.3	18	81.8
	Asmanex					11	1.1	0	0.0	9	0.9	8	88.9
	Other					5	0.5	0	0.0	5	0.5	5	100.0
	Arnuity					4	0.4	0	0.0	4	0.4	4	100.0
	Aldecin					1	0.1	0	0.0	1	0.1	1	100.0
	Unknown					1	0.1	0	0.0	1	0.1	1	100.0
	Inhaled corticosteroid/long-acting β2-agonist combination					922	89.8	40	4.3	861	89.8	781	90.7
	Relvar					334	32.5	15	4.5	315	32.8	294	93.3
	Adoair					135	13.1	1	0.7	131	13.7	117	89.3
	Symbicort					253	24.6	13	5.1	232	24.2	206	88.8
	Flutiform					207	20.2	11	5.3	190	19.8	171	90.0
	Other					4	0.4	0	0.0	4	0.4	4	100.0
	Trelegy					3	0.3	0	0.0	3	0.3	3	100.0
	BudeForu					1	0.1	0	0.0	1	0.1	1	100.0
	Oral corticosteroids		-			353	34.4	22	6.2	327	34.1	291	89.0
	Prednisolone/predonine	11.031±9.505	1.00	8.000	75.00	310	30.2	21	6.8	287	29.9	254	88.5
	Cortril	3.861±3.307	2.00	2.500	12.50	10	1.0	0	0.0	9	0.9	9	100.0
	Medrol	9.219±7.348	1.25	7.500	20.00	9	0.9	0	0.0	9	0.9	8	88.9
	Ledercort	3.750±1.768	2.50	3.750	5.00	2	0.2	0	0.0	2	0.2	2	100.0
	Orgadrone/decadron	8.667±7.764	1.67	5.000	20.00	5	0.5	1	20.0	5	0.5	4	80.0
	Rinderon	9.298±7.784	0.87	6.667	26.67	14	1.4	0	0.0	12	1.3	11	91.7
	Other		-			8	0.8	0	0.0	8	0.8	8	100.0
	Celestamine		-			8	0.8	0	0.0	8	0.8	8	100.0
	Unknown		-			1	0.1	0	0.0	1	0.1	0	0.0
	Long-acting β2 agonist alone					82	8.0	3	3.7	74	7.7	62	83.8
	Leukotriene receptor antagonists					685	66.7	29	4.2	644	67.2	579	89.9
	Theophylline sustained-release preparation					375	36.5	14	3.7	351	36.6	311	88.6
	Long-acting anticholinergics					484	47.1	18	3.7	457	47.7	404	88.4
	Anti-IgE antibody					74	7.2	3	4.1	69	7.2	59	85.5
	Antiallergic agents other than leukotriene receptor antagonists					255	24.8	17	6.7	236	24.6	198	83.9
	Unknown					5	0.5	0	0.0	5	0.5	5	100.0

*Calculated by prednisolone dose

CHMP comments

In the EU, Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older. In Japan, Nucala is indicated for the treatment of bronchial asthma in children aged six years or above and in adults with refractory asthma whose symptoms could not be controlled adequately with standard treatment. The differing indications between jurisdictions have contributed to differing patient characteristics between those enrolled in Study 204524 and pivotal studies submitted in support of the EU MA.

Generally, however, the majority of participants (n=995; 96.9%) enrolled in Study 204524 had severe disease; "severe persistent asthma" in 688 patients (67.0%), followed by "most severe persistent asthma" in 307 patients (29.9%). The most commonly used prior medications of participants were "inhaled corticosteroid/long-acting β2-agonist combination products" in 922 patients (89.8%), and "Oral corticosteroids" had been used as prior medications in 353 patients (34.4%).

In addition, the majority of patients 656 (63.9%) enrolled in Study 204524 had baseline blood eosinophil counts ≥150 cells/μL. Of note, all patients in the pivotal phase III studies (MEA115588 and MEA115575) supporting EU Nucala's severe eosinophilic asthma indication (in adults and paediatrics over 12 years of age) had peripheral blood eosinophil levels greater than or equal to 150 cells/μL at initiation of treatment or greater than or equal to 300 cells/μL within the past 12 months. Baseline blood eosinophil counts were not reported for 208 (20.3%) patients in Study 204524.

Although differing patient characteristics present challenges in comparing outcomes from Study 204524 to other (including pivotal) clinical studies supporting Nucala's EU clinical development, the applicant has provided an adequate qualitative comparative analysis under individual safety and effectiveness subheadings in the final CSR.

Of the 1027 patients included in the safety analysis set, the mean age was 62.7 ± 16.1 [(mean ± standard deviation (SD)] years, and 555 patients (54.0%) were "≥65" years of age. **There were 11**

paediatric patients (less than 15 years of age) and 3 adolescents (from 15 to less than 18 years of age). 14 patients less than 18 years of age were included in the effectiveness set.

The MAH is asked to provide summaries of baseline characteristics and prior medications for the 11 paediatric and 3 adolescent patients enrolled in the study **(OC).**

Patient exposure

In the 1,027 patients in the safety analysis set, 99.9% (1026/1027) of participants received at least one monthly dose of mepolizumab 100 mg. Mean ± SD of total number of doses was 9.4±5.2. Mean ± SD of duration of administration of the drug [days] was 272.6±163.0.

Among the 1,027 patients in the safety analysis set, Nucala treatment was "ongoing" in 559 patients (54.4%) and had been "discontinued/terminated" in 468 patients (45.6%) at the end of the observation period. The reasons for treatment discontinuation included "factors associated with effectiveness" in 146 patients, "patient's inconvenience other than the abovementioned" in 115 patients, and "financial reasons" in 59 patients (reasons for treatment discontinuation: duplicates included).

The extent of patient exposure and reasons for discontinuation in the observation period, by safety analysis and effectiveness analysis sets, are provided in the table below.

Subjects included in safety analysis, Subjects included in effectiveness analysis

Item/Category		Subjects included in safety analysis				Subjects included in effectiveness analysis			
		Number of subjects	Usage ratio (%)	Number of subjects with adverse drug reactions	Incidence of adverse drug reactions (%)	Number of subjects	Usage ratio (%)	Number of responders	Rate of responders (%)
Daily dose [mg](at the start of administration)	100	1026	99.9	42	4.1	958	99.9	865	90.3
	100<	1	0.1	0	0.0	1	0.1	1	100.0
Total number of doses [dose]	<1	0	0.0	0	-	0	0.0	0	-
Number of subjects: 1027/959	1≤ to <3	153	14.9	14	9.2	117	12.2	97	82.9
Mean ± SD: 9.4±5.2/9.8±5.0	3≤ to <6	141	13.7	12	8.5	121	12.6	84	69.4
Minimum: 1/1	6≤ to <9	118	11.5	5	4.2	112	11.7	96	85.7
Median: 11.0/11.0	9≤ to <13	221	21.5	9	4.1	218	22.7	204	93.6
Maximum: 20/20	13≤	394	38.4	2	0.5	391	40.8	385	98.5
Total dose [mg]	<100	0	0.0	0	-	0	0.0	0	-
Number of subjects: 1027/959	100≤ to <300	153	14.9	14	9.2	117	12.2	97	82.9
Mean ± SD: 941.4±528.1/984.2±513.1	300≤ to <600	141	13.7	12	8.5	121	12.6	84	69.4
Minimum: 100/100	600≤ to <900	118	11.5	5	4.2	112	11.7	96	85.7
Median: 1100.0/1100.0	900≤ to <1300	221	21.5	9	4.1	218	22.7	204	93.6
Maximum: 4500/4500	1300≤	394	38.4	2	0.5	391	40.8	385	98.5
Duration of administration of this drug [days]	<28	96	9.3	7	7.3	73	7.6	61	83.6
Number of subjects: 1027/959	28≤ to <84	101	9.8	9	8.9	74	7.7	55	74.3
Mean ± SD: 272.6±163.0/286.4±157.3	84≤ to <168	109	10.6	11	10.1	100	10.4	72	72.0
Minimum: 1/1	168≤ to <252	75	7.3	4	5.3	73	7.6	58	79.5
Median: 344.0/355.0	252≤ to <365	218	21.2	6	2.8	215	22.4	203	94.4
Maximum: 1418/1418	365≤	428	41.7	5	1.2	424	44.2	417	98.3
Administration of the drug at the end of the observation period	Treatment continued	559	54.4	5	0.9	553	57.7	543	98.2
(Reasons for discontinuation: duplicates included)	Discontinuation/termination of administration	468	45.6	37	7.9	406	42.3	323	79.6
	Onset of adverse events	54	5.3	28	51.9	41	4.3	31	75.6
	Pregnancy	2	0.2	0	0.0	1	0.1	1	100.0
	Factors associated with effectiveness	146	14.2	7	4.8	143	14.9	76	53.1
	Financial reasons	59	5.7	3	5.1	45	4.7	40	88.9
	No revisit after the first prescription date	0	0.0	0	-	0	0.0	0	-
	No revisit in the middle of the study	45	4.4	1	2.2	33	3.4	32	97.0
	Patient's inconvenience other than the above mentioned	115	11.2	0	0.0	97	10.1	93	95.9
	Physician's judgment other than the above mentioned	41	4.0	1	2.4	34	3.5	33	97.1
	Unknown	37	3.6	1	2.7	37	3.9	37	100.0

The "mean ± SD," "minimum," "median," and "maximum" for each item are presented in the order of "safety analysis set" / "effectiveness analysis set."

CHMP comments

A total of 1,027 patients were included in the safety analysis. Whilst the safety analysis set is not formally defined in the submission, it is presumed by the assessor, based on available data, that it included those that were enrolled in the study, according to the referenced implementation guideline, and received at least one full or partial dose of mepolizumab. Among these 1,027 patients, Nucala treatment was "ongoing" in 559 patients (54.4%) and had been "discontinued/terminated" in 468 patients (45.6%) at the end of the 52-week observation period. The most common cited reasons for discontinuation were "factors associated with effectiveness" (n=146; 14.2%), "patients inconvenience other than the above

mentioned” (n=115; 11.2%), “financial reasons" (n=56; 5.7%), and “onset of adverse events" (n=54; 5.3%).

The MAH is asked to provide summaries of patient exposure and reasons for discontinuation for the 11 paediatric and 3 adolecent patients enrolled in the study. **(OC)**

Efficacy results

Primary effectiveness outcome

Among the 959 patients in the effectiveness analysis set, the rate of responders was reported as 90.3% (866/959 patients).

Paediatric effectiveness data

Of the 959 patients treated with Nucala in the effectiveness analysis set, 11 were paediatric patients (under 15 years of age), and the rate of responders in the paediatric (< 15 years) patients was 81.8% (9/11 patients). No patients under 12 years of age were treated. Although the rate of non-responders in children (under 15 years of age) was slightly higher than that in the overall population, "age" was not detected as a factor affecting efficacy. No information on effectiveness of adolescent population was reported in the clinical study report as the 3 adolescent participants were included in the adult population effectiveness calculations.

Factors affecting effectiveness

Multivariate analysis was performed for the effectiveness based on patient characteristics to identify factors for which the adjusted odds ratio met the criteria "the asymptotic 95% confidence interval does not cross 1 and the point estimate exceeds 2 or is less than 0.5"; i.e., factors meeting the criteria were defined as factors affecting the effectiveness. Adjusted odds ratios were estimated using the following factors: "gender," "categorized age 1 [years]," "smoking history," "the primary disease (disease duration [years])," "comorbidities," "comorbidity (renal impairment)," "comorbidity (hepatic impairment)," "comorbidities (allergies)," "comorbidities (other conditions)," "blood eosinophil count (at the initiation of Nucala treatment) [/μL]," "prior medications for bronchial asthma," "concomitant medications," and "concomitant therapies (other than drug therapy) for bronchial asthma." Based on the analysis results, no factors meeting the criteria were detected.

The above variables were selected by Stepwise method (significance level 0.3: score chi-square was used in the step of placing factors in the model, and Wald chi-square was used in the step of excluding variables). The model variable "comorbidities" and "blood eosinophil count (at the initiation of Nucala treatment) [/μL]" were selected. According to the analysis results, "comorbidities" and "blood eosinophil count (at the initiation of Nucala treatment) [/μL]" did not meet the above criteria.

A summary of results from effectiveness analysis, including factors affecting effectiveness, is given below:

Table 23 Rate of responders by subject characteristics

As of September 27, 2023

Subjects included in effectiveness analysis

Subject characteristics		Number of subjects studied	Number of responders	Number of non-responders	Rate of responders (%)	95% confidence interval	
						Lower limit	Upper limit
Total		959	866	93	90.3	88.3	92.1
Gender	Male	355	317	38	89.3	85.6	92.3
	Female	604	549	55	90.9	88.3	93.1
Pregnancy status "Female only"	No	589	536	53	91.0	88.4	93.2
	Yes	1	1	0	100.0	2.5	100.0
	Unknown	14	12	2	85.7	57.2	98.2
Age 1 [years]	<15	11	9	2	81.8	48.2	97.7
Mean ± SD: 62.6±16.1	15≤ to <65	431	387	44	89.8	86.5	92.5
Minimum: 12	65≤ to <75	257	236	21	91.8	87.8	94.9
Median: 66.0	75≤	260	234	26	90.0	85.7	93.4
Maximum: 93							
Age 2 [years]	<65	442	396	46	89.6	86.4	92.3
	65≤	517	470	47	90.9	88.1	93.2
Hospitalization status	Inpatient	50	46	4	92.0	80.8	97.8
	Outpatient	909	820	89	90.2	88.1	92.1
Reason for use of this drug	Bronchial asthma	959	866	93	90.3	88.3	92.1
	Other	0	0	0	-	-	-
Comorbidity	No	280	262	18	93.6	90.0	96.1
	Yes	679	604	75	89.0	86.4	91.2
Comorbidity (renal impairment)	No	938	847	91	90.3	88.2	92.1
	Yes	21	19	2	90.5	69.6	98.8
Comorbidity (hepatic function disorder)	No	931	841	90	90.3	88.3	92.2
	Yes	28	25	3	89.3	71.8	97.7
Comorbidities (allergies)	No	592	544	48	91.9	89.4	94.0
	Yes	367	322	45	87.7	83.9	90.9
Comorbidities (other conditions)	No	392	362	30	92.3	89.3	94.8
	Yes	567	504	63	88.9	86.0	91.4
Smoking history	Never-smoker	668	612	56	91.6	89.3	93.6
	Ex-smoker	260	229	31	88.1	83.5	91.8
	Current-smoker	31	25	6	80.6	62.5	92.5
Primary disease (disease duration [years])	≤2	29	29	0	100.0	88.1	100.0
	2< to ≤5	60	55	5	91.7	81.6	97.2
	5< to ≤10	137	120	17	87.6	80.9	92.6
	10<	589	530	59	90.0	87.3	92.3
	Unknown	144	132	12	91.7	85.9	95.6
Primary disease (severity before administration)	Mild intermittent	0	0	0	-	-	-
	Mild persistent	2	2	0	100.0	15.8	100.0
	Moderate persistent	29	27	2	93.1	77.2	99.2
	Severe persistent	642	592	50	92.2	89.9	94.2
	Most severe persistent	286	245	41	85.7	81.1	89.5
Primary disease (disease type)	Atopic	485	433	52	89.3	86.2	91.9
	Non-atopic	364	336	28	92.3	89.1	94.8
	Unknown	110	97	13	88.2	80.6	93.6
Blood eosinophil count (9 to 52 weeks before start of administration of this drug)[/μL]	<150	97	88	9	90.7	83.1	95.7
Mean ±SD: 708.1±938.0	150≤ to <300	93	68	25	73.1	62.9	81.8
Minimum: 0	300≤ to <500	134	120	14	89.6	83.1	94.2
Median: 466.0	500≤	290	265	25	91.4	87.5	94.3
Maximum: 9999	Unknown	345	325	20	94.2	91.2	96.4
Blood eosinophil count (baseline)[/μL]	<150	150	132	18	88.0	81.7	92.7
Mean ± SD: 634.7±813.8	150≤ to <300	103	86	17	83.5	74.9	90.1
Minimum: 0	300≤ to <500	182	169	13	92.9	88.1	96.1
Median: 409.0	500≤	325	300	25	92.3	88.9	95.0
Maximum: 7500	Unknown	199	179	20	89.9	84.9	93.8
History of omalizumab use	No	813	748	65	92.0	89.9	93.8
	Yes	146	118	28	80.8	73.5	86.9
Prior medications for bronchial asthma	No	7	7	0	100.0	59.0	100.0
	Yes	952	859	93	90.2	88.2	92.0
Concomitant medications	No	69	59	10	85.5	75.0	92.8
	Yes	890	807	83	90.7	88.6	92.5
Concomitant therapies for bronchial asthma (other than drug therapy)	No	946	855	91	90.4	88.3	92.2
	Yes	13	11	2	84.6	54.6	98.1

Table 24 Multivariate logistic regression analysis (effectiveness)

As of September 27, 2023

Subjects included in effectiveness analysis

Odds ratio estimated by multivariate logistic regression

Item/Category			Number of subjects studied	Number of responders	Rate of responders (%)	Adjusted odds ratio		
						Point estimation	95% confidence	
							Lower limit	Upper limit
Total			959	866	90.3	-	-	-
Comorbidity	No	*	280	262	93.6	-	-	-
	Yes		679	604	89.0	0.476	0.217	1.044
Blood eosinophil count (baseline)[/μL]	<150	*	150	132	88.0	-	-	-
	150≤ to <300		103	86	83.5	0.768	0.360	1.639
	300≤ to <500		182	169	92.9	1.888	0.837	4.259
	500≤		325	300	92.3	1.898	0.974	3.699

*: Criteria

Other effectiveness outcomes

Exacerbation of bronchial asthma

The table below shows changes from baseline ("during the 52 weeks before the initiation of Nucala treatment") to after Nucala treatment ("at Week 52 of treatment or at the time of treatment discontinuation") in the 959 patients in the effectiveness analysis set for the frequency of all bronchial asthma exacerbations, for exacerbations requiring hospitalization, for exacerbations requiring emergency department visits, for exacerbations requiring the use of systemic corticosteroid, and for exacerbations requiring hospitalization (number of days of hospitalization). Decreasing incidence rates were observed for all types of exacerbations from baseline to Week 52 of Nucala treatment (or at time of discontinuation).

Table 25 Exacerbation of bronchial asthma

Subjects included in effectiveness analysis

As of September 27, 2023

Exacerbation of bronchial asthma	Period	Number of subjects	Total person-year *1	Number of exacerbation/ number of days	Rate *2	Number of subjects with events	Minimum *3	Median *3	Maximum *3	Rate Ratio *4	95% CI *4
The frequency of all bronchial asthma exacerbations	52 weeks before the initiation of Nucala treatment	943	943.0	3537	3.8	707	1	3.0	170	-	-
	Week 52 of treatment or at the time of treatment discontinuation	959	736.8	708	1.0	219	1	2.0	73	0.32	0.27-0.38
The frequency of exacerbations requiring hospitalization	52 weeks before the initiation of Nucala treatment	956	956.0	414	0.4	195	1	1.0	99	-	-
	Week 52 of treatment or at the time of treatment discontinuation	959	736.8	90	0.1	63	1	1.0	4	0.32	0.23-0.45
The frequency of exacerbations requiring emergency department visits	52 weeks before the initiation of Nucala treatment	943	943.0	892	0.9	260	1	2.0	99	-	-
	Week 52 of treatment or at the time of treatment discontinuation	959	736.8	170	0.2	81	1	1.0	12	0.27	0.20-0.37
The frequency of exacerbations requiring the use of systemic corticosteroid	52 weeks before the initiation of Nucala treatment	956	956.0	3017	3.2	674	1	3.0	156	-	-
	Week 52 of treatment or at the time of treatment discontinuation	959	736.8	523	0.7	183	1	2.0	68	0.26	0.22-0.31
Bronchial asthma exacerbations requiring hospitalization (number of days of hospitalization)	52 weeks before the initiation of Nucala treatment	956	956.0	3879	4.1	192	1	11.5	131	-	-
	Week 52 of treatment or at the time of treatment discontinuation	959	736.8	1597	2.2	63	1	12.0	233	0.89	0.54-1.48

*1: 52 weeks were converted to 1 year
*2: Number of exacerbation/number of days / total person-year
*3: Subjects with events were included
*4: Negative binomial regression model using administration period as an explanatory variable and observation period (log) as an offset variable

Respiratory function test (Peak Expiratory Flow)

The table below shows the mean peak expiratory flow (PEF, L/min) "at the initiation of Nucala treatment," "at 12 weeks after the initiation of Nucala treatment (at Week 12 of treatment)," "at Week 24 of treatment," and "at Week 52 of treatment" or "at the time of treatment discontinuation/termination" in the 959 patients in the effectiveness analysis set. Among patients for whom PEF measurements were performed, the mean PEF ± standard deviation (SD) at each time point was as follows: 304.4 ± 146.8 at the initiation of Nucala treatment (120 patients: n = 120), 333.7 ± 150.5 at Week 12 (n = 78), 334.2 ± 138.7 at Week 24 (n = 51), and 358.9 ± 129.8 at Week 52 (n = 45) or 349.5 ± 134.7 at the time of treatment discontinuation/termination (n = 43).

Table 26 Respiratory function test values

Subjects included in effectiveness analysis

As of September 27, 2023

Item/Category	Peak Flow (PEF)									
	Baseline		12 weeks after the initiation of Nucala treatment		24 weeks after the initiation of Nucala treatment		52 weeks after the initiation of Nucala treatment		At the time of treatment discontinuation/termination	
	Number of subjects (%)/ summary statistics		Number of subjects (%)/ summary statistics		Number of subjects (%)/ summary statistics		Number of subjects (%)/ summary statistics		Number of subjects (%)/ summary statistics	
Subjects included in analysis	120	(12.5)	78	(8.1)	51	(5.3)	45	(4.7)	43	(4.5)
Number of subjects	120		78		51		45		43	
Mean ± standard deviation	304.4±146.8		333.7±150.5		334.2±138.7		358.9±129.8		349.5±134.7	
Minimum	66		55		130		54		54	
Median	281.0		310.0		305.0		340.0		320.0	
Maximum	869		999		913		620		620	

Asthma Control Test (ACT)

The table below shows the mean asthma control test (ACT) 10) score "at the initiation of Nucala treatment," "at 12 weeks after the initiation of Nucala treatment (at Week 12 of treatment)," "at Week 24 of treatment," and "at Week 52 of treatment" in the 959 patients in the effectiveness analysis set. Among patients for whom ACT score measurements were performed, the mean ACT score ± SD at each time point was as follows: 16.2 ± 4.9 at the initiation of Nucala treatment (n = 352), 20.5 ± 4.3 at Week 12 (n = 317), 20.9 ± 4.2 at Week 24 (n = 261), and 21.4 ± 4.0 at Week 52 (n = 221). The mean ACT score was 16.2 ± 4.9 at the initiation of Nucala treatment (at baseline), indicating "poor control," while it was 20.5 ± 4.3 at Week 12, indicating "well control." ACT scores at Weeks 24 and 52 also indicated "well control"; i.e., this favorable condition "well control" was maintained throughout the treatment period. After the initiation of Nucala treatment, the minimal clinically important difference (MCID) of at least a 3-point increase from baseline in the ACT score 11) was achieved in 208 patients (65.6%) at Week 12, in 180 patients (69.0%) at Week 24, and in 163 patients (73.8%) at Week 52.

Table 27 ACT score (all subjects)

As of September 27, 2023

Subjects included in effectiveness analysis

Item/Category		ACT score	
Subjects included in effectiveness analysis		959	
Subjects included in ACT analysis		352	
Baseline	Number of subjects	352	
	Mean ± standard deviation	16.2±4.9	
	Minimum	5	
	25% point	13.0	
	Median	17.0	
	75% point	20.0	
	Maximum	25	
12 weeks after the initiation of Nucala treatment	Number of subjects	317	
	Mean ± standard deviation	20.5±4.3	
	Minimum	7	
	25% point	19.0	
	Median	22.0	
	75% point	24.0	
	Maximum	25	
24 weeks after the initiation of Nucala treatment	Number of subjects	261	
	Mean ± standard deviation	20.9±4.2	
	Minimum	5	
	25% point	19.0	
	Median	22.0	
	75% point	24.0	
	Maximum	25	
52 weeks after the initiation of Nucala treatment	Number of subjects	221	
	Mean ± standard deviation	21.4±4.0	
	Minimum	6	
	25% point	20.0	
	Median	23.0	
	75% point	25.0	
	Maximum	25	
ACT score (12 weeks after the initiation of Nucala treatment - at the initiation of Nucala treatment) ≥3	Number of subjects	208	(65.6)
ACT score (24 weeks after the initiation of Nucala treatment - at the initiation of Nucala treatment) ≥3	Number of subjects	180	(69.0)
ACT score (52 weeks after the initiation of Nucala treatment - at the initiation of Nucala treatment) ≥3	Number of subjects	163	(73.8)

CHMP comments

Of the 959 patients in the effectiveness analysis set, the rate of responders, those in whom the investigator deemed the treatment “effective” after 52 weeks of treatment or at the time of treatment

discontinuation/termination, was reported as 90.3% (866/959 patients). Based on multivariate analysis of 13 variables (including age, renal impairment, hepatic impairment, blood eosinophil count at initiation of Nucala treatment), no factors met the defined criteria to be considered to have affected effectiveness.

The rate of responders in the paediatric patients was 81.8% (9/11 patients), slightly higher than that in the overall population, but "age" was not determined to be a factor affecting effectiveness. No information on effectiveness in the adolescent population was reported in the clinical study report as the 3 adolescent participants were included in the adult population effectiveness calculations.

Other effectiveness measures, including change in the overall frequency of exacerbations and the frequency of specific types of exacerbations (e.g., those requiring hospitalisation, systemic corticosteroids etc) showed decreasing incidence rates from baseline to Week 52 of Nucala treatment (or at time of discontinuation). Notwithstanding the differences between patient characteristics, study design and study conditions, the extent of improvement of asthma exacerbations in Study 204524 were considered to be similar to those observed for Study MEA115588, the pre-approval, global, phase III study conducted in patients with severe asthma (including 50 Japanese patients).

Peak expiratory flow (PEF) and asthma control test (ACT) showed improvements in respiratory function and asthma control with Nucala at pre-defined times points during the 52-week observational part of the study.

Whilst acknowledging uncertainties (including definition of responder, correlation between relatively high rate of discontinuation/termination reported due to "factors associated with effectiveness" and the overall primary effectiveness outcome) pertaining to study design and conduct, Study 204524 has shown Nucala to be an effective treatment in adult and paediatric (from 12 years) Japanese patients when used in routine clinical practice for the treatment of bronchial asthma as determined by treating physicians during a 52-week observational study period. The primary effectiveness results were supported by additional effectiveness results, including reduced frequency of asthma exacerbations with time on Nucala treatment. These results are in line with those previously reported for mepolizumab.

As no new significant efficacy information has been generated as a result of this study, no update to the product information is necessary from an efficacy perspective.

As only 14 paediatric and adolescent patients (from 12 years to less than 18 years) were enrolled in this study, and data from the 3 adolescent patients (from 15 years to less than 18 years) were included in the adult population effectiveness calculations, the overall data generated are insufficient to make any comment on the efficacy of mepolizumab in this population, and no change to the product information is warranted. Nevertheless, additional data summaries restricted to the paediatric and adolescent patients are requested for completeness. **(OC)**

Safety results

Adverse drug reactions

As per the regulations of the Japanese PMDA, only adverse events which are considered to be related to study treatment are required to be reported in the clinical study report, i.e. adverse drug reactions (ADRs). Causality assessment between adverse events and the study drug was determined by treating physicians, and not the sponsor.

ADRs occurred in 42 (4.1%) of the 1,027 patients in the safety analysis set. The incidence rates of ADRs by system organ class (SOC) were "respiratory, thoracic and mediastinal disorders" 1.2% (12/1,027 patients), followed by "skin and subcutaneous tissue disorders" 1.0% (10/1,027). The most frequently

reported ADRs (in descending order) included "asthma" 0.7% (7/1,027 patients), "chronic eosinophilic rhinosinusitis" 0.4% (4/1,027), and "urticaria" 0.4% (4/1,027).

To investigate factors affecting the onset of ADRs based on patient characteristics, multivariate analysis was performed to identify factors for which the adjusted odds ratio/risk ratio met the criteria "the asymptotic 95% confidence interval does not cross 1 and the point estimate exceeds 2 or is less than 0.5"; i.e., factors meeting the criteria were defined as factors affecting the onset of ADRs. Based on the analysis results, no factors meeting the criteria were detected.

The time from the initiation of Nucala treatment to the onset of ADRs was examined for every type of ADRs reported in 42 of the 1,027 patients in the safety analysis set. No trend toward an increased incidence with long-term treatment was observed.

Serious adverse drug reactions

There were 9 (0.9%) reported serious ADRs. The types of ADRs included "asthma" with an incidence of 0.2% (2/1,027 patients) and "Chronic eosinophilic rhinosinusitis", "Angioedema", "Condition aggravated", "pneumonia", "myasthenia gravis", "gastric cancer", "Intraductal papillary mucinous carcinoma of pancreas", "Optic neuropathy" and "Vertigo positional" with an incidence of 0.1% (1/1,027).

The outcome of three of these serious ADRs ("pneumonia" in one patient, "gastric cancer" in one, and "asthma" in one) was reported as death. The outcome of all other serious ADRs was reported as "recovering" and "recovered".

Of those serious ADRs with a reported outcome of death, "gastric cancer" developed after the discontinuation of Nucala treatment (17 Apr 2018, drug was discontinued (85 days of treatment); adverse drug reaction occurred on 31 Oct 2019) and, as per CSR, it was difficult to ascertain any causal relationship with the drug.

"Pneumonia" and "asthma" causal relationship with Nucala is not excluded but the details, including the clinical courses resulting in fatalities, have not been obtained. Therefore, it was difficult to further evaluate causal relationship with the drug.

A summary of ADRs is given in the table below:

As of September 27, 2023

Subjects included in safety analysis

	Total		Serious	
Number of subjects studied	1027			
Number of subjects with adverse drug reactions, etc.	42		9	
Incidence of adverse drug reactions, etc. (%)	4.1		0.9	
Types of adverse drug reactions, etc.	Number of subjects with adverse drug reactions (%)			
Respiratory, thoracic and mediastinal disorders	12	(1.2)	3	(0.3)
Asthma	7	(0.7)	2	(0.2)
Chronic eosinophilic rhinosinusitis	4	(0.4)	1	(0.1)
Upper respiratory tract inflammation	1	(0.1)	0	(0.0)
Skin and subcutaneous tissue disorders	10	(1.0)	1	(0.1)
Urticaria	4	(0.4)	0	(0.0)
Pruritus	2	(0.2)	0	(0.0)
Rash	2	(0.2)	0	(0.0)
Alopecia	1	(0.1)	0	(0.0)
Angioedema	1	(0.1)	1	(0.1)
Eczema	1	(0.1)	0	(0.0)
General disorders and administration site conditions	9	(0.9)	1	(0.1)
Condition aggravated	4	(0.4)	1	(0.1)
Malaise	2	(0.2)	0	(0.0)
Oedema peripheral	1	(0.1)	0	(0.0)
Pain	1	(0.1)	0	(0.0)
Pyrexia	1	(0.1)	0	(0.0)
Infections and infestations	3	(0.3)	1	(0.1)
Bronchitis	1	(0.1)	0	(0.0)
Nasopharyngitis	1	(0.1)	0	(0.0)
Pharyngitis	1	(0.1)	0	(0.0)
Pneumonia	1	(0.1)	1	(0.1)
Nervous system disorders	3	(0.3)	1	(0.1)
Headache	2	(0.2)	0	(0.0)
Myasthenia gravis	1	(0.1)	1	(0.1)
Musculoskeletal and connective tissue disorders	3	(0.3)	0	(0.0)
Back pain	2	(0.2)	0	(0.0)
Arthralgia	1	(0.1)	0	(0.0)
Pain in extremity	1	(0.1)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(0.2)	2	(0.2)
Gastric cancer	1	(0.1)	1	(0.1)
Intraductal papillary-mucinous carcinoma of pancreas	1	(0.1)	1	(0.1)
Cardiac disorders	2	(0.2)	0	(0.0)
Palpitations	2	(0.2)	0	(0.0)
Gastrointestinal disorders	2	(0.2)	0	(0.0)
Nausea	2	(0.2)	0	(0.0)
Vomiting	1	(0.1)	0	(0.0)
Hepatobiliary disorders	2	(0.2)	0	(0.0)
Hepatic function abnormal	2	(0.2)	0	(0.0)

Paediatric safety data

There were no ADRs reported in this study for the 11 paediatric patients (under 15 years of age) Given the 3 participants aged between 15 and 18 years were included in the adult population it was not possible to ascertain whether ADRs were reported by them during the study period.

A review of the adverse event line listings revealed that five adverse events (AEs) were reported during the study for paediatric and adolescent participants. These AEs were not considered related to study

treatment by the investigator and therefore not classified by the Investigator as ADRs. These are summarised below:

Adverse Events List (<18years old)

'As of September 27, 2023

Subjects included in safety analysis

Types of Adverse events (PT)	Types of Adverse events (SOC)	Date of onset	Outcome	Date of Outcome	Seriousness
Influenza	Infections and infestations	2018	Recovered	2018	Non-serious
Asthma	Respiratory, thoracic and mediastinal disorders	2018	Recovered	2018	Non-serious
Asthma	Respiratory, thoracic and mediastinal disorders	2018	Recovered	2018	Non-serious
Anaphylactic reaction	Immune system disorders	2018	Recovered	2018	Serious
Asthma	Respiratory, thoracic and mediastinal disorders	2019	Recovered	2019	Serious

MedDRA/J (26.0)

One serious event of anaphylactic reaction was reported in a participant. The participant had a known history of milk allergy and was reported to have developed an anaphylactic reaction after accidentally consuming a cake that contained milk. The event was reported as recovered on the same day. The Investigator considered that the event of anaphylaxis had no causal relationship with mepolizumab.

Safety Specifications and Priority Investigation Matters

Hypersensitivity such as anaphylaxis: Of the 1027 patients in safety analysis set, the incidence rates of ADRs related to hypersensitivity such as anaphylaxis was 1.2% (12/1027). The type of ADRs include "urticaria" 0.4% 6 (4/1027), "rash" 0.2% (2/1027), "angioedema" 0.1% (1/1027), "eczema" 0.1% (1/1027), and "chronic eosinophilic rhinosinusitis" 0.4% (4/1027). "Angioedema" and "chronic eosinophilic rhinosinusitis" were reported as serious ADRs. The outcomes of each ADR were reported as "recovered" and "recovering" respectively.

Infections: Of the 1027 patients in safety analysis set, the incidence rates of ADRs related to "Infections" was 0.3% (3/1027). The type of ADRs include "bronchitis," "nasopharyngitis", "pharyngitis" and "pneumonia" in 0.1% (1/1027) each. Of these, one ("pneumonia") was serious, and the outcome was fatal. A causal relationship was not denied by the investigator. However, it was difficult to determine the relationship with Nucala because a detailed description of the course leading to death was not available.

Malignant tumor: The occurrence status of ADRs related to "malignant tumor" was investigated until 3 years after the initiation of Nucala treatment. Malignant tumor related ADRs occurred in 2 patients (0.2%): "gastric cancer" in one (0.1%) and "intraductal papillary mucinous carcinoma of pancreas" in one (0.1%). Both events were serious. "Gastric cancer" was found to have developed in one patient at 675 days after the initiation of Nucala treatment, and this event resulted in the outcome "fatal". "Gastric cancer" developed after the discontinuation of Nucala treatment (17 Apr 2018, drug was discontinued (85 days of treatment); adverse drug reaction occurred on 31 Oct 2019) and, as per CSR, it was difficult to ascertain any causal relationship with the drug.

"Intraductal papillary mucinous carcinoma of pancreas" was found to have developed at 304 days after the initiation of Nucala treatment, and the outcome was "recovered."

Other safety results

Blood eosinophil count: Among the 1,027 patients in the safety analysis set for whom blood eosinophil counts were performed "before treatment initiation (9 to 52 weeks before the initiation of Nucala treatment)," "at the time of treatment initiation (0 to 8 weeks before the initiation of Nucala treatment)," "at 12 weeks after the initiation of Nucala treatment (Week 12 of treatment)," "at Week 24 of treatment," and "at Week 52 of treatment or at the time of treatment discontinuation/termination", a decreasing trend in blood eosinophil count was observed from "Week 12 of Nucala treatment" onwards, and this trend was maintained until "Week 52 of treatment or the time of treatment discontinuation/termination."

Serum Total IgE Level: Serum total IgE concentration (IU/mL) before Nucala treatment and the presence or absence of "a history of omalizumab use" was investigated in the 1,027 patients in the safety analysis set. In addition, Serum total IgE levels were collected prior to omalizumab administration or at 1 year or later after discontinuation of omalizumab treatment if there was a history of omalizumab use. The patients "with" a history of omalizumab use were 15.2% (156/1027) and those "without" a history of omalizumab use were 84.8% (871/1027). The mean serum total IgE level ± SD in the patients "with" omalizumab use tended to be higher than in the patients "without." Analysis of ADRs by omalizumab status showed that there was no significant difference in the incidence of ADRs between both sets of patients.

CHMP comments

In line with Japanese regulations, only those adverse events considered related to the investigational product (IP) were required to be reported in the CSR.

ADRs occurred in 42 of the 1,027 patients in the safety analysis set, with the most frequently reported under the preferred term (PT) asthma, chronic eosinophilic rhinosinusitis and urticaria. The incidence of ADRs was 4.1% (42/1,027 patients) and for serious ADRs was 0.9% (9/1027). Of the reported serious ADRs, only PT asthma was reported in more than 1 patient. Whilst direct comparison with safety data reported in pivotal studies is confounded by differences in patient characteristics, study methods, and other study conditions, overall, the incidence of ADRs in Study 204524 was lower than pivotal placebo-controlled studies. No new safety concerns were noted.

Separate reporting and discussion of ADRs of special interest ("Safety Specifications and Priority Investigation Matters"), *hypersensitivity such as anaphylaxis*, *infection* and *malignant tumour* were provided. Although reporting of individual case studies was limited with unclear reporting of event timelines (for "gastric cancer"), no new safety concerns were identified. Of note, "Systemic Reactions including anaphylaxis" and "Alterations in immune response (malignancies)" continue to be monitored under important identified risks and important potential risks, respectively, in the current RMP for Nucala.

Among the patients in the safety analysis set, for whom blood eosinophil counts were performed, a decreasing trend in blood eosinophil count with time on treatment, consistent with that expected for Nucala, was observed.

Overall, the safety results from this study are in line with the known safety profile of mepolizumab. No new safety issues were identified as a result of this clinical trial such as to warrant a change in the safety information in the product information.

From a paediatric perspective, only 14 paediatric and adolescent patients were enrolled in this study. Of these, 11 patients were aged from 12 to less than 15 years of age, and adverse event line listings were available. Of the 5 adverse events reported for these patients, 3 were for PT asthma, 2 were considered serious (asthma and anaphylactic reaction). None were considered by the investigator to be related to

the IP. The 3 participants aged from 15 to less than 18 years were included in the adult population, and no individualised adverse event line listings were reported for this group. The MAH is, however, requested to confirm the number of ADRs (if any) reported for the 3 adolescent patients. **(OC)**

Overall, the data generated with respect to paediatric and adolescents patients is insufficient to allow any meaningful comment on the safety profile of the product in this population, and no update to product information is warranted.

2.3.3. Discussion on clinical aspects

Study 204524 was an open label, non-interventional study that was designed to collect and assess safety and efficacy data from the long-term use of Nucala in Japanese clinical practice. Due to enrollment of paediatric patients in the study, the MAH was obliged, under Article 46 of Regulation 1901/2006, to submit the final clinical study report (CSR) and critical expert overview within 6 months of the completion of the study. The study was not part of a PIP. There were 11 paediatric patients (less than 15 years of age) and 3 adolescents (from 15 to less than 18 years of age).

Lack of detail in the submission pertaining to study design and conduct presents challenges to the interpretation of the robustness of data generated. Comparing data to other studies in Nucala's clinical development is confounded by the differences in patient characteristics, study methods and study conditions between Study 204524 and other studies. That said, where possible, the applicant provided an adequate qualitative comparative analysis under pertinent safety and effectiveness subheadings in the final CSR.

Effectiveness/Efficacy

Of the 959 patients in the effectiveness analysis set, the rate of responders, those in whom the investigator deemed the treatment "effective" after 52 weeks of treatment or at the time of treatment discontinuation/termination, was reported as 90.3% (866/959 patients). Based on multivariate analysis of 13 variables (including age, renal impairment, hepatic impairment, blood eosinophil count at initiation of Nucala treatment), no factors met the defined criteria to be considered to have affected effectiveness.

The rate of responders in the paediatric (< 15 years) patients was 81.8% (9/11 patients), slightly higher than that in the overall population, but "age" was not determined to be a factor affecting effectiveness. No information on effectiveness in the adolescent population was reported in the clinical study report as the 3 adolescent participants were included in the adult population effectiveness calculations.

Other effectiveness measures, including change in the overall frequency of exacerbations and the frequency of specific types of exacerbations (e.g., those requiring hospitalisation, systemic corticosteroids etc) showed decreasing incidence rates from baseline to Week 52 of Nucala treatment (or at time of discontinuation). Notwithstanding the differences between patient characteristics, study design and study conditions, the extent of improvement of asthma exacerbations in Study 204524 were considered to be similar to those observed for Study MEA115588, the pre-approval, global, phase III study conducted in patients with severe asthma (including 50 Japanese patients).

Peak expiratory flow (PEF) and asthma control test (ACT) showed improvements in respiratory function and asthma control with Nucala at pre-defined times points during the 52-week observational part of the study.

Whilst acknowledging uncertainties pertaining to study design and conduct, Study 204524 has shown Nucala to be an effective treatment in adult and paediatric (from 12 years) Japanese patients when used

in routine clinical practice for the treatment of bronchial asthma as determined by treating physicians during a 52-week observational study period. The primary effectiveness results were supported by additional effectiveness results, including reduced frequency of asthma exacerbations with time on Nucala treatment. These results are in line with those previously reported for mepolizumab.

As no new significant efficacy information has been generated as a result of this study, no update to the product information is necessary from an efficacy perspective.

Effectiveness/efficacy and paediatric population

As only 14 paediatric and adolescent patients (from 12 years to less than 18 years) were enrolled in this study, and data from the 3 adolescent patients (from 15 years to less than 18 years) were included in the adult population effectiveness calculations, the overall data generated are insufficient to make any comment on the efficacy of mepolizumab in this population, and no change to the product information is warranted.

Safety

In line with Japanese regulations, only those adverse events considered related to the investigational product (IP) were required to be reported in the CSR.

ADRs occurred in 42 of the 1,027 patients in the safety analysis set, with the most frequently reported under the PT asthma, chronic eosinophilic rhinosinusitis and urticaria. The incidence of ADRs was 4.1% (42/1,027 patients) and for serious ADRs was 0.9% (9/1027). Of the reported serious ADRs, only the PT asthma was reported in more than 1 patient. Whilst direct comparison with safety data reported in pivotal studies is confounded by differences in patient characteristics, study methods, and other study conditions, overall, the incidence of ADRs in Study 204524 was lower than pivotal placebo-controlled studies. No new safety concerns were noted.

Separate reporting and discussion of ADRs of special interest ("Safety Specifications and Priority Investigation Matters"), *hypersensitivity such as anaphylaxis*, *infection* and *malignant tumour* were provided. No new safety concerns were identified. "Systemic Reactions including anaphylaxis" and "Alterations in immune response (malignancies)" continued to be monitored under important identified risks and important potential risks, respectively, in the current RMP for Nucala.

Overall, the safety results from this study are in line with the known safety profile of mepolizumab. No new safety issues were identified as a result of this clinical trial such as to warrant a change in the safety information in the product information.

Safety and paediatric population

From a paediatric perspective, for the 11 patients aged from 12 to less than 15 years of age, adverse event line listings were available. Of the 5 adverse events reported for these patients, 3 were for PT asthma, 2 were considered serious (asthma and anaphylactic reaction). None were considered by the investigator to be related to the IP. Safety data for adolescents were included in the adult population.

Overall, the data generated with respect to paediatric and adolescents patients is insufficient to allow any meaningful comment on the safety profile of the product in this population, and no update to product information is warranted.

3. CHMP overall conclusion and recommendation

The applicant has presented data on the effectiveness and safety of mepolizumab generated from a non-interventional study of the long-term use of mepolizumab in Japanese patients in routine clinical practice. Notwithstanding the uncertainties pertaining to the submitted dataset and the challenges in comparing these data to those generated by other clinical studies in Nucala's clinical development, no new safety and efficacy data have been generated by Study 204524 that warrant a change to the authorised product information. Data are consistent with those previously reported for mepolizumab.

Additional data summaries for paediatric/adolescents patients (< 18 years) included in the study were requested for completeness prior to making a final recommendation on this procedure (see sections 4 and 5). These did not impact the overall conclusion that no new data have been generated by this study that warrants update to product information or raises concerns regarding the benefit risk profile of Nucala. The MAH is considered to have fulfilled its obligations in accordance with Article 46 of Regulation (EC) No1901/2006, and this post-authorisation measure is considered fulfilled.

☒ Fulfilled:

☐ Not fulfilled:

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH is asked to provide summaries of baseline characteristics and prior medications for the 11 paediatric and 3 adolescent patients enrolled in the study.
2. The MAH is asked to provide summaries of patient exposure and reasons for discontinuation for the 11 paediatric and 3 adolescent patients enrolled in the study.
3. With respect to effectiveness, the MAH is requested to provide additional data summaries restricted to the paediatric and adolescent patients.
4. The MAH is requested to confirm the number of ADRs (if any) reported for the 3 adolescent patients.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to request for supplementary information

Question 1

The MAH is asked to provide summaries of baseline characteristics and prior medications for the 11 paediatric and 3 adolescent patients enrolled in the study.

Summary of applicant's response

Characteristics of the 14 patients included in the safety analysis are shown in Table 1 (Annex 1). There were 8 (57%) "male" patients. Nucala was administered for "bronchial asthma" in all patients.

The disease duration was "Over 10" years in 7 patients (50%), and "5≦to≦10" years in 7 patients (50%). The most common severity of asthma prior to Nucala administration was "most severe persistent asthma "in 11 patients (79%), followed by "severe persistent asthma" in 3 patients (21%). Type of asthma was "atopic asthma" in all patients.

All patients were "with" comorbidities including allergies. The names of comorbidities refer to Table 1 (Annex 1).

Prior medications other than Nucala are shown in Table 1 (Annex 1). All patients used "inhaled corticosteroid/long-acting β2-agonist combination products" as prior medications. Two patients (14%) used "Oral corticosteroids" as prior medications.

CHMP assessment of response

The MAH provided a summary of baseline characteristics of all paediatric/adolescent study participants, provided as Annex 1 to this report. Baseline disease characteristics were broadly in line with those reported for the general study population, consistent with severe persistent bronchial asthma, with all participants having undergone prior treatment with inhaled steroids/long acting β2 agonist combinations. The treated paediatric population was in keeping with that targeted by the authorised indication of Nucala in Japan.

Response accepted

Question 2

The MAH is asked to provide summaries of patient exposure and reasons for discontinuation for the 11 paediatric and 3 adolescent patients enrolled in the study.

Summary of applicant's response

Daily dose for all patients at the start of administration was 100 mg. Table 2 (Annex 2), shows the administration status of Nucala for the 14 patients.

Nucala treatment was "Continuation" in 4 patients (29%) and "Discontinued " in 10 patients (71%) at the end of the observation period.

The reasons for treatment discontinuation included "factors associated with effectiveness" in 7 patients, "Economic reasons" in 1 patient, and "Other reasons in the doctor's judgment" in 2 patients. It is important to note that "factors associated with effectiveness" could also be "discontinuation due to ineffectiveness" or "discontinuation due to enough efficacy". Of the 7 patients who discontinued for "factors associated with effectiveness", 3 patients were judged to have been effective.

CHMP assessment of response

Patient exposure and reasons for discontinuation specific to the paediatric/adolescent population were provided (provided as Annex 2 to this report). As per the authorised posology of Nucala in Japan, all participants from 12 years of age received mepolizumab 100 mg subcutaneously every 4 weeks. At the end of the 52-week observational period (or at the time of treatment discontinuation/ termination), a higher rate of discontinuation was observed for the paediatric participants (7/11; 63.6%) and the adolescent participants (3/3; 100%) when compared to the general study population (468/1027; 45.6%). As per the general study population, 'factors due to effectiveness' was the most commonly cited reason for discontinuation. Not all participants who discontinued for this reason were considered to have received "not effective" treatment. Due to the small number of paediatric/adolescent

participants enrolled, the study design, and reporting thereof, no meaningful conclusions can be drawn from these data.

Response accepted

Question 3

With respect to effectiveness, the MAH is requested to provide additional data summaries restricted to the paediatric and adolescent patients.

Summary of applicant's response

In this study, effectiveness was comprehensively assessed by the investigators as either "effective" or "not effective" at Week 52 of Nucala treatment or at the time of treatment discontinuation/ termination, based on all effectiveness items measured and any other feedback obtained from the participant obtained at each study visit. As a results, the responders were 71.4% (10/14 patients: 11 paediatric and 3 adolescent) in the effectiveness analysis set.

CHMP assessment of response

Data summaries pertaining to effectiveness outcomes in the paediatric/adolescent population were provided (Annex 2 to this report). In the effectiveness analysis set, a lower level of response was reported for the paediatric/adolescent population (10/14; 71.4%) when compared to the general study population (866/959; 90.3%). Within the former, the rate of responders in the paediatric (under 15 years) participants was 81.8% (9/11 participants) and 33.3% (1/3 participants) in the adolescents (over 15 and under 18 years). Again, the overall data generated are insufficient to allow for meaningful conclusions to be drawn on the efficacy of mepolizumab in this population.

Response accepted

Question 4

The MAH is requested to confirm the number of ADRs (if any) reported for the 3 adolescent patients.

Summary of applicant's response

The MAH confirms there were no ADRs reported for the 3 adolescent patients for the duration for the study.

CHMP assessment of response

No ADRs were reported for the (3) adolescent participants.

Response accepted