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Human Medicines Division

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

Nucala

Mepolizumab

Procedure no: EMA/PAM/0000327347

Note

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

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1. Introduction

On 5 February 2026, the MAH submitted a completed paediatric study for Nucala, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

The study has not been conducted according to an agreed paediatric investigation plan (PIP).

Following the approval of mepolizumab in Japan for the treatment of paediatric patients with bronchial asthma (limited to patients with refractory asthma whose symptoms are inadequately controlled with standard treatment) aged 6 to <12 years, the MAH met its regulatory commitment in Japan to collect safety and effectiveness data on mepolizumab in daily clinical practice in children aged 6 to <12 years with bronchial asthma.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Nucala (mepolizumab) is a monoclonal antibody targeting interleukin-5 (IL-5). It acts by specifically inhibiting IL-5 signalling, a central cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. In patients with type 2 inflammation–driven disease, IL-5 plays a key role in the pathogenic mechanisms underlying various inflammatory conditions, including asthma.

The MAH stated that Study 213135: Nucala for Subcutaneous Injection Special Drug Use Investigation (Paediatric Bronchial Asthma) is a standalone study. It was a regulatory commitment to collect safety and effectiveness data on mepolizumab in daily clinical practice in children aged 6 to <12 years with bronchial asthma in Japan, following the approval of mepolizumab in Japan for the treatment of paediatric patients with bronchial asthma.

Nucala was first authorised in the EU on 02-December-2015 as an "*add-on therapy for the treatment of severe refractory eosinophilic asthma (SUA) in adults, adolescents and children aged 6 years and older*".

The recommended dose of mepolizumab for adults and adolescents aged 12 years and over is 100 mg administered subcutaneously once every 4 weeks. The recommended dose of mepolizumab for children aged 6 to 11 years old is 40 mg administered subcutaneously once every 4 weeks.

2.2. Information on the pharmaceutical formulation used in the study

The evaluable IMP was the Japanese authorised Nucala [mepolizumab].

- Nucala solution for s.c. injection 100 mg
- Nucala solution for s.c. injection for Paediatric 40 mg Syringe

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study number: 213135

- Study report title: Nucala for Subcutaneous Injection Special Drug Use Investigation (Paediatric Bronchial Asthma)

2.3.2. Clinical study

Study number: 213135. Nucala for Subcutaneous Injection Special Drug Use Investigation (Paediatric Bronchial Asthma)

Description

This was a single-arm, open-label study to monitor the safety and effectiveness of mepolizumab used for the treatment of bronchial asthma in children aged 6 to <12 years administered as a part of clinical practice in Japan.

The observation period per participant will be one year (52 weeks) from the start date of Nucala administration. If a participant has withdrawn from/terminated Nucala administration, the observation period will be until the time of withdrawal/termination.

Methods

Study participants

The study will include paediatric participants aged 6 to <12 years, who receive Nucala for the first time after the indication in children has been obtained, in order to treat BA (refractory asthma in which asthma symptoms remain uncontrolled under the existing treatment), which is the indication of Nucala.

Treatments

All participants received mepolizumab 40 mg as a starting dose.

The maximum daily dose amount was 100 mg in 6 participants, and all of them continued to receive Nucala administration at a dose of 100 mg after undergoing dose modification during treatment, after reaching 12 years of age during Nucala treatment.

Objectives

Outcomes/endpoints

Primary and secondary objectives were not specifically defined; however, the following safety and effectiveness data were collected: asthma exacerbations, respiratory function test (peak flow), Childhood Asthma Control Test (C-ACT), and adverse events (AEs).

Observation Items collected:

1) Information about a medical institution as a study site

2) Participant characteristics (at the start of Nucala administration). Identification number, gender, year and month of birth, start date of Nucala administration, body weight, reason for Nucala use/disease type, disease duration, severity prior to Nucala administration, presence or absence of past medical histories/comorbidities (renal impairment, hepatic impairment, allergies, others) and names of diseases

3) Administration status of Nucala

4) Pre-treatment drugs (4 weeks before the start of Nucala administration) and concomitant drugs intended for BA

5) Concomitant drugs (except drugs intended for BA)

6) Concomitant therapies intended for BA (except drugs)

7) Blood test-related items

8) Asthma exacerbation

9) Respiratory function test (peak flow)

10) Childhood Asthma Control Test (C-ACT)

11) Body weight at the end of the observation period

12) Global assessment of effectiveness

13) Pregnancy

14) Adverse events (AEs)

Effectiveness assessment criteria:

Effective, not effective, indeterminable

Safety specification: collect information on incidences and related matters in daily clinical practice:

- Hypersensitivity including anaphylaxis
- Infections
- Malignant tumours

Sample size

The target sample size was 60 participants (as a safety analysis set).

Randomisation and blinding (masking)

Not applicable, open-label, single-arm design.

Statistical Methods

Primary and secondary objectives were not specifically defined.

A multivariate analysis was performed by participant characteristics to investigate factors affecting the effectiveness of study drug. The multivariate analysis was to confirm any factors in which adjusted odds ratios for effectiveness by participant characteristics met the criterion of "asymptotic 95% CIs not crossing 1, and point estimates exceeding 2 or less than 0.5." Variables were selected by the stepwise method (significance level of 0.3: score chi-square used for the step of including factors in the model and Wald chi-square used for the step of excluding variables) using the followings as explanatory variables: "gender," "age (years)," "body weight (kg) classification 2," "primary disease (disease duration [years])," "comorbidity (renal impairment)," "comorbidity (hepatic impairment)," "comorbidities (allergies)," "comorbidities (others)," "baseline blood eosinophil count (/μL) (at the start of Nucala treatment)," "pre-treatment drugs intended for bronchial asthma (BA)," "concomitant drugs

intended for BA," and "concomitant therapies intended for BA (except drugs)." No variables were included in the model. No factors meeting the criterion were detected in a univariate analysis (unadjusted odds ratios) performed as a preliminary step to the multivariate analysis.

There were no participants in whom ADRs occurred in this study; therefore, odds ratios and asymptotic 95% confidence intervals (CIs) were not calculated. In addition, no investigation was performed for factors affecting ADRs based on the results of the occurrence status of ADRs by participant characteristic.

Results

Participant flow

Of the 48 patients who were enrolled, mepolizumab was administered to a total of 45 patients (safety set).

All participants received mepolizumab 40 mg as a starting dose. 6 participants who reached 12 years of age during the study were escalated to a dose of 100 mg every 4 weeks. Among the 45 participants in the safety analysis set, the mepolizumab treatment status of continuation or withdrawal/termination at the end of the observation period was "treatment continued" in 84.4% (38/45 participants) and "treatment withdrawn/terminated" in 15.6% (7/45 participants). The most common reasons for withdrawal were "effectiveness-related factors" in 11.1% (5/45 participants) followed by "the participant's inconvenience other than the above" in 4.4% (2/45 participants).

Recruitment

The target sample size was 60 participants however due to recruitment challenges, the final number of enrolled patients was 48. This lower number was agreed with the Japan Pharmaceutical and Medical Devices Agency (PMDA). Of the 48 patients who were enrolled, mepolizumab was administered to a total of 45 patients (safety set).

Baseline data

Mepolizumab was administered to a total of 45 patients (safety set). 55.6% were male, and the mean age was 8.3 years (SD 1.7). The mean body weight was 29.52 kg (SD 10.85). 82.2% (37/45 participants) were in the <40kg body weight group, and 17.8% (8/45 participants) were in the ≥40 kg body weight group. All participants were diagnosed with bronchial asthma, and asthma severity prior to mepolizumab administration was "severe and persistent type" in 62.2% (28/45 participants), followed by "the most severe and persistent type" in 37.8% (17/45 participants).

Comorbidities were "present" in 91.1% (41/45 participants). Comorbidities (allergies) were "present" in 91.1% (41/45 participants) and comorbidities (others) were "present" in 22.2% (10/45 participants), the most common other comorbidity being "constipation" in 4.4% (2/45 participants).

The most commonly used pre-treatment drug was "Adoair" (salmeterol/fluticasone propionate) in 53.3% (24/45 participants). "A history of omalizumab use" was "present" in 13.3% (6/45 participants), and omalizumab had been used as a pre-treatment drug in 6.7% (3/45 participants).

The most common concomitant drug used for the treatment of bronchial asthma during the observation period was "montelukast sodium" in 93.3% (42/45 participants), followed by "salmeterol xinafoate/fluticasone propionate" in 51.1% (23/45 participants). The most common concomitant therapy was "desensitisation therapy" in 17.8% (8/45 participants).

Number analysed

A total of 44 participants were in the effectiveness analysis set.

A total of 45 patients were comprised as the safety set.

Efficacy results

Exposure

The mean total number of doses ± SD was 11.9 ± 3.2. The most common number of doses was "≥13" in 62.2% (28/45 participants), followed by "≥9 to <13" in 24.4% (11/45 participants).

Efficacy results

At Week 52 of Nucala treatment or at the time of withdrawal/termination, the investigators assessed effectiveness by either "effective" or "not effective", based on the course of subjective symptoms, course of clinical symptoms, etc. from the start date of administration to the end of the observation period. If effectiveness could not be determined for some reasons, it was to be assessed as "indeterminable."

Among the 44 participants in the effectiveness analysis set, the responder rate was 93.2% (41/44 participants). A responder analysis showed that participants weighing < 40kg were more likely to be responders (100%; 36/36 participants), compared to participants weighing ≥ 40kg (63%; 5/8 participants).

Blood Eosinophil Count

In 38 of the 45 participants, Nucala treatment was continued for 52 consecutive weeks. A decreasing trend was observed in the blood eosinophil count from "Week 12 of Nucala treatment" and this trend was maintained until "Week 52 of Nucala treatment or the time of withdrawal/termination."

Exacerbations of Bronchial Asthma

The "frequency of BA exacerbations" was 1.9 exacerbations/person-year before treatment, while it was 0.6 exacerbations/person-year after treatment (rate ratio = 0.33 [95% CI: 0.17-0.67]). The "frequency of BA exacerbations requiring hospitalisation" was 0.4 exacerbations/person-year before treatment, while it was 0.3 exacerbations/person-year after treatment (rate ratio = 1.07 [95% CI: 0.21-5.41]). The "frequency of BA exacerbations requiring emergency outpatient visits" was 0.4 exacerbations/person-year before treatment, while it was 0.0 exacerbations/person-year after treatment (rate ratio = 0.15 [95% CI: 0.03-0.88]). The "frequency of BA exacerbations requiring systemic corticosteroid use" was 1.2 exacerbations/person-year before treatment, while it was 0.2 exacerbations/person-year after treatment (rate ratio = 0.21 [95% CI: 0.09-0.47]). The "number of days of hospitalisation required for BA exacerbations" was 2.5 days/person-year before treatment, while it was 2.3 days/person-year after treatment (rate ratio = 2.60 [95% CI: 0.24-28.68]).

Respiratory Function Test (Peak Flow)

The mean peak flow ± SD among participants who underwent peak flow measurement at each timepoint was 266.2 ± 165.8 (n = 8) at baseline, 289.2 ± 126.0 (n = 9) at Week 12 of Nucala treatment, 221.6 ± 76.2 (n = 4) at Week 24 of Nucala treatment, 302.7 ± 57.7 (n = 5) at Week 52 of Nucala treatment, and 292.5 ± 51.3 (n = 7) at the time of withdrawal/termination. An increasing (= improving) trend was observed at Week 52 of Nucala treatment or at the time of withdrawal/termination, while a decreasing trend was observed at Week 24 of treatment. This

decreasing trend was possibly due to the fact that the number of participants whose test values at Week 24 of treatment were available was as small as 4.

Childhood Asthma Control Test (C-ACT)

The mean total C-ACT score ± SD among participants who took the C-ACT at each timepoint was 19.4 ± 6.1 (n = 37) at baseline, 22.6 ± 5.5 (n = 35) at Week 12 of Nucala treatment, 22.8 ± 4.7 (n = 33) at Week 24 of Nucala treatment, and 23.3 ± 4.3 (n = 32) at Week 52 of Nucala treatment, showing an increasing (= improving) trend from baseline.

Change in Systemic Corticosteroid Dose

Among the 44 participants in the effectiveness analysis set, 4 participants had used systemic corticosteroids "before the start of Nucala treatment." The mean systemic corticosteroid dose (mg/day) was 26.0 "before the start of Nucala treatment," while it was 2.7 "for up to Week 52 of Nucala treatment or until the time of withdrawal."

Safety results

The incidence rate of AEs was 40.0% (18/45 participants); serious AEs occurred in 7 of the 18 participants. Any relationship with mepolizumab was excluded in all events irrespective of seriousness, and no adverse drug reactions (ADRs) were reported. The most frequently reported AEs were "asthma" 20.0% (9/45 participants) followed by "sinusitis" 6.7% (3/45 participants). The most frequently reported serious AEs (SAEs) were "asthma" 8.9% (4/45 participants), followed by "sinusitis" 2.2% (1/45), "gastroenteritis" 2.2% (1/45), "pharyngitis" 2.2% (1/45), "beta haemolytic streptococcal infection" 2.2% (1/45), "neuropathy peripheral" 2.2% (1/45), and "dermatitis atopic" 2.2% (1/45). The outcomes of all types of SAEs were "recovering/resolving" or "recovered/resolved" at the end of the study.

In this study, "hypersensitivity including anaphylaxis," "infections," and "malignant tumours" were classified as safety specifications. Among the 45 participants in the safety analysis set, the incidence rate of AEs related to "hypersensitivity including anaphylaxis" was 6.7% (3/45 participants). The event in one participant was serious; however, a relationship with mepolizumab was ruled out for all these events, and no ADRs were reported. The incidence rate of AEs related to "infections" was 22.2% (10/45 participants). The events in 2 participants were serious; however, a relationship with mepolizumab was ruled out for all these events, and no ADRs were reported. The most frequently reported AEs by the type of events were "sinusitis" 6.7% (3/45 participants), followed by "bronchitis" 4.4% (2/45), "gastroenteritis" 4.4% (2/45), "influenza" 4.4% (2/45), "nasopharyngitis" 4.4% (2/45), and "pharyngitis" 4.4% (2/45). The incidence rates of AEs and ADRs related to "malignant tumours" were both 0.0% (0/45 participants).

Although effects on the cardiovascular system are not included in the safety specifications of the Risk Management Plan (RMP) for Nucala, it was determined necessary to collect further post-marketing information on possible effects of Nucala on the cardiovascular system, based on pooled data from placebo-controlled studies in adult and children aged ≥12 years who were suffering from severe asthma (Study MEA112997, Study MEA115588, Study MEA115575) and on pooled data from open-label, uncontrolled studies on the safety of long-term Nucala treatment (Study MEA115661, Study MEA115666 [interim data]). The incidence rates of AEs and ADRs related to effects on the cardiovascular system were both 0.0% (0/45 participants).

2.3.3. Discussion on clinical aspects

Study participants

Study 213135 included paediatric participants aged 6 to <12 years, with a diagnosis of BA (refractory asthma in which asthma symptoms remain uncontrolled under the existing treatment). The administered dose was in line with the recommended EU posology; however, the definition of bronchial asthma is unclear and from the provided data, the population included in Study 213135 differs from the Nucala EU authorised indication of "Severe eosinophilic asthma". Furthermore, as per the EU Nucala product information Section 5.1, the eosinophilic phenotype definition is defined as an elevated peripheral blood eosinophil count of ≥300/μL or ≥150/μL that is related to asthma, depending on symptom duration. The MAH has not specified a specific baseline blood eosinophil count as an inclusion criterion for Study 213135. In comparison, the 3 randomised, double-blind, parallel-group clinical studies, supporting the EU indication of severe eosinophilic asthma (MEA112997, MEA115588 and MEA115575) contained specific inclusion criteria for severe eosinophilic asthma and baseline blood eosinophil count.

Exposure

The target sample size of this study (60 participants to be enrolled) was not reached, and the final number of participants enrolled by the end of April 2024 was 48. Possible causes for there being an insufficient number of enrolled participants to meet the target sample size were that the number of participants for whom Nucala was indicated was small and that the number of potential participants was only one or 2 at each site, making it difficult to enrol new participants after entry into the contract with the site where Nucala was confirmed to be in use after the initial product supply to each site. In addition, during the COVID-19 pandemic, there were restrictions on outpatient visits and on visiting hours, and outpatients often refrained from visiting hospitals. These are possible background factors identified by the MAH that could be associated with the fact that the target sample size was not reached.

Among the 45 participants in the safety analysis set, the mepolizumab treatment status of continuation or withdrawal/termination at the end of the observation period was "treatment continued" in 84.4% (38/45 participants) and "treatment withdrawn/terminated" in 15.6% (7/45 participants). Compared to the available pivotal studies, results should be interpreted with caution given the low numbers of participants overall, particularly in the subgroup analysis of participants weighing ≥ 40kg.

Effectiveness

At Week 52 of Nucala treatment or at the time of withdrawal/termination, the investigators assessed effectiveness by either "effective" or "not effective", based on the course of subjective symptoms, course of clinical symptoms, etc. from the start date of administration to the end of the observation period. If effectiveness could not be determined, it was to be assessed as "indeterminable."

Among the 44 participants in the effectiveness analysis set, the responder rate was 93.2% (41/44 participants). A responder analysis showed that participants weighing < 40kg were more likely to be responders (100%; 36/36 participants), compared to participants weighing ≥ 40kg (63%; 5/8 participants), however this should be interpreted with caution given the low numbers of participants in the group weighing ≥ 40kg and that the odds ratio from a univariate analysis did not meet pre-specified criteria (asymptotic 95% confidence intervals not crossing 1, and point estimates exceeding 2 or less than 0.5).

The main effectiveness outcome of "responder rate" was undefined in terms of standard clinical outcomes and not consistent with primary endpoints used in the pivotal studies. Overall, however

there were positive efficacy trends and frequencies of asthma exacerbations, including those requiring medical attention, showed an improving trend, as did peak flow and the C-ACT.

Safety

Among the 45 participants in the safety analysis set, the incidence rate of AEs was 40.0% (18/45 participants). The events in 7 participants were serious; however, a relationship with Nucala was ruled out for all these events and the outcomes of these SAEs were "recovering/resolving" or "recovered/resolved." No ADRs were reported.

The MAH compares safety results in Study 200363, a pre-approval global phase II study in children aged 6 to 11 years who were suffering from severe asthma. The incidence rates of AEs in the Nucala 40 mg group were 77% (20/26 participants) in Part A of the study and 94% (15/16 participants) in Part B of the study. The incidence rates of ADRs in the Nucala 40 mg group were 31% (8/26 participants) in Part A and 31% (5/16 participants) in Part B. While differences in the population and methodology exist, the incidence rates of AEs and ADRs in Study 213135 were lower than the incidence rates in the phase II clinical study.

The most frequently reported AEs were "asthma" 20.0% (9/45 participants) followed by "sinusitis" 6.7% (3/45 participants).

In this study, "hypersensitivity including anaphylaxis," "infections," and "malignant tumours" were classified as safety specifications. Among the 45 participants in the safety analysis set, the incidence rate of AEs related to "hypersensitivity including anaphylaxis" was 6.7% (3/45 participants). The event in one participant was serious; however, a relationship with mepolizumab was ruled out for all these events, and no ADRs were reported. The incidence rate of AEs related to "infections" was 22.2% (10/45 participants). The events in 2 participants were serious; however, a relationship with mepolizumab was ruled out for all these events, and no ADRs were reported. The incidence rates of AEs and ADRs related to "malignant tumours" were both 0.0% (0/45 participants).

The MAH concluded, given the comparability of results to the Phase II Study 200363, and the known safety profile, it was considered unnecessary to provide additional precautions in the product information. This can be agreed. The most common AEs were consistent with the known safety profile of EU authorised Nucala or expected disease outcomes associated with severe eosinophilic asthma. The incidence of hypersensitivity including anaphylaxis and of infections were comparable to the known safety profile. In addition, anaphylaxis and hypersensitivity are mentioned in section 4.8 of the Nucala SmPC, and precautions concerning anaphylaxis and other related symptoms and specific infections are provided in the product information.

Based on Study 213135 findings, no new concerns regarding the effectiveness or safety of Nucala in the indication of severe eosinophilic asthma arose. A number of limitations and uncertainties are identified including lower than expected recruitment, small sample size (n= 38) with treatment-continued at the end of the observation period) and the open-label, single arm design.

In addition, the application of the data to the EU authorised Nucala is limited by the differing population, differences in disease definition (bronchial asthma versus severe eosinophilic asthma), inclusion criteria for blood eosinophil counts and differing efficacy endpoints to the pivotal phase III trials (definitions for "effective" and "not effective").

3. CHMP overall conclusion and recommendation

Study 213135, Nucala for Subcutaneous Injection Special Drug Use Investigation (Paediatric Bronchial Asthma) was a single-arm, open-label study to monitor the safety and effectiveness of mepolizumab

used for the treatment of bronchial asthma in children aged 6 to <12 years administered as a part of clinical practice in Japan.

Study 213135 has been submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Of the planned 60 participants, target recruitment was not reached, the final number of participants enrolled was 48 and the number with a status of "treatment continued" at the end of the observation period was 38.

The MAH has proposed no product information (PI) updates as a result of Study 213135 efficacy and safety outcomes. This is agreed. The study has been carried out in the Japanese population to obtain further data in relation to the BA authorisation in this jurisdiction. Aside from the different population, the study is an observational design with no blinding or comparator/control arms.

Efficacy endpoints cannot be compared directly with pivotal data due differences in disease definition (bronchial asthma) and inclusion criteria for blood eosinophil counts, also the main efficacy endpoint differs significantly to the pivotal phase III trials (i.e. definitions for "effective" and "not effective"). Overall, however there was evidence of positive efficacy trends and the frequencies of asthma exacerbations, including those requiring medical attention, showed an improving trend, as did peak flow and the C-ACT.

The most common AEs were consistent with the known safety profile of Nucala or expected disease outcomes associated with severe eosinophilic asthma. The incidence of hypersensitivity including anaphylaxis and of infections were comparable to the known safety profile and no ADRs were reported.

While the data is consistent with the known efficacy and safety profile of Nucala, it is not considered to contribute relevant data to the EU authorised indication of severe eosinophilic asthma and therefore does not warrant further updates to the PI.

The benefit-risk balance remains unchanged.

☒ **Fulfilled:**

No regulatory action required.