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

Nucala

mepolizumab

Procedure no.: EMA/H/C/003860/P46/005

Note

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



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1. Introduction

On 10 January 2017, the MAH submitted a completed study for Nucala that included 9 children from 12 to 17 years old, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH has stated that study 200862 'A randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control – the MUSCA study' is a stand-alone study.

This study is not part of the asthma agreed Paediatric Investigation Plan. However, the applicant has advised that, given this study enrolled 9 adolescents from 12 to 17 years old, the paediatric results from this study will be combined with the PIP agreed measures to support the evaluation of the effect of mepolizumab in the treatment of severe refractory eosinophilic asthma in patients from 6 to 17 years old. The paediatric results from this study will hence be part of an upcoming type II variation supporting an indication in paediatric patients.

2.2. Information on the pharmaceutical formulation used in the study

Nucala is a powder for solution for injection and is administered subcutaneously.

2.3. Clinical aspects

2.3.1. Introduction

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

The MAH submitted a final report for:

- Study 200862 – The MUSCA study; 'A randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control'

In the context of this procedure only the paediatric data has been reviewed (9 out of 556 randomised subjects). In the critical expert overview it is stated that the MAH has reviewed the results of this study (all subjects) and concluded that they are in-line with the approved product information in the EU.

2.3.2. Clinical study 200862

Description

This was a multi-centre, placebo-controlled, double-blind, parallel-group, twenty-four week study. Approximately 780 subjects with severe eosinophilic asthma were planned to be screened to ensure the randomisation of at least 544 subjects (272 subjects per treatment arm) into the study.

The primary objective of the study was to evaluate the efficacy of mepolizumab 100mg SC administered every 4 weeks for 24 weeks versus placebo on health-related quality of life (HR-QoL) (St. George's Respiratory Questionnaire [SGRQ] total score) in adult and adolescent subjects with severe eosinophilic asthma. The secondary objectives were to assess the effects of mepolizumab compared with placebo on lung function (pre-bronchodilator forced expiratory volume in 1 second [FEV1]), HR-QoL (SGRQ responder analysis) and asthma control (Asthma Control Questionnaire [ACQ-5]). The safety objective was to assess the safety and tolerability of mepolizumab compared with placebo.

The target population in this study was patients with severe eosinophilic asthma with evidence of eosinophilic airway inflammation as assessed by blood eosinophil level and who continue to experience exacerbations despite treatment with high dose ICS and additional controller therapy, a population which has been shown to have a positive benefit-risk assessment when treated with mepolizumab. In addition to study treatment, subjects were to receive standard of care treatment consisting of a high dose ICS and another controller (such as LABA), with or without maintenance oral corticosteroids (OCS).

The dose selection of mepolizumab was based on previous experience from two phase III placebo-controlled studies (MEA115588 and MEA115575) that demonstrated the safety and efficacy of mepolizumab at a dose of 100 mg SC. This is now the approved dose of mepolizumab for patients with severe eosinophilic asthma.

The optimal duration for assessment of HR-QoL is uncertain, but generally longer durations are recommended, with a time period of at least 3 to 6 months [European Medicines Agency, 2005]. This study used a 24-week treatment period, which is considered to be an adequate time period for the assessment of the impact of mepolizumab on SGRQ and other study endpoints.

Results

Recruitment/ Number analysed

Table 1: Study populations

Population	Number (%) of Subjects		
	Placebo	Mepolizumab 100 mg SC	Total
All Subjects Enrolled (ASE)			830
Randomised	280	276	556
Modified Intent-to-treat (mITT) ¹	277	274	551
Safety ¹	278	273	551
Per Protocol (PP)	238 (85)	242 (88)	480 (86)
Body Plethysmography (BP)	31 (11)	34 (12)	65 (12)
Physical Activity (PA)	40 (14)	37 (13)	77 (14)

Source: Table 1.01

1. 5 subjects (738, 796, 1660, 1959, 3154) were randomised in error and withdrawn without receiving any treatment.

In the age group 12-17years: 9 subjects were randomised and received at least one dose of study drug and were included in the mITT population. Of these 9 subjects; 6 received mepolizumab and 3 received placebo.

Efficacy results

Although a subgroup analysis of the primary endpoint was undertaken by age, the 12-17y age group only contained 9 patients out of a total of 556 subjects randomised (551 in the modified ITT). Consequently the results of the subgroup analysis in this subgroup are not shown in the CSR.

With regards to the overall efficacy results, in the conclusions section of the CSR it is stated that 'In a population of adult and adolescent subjects with severe eosinophilic asthma, mepolizumab 100 mg administered SC every 4 weeks was efficacious in improving HR-QoL over a 24-week treatment period, with statistically significant and clinically relevant improvements in SGRQ total score compared with placebo. A responder analysis showed that subjects treated with mepolizumab were statistically significantly more likely to have a clinically relevant improvement in SGRQ total score compared with placebo. Further benefit of treatment with mepolizumab was demonstrated by statistically significant and clinically relevant improvements in lung function (pre-bronchodilator FEV1) and statistically significant improvements in asthma control (ACQ-5) compared with placebo.'

Assessor's Comments:

It is agreed that, as only 9 adolescent patients were enrolled in this study (6 received mepolizumab) of a total of 556, it would be difficult to interpret any efficacy results in this subpopulation.

The applicant has confirmed that the paediatric results from this study will be combined with the PIP agreed measures to support the evaluation of the effect of mepolizumab in the treatment of severe refractory eosinophilic asthma in patients from 6 to 17 years old. The paediatric results from this study will hence be part of an upcoming type II variation supporting an indication in paediatric patients.

Safety results

Adverse events in adolescent subjects

There were 3 adolescent subjects in the placebo arm and each experienced an AE:

- Subject, a 12-year-old White female in the placebo arm, experienced AEs of headache, abdominal pain upper, influenza, and sinusitis that all resolved during the study. None of the

events were considered by the investigator to be related to study treatment and none led to withdrawal of study treatment.

- Subject, a 14-year-old White female in the placebo arm, experienced an SAE of gastroenteritis rotavirus that resolved within 7 days. This was the only SAE reported for an adolescent subject in either treatment arm. This subject also experienced AEs of helicobacter infection and headache that both resolved during the study. None of these events were considered by the investigator to be related to study treatment and none led to withdrawal.
- Subject, a 14-year-old White male in the placebo arm, experienced an AE of nasopharyngitis that resolved within 8 days. This AE was not considered by the investigator to be related to study treatment and did not lead to withdrawal.

There were 6 adolescent subjects in the mepolizumab 100 mg SC arm and 3 of these subjects experienced AEs:

- Subject, a 15-year-old White female in the mepolizumab 100 mg SC arm, experienced AEs of pharyngitis streptococcal that resolved within 15 days and upper respiratory tract infection that was resolving at the last contact. Neither event was considered by the investigator to be related to study treatment and neither led to withdrawal.
- Subject, a 13-year-old White female in the mepolizumab 100 mg SC arm, experienced AEs of injection-related reaction and local injection site reaction that were considered by the investigator to be related to study treatment but did not lead to withdrawal of study treatment. The injection-related reaction was considered to be both a local and systemic reaction by the investigator and was associated with the symptom headache. This event occurred after the first dose of mepolizumab 100 mg SC, was mild in intensity, non-serious and resolved within 1 day. This was the only AE in an adolescent subject in either treatment arm that was considered to be a systemic reaction. This subject also experienced AEs of hyperhidrosis, musculoskeletal stiffness and oral pain that resolved during the study. These AEs were not considered by the investigator to be related to the study treatment and did not lead to withdrawal.
- Subject, a 13-year-old White female in the mepolizumab 100 mg SC arm, experienced AEs of headache and respiratory tract infection that resolved within 4 and 8 days respectively. These AEs were not considered by the investigator to be related to study treatment and did not lead to withdrawal.

Adolescent subjects in the mepolizumab 100 mg SC arm did not experience any AEs.

Overall safety results

With regards to the overall safety results, in the conclusions section of the CSR it is stated that 'The safety of mepolizumab observed in this study was consistent with the known safety profile of mepolizumab 100 mg SC treatment in subjects with severe eosinophilic asthma. The incidence of adverse events was low and was similar between placebo and mepolizumab.'

Assessor's Comments:

Six of the 9 adolescent subjects in this study experienced an adverse event: 3 in the placebo arm and 3 in the mepolizumab arm.

Of these 6 subjects, only one experienced an AE that was considered by the investigator to be treatment related. This subject was in the mepolizumab treatment arm. This was an injection-related reaction that was considered to be both a local and systemic reaction by the investigator and was

associated with the symptom headache. This event occurred after the first dose of mepolizumab, was mild in intensity, non-serious, resolved within 1 day and did not result in withdrawal of study treatment. This is a listed event for nucala.

One subject experienced a serious adverse event; this subject was in the placebo arm. The event was gastroenteritis rotavirus and was assessed by the investigator as not related to the study treatment.

None of the adverse events led to withdrawal of study treatment.

2.3.3. Discussion on clinical aspects

This was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma. Of the 556 subjects randomised in the study, 9 were aged 12 to 17 years. Of these 9 subjects; 6 received mepolizumab and 3 received placebo.

The number of adolescent subjects in this study is too small to draw any conclusions on efficacy in this subpopulation.

Of the 6 adolescent subjects that received mepolizumab, 3 experienced adverse events none of which were serious or resulted in withdrawal of study treatment. One of the three subjects experienced an AE that was assessed by the investigator as related to the study drug: an injection-related reaction that was considered to be both a local and systemic reaction. This is a listed reaction for Nucala.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The MAH has submitted a completed study for Nucala that included 9 children from aged 12 to 17 years old, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This is a stand-alone study.

Based on the paediatric data submitted, there are no changes to the risk benefit balance of Nucala in the licensed indication and no changes to the product information are required at this time.

According to the applicant, the paediatric results from this study will be combined with the PIP agreed measures to support the evaluation of the effect of mepolizumab in the treatment of severe refractory eosinophilic asthma in patients from 6 to 17 years old. The paediatric results from this study will hence be part of an upcoming type II variation supporting an indication in paediatric patients.

Recommendation

☒ **Fulfilled:**

No regulatory action required.