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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: EMEA/H/C/003860/P46/020

Note

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

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1. Introduction

The MAH submitted a completed paediatric study for Nucala, mepolizumab, 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

Study no: 218952, title 'Association of Mepolizumab with Asthma-Related Outcomes in Pediatric and Adolescent Patients with Severe Asthma: A Pre/Post Assessment of Oral Corticosteroid and Asthma Medication Use, Asthma Exacerbations, and Healthcare Resource Utilization in the United States' is a standalone study.

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

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation is not specified as it is a retrospective registry-based study

2.3. Clinical aspects

2.3.1. Introduction

Real-world evidence on the association of mepolizumab initiation with clinical and economic outcomes in adolescent and pediatric patients with severe asthma remains sparse. Therefore, this study aimed to provide a comprehensive assessment of the effects of mepolizumab on endpoints related to the clinical and economic burden of severe asthma in adolescent and pediatric populations.

2.3.2. Clinical study

Study no: 218952

Title: Association of Mepolizumab with Asthma-Related Outcomes in Pediatric and Adolescent Patients with Severe Asthma: A Pre/Post Assessment of Oral Corticosteroid and Asthma Medication Use, Asthma Exacerbations, and Healthcare Resource Utilization in the United States.

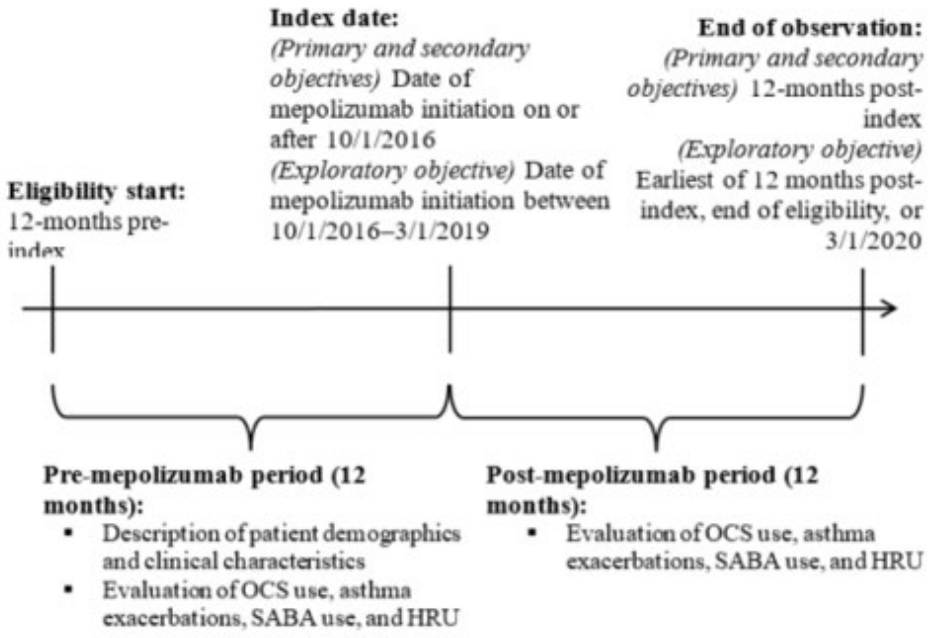
Study design

This retrospective pre-post study design used administrative claims from the Komodo Research Database, spanning from 01 January 2016 to 30 June 2023, to address the study objectives. The index date was defined as the first dispensing or administration of mepolizumab on or after 01 October 2016. The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date. The post-mepolizumab period was defined as the 12 months after the index date. Given the impact of the Coronavirus disease 2019 (COVID-19) pandemic on healthcare provisions, exploratory objective was conducted such that the end of the study period was conservatively set to 01 March

2020. The study design scheme for the primary, secondary, and exploratory objectives is depicted in Figure 1 below.

For all objectives, patient demographics and clinical characteristics were assessed during the pre-mepolizumab period or on the index date, and Oral Corticosteriod (OCS) use, asthma exacerbations, Short-Acting β2 Agonist (SABA) use, and Healthcare Resource Utilization (HRU) were evaluated during the pre- and post-mepolizumab periods.

Figure 1 Study Design Scheme



Methods

The Komodo Research Database is sourced from a variety of payers and healthcare organizations. It includes over 65 billion de-identified clinical, pharmacy, and laboratory encounters for more than 320 million patients enrolled in a health care plan in the US from 2012 till present. These encounters have census-level representation across patient populations (i.e., age, geography, risk pools), including hospital networks, physician networks, healthcare claim processing companies (i.e., claims clearinghouses), pharmacies, and health insurers.

The database consists of healthcare encounters that come directly from more than 150 payers, across Medicaid, Commercial, and Medicare insurers. Medical and pharmacy claims, medical and/or prescription benefit information, and insurance eligibility are available.

Study participants

Inclusion Criteria

- (Primary and secondary objectives) ≥1 medical or pharmacy claim for mepolizumab on or after 01 October 2016
- (Exploratory objective) ≥1 medical or pharmacy claim for mepolizumab between 01 October 2016 and 01 March 2019
- ≥12 months of continuous eligibility prior to the index date

- ≥12 months of continuous eligibility after the index date
- (Primary and secondary objectives) Between 6–17 years of age on the index date
- (Exploratory objective) Between 12–17 years of age on the index date
- ≥1 medical claim with a diagnosis of asthma in any position (ICD-10-CM: J45.3x–J45.5x, J45.9xx) during the pre-mepolizumab period or on the index date
- ≥2 medical or pharmacy claims for mepolizumab within the first 6 months on or after the index date, including the index dispensing or administration

Exclusion Criteria

- ≥1 medical or pharmacy claim for mepolizumab any time before the index date
- ≥1 medical or pharmacy claim for omalizumab, reslizumab, benralizumab, dupilumab, or tezepelumab during the pre- or post-mepolizumab period

Objective(s)

The aim of this study was to evaluate and compare OCS use, asthma exacerbations, SABA use, and Healthcare Resource Utilization (HRU) in the 12 months before and after mepolizumab initiation among pediatric and adolescent patients (age 6–17 years) with severe asthma in the US.

Outcomes/endpoints

OCS Dispensings

- Number of OCS dispensings

Asthma Exacerbations

- Rate of overall asthma exacerbations, including inpatient (IP)/emergency department (ED)-defined and systemic corticosteroid (SCS)-defined exacerbations
  - IP/ED-defined exacerbation: defined as an IP visit or as an ED visit that resulted in a hospitalization with a primary diagnosis of asthma within 1 day after the ED visit
  - SCS-defined exacerbation: defined as ED or outpatient (OP) visit with a primary diagnosis of asthma and an SCS (i.e., OCS or parenteral corticosteroid) medical or pharmacy claim within ±5 days
  - If 2 or more exacerbations were observed within 14 days of each other for a patient, they were considered as 1 exacerbation event and classified according to the highest severity of the contributing exacerbations, where IP/ED-defined exacerbations were considered more severe than SCS-defined exacerbations
  - Asthma exacerbations occurring on the index date were considered as part of the pre-mepolizumab period
- Medical claims for scheduled administrations of mepolizumab were excluded from OP visits used to identify asthma exacerbations.

OCS Treatment Patterns

- Patients with ≥1 OCS dispensing

    - Number of OCS bursts: defined as a pharmacy claim for OCS with 2–28 days of supply and an average daily dose of ≥20 mg prednisone equivalent
- Patients with chronic OCS use, defined as either:
    - Mean daily dose of ≥5 mg prednisone equivalent strength during the pre- and post-mepolizumab periods
    - Mean daily dose of ≥10 mg prednisone equivalent strength during the pre- and post-mepolizumab periods
    - Mean daily dose of ≥10 mg prednisone equivalent strength during the last 90 days of the pre- and post-mepolizumab periods
- Patients with maintenance OCS use: defined as ≥1 pharmacy claim for an OCS dispensing with >28 days of supply
- Average daily dose of OCS during the pre- and post-mepolizumab periods

SABA Use

- Number of SABA canisters
- Patients with ≥1 SABA canister

All-Cause, Asthma-Related, and Asthma Exacerbation-Related HRU

- All-cause HRU: defined as healthcare encounters due to any cause
- Asthma-related HRU: defined as healthcare encounters having a medical claim with a primary or secondary diagnosis of asthma
- Asthma exacerbation-related HRU: defined as healthcare encounters having a medical claim associated with an IP/ED-defined exacerbation or SCS-defined asthma exacerbation
- For all types of HRU, the following endpoints were evaluated:
    - Number of IP visits
    - Number of ED visits
    - Number of Outpatient (OP) visits
    - Claims for scheduled administrations of mepolizumab were excluded from the evaluation of OP visits
- For all-cause and asthma-related HRU, the following endpoint was evaluated:
    - Number of other visits

Sample size

The primary objectives of this study were to evaluate and compare the mean number of OCS dispensings and rate of asthma exacerbations before and after mepolizumab initiation among pediatric and adolescent patients with severe asthma. The reduction in the mean number of OCS dispensings and rate of asthma exacerbations before and after mepolizumab initiation among pediatric and adolescent patients with severe asthma was assumed a priori to fall within a range of rate ratios (RRs) spanning from 0.60–0.80 based on the reduction in the mean number of OCS dispensings and rate of asthma exacerbations observed in prior studies.

The sample size calculation was performed using a test for the ratio of 2 Poisson rates. Table 1 presents the minimum sample sizes required to detect statistically significant differences in the mean number of OCS dispensings and rate of asthma exacerbations before and after mepolizumab initiation based on a range of RRs (0.60–0.80). Assuming 80% power and a 2-tailed type I error rate of 0.05, a sample size of 365 patients was sufficient to detect a statistically significant RR of 0.80 in the mean number of OCS dispensings or rate of asthma exacerbations before and after mepolizumab initiation.

Assuming 90% power and a 2-tailed type I error rate of 0.05, a sample size of 494 patients was sufficient to detect a statistically significant RR of 0.80 in the mean number of OCS dispensings and rate of asthma exacerbations before and after mepolizumab initiation.

Table 1 Sample size calculations for a ratio of 2 Poisson rates (2-sided paired t-test, 80% or 90% power, type I error rate of 0.05)[1,2]

Power	RR	Sample size required
80%	0.60	84
	0.70	156
	0.80	365
90%	0.60	116
	0.70	213
	0.80	494

Notes:
1. Sample size calculations were performed using the software PASS (Copyright 1983-2022, NCSS, LLC)
2. Reference: Gu, K., Ng, H.K.T., Tang, M.L., and Schucany, W. 2008. 'Testing the Ratio of Two Poisson Rates.' Biometrical Journal, 50, 2, 283-298.

Given that 580 pediatric and adolescent patients with asthma initiating mepolizumab were selected into the study sample, the MAH considered the sample size to be sufficient to detect a statistically significant difference of 0.80 in the mean number of OCS dispensings and rate of asthma exacerbations.

Randomisation and blinding (masking)

NA

Statistical Methods

All analyses were conducted using SAS Enterprise Guide Software Version 8.3 (SAS Institute, Cary, North Carolina). For all comparative analyses, a 2-tailed type I error rate of 0.05 was used to determine statistical significance.

For primary analyses, the number of OCS dispensings was calculated as the mean, standard deviation (SD), and median number of events per patient-year (PPY) of observation and compared between the pre- and post-mepolizumab periods using RRs, 95% confidence intervals (CIs), and p-values obtained from Poisson regression models. For asthma exacerbations, the rates of overall, IP/ED-defined, and SCS-defined asthma exacerbations were calculated as the mean, SD, and median number of asthma exacerbations PPY of observation and compared between the pre- and post-mepolizumab periods using RRs, 95% CIs, and p-values obtained from Poisson regression models. The correlation of observations within the same patient between the pre- and post-mepolizumab periods was accounted for using generalized estimating equations (GEE), which provided population average effects.

CHMP comments

The MAH has submitted a retrospective study examining the effects of mepolizumab on severe asthma in the US in paediatric and adolescent patients. Little information has been provided about the administrative claims registry database utilised and, as is expected of such a database its source data cannot be verified. Compared to clinical trials, retrospective registry studies such as this one also have limitations including no data on actually taking medications which were dispensed/prescribed, and no safety data is collected. Nonetheless this database contains a large number of useable patients and is a valuable source of real-word data.

The outcomes of OCS, asthma exacerbations and HRU are important and relevant outcomes for patients' quality of life and impact on healthcare systems, although they are not as specific as clinical measures such as FEV1.

The exploratory end-points looking at the effects of mepolizumab on severe asthma in paediatric and adolescent patients in the pre-covid-19 period are relevant given the large impact covid-19 had on healthcare systems.

Results

Participant flow/recruitment

Of 68 485 patients with ≥1 medical or pharmacy claim for mepolizumab after 01 October 2016, 580 pediatric and adolescent patients with severe asthma initiating mepolizumab (0.85%) were selected into the study sample.

Results of Exploratory Objective

A total of 23 788 patients had ≥1 medical or pharmacy claim for mepolizumab between October 1, 2016 and March 1, 2019, of whom 114 adolescent patients with severe asthma initiating mepolizumab (0.48%) were selected into the study sample.

Baseline data

Mean age was 11.9 years and most patients were male (64.5%), Black or African American (33.1%), from the South (54.3%), and had Medicaid insurance (76.9%). Most patients initiated mepolizumab in 2020 (28.8%) or 2021 (30.2%).

Mean (SD) Quan-Charlson Comorbidity Index (Quan-CCI) score was 1.0 (0.3), and most patients (98.4%) had a Quan-CCI score in the range of 1–2. The most common asthma-related comorbidities were allergic rhinitis (86.0%), upper respiratory tract infection (61.6%), sinusitis (25.7%), obesity (19.1%), and gastroesophageal reflux disease (18.4%). Elixhauser comorbidities with prevalence ≥5% were obesity (19.1%) and cardiac arrhythmias (10.2%).

Nearly all patients used maintenance controller medications (95.9%) or rescue medications (97.8%) during the pre-mepolizumab period. The most common maintenance controller medications with prevalence greater than 20% were ICS (93.6%), ICS/LABA (88.4%), leukotriene modifiers (77.1%), and LAMA (28.3%). The most common rescue medications were SABA (93.4%), SCS (85.3%), antibiotics (60.0%), and SAMA (25.3%). Mean (SD) AMR was 0.5 (0.2).

Results of Exploratory Objective

Demographics and clinical characteristics in the adolescent population during the pre-COVID-19 pandemic period were similar to those observed in the primary study population, although mean age was higher (14.4 years) due to the exclusion of patients under the age of 12 years.

CHMP comments

580 paediatric and adolescent patients were included in the study: 274 children aged 6-11 years old and 306 adolescents aged 12-17 years old. Mepolizumab is not licenced in children under the age of 6. This sample size is sufficient to detect a statistically significant rate ratio of 0.8 for OCS dispensings and rate of asthma exacerbations with 90% power. 114 patients were included for the exploratory (pre-covid-19) end-points. No adults were included in the study.

The pre- and post-mepolizumab initiation design of the study allows patients to act as their own controls reducing confounding bias for demographics and clinical characteristics. However, it is possible that patients' health status changed over the course of the study and changed between the pre- and post- mepolizumab initiation periods, so while asthma-related and other co-morbidities are reported from the baseline period, it is not clear if these co-morbidities were present throughout both study periods and how a change in health status may affect the efficacy outcomes of the study. Allergic rhinitis (86%) and upper respiratory tract infection (62%) were the most common comorbidities reported pre-mepolizumab initiation.

Likewise, baseline respiratory medications (not including OCS) were recorded during the 12 month baseline period but again it is not known if or how these medications changed following mepolizumab initiation and how that may affect the efficacy outcomes of the study.

The licenced posology for children and adolescents receiving mepolizumab differs – 40mg every 4 weeks for children 6 to 11 years old and 100mg every 4 weeks for 12 years and over. The posology was not recorded in this retrospective study but presumed to be in line with licenced posology.

Efficacy results

OCS Dispensings

The number of OCS dispensings pre- and post-mepolizumab initiation is presented in Annex 2, Table 2. There was a 24% decrease in the mean number of OCS dispensings per patient year (PPY) during the post-mepolizumab period compared to the pre-mepolizumab period (2.8 vs. 3.6; RR [95% CI] = 0.76 [0.70, 0.83]; P<0.001).

OCS Treatment Patterns

Further OCS treatment patterns pre- and post-mepolizumab initiation are presented in Annex 2, Table 4. The mean number of OCS bursts PPY reduced from 2.0 burst PPY during the pre-mepolizumab period to 1.4 bursts PPY during the post-mepolizumab period, corresponding to a 29% reduction (RR [95% CI] = 0.71 [0.65, 0.78]; P<0.001). The proportion of patients with ≥1 OCS dispensing reduced by 16% between the pre- and post-mepolizumab period (82.6% vs. 69.7%; risk ratio [95% CI] = 0.84 [0.80, 0.89]; P<0.001). The proportion of patients with maintenance OCS use decreased by 16% during the post-mepolizumab period compared to the pre-mepolizumab period (9.3% vs. 11.0%; risk

ratio [95% CI] = 0.84 [0.66, 1.08]; P=0.182). The proportion of patients with chronic OCS use defined as mean daily dose ≥5 mg per period (risk ratio [95% CI] = 0.91 [0.68, 1.22]; P=0.517), mean daily dose ≥10 mg (risk ratio [95% CI] = 0.83 [0.32, 2.15]; P=0.706), and mean daily dose ≥10 mg over the last 90 days of the period (risk ratio [95% CI] = 0.60 [0.34, 1.04]; P=0.071) decreased during the post-mepolizumab period compared to the pre-mepolizumab period. The average daily dose of OCS per period decreased from a mean of 1.9 mg during the pre-mepolizumab period to 1.5 mg during the post-mepolizumab period (mean difference [95% CI] = -0.40 [-0.54, -0.27]; P<0.001).

Table 2 OCS Treatment Patterns Pre- Versus Post-Mepolizumab Initiation- Primary and Secondary Objectives

OCS treatment patterns[1]	Pre-mepolizumab period[2] N= 580	Post-mepolizumab period[3] N= 580	Percent reduction	Measures of effect	P-value
				Rate ratio (95% CI)[4]	
Number of OCS dispensings, PPY, mean ± SD [median]	3.6 ± 3.6 [3.0]	2.8 ± 3.7 [1.0]	24%	0.76 (0.70, 0.83)	<0.001*
Number of OCS bursts,[5] PPY, mean ± SD [median]	2.0 ± 1.9 [2.0]	1.4 ± 1.7 [1.0]	29%	0.71 (0.65, 0.78)	<0.001*
				Risk ratio (95% CI)[6]	
Patients with ≥1 OCS dispensing, n (%)	479 (82.6)	404 (69.7)	16%	0.84 (0.80, 0.89)	<0.001*
Maintenance OCS use,[7] n (%)	64 (11.0)	54 (9.3)	16%	0.84 (0.66, 1.08)	0.182
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg	43 (7.4)	39 (6.7)	9%	0.91 (0.68, 1.22)	0.517
Mean daily dose ≥10 mg	6 (1.0)	5 (0.9)	17%	0.83 (0.32, 2.15)	0.706
Mean daily dose ≥10 mg during the last 90 days of each period	25 (4.3)	15 (2.6)	40%	0.60 (0.34, 1.04)	0.071
				Mean difference (95% CI)[8]	
Average daily dose mg, mean ± SD [median]					
Per period[9]	1.9 ± 2.1 [1.4]	1.5 ± 2.1 [0.8]	–	-0.40 (-0.54, -0.27)	<0.001*

* $P<0.05$

Abbreviations: CI, confidence interval; HCPCS, Healthcare Common Procedural Coding System; GPI, generic product identifier; OCS, oral corticosteroid; PPY, per patient year; SD, standard deviation.

Notes:

[1] Oral OCS treatments were identified as all medications with a GPI codes starting with "22," excluding fludrocortisone, budesonide, and deflazacort. OCS treatments received in an inpatient or other institutional setting were identified using HCPCS codes. See **Appendices 5** and **6** for a complete list of GPI and HCPCS codes.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] An OCS burst was calculated as a pharmacy claim for an OCS medication with 2–28 days of supply and an average daily dose of ≥20 mg prednisone (or equivalent strength). If two or more bursts were observed for a patient within 14 days of each other, they were considered as one burst.

[6] Risk ratios, 95% CIs, and p-values were estimated from generalized estimating equations log-binomial regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[7] Maintenance OCS use was defined as ≥1 pharmacy claim for an OCS dispensing with >28 days of supply.

[8] Mean difference, 95% CIs, and p-values were estimated from generalized estimating equations linear regressions models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[9] The average daily dose of OCS per period was calculated from pharmacy claims as the sum of number of tablets × prednisone equivalent strength / duration of pre- or post-mepolizumab period or as sum of quantity (mL) × concentration / duration of pre- or post-mepolizumab period for syrups or solutions. OCS dosage was evaluated as prednisone equivalent strength. See **Appendix 8** for equivalent dosage.

Asthma Exacerbations

Asthma exacerbations pre- and post-mepolizumab initiation are presented in Annex 2, Table 3. The rate of overall asthma exacerbations decreased by 34% following mepolizumab initiation compared to before mepolizumab initiation (1.56 vs. 2.34 exacerbations PPY; RR [95% CI] = 0.66 [0.61, 0.72]; P<0.001), driven by a 35% reduction in SCS-defined exacerbations (1.33 vs. 2.05 exacerbations PPY; RR [95% CI] = 0.65 [0.59, 0.72]; P<0.001) and a 24% reduction in IP/ED-defined exacerbations (0.22 vs. 0.30 exacerbations PPY; RR [95% CI] = 0.76 [0.61, 0.95]; P=0.014).

Table 3 Asthma Exacerbations Pre- Versus Post-Mepolizumab – Primary and Secondary Objectives

Asthma exacerbations[1]	Pre-mepolizumab period[2] N= 580 [A]	Post-mepolizumab period[3] N= 580 [B]	Percent reduction	Rate ratio (95% CI)[4] [B]/[A]	P-value
Rate of asthma exacerbations, PPY, mean ± SD [median]					
Overall exacerbation[5]	2.34 ± 2.12 [2.0]	1.56 ± 1.98 [1.0]	34%	0.66 (0.61, 0.72)	<0.001*
SCS-defined exacerbation[6]	2.05 ± 1.92 [2.0]	1.33 ± 1.69 [1.0]	35%	0.65 (0.59, 0.72)	<0.001*
IP/ED-defined exacerbation[7]	0.30 ± 0.76 [0.0]	0.22 ± 0.77 [0.0]	24%	0.76 (0.61, 0.95)	0.014*

* *P*< 0.05

Abbreviations: CI, confidence interval; CPT, current procedural terminology; ED, emergency department; HCPCS, Healthcare Common Procedural Coding System; IP, inpatient; OCS, oral corticosteroid; OP, outpatient; PPY, per patient year; SCS, systemic corticosteroid; SD, standard deviation.

Notes:

[1] Medical claims for scheduled administrations of mepolizumab were excluded from OP visits used to identify asthma exacerbations if they met any of the following conditions: (1) the medical claim included a HCPCS code for mepolizumab (2) the medical claim had a procedure code for subcutaneous or intramuscular drug administration (J3590, CPT: 96372) within 28 days on or after a pharmacy claim for mepolizumab, and on or before the next medical claim with an HCPCS code specific to mepolizumab administration, and (3) if a person had two or more administrations of mepolizumab on a single day, all medical claims on that day were excluded from the exacerbation algorithm. See **Appendix 1** for a list of procedure code to identify mepolizumab.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] Overall exacerbations included both SCS-defined exacerbation and IP/ED-defined exacerbation. Two or more asthma exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity.

[6] SCS-defined exacerbation was defined as an ED visit or OP visit with a primary diagnosis of asthma and an SCS (i.e., OCS or parenteral corticosteroid) medical or pharmacy claim within ±5 days. See **Appendices 5** and **6** for a list of drug and procedure codes to identify SCS.

[7] IP/ED-defined exacerbation was defined as an IP visit with a primary diagnosis of asthma or as an ED visit with a primary diagnosis of asthma that resulted in a hospitalization within one day after the ED visit.

SABA Use

SABA use pre- and post-mepolizumab initiation is presented in Annex 2, Table 4. The mean number of SABA canisters PPY during the post-mepolizumab period did not differ from the pre-mepolizumab period (7.0 vs. 7.1 canisters PPY; RR [95% CI] = 0.98 [0.93, 1.04]; P=0.553). The proportion of patients with ≥1 SABA canister was lower during the post-mepolizumab period compared to the pre-mepolizumab period, decreasing from 91.4% to 88.6% (risk ratio [95% CI] = 0.97 [0.94, 1.00]; P=0.039).

Table 4 SABA Use Pre- Versus Post-Mepolizumab Initiation- Primary and Secondary Objectives

SABA use[1]	Pre-mepolizumab period[2] N= 580	Post-mepolizumab period[3] N= 580	Percent reduction	Measures of effect	P-value
				Rate ratio (95% CI)[4]	
Number of SABA canisters,[5] PPY, mean ± SD [median]	7.1 ± 5.9 [6.0]	7.0 ± 6.3 [5.0]	2%	0.98 (0.93, 1.04)	0.553
				Risk ratio (95% CI)[6]	
Patients with ≥1 SABA canister,[5] n (%)	530 (91.4)	514 (88.6)	3%	0.97 (0.94, 1.00)	0.039*

* *P*< 0.05

Abbreviations: CE, canister equivalent; CI, confidence interval; GINA, global initiative for asthma; GPI, generic product identifier; MDI, metered-dose inhaler; PPY, per patient year; SABA, short-acting β2 agonist; SD, standard deviation.

Notes:

[1] SABA was identified using GPI codes. See **Appendices 5** for a complete list of GPI codes.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] CEs were assigned to each dispensed SABA product to account for MDI and nebulized SABA use. A standard MDI canister size, or 1 CE, was defined as 200 metered actuations of albuterol; levalbuterol was considered to be equivalent in potency to albuterol. A 3-mL ampule of nebulized albuterol/levalbuterol was considered to be equivalent to 2 actuations of albuterol/levalbuterol from an MDI, so 100 3-mL ampules of nebulized SABA was considered 1 CE (based on the GINA guidelines: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf).

[6] Risk ratios, 95% CIs, and p-values were estimated from generalized estimating equations log-binomial regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

All-Cause, Asthma-Related, and Asthma Exacerbation-Related HRU

All-cause, asthma-related, and asthma exacerbation-related HRU pre- and post-mepolizumab initiation are presented in Annex 2, Table 5. Rates of all-cause HRU PPY following mepolizumab initiation reduced by 24% for IP visits (0.26 vs. 0.34 visits PPY; RR [95% CI] = 0.76 [0.61, 0.93]; P=0.009),

14% for ED visits (1.80 vs. 2.09 visits PPY; RR [95% CI] = 0.86 [0.77, 0.96]; P=0.008) and 12% for OP visits (20.36 vs. 23.20 visits PPY; RR [95% CI] = 0.88 [0.81, 0.95]; P=0.001).

Rates of asthma-related HRU PPY following mepolizumab initiation reduced by 23% for IP visits (0.23 vs. 0.30 visits PPY; RR [95% CI] = 0.77 [0.61, 0.98]; P=0.031), 15% for ED visits (0.97 vs. 1.15 visits PPY; RR [95% CI] = 0.85 [0.74, 0.98]; P=0.021), 26% for OP visits (6.46 vs. 8.73 visits PPY; RR [95% CI] = 0.74 [0.67, 0.81]; P<0.001), and 21% for other visits (0.66 vs. 0.84 visits PPY; RR [95% CI] = 0.79 [0.66, 0.96]; P<0.018). Rates of asthma exacerbation-related HRU PPY following mepolizumab initiation reduced by 24% for IP visits (0.23 vs. 0.30 visits PPY; RR [95% CI] = 0.76 [0.60, 0.97]; P=0.024), 19% for ED visits (0.71 vs. 0.89 visits PPY; RR [95% CI] = 0.81 [0.69, 0.95]; P=0.008), and 45% for OP visits (1.50 vs. 2.74 visits PPY; RR [95% CI] = 0.55 [0.49, 0.62]; P<0.001).

Table 5 All-Cause, Asthma-Related and Asthma Exacerbation-Realated HRU Pre- and Post-Mepolizumab[1]- primary and Secondary Objectives

All-Cause, Asthma-Related and Asthma Exacerbation-Related HRU	Pre-mepolizumab period[2] N= 580 [A]	Post-mepolizumab period[3] N= 580 [B]	Percent reduction	Rate ratio (95% CI)[4] [B]/[A]	P-value
All-cause					
HRU, PPY, mean ± SD [median]					
IP visits	0.34 ± 0.86 [0.0]	0.26 ± 0.85 [0.0]	24%	0.76 (0.61, 0.93)	0.009*
ED visits	2.09 ± 2.92 [1.0]	1.80 ± 2.82 [1.0]	14%	0.86 (0.77, 0.96)	0.008*
OP visits	23.20 ± 25.43 [16.0]	20.36 ± 25.62 [14.0]	12%	0.88 (0.81, 0.95)	0.001*
Other visits	2.83 ± 4.01 [2.0]	2.71 ± 4.97 [1.0]	4%	0.96 (0.84, 1.09)	0.497
Asthma-related[5]					
HRU, PPY, mean ± SD [median]					
IP visits	0.30 ± 0.77 [0.0]	0.23 ± 0.81 [0.0]	23%	0.77 (0.61, 0.98)	0.031*
ED visits	1.15 ± 2.03 [0.0]	0.97 ± 1.92 [0.0]	15%	0.85 (0.74, 0.98)	0.021*
OP visits	8.73 ± 10.90 [7.0]	6.46 ± 6.66 [5.0]	26%	0.74 (0.67, 0.81)	<0.001*
Other visits	0.84 ± 1.57 [0.0]	0.66 ± 1.69 [0.0]	21%	0.79 (0.66, 0.96)	0.018*
Asthma exacerbation-related[6]					
HRU, PPY, mean ± SD [median]					
IP visits	0.30 ± 0.77 [0.0]	0.23 ± 0.81 [0.0]	24%	0.76 (0.60, 0.97)	0.024*
ED visits	0.89 ± 1.73 [0.0]	0.71 ± 1.57 [0.0]	19%	0.81 (0.69, 0.95)	0.008*
OP visits	2.74 ± 3.32 [2.0]	1.50 ± 2.35 [1.0]	45%	0.55 (0.49, 0.62)	<0.001*

* *P*< 0.05

Abbreviations: CI, confidence interval; CPT, current procedural terminology; ED, emergency department; HCPCS, Healthcare Common Procedural Coding System; HRU, healthcare resource utilization; IP, inpatient; OP, outpatient; PPY, per patient year; SCS, systemic corticosteroid; SD, standard deviation.

Notes:

[1] OP visits associated with a mepolizumab administration were excluded. Claims associated with a mepolizumab administration were identified using the following algorithm: the medical claim is specific to a mepolizumab administration (i.e., the medical claim includes a HCPCS code for mepolizumab); or the medical claim has a procedure code for subcutaneous or intramuscular drug administration (CPT: 96372) that is within the earlier of the following two criteria: within 28 days on or after a pharmacy claim for mepolizumab and on or before the next medical claim with a HCPCS code specific to mepolizumab administration.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] Asthma-related HRU was defined as any medical visits with a primary or secondary diagnosis of asthma.

[6] Asthma exacerbation-related HRU was defined as any medical claim associated with an IP/ED-defined exacerbation or SCS-defined exacerbation as defined in **Table 5**.

Stratified Analyses

Analyses stratified by age group are presented. Consistent with the results of the primary and secondary analyses, reductions in the mean number of OCS dispensings (pediatric: RR [95% CI] = 0.79 [0.71, 0.89]; adolescent: RR [95% CI] = 0.74 [0.64, 0.84]) and rate of overall asthma exacerbations (pediatric: RR [95% CI] = 0.66 [0.59, 0.74]; adolescent: RR [95% CI] = 0.67 [0.59, 0.76]) were observed among pediatric and adolescent patients, separately (all P<0.001). Use of SABA canisters did not differ between the pre- and post-mepolizumab periods for both pediatric (mean number of SABA canisters: RR [95% CI] = 0.96 [0.88, 1.03], P=0.264; patients with ≥1 SABA canister: risk ratio [95% CI] = 0.97 [0.93, 1.00], P=0.083) and adolescent patients (mean number of SABA canisters: RR [95% CI] = 1.01 [0.93, 1.09], P=0.840; patients with ≥1 SABA canister: risk ratio [95% CI] = 0.97 [0.93, 1.02], P=0.223). Pediatric patients with severe asthma had lower rates of all cause (RR [95% CI] = 0.86 [0.77, 0.96]), asthma-related (RR [95% CI] = 0.73 [0.62, 0.87]), and

asthma exacerbation-related (RR [95% CI] = 0.61 [0.51, 0.71]) OP visits following initiation of mepolizumab (all P<0.05). Adolescent patients with severe asthma had lower rates of all-cause, asthma-related, and asthma exacerbation related HRU following initiation of mepolizumab, with the exception of other visits (RR [95% CI] = 0.95 [0.79, 1.15]; P=0.618).

Results of Exploratory Objective

OCS Dispensings

Among the adolescent population during the pre-COVID-19 pandemic period, a 22% decrease in the mean number of OCS dispensings PPY during the post-mepolizumab period compared to the pre-mepolizumab period was observed (3.4 vs. 4.4 dispensing PPY; RR [95% CI] = 0.78 [0.64, 0.95]; P=0.013; Annex 2, Table 19).

OCS Treatment Patterns

The proportion of adolescent patients with ≥1 OCS dispensing decreased from 86.0% during the pre-mepolizumab period to 73.7% during the post-mepolizumab period (risk ratio [95% CI] = 0.86 [0.77, 0.96]; P=0.006, Annex 2, Table 6). Decreases in the proportions of patients with chronic OCS use did not attain nominal statistical significance across all 3 definitions of chronic OCS use. The average daily dose of OCS decreased from 2.7 mg to 1.9 mg between the pre- and post-mepolizumab periods (mean difference [95% CI] = -0.72 [-1.12, -0.32]; P<0.001).

Table 6 OCS Treatment Patterns Pre- Versus Post-Mepolizumab Initiation- Primary and Secondary Objectives

OCS treatment patterns[1]	Pre-mepolizumab period[2] N= 114	Post-mepolizumab period[3] N= 114	Percent reduction	Measures of effect	P-value
				Rate ratio (95% CI)[4]	
Number of OCS dispensings, PPY, mean ± SD [median]	4.4 ± 4.1 [3.0]	3.4 ± 4.8 [2.0]	22%	0.78 (0.64, 0.95)	0.013*
Number of OCS bursts,[5] PPY, mean ± SD [median]	2.3 ± 2.0 [2.0]	1.5 ± 1.8 [1.0]	33%	0.67 (0.56, 0.80)	<0.001*
				Risk ratio (95% CI)[6]	
Patients with ≥1 OCS dispensing, n (%)	98 (86.0)	84 (73.7)	14%	0.86 (0.77, 0.96)	0.006*
Maintenance OCS use,[7] n (%)	19 (16.7)	16 (14.0)	16%	0.84 (0.60, 1.18)	0.318
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg	17 (14.9)	13 (11.4)	24%	0.76 (0.48, 1.21)	0.250
Mean daily dose ≥10 mg	3 (2.6)	3 (2.6)	0%	1.00 (0.27, 3.69)	1.000
Mean daily dose ≥10 mg during the last 90 days of each period	12 (10.5)	7 (6.1)	42%	0.58 (0.27, 1.26)	0.171
				Mean difference (95% CI)[8]	
Average daily dose mg, mean ± SD [median]					
Per period[9]	2.7 ± 2.6 [2.1]	1.9 ± 2.8 [0.8]	–	-0.72 (-1.12, -0.32)	<0.001*

* $P < 0.05$

Abbreviations: CI, confidence interval; HCPCS, Healthcare Common Procedural Coding System; GPI, generic product identifier; OCS, oral corticosteroid; PPY, per patient year; SD, standard deviation.

Notes:

[1] Oral OCS treatments were identified as all medications with a GPI codes starting with "22," excluding fludrocortisone, budesonide, and deflazacort. OCS treatments received in an inpatient or other institutional setting were identified using HCPCS codes. See **Appendices 5** and **6** for a complete list of GPI and HCPCS codes.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] An OCS burst was calculated as a pharmacy claim for an OCS medication with 2–28 days of supply and an average daily dose of ≥20 mg prednisone (or equivalent strength). If two or more bursts were observed for a patient within 14 days of each other, they were considered as one burst.

[6] Risk ratios, 95% CIs, and p-values were estimated from generalized estimating equations log-binomial regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[7] Maintenance OCS use was defined as ≥1 pharmacy claim for an OCS dispensing with >28 days of supply.

[8] Mean difference, 95% CIs, and p-values were estimated from generalized estimating equations linear regressions models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[9] The average daily dose of OCS per period was calculated from pharmacy claims as the sum of number of tablets × prednisone equivalent strength / duration of pre- or post-mepolizumab period or as sum of quantity (mL) × concentration / duration of pre- or post-mepolizumab period for syrups or solutions. OCS dosage was evaluated as prednisone equivalent strength. See **Appendix 8** for equivalent dosage.

Asthma Exacerbations

Asthma exacerbations in the adolescent population pre- and post-mepolizumab initiation are presented in Annex 2, Table 7. The rate of overall asthma exacerbations decreased by 28% following mepolizumab initiation (1.89 vs. 2.61 exacerbations PPY; RR [95% CI] = 0.72 [0.61, 0.86]; P<0.001), which was driven by a 29% decrease in SCS-defined exacerbations (1.55 vs. 2.19 exacerbations PPY; RR [95% CI] = 0.71 [0.58, 0.86]; P<0.001) and a 19% decrease in IP/ED-defined exacerbations (0.33 vs. 0.41 exacerbations PPY; RR [95% CI] = 0.81 [0.58, 1.12]; P=0.198).

Table 7 Asthma Exacerbations Pre- Versus Post-Mepolizumab Initiation- Exploratory Objectives

Asthma exacerbations[1]	Pre-mepolizumab period[2] N= 114 [A]	Post-mepolizumab period[3] N= 114 [B]	Percent reduction	Rate ratio (95% CI)[4] [B]/[A]	P-value
Rate of asthma exacerbations, PPY, mean ± SD [median]					
Overall exacerbation[5]	2.61 ± 2.19 [2.0]	1.89 ± 2.38 [1.0]	28%	0.72 (0.61, 0.86)	<0.001*
SCS-defined exacerbation[6]	2.19 ± 1.81 [2.0]	1.55 ± 1.95 [1.0]	29%	0.71 (0.58, 0.86)	<0.001*
IP/ED-defined exacerbation[7]	0.41 ± 0.92 [0.0]	0.33 ± 1.04 [0.0]	19%	0.81 (0.58, 1.12)	0.198

* *P*< 0.05

Abbreviations: CI, confidence interval, CPT, current procedural terminology, ED, emergency department, HCPCS, Healthcare Common Procedural Coding System, IP, inpatient, OCS, oral corticosteroid, OP, outpatient, PPY, per patient year, SCS, systemic corticosteroid, SD, standard deviation.

Notes:

[1] Medical claims for scheduled administrations of mepolizumab were excluded from OP visits used to identify asthma exacerbations if they met any of the following conditions: (1) the medical claim included a HCPCS code for mepolizumab (2) the medical claim had a procedure code for subcutaneous or intramuscular drug administration (J3590, CPT: 96372) within 28 days on or after a pharmacy claim for mepolizumab, and on or before the next medical claim with an HCPCS code specific to mepolizumab administration, and (3) if a person had two or more administrations of mepolizumab on a single day, all medical claims on that day were excluded from the exacerbation algorithm. See **Appendix 1** for a list of procedure code to identify mepolizumab.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] Overall exacerbations included both SCS-defined exacerbation and IP/ED-defined exacerbation. Two or more asthma exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity.

[6] SCS-defined exacerbation was defined as an ED visit or OP visit with a primary diagnosis of asthma and an SCS (i.e., OCS or parenteral corticosteroid) medical or pharmacy claim within ±5 days. See **Appendices 5 and 6** for a list of drug and procedure codes to identify SCS.

[7] IP/ED-defined exacerbation was defined as an IP visit with a primary diagnosis of asthma or as an ED visit with a primary diagnosis of asthma that resulted in a hospitalization within one day after the ED visit.

SABA Use

The number of SABA canisters PPY (RR [95% CI] = 0.89 [0.80, 1.01]; P=0.062) and the proportion of patients with ≥1 SABA canister (risk ratio [95% CI] = 0.96 [0.90, 1.03]; P=0.248) among adolescent patients with severe asthma trended lower following mepolizumab initiation (Annex 2, Table 8).

Table 8 SABA Use Pre- Versus Post-Mepolizumab Initiation- Exploratory Objectives

SABA use[1]	Pre-mepolizumab period[2] N= 114	Post-mepolizumab period[3] N= 114	Percent reduction	Measures of effect	P-value
				Rate ratio (95% CI)[4]	
Number of SABA canisters,[5] PPY, mean ± SD [median]	7.9 ± 6.5 [7.0]	7.1 ± 6.4 [6.0]	11%	0.89 (0.80, 1.01)	0.062
				Risk ratio (95% CI)[6]	
Patients with ≥1 SABA canister,[5] n (%)	100 (87.7)	96 (84.2)	4%	0.96 (0.90, 1.03)	0.248

* *P*< 0.05

Abbreviations: CE, canister equivalent, CI, confidence interval, GINA, global initiative for asthma, GPI, generic product identifier, MDI, metered-dose inhaler, PPY, per patient year, SABA, short-acting β- agonist, SD, standard deviation.

Notes:

[1] SABA was identified using GPI codes. See **Appendices 5** for a complete list of GPI codes.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] CEs were assigned to each dispensed SABA product to account for MDI and nebulized SABA use. A standard MDI canister size, or 1 CE, was defined as 200 metered actuations of albuterol; levalbuterol was considered to be equivalent in potency to albuterol. A 3-mL ampule of nebulized albuterol/levalbuterol was considered to be equivalent to 2 actuations of albuterol/levalbuterol from an MDI, so 100 3-mL ampules of nebulized SABA was considered 1 CE (based on the GINA guidelines: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf).

[6] Risk ratios, 95% CIs, and p-values were estimated from generalized estimating equations log-binomial regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

All-Cause, Asthma-Related and Asthma Exacerbation-Related HRU

Rates of all-cause, asthma-related, and asthma exacerbation-related HRU in the adolescent population pre- and post-mepolizumab initiation are presented in Annex 2, Table 9. Decreases were observed in

the rates of all-cause, asthma-related, and asthma exacerbation-related IP, ED, OP visits after mepolizumab initiation.

Table 9 All-Cause, Asthma-Related and Asthma Exacerbation-related HrU, Pre- and Post-Mepolizumab[1] – Exploratory Objective

All-Cause, Asthma-Related and Asthma Exacerbation-Related HRU	Pre-mepolizumab period[2] N= 114 [A]	Post-mepolizumab period[3] N= 114 [B]	Percent reduction
All-cause			
HRU, PPY, mean ± SD [median]			
IP visits	0.48 ± 1.14 [0.0]	0.37 ± 1.05 [0.0]	24%
ED visits	2.25 ± 2.83 [1.0]	1.82 ± 2.81 [1.0]	19%
OP visits	24.72 ± 20.10 [19.5]	21.26 ± 24.75 [16.0]	14%
Other visits	3.20 ± 4.92 [2.0]	3.01 ± 4.69 [1.0]	6%
Asthma-related[5]			
HRU, PPY, mean ± SD [median]			
IP visits	0.42 ± 0.93 [0.0]	0.32 ± 1.02 [0.0]	23%
ED visits	1.34 ± 2.37 [1.0]	1.08 ± 1.98 [0.0]	20%
OP visits	9.66 ± 11.99 [8.0]	7.64 ± 9.14 [6.0]	21%
Other visits	0.80 ± 1.23 [0.0]	0.68 ± 1.70 [0.0]	15%
Asthma exacerbation-related[6]			
HRU, PPY, mean ± SD [median]			
IP visits	0.42 ± 0.93 [0.0]	0.32 ± 1.02 [0.0]	23%	0.77 (0.53, 1.11)	0.165
ED visits	1.11 ± 2.31 [0.0]	0.73 ± 1.64 [0.0]	35%	0.65 (0.48, 0.89)	0.006*
OP visits	3.54 ± 4.62 [2.0]	1.85 ± 2.51 [1.0]	48%	0.52 (0.41, 0.67)	<0.001*

* $P < 0.05$

Abbreviations: CI, confidence interval; CPT, current procedural terminology; ED, emergency department; HCPCS, Healthcare Common Procedural Coding System; HRU, healthcare resource utilization; IP, inpatient; OP, outpatient; PPY, per patient year; SCS, systemic corticosteroid; SD, standard deviation.

Notes:

[1] OP visits associated with a mepolizumab administration were excluded. Claims associated with a mepolizumab administration were identified using the following algorithm: the medical claim is specific to a mepolizumab administration (i.e., the medical claim includes a HCPCS code for mepolizumab); or the medical claim has a procedure code for subcutaneous or intramuscular drug administration (CPT: 96372) that is within the earlier of the following two criteria: within 28 days on or after a pharmacy claim for mepolizumab and on or before the next medical claim with a HCPCS code specific to mepolizumab administration.

[2] The pre-mepolizumab period was defined as the 12 months prior to the index date, including the index date (i.e., the date of mepolizumab initiation).

[3] The post-mepolizumab period spanned from the day after the index date to 12 months after the index date.

[4] Rate ratios, 95% CIs, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation of observations within the same patient between the pre- and post-mepolizumab periods.

[5] Asthma-related HRU was defined as any medical visits with a primary or secondary diagnosis of asthma.

[6] Asthma exacerbation-related HRU was defined as any medical claim associated with an IP/ED-defined exacerbation or SCS-defined exacerbation as defined in **Table 20**.

Safety results

NA

CHMP comments

Results demonstrated that initiation of mepolizumab use resulted in a 24% reduction in the number of OCS dispensings, a 29% reduction in OCS bursts, a 16% reduction in the proportion of patients with ≥1 OCS dispensing, and a 9% and 40% decrease in the proportion of patients with a chronic mean daily dose ≥5 mg per period and ≥10 mg over the last 90 days OCS use, respectively. Similar results were also observed in the exploratory pre-covid-19 analyses following initiation of mepolizumab treatment.

Initiation of mepolizumab resulted in a 34% reduction in overall asthma exacerbations, a 35% reduction in systemic corticosteroid-defined exacerbations and a 24% reduction in in-patient or emergency department-defined exacerbations.

Healthcare resource utilisation rates were also examined and demonstrated decreases following mepolizumab initiation, with asthma related in-patient visits, ED visits and outpatient's visits reducing by 23%, 15% and 26% respectively. All cause and asthma exacerbation-related in-patient and emergency department visits also fell by similar percentages following mepolizumab initiation, while asthma exacerbation-related out-patient visits reduced by 45%. The number of SABA cannister used by patients did not significantly change following mepolizumab initiation.

Overall, similar results were also observed in the exploratory pre-covid-19 analyses following initiation of mepolizumab treatment. The MAH also analysed the results stratifying by age groups with similar trends observed in both children 6-11 years old and adolescents 12-17 years old with regards to OCS use and asthma exacerbations.

These results are supportive of the initiation of mepolizumab treatment for severe asthma in younger patients, despite the limitations of a retrospective registry-based study. The MAH does not propose any updates to the product information which is accepted. In pharmacodynamic studies, blood eosinophils were reduced by 84% in adults and adolescents, and 85% and 87% in children depending on the dose administered. Only adolescents and adults were included in the pivotal clinical trials however the SmPC does not refer to any difference in efficacy between children and adolescent patients.

2.3.3. Discussion on clinical aspects

The MAH has submitted a retrospective study examining the effects of mepolizumab on severe asthma in the US in paediatric and adolescent patients. Little information has been provided about the administrative claims registry database utilised and, as is expected of such a database its source data cannot be verified. Compared to clinical trials, retrospective registry studies such as this one also have limitations including no data on actually taking medications which were dispensed/prescribed, and no safety data is collected. Nonetheless this database contains a large number of useable patients and is a valuable source of real-word data.

The outcomes of OCS, asthma exacerbations and HRU are important and relevant outcomes for patients' quality of life and impact on healthcare systems, although they are not as specific as clinical measures such as FEV1.

The exploratory end-points looking at the effects of mepolizumab on severe asthma in paediatric and adolescent patients in the pre-covid-19 period are relevant given the large impact covid-19 had on healthcare systems.

580 paediatric and adolescent patients were included in the study: 274 children aged 6-11 years old and 306 adolescents aged 12-17 years old. Mepolizumab is not licenced in children under the age of 6. This sample size is sufficient to detect a statistically significant rate ratio of 0.8 for OCS dispensings and rate of asthma exacerbations with 90% power. 114 patients were included for the exploratory (pre-covid-19) endpoints. No adults were included in the study.

The pre- and post-mepolizumab initiation design of the study allows patients to act as their own controls reducing confounding bias for demographics and clinical characteristics. However, it is possible that patients' health status changed over the course of the study and changed between the pre- and post- mepolizumab initiation periods, so while asthma-related and other co-morbidities are reported from the baseline period, it is not clear if these co-morbidities were present throughout both study periods and how a change in health status may affect the efficacy outcomes of the study. Allergic

rhinitis (86%) and upper respiratory tract infection (62%) were the most common comorbidities reported pre-mepolizumab initiation.

Likewise, baseline respiratory medications (not including OCS) were recorded during the 12 month baseline period but again it is not known if or how these medications changed following mepolizumab initiation and how that may affect the efficacy outcomes of the study.

The licenced posology for children and adolescents receiving mepolizumab differs – 40mg every 4 weeks for children 6 to 11 years old and 100mg every 4 weeks for 12 years and over. The posology was not recorded in this retrospective study but presumed to be in line with licenced posology.

Results demonstrated that initiation of mepolizumab use resulted in a 24% reduction in the number of OCS dispensings, a 29% reduction in OCS bursts, a 16% reduction in the proportion of patients with ≥1 OCS dispensing, and a 9% and 40% decrease in the proportion of patients with a chronic mean daily dose ≥5 mg per period and ≥10 mg over the last 90 days OCS use, respectively. Similar results were also observed in the exploratory pre-covid-19 analyses following initiation of mepolizumab treatment.

Initiation of mepolizumab resulted in a 34% reduction in overall asthma exacerbations, a 35% reduction in systemic corticosteroid-defined exacerbations and a 24% reduction in in-patient or emergency department-defined exacerbations.

Healthcare resource utilisation rates were also examined and demonstrated decreases following mepolizumab initiation, with asthma related in-patient visits, ED visits and outpatient's visits reducing by 23%, 15% and 26% respectively. All cause and asthma exacerbation-related in-patient and emergency department visits also fell by similar percentages following mepolizumab initiation, while asthma exacerbation-related out-patient visits reduced by 45%. The number of SABA cannister used by patients did not significantly change following mepolizumab initiation.

Overall, similar results were also observed in the exploratory pre-covid-19 analyses following initiation of mepolizumab treatment. The MAH also analysed the results stratifying by age groups with similar trends observed in both children 6-11 years old and adolescents 12-17 years old with regards to OCS use and asthma exacerbations.

These results are supportive of the initiation of mepolizumab treatment for severe asthma in younger patients, despite the limitations of a retrospective registry-based study. The MAH does not propose any updates to the product information which is accepted. In pharmacodynamic studies, blood eosinophils were reduced by 84% in adults and adolescents, and 85% and 87% in children depending on the dose administered. Only adolescents and adults were included in the pivotal clinical trials however the SmPC does not refer to any difference in efficacy between children and adolescent patients.

3. CHMP overall conclusion and recommendation

Overall, the data submitted is accepted, and it is agreed no updates to the product information are warranted.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled: