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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/P46/019

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) No.1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study no. 217452, title 'Real-World Impact of Switching to Mepolizumab from Other Biologics among Patients with Severe Asthma in the United States' is a standalone study.

The study has not been conducted according to an agreed paediatric 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

While the benefit of mepolizumab treatment in biologic-naïve patients with severe asthma is well-established through clinical trials and observational studies, real-world data on the benefit of mepolizumab in biologic-experienced severe asthma patients is sparse. This study aimed to understand the real-world impact of biologic therapy switch between treatments available for severe asthma and mepolizumab on clinical outcomes and healthcare resource utilization (HRU) to provide insight into the clinical burden in this patient population and to support treatment decisions.

2.3.2. Clinical study

Study no: 217452

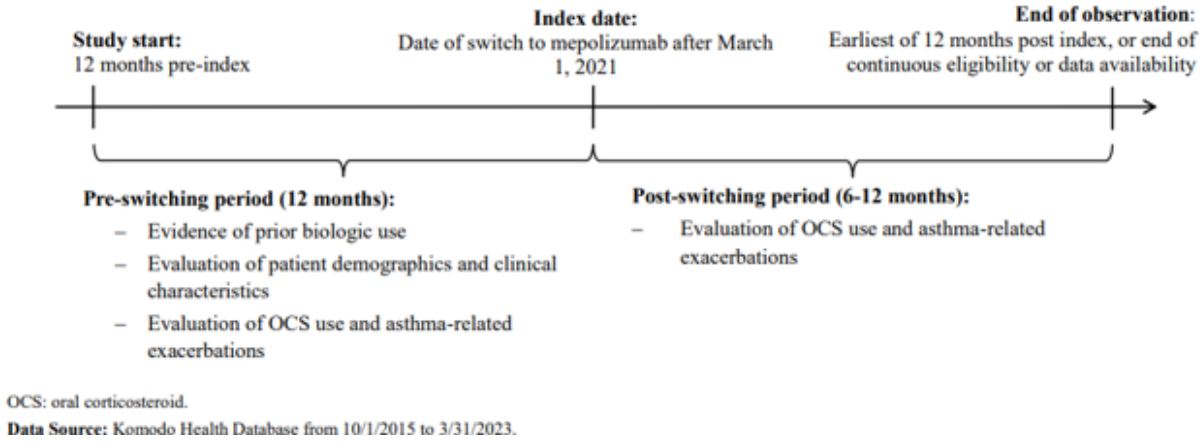
Title: Real-World Impact of Switching to Mepolizumab from Other Biologics among Patients with Severe Asthma in the United States

Study design

A retrospective pre/post study design was employed. In the post-Covid analysis, the index date was defined as the first dispensing/administration (i.e., date of switch) of mepolizumab after 01 March 2021. The latest possible index date was 01 October 2022 to allow for a minimum 6-month observation period prior to the end of data availability (i.e., 31 March 2023). The baseline (i.e., pre-switching) period was defined as the 12 months prior to the index date (i.e., date of switch to mepolizumab). The observation (i.e., post-switching) period was defined as the 6-12 months after the index date. Patient demographics and clinical characteristics were assessed during the baseline period or on the index date. Outcomes of interest (i.e., OCS use and asthma exacerbations) were evaluated for the same patients before and after switching to mepolizumab. The study design scheme for the post-Covid analysis is depicted in Figure 1.

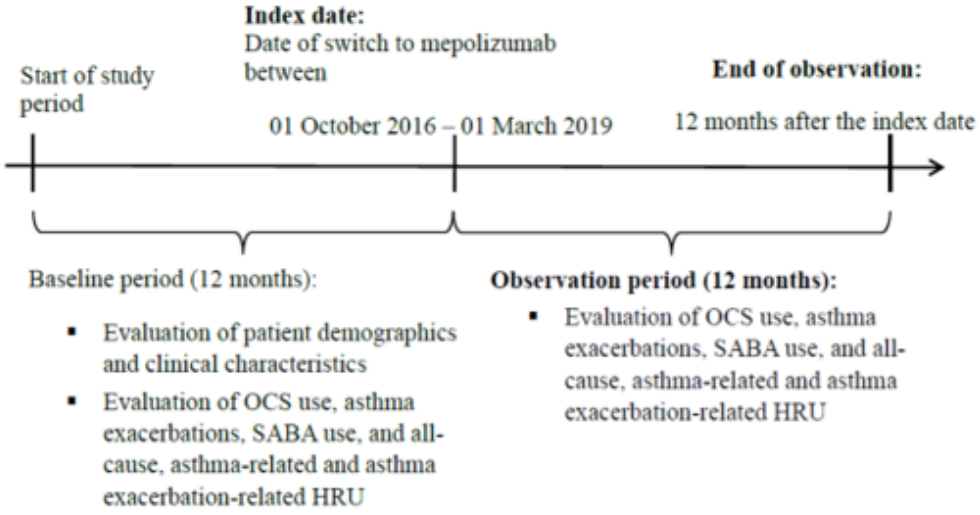
In the pre-Covid analysis, the index date was the date of switch to mepolizumab between 01 October 2016 and 01 March 2019, as presented in Figure 2. The observation period was defined as the 12 months following the index date. OCS use, asthma exacerbations, SABA use, and HRU were evaluated for the same patients before and after switching to mepolizumab.

Figure 1 Study Design Scheme



OCS: oral corticosteroid.
Data Source: Komodo Health Database from 10/1/2015 to 3/31/2023.

Figure 2 Study Design Scheme Pre-Covid Analysis



Methods

A pre-post study design was employed.

The Komodo Research Database, with data ranging from 01 March 2020 to 31 March 2023, was used to address the study objectives for the post-Covid analysis. Data from Komodo Health's comprehensive dataset was used for the pre-Covid analysis, ranging from 01 October 2015 to 01 March 2020. The Komodo databases are 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 United States from 2012 to present. The MAH states that the database captures a rich degree of encounter data for each patient due to the wide range of partnerships with 500+ payers across all US states and longitudinal capture of even patients who switched payers. These encounters have census-level representation across patient populations (e.g.,

age, geography, risk pools), including hospital networks, physician networks, health care claim processing companies (i.e., claims clearinghouses), pharmacies, and health insurers. The database consists of healthcare encounters that came 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. Data are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA).

Study participants

For the post-Covid analysis, the study inclusion criteria were as follows:

- ≥1 medical or pharmacy claim for mepolizumab after 01 March 2021 and before 01 October 2022 (first claim = index date)
- ≥12 years of age at the index date
- ≥12 months of continuous eligibility prior to the index date
- ≥6 months of continuous eligibility after the index date
- ≥1 diagnosis of asthma at any time during the baseline period or on index date (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]): J45.3x, J45.4x, J45.5x, J45.9xx)
- ≥2 medical or pharmacy claims for mepolizumab in the first 6 months after the index date (including the index date)
- ≥1 dispensing or administration of omalizumab, reslizumab, benralizumab, dupilumab, or tezepelumab during the baseline period
- ≥2 asthma exacerbations during the baseline period

For the pre-Covid analysis, the study inclusion criteria were as follows:

- ≥1 medical or pharmacy claim for mepolizumab between 01 October 2016, and 01 March 2019 (first claim = index date)
- ≥12 years of age at the index date
- ≥12 months of continuous eligibility prior to the index date
- ≥12 months of continuous eligibility after the index date
- ≥1 diagnosis of asthma at any time during the baseline period or on index date (ICD-10-CM: J45.3x, J45.4x, J45.5x, J45.9xx)
- ≥2 medical or pharmacy claims for mepolizumab in the first 6 months after the index date (including the index date)
- ≥1 dispensing or administration of omalizumab, reslizumab, benralizumab, or dupilumab during the baseline period

For the post-Covid analysis, the exclusion criteria were as follows:

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

For the pre-Covid analysis, the exclusion criteria were as follows:

- ≥1 diagnosis of active tuberculosis (ICD-10-CM: A15.x) or cystic fibrosis (ICD-10-CM: E84) at any time during the study period
- ≥1 medical or pharmacy claim for mepolizumab at any time before the index date
- ≥1 medical or pharmacy claim for omalizumab, reslizumab, benralizumab, or dupilumab during the follow-up period

Objective(s)

The overall objective of this study was to evaluate asthma medication use, asthma exacerbations, and HRU among patients with severe asthma who switched to mepolizumab from other biologics in the US. Analyses were conducted separately in the pre- and post-Covid eras (i.e., before and after 01 March 2020.

Outcomes/endpoints

OCS Use

The following OCS use measures were evaluated in the pre-and post-switching periods, separately

- Rate of OCS dispensings
- Number of patients receiving ≥1 OCS dispensing
- Rate of OCS bursts
    - OCS bursts were defined (as in GSK study #214181) as a pharmacy claim for an OCS with 2–28 days of supply and an average daily dose of ≥20 mg prednisone equivalent
- Chronic OCS use, defined as either:
    - ≥10 mg prednisone equivalent OCS mean daily dose during the last 90 days of the pre- or post-switching periods
    - ≥5 mg prednisone equivalent OCS mean daily dose during the pre- or post switching periods
- OCS average daily dose

Asthma Exacerbations

The following asthma exacerbation measures were evaluated in the pre-and post-switching periods, separately:

- Overall rate of asthma exacerbations: calculated as the total number of exacerbation events divided by total patient-years, including inpatient (IP)/Emergency Department (ED)-defined and Systemic Corticosteroid (SCS)-defined exacerbations.
- IP/ED-defined exacerbation: included hospitalization-defined and ED-defined exacerbations
    - Hospitalization-defined exacerbation: defined as an asthma-related hospitalization or asthma-related ED visit that resulted in a hospitalization within +1 day
    - ED-defined exacerbations: defined as an asthma-related1 ED visit

- SCS-defined exacerbation: defined as an asthma-related[1] ED visit or asthma-related[1] outpatient (OP) visit with an SCS (i.e., OCS or parenteral corticosteroid) medical or pharmacy claim within ±5 days
- If 2 or more exacerbations were observed for a patient within 14 days of each other, they will be considered as 1 exacerbation and classified according to the highest severity contributing event
- Claims for scheduled administrations of mepolizumab were excluded from OP visits used to identify asthma exacerbations

1 Asthma-related: healthcare encounters associated with any medical claim with a primary diagnosis of asthma (ICD-10-CM: J45.x)

SABA Use

The following SABA use measures were evaluated during the pre- and post-switching periods, separately:

- Proportion of patients with ≥1 SABA canister
- Mean number of SABA canisters

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

The following all-cause, asthma- related and asthma exacerbation-related HRU measures were evaluated during the pre- and post-switching periods, separately:

- All-cause HRU: defined as any medical visits, including IP, OP, or ED visits
- Asthma-related HRU: defined as any medical visits with a primary or secondary diagnosis of asthma
- Asthma exacerbation-related HRU: defined as any medical claim associated with an IP/OP-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 OP visits
- Claims for scheduled administrations of mepolizumab were excluded from the evaluation of OP visits

Sample size

The sample size calculations for rates of OCS dispensings and asthma exacerbations were performed using test for ratio of 2 Poisson rates.

Table 1 presents the minimum sample sizes required to detect statistically significant differences based on a range of different incidence rate ratios (IRRs), from 0.3 to 0.7. Assuming 80% power and 2-tailed type I error rate of 0.05, a target of 84 patients would be sufficient to detect a statistically significant rate ratio of 0.60 for OCS dispensings before and after switching to mepolizumab; a target of 35

patients would be sufficient to detect a statistically significant rate ratio of 0.4 for asthma exacerbation before and after switching to mepolizumab.

Given the post-Covid study population of 89 patients and the pre-Covid study population of 357 patients, the MAH considered the sample size was sufficient to detect statistically significant differences of IRRs for asthma exacerbation and OCS dispensings.

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

Power	IRR	Sample size required
80%	0.30	24
	0.40	35
	0.50	52
	0.60	84
	0.70	156

Notes:
1. Precision calculations based on these values were performed using the software PASS (Copyright 1983-2022, NCSS, LLC)
2. Reference: Gu K., Ng H.K.T., Tang M.L., et al. 'Testing the Ratio of Two Poisson Rates.' Biometrical Journal. 2008;50:(2):283-298.
Huffman Michael. 'An Improved Approximate Two-Sample Poisson Test.' Applied Statistics,. 1984;33(2):224-226.

Randomisation and blinding (masking)

NA

Statistical Methods

All analyses were conducted using SAS Enterprise Guide Software Version 7.1 (SAS Institute, Cary, North Carolina). For all comparative analyses, a 2-sided type I error rate of 0.05 was used to determine statistical significance.

For main analyses, the rate of OCS dispensings and rate of OCS bursts were calculated as number of OCS dispensings or number of OCS bursts per patient per year (PPPY) and described for both the pre- and post-switch periods using mean, SD, and median values. The rates in the pre and post-periods were compared using rate ratios (RRs), 95% confidence intervals (CIs), and p-values obtained from Poisson-family generalized estimating equations (GEE) model with a log link function to account for intra-subject correlation.

The number of patients receiving ≥1 OCS and patients with chronic OCS use were described in relative frequencies and proportions. and compared before and after switching to mepolizumab using log-binomial regression 55 with a log link function (GEE was applied to account for intra-subject correlation). Risk ratios and the associated 95% CIs and p values were reported.

Daily dose of OCS dispensing was described by mean, SD, and median and were compared using ordinary least squares regression. For each comparison, the mean difference and associated 95% CIs and p-values were reported.

The rate of asthma exacerbations was calculated as number of events PPPY and described for both the pre- and post-switch periods using mean, SD, and median values. The rate of asthma exacerbations in

the pre- and post-switch periods were compared using RRs, 95% CIs, and p-values obtained from Poisson-family GEE models with a log link function to account for intra-subject correlation.

Assessor's comments

The MAH has submitted a retrospective study examining the impact of switching to mepolizumab from other biologics in the US population. 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 wash out period before switching, 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 can be considered a valuable source of real-word data.

The inclusion/exclusion criteria and endpoints differed slightly depending on whether analyses were pre- or post-covid-19, however the overall objectives remained the same. 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 pre- and post-covid-19 analyses are relevant given the large impact covid-19 had on healthcare systems, but also at an individual level where asthma patients may be more vulnerable to other respiratory illnesses. Despite this, the proportion of patients who developed covid-19 or covid-19 related complications in the post-covid-19 analysis was not captured.

Results

Participant flow/recruitment

Post-Covid Analysis

A total of 37 198 patients with at least 1 dispensing or administration of mepolizumab were identified from the Komodo claims databases period after 01 March 2021. After applying all study eligibility criteria, 89 severe asthma patients switching to mepolizumab from other biologics with ≥2 baseline exacerbations were included in the study population. The earliest observed index date was March 3rd, 2021 and the latest observed index date was July 12th 2022. Most of these patients (88.8%) had ≥2 claims for the last biologic used prior to switching to mepolizumab.

Pre-Covid Analysis

A total of 19 159 patients with at least 1 dispensing or administration of mepolizumab were identified from the Komodo claims databases period between 01 October 2016 and 01 March 2019. After applying all study eligibility criteria, 357 patients severe asthma patients switching to mepolizumab from other biologics were included in the study population. The earliest observed index date was October 4th, 2016 and the latest observed index date was February 27th, 2019. After restricting to patients with ≥2 baseline exacerbations, 207 patients were included in the study population for the exploratory analysis.

Baseline data

Post-Covid Analysis

Mean age was 49.1 years, and 70.8% of switchers were female. Most patients were from the South and Midwest regions (39.3% and 28.1%, respectively) and had Medicaid (43.8%) or commercial insurance coverage (33.7%) The majority of patients had asthma-related comorbidities, the most

prevalent of which were allergic rhinitis (68.5%), gastroesophageal reflux disease (59.6%), and obesity (46.1%). The most common Elixhauser comorbidities were hypertension (47.2%), obesity (46.1%), and cardiac arrhythmias (28.1%). Mean (SD) Quan-CCI (Quan-Charlson comorbidity index) score was 2.1 (1.7), and mean Elixhauser comorbidity score was 4.7 (6.1).

All patients had prior asthma maintenance controller or rescue medications during the baseline period. All patients used rescue medications during the baseline period, among which the most prevalent classes were SCS (100.0%), SABA (93.3%), and antibiotics (79.8%). Maintenance controller medications were used by almost all patients (98.9%), among which the most commonly used were ICS (96.6%), ICS/LABA (83.1%), and leukotriene modifiers (75.3%). The mean (SD) AMR was 0.7 (0.2).

Patients switching to mepolizumab from omalizumab (39.3%) had mean (SD) 8.4 (5.7) dispensings/administrations of omalizumab during the baseline period. Patients switching to mepolizumab from benralizumab (31.5%) had mean (SD) 3.9 (2.3) dispensings/administrations of omalizumab during the baseline period, and patients switching from dupilumab (29.2%) had mean (SD) 6.8 (3.9) dispensings/administrations for dupilumab.

Pre-Covid Analysis

Mean age was 51.8 years, and 60.2% of switchers were female. Most patients were from the Northeast and South regions (30.0% and 28.3%, respectively) and had commercial (46.5%) and Medicaid (20.2%) insurance coverage.

In the pre-Covid analysis, mean (SD) Quan-CCI score was 1.6 (1.2), and mean (SD) Elixhauser comorbidity score was 3.9 (5.7). The most prevalent asthma-related comorbidities were allergic rhinitis (79.6%), sinusitis (52.7%), and gastroesophageal reflux disease (52.4%). The most common Elixhauser comorbidities were hypertension (48.5%), obesity (34.7%), and diabetes (24.6%).

Most patients (88.8%) used SCS during the baseline period, and use of OCS (79.6%) and antibiotics (76.5%) was also prevalent. Maintenance controller medications were used by the majority of the pre-Covid population (78.7%), with the most common medications being ICS/LABA (69.5%), LAMA (32.5%), and ICS (31.7%). The mean (SD) AMR was 0.6 (0.3). The majority of patients switched from omalizumab (96.4%), following by benralizumab (2.5%), and reslizumab (1.1%).

Assessor's comments

As per the CSR, 357 patients were included in the pre covid-19 analyses, while the data set for the post-covid-19 analyses was more limited with only 89 patients. However this smaller data-set is still large enough to detect a statistically significant rate ratio of 0.6 for OCS dispensings with 80% power.

The pre- and post- switching 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- switching 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. It also appears that the analyses are restricted to participants switching to mepolizumab who continued on mepolizumab for the entirety of the follow-up period or discontinued mepolizumab during the follow-up period without initiating another biologic treatment. This may have biased results in favour of mepolizumab.

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 the switch and how that may affect the efficacy outcomes of the study.

Despite this study being submitted under the paediatric regulation 1901/2006, only 7 (8%) patients were included in the post-covid-19 study population, these patients were aged 12-17 years old despite mepolizumab being licenced for children from the age of 6 upwards. No patients under the age of 18 were included in the pre-covid-19 study population. The number of paediatric patients with at least 1 dispensing or administration of mepolizumab identified in the claims databases was not stated.

For the pre-covid-19 analysis, 96% of patients received omalizumab, in effect making it the only biologic switch examined. For the post-covid-19 analyses, a broadly similar number patients switched from omalizumab, benralizumab and dupilumab. The majority of patients did not reach 60% of scheduled dispensings/administrations during the baseline period, this is based on an assumption of monthly dispensing/administration, which may not be a correct assumption. No patients were included that had switched from other biologics available for the treatment of severe asthma such as reslizumab and tezepelumab.

Efficacy results

Post-Covid Analysis

OCS Use

Results for OCS use in the post-Covid analysis are presented in ANNEX 2, Table 4. Patients had an average of 8.2 OCS dispensings per patient per year (PPPY) prior to switching to mepolizumab and 5.1 dispensing PPPY after switching, corresponding to a 38% reduction after mepolizumab initiation (RR = 0.62, 95% CI: 0.53, 0.72; p <0.001). The mean number of OCS bursts pre- to post-switching reduced from 3.0 to 1.9 events PPPY, corresponding to a 38% relative reduction (p<0.001). The proportion of patients with ≥1 OCS dispensing reduced 9% between the pre- and post-switching period (100.0% vs. 91.0%; p=0.005). The proportion of patients with chronic OCS use, defined as mean daily dose ≥5 mg per period, decreased 37% after switching to mepolizumab (risk ratio = 0.63, 95% CI: 0.46, 0.85; p=0.003). The proportion with chronic OCS use defined as mean daily dose ≥10 mg over the last 90 days of the period reduced by 57% (risk ratio = 0.43, 95% CI: 0.19, 0.95; p=0.038).

Table 2 OCS Treatment Patterns Pre- and Post- Switching to Mepolizumab

OCS treatment patterns[1]	Pre-switching period[2] N= 89 [A]	Post-switching period[3] N= 89 [B]	Percent reduction	Effect estimate	P-value
				Rate ratio (95% CI)[4] [B]/[A]	
Mean number of dispensings, PPPY, mean ± SD [median]	8.2 ± 5.1 [7.0]	5.1 ± 4.5 [4.0]	38%	0.62 (0.53, 0.72)	<0.001*
Mean number of OCS bursts,[5] PPPY, mean ± SD [median]	3.0 ± 1.9 [3.0]	1.9 ± 1.8 [1.4]	38%	0.62 (0.52, 0.74)	<0.001*
				Risk ratio (95% CI)[6] [B]/[A]	
Patients with ≥1 OCS dispensing, n (%)	89 (100.0)	81 (91.0)	9%	0.91 (0.85, 0.97)	0.005*
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg per period	40 (44.9)	25 (28.1)	37%	0.63 (0.46, 0.85)	0.003*
Mean daily dose ≥10 mg per period	14 (15.7)	6 (6.7)	57%	0.43 (0.19, 0.95)	0.038*
				Mean difference (95% CI)[7] [B] - [A]	
Average daily dose per dispensing,[8] mg, mean ± SD [median]	28.6 ± 16.5 [25.4]	27.0 ± 14.2 [25.3]	-	-1.58 (-5.22; 1.65)	0.360
Average daily dose per period,[9] mg, mean ± SD [median]	5.8 ± 4.4 [4.7]	3.9 ± 4.6 [2.5]	-	-1.92 (-2.79; -1.11)	<0.001*

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

Notes:

1. OCS were identified as all oral medications with GPI codes starting with "22," excluding fludrocortisone, budesonide, and deflazacort. OCS received in a hospital 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-switching period was defined as the 12 months prior to the index date, including the index date.
3. The post-switching period spanned from the day after the index date to the earliest of 12 months after the index date, or end of eligibility or data availability.
4. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation between the pre- and post-switching 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). 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% confidence intervals, and p-values were estimated from log-binomial regression models with robust standard errors to account for correlation between the pre- and post-switching periods.
7. Mean differences were calculated with mean differences were calculated from linear regression models using non-parametric bootstrap procedures with 999 replications to estimate 95% CIs and p-values.
8. The average daily dose of OCS per dispensing was calculated from pharmacy claims as number of tablets × prednisone equivalent strength / number of days supplied. OCS dosage was evaluated as prednisone equivalent. See **Appendix 8** for equivalent dosage.
9. The average daily dose of OCS per period was calculated from pharmacy claims as sum(number of tablets × prednisone equivalent strength)/ duration of pre or post mepolizumab period. OCS dosage was evaluated as prednisone equivalent. See **Appendix 8** for equivalent dosage.

Asthma Exacerbations

Switching to mepolizumab was associated with a 53% reduction in overall asthma exacerbations (3.4 PPPY vs. 1.4 PPPY; RR = 0.47, 95% CI: 0.38, 0.59; p<0.001) (ANNEX 2, Table 5). SCS-defined exacerbations decreased by 62% (2.1 PPPY vs. 0.7 PPPY; RR = 0.38, 95% CI: 0.27, 0.52; p<0.001), and IP/ED-defined exacerbations decreased by 37% (1.3 PPPY vs. 0.7 PPPY; RR = 0.63, 95% CI: 0.47, 0.83; p=0.001), driven by a 41% reduction in hospitalization-defined exacerbations (0.3 PPPY vs. 0.2 PPPY; RR = 0.59, 95% CI: 0.28, 1.26; p=0.173) and a 36% reduction in ED-defined exacerbations (1.0 PPPY vs. 0.5 PPPY; RR = 0.64, 95% CI: 0.48, 0.86; p=0.003).

Table 3 Exacerbations Pre- and Post- Switching to Mepolizumab

Asthma exacerbations	Pre-switching period[1] N= 89 [A]	Post-switching period[2] N= 89 [B]	Percent reduction	Rate ratio (95% CI)[3] [B]/[A]	P-value
Rate of exacerbations PPPY, mean ± SD [median]					
Overall exacerbation[4]	3.4 ± 1.9 [3.0]	1.4 ± 1.9 [1.0]	53%	0.47 (0.38, 0.59)	<0.001*
SCS-defined exacerbation[5]	2.1 ± 1.5 [2.0]	0.7 ± 1.1 [0.0]	62%	0.38 (0.27, 0.52)	<0.001*
IP/ED-defined exacerbation	1.3 ± 2.0 [1.0]	0.7 ± 1.6 [0.0]	37%	0.63 (0.47, 0.83)	0.001*
Hospitalization-defined exacerbation[6]	0.3 ± 0.8 [0.0]	0.2 ± 0.6 [0.0]	41%	0.59 (0.28, 1.26)	0.173
ED-defined exacerbation[7]	1.0 ± 1.9 [0.0]	0.5 ± 1.5 [0.0]	36%	0.64 (0.48, 0.86)	0.003*

ED: emergency department; IP: inpatient; OP: outpatient; PPPY: per patient per year; SCS: systemic corticosteroid; SD: standard deviation.

Notes:

1. The pre-switching period was defined as the 12 months prior to the index date, including the index date.
2. The post-switching period spanned from the day after the index date to the earliest of 12 months after the index date, or end of eligibility or data availability.
3. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation between the pre- and post-switching periods.
4. Overall asthma-related exacerbations include both SCS-defined exacerbation and IP/ED-defined exacerbation. Two or more exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity.
5. SCS-defined exacerbation was defined as an asthma-related ED visit or asthma-related OP visit (i.e., ED/OP visits that were associated with medical claims with a primary diagnosis of asthma) with an SCS (i.e., oral or parenteral corticosteroid) medical or pharmacy claim within ±5 days. OP visits related to a biologic administration were not considered.
6. Hospitalization-defined exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit that resulted in a hospitalization within +1 day. Asthma-related was defined as healthcare encounters associated with any medical claim with a primary diagnosis of asthma.
7. ED-defined exacerbations was defined as ED visit that are associated with any medical claim with a primary diagnosis of asthma.

OCS Use Stratified by Pre-Switch Biologic Agent

Patterns of OCS treatment stratified by last biologic agent used prior to switching to mepolizumab (i.e., omalizumab, benralizumab, or dupilumab) to mepolizumab are presented in ANNEX 2, Table 6. Switching to mepolizumab was associated with a decrease in the mean number of OCS dispensings as well as the mean number of OCS bursts, regardless of the pre-switch biologic. Switching from omalizumab to mepolizumab was associated with the largest magnitude of reduction (51% decrease in OCS dispensings and 46% decrease in OCS bursts, $p<0.001$), followed by dupilumab (31% decrease in OCS dispensings, $p=0.016$, and 39% decrease in OCS bursts, $p=0.032$), and benralizumab (29% decrease in OCS dispensings, $p=0.016$, and 28% decrease in OCS bursts, $p=0.032$). The proportion of patients with ≥1 OCS dispensing decreased from 100% pre-switch to 94.3% in switchers from omalizumab ($p=0.157$), 92.9% in switchers from benralizumab ($p=0.157$), and 84.6% in switchers from dupilumab ($p=0.046$).

Table 4 OCS Treatment Patterns Pre- and Post- Switching to Mepolizumab, Stratified by Pre-Switch Agent

OCS treatment patterns[1]	Pre-switching period[2] [A]	Post-switching period[3] [B]	Percent reduction	Effect Estimate	P-value
				Rate ratio (95% CI)[4] [B]/[A]	
Patients switching from omalizumab	**N = 35**	**N = 35**			
Mean number of dispensings, PPPY, mean ± SD [median]	7.9 ± 5.8 [6.0]	3.8 ± 2.9 [3.0]	51%	0.49 (0.39, 0.62)	<0.001*
Mean number of OCS bursts,[7] PPPY, mean ± SD [median]	2.8 ± 2.0 [3.0]	1.5 ± 1.4 [1.4]	46%	0.54 (0.41, 0.72)	<0.001*
Patients switching from benralizumab	**N = 28**	**N = 28**			
Mean number of dispensings, PPPY, mean ± SD [median]	7.1 ± 3.2 [7.0]	5.1 ± 3.7 [5.2]	29%	0.71 (0.54, 0.94)	0.016*
Mean number of OCS bursts,[7] PPPY, mean ± SD [median]	3.2 ± 1.7 [3.0]	2.3 ± 2.1 [1.6]	28%	0.72 (0.53, 0.97)	0.032*
Patients switching from dupilumab	**N = 26**	**N = 26**			
Mean number of dispensings, PPPY, mean ± SD [median]	9.9 ± 5.6 [9.5]	6.9 ± 6.3 [5.2]	31%	0.69 (0.54, 0.87)	0.002*
Mean number of OCS bursts,[7] PPPY, mean ± SD [median]	3.2 ± 2.2 [2.5]	1.9 ± 1.8 [1.2]	39%	0.61 (0.44, 0.85)	0.003*
				Risk ratio (95% CI)[6] [B]/[A]	
Patients switching from omalizumab	**N = 35**	**N = 35**			
Patients with ≥1 OCS dispensing, n (%)	35 (100.0)	33 (94.3)	6%	0.94 (0.87, 1.02)	0.157
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg per period	12 (34.3)	5 (14.3)	58%	0.42 (0.20, 0.89)	0.024*
Mean daily dose ≥10 mg per period	6 (17.1)	0 (0.0)	–	–	–
Patients switching from benralizumab	**N = 28**	**N = 28**			
Patients with ≥1 OCS dispensing, n (%)	28 (100.0)	26 (92.9)	7%	0.93 (0.84, 1.03)	0.157
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg per period	13 (46.4)	9 (32.1)	31%	0.69 (0.39, 1.23)	0.208
Mean daily dose ≥10 mg per period	2 (7.1)	3 (10.7)	-50%	1.50 (0.38, 6.00)	0.566
Patients switching from dupilumab	**N = 26**	**N = 26**			
Patients with ≥1 OCS dispensing, n (%)	26 (100.0)	22 (84.6)	15%	0.85 (0.72, 1.00)	0.046*
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg per period	15 (57.7)	11 (42.3)	27%	0.73 (0.50, 1.07)	0.024*
Mean daily dose ≥10 mg per period	6 (23.1)	3 (11.5)	50%	0.50 (0.18, 1.40)	<0.001*
				Mean difference (95% CI)[7] [B] - [A]	
Patients switching from omalizumab	**N = 35**	**N = 35**			
Average daily dose per dispensing,[8] mg, mean ± SD [median]	30.8 ± 17.1 [25.8]	30.3 ± 16.9 [27.0]	–	-0.14 (-4.58; 4.44)	0.977
Average daily dose per period,[9] mg, mean ± SD [median]	5.7 ± 5.1 [4.0]	2.7 ± 2.2 [1.9]	–	-3.04 (-4.06; -1.91)	<0.001*
Patients switching from benralizumab	**N = 28**	**N = 28**			
Average daily dose per dispensing,[8] mg, mean ± SD [median]	30.1 ± 19.8 [26.6]	27.4 ± 12.3 [24.2]	–	-2.67 (-7.29; 2.29)	0.388
Average daily dose per period,[9] mg, mean ± SD [median]	5.0 ± 2.9 [4.6]	4.0 ± 4.2 [3.3]	–	-0.98 (-2.23; 0.20)	0.118
Patients switching from dupilumab	**N = 26**	**N = 26**			
Average daily dose per dispensing,[8] mg, mean ± SD [median]	24.1 ± 10.5 [21.2]	21.7 ± 10.1 [21.6]	–	-2.34 (-6.18; 1.43)	0.236
Average daily dose per period,[9] mg, mean ± SD [median]	6.9 ± 4.6 [5.6]	5.4 ± 6.7 [3.5]	–	-1.44 (-2.79; -0.18)	0.022

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

Notes:

1. OCS were identified as all oral medications with GPI codes starting with "22," excluding fludrocortisone, budesonide, and deflazacort. OCS received in a hospital 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-switching period was defined as the 12 months prior to the index date, including the index date.
3. The post-switching period spanned from the day after the index date to the earliest of 12 months after the index date, or end of eligibility or data availability.
4. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation between the pre- and post-switching 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). 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% confidence intervals, and p-values were estimated from log-binomial regression models with robust standard errors to account for correlation between the pre- and post-switching periods.
7. Mean differences were calculated with mean differences were calculated from linear regression models using non-parametric bootstrap procedures with 999 replications to estimate 95% CIs and p-values.
8. The average daily dose of OCS per dispensing was calculated from pharmacy claims as number of tablets × prednisone equivalent strength / number of days supplied. OCS dosage was evaluated as prednisone equivalent. See **Appendix 8** for equivalent dosage.
9. The average daily dose of OCS per period was calculated from pharmacy claims as sum(number of tablets × prednisone equivalent strength)/ duration of pre or post mepolizumab period. OCS dosage was evaluated as prednisone equivalent. See **Appendix 8** for equivalent dosage.

Asthma Exacerbations Stratified by Pre-Switch Biologic Agent

Reductions in asthma exacerbations were consistent regardless of last biologic used prior to switching to mepolizumab (ANNEX 2, **Table 5**). The greatest reduction in overall exacerbations was observed for patients switching from benralizumab (RR = 0.45, p<0.001), followed by omalizumab (RR = 0.48,

p<0.001) and dupilumab (RR = 0.49, p<0.001). Reductions in SCS-defined exacerbations were larger in magnitude than reductions in IP/ED-defined exacerbations across all agents.

Table 5 Exacerbations Pre- and Post- Switching to Mepolizumab Stratified by Pre-Switch Agent

Asthma exacerbations	Pre-switching period[1] [A]	Post-switching period[2] [B]	Percent reduction	Rate ratio (95% CI)[3] [B]/[A]	P-value
Rate of exacerbations PPPY, mean ± SD [median]					
Patients switching from omalizumab	**N = 35**	**N = 35**			
Overall exacerbation[4]	3.5 ± 2.4 [2.0]	1.5 ± 2.3 [1.0]	52%	0.48 (0.35, 0.67)	<0.001*
SCS-defined exacerbation[5]	1.5 ± 1.4 [1.0]	0.4 ± 0.7 [0.0]	69%	0.31 (0.17, 0.60)	<0.001*
IP/ED-defined exacerbation[6]	1.9 ± 2.6 [1.0]	1.1 ± 2.2 [0.0]	41%	0.59 (0.41, 0.85)	0.004*
Patients switching from benralizumab	**N = 28**	**N = 28**			
Overall exacerbation[4]	3.2 ± 1.4 [2.5]	1.2 ± 1.7 [0.5]	55%	0.45 (0.28, 0.71)	<0.001*
SCS-defined exacerbation[5]	2.6 ± 1.2 [2.0]	0.7 ± 1.2 [0.0]	68%	0.32 (0.17, 0.60)	<0.001*
IP/ED-defined exacerbation[6]	0.6 ± 0.8 [0.5]	0.5 ± 1.0 [0.0]	6%	0.94 (0.45, 1.94)	0.864
Patients switching from dupilumab	**N = 26**	**N = 26**			
Overall exacerbation[4]	3.4 ± 1.7 [3.0]	1.4 ± 1.5 [1.0]	51%	0.49 (0.35, 0.69)	<0.001*
SCS-defined exacerbation[5]	2.3 ± 1.8 [2.0]	1.0 ± 1.4 [0.5]	50%	0.50 (0.32, 0.77)	0.002*
IP/ED-defined exacerbation[6]	1.1 ± 1.6 [0.5]	0.4 ± 1.0 [0.0]	49%	0.51 (0.29, 0.87)	0.015*

ED: emergency department; IP: inpatient; OP: outpatient; PPPY: per patient per year; SCS: systemic corticosteroid; SD: standard deviation.

Notes:

1. The pre-switching period was defined as the 12 months prior to the index date, including the index date.
2. The post-switching period spanned from the day after the index date to the earliest of 12 months after the index date, or end of eligibility or data availability.
3. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models with robust standard errors to account for correlation between the pre- and post-switching periods.
4. Overall asthma-related exacerbations include both SCS-defined exacerbation and IP/ED-defined exacerbation. Two or more exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity.
5. SCS-defined exacerbation was defined as an asthma-related ED visit or asthma-related OP visit (i.e., ED/OP visits that were associated with medical claims with a primary diagnosis of asthma) with an SCS (i.e., oral or parenteral corticosteroid) medical or pharmacy claim within ±5 days. OP visits related to a biologic administration were not considered.
6. Hospitalization-defined exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit that resulted in a hospitalization within +1 day. Asthma-related was defined as healthcare encounters associated with any medical claim with a primary diagnosis of asthma. ED-defined exacerbations was defined as ED visit that are associated with any medical claim with a primary diagnosis of asthma.

Pre-Covid Analysis

OCS Use

Results for OCS use in the pre-Covid analysis are presented in ANNEX 3, Table 4. On average, patients had 5.3 OCS dispensings PPPY prior to switching to mepolizumab and 4.3 after, corresponding to a 19% reduction after mepolizumab initiation (RR = 0.81, 95% CI: 0.73, 0.89; p <0.001). The proportion of patients with chronic OCS use defined as mean daily dose ≥5 mg per period decreased 39% after switching to mepolizumab (risk ratio = 0.61, 95% CI: 0.53, 0.71; p<0.001). The proportion of patients with chronic OCS use defined as mean daily dose ≥10 mg over the last 90 days of the period reduced by 30% (risk ratio = 0.70, 95% CI: 0.55, 0.89; p=0.004).

The mean number of OCS bursts pre- to post-switching reduced from 2.2 to 1.4 PPPY, corresponding to a 33% relative reduction (RR = 0.67, 95% CI: 0.60, 0.75; p<0.001). The proportion of patients with ≥1 OCS dispensing reduced 8% between the pre- and post-switching period (80.7% vs. 74.2%; RR = 0.92; 95% CI: 0.87, 0.97; p=0.003).

Table 6 Treatment Patterns Pre- and Post- Switching to Mepolizumab

OCS treatment patterns[1]	Pre-switching period[2] N= 357 [A]	Post-switching period[3] N= 357 [B]	Percent reduction	Ratio [B]/[A]	P-value
				Rate ratio (95% CI)[4]	
Mean number of dispensings, PPPY, mean ± SD [median]	5.3 ± 5.0 [4.0]	4.3 ± 5.2 [2.0]	19%	0.81 (0.73, 0.89)	<0.001*
Average daily dose per dispensing,[5] mg, mean ± SD [median]	44.6 ± 157.1 [27.9]	32.3 ± 33.9 [27.4]	28%	0.72 (0.48, 1.09)	0.125
Average daily dose per period,[6] mg, mean ± SD [median]	5.4 ± 8.8 [3.4]	4.2 ± 7.0 [1.6]	22%	0.78 (0.65, 0.93)	0.005*
Mean number of OCS bursts,[7] PPPY, mean ± SD [median]	2.2 ± 2.1 [2.0]	1.4 ± 1.8 [1.0]	33%	0.67 (0.60, 0.75)	<0.001*
				Risk ratio (95% CI)[8]	
Patients with ≥1 OCS dispensing, n (%)	288 (80.7)	265 (74.2)	8%	0.92 (0.87, 0.97)	0.003*
Chronic OCS use, n (%)					
Mean daily dose ≥5 mg per period	145 (40.6)	89 (24.9)	39%	0.61 (0.53, 0.71)	<0.001*
Mean daily dose ≥10 mg over the last 90 days of the period	84 (23.5)	59 (16.5)	30%	0.70 (0.55, 0.89)	0.004*

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

Notes:

1. OCS were identified as all oral medications with GPI codes starting with "22," excluding fludrocortisone, budesonide, and deflazacort. OCS received in a hospital or other institutional setting were identified using HCPCS codes.
2. The pre-switching period was defined as the 12 months prior to the index date, including the index date.
3. The post-switching period spanned from the day after the index date to 12 months after the index date (i.e., excluding the index date).
4. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models to account for correlation between the pre- and post-switching periods.
5. The average daily dose of OCS per dispensing was calculated from pharmacy claims as number of tablets × prednisone equivalent strength / number of days supplied. OCS dosage was evaluated as prednisone equivalent. See **Appendix 6** for equivalent dosage.
6. The average daily dose of OCS was calculated from pharmacy claims as Sum(number of tablets × prednisone equivalent strength)/ for all dispensings / number of days supplied. OCS dosage was evaluated as prednisone equivalent. See **Appendix 6** for equivalent dosage.
7. 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). If two or more bursts were observed for a patient within 14 days of each other, they were considered as one burst.
8. Risk ratios, 95% confidence intervals, and p-values were estimated from log-binomial regression models to account for correlation between the pre- and post-switching periods.

Asthma Exacerbations

Results for asthma exacerbations are presented in ANNEX 3, **Table 7**. In the pre-Covid population, switching to mepoliuzumab was associated with a 27% reduction in the rate of overall exacerbations PPPY (2.6 vs. 2.4; RR = 0.73, 95% CI: 0.66, 0.81; p<0.001). SCS-defined exacerbations decreased by 31% (1.6 vs. 1.1; RR = 0.69, 95% CI: 0.60, 0.80; <0.001), and IP/ED-defined exacerbations decreased by 22% (1.1 vs. 0.8; RR = 0.74, 95% CI: 0.61, 0.91; p<0.001), driven by a 26% reduction in hospitalization-defined exacerbations (0.7 vs. 0.5; RR = 0.74, 95% CI: 0.61, 0.91; p=0.003) and a 16% reduction in ED-defined exacerbations (0.4 vs. 0.3; RR = 0.84, 95% CI: 0.66, 1.06; p=0.143).

Table 7 Exacerbations Pre- and Post- Switching to Mepolizumab

Asthma exacerbations	Pre-switching period[1] N= 357 [A]	Post-switching period[2] N= 357 [B]	Percent reduction	Rate ratio (95% CI)[3] [B]/[A]	P-value
Rate of exacerbations PPPY, mean ± SD [median]					
Overall exacerbation[4]	2.6 ± 2.5 [2.0]	1.9 ± 2.4 [1.0]	27%	0.73 (0.66, 0.81)	<0.001*
SCS-defined exacerbation[5]	1.6 ± 1.7 [1.0]	1.1 ± 1.7 [1.0]	31%	0.69 (0.60, 0.80)	<0.001*
IP/ED-defined exacerbation	1.1 ± 1.9 [0.0]	0.8 ± 1.7 [0.0]	22%	0.78 (0.68, 0.90)	<0.001*
Hospitalization-defined exacerbation[6]	0.7 ± 1.4 [0.0]	0.5 ± 1.2 [0.0]	26%	0.74 (0.61, 0.91)	0.003*
ED-defined exacerbation[7]	0.4 ± 1.0 [0.0]	0.3 ± 0.9 [0.0]	16%	0.84 (0.66, 1.06)	0.143

ED: emergency department; IP: inpatient; OP: outpatient; PPPY: per patient per year; SCS: systemic corticosteroid; SD: standard deviation.

Notes:

1. The pre-switching period was defined as the 12 months prior to the index date, including the index date.
2. The post-switching period spanned from the day after the index date to 12 months after the index date (i.e., excluding the index date).
3. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models to account for correlation between the pre- and post-switching periods.
4. Overall asthma-related exacerbations include both SCS-defined exacerbation and IP/ED-defined exacerbation. Two or more exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity.
5. SCS-defined exacerbation was defined as an asthma-related ED visit or asthma-related OP visit (i.e., ED/OP visits that were associated with medical claims with a primary diagnosis of asthma) with an SCS (i.e., OCS or parenteral corticosteroid) medical or pharmacy claim within ±5 days. OP visits related to a biologic administration were not considered.
6. Hospitalization-defined exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit that resulted in a hospitalization within +1 day. Asthma-related was defined as healthcare encounters associated with any medical claim with a primary diagnosis of asthma.

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

Results for all-cause, asthma-related, and asthma exacerbation-related HRU are presented in ANNEX 3, Table 6. Rates of all-cause ED visits and OP visits PPPY reduced by 17% (1.6 vs. 1.3; RR = 0.83, 95% CI: 0.69, 0.99; p=0.042) and 9% (34.7 vs. 31.7; RR = 0.91, 95% CI: 0.86, 0.97; p=0.002), respectively from pre- to post-switching. All-cause hospitalization pre- to post-switching decreased by 6% from 1.8 to 1.7 (RR = 0.94, 95% CI: 0.77, 1.15; p=0.547). Rates of asthma-related hospitalizations PPPY reduced by 18% (1.2 vs. 1.0; RR = 0.82, 95% CI: 0.68, 0.99; p=0.037) after

switching to mepolizumab, and rates of asthma-related ED and OP visits PPPY reduced by 20% (0.9 vs. 0.7; RR = 0.80, 95% CI: 0.64, 1.00; p=0.05) and 25% (13.3 vs. 9.9; RR = 0.75, 95% CI: 0.69, 0.81; p<0.001), respectively. Rates of asthma exacerbation-related hospitalizations PPPY reduced 33% (0.9 vs. 0.6; RR = 0.67, 95% CI: 0.56, 0.81; p<0.001) after switching to mepolizumab, whereas rates of asthma exacerbation-related ED and OP visits PPPY reduced by 23% (0.6 vs. 0.4; RR = 0.77, 95% CI: 0.61, 0.98; p=0.031) and 34% (2.6 vs. 1.7; RR = 0.66, 95% CI: 0.57, 0.75; p<0.001), respectively.

Table 8 All-Cause, Asthma-Related and Asthma Exacerbation-Related HRU Pre- and Post-Switching to Mepolizumab

	Pre-switching period[1] N= 357 [A]	Post-switching period[2] N= 357 [B]	Percent reduction	Rate ratio (95% CI)[3]	P-value
All-cause healthcare resource utilization[4]					
HRU events, PPPY, mean ± SD [median]					
Hospitalizations	1.8 ± 4.4 [0.0]	1.7 ± 5.1 [0.0]	6%	0.94 (0.77, 1.15)	0.547
ED visits	1.6 ± 3.1 [0.0]	1.3 ± 2.6 [0.0]	17%	0.83 (0.69, 0.99)	0.042*
OP visits	34.7 ± 21.1 [31.0]	31.7 ± 23.6 [27.0]	9%	0.91 (0.86, 0.97)	0.002*
Asthma-related healthcare resource utilization[5]					
HRU events, PPPY, mean ± SD [median]					
Hospitalizations	1.2 ± 2.7 [0.0]	1.0 ± 2.3 [0.0]	18%	0.82 (0.68, 0.99)	0.037*
ED visits	0.9 ± 1.9 [0.0]	0.7 ± 1.8 [0.0]	20%	0.80 (0.64, 1.00)	0.050*
OP visits	13.3 ± 8.4 [12.0]	9.9 ± 8.1 [9.0]	25%	0.75 (0.69, 0.81)	<0.001*
Asthma exacerbation-related healthcare resource utilization[6]					
HRU events, PPPY, mean ± SD [median]					
Hospitalizations	0.9 ± 2.5 [0.0]	0.6 ± 1.7 [0.0]	33%	0.67 (0.56, 0.81)	<0.001*
ED visits	0.6 ± 1.5 [0.0]	0.4 ± 1.3 [0.0]	23%	0.77 (0.61, 0.98)	0.031*
OP visits	2.6 ± 3.0 [2.0]	1.7 ± 2.5 [1.0]	34%	0.66 (0.57, 0.75)	<0.001*

CI: confidence interval; ED: emergency department; HRU: healthcare resource utilization; OP: outpatient; PPPY; per patient per year; SD: standard deviation.

Notes:

1. The pre-switching period was defined as the 12 months prior to the index date, including the index date.
2. The post-switching period spanned from the day after the index date to 12 months after the index date (i.e., excluding the index date).
3. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models to account for correlation between the pre- and post-switching periods.
4. All-cause HRU defined as any medical visits, including hospitalizations, OP, or ED visits, excluding OP visits for a biologic administration.
5. Asthma-related HRU defined as any medical visits with a primary or secondary diagnosis of asthma (ICD-10-CM: J45.x), excluding OP visits for a biologic administration.
6. Healthcare encounters associated with any medical claim for asthma exacerbations, excluding OP visits for a biologic administration.

SABA Use

Results for SABA use are presented in ANNEX 3, Table 7. The mean rate of SABA canisters was 5.4 PPPY during the pre- switching period and 5.1 PPPY during the post-switching period, corresponding to a reduction of 6% (RR = 0.94, 95% CI: 0.87, 1.03; p=0.190). The proportion of patients using ≥1 SABA canister during the pre- switching period was 68.1%, which decreased to 65.0% during the post-switching period (risk ratio = 0.95, 95% CI: 0.90, 1.02; p=0.159).

Table 9 SABA Use Pre- and Post- Switching to Mepolizumab

SABA use	Pre-switching period[1] N= 357 [A]	Post-switching period[2] N= 357 [B]	Percent reduction	Ratio [B]/[A]	P-value
				Rate ratio (95% CI)[3]	
Rate of SABA canisters PPPY,[5] mean ± SD [median]	5.4 ± 7.0 [2.0]	5.1 ± 7.0 [2.0]	6%	0.94 (0.87, 1.03)	0.190
				Risk ratio (95% CI)[4]	
Proportion with ≥1 SABA canister, n (%)	243 (68.1)	232 (65.0)	5%	0.95 (0.90, 1.02)	0.159

CE: canister equivalent; CI: confidence interval; PPPY: per patient per year; SABA: short-acting β_2 agonist; SD: standard deviation.

Notes:

1. The pre-switching period was defined as the 12 months prior to the index date, including the index date.
2. The post-switching period spanned from the day after the index date to 12 months after the index date (i.e., excluding the index date).
3. Rate ratios, 95% confidence intervals, and p-values were estimated from generalized estimating equations Poisson regression models to account for correlation between the pre- and post-switching periods.
4. Risk ratios, 95% confidence intervals, and p-values were estimated from log-binomial regression models to account for correlation between the pre- and post-switching 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).

Exploratory Objective

OCS Use

Results for OCS use in the pre-Covid population of patients with ≥2 exacerbations during the baseline period: Patients had mean 7.4 OCS dispensings PPPY in the pre-switching period, which reduced to 6.0 PPPY after switch to mepolizumab (RR = 0.81, 95% CI: 0.73, 0.91; p<0.001). The rate of OCS bursts reduced from 3.1 bursts PPPY in the pre-switching period to 2.0 PPPY in the post-switching period (RR= 0.66, 95% CI: 0.57, 0.74; p<0.001).

The proportion of patients with chronic OCS use defined as mean daily dose ≥5 mg per period decreased 37% after switching to mepolizumab (risk ratio = 0.63, 95% CI: 0.54, 0.75; p<0.001). The proportion of patients with chronic OCS use defined as mean daily dose ≥10 mg over the last 90 days of the period reduced by 26% (risk ratio = 0.74, 95% CI: 0.58, 0.95; p=0.020).

Asthma Exacerbations

Results for asthma exacerbations in the pre-Covid population of patients with ≥2 exacerbations during the baseline period: In this population, switching to mepolizumab was associated with a 35% reduction in the rate of overall exacerbations (4.2 vs. 2.7; RR = 0.65, 95% CI: 0.59, 0.72; p<0.001). Rates of defined exacerbations decreased by 40% (2.5 vs. 1.5; RR = 0.60, 95% CI: 0.52, 0.70; p<0.001), and rates of IP/ED-defined exacerbations decreased by 28% (1.7 vs. 1.2, RR = 0.72, 95% CI: 0.62, 0.83; p<0.001), driven by a 35% reduction in hospitalization-defined exacerbations (1.1 PPPY vs. 0.7 PPPY, RR = 0.65, 95% CI: 0.53, 0.79; p<0.001) and a 15% reduction in ED-defined exacerbations (0.6 PPPY vs. 0.5 PPPY; RR = 0.85, 95% CI: 0.67, 1.10; p=0.215).

Safety results

NA

CHMP comments

Results demonstrated that switching to mepolizumab from any biologic in the post-covid-19 study period resulted in a 38% reduction in OCS use, a 38% reduction in OCS bursts, a 9% reduction in the proportion of patients with ≥1 OCS dispensing, and a 37% and 57% 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. A similar trend was observed in the pre-covid-19 analyses, although reductions were not as great in OCS use possibly due to lower OCS dispensings PPPY in the pre-switching period compared to the pre-switching period in the post-covid-19 study period.

Switching to mepolizumab from any biologic in the post-covid-19 analyses resulted in a 53% reduction in overall asthma exacerbations, a 62% reduction in systemic corticosteroid-defined exacerbations and a 37% reduction in in-patient or emergency department-defined exacerbations. In the pre-covid-19 analyses, a less effective, but still positive trend was observed for switching to mepolizumab.

When the post-covid-19 analyses were stratified by use of last prior biologic, OCS use and asthma exacerbations were reduced for all omalizumab, benralizumab or dupilumab.

Healthcare resource utilisation rates were also examined and demonstrated decreased rates pre and post switch, with asthma related hospitalisations, ED visits and outpatient's visits reducing by 18%, 20% and 25% respectively. SABA use was also slightly decreased in the pre-covid-19 study period.

Exploratory objectives looking at OCS use and asthma exacerbations patients with ≥2 exacerbations during the baseline period in the pre-covid-19 period also demonstrated similarly positive trends supporting the switch from other asthma biologics to mepolizumab.

Despite this study being submitted under the Article 46 of paediatric Regulation (EC) No.1901/2006, there was no subgroup analyses to assess outcomes based on paediatric patients in the post-covid-19 study. Following queries, the MAH clarified they 'did not report results for this subgroup due to the small number reporting rule that is widely adopted by various institutions and data source vendors. The small number reporting rule applies when reporting data that includes cells with fewer than a certain number of patients. It aims to protect the confidentiality of patients and avoid misinterpreting data of small sample size. Hence, we chose not to report results specifically for paediatric population that has <10 patients'. This can be accepted.

Overall, both the pre- and post-covid-19 outcomes demonstrated similar trends. Clinical trials for mepolizumab to obtain marketing authorisation were placebo controlled trials and included patients with background treatments including high doses of inhaled corticosteroids plus an additional maintenance treatment (LABA, LAMA and OCS, leukotriene, theophylline) or systemic corticosteroids. The results of this retrospective registry-based study therefore provide some support for switching to mepolizumab from other newer biologics for severe asthma.

The MAH does not propose any updates to the product information which may be acceptable, subject to resolution of the query raised. There is currently no reference in the product information with regards to other biologics and/or switching and this is appropriate.

2.3.3. Discussion on clinical aspects

The MAH has submitted a retrospective study examining the impact of switching to mepolizumab from other biologics in the US population. 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 wash out period before switching, 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 can be considered a valuable source of real-word data.

The inclusion/exclusion criteria and endpoints differed slightly depending on whether analyses were pre- or post-covid-19, however the overall objectives remained the same. 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 pre- and post-covid-19 analyses are relevant given the large impact covid-19 had on healthcare systems, but also at an individual level where asthma patients may be more vulnerable to other respiratory illnesses. Despite this, the proportion of patients who developed covid-19 or covid-19 related complications in the post-covid-19 analysis was not captured.

As per the CSR, 357 patients were included in the pre covid-19 analyses, while the data set for the post-covid-19 analyses was more limited with only 89 patients. However this smaller dataset is still large enough to detect a statistically significant rate ratio of 0.6 for OCS dispensings with 80% power.

The pre- and post- switching 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- switching 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. It also appears that the analyses are restricted to participants switching to mepolizumab who continued on mepolizumab for the entirety of the follow-up period or discontinued mepolizumab during the follow-up period without initiating another biologic treatment. This may have biased results in favour of mepolizumab.

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 the switch and how that may affect the efficacy outcomes of the study.

Despite this study being submitted under the paediatric regulation 1901/2006, only 7 (8%) patients were included in the post-covid-19 study population, these patients were aged 12-17 years old despite mepolizumab being licenced for children from the age of 6 upwards. No patients under the age of 18 were included in the pre-covid-19 study population. The number of paediatric patients with at least 1 dispensing or administration of mepolizumab identified in the claims databases was not stated.

For the pre-covid-19 analysis, 96% of patients received omalizumab, in effect making it the only biologic switch examined. For the post-covid-19 analyses, a broadly similar number patients switched from omalizumab, benralizumab and dupilumab. The majority of patients did not reach 60% of scheduled dispensings/administrations during the baseline period, this is based on an assumption of monthly dispensing/administration, which may not be a correct assumption. No patients were included that had switched from other biologics available for the treatment of severe asthma such as reslizumab and tezepelumab.

Results demonstrated that switching to mepolizumab from any biologic in the post-covid-19 study period resulted in a 38% reduction in OCS use, a 38% reduction in OCS bursts, a 9% reduction in the proportion of patients with ≥1 OCS dispensing, and a 37% and 57% 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. A similar trend was observed in the pre-covid-19 analyses, although reductions were not as great in OCS use possibly due to lower OCS dispensings PPPY in the pre-switching period compared to the pre-switching period in the post-covid-19 study period.

Switching to mepolizumab from any biologic in the post-covid-19 analyses resulted in a 53% reduction in overall asthma exacerbations, a 62% reduction in systemic corticosteroid-defined exacerbations and a 37% reduction in in-patient or emergency department-defined exacerbations. In the pre-covid-19 analyses, a less effective, but still positive trend was observed for switching to mepolizumab.

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Exploratory objectives looking at OCS use and asthma exacerbations patients with ≥2 exacerbations during the baseline period in the pre-covid-19 period also demonstrated similarly positive trends supporting the switch from other asthma biologics to mepolizumab.

Despite this study being submitted under the Article 46 of paediatric Regulation (EC) No.1901/2006, there was no subgroup analyses to assess outcomes based on paediatric patients in the post-covid-19 study. The MAH clarified that they 'did not report results for this subgroup due to the small number reporting rule that is widely adopted by various institutions and data source vendors. The small number reporting rule applies when reporting data that includes cells with fewer than a certain number of patients. It aims to protect the confidentiality of patients and avoid misinterpreting data of small sample size. Hence, we chose not to report results specifically for paediatric population that has <10 patients'. This can be accepted.

Overall, both the pre- and post-covid-19 outcomes demonstrated similar trends. Clinical trials for mepolizumab to obtain marketing authorisation were placebo controlled trials and included patients with background treatments including high doses of inhaled corticosteroids plus an additional

maintenance treatment (LABA, LAMA and OCS, leukotriene, theophylline) or systemic corticosteroids. The results of this retrospective registry-based study therefore provide some support for switching to mepolizumab from other newer biologics for severe asthma.

The MAH does not propose any updates to the product information which may be acceptable, subject to resolution of the queries raised. There is currently no reference in the product information with regards to other biologics and/or switching which is appropriate.

3. CHMP overall conclusion and recommendation

The MAH has submitted a retrospective study examining the impact of switching to mepolizumab from other biologics in the US population. Both the pre- and post-covid-19 outcomes demonstrated similar trends. Clinical trials for mepolizumab to obtain marketing authorisation were placebo-controlled trials and included patients with background treatments including high doses of inhaled corticosteroids plus an additional maintenance treatment (LABA, LAMA and OCS, leukotriene, theophylline) or systemic corticosteroids. The results of this retrospective registry-based study therefore provide some support for switching to mepolizumab from other newer biologics for severe asthma.

The MAH does not propose any updates to the product information which is acceptable. There is currently no reference in the product information with regards to other biologics and/or switching and this is appropriate.

The MAH is considered to have fulfilled its obligations in accordance with Article 46 of Regulation (EC) No1901/2006, and this post-authorisation measure is considered fulfilled.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled:

4. Request for supplementary information

None

MAH responses to Request for supplementary information

Queries raised:

1. The index dates and the dataset range dates do not appear aligned, for example for the pre-Covid analysis, the dataset ranges from 01 November 2015 to 05 Jun 2022 (CSR section 6.4) and index dates of between 01 Oct 2016 to 01 Mar 2019 which does not allow for a 12 month baseline period before the earliest index dates. In addition, Jun 2022 cannot be considered appropriate for a 'pre-covid-19' analysis. The MAH should clarify the earliest and latest observed index dates and dataset dates for patients included in the pre- and post-COVID analyses and update the CSR where appropriate**.**
2. The index date in Figure 1 of the CSR is incorrect, please correct and update the CSR**.**
3. The applicant is asked to update the CSR corrected for typos: the starting numbers of 37,198 appear to be incorrect for the pre-covid-19 analyses (page 31); the paragraph on % of patients switching from other biologics to mepolizumab doesn't mention benralizumab (page 31/32).

CHMP comments

The MAH responded to clarify inconsistencies raised and updated the CSR for the above queries. Acceptable.

4. Despite this study being submitted under the Article 46 of paediatric Regulation (EC) No.1901/2006, there was no subgroup analyses to assess outcomes based on paediatric patients in the post-covid-19 study. The MAH should clarify the number of paediatric patients at each stage of each analysis, and if feasible provide results separately for the paediatric subgroup and discuss whether similar outcome trends are observed as in the full study population

CHMP comments

The MAH clarified that they 'did not report results for this subgroup due to the small number reporting rule that is widely adopted by various institutions and data source vendors. The small number reporting rule applies when reporting data that includes cells with fewer than a certain number of patients. It aims to protect the confidentiality of patients and avoid misinterpreting data of small sample size. Hence, the MAH chose not to report results specifically for paediatric population that has <10 patients'. This can be accepted.