19 June 2025
EMADOC-1700519818-2025831
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

On 27 March 2025, the MAH submitted a completed study for Nucala, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Patients included in the study were ≥12 years of age at a defined index date which makes it fall under Article 46.

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

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 221029: *Burden of Being Eligible for Mepolizumab and Delaying Initiation in Patients with Severe Uncontrolled Asthma in the US,* is a stand-alone study. These data are not submitted as part of any post-authorisation measures or a specific obligation.

This is a retrospective observational study using insurance claims data to better understand the real-world use and effectiveness of mepolizumab.

No changes to the Summary of Product Characteristics (SmPC) for mepolizumab are proposed.

2.2. Information on the pharmaceutical formulation used in the study

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

The formulation, dose and exposure were not defined. Patient cohorts were defined by ≥1 pharmacy claim in the US, for mepolizumab, in the timeframe after the severe uncontrolled asthma (SUA) index date.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 221029: Burden of Being Eligible for Mepolizumab and Delaying Initiation in Patients with Severe Uncontrolled Asthma in the US

2.3.2. Clinical study

Study 221029: Burden of Being Eligible for Mepolizumab and Delaying Initiation in Patients with Severe Uncontrolled Asthma in the US

Description

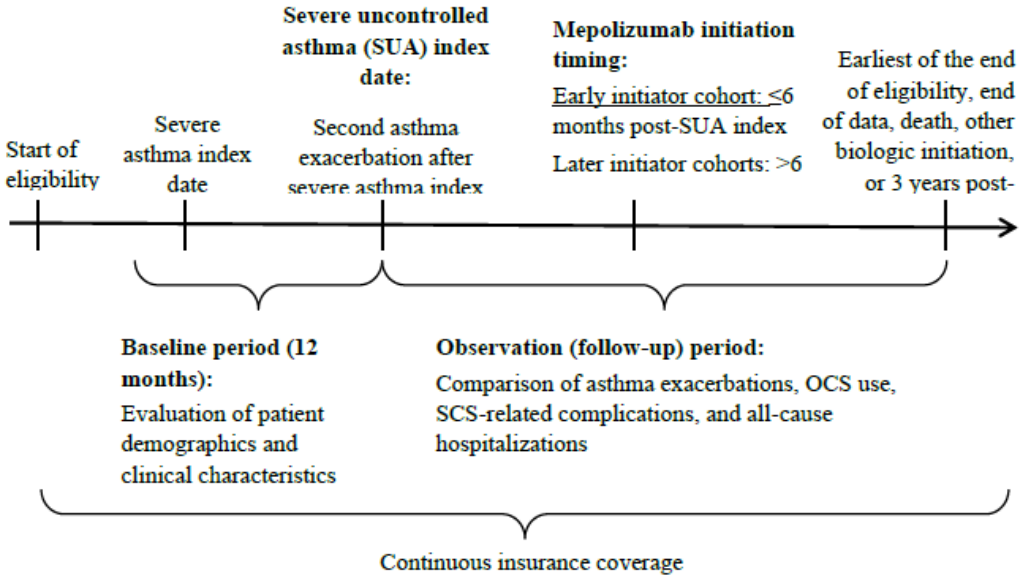
This is a retrospective observational study using insurance claims data, aiming to better understand the real-world use and effectiveness of mepolizumab.

Methods

A retrospective cohort study design was used with data from the Komodo Health database ranging from 01 January 2016 to 30 June 2023, which includes claims data from patients in the United States

of America (USA). Patients were eligible for the study upon identification of severe asthma. Patients with SUA were assigned to cohorts based on the timing of mepolizumab initiation after the diagnosis of SUA (i.e., SUA index date); early initiators began treatment in ≤6 months, later initiators began treatment between >6 to ≤24 months, and non-initiators were chronic systematic corticosteroids (SCS) users who never began treatment with mepolizumab or any other biologic.

Figure 1 Study Design Scheme



Severe asthma index date: The earliest date at which treatment for severe asthma was identified.

Severe uncontrolled asthma (SUA) index date: The second asthma exacerbation, used to define ongoing symptoms of severe asthma patients, within 12 months after the severe asthma index date.

Baseline period: The 12 months prior to the SUA index date. Patient demographics and clinical characteristics were assessed during the baseline period or on the SUA index date.

Follow-up period: The follow-up period was defined as the time from the SUA index date until the earliest of end of insurance eligibility, end of data availability, death, initiation of a non-mepolizumab biologic, or 3 years post-SUA index. Study outcomes (asthma exacerbations, OCS treatment patterns, SCS-related complications, and all-cause hospitalizations) were evaluated during this period.

The study period spanned from the earliest date of continuous eligibility (i.e., start of continuous health plan insurance coverage) to the earliest of the end of eligibility, end of data, death, initiation of a biologic therapy other than mepolizumab, or 3 years after the SUA index date.

Study participants

The study population consisted of patients treated for severe asthma with a subsequent asthma exacerbation within 12 months, in the US. The study inclusion criteria were as follows:

Inclusion criteria:

- Severe uncontrolled asthma, defined by the ongoing symptoms after treatment of severe asthma:
    - Severe asthma treatment, with the date that either of the below criteria was identified defined as the severe asthma index date:

        - ≥1 dispensing of high-dose inhaled corticosteroid (ICS) with ≥1 overlapping day of supply with a long-acting β2-agonist (LABA), leukotriene modifier, or theophylline during the study period,

      OR

        - ≥50% proportion of days covered by SCS during any 12-month period of the study period
    - Ongoing symptoms after severe asthma treatment:
        - ≥2 asthma exacerbations within 12 months of the severe asthma index date, with the date of the second observed exacerbation defined as the SUA index date
- ≥12 months of continuous health insurance coverage before the SUA index date
- ≥24 months of continuous eligibility after the SUA index date
- (early and late mepolizumab initiators only) ≥1 medical or pharmacy claim for mepolizumab during the follow-up period
- (non-initiators only) Evidence of chronic SCS use, defined as ≥6 months of continuous SCS use with an average daily dose equivalent to ≥6 mg of prednisone, during the follow-up period

Patients were excluded from the study if they had any of the following:

- <12 years of age at the SUA index date
- ≥1 medical or pharmacy claim for any biologic (i.e., benralizumab, dupilumab, omalizumab, reslizumab, tezepelumab, or mepolizumab) during the baseline period (non-initiators only) ≥1 medical or pharmacy claim for any biologic during the study period

Treatments

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

The formulation, dose and exposure were not defined. Patient cohorts, early and late mepolizumab initiators, were defined by ≥1 pharmacy claim in the US, for mepolizumab, in the timeframe after the severe uncontrolled asthma (SUA) index date.

The non-initiators cohort was defined as, evidence of chronic SCS use, defined as ≥6 months of continuous SCS use with an average daily dose equivalent to ≥6 mg of prednisone, during the follow-up period.

Objectives

The primary objective of this study was:

1. To evaluate and compare rates of overall asthma exacerbations among patients who initiated mepolizumab early versus those who remained at risk of initiating mepolizumab but did not initiate until later in a United States (US) population with SUA.

The secondary objectives of this study were:

1. To describe baseline demographic and clinical characteristics of early and late initiators of mepolizumab as well as non-initiators of any biologic who were chronic SCS users
2. To evaluate and compare rates of asthma exacerbations separately by exacerbation type (i.e., inpatient/Emergency Department [IP/ED]-defined and SCS-defined) among early versus late initiators of mepolizumab

3. To describe and compare OCS treatment patterns among early versus late initiators of mepolizumab
4. To describe and compare rates of SCS-related complications among early versus late initiators of mepolizumab
5. To describe and compare rates of all-cause hospitalizations among early versus late initiators of mepolizumab
6. To evaluate and compare asthma exacerbations, OCS treatment patterns, SCS-related complications, and all-cause hospitalizations between early initiators of mepolizumab and non-initiators of any biologic who were chronic SCS users

Outcomes/endpoints

Primary endpoint

- Asthma exacerbations
    - Overall exacerbations

Secondary endpoints

- Asthma exacerbations
    - IP/ED-defined exacerbations
    - SCS-defined exacerbations
- OCS use
    - OCS dispensing
    - OCS bursts
    - Mean daily dosage over the follow-up period
- SCS-related complications
- All-cause hospitalizations

Sample size

No sample size calculation was reported.

The Komodo Research Database with data ranging from 10 January 2016 to 30 June 2023 was used to address the study objectives. Komodo is a database sourced from a variety of payers and healthcare organizations. It includes over 65 billion deidentified clinical, pharmacy, and laboratory encounters for more than 320 million patients enrolled in a health care plan in the US from 2016 to present. The MAH states that encounters have US census-level representation across patient populations (e.g., age, geography, risk pools), including hospital networks, physician networks, healthcare claims processing companies (i.e., claims clearinghouses), pharmacies, and health insurers.

Randomisation and blinding (masking)

N/a

Statistical Methods

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

For all primary and secondary analyses, the sub-cohort of patients initiating mepolizumab ≤6 months after the SUA index date was the reference group to which subsequent initiators (i.e., initiation in >6

and ≤12 months or >12 and ≤24 months) were compared, as well as non-initiators. In the exploratory objective, patients initiating mepolizumab in >24 and ≤36 months were compared to the earliest initiators.

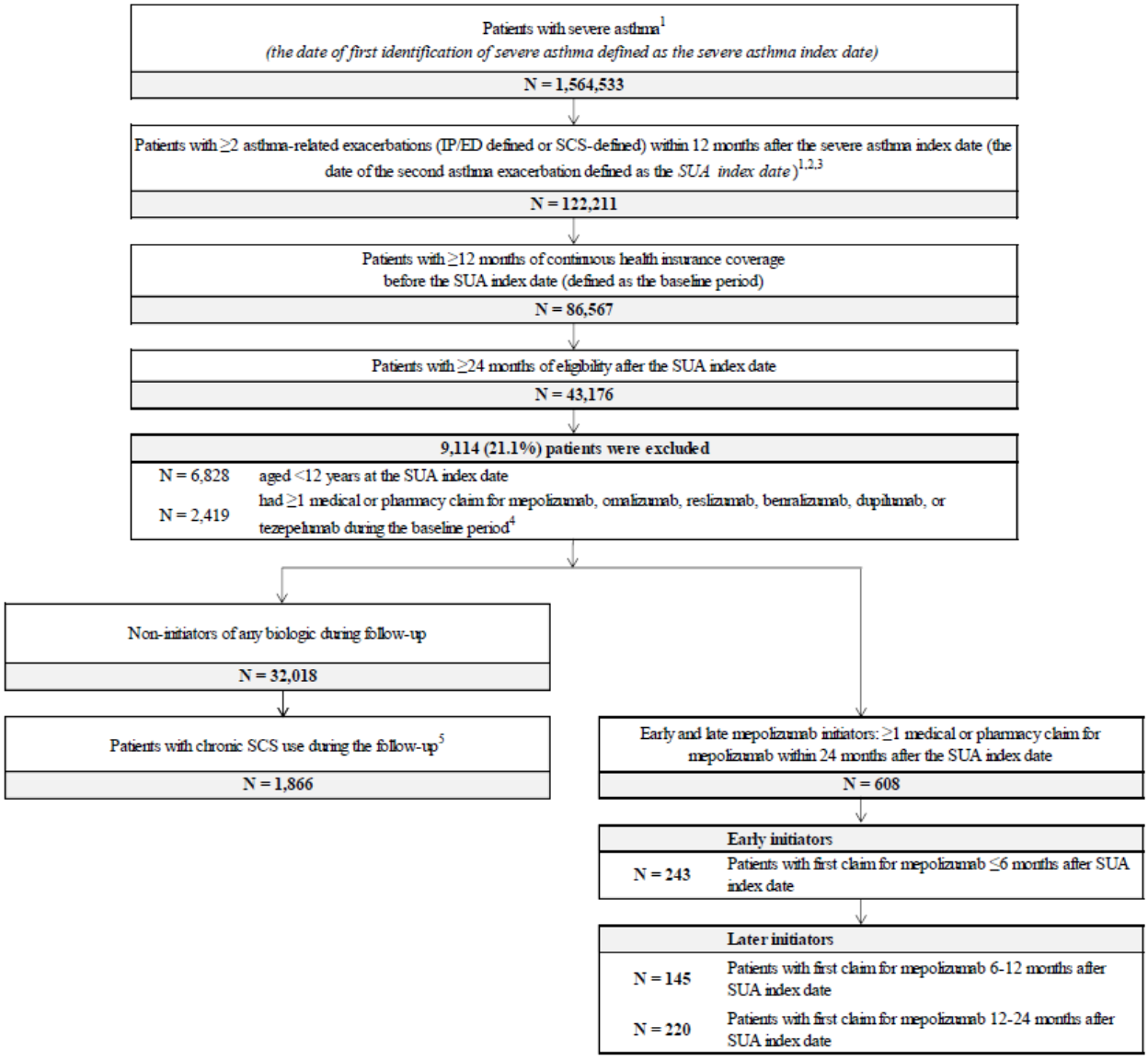
For the primary objective, rates of overall asthma exacerbations were calculated as the number of events per person-year (PPY) of observation and compared between sub-cohorts using rate ratios (RRs), 95% confidence intervals (CIs), and p-values obtained from adjusted Poisson regression models. Models were adjusted for all core demographics and baseline characteristics with prevalence ≥10% and standardized differences >10% between sub-cohorts.

Results

Participant flow

A total of 1,564,533 patients were identified to have severe asthma. Of those patients, 122,211 developed SUA. After applying all inclusion and exclusion criteria, the cohorts included the numbers analysed, below.

Figure 2 Patient Disposition



Abbreviations: ED: emergency department; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; ICS: inhaled corticosteroid; IP: inpatient; LABA: long-acting β2 agonist; OP: outpatient; SCS: systemic corticosteroid; SUA: severe uncontrolled asthma.

Notes:

[1] Patients with severe asthma were defined as those meeting either of the following criteria: (1) ≥1 dispensing of high-dose ICS (see Appendix 1 for classification of high-dose ICS) with ≥1 overlapping day of supply with a LABA (including ICS/LABA), leukotriene modifier, or theophylline (see **Appendices 2-4** for lists of codes used to identify medications), or (2) ≥50% proportion of days covered by SCS during a 12-month period (see **Appendices 5-6** for drug and procedure codes used to identify SCS). In the first case, the severe asthma index date was defined as the first day of overlapping supply; in the second case, the severe asthma index date was defined as the earliest day when ≥50% proportion of days covered by SCS during a 12-month period was met. For patients meeting both conditions, the earlier date was assigned.

Recruitment

Retrospective cohort design.

Baseline data

Mean age in the early initiators cohort was 49.0 years and most patients were female (68.7%), White (30.9%), from the South (35.8%), and had commercial health insurance (57.6%). Baseline demographic characteristics were largely similar across cohorts. Early initiators had the highest proportion of patients with a severe asthma diagnosis in baseline (58.4%).

Thirty-three patients included in the analyses were aged 12-17 years (cohorts who initiated mepolizumab.)

Figure 3 Demographics of Early and Late Mepolizumab Initiators with Severe Uncontrolled Asthma- Age

Characteristics[1]	Initiation timing of mepolizumab				
	≤ 6 months [A] N = 243	>6 months and ≤12 months [B] N = 145	Std.diff.[2,3] [A vs B] (%)	>12 months and ≤24 months [C] N = 220	Std.diff.[2,3] [A vs C] (%)
Age, years, mean ± SD [Q_1, median, Q_3]	48.98 ± 14.90 [40.7, 52.4, 58.8]	49.17 ± 14.32 [42.3, 52.7, 58.9]	1.3	48.45 ± 15.66 [37.5, 51.1, 59.0]	3.4
Age categories, n (%)					
12–17 years	14 (5.8)	7 (4.8)	4.2	12 (5.5)	1.3
18–29 years	16 (6.6)	9 (6.2)	1.5	19 (8.6)	7.7
30-39 years	29 (11.9)	14 (9.7)	7.3	37 (16.8)	13.9
40-49 years	43 (17.7)	32 (22.1)	11.0	33 (15.0)	7.3
50-59 years	87 (35.8)	53 (36.6)	1.6	67 (30.5)	11.4
60-69 years	43 (17.7)	25 (17.2)	1.2	35 (15.9)	4.8
≥ 70 years	11 (4.5)	5 (3.4)	5.5	17 (7.7)	13.3

Abbreviations: ED: emergency department; HRU: healthcare resource utilization; ICS: inhaled cortiocsteroid; IP: inpatient; ICS: inhaled corticosteroid; IQR, interquartile range; LABA: long-acting β_2 agonist; OP: outpatient; OCS: oral corticosteroid; SCS: systemic corticosteroid; SD, standard deviation; SUA, severe uncontrolled asthma.
Notes:
[1] Evaluated on the index date unless otherwise noted.
[2] For continuous variables, the standardized difference is calculated by dividing the absolute difference in means of the control and the case by the pooled standard deviation of both groups. The pooled standard deviation is the square root of the average of the squared standard deviations.
[3] For dichotomous variables, the standardized difference is calculated using the following equation where P is the respective proportion of participants in each group: $|(Pcase-Pcontrol)| / \sqrt{[(Pcase(1-Pcase)+Pcontrol(1-Pcontrol))/2]}$.

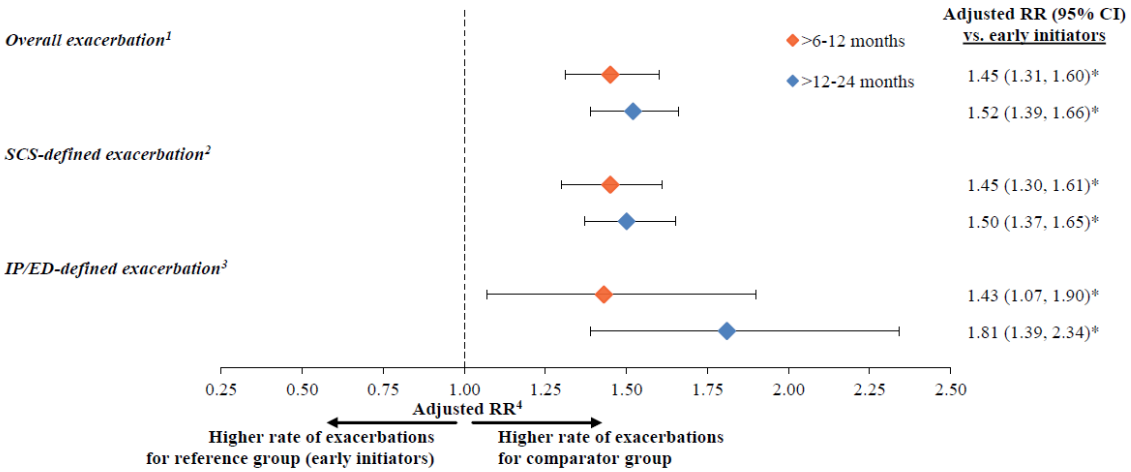
Number analysed

The early initiators cohort included 243 patients who initiated mepolizumab ≤6 months after the SUA index date. The later initiators cohorts included 145 patients who initiated mepolizumab >6 to ≤12 months after the SUA index date and 220 patients who initiated mepolizumab >12 to ≤24 months after the SUA index date. The non-initiators (chronic SCS use) cohort included 1,866 patients who did not initiate any biologic. In the exploratory analysis, 79 patients who initiated mepolizumab in >24 to ≤36 months after the SUA index date were identified.

Efficacy results

Compared with early initiators, higher rates of overall asthma exacerbations were observed in later initiators who initiated between >6 months and ≤12 months (RR [95% CI] = 1.45 [1.31, 1.60]; P<0.001) and >12 months and ≤24 months (RR [95% CI] = 1.52 [1.39, 1.66]; P<0.001). Similar trends were observed when considering asthma exacerbations by type (IP/ED- and SCS-defined exacerbations).

Figure 4 Asthma Exacerbations During Follow-Up



* P<0.05

Notes:

[1] 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.

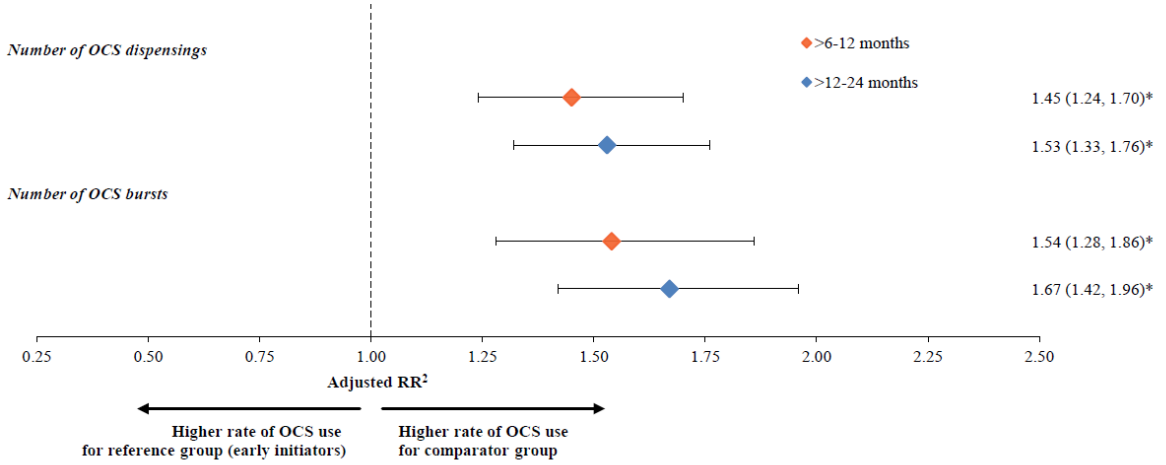
[2] SCS-defined exacerbation was defined as an ED visit or OP visit with a diagnosis of asthma and an SCS (i.e., OCS or parenteral corticosteroid) medical or pharmacy claim with 2-28 days of supply within ±5 days. See **Appendices 5** and **6** for a list of drug and procedure codes to identify SCS.

[3] 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.

[4] Rate ratios, 95% CIs, and p-values were estimated from Poisson regression models. Variables used to adjust for in the model include the following: all demographics as well as all clinical characteristics with ≥10% standardized differences and ≥10% prevalence.

Later initiators had higher OCS use compared with early initiators, as demonstrated by statistically significant higher rates of OCS dispensings (RRs ranging from 1.45 to 1.53, all P<0.001), rates of OCS bursts (RRs ranging from 1.54 to 1.67, all P<0.001), and mean differences in OCS daily dose (mean differences range: 1.13 mg to 1.69 mg, all P<0.001).

Figure 5 OCS Use During Follow-Up



* P<0.05

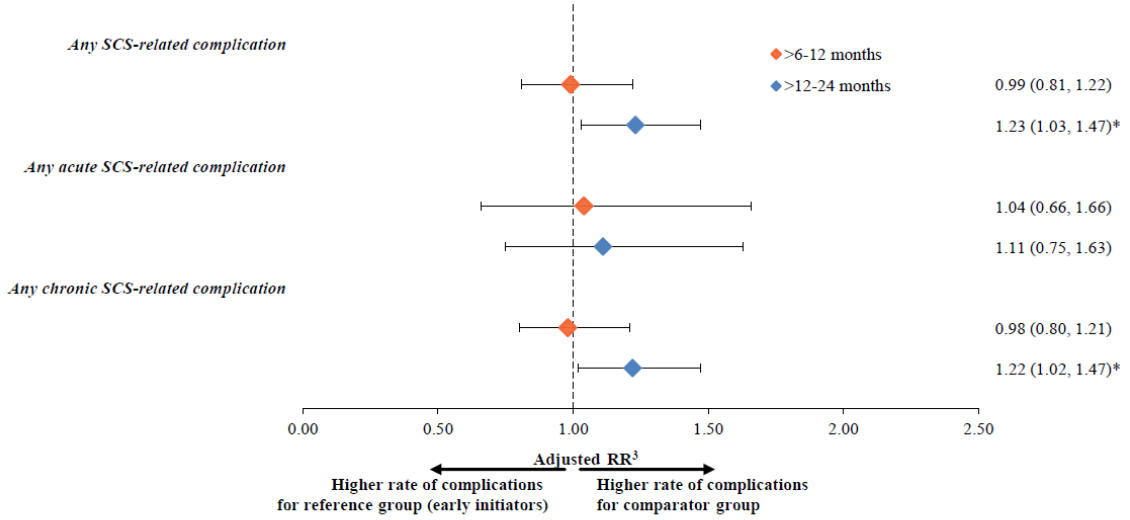
Notes:

[1] OCS burst was defined as cumulative daily dosage for OCS dispensings with 2–28 days of supply and an average daily dose of ≥20 mg prednisone equivalent.

[2] Rate ratios, 95% CIs, and p-values were estimated from negative binomial regression models. Variables used to adjust for in the model include the following: all demographics as well as all clinical characteristics with ≥10% standardized differences and ≥10% prevalence.

Higher rates of SCS-related complications and all-cause hospitalizations were also observed in those initiating in >12 months and ≤24 months (e.g., for any SCS-related complication, RR [95% CI] = 1.23 [1.03, 1.47]; P=0.021) but not in the initiators who initiated between >6 months and ≤12 months. Generally, larger differences in study outcomes relative to the early initiators were observed for those who had a longer delay in initiation (i.e., those who initiated between >12 months and ≤24 months and not those who initiated between >6 months and ≤12 months).

Figure 6 Any SCS-Related Complications During Follow-Up



* P<0.05

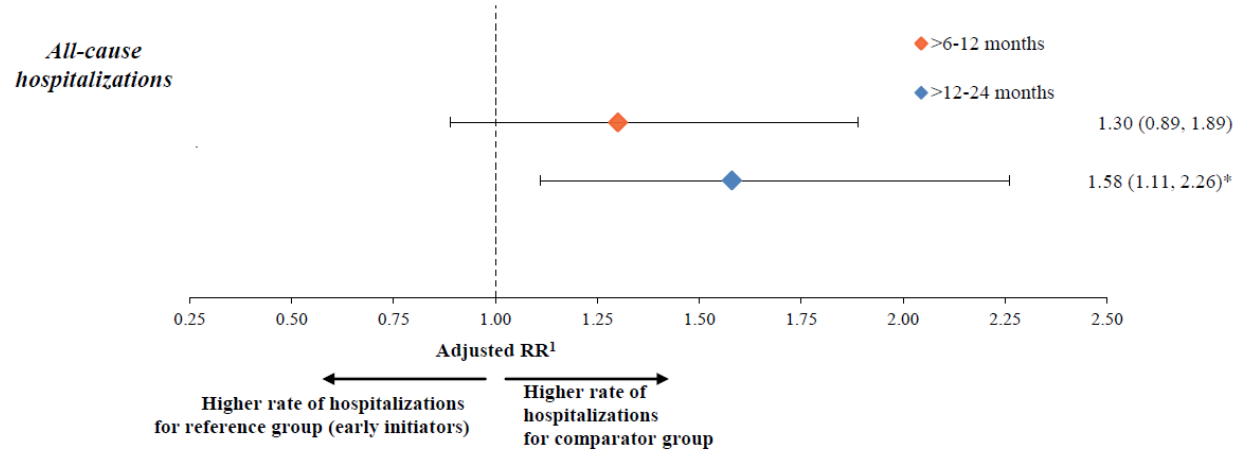
Notes:

[1] Acute complications are defined as IP or ER visits with a primary or secondary diagnosis. See **Appendix 12** for a list of codes used to identify SCS-related complications.

[2] Chronic complications are defined as taking place in any setting with a primary or secondary diagnosis.

[3] Rate ratios, 95% CIs, and p-values were estimated from negative binomial regression models.

Figure 7 All-Cause Hospitalizations During Follow-Up



* P<0.05
Note:
[1] Rate ratios, 95% CIs, and p-values were estimated from negative binomial regression models.

Similar trends were observed across outcomes for non-initiators (chronic SCS users) compared with early initiators.

In the exploratory analysis, delayed initiation of mepolizumab (between >24 and ≤36 months post-SUA index) was associated with higher rates of overall exacerbations (RR [95% CI] = 1.66 [1.46, 1.89]; P<0.001) and both SCS-defined and IP/ED-defined exacerbations. Similarly, rates of OCS bursts and dispensing were significantly higher in delayed initiators relative to early initiators (dispensing, RR [95% CI] = 1.37 [1.08, 1.72], P=0.008; bursts, RR [95% CI] = 1.46 [1.14, 1.87], P=0.003), and mean daily dose was also higher in the delayed initiators (mean difference [95% CI] = 0.83 [0.06, 1.60]; P=0.036).

In the sensitivity analysis of patients who were excluded due to having less than 24 months of follow-up, baseline demographic and clinical characteristics were not substantially different from the overall study population.

Safety results

The safety of mepolizumab was not investigated as part of this retrospective cohort study.

2.3.3. Discussion on clinical aspects

Study 221029 is a retrospective observational study using insurance claims data to better understand the real-world use and effectiveness of mepolizumab in US patients with severe uncontrolled asthma.

Patients with SUA were assigned to cohorts based on the timing of mepolizumab initiation after the diagnosis of SUA (i.e., SUA index date); early initiators began treatment in ≤6 months, later initiators began treatment between >6 to ≤24 months, and non-initiators were chronic SCS users who never began treatment with mepolizumab or any other biologic.

The early initiators cohort included 243 patients who initiated mepolizumab ≤6 months after the SUA index date. The later initiators cohorts included 145 patients who initiated mepolizumab >6 to ≤12 months after the SUA index date and 220 patients who initiated mepolizumab >12 to ≤24 months after the SUA index date. The non-initiators (chronic SCS use) cohort included 1,866 patients who did

not initiate any biologic. In an exploratory analysis, 79 patients who initiated mepolizumab in >24 to ≤36 months after the SUA index date were identified.

Mean age in the early initiators cohort was 49.0 years and most patients were female (68.7%), White (30.9%), from the South (35.8%), and had commercial health insurance (57.6%). **Thirty-three patients included in the analyses were aged 12-17 years**. Baseline demographic characteristics were largely similar across cohorts. Early initiators had the highest proportion of patients with a severe asthma diagnosis in baseline (58.4%). Compared with early initiators, higher rates of overall asthma exacerbations were observed in later initiators who initiated between >6 months and ≤12 months (RR [95% CI] = 1.45 [1.31, 1.60]; >12 months and ≤24 months (RR [95% CI] = 1.52 [1.39, 1.66]). Generally, larger differences in study outcomes relative to the early initiators were observed for those who had a longer delay in initiation (i.e., those who initiated between >12 months and ≤24 months). Similar trends were observed across outcomes for non-initiators (chronic SCS users) compared with early initiators.

Several limitations should be considered when interpreting findings from this retrospective, observational cohort study.

First, the generalizability of this study is limited due to the introduction of selection bias from conditioning on future information, as timing of mepolizumab initiation determined the cohorts to which patients were assigned.

Second, exposure misclassification may have been introduced through the attribution of person-time attributed to a treatment status despite the fact that initiation of mepolizumab did not occur until later; hence, results cannot be interpreted directly in terms of comparative effectiveness and exposure cannot be quantified.

Finally, there are various limitations inherent to all claims-based studies. For instance, the presence of a dispensed medication on outpatient pharmacy claims does not indicate that the medication was consumed or that it was taken as prescribed and not all medications are recorded in claims data (e.g., over the counter or drug samples, medications received during an IP stay). Moreover, administrative claims data may be subject to coding inaccuracies leading to misclassification bias, missing data, or a lack of information on specific clinical measures (e.g., lung function, asthma symptoms) and patient characteristics (e.g., tobacco use, socioeconomic factors). However, there is no reason to believe that one study sub-cohort would have been impacted more by these factors than the other.

Overall, the results of study 221029 suggest that in patients with SUA, longer delays in mepolizumab initiation may be associated with a greater burden of disease, as evidenced by higher rates of asthma exacerbations, OCS use, SCS-related complications, and all-cause hospitalizations. However, these results should be interpreted with caution due to limitations of the study design and analysis.

3. Rapporteur's overall conclusion and recommendation

This retrospective cohort study is likely informative to the MAH's development program. However, the data does not contribute to or impact the existing data supporting the marketing authorisation. Therefore, the MAH's conclusion that no updates to the SmPC are warranted as a result of Study 221029 is agreed. Study 221029 has been submitted in accordance with Article 46 of the regulation (EC) No 1901/2006 and is not part of any Paediatric Investigation Plan.

☒ **Fulfilled:**

No regulatory action required.