Statistical Analysis Plan

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STUDY ACCOUNTABLE PERSON	PPD VEO Study Delivery
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SPONSOR SIGNATORY

TITLE	**MEPOLYP**: - Real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal **POLYP**s
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LIST OF ABBREVIATIONS

ACQ-5	Asthma Control Questionnaire-5
ACT	Asthma Control Test
AE	Adverse Event
AERD	Aspirin Exacerbated Respiratory Disease
ATC	Anatomical Therapeutic Chemical
BEC	Blood Eosinophil Count
BMI	Body Mass Index
BSAR	Belgium Severe Asthma Registry
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without Nasal Polyps
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
DDD	Defined Daily Dose
DMP	Data Management Plan
EGPA	Eosinophilic Granulomatosis with Polyangiitis
ER	Emergency Room
EU	European Union
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
HRQoL	Health-Related Quality of Life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IL-13	Interleukin-13
IL-4	Interleukin-4
IL-5	Interleukin-5
INCS	Intranasal Corticosteroids
IgE	Immunoglobulin E
IHD	Individual Human Data
IPD	Individual Participant Data
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Muscurinic Antagonist
LTRA	Leukotriene Receptor Antagonist
MRI	Magnetic Resonance Imaging
MICE	Multiple Imputation by Chained Equations
NP	Nasal Polyps
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCS	Oral Corticosteroids
PDE4	Phosphodiesterase Type 4
PICO	Patients, Interventions, Comparators, Outcomes
RAMSES	Research on Severe Asthma
SABA	Short-Acting Beta2-Agonist
SABD	Short-acting Bronchodilator

SAMA	Short-Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEA	Severe Eosinophilic Asthma
SSAR	Swiss Severe Asthma Registry
T2	Type 2
Th2	Type 2 helper T cells
TSLP	Thymic Stromal Lymphopoietin
VEO	Value Evidence and Outcomes

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TRADEMARK INFORMATION

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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to detail the analyses to be conducted for the multicountry study that describes real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal POLYPs (MEPOLYP).

The SAP specifies the study populations, the variables and derived parameters that will be analysed, and the statistical methods that will be used. A separate document displays the shells of the tables, listings and figures (TLFs) that will be used for the analysis.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Study Objective(s) and Endpoint(s)

For the purpose of this study, two cohorts, comprising incident users of mepolizumab, will be described:

Cohort 1: SEA patients without comorbid CRSwNP. This cohort will include SEA patients without any mention of NP in the registries' databases.

Cohort 2: SEA patients with comorbid CRSwNP. This cohort will include SEA patients with any mention of NP historically (i.e., pre-mepolizumab treatment) or at index date (defined as date of mepolizumab initiation) in the registries' databases.

The **primary objective** of this study will be to evaluate the change of clinically significant asthma exacerbations rates defined as deterioration in asthma requiring (1) use of systemic corticosteroids and/or (2) emergency department (ED) visit and/or hospital admission, between the 12-month pre-mepolizumab treatment period and the 12-month post-exposure period, after initiating mepolizumab in cohorts 1 and 2.

Secondary objectives are:

1. Evaluate the change in rate of asthma exacerbations that required ER visits or hospitalization between the 12-month pre-mepolizumab treatment period and the 12-month post-exposure period after initiating mepolizumab in cohorts 1 and 2.
2. Evaluate the change in rate of asthma exacerbations that required hospitalization between the 12-month pre-mepolizumab treatment period and the 12-month post-exposure period after initiating mepolizumab in cohorts 1 and 2.
3. Compare the median OCS maintenance dose, when available, in the 12-month pre-mepolizumab treatment period with the median OCS maintenance dose at 6 and at 12 months after mepolizumab initiation in cohorts 1 and 2.
4. Compare FEV1 values, when available, in the pre-mepolizumab treatment period (using the historical value nearest to the index date in the pre-exposure period) with FEV1 values at 6 months and 12 months after mepolizumab initiation in cohorts 1 and 2.
5. Compare ACT scores, when available, in the pre-mepolizumab treatment period (using the historical score nearest to the index date in the pre-exposure period) with ACT scores, at 6 months and 12 months in cohorts 1 and 2.
6. Describe patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2.
7. Describe pre-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) in the pre-mepolizumab treatment period in cohorts 1 and 2.

The following exploratory objectives will be described for both cohorts.

1. Describe NP related outcomes, when available, in the pre-mepolizumab treatment period and at 12 months after mepolizumab initiation in datasets with sufficient patients in cohort 2.
    a. VAS loss of smell (Patient-reported assessment of size and symptom severity)
    b. SNOT-22 (Patient-reported assessment of symptom burden on quality of life)
    c. Bilateral Endoscopic NPS (Physician-reported assessment of size and extent of NP)
2. Describe clinical remission for patients who have achieved a clinically significant exacerbation reduction (as assessed in the primary endpoint) in the 12-month post-mepolizumab treatment periods for cohorts 1 and 2. Clinical remission is expressed as:
    a. No asthma exacerbations during the 12-month period and
    b. No OCS use for asthma during the 12-month period and
    c. ACQ-5 < 1.5 or ACT ≥ 20, assessed at the end of the 12-month period and
    d. Lung function stabilization (no decline of lung function measured using FEV1 from pre-exposure period ≥ 100 mL at 12 months)
3. Describe the change in peripheral blood eosinophils during the post treatment period compared with 6-month pre-mepolizumab levels in cohorts 1 and 2.
4. Describe post-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) in cohorts 1 and 2.
5. Evaluate the change in clinically significant asthma exacerbations annual rates between the 12-month pre-mepolizumab treatment and 24-month follow-up period after initiating mepolizumab in cohorts 1 and 2.
6. If cohort 1 and cohort 2 are balanced regarding their characteristics (i.e., similarity in their baseline demographic, clinical and treatment distributions) then:
    a. Compare the change in clinically significant asthma exacerbation rates from 12-months pre-mepolizumab treatment and 12-month post-mepolizumab initiation between cohorts 1 and 2.
7. In preparation for future registry-level meta-analyses:
    a. Evaluate the primary objective separately for each registry.
    b. Describe patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2 separately for each registry.

2.2. Study Design

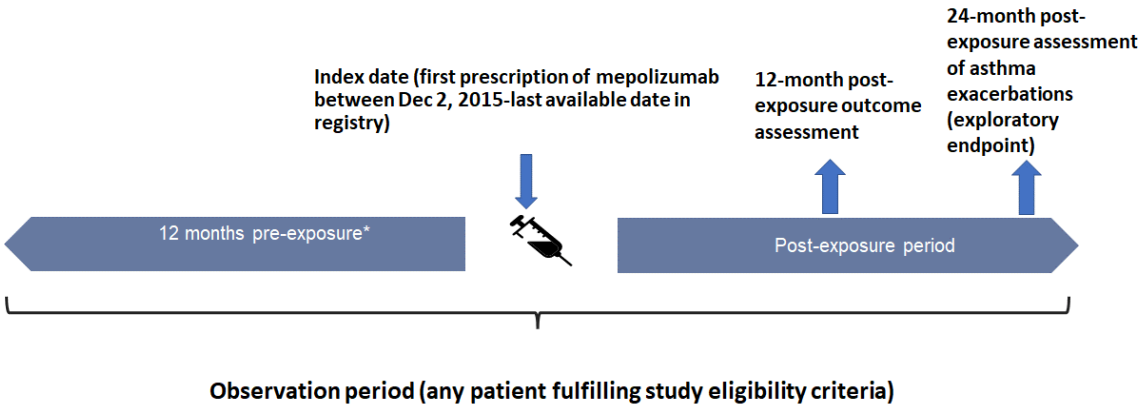
This study is an observational, multi-center retrospective cohort study examining real-world utilization of mepolizumab in SEA patients in established data registries from multiple countries (BSAR, REALITI-A, REDES, RELIght, and SSAR).

Objectives as described above will be assessed using the pooled individual participant data (IPD) from registries who provide raw data (REALITI-A, REDES, RELIght), as well as by combining registry-specific aggregated data from the BSAR and the SSAR. Adult patients clinically diagnosed with SEA and treated with mepolizumab without CRSwNP (Cohort 1) or comorbid SEA with CRSwNP (Cohort 2), will be identified through these data registries.

The index date for this study is defined as the first prescription record of mepolizumab during the patient identification period from December 02, 2015 (date of mepolizumab approval in the EU) till the last follow-up visit of the last patient in the registries. Follow-up will be up to 24 months post-index. Patients are expected to have a minimum follow-up observational period of 12 months post-index (See Figure 1).

Patient data on demographic characteristics, SEA/asthma and CRSwNP disease characteristics and history, comorbidities, treatment details, and laboratory assessments will be collected at different time points. Data from the pre-exposure period will be assessed to ensure that there was no mepolizumab usage prior to index date.

Figure 1 Study Design



2.3. Statistical Hypotheses / Data Analyses

The primary objective of this study is to compare the rates of clinically significant asthma exacerbations in the 12-month pre-exposure period and the 12-month post-exposure period of treatment with NUCALA using data from several registries. It is hypothesized that patients experienced a better response during the 12-month post-exposure period compared to the 12-month pre-exposure period, that is, the null hypothesis (H0) is the incidence rate of clinically meaningful asthma exacerbations is the same pre- and post-mepolizumab treatment, with the alternative hypothesis that there is a decrease in the incidence rate of clinically meaningful asthma exacerbations during the 12-month period following mepolizumab initiation.

3. STUDY DESCRIPTION

3.1. Study population

Patients aged ≥18 years at the index date with a clinical diagnosis of SEA (as diagnosed and documented by the physician per routine clinical care) during the pre-exposure period will be considered for this study. *For countries where there are two data sources of interest and it is possible to know whether a patient was also recruited into REALITI-A (e.g. Belgium), both REALITI-A and the registry data will be used, however, patients in REALITI-A will be excluded from the data registry. A patient will not be considered as duplicate if the mepolizumab initiation date in REALITI-A is after the last mepolizumab initiation date recorded in the other data source of interest.*

The first prescription record of mepolizumab will be considered as the index date for the patient. A mepolizumab prescription will be identified from the registries using the ATC/ DDD medication code R03DX09 (100 mg subcutaneous every 4 weeks for SEA) or any other specific criterion that the registries use to identify medications.

Detailed eligibility criteria for the current study are listed below in Section 173.2

3.2. Eligibility criteria

3.2.1. Inclusion criteria

- Informed Consent (described in the protocol)
- Patients must have a current clinical diagnosis of SEA and can be either included in prior published material or newly enrolled into the registry
- Physician decision to prescribe treatment with mepolizumab
- Relevant records available for at least 12-months prior to index date and at least 12-months post-index date
- Adults aged 18 years or over

3.2.2. Exclusion criteria

- Any mention of patient participation in an interventional clinical trial during the observational study period

4. DATA SOURCES

Data sources for this study are existing SEA registries or prospective studies in multiple countries that published data on mepolizumab effectiveness in real-world settings with available records of SEA patients with comorbid CRSwNP.

Data sources selected for all objectives (primary, secondary, exploratory) are:

- BSAR, Belgium
- REALITI-A (Belgium, Canada, Germany, Italy, Spain, the UK, the US; funded and owned by GSK)
- REDES, Spain; funded and owned by GSK
- RELIght, Greece
- SSAR, Switzerland

Description of Each data source is described in detail in sections below**Error! Reference s ource not found.**.

Note: For each registry, documented evidence about patient consent for inclusion into the registry and consent covering future research (including the current study) will be required.

4.1. BSAR (Belgium)

The BSAR is a national Belgian secured web database for severe asthma, collecting relevant demographic, clinical and social data of patients with severe asthma from 21 Belgian centers, enrolled after gaining fully informed written consent.

The prerequisite for inclusion in the registry was age ≥18 years, asthma follow-up by a respiratory physician for at least 12 months, education on the disease provided to the patient and compliance thought to be satisfactory.

Asthma was diagnosed based on symptoms of cough, breathlessness, or dyspnea, together with the demonstration of airflow variability (defined by one or more of the following: increase in FEV1 of 12% or greater following inhalation of 400 mg of salbutamol or inhaled concentration of methacholine provoking a 20% fall in FEV1 of less than 16 mg/ml).

Severe asthma was defined according to ATS criteria, i.e., definition requires one major criterion of either treatment with continuous or near continuous (>50% of year) OCS or requirement for combination high dose ICS (Beclomethasone or Budesonide > 1000 mg/d, Fluticasone > 500 mg/d) and long acting beta2 agonists (LABA) [Schleich, 2014, Graff, 2022].

For this study, only data from BSAR centers in the city of Liege are available and will be used. In addition, only patients who did not participate to REALITI-A study will be included in BSAR patients subgroups to avoid any duplicates.

4.2. REALITI-A (multiple countries)

REALITI-A (unique patients from Belgium, Canada, Germany, Italy, Spain, the UK, the US; GSK study identifier 204710) is a global, prospective, single-arm, observational cohort study enrolling patients diagnosed with asthma and on newly prescribed mepolizumab treatment.

Eligible patients were aged ≥18 years with a current clinical diagnosis of asthma, a physician decision to initiate mepolizumab treatment and relevant medical records for ≥12 months pre-enrolment, and who had provided informed consent for study participation. Prior use of other biological medications is permitted; those who received mepolizumab in the year pre-enrolment were excluded [Harrison, 2020].

Medical records of historical exacerbations during the pre-treatment were corroborated by patient recall, between clinic visits, to capture instances in which a patient self-medicated at home. Data for the 2 years after the index date (follow-up period) were collected at asthma health care visits (routine or unscheduled) following usual standard of care practices at each participating site.

4.3. REDES (Spain)

REDES (Spain) (GSK study identifier 213172) is a multicentric observational cohort study of SEA patients being treated with mepolizumab in Spain.

Sites were selected using a standard feasibility questionnaire ensuring they met the minimum relevant criteria for the study endpoints and geographic representativeness. Investigators needed to have followed up severe asthma patients regularly (i.e., every 6 months) for 12 months before mepolizumab initiation and at least 12 months after that date.

Key inclusion criteria were a diagnosis of SEA in individuals aged ≥ 18 years who provided informed consent, with at least 12 months since the start of mepolizumab treatment (regardless of their treatment continuation at data inclusion time), with a regular follow-up since treatment initiation (at least every 6 months), and the availability of continuous follow-up.

The key exclusion criteria was participation in an interventional asthma study in the 12 months prior or after initiating mepolizumab and missing key clinical information to defining the primary endpoint (asthma exacerbations rate as described by primary objective in Section 2.1) [Domingo Ribas, 2021].

4.4. RELIght (Greece)

RELIght is a prospective, multi-center study collecting data on clinical experience, effectiveness, and safety of mepolizumab treatment for patients with severe asthma.

Inclusion criteria were age ≥18 years, SEA characterized by inadequate symptom control despite continuous therapy with high doses of ICS and LABA, peripheral blood eosinophils≥150 cells/μL in a recent measurement or ≥300 cells/μL in any measurement during the previous year, newly initiated treatment with mepolizumab according to physicians' decision, and a history of at least two asthma exacerbations in the previous year despite optimal treatment. The only exclusion criterion was when patients do not consent to participating in the study [Kallieri, 2022].

4.5. SSAR (Switzerland)

SSAR (Switzerland) is a national registry for severe asthma originally built to get a better understanding about the heterogeneity of the disease. All patients with severe asthma were included in the register only after detailed information and written consent is provided. After four months (for specific therapies) and after 12 months, patients were re-evaluated for up to 15 years.

The registry originally started in 2018 and the first patients were enrolled in 2019. As of 2021, more than 150 patients were enrolled [[Jaun, 2023]

5. STUDY VARIABLES

In this section, the list of variables for the assessment of each objective is provided.

5.1. Primary outcomes

No.	Primary objective	Variables
1.	Change of clinically significant asthma exacerbations rates between 12-month pre- and post-exposure periods in cohorts 1 and 2	• Number of asthma exacerbations in the 12-month pre-exposure period that required at least one of the following events: hospitalization, ER visit or OCS burst [EX_HOSP_ER_OCS_PRE_N] • Number of asthma exacerbations in the 12-month post-exposure period that required at least one of the following events: hospitalization, ER visit or OCS burst [EX_HOSP_ER_OCS_POST_N]

ER, Emergency Room; OCS, Oral Corticosteroids
Note: The SAS variable names are specified into brackets.

Covariates included in IPD-based statistical models needed for the assessment of the primary objective will be defined in Section 8.4.

More details on variables definition are provided in Section 5.5 and data analysis specifications are described in Section 9.1.

5.2. Secondary outcomes

No.	Secondary Objectives	Variables
1.	Change in asthma exacerbation rates that required ER visits or hospitalization between 12-month pre- and post-exposure periods in cohorts 1 and 2	• Number of asthma exacerbations during the 12-month pre-exposure period that required at least one of the following events: hospitalization, ER visit [EX_HOSP_ER_PRE_N] • Number of asthma exacerbations during the 12-month post-exposure period that required at least one of the following events: hospitalization, ER visit [EX_HOSP_ER_POST_N]
2.	Change in asthma exacerbation rates that required hospitalization between 12-month pre- and post-exposure periods in cohorts 1 and 2	• Number of asthma exacerbations during the 12-month pre-exposure period that required at least one hospitalization [EX_HOSP_PRE_N] • Number of asthma exacerbations in the 12-month post-exposure period that

		required at least one hospitalization [EX_HOSP_POST_N]
3.	Compare median OCS maintenance dose, between pre- and post-exposure periods in cohorts 1 and 2	• Median daily maintenance OCS dose during the 12-month pre-exposure period [MEDIAN_OCS_PRE] • Median daily maintenance OCS dose during the 6-month post-exposure period [MEDIAN_OCS_6_POST] • Median daily maintenance OCS dose during the 12-month post-exposure period [MEDIAN_OCS_12_POST] • Total OCS maintenance dose during the 12-month pre-exposure period [TOTAL_OCS_PRE] • Total OCS maintenance dose during the 6-month post-exposure period [TOTAL_OCS_6_POST] • Total OCS maintenance dose during the 12-month post-exposure period [TOTAL_OCS_12_POST]
4.	Compare FEV1 values pre- and post-exposure in cohorts 1 and 2	• FEV1 (latest) value during the pre-exposure period [FEV1_PRE] • FEV1 (latest) value during the 6-month post-exposure period [FEV1_6_POST] • FEV1 (latest) value during the 12-month post-exposure period [FEV1_12_POST] *Note: The FEV1% predicted will be also used (in addition to FEV1) for the assessment of this objective. An assessment of the lung function stabilisation at later timepoints (e.g., 18 and 24 months) will be also provided.*
5.	Compare ACT scores pre- and post-exposure in cohorts 1 and 2	• ACT (latest) score during the pre-exposure period [ACT_PRE] • ACT (latest) score during the 6-month post-exposure [ACT_6_POST] • ACT (latest) score during the 12-month post-exposure period [ACT_12_POST]
6.	Describe patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2	• Same as in Section 5.4

7.	Describe pre-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) pre-exposure in cohorts 1 and 2	The following variables will be assessed during the pre-exposure period: • Use of OCS treatments (Yes/No) [OCS_PRE] • Use of ICS treatments (Yes/No) [ICS_PRE] • Use of inhaled treatments (Yes/No) [INH_PRE] • Mean daily dose of OCS [MEAN_DOSE_OCS_PRE] • Mean daily dose of ICS [MEAN_DOSE_ICS_PRE] • Mean daily dose of inhaled treatments [MEAN_DOSE_INH_PRE] • Minimum daily dose of OCS [MIN_DOSE_OCS_PRE] • Minimum daily dose of ICS [MIN_DOSE_ICS_PRE] • Minimum daily dose of inhaled treatments [MIN_DOSE_INH_PRE] • Maximum daily dose of OCS [MAX_DOSE_OCS_PRE] • Maximum daily dose of ICS [MAX_DOSE_ICS_PRE] • Maximum daily dose of inhaled treatments [MAX_DOSE_INH_PRE] • Total cumulative dose of OCS [TOTAL_DOSE_OCS_PRE] • Total cumulative dose of ICS [TOTAL_DOSE_ICS_PRE] • Total cumulative dose of inhaled treatments [TOTAL_DOSE_INH_PRE] • Frequencies of prescriptions for OCS [FREQ_OCS_PRE] • Frequencies of prescriptions for ICS [FREQ_ICS_PRE] • Frequencies of prescriptions for inhaled treatments [FREQ_INH_PRE] • Total treatment duration for OCS (in days) [DURATION_OCS_PRE] • Total treatment duration for ICS (in days) [DURATION_ICS_PRE] • Total treatment duration for inhaled treatments (in days) [DURATION_INH_PRE]

Note: The description of OCS, ICS and inhaled treatments is provided in Table 4.

ACT, Asthma Control Test; ER, Emergency Room; ICS, Inhaled Corticosteroids; OCS, Oral Corticosteroids

Note: The SAS variable name are in brackets.

Covariates included in IPD-based statistical models needed for the assessment of most secondary objectives will be defined in Section 8.4.

More details on variables definition (e.g., timing of assessment) are provided in Section 5.5 and data analysis specifications are described in Section 9.2.

5.3. Exploratory outcomes

No.	Exploratory Objectives	Variables
1.	Describe NP related outcomes[1] pre-and post-exposure in cohort 2, including: • VAS loss of smell score • SNOT-22 score • NPS score	The following variables will be assessed during the 12-month pre- and post-exposure periods: • (latest) VAS loss of smell score [VAS_PRE and VAS_POST] • (latest) SNOT-22 score [SNOT22_PRE and SNOT22_POST] • (latest) NPS score [NPS_PRE and NPS_POST] •
2.	Describe clinical remission for patients (who achieved clinically significant exacerbation reduction), post-exposure in cohorts 1 and 2	• Number of clinically significant asthma exacerbations during the 12-month post-exposure period [EX_HOSP_ER_OCS_POST_N] • Number of OCS use for asthma at 12-months post-exposure [OCS_ASTHMA_N] • ACQ-5 < 1 or ACT ≥ 20 at end of the 12-month post-exposure period (Yes/No) [ACQ5_ACT]

[1] Available only in the BSAR registry (Belgium)

No.	Exploratory Objectives	Variables
		• Lung function stabilization (no decline of lung function measured using FEV1 from pre-exposure period ≥100 mL at 12 months post-exposure) (Yes/No) [LUNG_STAB] • Clinical remission at 12 months post-exposure (Yes/No) [CLIN_REM] • Clinical remission at 12 months post-exposure considering at least two of the four criteria of clinical remission are satisfied (Yes/No) [CLIN_REM_C2] • Clinical remission at 12 months post-exposure considering at least three of the four criteria of clinical remission are satisfied (Yes/No) [CLIN_REM_C3]
3.	Describe the change in peripheral blood eosinophils during the post treatment period compared with 6-month pre-mepolizumab levels in cohorts 1 and 2	• Median number (per μL) of peripheral blood eosinophils during the 6-month pre-exposure period [MEDIAN_PER_BLD_6_PRE_N] • Median percentage of peripheral blood eosinophils during the 6-month pre-exposure period [PERCENT_PER_BLD_6_PRE] • Median number (per μL) of peripheral blood eosinophils during the 12-month post-exposure period [MEDIAN_PER_BLD_12_POST_N] • Median percentage of peripheral blood eosinophils during the 12-month post-exposure period [PERCENT_PER_BLD_12_POST]
4.	Describe post-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) after mepolizumab initiation in cohorts 1 and 2	The following variables will be assessed during the 12-month post-exposure period: • Use of OCS treatments (Yes/No) [OCS_POST] • Use of ICS treatments (Yes/No) [ICS_ POST] • Use of inhaled treatments (Yes/No) [INH_POST] • Mean daily dose of OCS [MEAN_DOSE_OCS_POST]

No.	Exploratory Objectives	Variables
		• Mean daily dose of ICS [MEAN_DOSE_ICS_POST] • Mean daily dose of inhaled treatments [MEAN_DOSE_INH_POST] • Total cumulative dose of OCS [TOTAL_DOSE_OCS_POST] • Total cumulative dose of ICS [TOTAL_DOSE_ICS_POST] • Total cumulative dose of inhaled treatments [TOTAL_DOSE_INH_POST] • Minimum daily dose of OCS [MIN_DOSE_OCS_POST] • Minimum daily dose of ICS [MIN_DOSE_ICS_POST] • Minimum daily dose of inhaled treatments [MIN_DOSE_INH_POST] • Maximum daily dose of OCS [MAX_DOSE_OCS_POST] • Maximum daily dose of ICS [MAX_DOSE_ICS_POST] • Maximum daily dose of inhaled treatments [MAX_DOSE_INH_POST] • Frequencies of prescriptions for OCS [FREQ_OCS_POST] • Frequencies of prescriptions for ICS [FREQ_ICS_POST] • Frequencies of prescriptions for inhaled treatments [FREQ_INH_POST] • Total treatment duration for OCS (in days) [DURATION_OCS_POST] • Total treatment duration for ICS (in days) [DURATION_ICS_POST] • Total treatment duration for inhaled treatments (in days) [DURATION_INH_POST] *Note: The description of OCS, ICS and inhaled treatments is provided in* Table 4.

No.	Exploratory Objectives	Variables
5.	Evaluate the change in clinically significant asthma exacerbations rates pre-and post-exposure (24 months post) in cohorts 1 and 2	• Number of clinically significant asthma exacerbations during the 12-month pre-exposure period [EX_HOSP_ER_OCS_PRE_N] • Number of clinically significant asthma exacerbations during the 24-month post-exposure period [EX_HOSP_ER_OCS_24_POST_N]
6.	Compare change in clinically significant asthma exacerbation rates from pre-and post-exposure between cohorts 1 and 2 (if cohorts are balanced)	• Number of clinically significant asthma exacerbations during the 12-month pre-exposure period [EX_HOSP_ER_OCS_PRE_N] • Number of clinically significant asthma exacerbations during the 12-month post-exposure period [EX_HOSP_ER_OCS_POST_N]
7.	In preparation for future registry-level meta-analyses: ❖ Evaluate the primary objective separately for each registry ❖ Evaluate secondary objective #6 by registry	• Outcomes as mentioned for primary and secondary objective # 6, at registry-level

ACT, Asthma Control Test; ACQ-5, Asthma Control Questionnaire-5; ICS, Inhaled Corticosteroids; NPS, Nasal Polyp Score; OCS, Oral Corticosteroids; SNOT-22, Sino-Nasal Outcome Test; VAS, Visual Analogue Score

Note: The SAS variable names are specified in brackets.

Covariates included in IPD-based statistical models needed for the assessment of most exploratory objectives will be defined in Section 8.4.

More details on variables definition (e.g., timing of assessment) are provided in Section 5.5 and data analysis specifications are described in Section 9.3.

5.4. Baseline characteristics

The following patients' characteristics will be described before or at index date for all patients included in the study. When necessary, details on variables definition are provided in Section 5.5. SAS variables are specified into square brackets. Unless otherwise stated, the baseline value will be that at treatment index date or the most recent value available prior to treatment index.

- Demographic variables:
  - Age at index (in years) [AGE_IDX]
  - Time since onset of SEA to index date (in years) [TIME_SEA_IDX]
  - Time since onset of CRSwNP to index date (in years) [TIME_CRSWNP_IDX] *(note: not available in the SSAR)*
  - Sex (Female/Male/Unknown/Other) [SEX]
  - BMI (in kg/m²) [BMI_IDX]
  - Smoking status (Current/Former/Never smoked/Unknown) [SMOKING_IDX]
    - If current/former smoker, number of packs per year [SMOKING_PACK_N]
    - If never smoked or passive smoker (Yes/No) [NEVER_PASS_SMOKER]
- Clinical variables: (Value at index or historical value nearest to the index date during the 90 days prior to treatment index if value at index is missing.)
  - Peripheral BEC (10^9 cells/L) [PERPH_BEC] *(note: conversion needed in some data sources: 1 Cells/µL = 1000000 Cells/L)*
  - Total IgE (kU/L) [TOTAL_IGE]
  - FEV1 (L) [FEV1]
  - FeNO (ppb) [FENO]
  - T2 Biomarkers [T2_BIOMARKER]
- Comorbidities, assessed during the entire pre-exposure period
  - AERD (Yes/No) [AERD]
  - COPD (Yes/No) [COPD]
  - Diabetes (Yes/No) [DIABETES]
  - Churg Strauss Syndrome (Yes/No) [CH_STR_SYND]
  - EGPA (Yes/No) [EGPA]
  - HES (Yes/No) [HES]
  - CRS (Yes/No) [CRS]
    - CRSwNP (Yes/No) [CRSWNP]
    - CRSsNP (Yes/No) [CRSSNP]
  - Vasculitis (Yes/No) [VASCULITIS] *(note: not available in SSAR)*
  - Gastro esophageal reflux syndrome (Yes/No) [GAS_ESO_REF_SYND]
  - Allergic rhinitis (Yes/No) [ALLER_RHIN]
  - Anxiety (Yes/No) [ANXIETY]
  - Depression (Yes/No) [DEPRESSION]
  - Atopic dermatitis (Yes/No) [ATOP_DERM]
  - Non-cystic fibrosis bronchiectasis (Yes/No) [BRONCHIEC]
  - Eosinophilic esophagitis (Yes/No) [EOSIN_ESOPH]
  - Obesity (Yes/No: Yes if BMI >30) [OBESITY]
  - Allergy diagnosis (Yes/No) [ALLER_DIAG]
    - If yes, Allergic asthma diagnosis (Yes/No) [ALLER_ASTHMA_DIAG]
  - Sensitization to common inhalants (Yes/No) [SENSIT_COM_INH]
  - Number of exacerbations [EX_N]
- Nasal polyp-related variables, assessed during the entire pre-exposure period

- Nasal polyp surgery (polypectomy) (Yes/No) [NASAL_POLYP_SURG]. If yes
  - Type of surgery
    - Functional endoscopic sinus surgery (FESS) (Yes/No) [SURG_TYPE_FESS]
    - Endoscopic polyp removal (Yes/No) [SURG_TYPE_EN_PO]
  - Number of polyps removed [POLYP_REMOV_N]
  - Median size of polyps removed (in cm) [MEDIAN_POLYP_SIZE]
  - Surgical complications (Yes/No) [SURG_COMPLIC]
  - Time since last surgery (in days) [TIME_LAST_SURG]

  Note: In SSAR, it is assessed if surgery was performed and how many times, but details on the surgery is not captured

- *Treatment-related variables*, assessed during the entire pre-exposure period
  - Mepolizumab treatment (Yes/No) [MEPOLIZUMAB_TRT]
  - Other Asthma/CRSwNP related treatment (Yes/No) [OTH_ASTHMA_TRT]
    - If yes, same variables as in Secondary objective #7.
  - History of previous biological treatments (Yes/No) [HIST_BIO_TRT]
  - Presence of NSAID intolerance (Yes/No) [NSAID_INT]

5.5. Definition

This section provides details on the definition of some variables listed in Sections 5.1, 5.2, 5.3, and 5.4. as they were recorded in the different datasets. Self-explanatory variables (e.g., Age at index date, sex) are not mentioned. All variables required for the analysis will be directly available in the different datasets, without need to specify any complex algorithms to define them. In case a variable definition in a registry is not aligned with other registries, the approach to derive a common definition will be outlined in sections below. Handling of missing variables will be addressed in Section 8.7.

Section 5.5.18 will address the case of several measurements recorded during the same reference period.

5.5.1. CRS

CRS is a disease characterized by chronic inflammation of the sinonasal tissue. The primary phenotypes of CRS are based on the presence or absence of NP as assessed via endoscopic findings. CRS has traditionally been classified into with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP).

5.5.2. CRS with nasal polyps

It corresponds to the presence of bilateral polyps in middle meatus identified using endoscopic examination or CT/MRI scan. A patient will also be classified in the CRSwNP cohort if they had a historical record of nasal polyps in pre-exposure period,

that is, the occurrence of one of the following events (independently of CRS) during the pre-exposure period:

- Nasal polyps
- Nasal polypectomy

5.5.3. Asthma exacerbations

An asthma exacerbation is a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome (Fuhlbrigge et al., 2012).
Asthma exacerbations occurring within 7 days of each other will be considered a single episode.

5.5.4. Clinically significant asthma exacerbations

A clinically significant asthma exacerbation is defined as deterioration in asthma requiring use of systemic corticosteroids and/or ED visit and/or hospital admission. In the different datasets, a clinically significant asthma exacerbation will be defined following the European Respiratory Society/American Thoracic Society consensus, that is, by the occurrence of one of the following events:

- Any asthma-related referral or hospitalization with a discharge diagnosis of asthma; OR another criterion as specified by the registry (Hospitalization)
- Any record of an ER visit related to an asthma diagnosis code; OR another criterion as specified by the registry (ER visit)
- A treatment with short-term OCS, for ≥3 days but ≤28 days (or 4 weeks) with an asthma exacerbation diagnosis code recorded within ±2 weeks of the start of the OCS treatment (OCS burst)

5.5.5. OCS dose

OCS treatments will be mainly identified in the datasets by the medication type ‘oral corticosteroid’, and confirmed by clinical opinion. Other medication types will also be used to identify OCS treatments: ‘asthma’, ‘inhaled corticosteroid’, ‘intramuscular corticosteroid medication’ or ‘intravenous corticosteroid’.

All OCS medications daily dose will be expressed as prednisone equivalent dose in mg per day using scaling factor in Table 1. OCS medications scaling factor for prednisone equivalent conversion

, as in REALITI-A.

Table 1. OCS medications scaling factor for prednisone equivalent conversion

OCS medication name	Dose scaling factor (in prednisone equivalent)
Betamethasone	8.33
Betamethasone Dipropionate	8.33
Betamethasone Sodium Phosphate	8.33
Cortisone	0.2

Cortisone Acetate	0.2
Cortivazol	17
Deflazacort	0.833
Dexamethasone	6.67
Dexamethasone Sodium Phosphate	6.67
Fludrocortisone Acetate	0
Hydrocortisone	0.25
Hydrocortisone Sodium Succinate	0.25
Hydrocortisone Sodium Phosphate	0.25
Meprednisone	1
Methylprednisolone	1.25
Methylprednisolone Acetate	1.25
Methylprednisolone Sodium Succinate	1.25
Methylprednisone	1.25
Methylprednisone Acetate	1.25
Methylprednisolone Sodium Succinate	1.25
Methylprednisone	1.25
Methylprednisone Acetate	1.25
Prednisolone	1
Prednisolone Acetate	1
Prednisolone Hemisuccinate	1
Prednisolone Sodium Succinate	1
Prednisone	1
Prednisone Acetate	1
Triamcinolone	1.25
Triamcinolone Acetonide	1.25

5.5.6. OCS burst

Treatment with short-term OCS for ≥3 days but ≤28 days (or 4 weeks)

5.5.7. OCS maintenance dose

This corresponds to an increase of the prescribed dose by at least 2 times, for ≥3 days, but ≤28 days (or 4 weeks).

5.5.8. ICS dose

All ICS medications daily dose will be expressed as fluticasone propionate (FP) equivalent dose in mg per day using scaling factor in Table 2. ICS medications scaling factor for FP equivalent conversion

, as in REALITI-A

Table 2. ICS medications scaling factor for FP equivalent conversion

ICS medication name	Dose scaling factor (in FP equivalent)
Beclometasone Dipropionate (CFC)	0.5
Beclometasone Dipropionate (HFA)	1.25
Budesonide	0.625
Ciclesonide	1.5625

Fluticasone Furoate	5
Fluticasone Propionate	1
Mometasone Furoate	1.13636
Triamcinolone Acetonide	0.25

5.5.9. Total cumulative dose

It is the total dose of the treatment (e.g., OCS, ICS) a patient received during a given period. It can be obtained as the sum of the daily treatment dose.

5.5.10. Daily treatment dose

It is the total dose of treatments of the same category (e.g., OCS, ICS) a patient received in a day.

5.5.11. FEV1 values

FEV1 is the volume of air (in liters) exhaled in the first second during forced exhalation after maximal inspiration. Normally, at least 80% of the forced vital capacity (FVC) is exhaled in the first second. The FEV1 is used with the FVC to differentiate between obstructive lung disease (FEV1/FVC < 70%) and restrictive lung disease (reduced FEV1 and FVC but normal FEV1/FVC relationship). An FEV1 of less than 1 liter indicates significant lung disease. FEV1/FVC, also called FEV1%, is the percentage of the FVC expired in one second [Barreiro, 2004]. The FEV1% predicted value is the FEV1% divided by the FEV1% of a person with similar characteristics in the general population.

5.5.12. ACT scores

ACT score assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. This is a 5-point Likert scale (for symptoms and activities: 1=all the time to 5= not at all; for asthma control rating: 1=not controlled at all to 5=completely controlled). The scores range from 5 (poor control of asthma) to 25 (complete control of asthma), (continuous variable) with higher scores reflecting greater asthma control. An ACT score >19 indicates well-controlled asthma [American Thoracic Society, 2023].

5.5.13. Nasal polyp-related variables

The following nasal polyp-related variables have been collected in the BSAR registry:

- NPS score is a physician-reported assessment of size and extent of NP.
  - Scores ranging from 0 to 8 (continuous variable) (sum of the right and left scores; average of 2 independent raters) [Han, 2022]
    - No polyps (“0”)

        - Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate ("1")
        - Polyps reaching below the lower border of the middle turbinate ("2")
        - Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate ("3")
        - Large polyps causing complete obstruction of the inferior nasal cavity ("4")
- VAS loss of smell is a patient-reported assessment of size and symptom severity.
    - Scores ranging from no smell ("0") to normal smell ("10") (continuous variable) [Prajapati, 2021]
    - Patient selects best description of odour out of 40 choices.
- SNOT-22 score is a patient-reported assessment of symptom burden on quality of life.
    - Scores ranging from 0 to 110 (continuous variable) (sum of the 22 items). Higher scores indicate greater impacts of CRS on HRQoL [Han, 2022]. For each item, the scores are as following:
        - No problem ("0")
        - Very mild problem ("1")
        - Mild or slight problem ("2")
        - Moderate problem ("3")
        - Severe problem ("4")
        - Problem as bad as it can be ("5")
- Nasal polyp surgical history (type of surgery, number, size of polyps removed, surgical complications, time since last surgery)

5.5.14. ACQ-5

The validated ACQ-5 has been shown to correlate with a measure of control based on the GINA/NIH criteria. This instrument includes five questions on symptoms and activity limitation. Each question is scored from 0 to 6 with the total score being the average of the questions. The ACQ score ranges between 0 (well controlled) and 6 (extremely poorly controlled). Recent studies show that a score of 1.5 or more indicates that a patient has inadequate asthma control and a score of 0.75 or lower indicates that the patient has well-controlled asthma [American Thoracic Society, 2023].

Note: ACQ-5 score at initiation of mepolizumab have not been assessed in the SSAR and REDES registries, only ACT.

5.5.15. Peripheral blood eosinophils

It is the number of eosinophils in the peripheral blood expressed in cells per microliter (μL) as given by the lab blood test. Eosinophilia is considered when absolute eosinophil count exceeds 500/µL in peripheral blood. Eosinophilia can be categorized as mild (absolute eosinophil count ranges from 500/µL to 1,500/µL), moderate (absolute eosinophil count ranges from 1,500/µL to 5,000/µL), or severe (absolute eosinophil count >5,000/µL) [Park et al, 2018].

5.5.16. Clinical remission

Clinical remission will be defined as:

- No asthma exacerbations during the 12-month period AND
- No OCS use for asthma during the 12-month period AND
- ACQ-5 < 1 or ACT ≥ 20, assessed at the end of the 12-month period AND
- Lung function stabilization (no decline of lung function measured using FEV1 from pre-exposure period ≥ 100 mL at 12 months)

5.5.17. Mepolizumab treatment

Mepolizumab treatment will be identified in the datasets using medication code R03DX09 (100 mg subcutaneous every 4 weeks for SEA) or any other specific criterion that the registries use to identify mepolizumab medications

5.5.18. Measurement/score variables

For all variables except baselines characteristics (See Section 5.4), Table 3 gives the rule to define the value to be considered for the assessment of the different study objectives.

Table 3. Rule to be applied in case of multiple values in the same assessment window

Measurement/score variables	Value to be considered
• FEV1 • ACT	The latest value in the reference period
• NP-related outcomes (e.g., NC score)	The latest value in the reference period
• Peripheral blood eosinophils count (BEC)	The median value during the reference period
• ACQ	The value closest to the target day

Note: For these variables, only on-treatment values will be considered for the post-exposure outcomes.

6. DERIVED/INTERMEDIATE VARIABLES

6.1. Exposure

Patients will be censored in case of the following events, whichever comes first: at the end of the 24-month observation period, withdrawal of consent or death.

The mepolizumab treatment period will be defined as the period starting from the index date until the earliest of the censoring date or discontinuation of prescribing. Discontinuation is considered to have occurred if there is either:

- A Break in exposure, that is, at least 90 days between prescriptions to align with REALITI-A study protocol [GSK document number 2016N286379_03]. The 90-day time window between two prescriptions will be assessed from the end of the first prescription and/or dispensation (prescription start date plus 28 days) to the start of the subsequent one. If discontinuation date is not reported, then the discontinuation date will be set at 28 days after the last known final prescription (prescription start date plus 28 days).

or

- Never receiving another mepolizumab prescription within the study period (withdrawal). The discontinuation date is set at 28 days after the last known final prescription (prescription start date plus 28 days). *It will not be possible to determine whether a patient discontinued mepolizumab if they are censored between 29 and 90 days after their last prescription. For these patients, the period up to 28 days following last prescription will be included in the currently exposed period.*

The duration of mepolizumab exposure will be defined as the number of days from the day of the first administration of NUCALA (treatment index) to the day of the last administration of NUCALA + 28 days inclusive (i.e. all gaps between consecutive NUCALA doses are counted regardless of possible breaks in exposure that are 90 days or less).

For the Mepolizumab treatment, the following variables will be defined:

- Start date (at index date)
- Dosage (at index date and 12-, 24- months post-exposure period)
- Frequency (at index date and post-exposure period)
- Days supplied (post-exposure period)
    - Days supplied will be calculated as number of doses in the prescription by the number of doses per day
- Formulation (at index date and post-exposure period)
- Mode of administration (at index date and post-exposure period)
- Cessation (at 12-, 24- months post-exposure period)
- Change in treatment (at 12-, 24- months post-exposure period)
- Interruption in treatment (at 12-, 24- months post-exposure period)

6.2. Asthma and CRSwNP medications

Asthma medication groups will be described according to the categories listed in Table 4. Individual drugs listed under each category, their respective ATC codes and DDD are also detailed in Table 6 in Appendix. Some specific treatments will be described separately as reported in Table 6 in Appendix.

Table 4. Asthma and/or CRSwNP Medications

Category	Description
OCS	Oral corticosteroids (See Table 6)
ICS mono	Inhaled corticosteroids (See Table 6)
INCS	Intranasal corticosteroids (See Table 6)
ICS combination (ICS and Bronchodilator)	See Table 6 *Including:* ○ *ICS and bronchodilators* ○ *Fixed Combination of SABA and ICS* ○ *Open combination of ICS and LAMA in two devices* ○ *Fixed Combination of ICS and LABA* ○ *Open combination of ICS and LABA in two devices (LABA script overlaps with ICS by at least one day)* ○ *ICS and double bronchodilators* ○ *Fixed Combination of ICS and LABA along with a LAMA in two devices* ○ *Open combination of ICS and LABA and LAMA in three devices* ○ *Fixed combination of LABA and LAMA along with ICS in two devices* ○ *Fixed combination of ICS and LABA and LAMA*
Bronchodilator (without corticosteroids)	See Table 6 *Including:* ○ *SABA, SAMA, LAMA* ○ *Double bronchodilator* ○ *Fixed Combinations of SABA/ Cromoglycate* ○ *Fixed Combinations of SABA/SAMA Long-Acting Beta2-Agonists* ○ *Fixed Combination of LABA along with a LAMA* ○ *Open combination of LABA and LAMA in two devices* ○ *Theophylline and its derivates*
Other medications for asthma/CRSwNP	See Table 6

CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; ICS, Inhaled Corticosteroids; INCS, Intranasal Corticosteroids; LABA, Long-Acting Beta2-Agonists; LAMA, Long-Acting Muscurinic Antagonist; LTRA, Leukotriene Receptor Antagonist; PDE4, phosphodiesterase type 4 inhibitor; SABA, Short-Acting Beta2-Agonist; SABD, Short-acting bronchodilator; SAMA, Short-Acting Muscarinic Antagonist;

6.3. Study period

6.3.1. Index date

The index date for this study is defined as the first prescription record of mepolizumab during the patient identification period from December 02, 2015 (date of mepolizumab approval in the EU) till the last follow-up visit of the last patient in the registries.

6.3.2. Pre-exposure period

The pre-exposure period will start from the index date (included) and finish at a minimum of 365 days prior. In case the patient enrolment occurred after the initiation of mepolizumab, the pre-exposure period will start from the enrolment date and finish at a minimum of 365 days prior.

6.3.3. Post-exposure period

The post-exposure period corresponds to the mepolizumab treatment period starting from index date + 1 day to their censoring date, which is the earliest of the following:

- End of the 24-month follow-up period
- Withdrawal of consent
- Death

After index date, patients' follow-up duration will be up to 24 months post-index. Based on previous analyses, patients are expected to have a minimum follow-up observational period of 12 months post-index.

7. DATA MANAGEMENT AND STANDARDISATION

Syneos Health (the CRO) will carry out the management and analysis of the IPD from the following sources: REALITI-A, REDES, RELIght. For the BSAR and the SSAR, only aggregated data (results tables) will be shared with the CRO for incorporation into the study report.

Syneos Health will receive registries IPD data through an internal encrypted file transfer system. A first quality control process will be conducted to make sure that datasets received contain all variables needed for the analysis. If needed, study variables will be derived based on available information in each dataset, in accordance with the variable definition in Section 5.5. Any deviation from the common definition will be documented and justified in the final report. Missing data strategy will be defined in Section 8.7.

To ensure standardization of patent data and variables definitions across data sources, Syneos Health will ensure that the same process is internally conducted by the BSAR and the SSAR registries.

After standardization, IPD from all data sources will be pooled together to create a unique analysis dataset that will contain a variable for the identification of the registry each patient belongs to. Registries for which IPD will not be available will share aggregated outcomes and patients' characteristics at index, by populating the results table shell developed by Syneos Health.

A DMP will be created before the start of the data collection and will describe all functions, processes, and specifications for data transfer from registry holders including data collection, cleaning, and validation.

8. STATISTICAL AND DATA ANALYSIS CONSIDERATIONS

8.1. General statistical considerations

The fit of the negative binomial generalized linear model will be investigated by calculating standardised deviance residuals and plotting these on a “Q-Q” plot. In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced. Distributional assumptions underlying the model used for analysis will be examined by assessing if a sufficient number of events occurred within covariate categories. The level of significance will be set to 5% for all statistical tests.

8.2. Descriptive summary statistics

Continuous variables will be described (distribution) by their mean, standard deviation, median, first and third quartile (Q1 and Q3), extreme values (minimum and maximum) and the number of non-missing and missing data. Categorical variables will be described using frequency counts and percentages, including counts of missing observations. Unless otherwise stated, the calculation of proportions/percentages for a given qualitative variable will include patients with non-missing values in the denominator. The percentage of missing values will be reported for each variable.

8.3. Feasibility patient count

Based on initial feasibility counts and data from publications, Table 5 provides approximate patient counts across countries.

Table 5 Feasibility counts of patients in Cohort 1 and Cohort 2 across registries with available data

	GSK-owned IPD data							Other IPD data	Total IPD	Aggregated data		Total (IPD + aggregated
	REALITI-A						REDES	RELIght[#]		BSAR	SSAR	
	Belgium	Canada	Germany	Italy	UK	US	Spain	Greece		Belgium	Switzerland	
SEA	29	19	44	178	98	35	318	87	808[¥]	80	30	918[¥]
SEA with NP	13	9	16	109	30	4	147	46	374[¥]	40	21	435[¥]
SEA without NP	16	10	28	69	68	31	171	41	434[¥]	40	9	483[¥]

BSAR, Belgium Severe Asthma Registry; NP, Nasal Polyps; RELIght, REal-LIfe study of mepolizumab in patients with severe eosinophilic asTHma in Greece; SEA, Severe Eosinophilic Asthma; SSAR, Swiss Severe Asthma Registry

[#]Based on published numbers. [¥]Patients count excluding patients who were participating to the REALITI-A study

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8.4. Covariates

The following list of covariates will be included in some IPD-based regression models:

- Registry (REALITI-A, REDES, RELIght)
- Country (Belgium, Canada, Germany, Greece, Italy, Spain, UK, US)
- Number of clinically significant asthma exacerbations in the 12-month pre-exposure period (0, 1–3, 4+)
- The pre-exposure value of the outcome variable to be analysed
- Use of maintenance oral corticosteroids during the 12-month pre-exposure period (Yes/No)
- Peripheral BEC at baseline [only considered for the trend analysis described in Section 9.1.1.4]
- Time period (pre-exposure/post-exposure)

If the percentage of participants is small (n<10) within a country, countries may be grouped into regions. The following regions are defined with consideration for reimbursement criteria and geographic location:

- Region 1: UK, Belgium
- Region 2: Italy, Germany, Spain
- Region 3: Rest of the World (US and Canada)

If the percentage of participants is small (n<10) within Regions 1 or 2, both may be grouped into one region called Europe.

The registry covariate will not be considered for registry subgroups analyses. Country will be included as covariate only for IPD pooled and REALITI-A regression models. The pre-exposure value of the outcome variable will not be used as covariate for analyses mentioned in Section 9.1.1 (primary objective), 9.3.5 (exploratory objective 5), and 9.3.6 (exploratory objective 6) as it would correspond to the number of clinically significant asthma exacerbations which will be already included as covariate. The use of maintenance OCS during the 12-month pre-exposure period will not be included in the list of covariates for the analysis mentioned in Section 9.2.2 (secondary objective 3), as it would correspond to the baseline value of the outcome variable which will be already considered as covariate.

For the exploratory objective 6 (comparing the change in clinically significant asthma exacerbation rates from 12-month pre-mepolizumab treatment and 12-month post-mepolizumab initiation between cohorts 1 and 2), in addition to covariates mentioned above, the following variables will be used as covariates:

- Age at index, BMI at index, blood eosinophil count at baseline, gender, smoking status

If model convergence issues arise, the following covariates will be removed one by one until convergence in the order below, and a note will be added to the corresponding results tables:

1. Number of clinically significant asthma exacerbations in the 12-month pre-exposure period (0, 1–3, 4+)
2. The pre-exposure value of the outcome variable to be analysed

8.5. Subgroups definition

To implement registry-level pooling methods and account for data from BSAR and SSAR registries, IPD-based regression model will be estimated separately for each registry.

The analysis of the change in peripheral BEC (exploratory objective #3) will be also conducted for subgroups defined based on specific threshold of peripheral BEC at baseline as described in Section 9.3.3.4.

The primary objective will be also assessed for each subgroup defined by quartiles of peripheral at baseline as described in Section 9.1.1.4.

No other subgroup analysis will be conducted.

8.6. Multiple Comparisons and Multiplicity

Adjustments for multiplicity are not being performed in this study. There is a single primary endpoint, secondary endpoints will contribute to the totality of the evidence.

8.7. Missing data

Missing data for the primary analysis will not be imputed, and the data will be analysed as recorded in the study under the missing at random assumption (MAR). Therefore, no imputation method will be implemented.

For secondary and exploratory analyses, the percentage of missing data for each variable (between patients) and each patient (between variables) will be computed, to help decide which variables and/or patients should be considered candidates for removal. The amount of missing data may be considered negligible if less than 5% [Schafer, 1999]. In case a given variable is not reported or completely missing in one or several registries, IPD-based statistical model and standard pooling methods described in Section 9 will be estimated using other registries data. However, the associated results will be interpreted with caution and a note will be added to the corresponding results table.

8.8. Statistical software and tools

Data will be analysed using SAS software (SAS Institute, North Carolina), version 9.3 or higher, and registry-level pooling methods will be implemented in R version 4.2.1.

9. DATA ANALYSIS

9.1. Primary analysis

The analysis described in this section will be applied separately to cohorts 1 and 2.

9.1.1. Analysis of change in asthma exacerbations rates – Primary objective

9.1.1.1. Summary measure

The summary measure will be the ratio between the exacerbation rate during the 12-month post-exposure period and the exacerbation rate during the pre-exposure period. This will be obtained as a parameter estimate of an IPD-based statistical model or as the pooled effect measure of registry-level results.

9.1.1.2. Population of interest

The population of interest for the primary analysis will be the treated population, that is, all participants with severe eosinophilic asthma who received an injection of NUCALA 100mg SC (the approved dose for use in asthma) at index date, and who will satisfy all inclusion and exclusion criteria.

9.1.1.3. Strategy for the intercurrent events

Four main intercurrent events have been identified for the primary analysis:

- **Discontinuation of NUCALA:** It is the key expected intercurrent event. Discontinuation will not affect the duration of the post-exposure period (12 or 24 months), that is, periods of breaks in exposure will not be excluded.
- **Interruptions to treatment:** Same strategy than treatment discontinuation
- **Switch to another biologic:** The purpose of this study is to evaluate the treatment effect attributable NUCALA. Therefore, data recorded after a treatment switching will not be considered for the definition of post-exposure variables.
- **Modified dose of NUCALA:** The purpose of this study is to evaluate the treatment effect attributable NUCALA 100mg. Therefore, data recorded after a change in NUCALA dose will not be considered for the definition of post-exposure variables.

9.1.1.4. Statistical analysis

A summary measure value will be first obtained using all available IPD data, and then using registry-specific results, including data from BSAR and SSAR registries.

IPD-based statistical models

The number of exacerbations in the pre- and post-exposure period will be analysed using a Negative Binomial regression with a covariate of time period (pre-exposure, post-exposure). The variance of the estimate of the mean number of exacerbations will be

corrected for the within-subject correlation. This will be implemented in SAS by inclusion of the REPEATED statement for subject in the GENMOD procedure. The logarithm of the total length of time (in years) of pre-exposure and post-exposure periods for which exacerbation data have been recorded will be included in the model as an offset variable. This will allow to interpret the summary measure as the ratio of annual rates of asthma exacerbations. Length of time (years) in study will be calculated as length of time (days)/365.25.

To control for heterogeneity across registries and countries, Registry and Country will be included as covariates in the regression models. Other covariates will be also considered as mentioned in Section 8.4. The summary measure will be derived from the parameter associated to the covariate Time Period. In case this model fails to converge, the list of covariates may be adjusted and/or reduced. If model convergence is not achieved, the list of covariates may be adjusted and/or reduced.

Registry-level pooling method

To take into account data from BSAR and SSAR registries, an inverse-variance weighting method will be implemented to obtain a pooled summary measure from registry-level aggregated data. Registry-specific summary measure will be estimated using the same methodological approach than for IPD-based models.

Fixed and random effect pooled summary effect will be obtained following the inverse-variance weighting approach described in *Deeks et al. (2023)* [Deeks, 2023], assuming the logarithm of the rate ratio of exacerbations rate will be normally distributed. Statistical heterogeneity across registries will be assessed by the heterogeneity index I^2. A value of I^2 greater than 50% will indicate a high level of heterogeneity.

This analysis will be implemented using the software R version 4.3.1 (package *netmeta* version *2.9.0*).

Subgroups analysis

Specifically for the assessment of the primary objective, the analysis described above will be repeated for subgroups defined based on quartiles of peripheral BEC at baseline. Registry-level pooling methods will be based on summary measures associated to each registry-specific quartile subgroups. Because quartiles of the IPD pooled dataset cannot be derived from quartiles of each specific registry, the total number of patients for REALITI-A, REDES and RELIGHT registries included in a specific subgroup analysis do not necessarily sum up to the number of patients of the corresponding subgroup analysis of IPD pooled dataset.

Trend analysis

Specifically for the assessment of the primary objective, an analysis of the relationship between the response and the peripheral BEC at baseline will be conducted. For the implementation of this trend analysis, the peripheral BEC will be added as covariate in IPD-based models described above and an interaction term between the time period and peripheral BEC will be considered. The summary measure (annual incidence rate ratio),

as well as its 95% confidence interval (CI), will then depend on value of the peripheral BEC at baseline. The associated 95% CI will be derived from the estimated variance-covariance matrix of the regression model and assuming parameter estimates will follow a normal distribution. The statistical significance of the interaction term (two-sided alpha of 5%), measured by p_value, would suggest the existence of a relationship between response to mepolizumab and peripheral BEC at baseline.

9.2. Secondary analysis

Each analysis described in this section will be applied separately to cohorts 1 and 2.

9.2.1. Analysis of change in asthma exacerbation rates – Secondary objectives 1 & 2

9.2.1.1. Summary measure

The summary measure will be the ratio between the exacerbation rate during the 12-month post-exposure period and the exacerbation rate during the pre-exposure period. This will be obtained as a parameter estimate of an IPD-based statistical models or as the pooled effect measure of registry-level results.
In case an ER visit that follows exacerbation results in a hospitalization, then the exacerbation will be considered as hospitalization-related.

9.2.1.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.2.1.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.2.1.4. Statistical analysis

As for primary analysis (See Section 9.1.1.4).

9.2.2. Analysis of change in median OCS – Secondary objective 3

9.2.2.1. Summary measure

The summary measure will be the mean difference in median daily OCS maintenance dose between the 6- and 12-month post-exposure period and 12-month pre-exposure period. Similar summary measures will be used for the total OCS dose. All summary measures will be obtained as parameter estimates of IPD-based statistical models or as pooled effect measures of registry-level results.

9.2.2.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.2.2.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.2.2.4. Statistical analysis

A summary measure value will be first obtained using all available IPD data, and then using registry-specific results, including data from BSAR and SSAR registries.

IPD-based statistical models

It will be assumed median daily OCS maintenance dose and total OCS dose follow a Normal distribution and they will be analysed using a linear regression model with a covariate of time period (pre-exposure, post-exposure). The variance of the parameter estimate will be corrected for the within-subject correlation. This will be implemented in SAS by inclusion of the REPEATED statement for subject in the GENMOD procedure.

To control for heterogeneity across registries and countries, Registry and Country will be included as covariates in the regression models. Other covariates will be also considered as mentioned in Section 8.4. The summary measure will be derived from the parameter associated to the covariate Time Period. If model convergence is not achieved, the list of covariates may be adjusted and/or reduced.

Registry-level pooling method

As for primary analysis (See Section 9.1.1.4), assuming mean differences will be normally distributed.

9.2.3. Analysis of FEV1 values – Secondary objective 4

9.2.3.1. Summary measure

The summary measure will be the mean difference in FEV1 value (or FEV1% predicted) at 6- and 12-month after mepolizumab initiation compared to baseline. Summary measures will be obtained as parameter estimates of IPD-based statistical models or as pooled effect measures of registry-level results.

A similar summary measure will be also used to assess lung function stabilisation at 18 and 24 months using FEV1 values and FEV1% predicted. For this specific analysis, the last value recorded in 3-month period prior to the timepoint of interest will be considered.

9.2.3.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.2.3.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.2.3.4. Statistical analysis

As for secondary analysis of change in median OCS (See Section 9.2.2.4).

9.2.4. Analysis of ACT scores – Secondary objective 5

9.2.4.1. Summary measure

The summary measure will be the mean difference in ACT score at 6- and 12-month after mepolizumab initiation compared to baseline. Summary measures will be obtained as parameter estimates of IPD-based statistical models or as pooled effect measures of registry-level results.

9.2.4.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.2.4.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.2.4.4. Statistical analysis

As for secondary analysis of change in median OCS (See Section 9.2.2.4).

9.2.5. Analysis of patient demographic, clinical and disease characteristics at initiation of mepolizumab – Secondary objective 6

9.2.5.1. Summary measure

Patient demographic, clinical and disease characteristics from Section 5.4 will be summarized as described in Section 8.2.

9.2.5.2. Population of interest

The population of interest will correspond to all patients satisfying all inclusion and exclusion criteria.

9.2.5.3. Strategy for the intercurrent events

No specific intercurrent event will be considered for this analysis.

9.2.5.4. Statistical analysis

Patient demographic, clinical and disease characteristics from Section 5.4 will be analysed as described in Section 8.2.

9.2.6. Analysis of pre-mepolizumab asthma treatment patterns – Secondary objective 7

9.2.6.1. Summary measure

The dosage and frequency of treatments listed in Table 6 will be summarized during the pre-exposure period as described in Section 8.2.

9.2.6.2. Population of interest

The population of interest will correspond to all patients satisfying all inclusion and exclusion criteria. For ICS-related outcomes, subgroup analyses on patients who achieved clinical remission and on patients who did not experience an increase in their number of exacerbations in the post-exposure period will be carried out.

9.2.6.3. Strategy for the intercurrent events

No specific intercurrent event will be considered for this analysis.

9.2.6.4. Statistical analysis

The dosage and frequency of treatments listed in Table 6 will be analysed during the pre-exposure period as described in Section 8.2.

9.3. Exploratory analysis

9.3.1. Analysis of NP-related outcomes – Exploratory objective 1

The analysis described in this section will be only applied to cohort 2.

9.3.1.1. Summary measure

For each of VAS loss of smell, SNOT-22, and NPS scores, the summary measure will be the mean difference in scores between the 12-month post-exposure period and the pre-exposure period. Summary measures will be obtained as parameter estimates of IPD-based statistical models or as pooled effect measures of registry-level results.

9.3.1.2. Population of interest

As for primary analysis (See Section 9.1.1.2). In addition, only patients who have not undergone polypectomy in the 12-months pre-exposure or 12-months post-exposure period will be considered for this analysis.

9.3.1.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.3.1.4. Statistical analysis

As for secondary analysis of change in median OCS (See Section 9.2.2.4).

9.3.2. Analysis of clinical remission – Exploratory objective 2

The analysis described in this section will be applied separately to cohorts 1 and 2.

9.3.2.1. Summary measure

Corresponding variables listed in Section 5.3 will be summarized as described in Section 8.2.

9.3.2.2. Population of interest

As for primary analysis (See Section 9.1.1.2). In addition, patients should have experienced a decrease in the number of asthma exacerbation when comparing the pre-

and post-exposure period. They should also be under mepolizumab treatment during the entire 12-month post-exposure period.

9.3.2.3. Strategy for the intercurrent events

No specific intercurrent event will be considered for this analysis. Patients will not be included if they discontinue treatment before 12 months in the post-exposure period.

9.3.2.4. Statistical analysis

Corresponding variables listed in Section 5.3 will be analysed as described in Section 8.2. In addition, the inverse-variance pooling method specific to dichotomous endpoints will be implemented to obtain fixed- and random-effect summary measures [Deeks, 2023]. Random-effects estimates account for the heterogeneity across registries, which will be measured by the heterogeneity index I^2. A value of I^2 greater than 50% will indicate a high level of heterogeneity.

This analysis will be implemented using the software R version 4.3.1 (package *meta* version *7.0.0*).

9.3.3. Analysis of change in peripheral blood eosinophils – Exploratory objective 3

The analysis described in this section will be applied separately to cohorts 1 and 2.

9.3.3.1. Summary measure

Summary measures will be the mean difference in median number or percentages of peripheral blood eosinophils between the 6-month pre-baseline period and the 12-month post-exposure period. Summary measures will be obtained as parameter estimates of IPD-based statistical models or as pooled effect measures of registry-level results.

9.3.3.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.3.3.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.3.3.4. Statistical analysis

As for secondary analysis of change in median OCS (See Section 9.2.2.4). In addition, a subgroups analysis will be conducted using each of the following categories:

- Eosinophils count at treatment initiation (by range)
  - < 150 eosinophils/µL;
  - ≥ 150 eosinophils/µL and < 300 eosinophils/µL;
  - ≥ 300 eosinophils/µL and < 500 eosinophils/µL;
  - ≥ 700 eosinophils/µL at treatment initiation.
- Eosinophils count at treatment initiation (by lower thresholds)
  - ≥ 150 eosinophils/µL;
  - ≥ 300 eosinophils/µL;
  - ≥ 500 eosinophils/µL;

- ≥ 700 eosinophils/µL.

9.3.4. Analysis of post-mepolizumab asthma treatment patterns – Exploratory objective 4

The analysis described in this section will be applied separately to cohorts 1 and 2.

9.3.4.1. Summary measure

Corresponding variables listed in Section 5.3 will be summarized as described in Section 8.2.

9.3.4.2. Population of interest

As for primary analysis (See Section 9.1.1.2). For ICS-related outcomes, subgroup analyses on patients who achieved clinical remission and on patients who did not experience an increase in their number of exacerbations in the post-exposure period will be carried out.

9.3.4.3. Strategy for the intercurrent events

No specific intercurrent event will be considered for this analysis.

9.3.4.4. Statistical analysis

Corresponding variables listed in Section 5.3 will be analysed as described in Section 8.2.

9.3.5. Analysis of change in asthma exacerbations rate – Exploratory objective 5

The analysis described in this section will be applied separately to cohorts 1 and 2.

9.3.5.1. Summary measure

As for primary analysis (See Section 9.1.1.1), considering a 24-month post-exposure period.

9.3.5.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.3.5.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.3.5.4. Statistical analysis

As for primary analysis (See Section 9.1.1.4).

9.3.6. Analysis of change in asthma exacerbations rate between cohorts – Exploratory objective 6

9.3.6.1. Summary measure

The summary measure will be the ratio of cohort-specific exacerbation rate ratios as defined in Section 9.1.1.1. This will be obtained as a parameter estimate of an IPD-based statistical model or as the pooled effect measure of registry-level results.

9.3.6.2. Population of interest

As for primary analysis (See Section 9.1.1.2).

9.3.6.3. Strategy for the intercurrent events

As for primary analysis (See Section 9.1.1.3).

9.3.6.4. Statistical analysis

As for primary analysis (See Section 9.1.1.4), with the following differences:

- Cohort (1 or 2) will be included as covariate in the IPD-based regression models.
- There will be an interaction term between Cohort and Time period, from which will be derived the summary measure for the assessment of this objective.
- To control for potential imbalances in baseline characteristics across cohorts, adjusted IPD-based statistical models in which patients' characteristics (See Section 5.4) are added as covariates will be also estimated. Only characteristics associated with highest levels of imbalance across cohorts, as measured by the p-value of the between-cohort comparison test, will be considered.

9.3.7. Analysis in preparation for future registry-level meta-analysis – Exploratory objective 7

A part of analysis associated to Exploratory objective #7 will correspond to registry-level implementation of the analysis described in Section 9.2.5 (Secondary objective #6). The other part (Primary objective) will be conducted in the primary analysis while implementing the registry-level pooling method (See Section 9.1.1.4).

9.4. Sensitivity analyses

9.4.1. Excluding patients with treatment initiation before the enrolment

In some datasets like REALITI-A, patients may be enrolled after the mepolizumab treatment initiation. For those patients, baseline variables may include data from a certain period of time after exposure, and this could bias our analysis. For this reason, a sensitivity analysis excluding patients enrolled after treatment initiation will be conducted for primary analysis.

9.4.2. Taking into account COVID-19

To determine the effect of COVID-19 on primary and secondary analyses' results, patients with an index date prior to COVID-19 (January 1, 2020) will be compared at baseline with those with an index date from December 31, 2020 onwards on variables listed in Section 5.4, using t-test and Wilcoxon test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables.

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11. APPENDIX

Table 6. List of asthma treatments

Treatment	ATC Code	Asthma treatment category	Individualized analysis (Pre-post)	Rescue/ Maintenance treatment
Alpha-and beta-adrenoreceptor agonists	R03AA		No	
Epinephrine	R03AA01	Bronchodilator	No	
Non-selective beta-adrenoreceptor agonists	R03AB R03CB		No	
Isoprenaline	R03AB02 R03CB01	Bronchodilator	No	
Isoprenaline, combinations	R03CB51	Bronchodilator	No	
Orciprenaline	R03AB03 R03CB03	Bronchodilator	No	
Orciprenaline, combinations	R03CB53	Bronchodilator	No	
Methoxyphenamine	R03CB02	Bronchodilator	No	
Selective beta-2-adrenoreceptor agonists	R03AC R03CC			
Salbutamol / Albutamol	R03AC02	Bronchodilator	**Yes**	Rescue
Terbutaline	R03AC03	Bronchodilator	**Yes**	Rescue
Fenoterol	R03AC04 R03CC04	Bronchodilator	No	
Rimiterol	R03AC05	Bronchodilator	No	
Hexoprenaline	R03AC06 R03CC05	Bronchodilator	No	
Isoetarine	R03AC07 R03CC06	Bronchodilator	No	
Pirbuterol	R03AC08 R03CC07	Bronchodilator	No	
Tretoquinol	R03AC09 R03CC09	Bronchodilator	No	
Carbuterol	R03AC11 R03CC10	Bronchodilator	No	
Tulobuterol	R03AC12 R03CC11	Bronchodilator	No	
Formoterol	R03AC13	Bronchodilator	**Yes**	Rescue
Clenbuterol	R03AC14 R03CC13	Bronchodilator	No	
Clenbuterol and ambroxol	R03CC63	Bronchodilator		
Reproterol	R03AC15 R03CC14	Bronchodilator	No	
Procaterol	R03AC16 R03CC08	Bronchodilator	No	
Bambuterol	R03CC12	Bronchodilator	No	

Bitolterol	R03AC17	Bronchodilator	No	
Indacaterol	R03AC18	Bronchodilator	**Yes**	Maintenance
Olodaterol	R03AC19	Bronchodilator	**Yes**	Maintenance
Terbutaline	R03CC03	Bronchodilator		
Terbutaline, combinations	R03CC53	Bronchodilator		
Combinations of adrenergics	R03AH			
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	R03AK			
Epinephrine and other drugs for obstructive airway diseases	R03AK01	Bronchodilator	No	
Isoprenaline and other drugs for obstructive airway diseases	R03AK02	Bronchodilator	No	
Salbutamol and sodium cromoglicate	R03AK04	Bronchodilator	**Yes**	Rescue
Reproterol and sodium cromoglicate	R03AK05	Bronchodilator	No	
Salmeterol and fluticasone	R03AK06	ICS and Bronchodilator	**Yes**	Maintenance
Formoterol and budesonide	R03AK07	ICS and Bronchodilator	**Yes**	Maintenance
Formoterol and beclometasone	R03AK08	ICS and Bronchodilator	**Yes**	Maintenance
Formoterol and mometasone	R03AK09	ICS and Bronchodilator	**Yes**	Maintenance
Vilanterol and fluticasone furoate	R03AK10	ICS and Bronchodilator	**Yes**	Maintenance
Formoterol and fluticasone	R03AK11	ICS and Bronchodilator	**Yes**	Maintenance
Salmeterol and budesonide	R03AK12	ICS and Bronchodilator	**Yes**	Maintenance
Salbutamol and beclometasone	R03AK13	ICS and Bronchodilator	No	Rescue
Indacaterol and mometasone	R03AK14	ICS and Bronchodilator	**Yes**	Maintenance
Adrenergics in combination with anticholinergics including triple combinations with corticosteroids	**R03AL**			
Fenoterol and ipratropium bromide	R03AL01	Double bronchodilator	**Yes**	Rescue
Salbutamol and ipratropium bromide	R03AL02	Double bronchodilator	**Yes**	Rescue
Formoterol and glycopyrronium bromide	R03AL07	Double bronchodilator	**Yes**	Maintenance
Formoterol and tiotropium bromide	R03AL10	Double bronchodilator	**Yes**	Maintenance
Vilanterol, umeclidinium bromide and fluticasone furoate	R03AL08	ICS and double bronchodilator	**Yes**	Maintenance
Formoterol, glycopyrronium bromide and beclometasone	R03AL09	ICS and double bronchodilator	**Yes**	Maintenance
Formoterol, glycopyrronium bromide and budesonide	R03AL11	ICS and double bronchodilator	**Yes**	Maintenance

Indacaterol, glycopyrronium bromide and mometasone	R03AL12	ICS and double bronchodilator	**Yes**	Maintenance
Other drugs for obstructive airway diseases, inhalants	**R03B**			
Glucocorticoids	**R03BA**			
Beclometasone	R03BA01	ICS	**Yes**	Maintenance
		Intranasal corticosteroid		Maintenance
Budesonide	R03BA02	ICS	**Yes**	Maintenance
		Intranasal corticosteroid		Maintenance
Flunisolide	R03BA03	ICS	**Yes**	
		Intranasal corticosteroid		
Betamethasone	R03BA04	OCS	**Yes**	
		ICS		
		Intranasal corticosteroid		
Fluticasone	R03BA05	ICS	**Yes**	Maintenance
		Intranasal corticosteroid		
Triamcinolone	R03BA06	OCS	**Yes**	
		ICS		
		Intranasal corticosteroid		
Mometasone	R03BA07	ICS	**Yes**	
		Intranasal corticosteroid		
Ciclesonide	R03BA08	ICS	**Yes**	Maintenance
		Intranasal corticosteroid		
Fluticasone furoate	R03BA09	ICS	**Yes**	Maintenance
		Intranasal corticosteroid		
Methylprednisolone, combinations	H02BX01	OCS	No	rescue
				Maintenance
Prednisolone		OCS	No	rescue
				Maintenance
dexamethasone		OCS	No	rescue
Anticholinergics	**R03BB**			
Tiotropium bromide	R03BB04	Bronchodilator	Yes	Maintenance
Tiotropium bromide, combinations	R03BB54	Bronchodilator	Yes	Maintenance
Antiallergic agents, excluding corticosteroids	**R03BC**			
Ephedrine	R03CA02	Bronchodilator	No	
Xanthines	**R03DA**			
Theophylline	R03DA04	Bronchodilator	No	maintenance
Aminophylline	R03DA05	Bronchodilator	No	maintenance
Mineralocorticoids	**H02AA**	**OCS**		
Fludrocortisone	H02AA02	OCS	No	

Desoxycortone	H02AA03	OCS	No	
Hydrocortisone		OCS	No	maintenance
Other systemic drugs for obstructive airway diseases	**R03DX**			
Amlexanox	R03DX01		No	
Eprozinol	R03DX02		No	
Omalizumab	R03DX05		No	maintenance
Seratrodast	R03DX06		No	

Source: WHO Collaborating Centre for Drug Statistics Methodology. https://www.whocc.no/
ATC: Anatomical Therapeutic Chemical DDD: defined daily dose; N/A: Not applicable

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