Protocol

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Official Title of Study: MEPOLYP: - Real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal POLYPs

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NON-INTERVENTIONAL STUDY PROTOCOL

UNIQUE IDENTIFIER	219821
TITLE	**MEPOLYP**: - Real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal **POLYP**s
STUDY ACCOUNTABLE PERSON	PPD VEO Study Delivery
CONTRIBUTING AUTHORS	GSK: PPD Syneos Health: PPD

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SPONSOR SIGNATORY

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UNIQUE IDENTIFIER	219821
ASSET ID	SB-240563

Thomas Paulsson
Head – Evidence Generation Europe

Date (DD Month YYYY)

Note: Not applicable if an eSignature process is used to get the sponsor approval.

PROTOCOL/ PROTOCOL AMENDMENT INVESTIGATOR AGREEMENT

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the marketed product and study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
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- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

Investigator Name:

_____

_____ _____

Investigator Signature Date (DD Month YYYY)

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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
ATS	American Thoracic Society
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
CRC	Clinical Research Collaboration
CRO	Contract Research Organisation
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without Nasal Polyps
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CT	Computed Tomography
DDD	Defined Daily Dose
DMP	Data Management Plan
ED	Emergency Department
EGPA	Eosinophilic Granulomatosis with Polyangiitis
ERS	European Respiratory Society
EU	European Union
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GDPR	General Data Protection Regulation
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
ICSR	Individual Case Safety Reports
IgE	Immunoglobulin E
IHD	Individual Human Data
IL-13	Interleukin-13
IL-4	Interleukin-4
IL4R	Interleukin-4 Receptor
IL-5	Interleukin-5
INCS	Intranasal Corticosteroids
IPD	Individual Patient Data
IRM	Individual Rights Management
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Muscurinic Antagonist
LTRA	Leukotriene Receptor Antagonist
MRI	Magnetic Resonance Imaging
NP	Nasal Polyps

NSAID	Non-Steroidal Anti-Inflammatory Drug
OCS	Oral Corticosteroids
PDE4	Phosphodiesterase Type 4
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
SHARP	Severe Heterogeneous Asthma Research collaboration, Patient-centred
SSAR	Swiss Severe Asthma Registry
T2	Type 2
TSLP	Thymic Stromal Lymphopoietin
UAD	United Airways Disease
UK	United Kingdom
US	United States
VEO	Value Evidence and Outcomes

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1. BACKGROUND AND RATIONALE

Asthma is a prevalent chronic inflammatory disease of the airways, defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [GINA, 2022]. The global prevalence of asthma has been estimated at 262 million people as of 2019 and has caused an estimated 455,000 deaths [GBD, 2019]. In 2019, the global prevalence estimates of asthma in people aged 5-69 years by various definitions, namely current wheezing, ever wheezing, current asthma, and ever asthma were 11.5%, 17.9%, 5.4% and 9.8%, respectively [Song, 2022]. Around 3.7% of patients with asthma have severe asthma, defined as asthmatic disease that can only be controlled with high-dose ICS in combination with a second maintenance medication and/or systemic corticosteroids, or that remains uncontrolled despite optimal therapy [Hekking, 2015; GINA, 2022].

Severe asthma is a heterogeneous condition, characterized by different clinical and physiological features [Wener, 2013]. Phenotyping of patients with severe asthma is increasingly important to enable the use of targeted therapies in addition to conventional ones. Patients with eosinophilic phenotype i.e., SEA, have been shown to have greater airway remodeling and more frequent exacerbations [Bakakos, 2019]. The number of eosinophils tends to correlate with asthma severity and the frequency of exacerbations [Vedel-Krogh, 2017].

SEA is characterized by Type 2 inflammation and patients with SEA experience recurrent asthma exacerbations even when treated with high doses of ICS and controllers including long-acting bronchodilators, LTRA and OCS. SEA patients also, generally, have high blood and sputum eosinophil levels despite receiving high-dose ICS and systemic corticosteroids [Chung, 2014]. Patients with SEA have significant morbidity including an increase in ED visits and a decrease in productivity due to missed school and workdays, which results in significant economic burden [Nunes, 2017]. This economic burden translates into high healthcare costs for both the patient and the payer. Moreover, the cost of asthma has been found to significantly increase as disease control decreases, whilst cost savings may be obtained through appropriate management of the disease [Nunes, 2017].

SEA patients have been reported to have significant comorbidities, such as CRS [Staniorski, 2018]. CRS, a disease characterized by chronic inflammation of the sinonasal tissue, affects 5.5% to 28% of the general population [Wang, 2020]. The primary phenotypes of CRS are based on the presence or absence of NP as assessed via endoscopic findings. Chronic rhinosinusitis has traditionally been classified into with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). CRSwNP is diagnosed with bilateral, endoscopically visualized polyps in middle meatus; and CRSsNP is diagnosed with no visible polyps in middle meatus [Fokkens, 2020]. CRSwNP accounts for approximately 20% of all CRS and has greater severity of clinical disease [Wang, 2020]. CRSwNP patients experience high symptom burden including loss of smell, nasal congestion, and sinus infections, which impacts physical and mental health, is associated with greater healthcare costs and a higher loss of productivity compared to the general population [Bachert, 2021]. Current treatment options for CRSwNP are limited to

intranasal and OCS, long-term antibiotics, systemic corticosteroids and surgery [Bachert, 2015].

Patients with comorbid asthma and CRSwNP have been reported to have greater asthma severity, higher recurrence rates of NP after surgery, poorer asthma control and higher treatment costs [Bachert, 2019; Bhattacharyya, 2019; Fokkens, 2020]. Increased blood eosinophil counts (BEC), airway obstruction, and inflammatory cells, as well as reduced asthma control have been reported for patients with asthma and CRSwNP compared with CRSsNP [Van Zele, 2006; Bilodeau, 2010; Bachert, 2015]. Therefore, the combination of asthma and CRSwNP provides significant treatment challenges and substantial disease burden, along with a significantly greater number of asthma exacerbations per year, which negatively impact HRQoL [Bilodeau 2010; Canonica, 2020].

CRSwNP has been reported to affect around 40% to 60% of SEA patients [Denlinger, 2017; Staniorski, 2018; Heffler, 2019; Canonica, 2020]. Core underlying pathophysiological mechanisms are shared between CRSwNP and SEA, including T2 inflammation [Bakakos, 2022]. T2 inflammation is characterized by pronounced levels of eosinophilia and high levels of IL-4, IL-5 and IL-13 cytokines [Bakakos, 2019]. IL-5 appears to have a key role in the pathogenesis of NP: (1) NP are associated with IL-5 expression; (2) the expression of IL-5 within NP tissue has been associated with asthma comorbidity, and (3) eosinophilic inflammation is associated with polyp recurrence after surgery. Consequently, IL-5 is a major target for therapeutic intervention, and previous studies with small numbers of patients have shown that inhibiting IL-5 with anti–IL-5 treatments can successfully reduce NP size [Bachert, 2015].

A relative new concept of UAD, that proposes that upper and lower airway diseases are infections of a single inflammatory process within the respiratory tract is particularly relevant in the context of multimorbidity due to SEA and CRSwNP [Domínguez-Ortega, 2023]. Therapeutic approaches in patients with UAD are mainly focused on minimizing the dose of systemic corticosteroids and increasing the use of biologics. Studies have reported the clinical benefit of biologics in upper and lower respiratory tract disease including in SEA and CRSwNP [Bachert, 2019; Han, 2021].

Mepolizumab (NUCALA™) is a humanized IL-5 antagonist monoclonal antibody indicated for the treatment of uncontrolled SEA as well as of CRSwNP. Targeting IL-5 with mepolizumab, which is a central protagonist of eosinophilic type 2 inflammation, has achieved good results in reducing asthma exacerbations as well as reduction in NP size as demonstrated in previous randomized controlled trials (RCTs) [Pavord, 2022]. The SYNAPSE trial showed that mepolizumab is effective at multiple levels, in decreasing the occurrence of nasal surgeries, use of OCS and in improving nasal symptoms [Han, 2021].

The effectiveness of mepolizumab in SEA has been demonstrated in the REALITI-A study, BSAR, REDES study, RELIght study, SSAR and RAMSES study, among others [Harrison, 2020; Kallieri, 2020; Schleich, 2020; Domingo Ribas, 2021; Fong, 2021; Jackson, 2021; Pini, 2021; Koistinen, 2022]. Whilst SEA patients have been evaluated in recent publications using a few real-world registries [Domingo Ribas, 2021; Harrison,

2020], there remains limited evidence, on the effectiveness of mepolizumab on reducing asthma exacerbations in SEA and CRSwNP comorbid patients, in a real-world setting.

The aim of this multi-country study is to assess patient characteristics as well as treatment outcomes pre- and post-mepolizumab initiation in SEA patients with or without comorbid CRSwNP from existing SEA registries (BSAR, RELight, REALITI-A, REDES, SSAR). This study will provide a more complete understanding of the value of mepolizumab in SEA patients with and without comorbid CRSwNP. This study can also provide a better understanding of the baseline characteristics of patients with multimorbid conditions and allow a more comprehensive evaluation of the effect of mepolizumab in both diseases under the UAD concept.

2. OBJECTIVES

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.

There may be inconsistencies in the diagnosis criteria of NP between registries. See Section 8 for NP diagnosis criteria through endoscopic findings, CT scans or MRI scans, which may be different across registries. As a result, this study will only descriptively compare the two cohorts and will not assess any statistical differences between the cohorts for the primary and secondary objectives. Objectives described below will be analyzed by pooling data from all registries (see Section 3.2 for additional details).

2.1. Primary objective

1. Evaluate the change of clinically significant asthma exacerbations rates defined as deterioration in asthma requiring (1) use of systemic corticosteroids and/or (2) 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.

2.2. Secondary objectives

1. Evaluate the change in rate of asthma exacerbations that required ED 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.

2.3. Exploratory objectives

The following objectives are considered exploratory as these objectives will be described dependent on the availability of the below measures and/or patients 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.
    - VAS loss of smell (Patient-reported assessment of size and symptom severity)
    - SNOT-22 (Patient-reported assessment of symptom burden on quality of life)
    - 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:
        - No asthma exacerbations during the 12-month period and
        - No OCS use for asthma during the 12-month period and
        - ACQ-5 < 1.5 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)

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 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:
    - 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:
    - Evaluate the primary objective separately for each registry.
    - Describe patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2 separately for each registry.

3. RESEARCH METHODOLOGY

3.1. 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 (BSAR, REALITI-A, REDES, RELIght, SSAR) from multiple countries. Details about the registries are provided in Section 3.2.

Objectives as described above will be assessed using the pooled 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.

The study will be overseen by Syneos Health, a CRO, on behalf of GSK.

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. Safety events will therefore not be systematically collected for the purposes of this study.

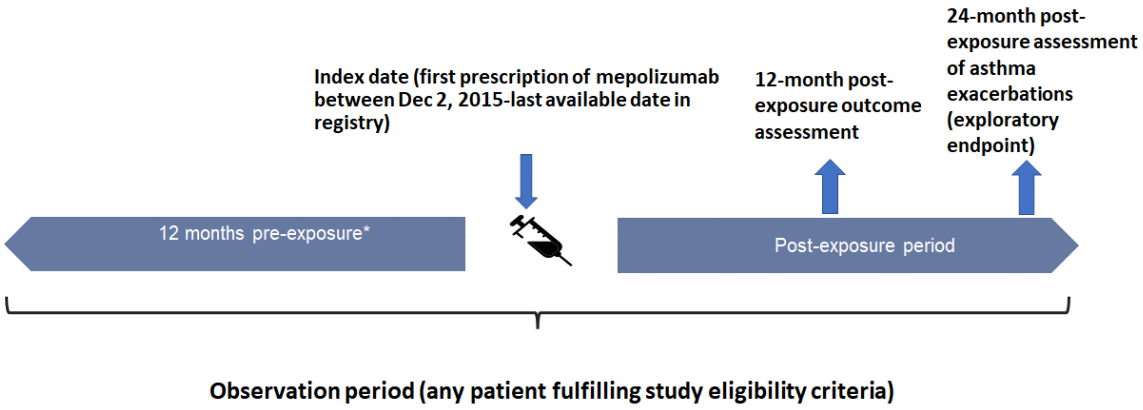
The index date for this study is defined as the first prescription record of mepolizumab during the patient identification period from December 02, 2015 (date of mepolizumab approval in the EU) till the last follow-up visit of the last patient in the registries. Follow-up will be up to 24 months post-index. Based on previous analyses, patients are expected

to have a minimum follow-up observational period of 12 months post-index. Figure 1 provides the study schematic.

Since the study time period may include the start of the COVID-19 pandemic, sensitivity analyses may be undertaken to estimate the impact of COVID-19 on primary and secondary objectives (see Section 3.9 for additional details).

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 as specified in Table 1 in Section 3.5.2. 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



3.2. Data Source / Data Collection

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

Each data source is described in detail in Section 3.2.2 below.

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.

3.2.1. Justification for selection of the data sources

The data sources considered for this study were selected for the following reasons:

1. Based on previous analyses and discussions with the registries:
   - They describe asthma exacerbations within 12 months prior and after initiation of mepolizumab (primary objective), using the same definition.
   - Blood eosinophil level is assessed and reported prior or at initiation of mepolizumab in a large majority of patients, if not all.
   - REALITI-A and REDES are two longitudinal prospective studies funded and housed by GSK, ensuring high-level of compliance with GSK requirements for this study.
   - SSAR and BSAR have been actively participating in a CRC called SHARP financially supported by the ERS that aims at harmonizing patient data from different disease registries for the purpose of data analysis.
   - Each registry has a track record of published study results arising from the analysis of their data.
2. Based on the results of the preliminary feasibility assessment:
   - They are expected to have enough information to identify patients with SEA and patients with comorbid CRSwNP.
   - They will have sufficient information on demographics, clinical characteristics, treatment regimens and secondary endpoints.

The feasibility assessment is ongoing and requests information from the data holders on the number of patients satisfying different criteria (e.g., number of patients with SEA treated with mepolizumab and with comorbid CRSwNP), data access (access to database for external parties, contracting process with the registries), availability of clinical parameters including BEC, FEV1 (% predicted), total IgE, FeNO, T2 biomarkers, comorbid CRSwNP, asthma exacerbations, patient demographics, medical procedures, treatment options, treatment-related AEs, and presence of nasal polyp-related outcomes (e.g., NPS, SNOT-22) among other information. Please see the detailed feasibility questionnaire in Section 7.

3.2.2. General description of the data sources

3.2.2.1. 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 is 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.

3.2.2.2. 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 are 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 are 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.

3.2.2.3. REDES (Spain)

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

Sites are 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 are 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 are 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].

3.2.2.4. 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 are 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 is when patients do not consent to participating in the study [Kallieri, 2022].

3.2.2.5. 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 are included in the register only after detailed information and written consent is provided. After four months (for specific therapies) and after 12 months, patients are 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, 2021].

3.2.3. Informed Consent

Consent for participation in each data source is described above, but consent in relation to this study is described here. For GSK databases (REALITI-A and Redes) in-house processes are being followed to confirm if patients have provided consent and to access data. For non-GSK databases and for two data sources (SSAR and BSAR) the teams are analyzing data themselves and will transfer aggregated data to the vendor, hence consent is not necessary. For the other non-GSK databases (Greece Relight) where individual anonymized patient data will be transferred, the vendor will be requesting registries to send only data for patients who have consented.

3.3. 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 3.4.

3.4. Eligibility Criteria

3.4.1. Inclusion Criteria

- Informed Consent (covered in Section 3.2.3 above)
- 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

3.4.2. Exclusion Criteria

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

3.5. Variables

3.5.1. Exposure definitions

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 of at least 90 days between prescriptions to align with REALITI-A study protocol [GSK document number 2016N286379_03]. Ninety days will be measured from the end of the last known prescription and/or dispensation (prescription start date plus 28 days). 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. 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.*

3.5.2. Variables to be extracted for each objective

Table 1 details the study objectives, endpoints and variable definitions and assessment time points.

Categorization details for demographic, clinical and disease characteristic variables are provided in Appendix 2 (Section 8). Additional variable definitions related to OCS burst, ED visit and hospitalization is provided in Section 8.

If multiple laboratory values for peripheral blood eosinophils are recorded, then the median of these values will be considered for analyses (median values estimated over 6 months pre-exposure and 12-months post-exposure).

Table 1 Objectives and variables extracted for each objective

No.	Primary objective	Endpoint variables	Definition	Timing of endpoint measurement
1.	Change of clinically significant asthma exacerbations rates pre- and post-exposure in cohorts 1 and 2	Asthma exacerbations (use of systemic corticosteroids and/or ED visit and/or hospital admission)	Continuous variable (See Section 8 for additional details)	Asthma exacerbations in the 12-month pre-exposure period and 12-months post-exposure period

No.	Secondary objectives	Endpoint variables	Definition	Timing of endpoint measurement
1.	Change in rate of asthma exacerbations that required ED visits/ hospitalization pre- and post-exposure in cohorts 1 and 2	Asthma exacerbations (that required an ED visit, or hospitalization)	Continuous variable (See Section 8 for additional details)	Asthma exacerbations in the 12-month pre-exposure period and 12-months post-exposure period
2.	Change in rate of asthma exacerbations that required hospitalization pre- and post-exposure in cohorts 1 and 2	Asthma exacerbations (that required hospitalization)	Continuous variable (See Section 8 for additional details)	Asthma exacerbation in the 12-month pre-exposure period and 12-months post-exposure period
3.	Compare median OCS maintenance dose, pre- and post-exposure in cohorts 1 and 2	• Dosage • Frequency • Days supplied • Cessation • Change in treatment	Continuous variable (See Section 8 for additional details)	If multiple values available, then: median daily maintenance OCS dose and total OCS maintenance dose during the pre-exposure period

		• Interruption in treatment		and the post-exposure period
4.	Compare FEV1 values pre- and post-exposure in cohorts 1 and 2	FEV1 values (in liters)	Continuous variable (See Section 8 for additional details)	Latest available value in pre-exposure period, at index date and at 6-, 12-months post-exposure period)
5.	Compare ACT pre- and post-exposure in cohorts 1 and 2	ACT scores	Continuous variable (See Section 8 for additional details)	Latest available value in pre-exposure period, at index date and at 6-, 12-months post-exposure period)
6.	Describe patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2	Demographic variables: • Age at index • Time since onset of SEA to index date (in years) • Time since onset of CRSwNP to index date (in years) (dependent on data availability) • Sex • BMI • Smoking status (Current/Former/Never smoked/Unknown) • Pack years Clinical variables: • Peripheral BEC (10^9 cells/L) • Total IgE (kU/L) • FEV1 (L) • FeNO (ppb) • T2 Biomarkers Disease variables: • *Comorbidities* ○ AERD ○ COPD ○ Diabetes ○ Churg Strauss Syndrome	See Section 8 for additional details	Demographic variables Latest available value collected at pre-exposure period or index Clinical variables Value at index. If value at index is missing, then historical value nearest to the index date 90 days prior to index will be extracted Comorbidities Any available value collected during pre-exposure period Nasal polyp-related variables Any available value

		○ EGPA ○ HES ○ CRS ▪ CRSwNP ▪ CRSsNP ○ Vasculitis ○ Gastro esophageal reflux syndrome ○ Nonsteroidal anti-inflammatory drug intolerance ○ Allergic rhinitis ○ Anxiety ○ Depression ○ Atopic dermatitis ○ Bronchiectasis ○ Eosinophilic esophagitis ○ Obesity • *Nasal polyp-related variables (dependent on data availability)* ○ Nasal polyp surgery (polypectomy) ○ Type of surgery (e.g., Functional endoscopic sinus surgery (FESS)) ○ Number and size of polyps removed ○ Surgical complications ○ Time since last surgery • *Treatment-related variables* ○ Mepolizumab treatment ○ Other Asthma/CRSwNP related treatment ○ History of previous biological treatments ○ Presence of NSAID intolerance • *Additional variables* ○ Allergy diagnosis ○ Allergic asthma diagnosis ○ Sensitization to common inhalants ○ Number of exacerbations		collected during pre-exposure period Treatment-related variables Any available value collected during pre-exposure period Additional variables (i.e., allergy diagnosis, allergic asthma diagnosis, sensitization to common inhalants) to be collected during pre-exposure period
7.	Describe pre-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled	• Dosage • Frequency	Continuous variables (See Section 8 for	If multiple values available, then: mean value, minimum, maximum and total

	treatments) pre-exposure in cohorts 1 and 2		additional details)	cumulative dose during the pre-exposure period

No.	Exploratory objectives	Endpoint variables	Definition	Timing of endpoint measurement
1.	Describe NP related outcomes pre-and post-exposure in cohort 2	• VAS loss of smell • SNOT-22 score • NPS score	Continuous variables (See Section 8 for additional details)	If multiple values available, then: latest value during 12-month pre-exposure period, and latest value during 12-month post-exposure period
2.	Describe clinical remission for patients (who achieved clinically significant exacerbation reduction), post-exposure in cohorts 1 and 2	• Asthma exacerbations • Absence of OCS use for asthma • ACQ-5 or ACT scores • FEV1 values	Continuous variables (See Section 8 for additional details on ACQ-5, ACT and FEV1)	Asthma exacerbations and/or absence of OCS use and/or ACQ-5 < 1.5 or ACT ≥ 20 and/or lung function stabilization at 12-months post-exposure period
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	• Peripheral BEC; number and percentage (10^9 cells/L)	Continuous variable	If multiple values available, then: median value during 6-months pre-exposure period and median value during 12-months post-exposure period
4.	Describe post-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled	• Dosage • Frequency	Continuous variables (See Section 8 for	If multiple values available, then: mean value, minimum, maximum and total cumulative dose collected

	treatments) in cohorts 1 and 2		additional details)	in the 12-months post-exposure period
5.	Evaluate the change in clinically significant asthma exacerbations rates pre-and post-exposure (24 months post) in cohorts 1 and 2	• Asthma exacerbations (use of systemic corticosteroids and/or ED visit and/or hospital admission)	Continuous variable (See Section 8 for additional details)	Number of asthma exacerbations in the 12-month pre-exposure period and 24-months post-exposure period
6.	Compare change in clinically significant asthma exacerbation rates from pre-and post-exposure between cohorts 1 and 2 (if cohorts are balanced)	• Asthma exacerbations (use of systemic corticosteroids and/or ED visit and/or hospital admission)	Continuous variable (See Section 8 for additional details)	Number of asthma exacerbations in the 12-month pre-exposure period and 12-month post-exposure period
7.	In preparation for future registry-level meta-analyses: ❖ Evaluate the primary objective separately for each registry ❖ Evaluate Secondary objective #6 by registry	• Variables as mentioned for primary objective and secondary objective # 6	See under primary objective and secondary objective # 6	See under primary objective and secondary objective # 6

ACT, Asthma Control Test; AERD, Aspirin Exacerbated Respiratory Disease; ACQ-5, Asthma Control Questionnaire-5; BEC, Blood Eosinophil Count; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRS, Chronic Rhinosinusitis; CRSsNP, Chronic Rhinosinusitis without Nasal Polyps; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; EGPA, Eosinophilic Granulomatosis with Polyangiitis; ER, Emergency Room; FeNO, Fractional Exhaled Nitric Oxide; FEV1, Forced Expiratory Volume in 1 second; HES, Hypereosinophilic Syndromes; ICS, Inhaled Corticosteroids; IgE, Immunoglobulin E; Computed Tomography; NPS, Nasal Polyp Score; OCS, Oral Corticosteroids; SEA, Severe Eosinophilic Asthma; SNOT-22, Sino-Nasal Outcome Test; VAS, Visual Analogue Score kU/L, 1000 units/liter; L, Liter; ppb, parts per billion

3.5.2.1. Asthma and CRSwNP Medications

Asthma medication groups will be described according to the categories listed in

Table 2. Individual drugs listed under each category, their respective ATC codes and DDD are also detailed in Appendix 2 (Section 8).

Table 2 Asthma and/or CRSwNP Medications

Category	Description
SABD	○ SABA ○ SAMA ○ Fixed Combinations of SABA/ Cromoglycate ○ Fixed Combinations of SABA/SAMA
INCS	○ Intranasal corticosteroids (INCS)
ICS and SABA/ICS	○ ICS OR ○ Fixed Combination of SABA and ICS
LABA	○ Long-Acting Beta2-Agonists
ICS/LABA	○ Fixed Combination of ICS and LABA OR ○ Open combination of ICS and LABA in two devices (LABA script overlaps with ICS by at least one day)
LAMA	○ LAMA
ICS/LAMA	○ Open combination of ICS and LAMA in two devices
LAMA/LABA	○ Fixed Combination of LABA along with a LAMA OR ○ Open combination of LABA and LAMA in two devices
ICS, LABA, LAMA	○ Fixed Combination of ICS and LABA along with a LAMA in two devices OR ○ Open combination of ICS and LABA and LAMA in three devices OR ○ Fixed combination of LABA and LAMA along with ICS in two devices OR ○ Fixed combination of ICS and LABA and LAMA
Theophylline	○ Theophylline and its derivates
Other non-biologics	○ Roflumilast (oral PDE4 inhibitor)
Oral corticosteroids	

Category	Description
Omalizumab	○ Anti-IgE
Benralizumab	○ Anti-IL5
Dupilumab	○ Anti-IL4R
Tezepelumab	○ Anti-TSLP
Reslizumab	○ Anti-IL5
Other medications for asthma/CRSwNP	

CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; ICS, Inhaled Corticosteroids; IgE, Immunoglobulin E ; IL4R, Interleukin-4 Receptor; IL-5, Intraleukin-5; 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; TSLP, Thymic Stromal Lymphopoietin

3.5.2.2. Primary Outcome: Clinically Significant Asthma Exacerbations

A reduction in asthma exacerbations will be considered clinically significant if exacerbation rates are reduced by 35% in the post-exposure period [GSK document number 2016N286379_03] .

The annualized rate of clinically significant asthma exacerbations 12- month pre- and 12-months post-mepolizumab treatment periods will be computed and described by using the information below. The definition for clinically significant asthma exacerbations according to the ERS/ATS consensus (and in order of decreasing severity) is based on presence of hospitalization or ED visits or treatment with short-term OCS or OCS-burst. The definition of clinically significant asthma exacerbations is provided in Section 8.

To assess the annualized rate of asthma exacerbations, the following information will be collected (dependent on data availability):

- Number of asthma exacerbations in the 12-month pre-exposure period (all):
  - Number that required hospitalization
  - Number that required an ED visit
  - Number that required an OCS burst
- Number of asthma exacerbations in the 12-month post-exposure period (all):
  - Number that required hospitalization
  - Number that required an ED visit
  - Number that required an OCS burst

This information will be used to calculate the annualized rate of asthma exacerbations.

3.5.2.3. Secondary Outcomes

Outcomes for secondary objectives are provided in Table 3.

For secondary objectives 1 and 2, the reduction in asthma exacerbations will be considered clinically significant if exacerbation rates are reduced by 35% in the post-exposure period [GSK document number 2016N286379_03].

For secondary objective 3, (related to median OCS maintenance dose), a conservative estimate of a 40%-60% reduction in median daily OCS maintenance dose in the post-exposure period will be considered a clinically meaningful change. This is based on the results provided in the real-world study on REDES registry where a reduction of mean daily OCS maintenance dose was reported at 50.4% and 59.9% at 6 and 12 months, respectively [Domingo Ribas, 2021].

For secondary objective 4, related to FEV1 values, a change from baseline of ≥15% in long-term trials (i.e., ≥1 year) will be considered a clinical meaningful change [Pellegrino, 2005].

For secondary objective 5, related to ACT scores, an increase in ≥3 points from baseline will be considered a clinical meaningful change [Schatz, 2009].

Table 3 Secondary objectives and outcomes

No.	Secondary Objectives	Outcome
1.	Change in asthma exacerbation rates that required ED visits/ hospitalization pre- and post-exposure in cohorts 1 and 2	• Number of asthma exacerbations requiring ED visits and/or hospitalization (pre-exposure and 12-month post-exposure period)
2.	Change in asthma exacerbation rates that required hospitalization pre- and post-exposure in cohorts 1 and 2	• Number of asthma exacerbations requiring hospitalization (pre-exposure and 12-month post-exposure period)
3.	Compare median OCS maintenance dose, pre- and post-exposure in cohorts 1 and 2	• Change in median daily maintenance OCS dose (pre-exposure to 6- and 12-month post-exposure period) • Change in total OCS dose (pre-exposure to 6- and 12-month post-exposure periods)
4.	Compare FEV1 values pre- and post-exposure in cohorts 1 and 2	• Change in FEV1 values (pre-exposure to 6- and 12-months post-exposure periods)
5.	Compare ACT scores pre- and post-exposure in cohorts 1 and 2	• Change in ACT (pre-exposure to 6- and 12-months post-exposure periods)
6.	Describe patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2	Mean [SD] (continuous variables), number [percentages] (categorical variables) for variables mentioned in Table 1

No.	Secondary Objectives	Outcome
7.	Describe pre-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) pre-exposure in cohorts 1 and 2	• Mean daily dose of OCS, ICS, inhaled treatments during the pre-exposure period • Total cumulative dose of OCS, ICS, inhaled treatments during the pre-exposure period • Frequencies of OCS, ICS, inhaled treatments usage during the pre-exposure period

ACT, Asthma Control Test; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; ER, emergency room; FEV1, forced expiratory volume in 1 second; FeNO, Fractional exhaled nitric oxide; ICS, inhaled corticosteroids; kU/L, 1000 units/liter; L, Liter; OCS, oral corticosteroids; ppb, parts per billion; SD, Standard Deviation

3.5.2.4. Exploratory Outcomes

Outcomes for exploratory objectives are provided in Table 4. Since the original registries were not designed to evaluate nasal polyp-related outcomes, the exploratory outcomes will be assessed only in registries with CRSwNP cohorts of adequate sample size.

Table 4 Exploratory objectives and outcomes

S. No.	Exploratory Objectives	Outcome
1.	Describe NP related outcomes pre- and post-exposure in cohort 2, including: • VAS loss of smell core • SNOT-22 score • NPS score	• Mean change in VAS loss of smell score from 12 months pre-exposure to 12 months post-exposure • Mean change in SNOT-22 score from 12 months pre-exposure to 12 months post-exposure • Mean change in NPS score from 12 months pre-exposure to 12 months post-exposure
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 • Number of OCS use for asthma at 12-months post-exposure • ACQ-5 < 1.5 or ACT ≥ 20, (Yes/No) assessed at end of the 12-month post-exposure period and • Lung function stabilization (no decline of lung function measured using FEV1 from pre-exposure period ≥100 mL) at 12 months post-exposure
3.	Describe the change in peripheral blood eosinophils during the post treatment period compared with 6-	• Median number (per µL) of peripheral blood eosinophils during the 6-month pre-exposure period

S. No.	Exploratory Objectives	Outcome
	month pre-mepolizumab levels in cohorts 1 and 2	• Median percentage of peripheral blood eosinophils during the 6-month pre-exposure period • Median number (per µL) of peripheral blood eosinophils during the 12-month post-exposure period • Median percentage of peripheral blood eosinophils during the 12-month post-exposure period
4.	Describe post-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) after mepolizumab initiation in cohorts 1 and 2	• Mean daily dose of OCS, ICS, inhaled treatments during the post-exposure period • Total cumulative dose of OCS, ICS, inhaled treatments during the post-exposure period • Frequencies of prescriptions for OCS, ICS, inhaled treatments during the post-exposure period
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 Number of clinically significant asthma exacerbations during the 24-month post-exposure period
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 • Number of clinically significant asthma exacerbations during the 12-month post-exposure period
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; CRS, Chronic Rhinosinusitis; ER, Emergency Room; NPS, Nasal Polyp Score; SNOT-22, Sino-Nasal Outcome Test; VAS, Visual Analogue Score

3.6. Sample Size / Power Calculations

Table 5 provides samples sizes needed to assess each objective with 80% and 90% statistical powers considering a two-sided 5% significance level.

For objectives that assume a negative binomial distribution (i.e., primary objective, secondary objectives 1 and 2), the sample size was estimated following [Zhu, 2014] as implemented in the package *PASSED* of R software (version 4.2.1).

For the primary objective, 290 patients from all registries per cohort are needed to detect, with 90% statistical power, a 35%-decrease in the asthma exacerbations rate between the

12-month pre-mepolizumab treatment period and the 12-month post-exposure period assuming a dispersion parameter of 2 and a dropout rate of 20% at the end of the pre-exposure period. The higher the dispersion parameter, the larger the sample size needed. A smaller number of patients may be required when the repeated data structure is accounted for in the analysis step.

For the other objectives (secondary objectives 3, 4, 5), a paired t-test was considered using the effect size as defined by [Cohen, 1988]. The power calculation was obtained using the package *pwr* of the R software (version 4.2.1).

Table 5 Cohort-specific sample sizes to assess a change in primary and secondary outcomes between pre- and post-exposure periods at 80% and 90% statistical powers (two-sided test)

No.	Objectives	Assumptions	Difference to be detected	Sample size (power=80%)	Sample size (power=90%)
	Primary Objective				
1.	Change of clinically significant asthma exacerbations rates pre- and post-exposure in cohorts 1 and 2	• Exacerbation rate of 4.5/year in the 12-month pre-exposure period [Domingo Ribas, 2021] • The number of exacerbations follows a negative binomial distribution with a dispersion parameter* of θ=2 (greater dispersion compared to REALITI-A where θ=0.8) • Dropout rates of 20% during the pre-exposure period • Dropouts occur at the end of the pre-exposure period	Reduction by 35% in exacerbation rate during the 12-month post-exposure period	n=216 (θ=2) Sensitivity analysis on the dispersion parameter: • n=121 (θ=1) • n=312 (θ=3)	n=290 (θ=2) Sensitivity analysis on the dispersion parameter: • n=162 (θ=1) • n=417 (θ=3)
	Secondary Objectives				
1.	Change in asthma exacerbations that required ED visits/ hospitalization pre- and post-exposure in cohorts 1 and 2	• Exacerbation rate of 1.6/year in the 12-month pre-exposure period [Domingo Ribas, 2021] • The number of exacerbations follows a negative binomial distribution with a dispersion parameter* of θ=5 (greater dispersion compared to REALITI-A where θ=3) • Dropout rates of 20% during the pre-exposure period • Dropouts occur at the end of the pre-exposure period	Reduction by 35% in exacerbation rate during the 12-month post-exposure period	n=549 (θ=5) Sensitivity analysis on the dispersion parameter • n=359 (θ=3) • n=454 (θ=4) • n=644 (θ=6) • n=739 (θ=7)	n=735 (θ=5) Sensitivity analysis on the dispersion parameter • n=481 (θ=3) • n=608 (θ=4) • n=863 (θ=6) • n=990 (θ=7)
2.	Change in asthma exacerbations that required hospitalization pre- and post-exposure in cohorts 1 and 2	• Exacerbation rate of 0.3/year in the 12-month pre-exposure period [Domingo Ribas, 2021] • The number of exacerbations follows a negative binomial distribution with a dispersion parameter* of θ=5 • Dropout rates of 20% during the pre-exposure period • Dropouts occur at the end of the pre-exposure period	Reduction by 35% in exacerbation rate during the post-exposure period	n=863 (θ=5) Sensitivity analysis on the dispersion parameter • n=676 (θ=3) • n=767 (θ=4) • n=958 (θ=6) • n=1,053 (θ=7)	n=1,160 (θ=5) Sensitivity analysis on the dispersion parameter • n=905 (θ=3) • n=1,032 (θ=4) • n=1,287 (θ=6) • n=1,415 (θ=7)

No.	Objectives	Assumptions	Difference to be detected	Sample size (power=80%)	Sample size (power=90%)
3.	Compare median OCS maintenance dose, pre- and post-exposure in cohorts 1 and 2	• SD[pre-exposure] = 10.0; SD[6-month post-exposure] = 7.3; SD[12-month post-exposure] = 6.9 [Domingo Ribas, 2021] • Correlation between pre- and post- exposure values: 0.1 (low), 0.4 (medium), 0.7 (high) • Assuming OCS maintenance follows a normal distribution	Reduction by 6.0 at 6 months Reduction by 7.0 at 12 months	Change in median OCS maintenance dose at 6 months • n=33 (low correlation) • n=23 (medium correlation) • n=14 (high correlation) Change in median OCS maintenance dose at 12 months • n=24 (low correlation) • n=17 (medium correlation) • n=11 (high correlation)	Change in median OCS maintenance dose at 6 months • n=43 (low correlation) • n=30 (medium correlation) • n=17 (high correlation) Change in median OCS maintenance dose at 12 months • n=31 (low correlation) • n=22 (medium correlation) • n=14 (high correlation)
4.	Compare FEV1 values pre- and post-exposure in cohorts 1 and 2	• Mean FEV1 during the pre-exposure period: 1.88L • SD [Change in FEV1 at 6 months] = 0.48 • SD [Change in FEV1 at 12 months] = 0.46 [Domingo Ribas, 2021]	Reduction by 15% at 6 and 12 months (1.6L)	• n=25 (at 6 months) • n=23 (at 12 months) Sensitivity analysis on the dispersion parameter at 6 and 12 months • n=18 (SD=0.4); • n=38 (SD=0.6)	• n=33 (at 6 months) • n=30 (at 12 months) Sensitivity analysis on the dispersion parameter at 6 and 12 months • n=24 (SD=0.4); • n=50 (SD=0.6)
5.	Compare ACT scores pre- and post-exposure in cohorts 1 and 2	• SD[Change in ACT score at 6 months] = 1.9; • SD[Change in ACT score at 12 months] = 1.9; [Domingo Ribas, 2021]	Increase by 3 points in mean ACT score at 3 and 12 months during the post-exposure period	n=6 (at 6 and 12 months) Sensitivity analysis on the dispersion parameter (6 and 12 months) • n=24 (SD=5) • n=58 (SD=8)	n=7 (at 6 and 12 months) Sensitivity analysis on the dispersion parameter (6 and 12 months) • n=32 (SD=5) • n=77 (SD=8)

ACT, Asthma Control Test; ER, Emergency Room; FEV1, forced expiratory volume in 1 second; OCS, oral corticosteroids; SD, Standard deviation
** A higher dispersion parameter (θ) indicates a higher dispersion/variance of the negative binomial distribution*

Table 6 provides the 95% CI (Clopper-Pearson method) for categorical baseline characteristics (secondary objectives 6 and 7) considering a range of sample sizes for a given cohort.

Ranges of samples sizes are based on preliminary results of the feasibility assessment and will be updated in the SAP in accordance with final results of the feasibility assessment. E.g., assuming that the proportion of males in the sample is 5%, the CI will vary between 2 and 11 for a sample size of 100, 2 and 10 for a sample size of 150 and so on.

Table 6 95% CI of categorical baseline characteristics

95% CI		Sample size (for a given cohort)						
		100	150	200	250	300	350	400
Proportion (in %) of patients with a given characteristic	1	0 - 5	0 - 5	0 - 4	0 - 3	0 - 3	0 - 3	0 - 3
	5	2 - 11	2 - 10	2 - 9	3 - 8	3 - 8	3 - 8	3 - 8
	10	5 - 18	6 - 16	6 - 15	7 - 14	7 - 14	7 - 14	7 - 13
	15	9 - 24	9 - 21	10 - 21	11 - 20	11 - 20	11 - 19	12 - 19
	20	13 - 29	14 - 27	15 - 26	15 - 26	16 - 25	16 - 25	16 - 24
	25	17 - 35	19 - 33	19 - 32	20 - 31	20 - 30	21 - 30	21 - 30
	30	21 - 40	23 - 38	24 - 37	24 - 36	25 - 36	25 - 35	26 - 35
	35	26 - 45	27 - 43	28 - 42	29 - 41	30 - 41	30 - 40	30 - 40
	40	30 - 50	32 - 48	33 - 47	34 - 46	34 - 46	35 - 45	35 - 45
	45	35 - 55	37 - 54	38 - 52	39 - 51	39 - 51	40 - 51	40 - 50
	50	40 - 60	42 - 58	43 - 57	44 - 56	44 - 56	45 - 55	45 - 55
	55	45 - 65	46 - 63	48 - 62	49 - 61	49 - 61	50 - 60	50 - 60
	60	50 - 70	52 - 68	53 - 67	54 - 66	54 - 66	55 - 65	55 - 65
	65	55 - 74	57 - 73	58 - 72	59 - 71	59 - 70	60 - 70	60 - 70
	70	60 - 79	62 - 77	63 - 76	64 - 76	64 - 75	65 - 75	65 - 74
	75	65 - 83	67 - 81	68 - 81	69 - 80	70 - 80	70 - 79	70 - 79
	80	71 - 87	73 - 86	74 - 85	74 - 85	75 - 84	75 - 84	76 - 84
	85	76 - 91	79 - 91	79 - 90	80 - 89	80 - 89	81 - 89	81 - 88
	90	82 - 95	84 - 94	85 - 94	86 - 93	86 - 93	86 - 93	87 - 93
	95	89 - 98	90 - 98	91 - 98	92 - 97	92 - 97	92 - 97	92 - 97
	100	96 - 100	98 - 100	98 - 100	99 - 100	99 - 100	99 - 100	99 - 100

3.7. Feasibility patient count

Based on initial feasibility counts and data from publications, Table 7 provides approximate patient counts across countries.

Table 7 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

3.8. Data management, standardization, and consolidation

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

All data sources considered for this study have sufficient information to identify patients with severe asthma and patients with CRSwNP. Based on the result of the preliminary feasibility assessment, demographics, clinical characteristics, treatment regimens, and clinical outcomes of patients with SEA are also recorded in these data sources.

Each study variable will be defined and derived based on available information in each dataset for which the IPD are available, in accordance with the variable definition included in the SAP. Any deviation from the common definition will be documented and justified in the final report.

The CRO will ensure that the same process is internally conducted by the BSAR and the SSAR registries. This will allow for the standardization of patient data and variables definitions across data sources.

After this 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 with the CRO to be included in the final results.

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.

3.9. Data Analysis Considerations

All data analyses will be performed using SAS® statistical software 9.4 or higher (SAS Institute Inc., Cary, NC), or any statistical software used by the registry holder (if the data holder prefers conducting their own analyses). Detailed methodology of statistical analyses will be documented in the SAP.

All patients who meet the eligibility criteria will be considered as the enrolled population for evaluating demographic, clinical and disease characteristics.

Patients with one dose of mepolizumab will be considered as the analysis set. Primary, secondary and exploratory objectives will be evaluated on the analysis set.

Descriptive analysis of the data will be performed using summary statistics for categorical and continuous data. Frequency tables will be generated for categorical data. Counts of missing data will be provided in all tables for information only. Percentages will not include the missing category and will be calculated from the number of patients

with available (non-missing) data. Continuous data will be described by the number of non-missing values, median, mean, SD, minimum, maximum, lower quartile (25 percentile) upper quartiles (75 percentile) and 95% CI, where applicable. Continuous variables will be described by absolute value and as change from pre-exposure period per analysis time point, if applicable.

If data is not normally distributed (e.g., distribution of blood eosinophils, total IgE), then these data may be logarithmically transformed to provide geometric means.

When applicable, comparison of categorical variables between pre-and post-exposure periods will be performed using the Chi-squared test or Fisher's exact test. Depending on distribution of variables, either a t-test (for normal distribution) or the Wilcoxon sum of ranks/Mann-Whitney U test for non-normal distributions will be considered. To test normality of data distribution, Kolmogorov-Smirnov tests may also be performed.

To determine the effect of COVID-19 on the cohorts, sensitivity analyses may be undertaken by comparing baseline characteristics between patients with an index date prior to COVID-19 (January 1, 2020) and those with an index date from December 31, 2020, onwards including a 12-month pre-exposure period during COVID-19, for the primary and secondary objectives. Additional details will be provided in the SAP.

For patients who discontinued treatment before the 6-, 12- or 24-month timepoint, their last available measurement during treatment will be used for the analyses.

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

Depending on data availability, endpoints for each registry (in the exploratory objectives) may only be described, if comparisons between cohorts are not deemed to be feasible.

Statistical analysis details will be documented in the SAP, which will be finalized and approved before the initiation of data analysis. For registries that will perform the analyses themselves rather than the CRO (i.e., will share aggregated data only for inclusion into the study report), the CRO will ensure that analyses will be conducted as specified in the study protocol and the SAP.

3.9.1. Primary Analysis

Analysis of the primary objective will be achieved by performing an analysis of the frequency of clinically significant exacerbations 12-months after the index date (initiation of mepolizumab treatment) compared to the pre-exposure period. The overall estimate will be obtained using pooled IPD data from registries who provide raw data. The overall estimate will also be derived combining registry-specific aggregated data including the BSAR and the SSAR.

All available data up to 12 months post-exposure will be included for all patients, including those withdrawing prematurely. Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. In case an ED visit results in a hospitalization, then the exacerbation will be considered as a hospitalization.

Additionally, to get a first estimate of the change in asthma exacerbation rates, an unadjusted negative binomial generalized linear model will be applied. Additional models will be developed to adjust for confounders using all available individual patient data. A variable for person-years will be included into the model as an offset (applying the logarithm function) to account for each individual follow-up. The exacerbation rate will be analyzed with time period (pre-, post-exposure), demographic variables and clinical/biomarker variables as covariates (see Table 1). The variance of the mean estimate will be corrected for within-subject correlation.

IPD-based models will also account for the clustering of patients within registries. This will allow to control for the heterogeneity across data sources. Further model specification details will be provided in the SAP.

The obtained IPD registry-specific results will be pooled with aggregated data from the BSAR and the SSAR registries using standard pooling methods like inverse variance weighting (fixed or random effects). Further details will be provided in the SAP.

3.9.2. Secondary Analyses

For each objective, the analysis will be conducted using pooled IPD data from registries that will provide IPD to the CRO. Registry-specific aggregated data including the BSAR and the SSAR will be also analyzed using standard pooling methods like inverse variance weighting (fixed or random effects). Further details will be provided in the SAP.

Change in asthma exacerbation rates that required ED visits/hospitalization between the 12-month pre-mepolizumab treatment period and the 12-month post-exposure period, after initiating mepolizumab in cohorts 1 and 2.

The number of asthma exacerbations requiring an ED visit and/or a hospital admission with an overnight stay will be collected and compared for each cohort during the pre-exposure and 12-month post-exposure periods. The proportion of patients experiencing 1 or more exacerbations requiring ED visits and/or hospitalization during the pre-exposure and 12-month post-exposure periods will also be collected and compared for each cohort.

Change in exacerbation rates requiring ED visits and/or hospitalization will be analyzed using a generalized linear model, as described for the primary objective.

Change in asthma exacerbation rates 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.

The number of asthma exacerbations requiring hospital admission with overnight stay and the length of stay will be collected and compared for each cohort during the pre-exposure and 12-month post exposure periods. The proportion of patients experiencing 1 or more exacerbation requiring hospitalization during the pre-exposure and 12-month post-exposure periods will also be collected and compared for each cohort.

Change in exacerbation rates requiring hospitalization will be analyzed using generalized linear model, as described for the primary objective.

Comparison of change in the median OCS maintenance dose, when available, between the 12-month pre-mepolizumab treatment period and the median OCS maintenance dose at 6 and at 12 months after mepolizumab initiation, in cohorts 1 and 2.

The OCS prescription and the associated dose, days supplied, and the dates of administration (start date and end date) will be captured for the pre-exposure and 6- and 12-month post-exposure periods.

The average OCS daily dose will be expressed as the prednisone equivalent dose in mg per day over a pre-defined period of time. The median daily dose of patients on maintenance OCS at baseline and in the 6- and 12-month observation period will also be compared.

The mean difference in daily dose utilization from baseline to 6-, and 12-months will be estimated by using mixed effects models for repeated measures.

Comparison of FEV1 values, when available, between the pre-mepolizumab treatment period (using the historical value nearest to the index date in the pre-exposure period) and post-exposure values after mepolizumab initiation, at 6 months and 12 months in cohorts 1 and 2.

Where available, FEV1 (in liter) will be compared using the historical values nearest to the index date in the pre-exposure period. The change from baseline in FEV1 value will be estimated as the mean difference in FEV1 at 6- and 12-months post-exposure using a mixed effects models for repeated measures.

Comparison of ACT scores, when available, between the pre-mepolizumab treatment period (using the historical score nearest to the index date in the pre-exposure period) and post-exposure values after mepolizumab initiation, at 6 months and 12 months in cohorts 1 and 2.

Where available, ACT scores will be compared using the historical score nearest to the index date in the pre-exposure period. The change from baseline in ACT score will be estimated as the mean difference in ACT scores at 6- and 12-months post-exposure using a mixed effects models for repeated measures.

Description of patient demographic, clinical and disease characteristics at initiation of mepolizumab in cohorts 1 and 2.

Summary statistics including frequency tables for categorical data and mean, median, SD, minimum, and maximum for the continuous variables will be provided for the variables defined in Table 1.

Description of pre-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) in cohorts 1 and 2.

Descriptions of treatment patterns during pre-mepolizumab treatment will be summarized including frequency tables for categorical data and mean, median, SD, minimum, and maximum for the following:

- Mean and SD of dosing and frequency (i.e., number and percentage) of use of treatments as detailed in Section 8.

3.9.3. Exploratory Analyses

For each objective, the analysis will be first conducted using pooled data from registries that will provide IPD to the CRO. Registry-specific aggregated data including BSAR and SSAR will be also analyzed using standard pooling methods like inverse variance weighting (fixed or random effects). Further details will be provided in the SAP.

Description of nasal polyps related outcomes, when available, in the 12-month pre- and post-mepolizumab treatment periods in cohort 2.

Change in VAS loss of smell, SNOT-22, and NPS scores will be estimated as the mean difference from pre-exposure to 12-months post-exposure for each score, separately. Mixed effects models for repeated measures using ordinary linear regression will be used.

These outcomes will only be analyzed for patients who have not undergone polypectomy in the 12-months pre-exposure or 12-months post-exposure period.

Description of clinical remission in cohorts 1 and 2 for those patients who have achieved clinically significant exacerbation reduction (as assessed in primary endpoint) in the 12-months post-exposure period.

Proportion of patients with clinically significant exacerbation reduction also achieving clinical remission within the 12-month post-period of mepolizumab treatment will be described in frequency tables (i.e., number and percentage of patients).

Patients will not be included if they discontinue treatment before 12 months in the post-exposure period.

Proportion of patients who do not satisfy all criteria for clinical remission will be reported and further details will be provided in the SAP.

Description of post-mepolizumab asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) in cohorts 1 and 2.

Descriptions of treatment patterns during pre-mepolizumab treatment will be summarized including frequency tables for categorical data and mean, median, SD, minimum, and maximum for the following:

Mean and SD of dosing and frequency (i.e., number and percentage) of use of treatments as detailed in Section 8.

Description of the change in peripheral blood eosinophils during the post treatment period compared with 6-month pre-mepolizumab levels in cohorts 1 and 2.

Median peripheral blood eosinophil levels in the pre-exposure period will be compared to median levels in the post-exposure levels. Any relevant cell count data available during

the post-exposure period will be also collected. Both percent of eosinophils and cells per microliter (μL) will be collected.

Two stratifications may be carried out to compare pre-exposure and post-exposure eosinophil levels: by ranges (< 150 eosinophils/μL, ≥ 150 eosinophils/μL and < 300 eosinophils/μL, ≥ 300 eosinophils/μL and < 500 eosinophils/μL and ≥ 700 eosinophils/μL at treatment initiation) and by lower thresholds (≥ 150 eosinophils/μL, ≥ 300 eosinophils/μL, ≥ 500 eosinophils/μL and ≥ 700 eosinophils/μL at treatment initiation).

Evaluating change in clinically significant asthma exacerbations rates between the 12-month pre-mepolizumab treatment and 24-month follow-up period after initiating mepolizumab in cohorts 1 and 2.

The annualized rate of clinically significant asthma exacerbations 12- month pre- and 24-month post-exposure periods will be analyzed as previously described for the primary endpoint.

Comparison of change in clinically significant asthma exacerbation rates from 12-months pre-mepolizumab treatment and 12-month post-mepolizumab initiation between cohorts 1 and 2 (if cohorts 1 and 2 are balanced in baseline characteristics)

Baseline characteristics (demographic, clinical and treatment) will be compared between cohorts 1 and 2 to see if they are statistically similar. If cohorts are considered similar, and if appropriate, difference-in-differences method will be used where annualized rate of clinically significant asthma exacerbation (pre-post) rates between cohort 1 and cohort 2 will be estimated. Summary statistics (i.e., mean, SD, 95% CI, p-value) will be estimated for the differences in annualized rate between the cohorts, if sample sizes between the cohorts is adequate.

In preparation for future registry-level meta-analysis, assessment of primary objective and secondary objective #6 to be conducted at registry-level.

Endpoints related to primary and secondary objective description of patient demographic, clinical and disease characteristics) will be assessed for each registry, separately.

3.9.4. Handling of missing data

Missing data for the primary analysis will not be imputed, and the data will be analyzed as recorded in the study; the mixed model for repeated measurements offers a simple alternative to handle missing data without requiring imputation.

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 or data imputation.

The amount of missing data may be considered negligible if less than 5% [Schafer, 1999]; however if patients with missing data differ from those with complete data, or

where data for key variables are unavailable, the resulting estimates could be biased [Little, 2002].

If the amount of missing data for any variable during pre-exposure period or post-exposure period is greater than 5%, then patterns in missing data may be examined to determine an appropriate technique to analyze the data. Missing data methods will be further defined in the SAP.

3.10. Quality control and Quality Assurance

3.10.1. Data Quality Assurance

This study will be conducted according to relevant SOPs from the CRO which will guide the correct interpretation and execution of the current study protocol, DMP and SAP to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All revisions to the study documents (e.g., protocol, DMP, SAP) will be properly documented. All study documents will undergo quality control review and senior scientific review. An independent quality check analyst will document their review of the work of the project analyst. Analysts will reach and document agreement that the study results are complete, internally consistent, and accurately reflect the source data and intended purpose of this protocol.

3.10.2. Access to Source Data/Documents

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and ethics committees to have direct access to all documents pertaining to the study.

3.10.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. All study materials will be returned to the Sponsor after the study has been completed.

Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

3.11. LIMITATIONS

Study design: This study is based on retrospective data collection, which may be subject to missing data and time-varying confounders. To minimize this, data registries in the study have a study entry criterion indicating that patients need 12 months of relevant

medical records available to be eligible for enrolment (e.g., REALITI-A study registry). The REDES study registry has participating centers with specialized dedicated asthma units to maximize the data extracted from this specific study population [Domingo Ribas, 2021]. However, limiting the patient observational period to 12 months will limit generalizability to the study findings and has the potential to introduce selection bias and immortal time bias.

Consistency between variable definition across registries: Definition of variables (e.g., identification of SEA, CRSwNP) may be inconsistent across registries, precluding a statistical comparison of SEA cohorts with and without CRSwNP.

Real-world treatment practices: Additionally, as this data is sourced from real-world registries, therapy could be discontinued or changed by the patient or physician. Patient behavior may be harder to control in real-world studies and discontinuation rates in real-world studies have been shown to be higher than those observed in clinical trials, with patient decision and lack of efficacy accounting for most treatment withdrawals. Another limitation can be the limited number of patients with detailed allergic characteristics and the recruitment at tertiary care university hospitals with potential selection bias as reported for the BSAR registry [Schleich, 2014].

Missing data bias: Increased percentages of missing data (50% or higher) for nasal polyp outcomes recorded in the registry and for outcomes recorded beyond 12 months of follow-up may increase the risk of bias in results or loss of statistical power.

Representativeness of SEA with comorbid CRSwNP population: Although the selection of the registries is planned to be as reflective of the subpopulation of CRSwNP patients initiating treatment with mepolizumab, there may be challenges in obtaining required sample sizes for comparison with the SEA-only cohort.
The purpose of the original registries was not to examine the effectiveness of mepolizumab specifically in SEA patients with comorbid CRSwNP. Instead, by using existing registries of SEA patients, this is an attempt to gain additional insights into mepolizumab on comorbid CRSwNP patients. Registries used in this study are established registries with published data focusing on outcomes pertaining to SEA patients, and therefore may not accurately record CRSwNP or CRSsNP diagnoses. As a result, the number of comorbid CRSwNP patients in the registries might be underestimated, precluding extrapolation of results.

Also, detailed methodology for summary and statistical analysis of data collected in this study will be documented in the SAP, which will be finalized, accepted and approved before the initiation of data analysis. For those registry holders that will perform the analyses themselves rather than the CRO (i.e., internally and will share aggregated data only for inclusion into the study report), the CRO will ensure that the registry investigators conduct the analyses as specified in the study protocol and the SAP. When comparing the two cohorts for the exploratory objective, differences between cohort 1 and 2 might have been underestimated due to patients with non-recorded/non-diagnosed CRSwNP or CRSsNP being included in cohort 1 and CRSsNP patients actually being CRSwNP.

The study does not compare the cohorts treated with mepolizumab with a control group (e.g., a group that is not treated with mepolizumab). As a result, caution must be exercised in interpreting the findings of studies examining pre-and post-treatment effects. Specifically, any observed associations cannot be considered causal.

4. STUDY CONDUCT, MANAGEMENT & ETHICS

This study will comply with all applicable laws regarding patient privacy. Where data has already been collected in registries, no direct subject contact or primary collection of individual human subject data will occur. Should additional patient data be required, individual consent will be obtained to use pre-existing patient data. Prior to use of any additional data, patients will consent to their data being used on the study via a consent form which has been approved by an Ethics Committee and/or Institutional Review Board and which is in compliance with GDPR and any local requirements.

Study results will be in tabular form and aggregate analyses that omits subject identification, Any publications and reports will not include subject identifiers. This study will be conducted in accordance with the Declaration of Helsinki and in compliance with the applicable laws and regulatory requirements in the countries where the study is conducted.

4.1. Legal Basis for Processing Individual Human Data

The authors confirm that study data from REALITI-A and REDES registries are IHD owned by GSK and that the study IHD use is **Further Research** (as described in VQD-STD-0004982 i.e., the use is anything other than Study Use*) **AND** The research participants consented to their IHD being processed for Further Research and have NOT submitted an IRM request that limits the use of their IHD.

* Study Use means - the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studied and the disease/condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

The authors confirm that study data from other registries including BSAR, RELight, SSAR are IHD not owned by GSK, but that the proposed use of the IHD aligns with the 'purpose of use' outlined in the source contract and/or the terms and conditions of use of the data source and will it comply with any specified prohibitions of use.

4.2. Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

Collection of adverse events/reactions

This study does not evaluate the safety of mepolizumab. Safety events will therefore not be systematically collected according to the study objectives. As an effectiveness study the study outcomes are effectiveness endpoints that will not be collected and reported as safety events.

Study type 6: Secondary data collection studies including unstructured data with human review without safety objectives. An example is human review of verbatim text in a medical record as part of a chart review study.	*These studies will not identify solicited events as per study objective and cannot identify spontaneous events*

Definitions of Solicited and Spontaneous Events

Solicited events are defined as those adverse events related to the GSK/ViiV product under evaluation and identified for collection in the study database as per study objectives.

Solicited events must be collected in the study database and reported to GSK for entry into the GSK Safety database. Onward reporting to regulators, in the form of Individual Case Safety Reporting (ICSR)s, is only applicable for primary data collection studies (further information below). For secondary data collection studies, information on solicited events will be contained in the study report.

Spontaneous events are defined as:

- Those unsolicited AEs observed related to the GSK product under evaluation but exempted from collection, as justified in the protocol. (Only applicable to studies capturing solicited events).
- Those AEs observed related to any GSK product not under evaluation in the study.
- Any Adverse Drug Reactions observed related to non-GSK product(s), for which the ADRs should be reported to the appropriate marketing authorization application of the product(s) or Health Authority per local regulations.

Spontaneous events are not collected in the study database BUT are still reported to GSK for entry in the GSK Safety database.

Collection of adverse events/reactions (Solicited Events)

The study outcomes are endpoints unrelated to safety that will not be collected and reported as safety events.

Reporting of adverse events/reactions (Spontaneous Events)

This study is based on data previously collected for other purposes e.g., routine healthcare encounters. As such, there is no requirement for the collection and reporting

of ICSRs Although the study is based on human review of unstructured data, the nature of the secondary data protocol driven data collection and analysis does not allow for reporting of serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK/ViiV product during the conduct of this research. In addition, the minimum criteria of identifiable patient, reporter, exposure and event, needed to report individual case safety reports may not be present in the information reviewed within the context of the study. The data also may lack an identifiable patient and reporter and may be insufficient to establish attribution between a potential safety event and an individual patient using a GSK/ViiV product.

This study is based on secondary use of existing health data and as such Individual Case Safety Reporting to regulatory agencies is not required.

5. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Upon finalization of the study reports and completion of the study, the Sponsor intends to use study data to prepare publication for submission to peer-reviewed journals and other scientific communications, such as abstracts, posters, and oral presentations. All publications will comply with the International Committee of Medical Journal Editors guidelines.

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7. APPENDIX 1: FEASIBILITY QUESTIONNAIRE FOR DATA REGISTRY HOLDERS

Questions

Database access

[Access] Do you agree to provide Syneos Health with access to the data directly for analysis?

☐ YES

☐ NO

If NO, is your registry willing to perform analyses and provide summary tables with results?

☐ YES

☐ NO

Please explain:

[Process] What is the contracting process required for your institution and associated timelines?

Please describe:

[Timelines] Once protocol has been approved and contracting completed, what are the data access timelines?

months

[Transfer] Do you have specific data transfer and storage processes or requirements you would like us to follow?

☐ YES Please explain:

☐ NO

Data contents

Population

Suggestion of criteria to select the population of interest i.e., patients with severe eosinophil asthma at initiation of mepolizumab:

A patient will be eligible for inclusion in this study if all of the following criteria apply:

Informed Consent: Prior to commencing any study related activities, participants must be able and willing to provide written informed consent.

Participants must have a current clinical diagnosis of asthma.

Physician decision to initiate treatment with NUCALA.

Data available for at least 12-months prior to enrolment date (i.e. mepolizumab initiation).

Adults aged 18 years or over.

[Severe eosinophil asthma definition] Are blood eosinophil levels systematically reported within 12 months prior or at initiation of mepolizumab?

☐ YES

☐ NO

Please describe:

[Patients with CRSwNP] Does the registry have enough elements to identify patients with comorbid chronic rhino sinusitis with nasal polyps (CRSwNP)?

☐ YES

☐ NO

Please describe approximate % of CRSwNP comorbid patients in your cohort:

Sample size

Could you please provide some preliminary patient counts:

Patients with severe eosinophilic asthma with mepolizumab:

N=

With pre-mepolizumab treatment period ≥ 12 months N=

Among them:

With post-initiation follow-up (FU) periods ≥ 12 months N=

With post-initiation FU periods ≥ 24 months N=

Patients with severe eosinophilic asthma with CRSwNP treated with mepolizumab

N=

With pre-mepolizumab treatment period ≥ 12 months N=

Among them:

With post-initiation FU periods ≥ 12 months N=

With post-initiation FU periods ≥ 24 months N=

Treatment

[Treatment] Do the data allow for a detailed description of treatment lines with dates (start, end), product information, dose at initiation, dose changes and reason for withdrawal?

☐ YES

☐ NO

Please describe:

[Treatment withdrawal] Is treatment withdrawal within 12 months after initiation of mepolizumab well documented (date, reason of withdrawal)?

☐ YES

☐ NO

Please describe:

Secondary Outcomes

[FEV1] Does the registry allow to describe FEV1 at initiation of mepolizumab, and at 6 months and 12 months after initiation? *[Note: at initiation here would mean there is a test value recorded within 90 days preceding mepolizumab initiation]*

☐ YES

☐ NO

Please describe:

[Asthma exacerbations] Do the data allow to describe asthma exacerbations requiring hospitalization and/or an emergency department (ED) visit, within 12 months prior and after initiation of mepolizumab?

☐ YES

☐ NO

Please describe:

[ACT score] Will it be possible to describe ACQ-5 < 1 or ACT ≥ 20 scores at initiation of mepolizumab, at 6 and 12 months after treatment initiation? *[Note: at initiation = with a test value within 90 days preceding initiation of the treatment]*

Please describe:

[Adverse events] Do the data allow a comprehensive description of treatment-related adverse events, with dates and clear identification of events?

☐ YES

☐ NO

[Quality of life] Will it be possible to describe quality of life at initiation of mepolizumab and at 6 and 12 months after treatment initiation?

☐ YES

☐ NO

If yes, please specify the Health-Related Quality of Life questionnaire used?

Exploratory outcomes

Potential exploratory outcomes:

NP related outcomes in the 12-month pre and post mepolizumab initiation period in cohort 2, including: Nasal Congestion/Obstruction (NC) Score, Bilateral Endoscopic Nasal Polyp Score (NPS), Daily Loss of Smell, University of Pennsylvania Smell Identification Test (UPSIT), Sino-Nasal Outcome Test (SNOT-22), Lund-Mackay Computed Tomography (LMK-CT).

Clinically remission expressed as:

No asthma exacerbations during the 12-month period,

No OCS (burst or maintenance) use for asthma during the 12-month period,

ACQ-5 < 1 or ACT≥20, assessed at end of 12-month period,

Lung function stabilisation (no decline of FEV1 from baseline ≥-100 observed at 12 months.

To describe the change in peripheral blood eosinophils during the post treatment period compared with initial levels.

[NP-related outcomes] Will it be possible to describe the following NP-related outcomes at initiation of mepolizumab and at 6 and 12 months after mepolizumab initiation? (Please select all that apply)

☐ Nasal Congestion/Obstruction (NC) Score

☐ Bilateral Endoscopic Nasal Polyp Score (NPS)

☐ Daily Loss of Smell Please describe (e.g. VAS):

☐ University of Pennsylvania Smell Identification Test (UPSIT)

☐ Sino-Nasal Outcome Test (SNOT-22)

☐ Lund-Mackay Computed Tomography (LMK-CT)

☐ Other Please describe:

Data to define baseline characteristics of interest

Do the data in your cohort allow a comprehensive description of the patient demographic, clinical and disease characteristics at initiation of mepolizumab (please tick all that apply):

☐ Body Mass Index (kg/m2)

☐ Pre/post bronchodilator FEV1 (%pred)

☐ Blood eosinophil count (10^9 cells/L)

☐ Smoking habits (current smoker, previous smoker, non-smoker)

☐ Pack years (n)

☐ Total IgE (kU/L)

☐ FeNO (ppb)

☐ Year since diagnosis

☐ T2 Biomarkers

☐ Chronic rhinosinusitis (CRS) and asthma onset

☐ Nasal polyps

☐ Non-steroidal anti-inflammatory drug (NSAID) intolerance

☐ Sensitisation to common inhalants

☐ Type of ongoing nasal therapies

☐ Oral corticosteroids (OCS) maintenance (mg/day)

☐ Daily OCS dose (mg/day)

☐ History of previous biological treatments

☐ History of sinonasal surgeries

☐ Frequent exacerbations (≥2/year)

☐ Comorbidities (COPD, Diabetes….)

Please describe:

Ethic committee submission

Does this study require a (re-)submission to an ethic committee (EC)? If so, what are the steps and related timelines?

☐ YES Please describe:

☐ NO

Language

Are there key information/variables in the database reported in native language?

☐ YES

☐ NO

8. APPENDIX 2: VARIABLE DEFINITIONS

Diagnosis of 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

Mepolizumab prescription

- Identified using medication code R03DX09 (100 mg subcutaneous every 4 weeks for SEA) OR
- any other specific criterion that the registries use to identify medications

Treatment-related variables

- Mepolizumab treatment
    - 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)

- Other asthma/CRSwNP treatment
    - Dosage (pre-exposure period, at index date and at 6-,12 months post-exposure period)
    - Frequency (pre-exposure period, at index date and at 6-,12 months post-exposure period)
    - Days supplied (pre-exposure period and post-exposure period)
        - Days supplied will be calculated as number of doses in the prescription by the number of doses per day
    - Cessation (pre-exposure period, at index date and at 6-,12- months post-exposure period)
    - Change in treatment (pre-exposure period, at index date and at 6-,12-months post-exposure period)
    - Interruption in treatment (pre-exposure period, at index date and at 6-,12-months post-exposure period)

- Presence of NSAID intolerance (yes/no)
- History of previous biological treatments (yes/no)

List of asthma treatments:

Treatment	ATC Code	DDD	Dosage form
Obstructive airway diseases (Asthma)	R03		
Adrenergics, Inhalants	*R03A*		
Alpha-and beta-adrenoreceptor agonists	R03AA	N/A	N/A
Epinephrine	R03AA01	2.24 (mg) 20 (mg)	Inhal.aerosol Inhal.solution
Non-selective beta-adrenoreceptor agonists	*R03AB*		
Isoprenaline	R03AB02	0.64 (mg) 10 (mg)	Inhal.aerosol Inhal.solution
Orciprenaline	R03AB03	6 (mg)	Inhal.aerosol
Selective beta-2-adrenoreceptor agonists	*R03AC*	N/A	N/A
Salbutamol	R03AC02	0.8 (mg) 0.8 (mg) 10 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Terbutaline	R03AC03	10 (mg) 10 (mg) 20 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Fenoterol	R03AC04	0.6 (mg) 0.6 (mg) 4 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Rimiterol	R03AC05	1.6 (mg)	Inhal.aerosol
Hexoprenaline	R03AC06	1.5 (mg)	Inhal.aerosol
Isoetarine	R03AC07	N/A	N/A
Pirbuterol	R03AC08	N/A	N/A
Tretoquinol	R03AC09	1.2 (mg)	Inhal.aerosol
Carbuterol	R03AC11	1.6 (mg)	Inhal.aerosol
Tulobuterol	R03AC12	0.1 (mg) 0.1 (mg)	Inhal.aerosol Inhal.powder
Formoterol	R03AC13	24 (mcg) 24 (mcg)	Inhal.aerosol Inhal.powder
Clenbuterol	R03AC14	N/A	N/A
Reproterol	R03AC15	N/A	N/A
Procaterol	R03AC16	60 (mcg)	Inhal.aerosol
Bitolterol	R03AC17	N/A	N/A
Indacaterol	R03AC18	0.15 (mg)	Inhal.powder
Olodaterol	R03AC19	5 (mcg)	Inhal.solution
Combinations of adrenergics	*R03AH*	N/A	N/A
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	*R03AK*	N/A	N/A
Epinephrine and other drugs for obstructive airway diseases	R03AK01	N/A	N/A
Isoprenaline and other drugs for obstructive airway diseases	R03AK02	N/A	N/A

Treatment	ATC Code	DDD	Dosage form
Salbutamol and sodium cromoglicate	R03AK04	N/A	N/A
Reproterol and sodium cromoglicate	R03AK05	N/A	N/A
Salmeterol and fluticasone	R03AK06	N/A	N/A
Formoterol and budesonide	R03AK07	N/A	N/A
Formoterol and beclometasone	R03AK08	N/A	N/A
Formoterol and mometasone	R03AK09	N/A	N/A
Vilanterol and fluticasone furoate	R03AK10	N/A	N/A
Formoterol and fluticasone	R03AK11	N/A	N/A
Salmeterol and budesonide	R03AK12	N/A	N/A
Salbutamol and beclometasone	R03AK13	N/A	N/A
Indacaterol and mometasone	R03AK14	N/A	N/A
Adrenergics in combination with anticholinergics including triple combinations with corticosteroids	*R03AL*	N/A	N/A
Fenoterol and ipratropium bromide	R03AL01	N/A	N/A
Salbutamol and ipratropium bromide	R03AL02	N/A	N/A
Vilanterol and umeclidinium bromide	R03AL03	N/A	N/A
Indacaterol and glycopyrronium bromide	R03AL04	N/A	N/A
Formoterol and aclidinium bromide	R03AL05	N/A	N/A
Olodaterol and tiotropium bromide	R03AL06	N/A	N/A
Formoterol and glycopyrronium bromide	R03AL07	N/A	N/A
Vilanterol, umeclidinium bromide and fluticasone furoate	R03AL08	N/A	N/A
Formoterol, glycopyrronium bromide and beclometasone	R03AL09	N/A	N/A
Formoterol and tiotropium bromide	R03AL10	N/A	N/A
Formoterol, glycopyrronium bromide and budesonide	R03AL11	N/A	N/A
Indacaterol, glycopyrronium bromide and mometasone	R03AL12	N/A	N/A
Other drugs for obstructive airway diseases, inhalants	*R03B*	N/A	N/A

Treatment	ATC Code	DDD	Dosage form
Glucocorticoids	*R03BA*	N/A	N/A
Beclometasone	R03BA01	0.8 (mg) 0.8 (mg) 1.5 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Budesonide	R03BA02	0.8 (mg) 0.8 (mg) 1.5 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Flunisolide	R03BA03		
Betamethasone	R03BA04		
Fluticasone	R03BA05	0.6 (mg) 0.6 (mg) 1.5 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Triamcinolone	R03BA06		
Mometasone	R03BA07		
Ciclesonide	R03BA08	0.4 (mg)	Inhal.powder
Fluticasone furoate	R03BA09	1.6 (mg)	Inhal.aerosol
Anticholinergics	*R03BB*	N/A	N/A
Ipratropium bromide	R03BB01	N/A	N/A
Oxitropium bromide	R03BB02	N/A	N/A
Stramoni preparations	R03BB03	N/A	N/A
Tiotropium bromide	R03BB04	N/A	N/A
Aclidinium bromide	R03BB05	N/A	N/A
Glycopyrronium bromide	R03BB06	N/A	N/A
Umeclidinium bromide	R03BB07	N/A	N/A
Revefenacin	R03BB08	N/A	N/A
Tiotropium bromide, combinations	R03BB54	N/A	N/A
Antiallergic agents, excluding corticosteroids	*R03BC*	N/A	N/A
Cromoglicic acid	R03BC01	40 (mg) 40 (mg) 80 (mg)	Inhal.aerosol Inhal.powder Inhal. solution
Nedocromil	R03BC03	8 (mg)	Inhal.aerosol
Other drugs for obstructive airway diseases, inhalants	R03BX	N/A	N/A
Fenspiride	R03BX01	N/A	N/A
Adrenergics for systemic use	*R03C*	N/A	N/A
Alpha- and beta-adrenoreceptor agonists	*R03CA*	N/A	N/A
Ephedrine	R03CA02	50 (mg)	
Non-selective beta-adrenoreceptor agonists	*R03CB*	N/A	N/A
Isoprenaline	R03CB01	40 (mg)	
Methoxyphenamine	R03CB02	0.4 (g)	
Orciprenaline	R03CB03	60 (mg)	
Isoprenaline, combinations	R03CB51	N/A	N/A
Orciprenaline, combinations	R03CB53	N/A	N/A
Selective beta-2-adrenoreceptor agonists	*R03CC*	N/A	N/A
Salbutamol	R03CC02	12 (mg)	
Terbutaline	R03CC03	15 (mg)	

Treatment	ATC Code	DDD	Dosage form
Fenoterol	R03CC04	10 (mg)	
Hexoprenaline	R03CC05	1.5 (mg)	
Isoetarine	R03CC06	40 (mg)	
Pirbuterol	R03CC07	30 (mg)	
Procaterol	R03CC08	0.1 (mg)	
Tretoquinol	R03CC09	9 (mg)	
Carbuterol	R03CC10	6 (mg)	
Tulobuterol	R03CC11	4 (mg)	
Bambuterol	R03CC12	20 (mg)	
Clenbuterol	R03CC13	40 (mcg)	
Reproterol	R03CC14	N/A	N/A
Formoterol	R03CC15	0.16 (mg)	
Terbutaline, combinations	R03CC53	N/A	N/A
Clenbuterol and ambroxol	R03CC63	N/A	N/A
Xanthines	*R03DA*	N/A	N/A
Diprophylline	R03DA01	1 (g)	
Choline theophyllinate	R03DA02	0.6 (g)	
Proxyphylline	R03DA03	1.2 (g)	
Theophylline	R03DA04	0.4 (g)	
Aminophylline	R03DA05	0.6 (g)	
Etamiphylline	R03DA06	N/A	N/A
Theobromine	R03DA07	N/A	N/A
Bamifylline	R03DA08	N/A	N/A
Acefylline piperazine	R03DA09	N/A	N/A
Bufylline	R03DA10	N/A	N/A
Doxofylline	R03DA11	0.8 (g)	
Mepyramine theophyllinacetate	R03DA12	N/A	N/A
Combinations of xanthines	R03DA20	N/A	N/A
Diprophylline, combinations	R03DA51	N/A	N/A
Theophylline, combinations excl. psycholeptics	R03DA54	N/A	N/A
Aminophylline, combinations	R03DA55	N/A	N/A
Theobromine, combinations	R03DA57	N/A	N/A
Theophylline, combinations with psycholeptics	R03DA74	N/A	N/A
Xanthines and adrenergics	*R03DB*	N/A	N/A
Diprophylline and adrenergics	R03DB01	N/A	N/A
Choline theophyllinate and adrenergics	R03DB02	N/A	N/A
Proxyphylline and adrenergics	R03DB03	N/A	N/A
Theophylline and adrenergics	R03DB04	N/A	N/A

Treatment	ATC Code	DDD	Dosage form
Aminophylline and adrenergics	R03DB05	N/A	N/A
Etamiphylline and adrenergics	R03DB06	N/A	N/A
Other systemic drugs for obstructive airway diseases	*R03DX*	N/A	N/A
Amlexanox	R03DX01	N/A	N/A
Eprozinol	R03DX02	N/A	N/A
Fenspiride	R03DX03	N/A	N/A
Omalizumab	R03DX05	16 (mg)	
Seratrodast	R03DX06	N/A	N/A
Roflumilast	R03DX07	0.5 (mg)	N/A
Reslizumab	R03DX08	7.1 (mg)	N/A
Mepolizumab	R03DX09	3.6 (mg)	N/A
Benralizumab	R03DX10	0.54 (mg)	N/A
Tezepelumab	R03DX11	N/A	N/A
Corticosteroids for systemic use	*H02*	N/A	N/A
Mineralocorticoids	*H02AA*	N/A	N/A
Ludrocortisone	H02AA02	0.1 (mg)	N/A
Desoxycortone	H02AA03	5 (mg)	N/A
Methylprednisolone, combinations	H02BX01	N/A	N/A
Trilostane	H02CA01	0.36 (g)	N/A
Osilodrostat	H02CA02	N/A	N/A
Ketoconazole	H02CA03	0.6 (g)	N/A
Levoketoconazole	H02CA04	N/A	N/A

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

Demographic variables

Demographic variables will be categorized as below:

- Age: continuous variable (years)
- Sex at birth: categorical variable (male, female, unknown, other)
- Physical examination: weight, height, BMI (kg/m^2) (calculated using weight and height)
- Smoking status: categorical variable
  - Smoker: number of packs/year
  - Ex-smoker: number of packs/year
  - Non-smoker
  - Passive smoking
  - Unknown

Nasal polyp-related variables

Nasal polyp-related variables that may be collected (dependent on feasibility data results):

- NPS score:

  - 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:
  - Scores ranging from no smell (“0”) to normal smell (“10”) (continuous variable) [Prajapati, 2021]
- SNOT-22 score :
  - 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)

Other Variables

The 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. ACT scores will be extracted from the pre-exposure period and at the 6-, 12- months post-exposure period [American Thoracic Society, 2023].

ACQ-5 score: 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].

FEV1 score: 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 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 [Barreiro, 2004].

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.

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

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, 2018].

Clinically significant asthma exacerbation

The definition for clinically significant asthma exacerbations according to the European Respiratory Society/American Thoracic Society consensus (and in order of decreasing severity) is:

Hospitalization definition: any asthma-related referral or hospitalization with a discharge diagnosis of asthma; OR another criterion as specified by the registry;

ED visit definition: any record of an ED visit related to an asthma diagnosis code; OR another criterion as specified by the registry;

OCS-definition: Treatment with short-term OCS, a so-called OCS burst for ≥3 days, but ≤28 days (or 4 weeks) with an asthma exacerbation code recorded within ±2 weeks. For maintenance OCS users, increase of the prescribed dose by at least 2 times, for ≥3 days, but ≤28 days (or 4 weeks) with asthma exacerbation code recorded within ±2 weeks. All other OCS therapy use will be considered maintenance therapy or non-asthma related.

Asthma exacerbations occurring within 7 days of each other will be considered a single episode. All these categories of asthma exacerbations are considered as clinically significant for the patient.

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