Study Protocol

Associations between biological and clinical response following treatment with anti-IL5/5R biologics (FLAME)

A study of changes in blood eosinophil count, FEV_1 and exacerbations and factors related to these, following initiation of treatment with anti-IL5/5R biologics in severe asthma patients

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TITLE	**Associations between biological and clinical response following treatment with anti-IL5/5R biologics**
Subtitle	Not applicable
Protocol version number	V1.2
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Product code	Not applicable
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Marketing authorisation number	Not applicable
Study aims and objectives	**Aim:** To identify and describe patient characteristics associated with biological and/or clinical treatment failure at different times after initiation of anti-IL5/5R biologics and the extent to which these are linked or independent events. **Objective 1:** Test for associations between changes in BEC and changes in FEV_1 and exacerbations (compared to their baseline values) one year after biologic initiation, and to identify factors that modify these associations or explain the remaining variability **Objective 2:** Describe patterns of change over time in BEC, FEV_1 and exacerbations following initiation of anti-IL5/5R treatments **Objective 3:** Test for associations between baseline patient characteristics and different patterns of change over time in BEC and/or FEV_1 and exacerbations following initiation of anti-IL5/5R BEC - blood eosinophil count; FEV_1 - forced expiratory volume in 1 second
Countries of study	Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, France, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, Spain, Taiwan, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA)
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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency
BEC	Blood eosinophil count
BMI	Body mass index
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FVC	For
GINA	Global INitiative for Asthma
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL5	Interleukin 5
IL5R	Interleukin 5 receptor
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-Acting Beta-Agonists
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
LTOCS	Long-term oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute

1.0 Background

Asthma is a chronic inflammatory disorder of the airways affecting approximately 262 million people worldwide and the cause of 455 000 deaths in 2019 [1]. Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled [2]. It has been estimated that around 3-10% of people with asthma have severe asthma [2]. However, severe asthma is a heterogeneous disease consisting of multiple phenotypes. In recent years phenotype-targeted biologic therapies are increasingly showing efficacy [3].

Eosinophils affect the severity of asthma through their role in tissue damage and airway remodelling, inflammatory response, and hyperresponsiveness [4, 5]. The deleterious effect of a high blood eosinophil count is therefore a combination of both permanent and reversible effects. High blood eosinophil counts are associated with faster decline in FEV_1 [6] and greater exacerbation rates in asthma patients [7, 8].

Anti-IL5 biologics target the IL5 cytokine or its receptor thereby interfering with the production and/or survival of eosinophils in the blood and have been shown to reduce exacerbation rates [9, 10, 11, 12] and increase FEV_1 [10, 11]. The half life of blood eosinophils is around 18 hours [13], therefore decreases in blood eosinophils are often seen quickly (within the first few months) after initiating biologics [14, 15]. The effects are sustained over long periods while the patient remains on treatment [16, 17]. Bel et al [18] observed a very rapid decrease in the occurrence of exacerbations in a cohort of patients treated with mepolizumab. FEV_1 can also improve within the first 3 months following initiation of anti-IL5 [19]. Given the important role that IL5 cytokines play in the production of eosinophils and the known associations between eosinophil levels and clinical outcomes, it might be expected that a decrease in blood eosinophils following initiation of anti-IL5/5R biologics (biological response) would correspond to improvement in FEV_1 and decreased exacerbation rates. However, perfect correlation will only occur if there is a direct causal link. Describing the strength of these links, and factors which confound or mediate them, is the focus of this study. Denton et al [36] found that 40-50% of a cohort of biologics initiators (of which 59% initiated anti-IL5/5R) showed sub-optimal response in FEV_1 and exacerbation rates [36], demonstrating the need for greater understanding of the determinants of successful treatment with biologics.

A number of factors can affect patients' response to treatment including comorbid conditions [20, 21, 22], severity of disease at biologic initiation [23, 24], and age of asthma onset [5, 23]. The improvement in FEV_1 is greater in patients with high pre-biologic levels of BEC [14, 23].

Clinical trials have found that the difference in follow-up exacerbation rates with anti-IL5/5R compared to a placebo group is also greater in patients with high levels of baseline BEC. However, this difference was largely due to greater exacerbation rates with high levels of BEC in the placebo group [25, 26]. When the effect of biologic treatment was evaluated as the change from a patient's baseline level, although all biologics led to substantial decreases in exacerbation rates, no association was found between baseline BEC and the change in exacerbations [14]. Pavord et al [27] also found no association between change in BEC and decrease in exacerbation rate following initiation of dupilumab.

Response to biologics in terms of biomarkers and clinical outcomes depends partly on baseline levels of these factors [28]. Therefore, patients with a high percent predicted FEV_1 at baseline are unlikely to show a large absolute improvement in FEV_1 following biologic initiation. Similarly, patients with low exacerbation rates before initiating biologics can have only a modest absolute decrease in this outcome. Baseline levels of outcomes must, therefore, be taken into account when assessing the response to biologic treatments. The absolute change in biomarkers is also related to their pre-biologic levels. In patients on long-term oral corticosteroids (LTOCS) the decrease in BEC may be less pronounced because LTOCS suppresses BEC levels at baseline [29, 30].

A number of studies have examined baseline patient characteristics and biomarkers predictive of good response to biologics, usually around six months or one year after initiation of the drug [31]. However, relatively little is known about the timing of and reasons for changes in clinical and biological response to biologics over time after biologic initiation, particularly at the individual patient level. In some patients, the response of biomarkers to biologics is either poor or decreases over time. This may be due to poor adherence but can also be due to development of resistance to the drug through development of anti-drug antibodies [32]. The improvement in clinical outcomes may also diminish over time due to progression of the disease, change in the inflammatory endotype, or other comorbidities developing [33].

Although biologics have been shown to be very effective drugs for improving outcomes in severe asthma, there is wide variation in response of individual patients often leading to switching of biologics [34]. Further information from the post-initiation phase of biologics treatment could help to predict which patients will have the best long-term response and which biomarkers or other characteristics should be monitored during patient follow-up. This could help in early identification of patients who should switch or stop biologics or to suggest other interventions that may improve the efficacy of the current treatment.

This study will consider biological response (changes in BEC) and clinical response (changes in FEV_1 and exacerbations) following initiation of anti-IL5/5R treatments and the associations between the changes in biomarker and clinical outcomes over time in individual patients. Focussing on a single biologic and a limited set of outcomes will allow us to study these relationships in detail, perhaps suggesting useful approaches to study other biologics and outcomes subsequently.

2.0 Study Aims and Objectives

2.1 Study Aims

To identify and describe patient characteristics associated with biological and/or clinical treatment failure at different times after initiation of anti-IL5/5R biologics and the extent to which these are linked or independent events.

The study will reveal whether biological and/or clinical failure of anti-IL5/5R treatments in the short or long term can be predicted from patient characteristics known pre-biologic initiation, or whether subsequent failure can be predicted from early follow-up data. This information will help clinicians in selecting the best treatment for patients and provide important evidence on the information that should be collected before and after biologic initiation.

2.2 Study Objectives

Objective 1: Test for associations between changes in BEC and changes in FEV_1 and exacerbations (compared to their baseline values) one year after biologic initiation, and to identify other factors that modify these associations or explain the remaining variability

- Preliminary work has shown an association between changes in BEC and changes in FEV_1. Other factors may explain residual unexplained variation in this association (e.g. high baseline percent predicted FEV_1 might limit the potential improvement in FEV_1) or may substantially change the association (e.g. long-term oral corticosteroid (LTOCS) use might reduce levels of BEC at baseline). The association between change in BEC and change in exacerbation rate will be investigated in a similar way.

Objective 2: Describe patterns of change over time in BEC, FEV_1 and exacerbations following initiation of anti-IL5/5R treatments

- For patients with sufficient longitudinal data, patterns of change in BEC and FEV_1 over time will be described and patients will be classified according to biologically or clinically relevant patterns of change. Groups with poor initial response in BEC or FEV_1, or with an initial strong response which later diminishes, will be of particular interest. Changes in exacerbation rate over time will also be investigated and related to changes in BEC over time if temporal variations in follow-up exacerbation rates are detected in the data.

<u>Objective 3</u>: Test for associations between baseline patient characteristics and different patterns of change over time in BEC and/or FEV_1 and exacerbations following initiation of anti-IL5/5R

- This objective will use the groups identified in objective 2 and is intended to look for identifiable characteristics of patients who are likely to have short term or long term failure of the biologic treatments.

3.0 Study Design

This study is a registry-based cohort study. The study consists of pre-biologic (baseline) and post-biologic (follow-up) periods.

Variables describing the patient baseline demographic and clinical characteristics are obtained during pre-biologic visits, prior to or on the biologic treatment initiation date. Patient baseline characteristics are available at biologic initiation (e.g. age and long-term OCS use), in the year preceding biologic initiation (e.g. count of exacerbation episodes), or at any time pre-biologic initiation (e.g. highest recorded blood eosinophil count and presence of comorbidities). For FEV_1 the most recent recorded value before or at biologic initiation will be used. Follow-up data are recorded at any visits post-biologic initiation, which are generally at approximately 1-year intervals, but may be more or less frequent depending on the practice at individual sites.

For objective 1 (analysis of changes in outcomes and biomarkers at 1-year post-biologic initiation) FEV_1 and exacerbations data will be used from the follow-up visit closest to 1-year, with a minimum of 24 weeks after biologic initiation for FEV_1 and a minimum of 48 weeks after initiation for exacerbations. The BEC result closest to 1-year post-biologic initiation will be used, with no minimum time limit, in order to include as many patients as possible in this analysis (Figure 1).

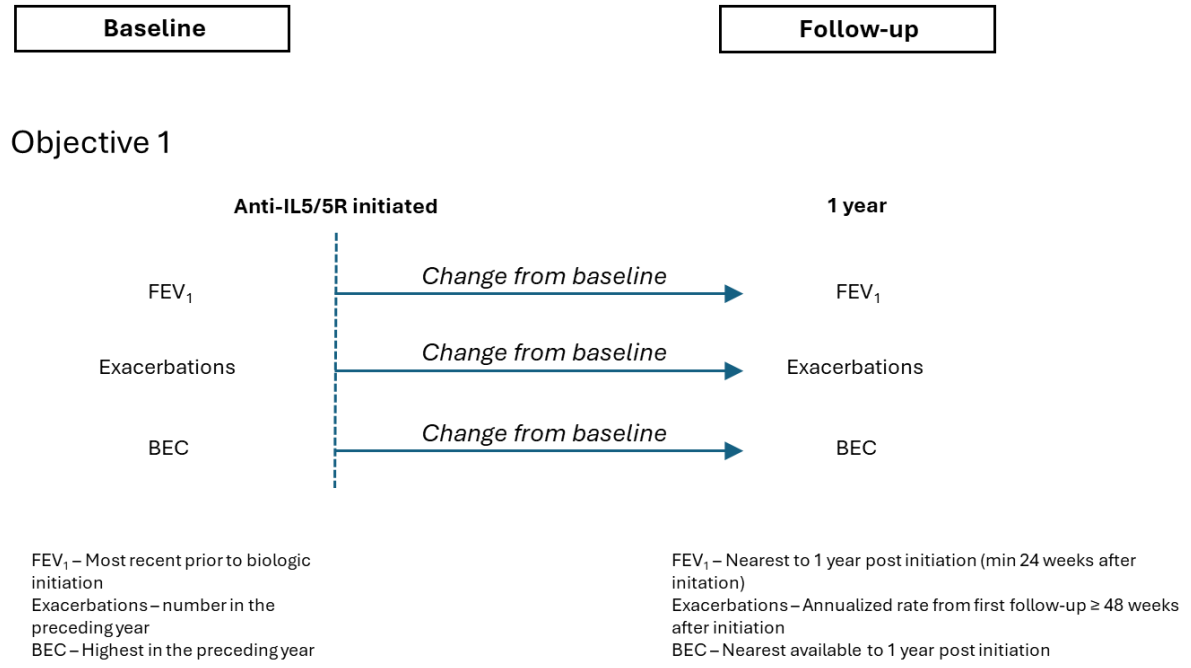

Figure 1. Study design for objective 1

For objectives 2 and 3 (patterns of change in biomarkers and outcomes over time) all available relevant follow-up data on BEC, FEV_1 and exacerbations will be used to describe changes over time following biologic initiation (Figure 2). For BEC and FEV_1, the result and date of any recorded values will be used in the analysis. For exacerbations, the number since the last visit will be used to assess changes in the rate over time. Patients with less than 48 weeks follow-up will be excluded from the analysis of exacerbations.

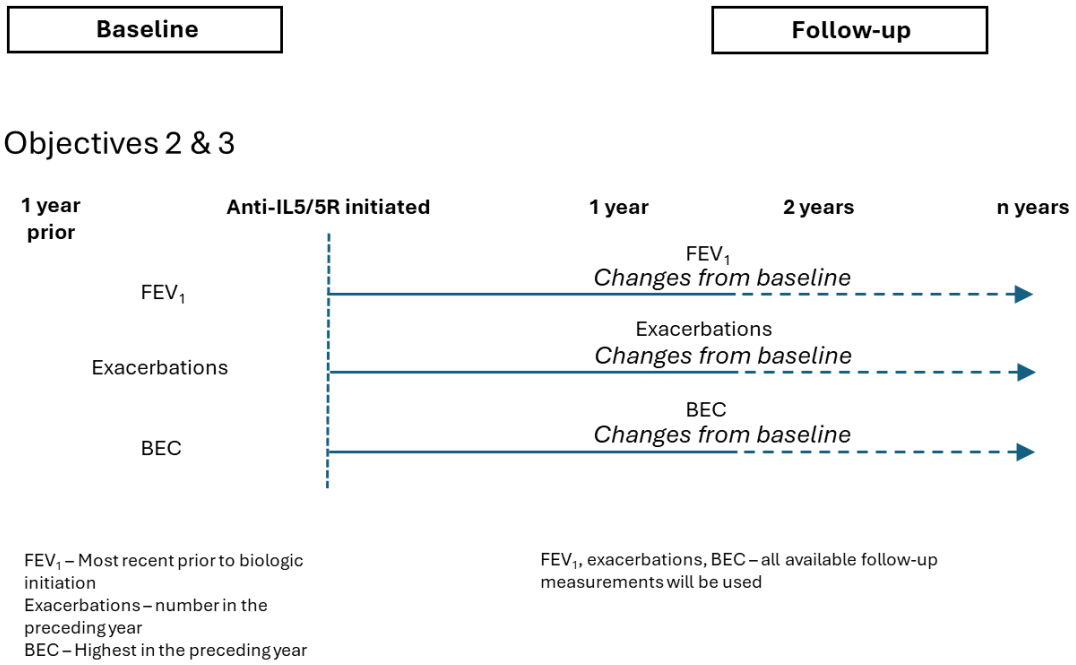

Figure 2. Study design for objectives 2 & 3

Patients who stop anti-IL5/5R treatment and/or switch to another biologic type will be included in the study, but their follow-up will not be included from the point of stopping or switching to a non-anti-IL5/5R biologic, so that we can identify any effects on BEC and FEV_1 as being due to anti-IL5/5R. If there are sufficient patients who stopped or switched from anti-IL5/5R, stratified analyses will also be undertaken to compare these patients with patients who were still on anti-IL5/5R at their last available follow-up. This analysis is included because patients who stopped or switched are particularly likely to have experienced failure of the treatment.

4.0 Study Population

4.1 Data Sources

Data will be sourced from the International Severe Asthma Registry (ISAR) [35]. ISAR is a multi-country, multicentre, observational initiative gathering longitudinal data on severe asthma patients, with retrospective and prospective data collection. Data collection started in 2017 and is currently ongoing. As of April 2024, ISAR had 18,290 patients registered in the database, out of whom 9,702 had a history of biologic treatment. Those eligible for enrolment are patients aged 18 or over, visiting a participating centre. They must have been diagnosed with severe asthma and provided informed consent for their data to be collected. Data are collected via electronic Case Report Forms (eCRF) made available by a common web-based platform or using countries' own eCRF systems, and for the USA data are extracted from electronic medical records (EMR). Data are then subjected to quality control checks and processed in a standardized manner to produce overall ISAR datasets.

4.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Receiving treatment according to GINA (2020 Criteria) step 5 or are uncontrolled at step 4 (uncontrolled is defined as having severe asthma symptoms or frequent exacerbations (≥2/year) requiring oral corticosteroids);
- Prescribed with an anti-IL5 or anti-IL5R biologic for the first time and as their first biologic therapy;
- 18 years or older at biologic initiation;
- Available data on BEC from a visit prior to or on the date of first anti-IL5/5R initiation, and from at least one visit after the date of first biologic initiation.
- Available data on FEV_1 and/or exacerbations in the year prior to anti-IL5/5R initiation and from at least one visit after the date of first biologic initiation for the same outcome(s).

Exclusion Criteria

- Received bronchial thermoplasty prior to initiating biologics.

5.0 Study Variables and Study Outcome Definitions

5.1 Patient characteristics

Patient characteristics used to describe the patients at the time of biologic initiation will include those in Table 1:

Table 1. Patient characteristics
Sex
Age at time of first biologic initiation (index date)
Body mass index (BMI)
Ethnicity
Country
Smoking status
Age at asthma onset
Duration of asthma
Highest pre-biologic blood eosinophil count (BEC)
Highest pre-biologic fractional exhaled nitric oxide (FeNO)
Highest pre-biologic serum immunoglobulin E (IgE)
One or more allergies detected from skin prick test and/or serum allergy test
Baseline asthma control
Baseline FEV_1 (post-bronchodilator)
Baseline FEV_1 percent predicted
Baseline FVC (post-bronchodilator)
Baseline FVC percent predicted
Baseline Exacerbation rate
Eosinophilic grade
Comorbidities Anxiety, depression, osteoporosis, type 2 diabetes, peptic ulcer, pneumonia, obstructive sleep apnoea, chronic kidney disease, heart failure, myocardial infarction, stroke, venous thromboembolism / pulmonary embolism, cataracts, glaucoma, chronic rhinosinusitis, nasal polyps, allergic rhinitis, eczema / atopic dermatitis
Receiving LTOCS at biologic initiation
Mean Daily LTOCS dose, mg
Add-on therapies to ICS/LABA LAMA, LTRA, macrolides, theophylline

(BEC - Blood eosinophil count; FeNO - Fractional exhaled nitric oxide; IgE - serum immunoglobulin E; FEV_1 - forced expiratory volume in 1 second; FVC - forced vital capacity)

5.2 Biological and clinical outcomes

The main variables of interest will be blood eosinophil count (BEC), forced expiratory volume in 1 second (FEV_1) and exacerbation rates, both before and after biologic initiation. BEC values known to be during exacerbations will be excluded. FEV_1 measurements post-bronchodilator will be used. Exacerbation rates will be the number of exacerbations in the year preceding biologic initiation or the annualised rate calculated since the previous visit during follow-up.

All available BEC, FEV_1 and exacerbation records pre- and post- biologic initiation will be included in the dataset. These will be summarized at time points, and over periods, according to the frequency and completeness of data available.

6.0 Statistical Analysis

6.1 Sample Size

As of 09 July 2024, a total of 5117 patients who initiated anti-IL5/5R and met the inclusion criteria are recorded in ISAR. All patients who meet the inclusion / exclusion criteria and have sufficient data will be included in the analyses. 2534 patients meet the inclusion / exclusion criteria and have at least one baseline and one follow-up BEC measurement. Of these 2062 have at least one pre- and post- FEV_1 result and 1276 have at least one pre- and post-exacerbation result available (Table 2).

Table 2. Patient flow		
Criterion	**Included**	**Excluded**
All patients in ISAR	20115	
18 years or over at biologic initiation	19806	309
Not received bronchial thermoplasty	19527	279
Initiated anti-IL5/5R as first biologic	5117	14410
BEC available from at least one pre- and one post- initiation visit	2534	2583
FEV_1 data available for year prior and at least one post-initiation visit	2062	
Exacerbations data available for year prior and at least one post-initiation visit (minimum 48 weeks after initiation)	1276	

6.2 Software

The analysis will be conducted with STATA version 18.0.

6.3 Demographic and Clinical Characteristics

Demographic and clinical characteristics shown in Table 1 will be summarised using the mean (standard deviation), median (inter-quartile range) or percentage.

6.4 Analysis for objective 1

Test for associations between changes in BEC and changes in FEV_1 and exacerbations one year after biologic initiation, and to identify other factors that modify these associations or explain the remaining variability

The associations between changes in BEC, and FEV_1 from their baseline values to the values closest to 1 year after initiation of anti-IL5/5R (defined in section 3.0) will be tested using linear regression with change in FEV_1 as the response variable and change in BEC as the predictor. The fitted line represents the average change in FEV_1 for a given change in BEC.

The analysis will then look for factors that predict above average or below average change in FEV_1, beyond that predicted by BEC alone. This will be done by treating the residuals (unexplained variation in FEV_1) from the regression as the response variable and testing for associations with other patient characteristics including:

- Long-term oral corticosteroid (LTOCS) use at baseline,
- Baseline FEV_1
- Percent predicted FEV_1 at baseline
- Baseline BEC
- All other patient characteristics listed in Table 1
- Highest recorded FeNO ≥ 90 days after biologic initiation
- Background maintenance therapy (ICS/LABA, LAMA) at the time of the follow-up
- BEC measurement used
- LTOCS use at the time of the follow-up BEC measurement used

Multivariable modelling will be used to identify any important interactions. Note, it will probably not be possible to include all potential predictors in the same model as only patients with complete data would be retained. Therefore, model building will proceed through a process of clinical and statistical judgement to obtain the best model.

The effect of baseline LTOCS use on the association between change in FEV_1 and change in BEC will be studied through stratification and inclusion of interaction terms, as LTOCS is likely to affect baseline BEC measurements without an equivalent effect on FEV_1.

An investigation of the association between change in exacerbation rates and change in BEC will be carried out using similar methods. The IGNITE study found that there was little association between baseline BEC and change in exacerbation rates (with most patients having a strong decrease in exacerbations, irrespective of baseline BEC) [14]. If a similar effect is observed for the association between change in BEC and change in exacerbation rates, model building will focus on identifying factors which predict a poor improvement in exacerbations, despite a good biological response in BEC.

Frequency distributions of changes in BEC, FEV_1 and exacerbation rates (change from baseline to 1 year follow-up) will also be produced to show if there are any groups of interest in the tails of these distributions for whom additional analyses should be carried out.

6.5 Analysis for objective 2

Describe patterns of change over time in BEC, FEV_1 and exacerbations following initiation of anti-IL5/5R treatments

Analysis for this objective will be largely graphical and based on the individual data points and dates recorded in the ISAR database. Methods of grouping the follow-up data into time periods will be derived empirically, depending on the timings of follow-ups available (which are likely to vary between countries and between patients).

For BEC, the IGNITE study showed that many patients experienced a large drop in BEC within a few months after initiating anti-IL5/5R and that BEC remained low for >3 years. The focus will therefore be on patients who exhibit different patterns, such as a poor initial response or a good initial response followed by an increase over time. Criteria defining typical, poor, or unsustained BEC response will be defined and used to create a grouping variable for the type of BEC response.

FEV_1 measurements over time will initially be plotted as line graphs using one line for each patient. If distinct patterns emerge then criteria will be defined to group patients by the pattern of response over time.

Exacerbation rates are only available for the periods between visits (though the length of time between visits varies between patients). These will also be plotted as line graphs with one line per patient. If distinct patterns of change over time are seen, criteria will be defined to group patients by the different patterns observed.

6.6 Analysis for objective 3

Test for associations between baseline patient characteristics and different patterns of change over time in BEC and/or FEV_1 and exacerbations following initiation of anti-IL5/5R

The analyses for Objective 2 (above) will identify any distinct patterns of changing response over time for BEC, FEV_1 and exacerbations, following initiation of anti-IL5/5R. Associations between response pattern and baseline patient characteristics will be tested using logistic regression (if 2 response pattern groups) or multinomial regression (if >2 response patterns identified).

Associations between the patterns for different clinical and biological responses will also be tested (e.g. are patients with an unsustained response in BEC more likely to have an unsustained response in FEV_1).

For all analyses in this section, consideration will be given to including any variables shown in objective 1 to modify the association between BEC and FEV_1 or between BEC and exacerbations, as covariates in the models. Stratified analyses will also be carried out for patients on / not on LTOCS at biologic initiation. This will provide information about how BEC measurements can or cannot be used to measure biological response in the presence of LTOCS. Stratified analyses will also be carried out for patients who stopped or switched biologic during their follow-up period to determine whether the decision to switch or stop was reflected in the pattern of biological or clinical response up to that point.

7.0 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)” and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with ENCePP (www.encepp.eu).

ISAR is approved by the Health Research Authority for clinical research use and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. We will submit the finalised version of this protocol to the ADEPT committee (https://www.regresearchnetwork.org/adept-committee/) for approval.

All sites will enter into a regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country and its relevant ethical boards and organisations. Further, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymised patient IDs. The data will be retrieved by Optimum Patient Care (OPC) data analysts and utilised as an anonymised dataset to perform the analysis according to protocol. This study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practice.

8.0 Data Dissemination

Results from the study will be submitted for publication in asthma focused peer-reviewed scientific journals. We will also consider submitting abstracts for distinct results to relevant international conferences. Authorship will follow the ISAR authorship policy.

9.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other members of the committee, as listed in the following table, will form the Advisory Group.

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11.0 Timelines

Action	Timeline
Protocol sign-off	July 2024
Dataset delivery + ADEPT approval	August 2024
Analyses	October 2024
Final study report	Jan 2025
Manuscript	May 2025

12.0 References

[1] World Health Organization (WHO). (2024). Asthma. https://www.who.int/news-room/fact-sheets/detail/asthma (accessed 29/05/2024)

[2] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. www.ginasthma.org (accessed 29/05/2024)

[3] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European respiratory journal. 2014 Feb 1;43(2):343-73.

[4] Gleich GJ. Mechanisms of eosinophil-associated inflammation. Journal of Allergy and Clinical Immunology. 2000 Apr 1;105(4):651-63.

[5] Mormile M, Mormile I, Fuschillo S, Rossi FW, Lamagna L, Ambrosino P, de Paulis A, Maniscalco M. Eosinophilic airway diseases: from pathophysiological mechanisms to clinical practice. International Journal of Molecular Sciences. 2023 Apr 14;24(8):7254.

[6] Backman H, Lindberg A, Hedman L, Stridsman C, Jansson SA, Sandström T, Lundbäck B, Rönmark E. FEV_1 decline in relation to blood eosinophils and neutrophils in a population-based asthma cohort. World Allergy Organization Journal. 2020 Mar 1;13(3):100110.

[7] Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, Wenzel SE, Wilson AM, Small MB, Gopalan G, Ashton VL. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. The lancet Respiratory medicine. 2015 Nov 1;3(11):849-58.

[8] Kimura, H., Makita, H., Taniguchi, N., Takei, N., Matsumoto, M., Kimura, H., Goudarzi, H., Shimizu, K., Suzuki, M., Nishimura, M. and Konno, S., 2021. Determination of the cutoff values of Th2 markers for the prediction of future exacerbation in severe asthma: an analysis from the Hokkaido Severe Asthma Cohort Study. Allergology International, 70(1), pp.68-73.

[9] Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. The Lancet. 2012 Aug 18;380(9842):651-9.

[10] Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P. Mepolizumab treatment in patients with severe eosinophilic asthma. New England journal of medicine. 2014 Sep 25;371(13):1198-207.

[11] Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, Goldman M. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. The Lancet. 2016 Oct 29;388(10056):2115-27.

[12] Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeyer L, Khurana S, Knight S, McDonald VM. Management of severe asthma: a European respiratory society/American thoracic society guideline. European respiratory journal. 2020 Jan 1;55(1).

[13] Katz LE, Gleich GJ, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. Annals of the American Thoracic Society. 2014 May;11(4):531-6.

[14] Porsbjerg CM, Townend J, Bergeron C, Christoff GC, Katsoulotos GP, Larenas-Linnemann D, Tran TN, Al-Lehebi R, Bosnic-Anticevich SZ, Busby J, Hew M. Association between pre-biologic T2-Biomaker combinations and response to biologics in patients with severe asthma. Frontiers in immunology. 2024 Apr 19;15:1361891.

[15] Li H, Zhang Q, Wang J, Gao S, Li C, Wang J, Zhang S, Lin J. Real-world effectiveness of mepolizumab in severe eosinophilic asthma: a systematic review and meta-analysis. Clinical Therapeutics. 2021 Jun 1;43(6):e192-208.

[16] Busse, W.W., Bleecker, E.R., FitzGerald, J.M., Ferguson, G.T., Barker, P., Sproule, S., Olsson, R.F., Martin, U.J., Goldman, M., Yañez, A. and Fernández, M., 2019. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. The lancet respiratory medicine, 7(1), pp.46-59.

[17] Chupp G, Wechsler ME. Biologic medications in asthma: What have we learned from long-term studies?. Annals of Allergy, Asthma & Immunology. 2022 Aug 1;129(2):138-9.

[18] Bel, E. H., Wenzel, S. E., Thompson, P. J., Prazma, C. M., Keene, O. N., Yancey, S. W., & Ortega, H. G. (2014). Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. New England Journal of Medicine, 371(13), 1189-1197.

[19] Jang JH, Woo SD, Lee Y, Kim CK, Shin YS, Ye YM, Park HS. Changes in type 2 biomarkers after anti-IL5 treatment in patients with severe eosinophilic asthma. Allergy, Asthma & Immunology Research. 2021 Mar;13(2):330.

[20] Boulet LP. Influence of comorbid conditions on asthma. European Respiratory Journal. 2009 Apr 1;33(4):897-906.

[21] Scelo G, Torres-Duque CA, Maspero J, Tran TN, Murray R, Martin N, Menzies-Gow AN, Hew M, Peters MJ, Gibson PG, Christoff GC. Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry. Annals of Allergy, Asthma & Immunology. 2024 Jan 1;132(1):42-53.

[22] Wechsler ME, Scelo G, Larenas-Linnemann DE, Torres-Duque CA, Maspero J, Tran TN, Murray RB, Martin N, Menzies-Gow AN, Hew M, Peters MJ. Association between T2-related comorbidities and effectiveness of biologics in severe asthma. American journal of respiratory and critical care medicine. 2024 Feb 1;209(3):262-72.

[23] Scelo G, Tran TN, Le TT, Faregås M, Dorscheid D, Busby J, Al-Ahmad M, Al-Lehebi R, Altraja A, Beastall A, Bergeron C. Exploring definitions and predictors of response to biologics for severe asthma. The Journal of Allergy and Clinical Immunology: In Practice. 2024 May 19.

[24] Perez-de-Llano L, Scelo G, Tran TN, Le TT, Fagerås M, Cosio BG, Peters M, Pfeffer PE, Al-Ahmad M, Al-Lehebi RO, Altraja A. Exploring definitions and predictors of severe asthma clinical remission post-biologic in adults. American journal of respiratory and critical care medicine. 2024 May 3(ja).

[25] Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, Brightling CE, Pavord ID. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. The Lancet Respiratory Medicine. 2016 Jul 1;4(7):549-56.

[26] FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, Newbold P, Goldman M. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. The Lancet Respiratory Medicine. 2018 Jan 1;6(1):51-64.

[27] Pavord ID, Casale TB, Corren J, FitzGerald MJ, Deniz Y, Altincatal A, Gall R, Pandit-Abid N, Radwan A, Jacob-Nara JA, Rowe PJ. Dupilumab reduces exacerbations independent of changes in biomarkers in moderate-to-severe asthma. The Journal of Allergy and Clinical Immunology: In Practice. 2024 Mar 29.

[28] Kroes JA, Zielhuis SW, Van Roon EN, Ten Brinke A. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. Biochemical pharmacology. 2020 Sep 1;179:113978.

[29] Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nature medicine. 2012 May;18(5):716-25.

[30] Prazma CM, Bel EH, Price RG, Bradford ES, Albers FC, Yancey SW. Oral corticosteroid dose changes and impact on peripheral blood eosinophil counts in patients with severe eosinophilic asthma: a post hoc analysis. Respiratory research. 2019 Dec;20:1-4.

[31] Menzella F. Baseline characteristics of patients enrolled in clinical trials of biologics for severe asthma as potential predictors of outcomes. Journal of Clinical Medicine. 2023 Feb 15;12(4):1546.

[32] Chen ML, Nopsopon T, Akenroye A. Incidence of anti-drug antibodies to monoclonal antibodies in asthma: a systematic review and meta-analysis. The Journal of Allergy and Clinical Immunology: In Practice. 2023 May 1;11(5):1475-84.

[33] Pérez de Llano L, Cisneros C, Domínguez-Ortega J, Martínez-Moragón E, Olaguibel JM, Plaza V, Quirce S, Dávila I. Response to monoclonal antibodies in Asthma: definitions, potential reasons for failure, and Therapeutic Options for suboptimal response. J. investig. allergol. clin. immunol. 2023:1-3.

[34] Eger K, Kroes JA, Ten Brinke A, Bel EH. Long-term therapy response to anti–IL-5 biologics in severe asthma—a real-life evaluation. The Journal of Allergy and Clinical Immunology: In Practice. 2021 Mar 1;9(3):1194-200.

[35] Bulathsinhala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, et al. Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study. J Allergy Clin Immunol Pract. 2019;7(2):578-88.e2.

[36] Denton E, Hew M, Peters MJ, Upham JW, Bulathsinhala L, Tran TN, Martin N, et al. Real-world biologics response and super-response in the International Severe Asthma Registry cohort. Allergy. 2024 Jun 22.