Study Protocol

"Impact of biologics on inhaled corticosteroids reduction" (MOON LIGHT)

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TITLE	**Impact of biologics on ICS reduction (MOON LIGHT)**
Subtitle	
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Study aims and objectives	**Study aims:** To evaluate the effect of biologic initiation on the level of inhaled corticosteroid, SABA, and triple therapy exposure among patients with severe asthma **Study objectives:** **Objective 1:** To study the extent patients achieve ICS dose, SABA, and triple therapy use reduction after biologic initiation. **Objective 2:** To identify potential predictors of successful down titration of ICS, SABA and triple therapy use after biologic therapy.
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 Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
FAO	Fixed airway obstruction
FDA	U.S. Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
GINA	Global Initiative for Asthma
HD	High dose
IgE	Immunoglobulin E
ICS	Inhaled corticosteroids
IL-4, -5, -13	Interleukin-4, -5, -13
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
LTOCS	Long-Term Oral Corticosteroid
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
R	R software from the R Project for Statistical Computing
SABA	Short-acting beta-agonist
STATA	Stata software suite

1.0 Background

Severe asthma, defined by the Global Initiative for Asthma (GINA) as asthma that either remains uncontrolled despite good adherence to high-dose treatments or requires such treatments to achieve adequate control, affects 5-10% of all patients with asthma globally and poses higher economic burden than non-severe asthma[1,2]. Its disproportionate contribution to asthma morbidity significantly impacts healthcare systems[3,4]. Raising inhaled corticosteroids (ICS) levels along with prescription of rescue or long-term oral corticosteroids in patients with uncontrolled asthma on medium to low dose ICS is a conventional clinical management pathway that is recommended by national and international asthma guidelines[2,17]. The below table represents the dosage of ICS drugs that are currently available in the market globally:

Inhaled corticosteroid (mcg/day)	Low	Medium	High
Beclometasone dipropionate (standard particles) *	≤500	>500 to <1000	≥1000
Beclometasone dipropionate (extra-fine particles) *	≤200	>200 to <400	≥400
Budesonide*	≤400	>400 to 800	>800
Ciclesonide (extrafine particles)	80-160	>160-320	>320
Fluticasone furoate*	<200		≥200
Fluticasone propionate*	≤250	>250 to 500	>500
Flunisolide+	≤1000	1000 to 2000	>2000
Mometason furoate (standard particle)	200-400		>400

Table 1 Inhaled molecules and daily dosage categories
* NICE: https://www.nice.org.uk/guidance/ng80/resources/inhaled-corticosteroid-doses-pdf-4731528781 (page 3). GINA 2024: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf (page 71). + National Asthma Education and Prevention Program: https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf (page 349)

Since 2013, biologics that target various cytokines, their receptors, or immunoglobulin E (IgE), have provided an OCS-sparing approach to treating uncontrolled asthma with reduction in exacerbations and improvement in symptom control [5-8]. These patients however are exposed to high levels of ICS that were initiated before biologic therapy. For example, the Danish Severe Asthma Registry found that 24% of its biologic users were receiving high (> 1600 µg budesonide daily) dose of ICS at baseline, prior to biologic initiation[11]. GINA recommends

reducing ICS after asthma is well controlled on biologic therapy for 3-6 months[2]. In a phase 4, open label, randomized multicentre study SHAMAL, made up of patients achieving asthma control with Benralizumab, 91% of those assigned to the ICS tapering group maintained the ICS reductions for 48 weeks without exacerbations[18]. This study demonstrates that once asthma is well controlled with biologics, it may be possible for patients to reduce and maintain a lower ICS dose. However, there is a lack of real-world evidence, therefore consensus, on the approach of tapering ICS for biologic users.

Despite emerging evidence of safe-ICS reduction among patients attaining asthma control following biologic initiation, there may be lag in adaptation in clinical practice due to reimbursement requirements and/or until repeated real-life evidence is provided for firmer clinical guidelines. Thus, while we may not be able to fully demonstrate the full potential of ICS reduction. However, describing the evidence of ICS reduction in the real-world is the first step towards exploring and demonstrating the clinical management strategies of ICS reduction while on biologic therapy and providing the confidence that clinicians need. ICS reduction is a key factor in the management of asthma as chronic ICS exposure, in mono or combination therapy, such as triple therapy.

Frequent use of SABA and ICS exposure also poses risk of adverse events, such as osteoporosis, pneumonia, obesity, and diabetes mellitus[12-16,20]. These health risks are similar to OCS-related adverse outcomes. There is substantial evidence supporting and guiding clinicians on the down titration of OCS once biologic therapy is initiated, yet there remains an unmet need to do the same for ICS therapy. Those that switch from fixed dose ICS-LABA to moderate or low dose MART maybe difficult to capture with registry data, therefore, we will endeavour to look at cessation of SABA usage as a marker of this occurrence via the use of an electronic medical records database, OPCRD (UK primary care)[10]

This study aims to evaluate the effect of biologic initiation on inhaled corticosteroid, SABA and triple therapy exposure among patients with severe asthma. We hypothesize that initiation of biologic therapy reduces the cumulative ICS and SABA exposure among patients with uncontrolled asthma.

The International Severe Asthma Registry (ISAR) is a data source that allows us to assess the potential ICS dose reduction after initiating biologic therapy globally[9]. To enhance our understanding further, integrating electronic medical records data from UK's primary care

sector via OPCRD[10] will increase our study population while offering more granularity of the data.

2.0 Study Aims and Objectives

Aim: To evaluate the effect of biologic initiation on level of inhaled corticosteroid exposure, SABA and triple therapy after biologic initiation.

Hypothesis: Biologic therapy has an ICS dose, SABA, and triple therapy use reduction effect

Study Objectives:

Objective 1: To calculate the extent of reduction in ICS, SABA, and triple therapy use after biologic initiation.

Objective 2: To identify potential predictors of successful down titration of ICS, SABA, and triple therapy use for those receiving biologic therapy.

3.0 Study Design

This is a prospective, single-arm, cohort study that will examine the down titration of background therapy after biologic treatment has been commenced. For objective 1, pattern of ICS dose change (decrease/stable/no-change vs increase), SABA and triple therapy exposure from before and at 6- month (where feasible, e.g. OPCRD, Japan) or 12-month intervals after biologic therapy will be assessed. Frequency of SABA use (OPCRD only), and stepping down (i.e., triple to dual) or maintained on the same therapy from before and at 6-month or 12-month intervals after biologic therapy will also be explored. For patients on triple therapy, we will be able to see which down titration approach (e.g. triple therapy or ICS dose) was practiced first in the real-world.

The following terms will be used:

- **Baseline period** – The year prior to initiation of a first biologic initiation
- **Baseline dose** – The latest recorded dose rate prior to biologic initiation
- **Index date** – The date of biologic initiation
- **Study period** – 2003 – 2025 (1 year prior to earliest biologic initiation date to most recent data available)
- **Follow-up period** – The time from biologic initiation to latest data available at the time of closing the dataset. In ISAR this will correspond to the latest patient visit prior to the most recent data submission from each contributing centre. For OPCRD this will correspond to the latest patient visit, or death, prior to the data extraction date from each GP practice.

For ISAR, ICS data is available for up to five years post biologic initiation (post-bx) and has a mean follow-up of 3.1 years in OPCRD, providing a complete capture of the comprehensive patient record. ICS dose, at or before biologic therapy, will be used as the baseline dose. The final ICS prescription in the follow up period (6 months, 1 year 2 years etc.), following biologic initiation, will be used to determine if the patient has changed their ICS dose (medication). All ICS doses will be converted to beclomethasone equivalents. We will also explore methods to report OCS equivalence results as well as describing the patterns of formulation changes (drug) for those that reduce. All ICS doses will be converted to beclomethasone equivalents. We also plan to report OCS equivalence results as well as describing the patterns of formulation changes (drug) for those that reduce.

For objective 2, baseline clinical characteristics pre biologic initiation (pre-bx) will be assessed for association with ICS reduction via a two-group comparison (reducer [decreasing] vs non-reducer [stable/increasing] at 6-, 12- or 24- months (three analyses) as sample size will progressivly decline after 24 months. Similar assessments will be conducted for exploring predictors of stepping down from triple to dual therapy (i.e. stepped down [triple -> dual] vs not stepped down [triple -> triple]) amongst patients on triple therapy in the baseline year. Assessment of long follow-up will be investigated using a survival analysis approach to allow for varying durations of follow-up (see section 6.0 for more details).

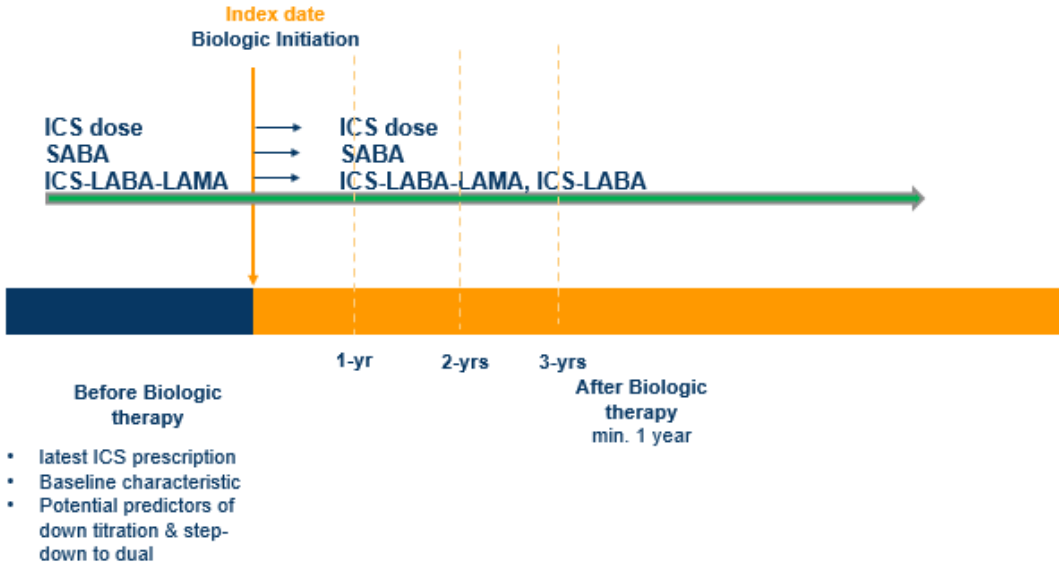


Figure 1 Study Design

ICS: Inhaled Corticosteroid, LABA: long-acting beta agonists, LAMA: long-acting muscarinic antagonists, SABA: Short-acting beta-agonist

4.0 Study Population

Data Sources

ISAR

The International Severe Asthma Registry (ISAR) is a global cooperative project designed to collect ongoing data from patients with severe asthma. To be included in this registry, patients must be 18 years of age or older, visit a participating centre, and have a diagnosis of severe asthma[20]. Additionally, they need to provide appropriate consent for their data to be used in ISAR research. Severe asthma is characterised either by its lack of control despite therapeutic efforts, or by the necessity for comprehensive treatment as described in steps 4 and 5 of the GINA guidelines[2]. Data collection began in 2018, and as of June 2025, there are 34,681 participants from 26 countries enrolled into ISAR. Of these enrolled participants, at least 12,875 have initiated a biologic, with an average follow-up time of 4.87 years (min: 0.01, max: 21.1). The data is comprised of routine clinical and demographic information collected from patients at each visit and extracted from medical records.

OPCRD

The Optimum Patient Care Research Database (OPCRD) collects and analyses anonymised primary care records from UK patients. Eligibility requires relevant medical histories from participating practices. The OPCRD, focusing on diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD), captures data that reflect real-world treatment patterns, outcomes, and healthcare interactions in line with clinical guidelines. Since its inception in 2008, the OPCRD has compiled records from 29 million patients. The database features details on 2,047 patients prescribed biologics for severe asthma, with 1,704 providing longitudinal data for ongoing research.

Inclusion and Exclusion Criteria

Patients meeting the following inclusion criteria will be included in this study

- Documented initiation of biologic therapy, AND
- Severe Asthma diagnosis (severe defined as ≥2 exacerbations and medium dose ICS/LABA OR high ICS/LABA)
- Age 18 years or older at the time of biologic initiation, AND
- Record of biologic initiation date, AND
    - Pre-bx ICS dose data (before bx initiation date) and at least one follow-up visits with ICS dose data post-bx,
- Patient data / recorded assessment available in baseline

Patients with the following exclusion criteria will not be included in this study:

- Biologic received for other (non-asthma) conditions (e.g. Urticaria, atopic dermatitis, EGPA, CRSwNP without severe asthma)

Study Variables

The following variables will be used to derive an analysis dataset suitable for the objectives of the study. Baseline values of the following variables will be used to describe the baseline characteristics of the study population. Please see section 6.2 for detail so the analyses that will involve these variables.

Patient Identifier and Demographic Variables

Label	Values
Record ID	string
DOB	string
Biological Sex	Male, Female
Height	numerical
Ethnicity	1, Caucasian | 2, South East Asian | 3, North East Asian | 4, African | 5, Mixed | 6, Other | 7, Unknown
Weight	numerical
BMI	numerical
Smoking status	1. Current 2. Past 3. Never
History of Bronchial Thermoplasty	yes, no

Diagnosis Variables

Label	Values
On GINA Step 5 Treatment	yes, no
Uncontrolled on GINA step 4 treatment	yes, no
Age at asthma onset	numerical

Biomarker Variables

Label	Values

Highest blood eosinophil count within the year before bx initiation or in the past three years (outside of an exacerbation)	numerical
Date of highest blood eosinophil count	date
FeNO test result (ISAR only)	numerical
FeNO count within the period (ISAR only)	yes, no
Date of FeNO test (ISAR only)	date
Blood IgE count (mostly in ISAR only)	numerical
Specific IgE positivity, serum or skin prick test	yes, no
Date of blood IgE count within the period	date

Therapy

Label	Values
Biologic Start Date	string
Biologic name	Omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab
Biologic class	Anti-IgE Anti- IL5/5R Anti-IL5 Anti-IL 5R Anti-IL4Rα Anti-TSLP
Start Date of ICS+LABA combination therapy	date
Start Date of ICS	date
Start Date of LABA	date
Start Date of LAMA	date
Start Date of SABA*	date
Number of SABA prescriptions	numerical
ICS dose (mcg)	numerical
Start date of long-term oral corticosteroids	date

Long-term OCS use + daily dose (mg)	numerical

*OPCRD only

Clinical outcomes and domain of defining Biologic Responsiveness/Remission

Label	Values
Asthma control as defined by GINA, ACT, AIRQ, ACQ	Uncontrolled, Well- or Partly controlled
Date of spirometry result	date
Pre-bronchodilator FEV1 (actual or predicted %)	numerical
Pre-bronchodilator FVC (actual or predicted %)	numerical
Post-bronchodilator FEV1 (actual or predicted %)	numerical
Post-bronchodilator FVC (actual or predicted %)	numerical
FEV1/FVC ratio post bronchodilator (%) - Auto calculated	numerical
Total number of severe exacerbations*	numerical
Total number of hospital admissions for asthma*	numerical
Total number of A&E attendances (Emergency room visit) for asthma*	numerical
Total number of episodes of invasive ventilation ever	numerical
Start and end date for each exacerbation	date

*requiring rescue steroids

Comorbidities

Label	Values

Indication of: Nasal Polyps (NP)	yes, no
Indication of: Chronic Rhinosinusitis (CRS)	yes, no
Indication of: CRS +/- NP	CRS + NP, CRS -NP
Indication of: Eczema	yes, no
Indication of: Allergic Rhinitis	yes, no
Diagnosis of osteoporosis	yes, no
Diagnosis of type II diabetes	yes, no
Start/diagnosis date of osteoporosis	date
Start/diagnosis date of type II diabetes	date

5.0 Study Outcomes

- **Objective 1:**

  - SABA prescriptions (count)
  - ICS dosing change (mcg, continuous) – change from baseline and final ICS dose in the follow up period (6 months, 1 year 2 years etc.)
  - ICS reducer – baseline is higher than the final ICS dose at follow-up times (6 months, 1 year, 2 year)
  - ICS non-reducer – baseline is equal to or lower than the final ICS dose at follow-up times (6 months, 1 year, 2 year)
  - Triple therapy (binary [stepped down to dual – yes or no])

- **Objective 2:**
  - ICS reduction (yes or no)
    - **Yes (reducer):** final ICS dose of interest time point less than baseline dose
    - **No (non-reducer):** final ICS dose of interest time point equal to or greater than dose at baseline
  - ICS mean daily dose (mcg)
  - Comparison groups:
    - reducers vs non-reducers of ICS dose
    - those that stepped down from triple therapy vs those that did not (patients on triple therapy in the baseline year).
    - reducers vs non-reducers of SABA (OPCRD only).

6.0 Statistical Analysis

6.1 Sample Size

The final sample size will depend on the number of individuals with available data meeting inclusion criteria. All patients meeting the eligibility criteria and with sufficient relevant data will be included (i.e. patients will be included in each analysis if they have non-missing data for the variables concerned, irrespective of whether they have non-missing data for all other variables (e.g. ICS dose vs record of combination therapy)).

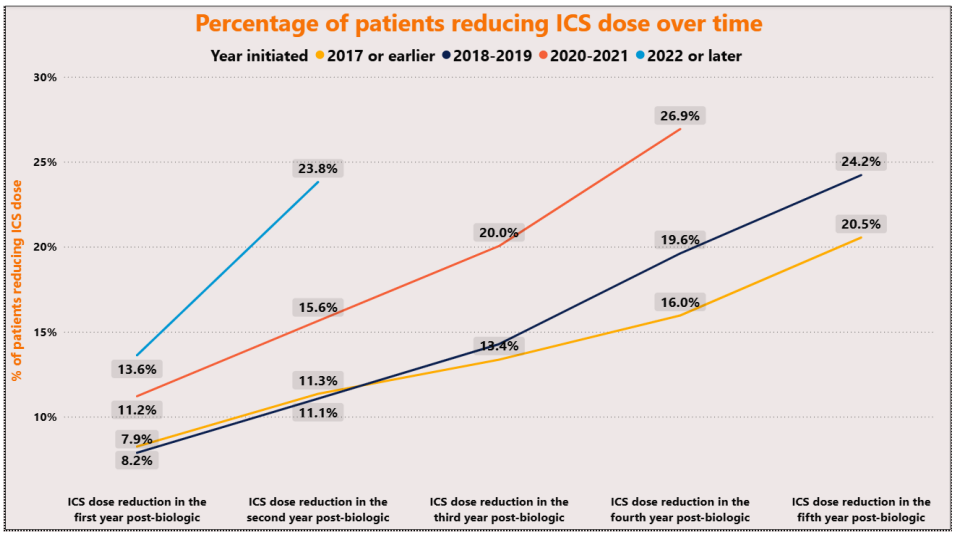
ISAR has 4,524 biologics patients that were on triple therapy (ICS+LABA+LAMA) before initiating a biologic. Rough feasibility estimates of the numbers of patients with pre- and post-bx ICS dose are shown below for ISAR and OPCRD. Additionally, an initial assessment of SABA feasibility is shown only for OPCRD. For ISAR, only the countries with consistent, reliable ICS dose data collection will be included in the analysis.

OPCRD (feasibility analysis) and ISAR ICS cohorts by total follow-up years

	ICS dose data Pre-bx and 1 yr post-bx	ICS dose data Pre-bx and 2 yrs post-bx	ICS dose data Pre-bx and 3 yrs post-bx	ICS dose data Pre-bx and 4 yrs post-bx	ICS dose data Pre-bx and ≥5 yrs post-bx
OPCRD	887	623	448	374	227
ISAR	6,457	4,855	3,751	2,838	1,823

Table 2 Feasibility by database

ISAR Initial Assessment of ICS reductions



Notes: ICS reduction shown above is if the ICS daily dose in the given period is smaller than what was seen in the pre-biologic period. If a patient had multiple ICS prescriptions in the same period, the maximum dose across the prescriptions was used. The y*ear initiated* categories were chosen to each contain 25% of the biologic population in ISAR

OPCRD SABA & Triple Therapy Cohorts (feasibility analysis) by Total Follow-up Years

	Annual SABA Pre-bx and 1 yr post-bx	**Annual SABA Pre-bx and 2 yrs post-bx**	**Annual SABA Pre-bx and 3 yrs post-bx**
OPCRD	887	623	448
	Annual Triple RX data Pre-bx and 1 yr post-bx	**Annual Triple RX data Pre-bx and 1 yr post-bx**	**Annual Triple RX data Pre-bx and 1 yr post-bx**
OPCRD	511	349	248

6.2 Analysis

Objective 1

Descriptive Analysis: Patient characteristics for each of the data sources will be described in tables. Baseline characteristics of the two groups (reducer, non-reducer) will be described, including numbers of patients with available data for each of the characteristics. We will also describe clinical events (e.g. exacerbations, hospital visits, LTOCS) that occur after biologic initiation at 6, 12 and 24 months, in line with objective 2 analysis time points. Distributions at the overall global and country level will be explored to allow for health system and/or data collection differences. The probability of being an ICS reducer will also be described by biologic initiation year (≤2020, 2021 - 2023 and ≥2024), with ≥2024 corresponding to after the publication of the SHAMAL study, and by those who switched or discontinued a biologic prescription vs those who did not.

- **Continuous variables** –will be summarized as: n (non-missing sample size), mean (or median for skewed and ordinal data) and standard deviation or inter-quartile range (IQR). We also plan to explore methods of reporting OCS equivalence results as well**.**
- **Categorical variables** will be presented as frequency and percentage (based on the non-missing sample size) or range (if applicable).
- **Graphical presentations**
    - **River plots** – to illustrate changes from pre-biologic initiation high/medium/low ICS to post-biologic initiation high/medium/low. Proportions, such as those that move form high pre-bx ICS to medium or low ICS dose, can be shown.

        - Similar approach will be taken to demonstrate the change in the frequency of SABA prescriptions, as shown in the above sample size section 6.1.
        - Describing the patterns of formulation changes (drug) for those that reduce.
    - **Bar charts –**
        - to demonstrate proportion with medium-, low-dose ICS as well as as-needed (anti-inflammatory) of those that had any reduction.
        - Multiple graphs by years of follow-up cohort to show mean daily ICS dose change from pre- to post-bx: 1.pre-bx and one year of post-bx ICS dose information 2. Pre-bx and two years of post-bx ICS dose information 3. pre-bx and three years of post-bx ICS dose information, pre-bx 4. four years of post-bx ICS dose information.
            - Similar assessments for SABA will be explored via illustrating the mean number of SABA prescription by year
        - 95 % confidence intervals will be provided for each chart
    - Line graphs showing the proportion of patients who reduced their ICS doses by various percentages (e.g. 5%, 10%, 20%) will be compared to pre-biologic levels at different points in time after starting biologics.

    - **Scatter plots -** Display the association between pre-Bx (baseline) and post-Bx ICS dose at 12 and 24 months after biologic initiation.
- Tables and charts will be annotated with the total population size including any missing observations (frequency and %).

Objective 2

Logistic regression models will be used to test for associations between baseline characteristics (including year of biologic initiation) and the odds of being an ICS reducer vs non-reducer at 12 months and 24 months after biologic initiation. Upon assessment of the distribution of ICS reduction, we may choose a binary cut-off point (e.g. 20%) as ‘reduction’ and conduct a sensitivity analysis.

The following variables (collected at baseline) will be assessed for potential confounding and may be included as covariates of the multivariable regression:

- Biologic class initiated
- ICS dose
- Other inhaled asthma therapies (LABA, LAMA, SABA)
- LTOCS use and / or dose
- Clinical characteristics (exacerbation rate, asthma control, percent predicted FEV_1)
- Age
- Sex
- BMI
- Smoking history
- Comorbidities (nasal polyps, chronic rhinosinusitis, eczema, allergic rhinitis)
- Year of biologic initiation (continuous or categorical)

Consideration will be given to using multiple imputation to derive data for missing variables or alternatively omitting some covariates from the regressions, depending on the numbers of missing values found and the relative importance of the covariates in the regressions.

Further timepoints (e.g. 6 months) may be added if there are sufficient patients with complete data (for ICS use and baseline characteristics). Logistic regressions will be used to determine whether the odds of being a reducer at 24 months (reducer/non-reducer) is predicted by the status at 6 months or at 12 months, as well as graphical and tabular summary statistics.

Logistic regression models (including the same covariates as listed above) will similarly be used to assess the association between baseline patients' characteristics and:

i) The odds of stepping down from triple therapy vs not at 12 and 24 months after biologic initiation (in patients on triple therapy in the baseline year).
ii) The odds of reducing SABA use (compared with pre-biologic level) at 12, 24 and 36 months after biologic initiation (OPCRD only).

The sample size of patients with complete data is likely to decrease with longer follow-up, therefore a survival analysis approach will be used using Cox regression models to test for associations between baseline patient characteristics and (i) duration of ICS reduction in patients, who are reducers in the first year, and (ii) time until reduction is first observed in non-reducers in the first year. Patients will be included using as much follow-up data as they have available.

i) For patients who are ICS reducers in the first year the failure event of interest will be an ICS dosing regimen equal to or greater than their pre-biologic dose. Patients who are still on a reduced dose at the point of their last follow-up data will be censored at that point. This analysis will allow us to determine whether the duration of reduction is related to any of the patient's baseline characteristics. Reducers who do not have the failure event (i.e. a return to ≥ pre-biologic ICS dose) will be censored at the time of their last follow-up data available.

ii) For patients, who are non-reducers in the first year post-bx, the failure event of interest will be an ICS dosing regimen less than their baseline dose. This analysis will allow us to study whether time to ICS dose reduction (if it occurs) is related to the patient's baseline characteristics. Patients who are still on their pre-biologic dose or a higher dose at the time of their last follow-up data will be censored at that point.

Note that for these analyses patients are censored at the time of their last follow-up data available. In ISAR this will correspond to the latest patient visit prior to the most recent data submission from each contributing centre. For OPCRD this will correspond to the latest patient visit, or death, prior to the data extraction date from each GP practice.

The primary analysis will follow an intention to treat principle (including all patients who initiate a first biologic) with sensitivity analyses i) excluding patients who stop biologic treatment during follow-up, and ii) excluding patients who stop or switch biologic treatment during follow-up. This will give us insight into whether the biologic treatment itself reduces the need for ICS in patients who tolerate the new treatment.

Software

Analysis will be undertaken in Stata or R. Datasets will be received from the data analytics team in either XLS or CSV format, which can be easily imported into the analysis software.

7.0 Regulatory and Ethical Compliance

This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPASXXXX#) and with all applicable local and international laws and regulation.

Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPTXXXX#).

All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.

8.0 Data Dissemination

This study will provide evidence from real-world data on whether initiation of biologic treatment in severe asthma patients is associated with successful reduction in ICS and other inhaled therapies. The evidence may be useful in recommending dosing strategies for physicians treating severe asthma patients after starting them on a biologic.

Publications:

The findings will be submitted for publication in peer-reviewed journals that focus on respiratory diseases, biologic therapies, and clinical outcomes.

Conferences:

Results will also be presented at relevant medical and scientific conferences, through abstract presentations and/or discussions.

Authorship:

Authorship will be determined in accordance with the ISAR authorship policy as outline in the ISAR publication charter, which has been approved by the ISAR steering committee. Authorship will recognise significant contributions to the study's conception, analysis, and writing.

9.0 Advisory Group

Professor David Price, Chief Investigator for this 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.

No	Name	Country / Institution
1	Jorge Máspero	Argentina
2	Olivier Chambenoit	AstraZeneca
3	James M. Eudicone	AstraZeneca
4	Amit D. Parulekar	AstraZeneca
5	Trung N. Tran	AstraZeneca
6	Tancy C. Zhang	AstraZeneca
7	Florence Schleich	Belgium
8	Paulo Márcio Pitrez	Brazil
9	George C. Christoff	Bulgaria
10	Todor A. Popov	Bulgaria
11	M. Diane Lougheed	Canada
12	Carlos A. Torres-Duque	Colombia
13	Kjell Erik Julius Håkansson	Denmark
14	Ivan Cherrez-Ojeda	Ecuador
15	Alan Altraja	Estonia
16	Arnaud Bourdin	France
17	Camille Taillé	France
18	Christian Taube	Germany
19	Maria Kallieri	Greece
20	Nikolaos G. Papadopoulos	Greece
21	Sundeep Salvi	India
22	Richard W. Costello	Ireland
23	Patrick D. Mitchell	Ireland
24	Giorgio Walter Canonica	Italy
25	Enrico Heffler	Italy
26	Takashi Iwanaga	Japan
27	Mona S. Al-Ahmad	Kuwait
28	Désirée Larenas-Linnemann	Mexico
29	Job F.M. Van Boven	Netherlands
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10.0 Research Team

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11.0 Project Timeline

Action	Timeline
Protocol finalisation	July 2025
Ethics approval	July 2025
Dataset preparation	July-August 2025
Analysis & preliminary results	September 2025
Study report	December 2025
Conference abstract	January 2026
Manuscript Draft	February 2026

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