Study Report

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

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Study aims and objectives	**Aim:** To evaluate changes in inhaled corticosteroid, SABA, and triple therapy exposure among patients with severe asthma following biologic initiation. **Objective 1:** To assess 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, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, UAE/Dubai, UK, USA
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics & Protocol Transparency
BEC	Blood eosinophil count
BMI	Body mass index
Bx, bx	Shorthand for Biologic
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CRSwNP	Chronic rhinosinusitis with nasal polyps
ED	Emergency Department
EGPA	Eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome)
ENCePP	European Network of 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
FEV_1/FVC	Ratio of forced expiratory volume in 1 second to forced vital capacity
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General Practitioner
GLI	Global Lung Function Initiative
HD	High dose
HR	Hazard ratio
IgE	Immunoglobulin E
ICS	Inhaled corticosteroids
IL-4, IL-5, IL-13	Interleukin-4, interleukin-5, interleukin-13
IQR	Interquartile range
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
MART	Maintenance and reliever therapy

mcg (µg)	Microgram
mg	Milligram
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
OPRI	Observational and Pragmatic Research Institute
OR	Odds ratio
ppb	Parts per billion
R	R software from the R Project for Statistical Computing
RDAC	Risk domain asthma control
SABA	Short-acting beta-agonist
SHAMAL	Study of High-dose vs. Moderate-dose steroid tapering in Asthma management with OCS reduction
SMD	Standardised mean difference
STATA	Stata software suite
T2	Type 2 (inflammatory endotype)
TSLP	Thymic stromal lymphopoietin

1.0 Executive Summary

The MOONLIGHT study evaluated real-world patterns of inhaled corticosteroid (ICS), short-acting β-agonist (SABA), and triple therapy use following biologic initiation among adults with severe asthma. Using data from 8,392 patients across the International Severe Asthma Registry (ISAR) and the UK OPCRD, this study provides the largest global assessment to date of inhaled therapy down-titration after biologic therapy in routine clinical care.

Biologic therapy was initiated between 2004 and 2025 across 26 countries, with anti-IL5/5R agents the most used. Prior to initiation, most patients were prescribed high-dose ICS, with substantial use of SABA and triple therapy.

ICS Use

ICS dose remained stable for most patients (73%), but reductions increased over time (10% at 6 months to 22% at 5 years). When reductions occurred, they were clinically meaningful (median 800–1,000 mcg) but often insufficient to shift dose category. Most reductions occurred within 1-2 years after biologic initiation and were highly persistent (>90% over follow-up). While patients who reduced ICS showed slightly greater improvements in lung function, these differences were small and unlikely to be clinically meaningful.

SABA Use

SABA use remained highly prevalent but declined modestly over time. Median annual prescriptions decreased from 7 at baseline to 4 by Year 5. Over half of patients experienced at least one reduction, although reliever therapy remained substantial.

Triple Therapy

Triple therapy use declined modestly (55% to 46% at 5 years), with approximately 21% of patients experiencing at least one reduction. Unlike ICS, reductions occurred gradually over time rather than being concentrated early after biologic initiation, and most patients remained on triple therapy.

Predictors of Reduction

Few strong predictors of treatment reduction were identified. Higher baseline ICS dose was the only consistent predictor of ICS reduction. Improved asthma control and fewer exacerbations were associated with SABA reduction, limited and inconsistent associations were observed for triple therapy reduction, with no strong or consistent predictors identified. Most demographic and clinical variables showed limited independent association.

Treatment Pathways

Treatment patterns were dynamic, with approximately 22% of patients switching biologics during follow-up. ICS reduction was more frequently observed among patients who switched biologic therapy than among those who did not switch. These findings suggest that inhaled therapy reduction and biologic treatment modification may occur concurrently in some patients, although the observational nature of the data precludes conclusions regarding causality.

Overall Interpretation

Biologic initiation was associated with modest but progressive reductions in ICS, SABA, and triple therapy use. While most patients remained on baseline inhaled therapy, a substantial minority achieved sustained reductions, particularly for ICS. There was marked variation between countries, suggesting that treatment de-escalation is influenced by local clinical practice and may be achievable to a greater extent in some settings.

These findings provide robust real-world evidence that inhaled therapy reduction may be feasible following biologic initiation and generally durable. However, given the observational design, associations should not be interpreted as causal. Overall, the results support optimisation of treatment burden and reduction of corticosteroid exposure while highlighting opportunities for more consistent implementation in practice.

2.0 Background

Severe asthma, as defined by the Global Initiative for Asthma (GINA), is characterised by asthma that remains uncontrolled despite good adherence to optimised high-dose therapy or that requires such treatment to achieve adequate control. Severe asthma affects approximately 5–10% of patients with asthma globally and imposes a disproportionate clinical and economic burden compared with non-severe asthma.[1,2] Its contribution to healthcare utilisation, morbidity, and mortality remains substantial.[3,4] Optimisation of long-term treatment strategies in this population therefore represents a key clinical and health system priority.

Inhaled corticosteroids (ICS) remain the foundation of asthma management across all severities. In patients with uncontrolled disease, escalation to high-dose ICS in combination with long-acting bronchodilators and, where required, rescue or maintenance oral corticosteroids (OCS), has historically represented standard care in alignment with national and international guidelines.[2,5] However, prolonged exposure to high cumulative doses of ICS and frequent short-acting beta-agonist (SABA) use are increasingly recognised to be associated with clinically meaningful adverse outcomes, including osteoporosis, pneumonia, metabolic disorders, cardiovascular events, obesity, and diabetes mellitus.[12–17] These risks are additive to the well-described adverse effects associated with long-term systemic corticosteroid use.

The table below summarises commonly used global thresholds for low-, medium-, and high-dose ICS therapies across key molecules currently used in clinical practice (table 1).

Table 1: Inhaled molecules and daily dosage categories

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 (extra fine particles)	80-160	>160-320	>320
Fluticasone furoate*	<200		≥200
Fluticasone propionate*	≤250	>250 to 500	>500
Flunisolide+	≤1000	1000 to 2000	>2000
Mometasone furoate (standard particle)	200-400		>400

* 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 for treating uncontrolled asthma with reduction in exacerbations and improvements in symptom control[6-9]. However, these patients often continue to be 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 (> 1600µg budesonide daily) dose of ICS at baseline, prior to biologic initiation[10]. GINA recommends reducing ICS after asthma is well controlled on biologic therapy for 3-6 months[2]. In the phase 4, open-label, randomised multicentre SHAMAL study of patients achieving asthma control with benralizumab, 92% of patients reduced their ICS dose by Week 32, and 96% maintained the reduced dose through Week 48[11]. 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 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. Consequently, describing the patterns and consequences of ICS reduction in the real-world is necessary in providing evidence that ICS-reduction strategies can be safe and effective in biologic-treated populations.

Frequent use of SABA and ICS exposure also poses risk of adverse events, such as osteoporosis, pneumonia, obesity, and diabetes mellitus[12-17]. 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 examined the 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 is associated with reductions in 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[18]. To enhance our understanding further, integrating electronic medical records data from UK's primary care

sector via OPCRD[11] will increase our study population while offering more granularity of the data.

3.0 Study Aims and Objectives

3.1 Study Aim

To evaluate changes in inhaled corticosteroid, SABA, and triple therapy exposure following biologic initiation.

Hypothesis: Biologic therapy is associated with reductions in ICS dose, SABA use, and triple therapy exposure

3.2 Study Objectives

Objective 1: To assess 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.

4.0 Materials and Methods

4.1 Data Source

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[17]. 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; however, participating centres may contribute retrospectively extracted historical clinical data from medical records, allowing capture of data prior to registry enrolment. 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.

4.2 Study Design

This is a prospective, single-arm, cohort study that examined the down titration of background therapy after biologic treatment has been commenced. For objective 1, pattern of ICS dose change (decrease/stable 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 was assessed. Frequency of SABA use (OPCRD only), and stepping down inhaled therapy (i.e., triple to dual) or maintained on the same therapy from before and at 6-month or 12-month

intervals after biologic therapy was also explored. For patients on triple therapy, we assessed which down titration approach (e.g. triple therapy or ICS dose) was practiced first in the real-world.

The following terms were used:

- Baseline period – The year prior to initiation of a first biologic initiation
- Baseline dose – The highest recorded dose rate prior to biologic initiation
- Index date – The date of biologic initiation
- Study period – 2003 to 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). In OPCRD, mean follow-up of 3.1 years in OPCRD, providing a complete capture of the comprehensive patient record.

ICS daily dose was derived from prescription records during the baseline and follow up period. For each prescription, the prescribed daily dose was calculated using product strength, quantity prescribed, and dosing instructions where available. ICS doses were standardised to beclometasone dipropionate equivalent doses using established equivalence tables to allow comparison across inhaled corticosteroid preparations (table 2). For prescriptions with missing or incomplete dosing instructions, daily dose was imputed using the most recent valid dosing instruction for the same product where available; otherwise, standard maintenance dosing assumptions based on product licensing/guidelines were applied. The maximum recorded ICS daily dose during the baseline year was used as the baseline ICS dose for these analyses.

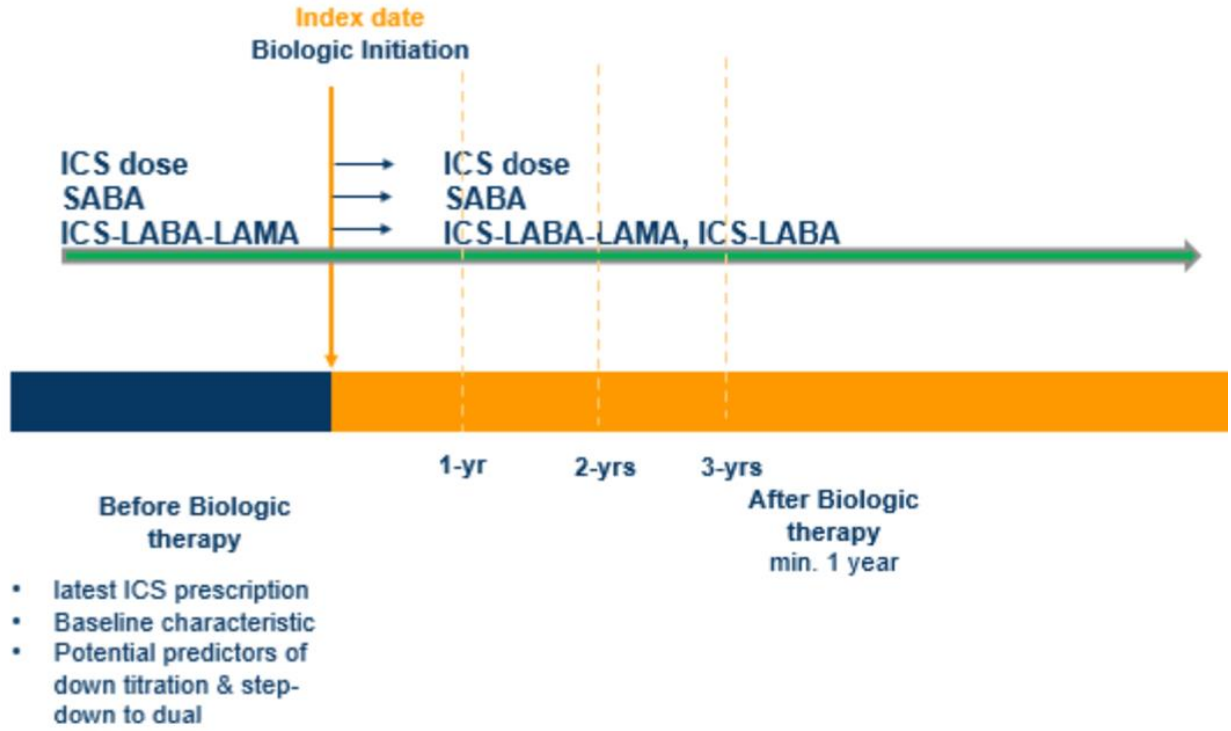
For objective 2, baseline clinical characteristics pre-biologic initiation (pre-bx) were assessed for association with ICS reduction via a two-group comparison (reducer [decreasing] vs non-reducer [stable/increasing] at 1 and 2 years. Analysis after 2 years post-initiation was not attempted due to an insufficient sample size.

Table 2: Oral corticosteroid drugs

Drug name	Prednisolone equivalent conversion
Betamethasone	6.67
Cortisone	0.27
Deflazacort	0.67
Dexamethasone	6.67
Hydrocortisone	0.33
Methylprednisolone	1.33
Prednisolone	1.0
Prednisone	1.0
Triamcinolone	1.33

Figure 1 illustrates the study design and key assessment time points.

Figure 1: Study Design: ICS: Inhaled Corticosteroid, LABA: long-acting beta agonists, LAMA: long-acting muscarinic antagonists, SABA: Short-acting beta-agonist



Inclusion and exclusion criteria

To be eligible for the project, patients had to meet all the following criteria:

- 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 will be excluded if

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

5.0 Study Variables

5.1 Baseline (pre-biologic) patient characteristics

Patient characteristic variables that have been used for the study are described in Table 3Error! Reference source not found.. They have served to describe the study population, and as variables of interest and/or adjustment and/or stratification variables in Objectives 1 and 2.

Table 3: Patient characteristic variables.

Label	Type	Value	Construct/comments
Demographic characteristics			
Biologic initiation date (index date)	Date	-	First biologic initiated
Age at biologic initiation (years)	Numerical	-	
Sex	Nominal	Female, male	
Country	Nominal	Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, UAE/Dubai, UK, USA	
Body mass index (BMI) at biologic initiation (kg/m^2)	Numerical	-	Weight in kg/(height in m)^2
Smoking status at biologic initiation	Ordinal	Current smoker, ex-smoker, never smoker	
Asthma-related key clinical characteristics			
Number of asthma exacerbations in the year preceding biologic initiation	Discrete	-	A time window of 12 months prior to initiation. Exacerbations were defined as requiring a course of OCS of at least 3 days.

Label	Type	Value	Construct/comments
Asthma symptom control at biologic initiation	Ordinal	Well controlled Partly controlled Uncontrolled	Assessment in the year preceding biologic initiation, and closest to biologic initiation. In OPCRD Risk Domain Asthma Control (RDAC)was used.[19,20] Patients whose asthma was "uncontrolled" in terms of RDAC were those who had any of the following during the 12-month assessment period: asthma-related hospital admission, ED or outpatient department attendance; acute use of OCS with evidence of respiratory review; or antibiotics prescribed with evidence of respiratory review. Asthma was "controlled" in terms of RDAC for those who had none of the above events/prescriptions over the assessment period. In ISAR, GINA 2020 classification is collected by most participating ISAR centres. For centres reporting asthma symptom control assessment based on ACT (Nathan et al., 2004) and/or ACQ (Juniper et al., 1999), algorithms were used to fit available data to GINA 2020 categories: - ACQ: Mean ACQ ≤0.75: Well controlled 0.75< Mean ACQ <1.5: Partly controlled Mean ACQ ≥1.5: Uncontrolled - ACT: Total ACT >19: Well controlled 15< Total ACT ≤19: Partly controlled Total ACT ≤15: Uncontrolled
FEV_1 at biologic initiation (mL)	Numerical		Assessment in the year preceding biologic initiation and closest to biologic initiation. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available.
FEV_1 percent predicted at biologic initiation (%)	Numerical	-	Assessment in the year preceding biologic initiation and closest to biologic initiation. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available. Reference equations: GLI 2022 race-neutral equations (Bowerman et al., 2023)
FEV_1/FVC ratio at biologic initiation	Numerical	-	Assessment in the year preceding biologic initiation and closest to biologic initiation. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available.
Biomarkers and other clinical features			
Blood eosinophil count at biologic initiation (cells/mcL)	Numerical	-	Highest measure recorded up to index date
FeNO concentration at biologic initiation (ppb)	Numerical	-	Latest measure recorded up to index date
Asthma-related medications			
ICS dose (mcg)	Numerical	-	Highest measure recorded in year prior to index date and in interested periods (6m, 12m, 24m, 36m, 48m, 60m)
Biologic class	Nominal	Anti-IL5/5R Anti-IgE Anti-IL4Ralpha Anti-TSLP	First biologic initiated
Long-term OCS use in the year preceding biologic initiation	Binary	Yes, no	LTOCS is defined as using OCS daily (or every other day) for at least 3 months in the year preceding biologic initiation.
Long-term OCS daily dose during in the year	Numerical	-	Prednisone-equivalent dosages over the period of use (most recent dosage if dosages changed over the year).

Label	Type	Value	Construct/comments
preceding biologic initiation (mg/day)			
Potentially T2-related comorbidities			
Allergic rhinitis	Binary	Ever, never	-
Chronic rhinosinusitis	Binary	Ever, never	-
Nasal polyps	Binary	Ever, never	-
Eczema/atopic dermatitis	Binary	Ever, never	-
History of potentially OCS-related comorbidities at biologic initiation			
Osteoporosis	Binary	Yes, no	
Type II diabetes	Binary	Yes, no	

5.2 Objective 1: Outcomes of asthma variables

- **Objective 1:**
  - ICS daily dose (mcg) (continuous)
  - ICS dosing change (categorical [stable, deceasing, increasing])
    - Stable - same dose at all visits
    - Decreasing - visits with lower (any decrease) ICS dose vs baseline
    - Increasing - visits with higher ICS dose (any increase)
    - Mixed – patients who have increasing, and decreasing doses during follow-up.
  - SABA prescriptions (count)
  - Triple therapy (binary [stepped down to dual – yes or no])

5.3 Objective 2: Outcomes of asthma variables

- **Objective 2:**
  - ICS reduction (yes or no)
    - **Yes:** decreased visits with lower (any decrease) ICS dose vs baseline
    - **No:** visits with higher ICS dose (any increase)
  - ICS mean daily dose (mcg)
  - Comparison groups:
    - reducers vs non-reducers of ICS dose
    - reducers vs non-reducers of SABA (OPCRD only)
    - those that stepped down from triple therapy vs those that did not (patients on triple therapy in the baseline year).

6.0 Statistical Analysis

6.1 Objective 1

Descriptive Analysis: Patient characteristics for each of the data sources were described in tables. Baseline characteristics of the ICS dose trajectory groups (reducers, increasers, stable and mixed) will be described. ICS reduction was defined as any decrease from baseline ('ever reduction'). Timepoint-specific and sustained reductions are reported separately. For the main ICS trajectory analysis, patients were classified by comparing the maximum ICS dose recorded during the baseline period with the maximum ICS dose recorded during follow-up. Reducers were defined as patients whose maximum follow-up ICS dose was lower than their maximum baseline ICS dose; increasers were those whose maximum follow-up ICS dose was higher than their maximum baseline ICS dose; and stable patients were those whose maximum follow-up ICS dose was unchanged from their maximum baseline ICS dose.We described clinical events (e.g. exacerbations, hospital visits) that occur after biologic initiation at 1 year, in line with objective 2 analysis time points.

Patients were also classified according to their longitudinal ICS dose trajectory during follow-up relative to baseline ICS dose. Patients were categorised as reducers (at least one reduction below baseline and no increases above baseline), increasers (at least one increase above baseline and no reductions below baseline), stable (no change from baseline throughout follow-up), or mixed (both increases and reductions relative to baseline during follow-up). Baseline characteristics were summarised descriptively across these trajectory groups.

Analysis of ISAR data will allow distributions at the overall global and country level were explored to allow for health system and/or data collection differences. Patients were also stratified by biologic initiation year (≤2019, 2020 - 2023 and ≥2024), with ≥2024 corresponding to after the publication of the SHAMAL study.

- **Continuous variables** –were summarized as: n (non-missing sample size), mean (or median for skewed and ordinal data) and standard deviation or inter-quartile range (IQR).
- **Categorical variables** were 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.

- **Bar charts –**
  - to demonstrate proportion with medium, low-dose ICS as well as 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 chart that aren't stacked

- **Scatter plots -** Display the association between pre-Bx (baseline) and post-Bx ICS dose at 1 and 2 years after biologic initiation.

Handling of Missing Data and Incomplete Follow-up: Where ICS dose was not recorded at a scheduled follow-up assessment, the missing value was imputed using the most recent prior recorded ICS dose. Patients were therefore not assumed to have changed ICS dose in the absence of a newly recorded prescription. Analyses at each follow-up time point were restricted to patients with available follow-up data and complete data for required model covariates, and denominators therefore varied according to data availability at each assessment (including 12- and 24-month follow-up). For time-to-event analyses, patients contributed follow-up until their last available recorded assessment and were right-censored thereafter if the event of interest had not occurred.

6.2 Objective 2

Logistic regression models were used to test for associations between baseline characteristics and the odds of being an ICS "reducer" (group decreasing) vs "non-reducer" (groups stable and increasing) at 1 and 2 years after biologic initiation.

Multivariable regression models included the following variables relating to the baseline year or time of biologic initiation:

- ICS dose
- OCS 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)

McNemar's test were used to test for an association between reduction status (reducer/non-reducer) at 1 and 2 years (compared to pre-biologic level in both cases).

Year-on-year persistence of a reduced ICS state was quantified as the conditional probability of remaining in that state in year $t + 1$ among patients observed and classified as State 1 in year t.

For each consecutive year pair (Y1→Y2 through Y4→Y5), the analysis was restricted to patients with non-missing values in both years, reflecting continued participation in the dataset. The number of patients who remained on a reduced ICS dose was divided by the total number of patients who reduced ICS dose in the prior year ("Total at Risk") to estimate the transition probability $P(1 \rightarrow 1)$. Patients with missing ICS reduction status at the subsequent time point were excluded from the corresponding transition denominators. Ninety-five percent confidence intervals for each persistence estimate were calculated using the Wilson score method for binomial proportions to provide accurate interval coverage, particularly under moderate sample sizes. These probabilities and confidence intervals form the basis of the year-on-year persistence plot with error bars.

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

i) The odds of reducing SABA use (compared with pre-biologic level) at 1, and 2 years after biologic initiation (OPCRD only).
ii) The odds of stepping down from triple therapy vs not at 1 and 2 years after biologic initiation (in patients on triple therapy in the baseline year).

The sample size of patients with complete data is likely to decrease with longer follow-up, therefore a survival analysis approach were 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 and will be right censored at the end of available follow-up if the event of interest has not occurred"

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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 allowed 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 allowed us to study whether time to 'late' 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 included all patients who initiate a first biologic regardless of whether they stopped or switched during follow. We conducted additional 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 may be associated with reduced ICS requirements in patients who tolerate the new treatment.

6.3 Software

All analyses were conducted using Stata version 15.1.

7.0 Results

7.1 Description of the study population and patient disposition

A description of the number of biologic initiator patients considered for and included in the study is provided in Table 4Error! Reference source not found.. Numbers by geographical settings contributing to ISAR are available in **14.1 Appendix 1**.

Table 4: Patient Flow.

	Patients	Excluded	% of Bx Pats
All OPCRD Patients	29,968,686		
Biologic patients	3,757		
Age ≥18 years	3,524	233	93.8%
Current asthma diagnosis 'ever'[1]	3,231	293	7.8%
At least 1 ICS Rx in the year prior	2,290	941	61.0%
≥2 exacerbations and medium dose ICS/LABA, OR high dose ICS/LABA[2]	1,928	362	51.3%
Same Day Dx Exclusion for Derm. or Rheum[3]	1,872	56	49.8%
Less than 6 months data	1,610	262	42.9%
OPCRD Patients meeting inclusion criteria	1,610		42.9%

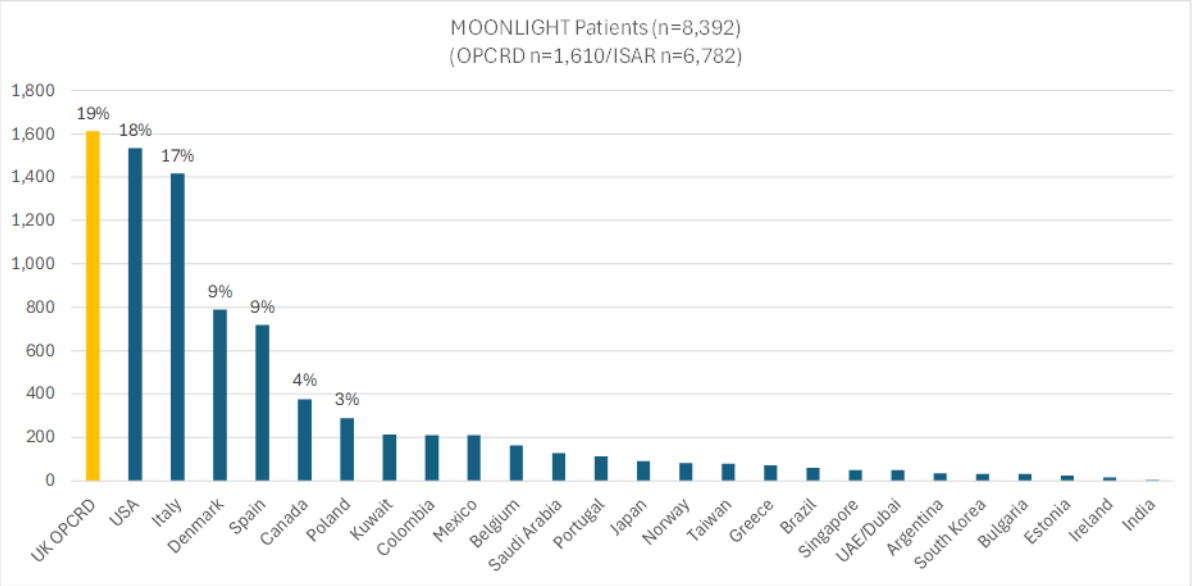
	Patients	Excluded	% of Bx Pats
All ISAR Patients	34,681		
Biologic patients	12,486		
Age ≥18 years	11,856	630	95.0%
At least 1 ICS In the year prior	9,046	2,810	72.4%
With a definitive Bx initiation date	8,916	130	75.2%
Patients with poor ISC follow up data	6,782	2,134	54.3%
ISAR Patients meeting inclusion criteria	6,782		54.3%

Total Study Population	8,392

1. QOF Dx, asthma general, asthma action plan, asthma review
2. Based on sensitive exacerbation definition of >1 acute OCS Rx's or maintenance OCS & patients' maximum dose in the last year
3. OPCRD: Same day (+/- 3 days) for Dermatology or Rehumatology and receiving dupilumab, omalizumab, or mepolizumab; ISAR: Patients have confirmed severe asthma, and biologic prescription is associated with asthma.

A total of 8,392 patients (6,782 Patients from ISAR, and 1,610 patients from OPCRD) were eligible for this analysis (see Table 4 for the patient flow). Patient characteristics are described in Table 5. In this study population, biologic therapy was initiated between 2004 and March 2025. The most frequent initiated class was anti-IL5/5R (4,271 patients 51.4%). Patients were from 26 countries, with UK (9%), USA (18%) Italy (17%), and Denmark (9%) encompassing most patients (Figure 2).

Figure 2: Distribution of patients by location



The mean age was similar between data sources (ISAR: 53.5 years; UK OPCRD: 50.9 years; SMD = 0.17), indicating good balance. The proportion of male patients was also comparable (ISAR: 37.0%; UK OPCRD: 39.5%; SMD = 0.05. In contrast, body mass index (BMI) showed moderate between-group imbalance (SMD = 0.47). A substantial imbalance was observed for smoking status (SMD = 2.40), indicating marked differences in smoking distributions between datasets. Clinical biomarkers and lung function measures were well balanced, including maximum eosinophil count (ISAR mean 524 cells/μL vs UK OPCRD 571 cells/μL; SMD = 0.07), FEV_1 (2.16 vs 2.13 L; SMD = 0.04), and FVC (3.17 vs 3.12 L; SMD = 0.04). Overall, the two data sources were well matched for most demographic and clinical characteristics, except for smoking status and, to a lesser extent, BMI. (Table 5).

Table 5: Baseline patient characteristics: biologic initiation, and pre-biologic demographic and clinical characteristics.

	Variables			ISAR			UK OPCRD			SMD
			n=	6,782			1,610			
Patient Demographics	**Age**	Mean (SD)		53.47	13.89		50.88	16.01		0.173
		Median (IQR)		55	44	64	53	38	63	
	Gender	Male (%)		2,512	37.0%		636	39.5%		0.052
	BMI Recorded or calculated	[1] Mean (SD)		28.03	7.57		31.66	8.58		0.470
		Median (IQR)		27.05	23.67	31.40	30.10	25.47	36.17	
	<18.5			173	2.6%		23	1.5%		
	18.5 to <25			2,132	32.0%		332	21.0%		
	25 to <30			2,237	33.6%		425	26.9%		
	30 to <35			1,291	19.4%		341	21.6%		
	35 to <40			509	7.6%		206	13.0%		
	40 to <80			316	4.7%		253	16.0%		
	Missing	n (%)		124	1.8%		30	1.9%		
	Smoking	[2]								2.396
	Non Smoker			4,611	68.7%		999	62.1%		
	Ex			1,903	28.3%		584	36.3%		
	Current			201	3.0%		25	1.6%		
	Missing	n (% total)		67	1.0%		2	0.1%		
Clinical Measurements	**Max Eosinophil**	[3] Mean (SD)		524	735		571	533		0.073
	<150	n (% non missing)		1,655	33.1%		57	4.4%		
	150 to <300			661	13.2%		295	23.0%		
	≥300			2,690	53.7%		930	72.5%		
	Missing	n (% total)		1,776	26.2%		328	20.4%		
	FEV_1	[4] Mean (SD)		2.16	0.84		2.13	0.81		0.036
	0 to <0.7	n (%)		14	0.3%		59	6.6%		
	Missing	n (% total)		2374	35.0%		715	44.4%		
	FVC	Mean (SD)		3.17	1.07		3.12	1.05		0.036
	0 to <0.8	n (% non missing)		3	0.0%		1	0.1%		
	Missing	n (% total)		2,365	34.9%		715	44.4%		
	FEV_1/FVC	Mean (SD)		0.70	0.26		0.68	0.13		0.080
	0 to <0.7	n (% non missing)		2,283	51.7%		483	51.1%		
	Missing	n (% total)		2,364	34.9%		664	41.2%		
	% Predicted FEV_1	Mean (SD)		75	22.02		68	25.78		0.293
	Missing	n (% total)		2438	35.9%		919	57.1%		
	Feno	Median (IQR)		32	16	63	33	17	65	0.004
	Missing	n (% total)		3,978	35.9%		1,444	57.1%		
Prescribing	**Acute OCS count in the year prior**	Mean (SD)		2	3.35		2	5.06		0.011
	GINA step									
	Step 4	n (% non missing)		6,476	95.5%		1,557	96.7%		0.063
	Step 5			306	4.5%		53	3.3%		
	Biologic initiation									0.425
	Benralizumab	n (% non missing)		1114	16.4%		452	28.1%		
	Dupilumab			976	14.4%		233	14.5%		
	Mepolizumab			2076	30.6%		422	26.2%		
	Omalizumab			2424	35.7%		413	25.7%		
	Reslizumab			94	1.4%		1	0.1%		
	Tezepelumab			98	1.4%		89	5.5%		
Comorbidity	Allergic rhinitis	%		61%			52%			
	Chronic rhinosinusitis			65%			15%			
	Chronic rhinosinusitis + Nasal polyps			39%			8%			
	Eczema			17%			46%			
	Osteoporosis			16%			10%			
	Diabetes			11%			12%			

1. BMI nearest index date. Either recorded or calculated (when height and weight recordings are within 1 month of each other). N.B. BMI<10 & >80, height <40 & >220, and weight<2 & >400 excluded; 2. Smoking nearest, and prior to index date; 3. Maximum Eosinophil reading prior to index date; 4. Spirometry measurements and FeNo made nearest prior to index date

Mean age was similar across groups, with minimal between-group imbalance (Reducers 53.4 years; Increasers 51.4 years). Sex distribution was also comparable between groups with small SMDs. Baseline clinical characteristics, including eosinophil counts and spirometry indices, were broadly similar across ICS change categories with low SMDs, suggesting adequate comparability of lung function and inflammatory burden prior to biologic initiation.

Patients were classified according to their ICS dose trajectory over follow-up based on comparison with baseline ICS dose at all available post-biologic assessments: reducers ever (n=1,632) were patients with at least one recorded ICS dose lower than baseline and no increases above baseline; increasers ever (n=502) had at least one recorded ICS dose higher than baseline and no reductions below baseline; stable (n=6,152) had a stable ICS dose throughout follow-up; and mixed treatment patterns (n=106) had both increases and reductions relative to baseline at different follow-up time points. Baseline characteristics of these groups were compared descriptively to explore whether patients with differing longitudinal ICS dose trajectories differed in their pre-biologic clinical characteristics (Table 6).

Follow-up duration differed across ICS trajectory groups (Table 6). Patients with no change in ICS dose had the shortest follow-up, whereas those with mixed dose trajectories had the longest follow-up. This pattern is consistent with longer observation periods providing greater opportunity to observe changes in ICS dose over time.

Table 6: Patient Characteristics according to whether patients reduced, increased, remained the same or had a mixed increase/reduction during follow up period

	Variables		Reducers			Increasers			Stable			Mixed		
		n=	1,632	19%		502	6%		6,152	73%		106	1%	
Patient Demographics	**Age**	Mean (SD)	53.37	14.53		51.40	14.81		52.99	14.26		53.01	14.72	
		Median (IQR)	55	43	64	54	42	62	54	44	63	55	45	64
	Gender	Male (%)	617	37.8%		194	38.6%		2,304	37.5%		33	31.1%	
	BMI Recorded or calculated [1]	Mean (SD)	28.86	9.55		29.28	7.07		28.65	7.50		28.49	5.49	
		Median (IQR)	27.34	23.87	32.45	28.58	24.22	32.95	27.48	23.92	32.07	28.22	24.22	31.56
	<18.5		36	2.2%		8	1.6%		151	2.5%		1	0.9%	
	18.5 to <25		505	31.3%		134	27.1%		1,794	29.8%		31	29.2%	
	25 to <30		508	31.5%		156	31.6%		1,965	32.6%		33	31.1%	
	30 to <35		315	19.5%		101	20.4%		1,189	19.7%		27	25.5%	
	35 to <40		129	8.0%		61	12.3%		515	8.5%		10	9.4%	
	40 to <80		121	7.5%		34	6.9%		410	6.8%		4	3.8%	
			1614			494			6024			106		
	Missing	n (%)	18	1.1%		8	1.6%		128	2.1%		0	0.0%	
	Smoking [2]													
	Current		941	57.7%		247	49.4%		3,392	55.7%		56	53.3%	
	Ex		494	30.3%		170	34.0%		1,782	29.3%		41	39.0%	
	Non Smoker		195	12.0%		83	16.6%		914	15.0%		8	7.6%	
			1630			500			6088			105		
	Missing	n (% total)	2	0.1%		2	0.4%		64	1.0%		1	0.9%	
	Follow up (days)	Median (IQR)	1,441	834	2,151	1,711	1,058	2,290	1,042	520	1,863	1,909	1,419	2,454
Clinical Measurements	**Max Eosinophil** [3]	Mean (SD)	387	623		485	706		588	717		310	444	
	<150	n (% non missing)	625	45.0%		122	31.7%		923	20.8%		42	50.6%	
	150 to <300		170	12.2%		72	18.7%		702	15.8%		12	14.5%	
	≥300		594	42.8%		191	49.6%		2,806	63.3%		29	34.9%	
	Missing	n (% total)	243	14.9%		117	23.3%		1,721	28.0%		23	21.7%	
	FEV1 [4]	Mean (SD)	3.17	1.07		2.24	0.88		2.14	0.83		2.34	0.92	
	0 to <0.7	n (%)	17	1.3%		2	0.5%		54	1.5%		0	0.0%	
	Missing	n (% total)	313	19.2%		135	26.9%		2619	42.6%		20	18.9%	
	FVC	Mean (SD)	3.12	1.05		3.19	1.08		3.15	1.06		3.27	1.14	
	0 to <0.8	n (% non missing)	723	54.0%		1	0.3%		3	0.1%		86	100.0%	
	Missing	n (% total)	293	18.0%		134	26.7%		2,613	42.5%		20	18.9%	
	FEV1/FVC	Mean (SD)	0.68	0.15		0.71	0.15		0.68	0.16		0.71	0.12	
	0 to <0.7	n (% non missing)	723	54.4%		165	44.6%		1,844	51.6%		34	32.1%	
	Missing	n (% total)	302	18.5%		132	26.3%		2,575	41.9%			0.0%	
	% Predicted FEV1	Mean (SD)	74	22.56		75	24.26		74	22.55		82	22.96	
	Missing	n (% total)	875	53.6%		308	61.4%		4,158	67.6%		73	68.9%	
	Feno	Median (IQR)	31	17	64	31	14	63	32	16	62	33	19	73
	Missing	n (% total)	830	50.9%		313	62.4%		4,222	68.6%		57	53.8%	
Prescribing	**Acute OCS count in the year prior**	Mean (SD)	1.8	3.11		2.9	3.80		2.7	4.13		1.9	3.83	
	GINA step													
	Step 4	n (% non missing)	1,561	95.6%		475	94.6%		5,895	95.8%		102	96.2%	
	Step 5		71	4.4%		27	5.4%		257	4.2%		4	3.8%	
	Biologic initiation													
	Benralizumab	n (% non missing)	323	19.8%		66	13.1%		1161	18.9%		16	15.1%	
	Dupilumab		315	19.3%		54	10.8%		825	13.4%		15	14.2%	
	Mepolizumab		451	27.6%		163	32.5%		1846	30.0%		38	35.8%	
	Omalizumab		497	30.5%		212	42.2%		2092	34.0%		36	34.0%	
	Reslizumab		19	1.2%		6	1.2%		69	1.1%		1	0.9%	
	Tezepelumab		27	1.7%		1	0.2%		159	2.6%		0	0.0%	
Comorbidity	Allergic rhinitis	%	872	53.4%		295	58.8%		3321	54.0%		55	51.9%	
	Chronic rhinosinusitis		940	57.6%		231	46.0%		2982	48.5%		48	45.3%	
	Chronic rhinosinusitis + Nasal polyps		484	29.7%		129	25.7%		1278	20.8%		23	21.7%	
	Eczema		346	21.2%		131	26.1%		1897	30.8%		22	20.8%	
	Osteoporosis		254	15.6%		73	14.5%		785	12.8%		23	21.7%	
	Diabetes		174	10.7%		58	11.6%		558	9.1%		15	14.2%	

1. BMI nearest index date. Either recorded or calculated (when height and weight recordings are within 1 month of each other). N.B. BMI<10 & >80, height <40 & >220, and weight<2 & >400 excluded; 2. Smoking nearest, and prior to index date; 3. Maximum Eosinophil reading prior to index date; 4. Spirometry measurements and FeNo made nearest prior to index date

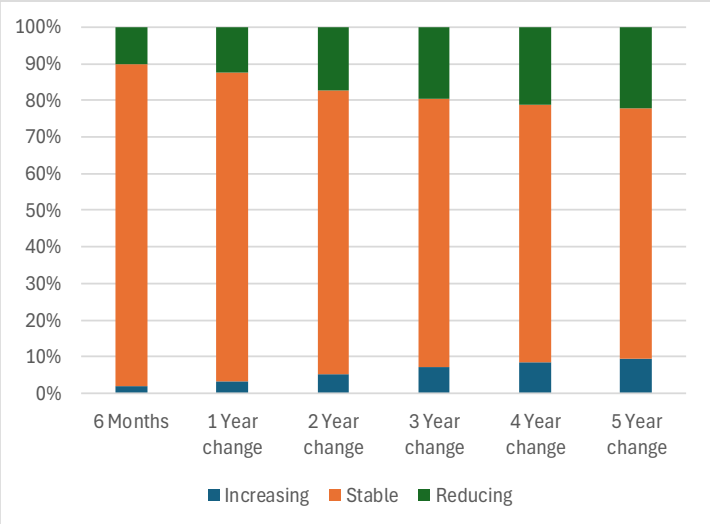
7.2 Objective 1

Change in ICS use

At baseline, most patients 59% were receiving high-dose ICS therapy, with 35% on medium dose and 6% on low dose, indicating a predominantly high-treatment population prior to biologic initiation. ICS Daily Dose were also measured as a change from baseline (before biologic initiation) at 6 months, 1, 2, 3, 4 and 5 years after biologic initiation. 837 (10%) patients were shown to have reduced ICS at 6 months, rising to 22% after 5 years (Figure 3).

These estimates are cumulative, such that patients with a reduction at earlier time points (e.g. 6 or 1 year) are included in subsequent time points providing their ICS daily dose remains lower than baseline. Time-to-event analysis (Figure 4) showed that most first ICS reductions occurred within the first 1–2 years following biologic initiation, with a plateau thereafter.

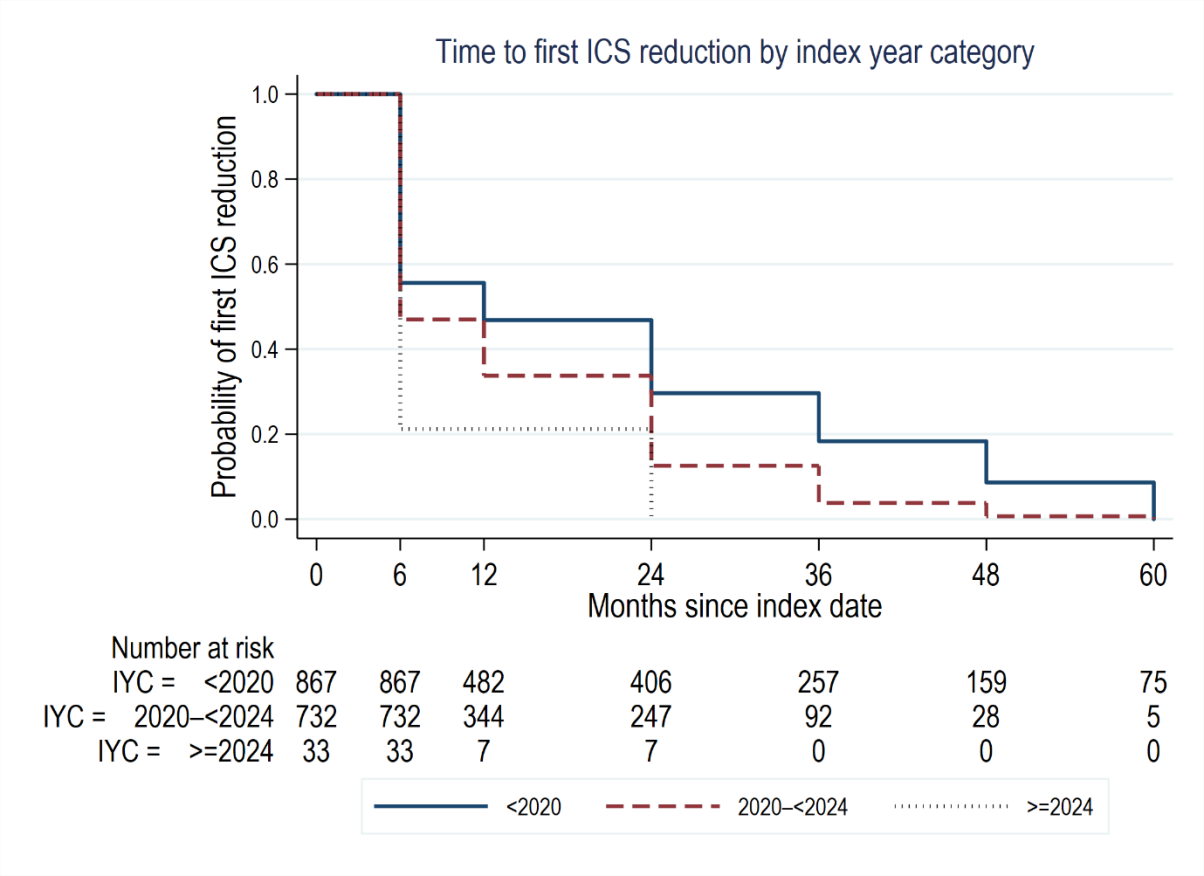
Figure 3: Number and percentage of patients changing ICS dose after biologic initiation



	Increasing		Stable		Reducing		
6 Months	166	2%	7389	88%	837	10%	8392
1 Year change	236	3%	6161	84%	900	12%	7297
2 Year change	306	5%	4433	77%	982	17%	5721
3 Year change	309	7%	3227	73%	859	20%	4395
4 Year change	272	8%	2305	71%	689	21%	3266
5 Year change	224	10%	1608	68%	524	22%	2356

To further characterise the timing of ICS reduction following biologic initiation, Kaplan–Meier analysis was undertaken to assess time to first ICS dose reduction stratified by biologic initiation year category (Figure 5). Patients initiating biologic therapy in more recent years demonstrated earlier time to first ICS reduction, suggesting increasing adoption of ICS down-titration in contemporary clinical practice. Interpretation of the ≥2024 cohort should be cautious due to limited follow-up and small sample size.

Figure 4: Kaplan–Meier Curve Showing Time to First sustained ICS Reduction by Biologic Initiation Year Category

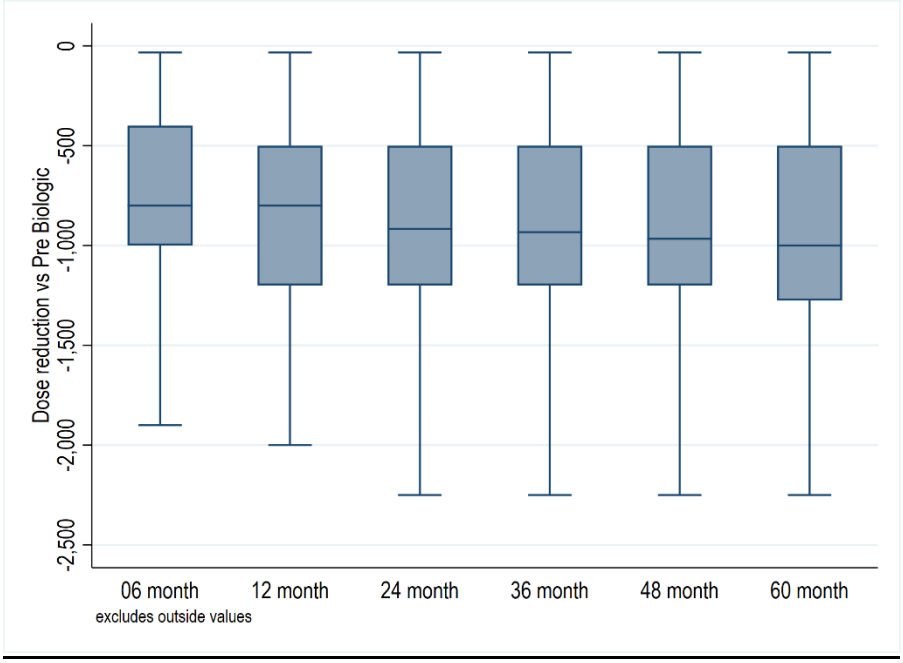


For patients that had a reduction in ICS dose the median reduction was 800mcgs (IQR 400-1000) at 6 months rising to 1000mcgs at 5 years (IQR 500-1275) (Table 7, Figure 5).

Table 7: Number of patients with an ICS reduction and median ICS change.

Patients ICS reducers	Pre Biologic	6 Month			1 Year			2 Years			3 Years			4 Years			5 Years		
ICS reduction (n, %)	8,392	837	8,392	10%	900	7,297	12%	982	5,721	17%	859	4,395	20%	689	3,266	21%	524	2,356	22%
Median Reduction (IQR)	-	800	400	1000	800	500	1200	916	500	1200	933	500	1200	966	500	1200	1,000	500	1275
Mean (95% CI's)	-	921	871	970	952	866	981	1,012	870	1016	1,031	868	1042	1,042	845	1069	1,081	833	1128

Figure 5: Boxplots showing spread of ICS dose reduction



Change in ICS dose by Location

Reducing patients vary greatly across the countries with USA (n=706 [46%]), Belgium (n=57 [35%]), Japan (n=28 [31%]), Canada (n=97 [26%]), and Singapore (n=12 [23%]) having the largest % of patients with a reducing ICS dose (Figure 6, Table 8).

Figure 6: Change in ICS by country

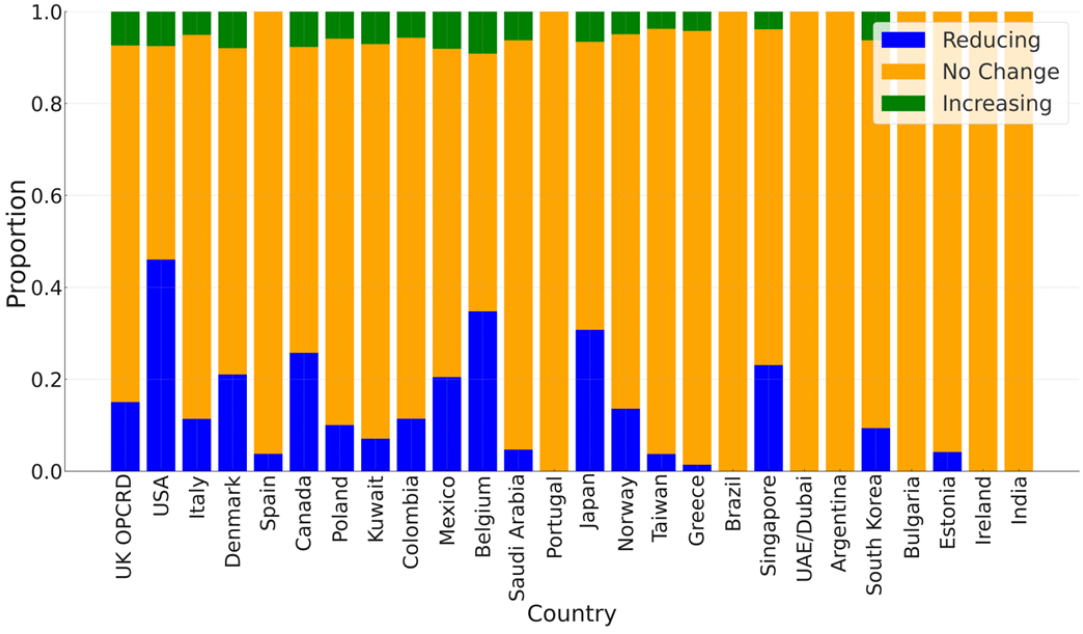


Table 8: Number of patients Increasing, Stable and Reducing, by location

	Reducing		No Change		Increasing		Total
UK OPCRD	242	15.0%	1,249	77.6%	119	7.4%	1,610
USA	706	46.1%	712	46.4%	115	7.5%	1,533
Italy	161	11.4%	1,183	83.5%	72	5.1%	1,416
Denmark	166	21.0%	560	71.0%	63	8.0%	789
Spain	27	3.8%	690	96.2%	0	0.0%	717
Canada	97	25.7%	251	66.6%	29	7.7%	377
Poland	29	10.0%	243	84.1%	17	5.9%	289
Kuwait	15	7.1%	182	85.8%	15	7.1%	212
Colombia	24	11.4%	174	82.9%	12	5.7%	210
Mexico	43	20.5%	150	71.4%	17	8.1%	210
Belgium	57	34.8%	92	56.1%	15	9.1%	164
Saudi Arab	6	4.7%	114	89.1%	8	6.3%	128
Portugal	0	0.0%	112	100.0%	0	0.0%	112
Japan	28	30.8%	57	62.6%	6	6.6%	91
Norway	11	13.6%	66	81.5%	4	4.9%	81
Taiwan	3	3.8%	74	92.5%	3	3.8%	80
Greece	1	1.4%	67	94.4%	3	4.2%	71
Brazil	0	0.0%	61	100.0%	0	0.0%	61
Singapore	12	23.1%	38	73.1%	2	3.8%	52
UAE/Duba	0	0.0%	50	100.0%	0	0.0%	50
Argentina	0	0.0%	35	100.0%	0	0.0%	35
South Kore	3	9.4%	27	84.4%	2	6.3%	32
Bulgaria	0	0.0%	31	100.0%	0	0.0%	31
Estonia	1	4.2%	23	95.8%	0	0.0%	24
Ireland	0	0.0%	16	100.0%	0	0.0%	16
India	0	0.0%	1	100.0%	0	0.0%	1
Total	1,632		6,258		502		8,392

Change in ICS dose 1 versus 2 years

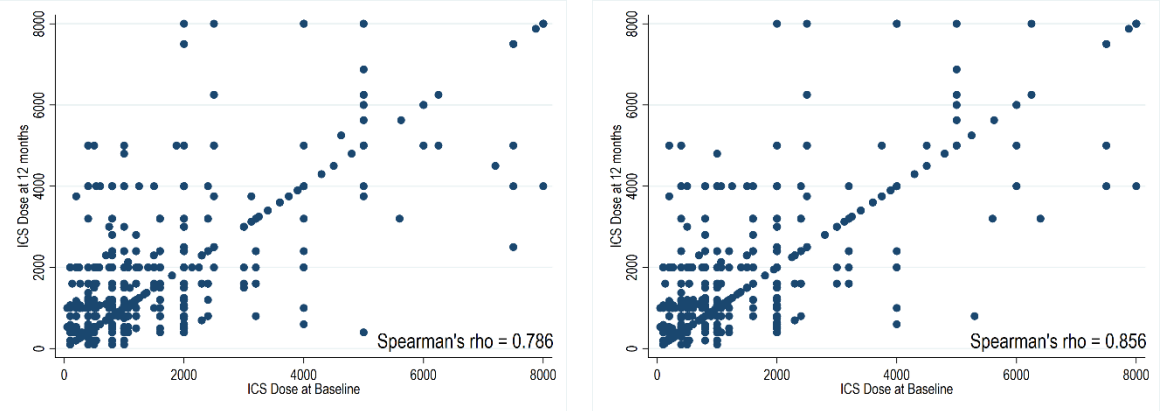
Scatterplots were drawn to illustrate the relationship between inhaled corticosteroid (ICS) dose at baseline and ICS dose at 1 and 2 years (Figure 7).

A total of 7,297 patients contributed data at 1 year and 5,721 at 2 years, with analyses restricted to patients with available follow-up at each timepoint.

As discussed, above the majority of patients didn't change ICS dose and thus spearman's correlation showed a strong correlation of 0.856 baseline to 1 year, and 0.786 baseline to 2 years (Figure 7). However, to specifically assess whether reductions are sustained, analyses were restricted to patients who achieved an ICS reduction in the first year; among

these patients, persistence of reduction was high, with over 90% remaining at a reduced dose at subsequent timepoints.

Figure 7: Scatterplot showing ICS dose at baseline and at 1 and 2 years



Change in ICS dose and Low, Medium, High Category

Among patients who reduced ICS dose between baseline and 1 year (n = 900), 672 (75%) also had a decrease in LMH category, where categories were defined as low (≤500 mcg/day), medium (>500 to <1000 mcg/day), and high (≥1000 mcg/day) (Table 9).

Table 9: Transition Matrix of ICS Dose Category from Baseline to Year 1

	Patient Count			Median Dose Change		
	Low	Medium	High	Low	Medium	High
Low	22			-200		
Medium	187	60		-500	-200	
High	123	362	146	-1500	-1000	-933
Total			900			

Category Change=672

Change in FEV_1 by ICS dose trajectory

Sample sizes in this analysis are smaller than in previous sections due to missing FEV_1 data at baseline and/or 1 year. Median change in FEV_1 % predicted was highest among reducers (2.4, IQR −2.3 to 12.5), compared with increasers (1.0, IQR −3.8 to 9.8) and those with a stable dose (0.4, IQR −2.2 to 10.3) (Figure 8).

Figure 8: Change in FEV_1 % predicted from baseline to 1 year by ICS Dose Change group.

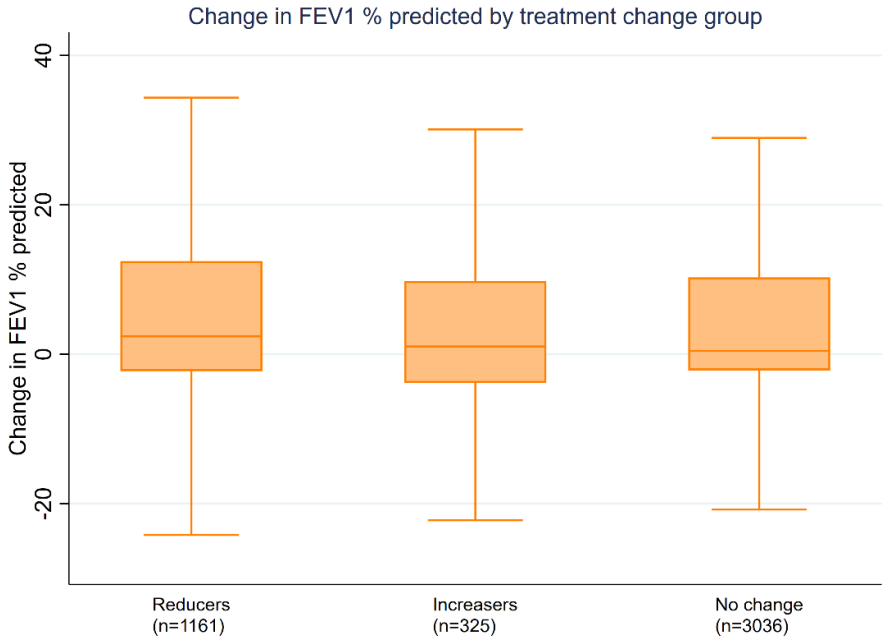


Table 10: Change in FEV_1 % predicted from Baseline to year 1 by ICS Dose Change Group

Group	N	FEV change, median (IQR)	Pairwise Comparison p-value*
Reducers	1161	2.40 (-2.27 to 12.46)	Reference
Increasers	325	1.03 (-3.85 to 9.79)	0.016 vs Reducer
No change	3036	0.44 (-2.17 to 10.29)	0.022 vs Reducers; 0.208 vs Increasers
Total	4604	1.04 (-2.37 to 10.87)	

*Pairwise Wilcoxon rank-sum tests with Bonferroni correction (significance threshold p<0.0167)

Median change in FEV_1 % predicted from baseline to year 1 was numerically greatest among patients who reduced ICS dose (2.4, IQR −2.3 to 12.5), compared with those who increased ICS dose (1.0, IQR −3.8 to 9.8) and those with a stable dose (0.4, IQR −2.2 to 10.3).

Overall differences across groups were modest but statistically significant (Kruskal–Wallis p=0.019). Pairwise comparisons suggested a difference between reducers and increasers (Bonferroni-adjusted p=0.016; adjusted significance threshold 0.017), while no other pairwise comparisons were statistically significant (Table 10).

Despite the numerically greater improvement among reducers, the magnitude of change was small and unlikely to be clinically meaningful at the population level, and distributions overlapped substantially across groups.

Change in ICS dose over time

Analysis on the number of patients receiving high dose ICS at each year by year of initiation showed that among patients who underwent ICS dose reduction, the proportion receiving high-dose ICS showed a consistent decline over time following biologic initiation across all index-year strata. Patients initiated before 2020 showed a gradual decline from approximately 70% at baseline to around 25% by 5 years, while those initiated in 2020–2023 declined more steeply from 70% to 10% by 5 years with a more pronounced early reduction followed by a continued downward trend. Patients initiated in 2024–2025 had the highest baseline prevalence of high-dose ICS use (85%), although follow-up remained limited in this most recent cohort.

Median ICS dose also decreased over time. The greatest reduction was observed in the 2020–2023 cohort, in whom median dose declined from 2000 at baseline to approximately 800 by 4-5 years. In contrast, median dose in the <2020 cohort decreased to approximately 1000 by 6 months and continued to decline gradually to around 800 by 4–5 years. Estimates for the 2024–2025 cohort should be interpreted cautiously due to limited follow-up and small sample size (Figure 9).

Figure 9: Changes in High-Dose ICS Use and Dose After Biologic Initiation, among those who reduced their ICS dose during the study

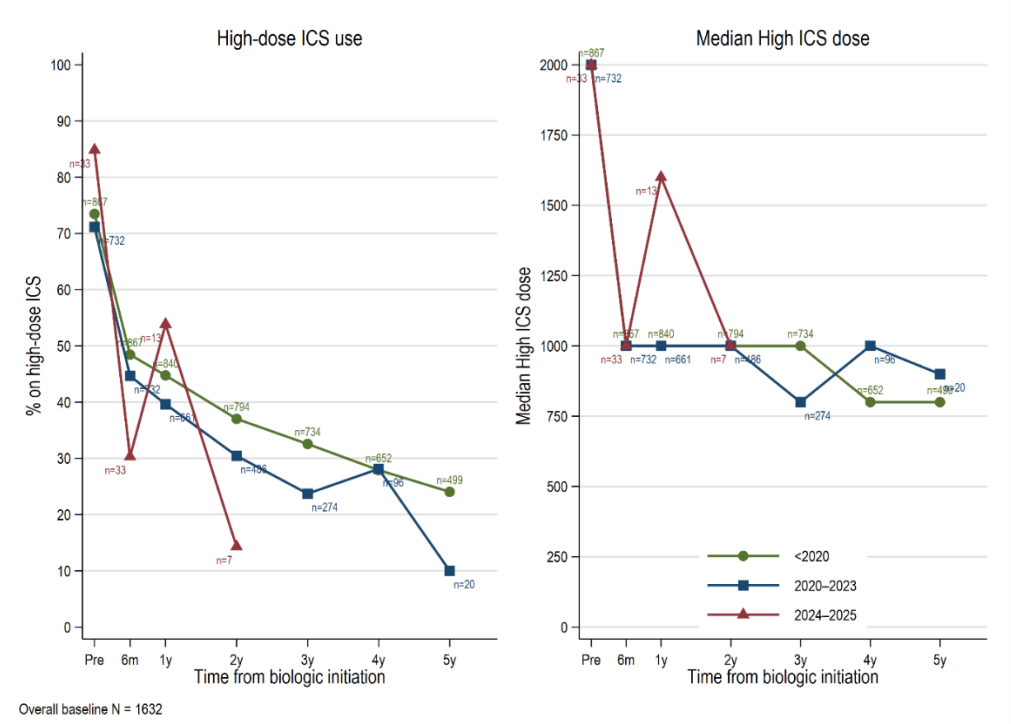
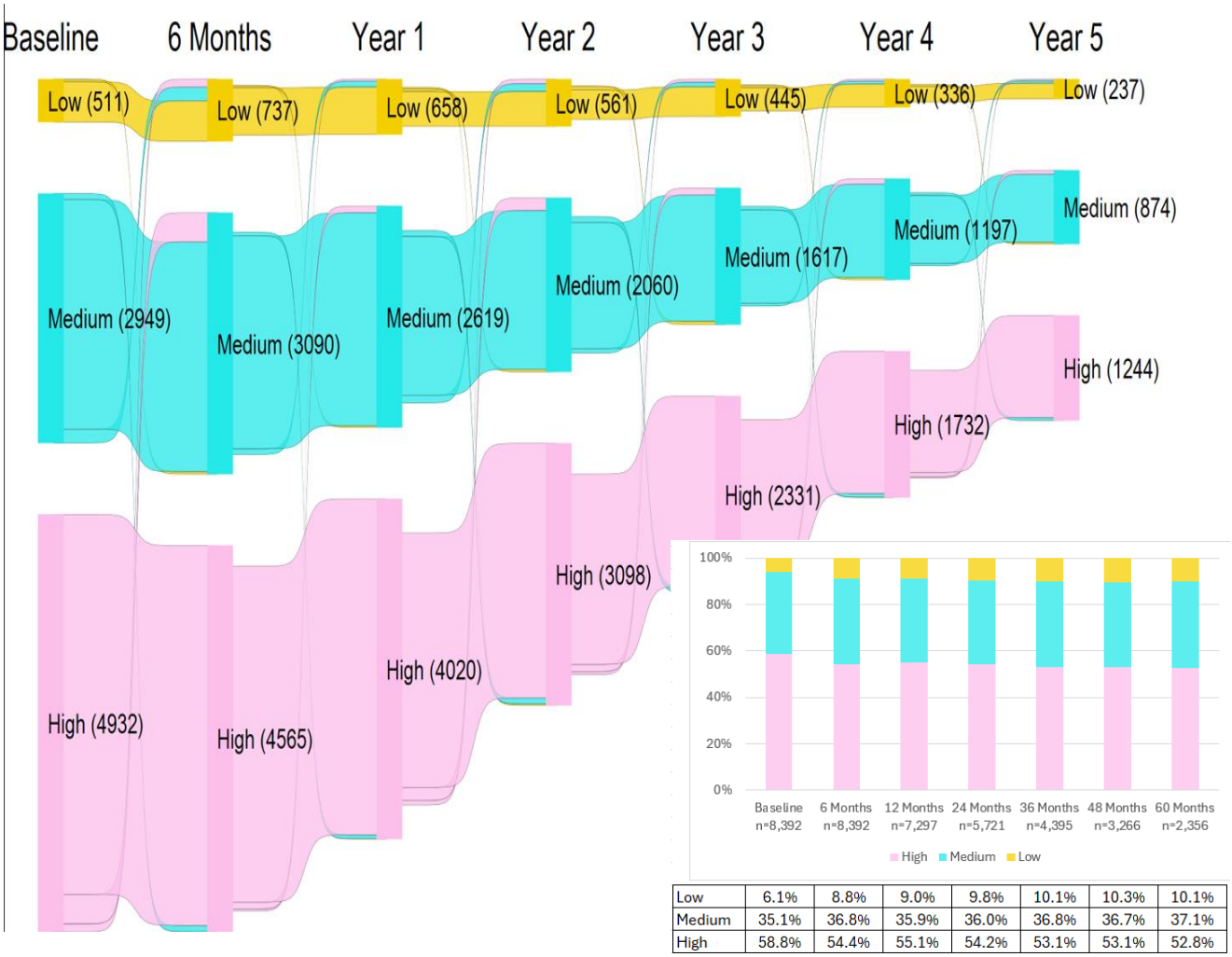


Figure 10: River plot showing transitions in ICS dose category over 5-year follow-up (all patients)

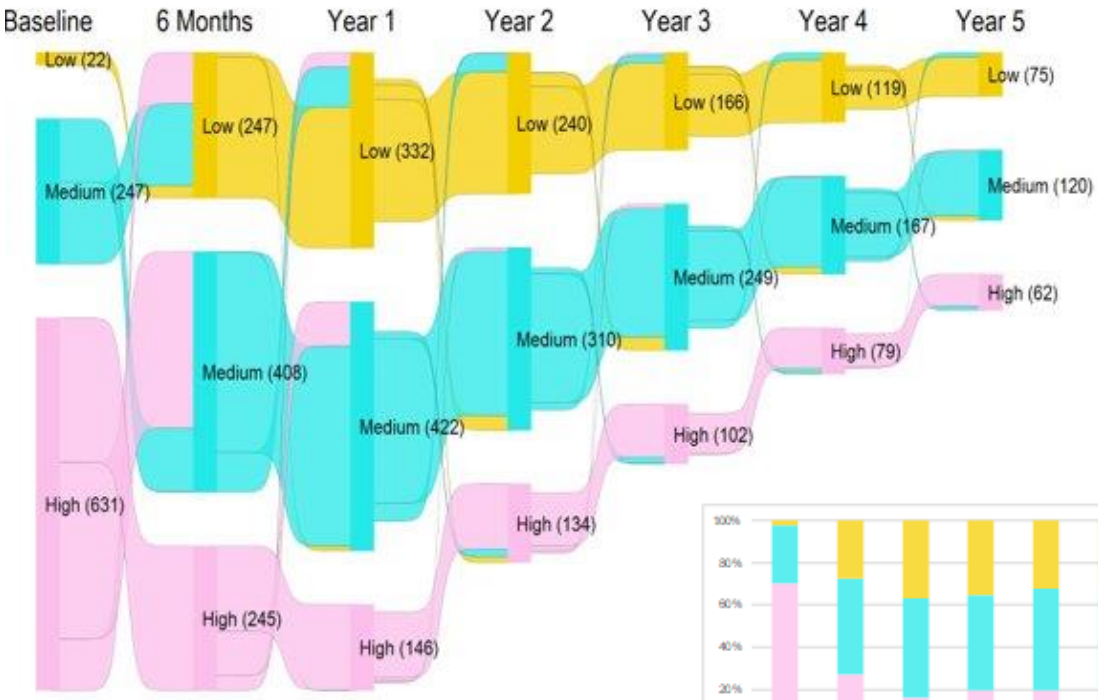


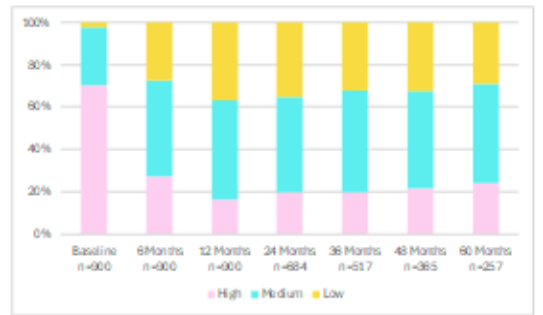
Low	6.1%	8.8%	9.0%	9.8%	10.1%	10.3%	10.1%
Medium	35.1%	36.8%	35.9%	36.0%	36.8%	36.7%	37.1%
High	58.8%	54.4%	55.1%	54.2%	53.1%	53.1%	52.8%

In contrast to the limited category transitions observed in the overall cohort, a Sankey-style diagram was constructed to characterise patterns among patients who reduced ICS dose (Figure 10).

Figure 11 shows changes in ICS dose categories (low, medium, high) over time among patients who reduced ICS dose, demonstrating directional movement toward lower dose categories within this subgroup. Most patients began in the high-dose category and transitioned to medium and low categories by 6 months, with continued movement over time. The high-dose group declined steadily, while the medium-dose group appeared to act as a transitional state. By Years 3–5, a greater proportion of patients were in the low-dose category, although some variability remained. The accompanying bar chart, presented as percentages, confirms the increasing proportion of patients in lower dose categories over time.

Figure 11: River plot showing transitions in ICS dose category over 5-year follow-up among patients who reduced ICS dose





Low	2.4%	27.4%	36.9%	35.1%	32.1%	32.6%	29.2%
Medium	27.4%	45.3%	46.9%	45.3%	48.2%	45.8%	46.7%
High	70.1%	27.2%	16.2%	19.6%	19.7%	21.6%	24.1%

This contrasts with the overall cohort, where transitions between dose categories were relatively uncommon. This reflects that category transitions are concentrated among patients who undergo dose reduction, rather than being widely distributed across the overall cohort.

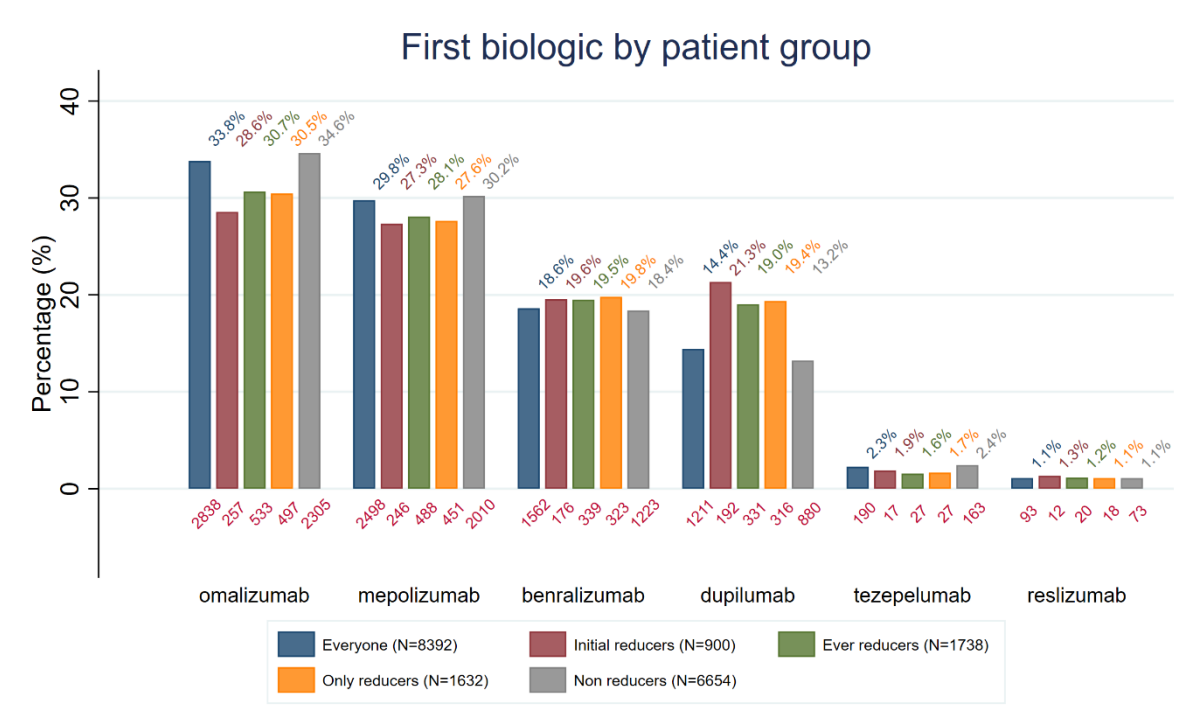
Biologic treatment patterns and switching

To further characterise treatment pathways following biologic initiation, biologic initiation patterns and switching during follow-up were examined according to ICS dose reduction status.

First biologic distribution

The distribution of first biologic therapy was broadly similar across ICS dose trajectory groups. Omalizumab (29–35%) and mepolizumab (27–30%) were the most initiated therapies across all groups, with minimal variation. Benralizumab accounted for approximately 18–20% of initial treatments. Dupilumab use varied more noticeably, being less frequent among non-reducers (~13%) and more common among reducers (~19–21%). Tezepelumab and reslizumab were used infrequently across all groups (<3%) (Figure 12).

Figure 12: Distribution of First Biologic Therapy by ICS Dose Reduction Group



Biologic switching patterns

Overall, 22.4% of patients switched biologic therapy during follow-up. Switching was more frequent among patients who experienced ICS reduction (27.6%) compared with those who did not (21.0%), with a higher proportion undergoing one or multiple switches. Patients without ICS reduction were more likely to remain on their initial therapy (79.0%).

Among those who switched, median time to first switch was similar across groups, ranging from approximately 747 to 779 days. Statistical comparisons between groups were significant (all p<0.001), although these findings reflect associations rather than causal relationships (Table 11).

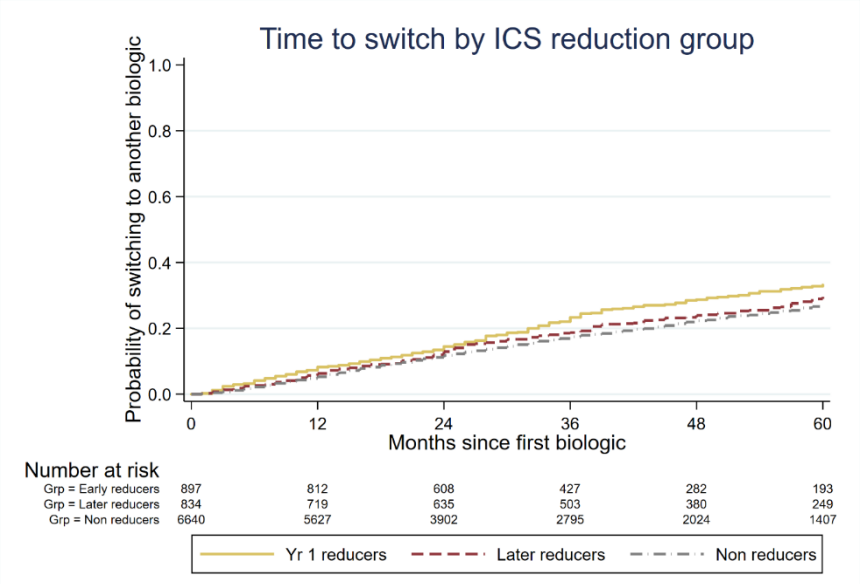
Table 11: Biologic Switching Patterns by ICS Dose Reduction Status

Group	Patients	Switched	Didn't switch	One Switch	>1 Switch	Median days to switch (IQR)
Whole population	8,392	1,879 (22.4%)	6,513 (77.6%)	1,466 (17.5%)	413 (4.9%)	774 (371 to 1463)
Initial Reducers (Year 1)	900	248 (27.6%)	652 (72.4%)	181 (20.1%)	67 (7.4%)	747 (316 to 1173)
Ever Reduced	1,738	479 (27.6%)	1,259 (72.4%)	356 (20.5%)	123 (7.1%)	777 (364 to 1310)
Never Reduced	6,654	1,400 (21.0%)	5,254 (79.0%)	1,110 (16.7%)	290 (4.4%)	773 (378 to 1518)
Only Reducers	1,632	438 (26.8%)	1,194 (73.2%)	326 (20.0%)	112 (6.9%)	779 (357 to 1310)
P value: Ever Reduced vs Never Reduced		<0.001	<0.001	<0.001	<0.001	.

Time to biologic switching

Kaplan–Meier analysis demonstrated a gradual increase in the cumulative probability of switching over 5 years across all groups. Patients who reduced ICS in the first year showed a consistently higher probability of switching over time, followed by later reducers, while non-reducers had the lowest probability throughout follow-up. Separation between groups was modest but persistent and became more apparent after approximately 1-2 years. By 5 years, approximately one-third of early reducers had switched biologic therapy, compared with lower proportions among later reducers and non-reducers (Figure 13).

Figure 13: Time to Biologic Switching by ICS Dose Reduction Group



These findings indicate that biologic treatment pathways are dynamic in clinical practice, with a substantial minority of patients requiring treatment optimisation over time, including both switching of biologic therapy and simplification of inhaled treatment regimens.

Change in SABA Use

In the OPCRD cohort (n=1,610) SABA use among patients receiving biologics remained highly prevalent across follow-up. Pre-biologic, 92% of patients were SABA users; this proportion declined modestly to 87% at 1 year and 82% at 2 years and remained broadly stable thereafter at 80–82% through Year 5 as the cohort size declined. The proportion of patients with no recorded SABA use increased from 8% pre-biologic to 18% by Year 5

932 of the 1,610 patients (58%) experienced at least one reduction in SABA during the 5 years follow-up. However, this represents a cumulative measure, and the likelihood of observing any reduction increases over time, so this estimate should be interpreted cautiously. Median annual SABA prescriptions decreased from 7 at baseline to 6 at Year 1, 5 at Year 2, and remained at 5 through Year 4 before declining to 4 at Year 5. These estimates reflect the overall cohort rather than being restricted to patients who reduced SABA use (Table 12a, Figure 14).

Additional analysis was undertaken to investigate whether patients who experienced an ICS reduction in the first year had differing reductions in SABA use. Patients who had an initial reduction in ICS started with lower baseline SABA use (85% vs 92%), and showed greater reductions in SABA use over time (76% at Year 1 and 69% at Year 2) and maintained lower median SABA use compared with the overall patient population (baseline 5 vs 7; Year 2 onward 2 vs 5) (Table 12b).

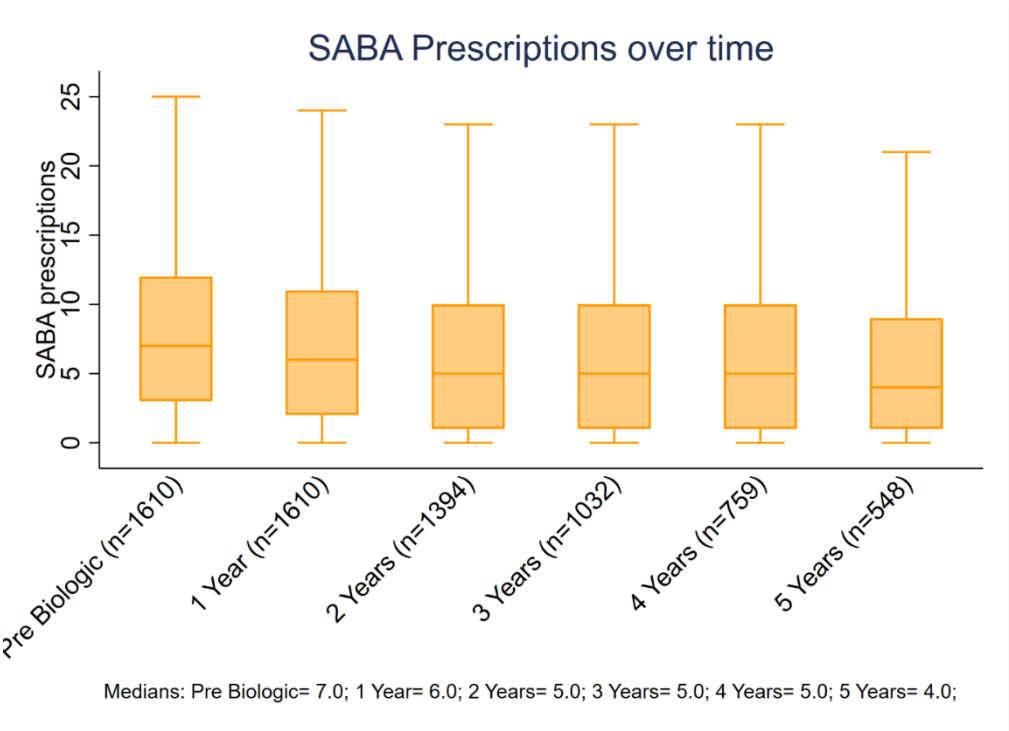
Table 12a): All patients - SABA reduction and median change.

OPCRD Patients	Pre Biologic	1 Year	2 Years	3 Years	4 Years	5 Years
SABA Patients	1,610	1,610	1,394	1,032	759	548
No SABA	132 (8%)	208 (13%)	248 (18%)	203 (20%)	143 (19%)	97 (18%)
SABA	1,478 (92%)	1,402 (87%)	1,146 (82%)	829 (80%)	616 (81%)	451 (82%)
Median SABAs	7	6	5	5	5	4

Table 12b): Patients with ICS reduction in the first year - SABA reduction and median change

OPCRD Patients	Pre Biologic	1 Year	2 Years	3 Years	4 Years	5 Years
SABA Patients	103	103	85	65	47	31
No SABA	15 (15%)	25 (24%)	26 (31%)	26 (40%)	17 (36%)	7 (23%)
SABA	88 (85%)	78 (76%)	59 (69%)	39 (60%)	30 (64%)	24 (77%)
Median SABAs	5	3	2	2	2	2

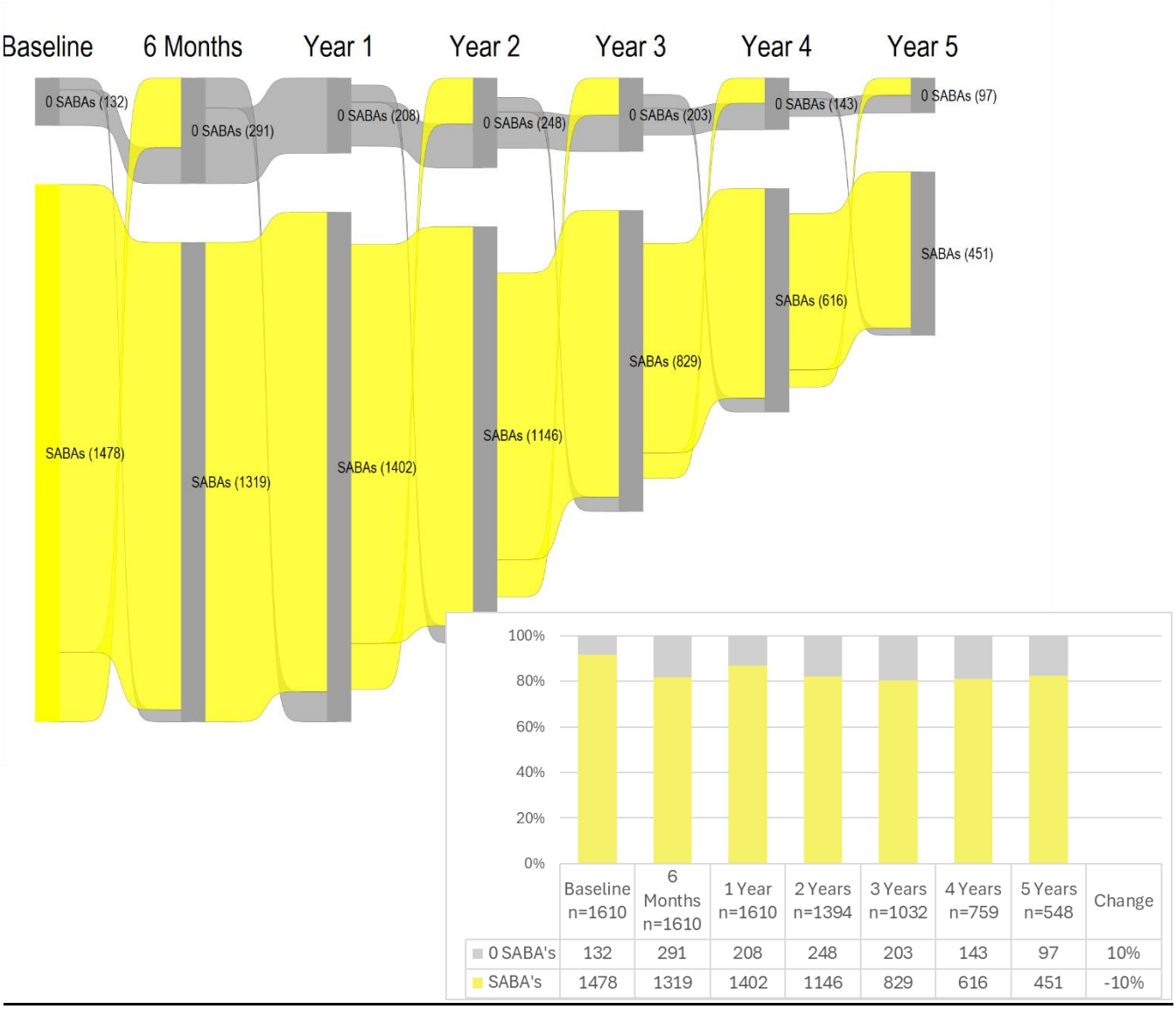
Figure 14: Boxplots showing spread of SABA prescriptions reduction



Change in SABA use at all timepoints

SABA use showed modest reductions over the 5-year follow-up. At baseline median annual SABA prescriptions were 7, decreasing to 6 at 1 year and 5 by 2 years. By Years 2–4, median SABA prescriptions remained stable at 5, before declining to 4 by Year 5. Boxplot distributions demonstrated that although median SABA prescriptions decreased over time, substantial variability in prescribing remained, with persistent upper-range SABA use across follow-up. Overall, SABA reliance remained high despite modest reductions in prescribing burden over time (Figure 15).

Figure 15: River plot showing how SABA use changed over the 5-year follow-up



	Baseline n=1610	6 Months n=1610	1 Year n=1610	2 Years n=1394	3 Years n=1032	4 Years n=759	5 Years n=548	Change
0 SABA's	132	291	208	248	203	143	97	10%
SABA's	1478	1319	1402	1146	829	616	451	-10%

Change in Triple (ICS/LABA/LAMA) Use

In the ISAR and OPCRD cohorts, 56% of patients were receiving triple therapy at baseline. This reduced to 51% in the first 6 months and declined to 48% at the end of the 5 years follow-up, representing an overall reduction of approximately 10 percentage points (Figure 16).

Figure 3: Triple therapy use: Proportion of patients receiving triple therapy over time

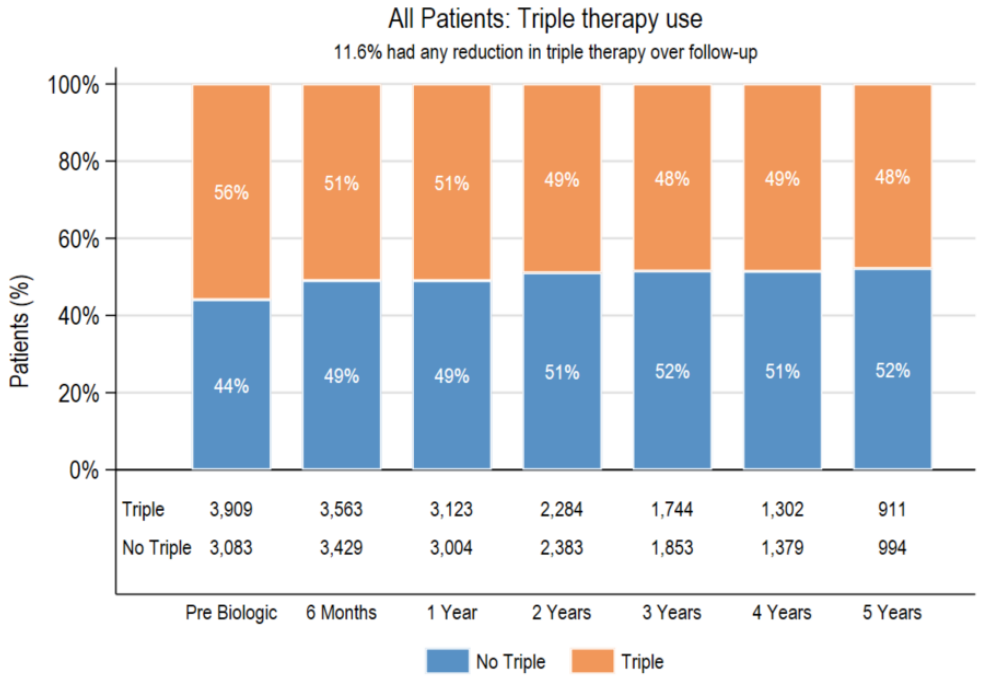
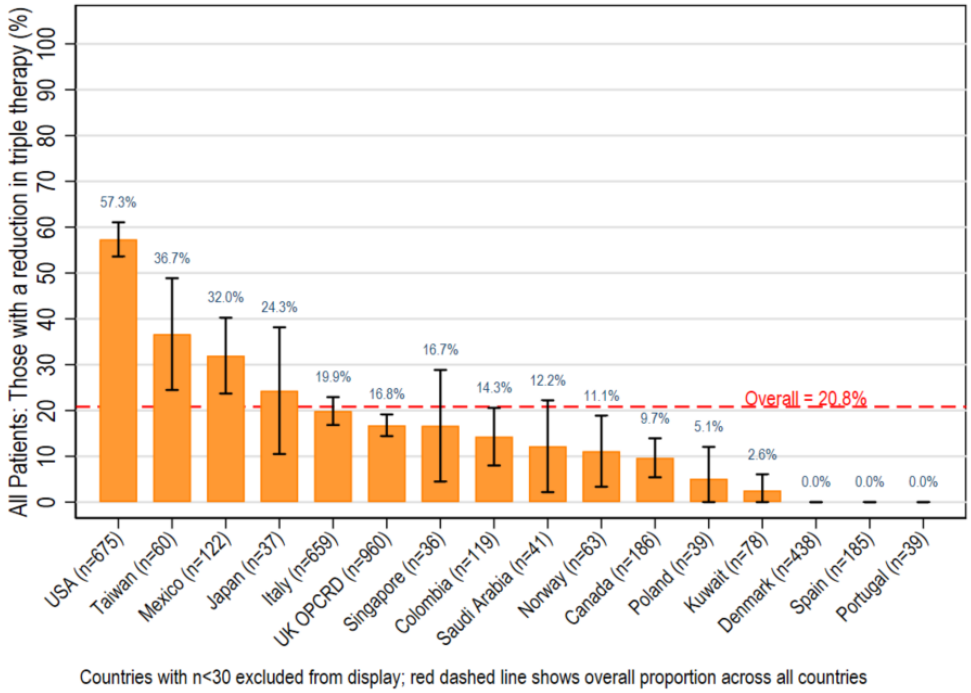


Figure 17 shows the proportion of patients by country who were on triple therapy at baseline and experienced a reduction at any time over follow-up, the bars representing percentages and error bars showing 95% confidence intervals.

Approximately 21% of patients had a reduction in triple therapy at some point (red dashed line), but there is marked variation between countries. Some countries have relatively high proportions of patients reducing therapy (approaching or exceeding ~40%), while others are much lower, indicating that in many settings most patients remained on triple therapy throughout follow-up.

Figure 17: Proportion of Patients with Any Reduction in Triple Therapy by Country



Countries with n<30 excluded from display; red dashed line shows overall proportion across all countries

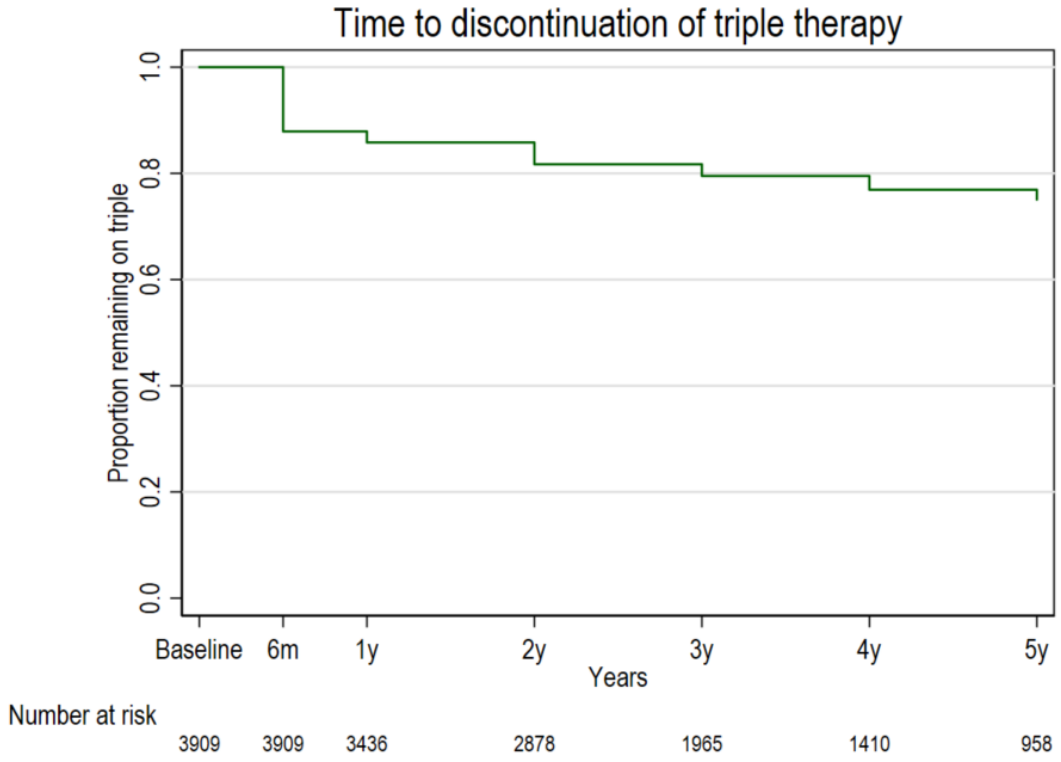
Change in Triple Therapy Use at all timepoints

Triple therapy use declined over time following biologic initiation. Overall, approximately 21% of patients experienced a reduction in triple therapy during follow-up, with most patients remaining on triple therapy throughout the study period. Changes were gradual, with relatively small shifts in the proportion of patients receiving triple therapy at each timepoint.

To further characterise the timing of treatment de-escalation, a Kaplan–Meier analysis was conducted among patients receiving triple therapy at baseline. This showed a gradual discontinuation of triple therapy by 5 years (Figure 18). In contrast to Figure 16, which captures whether any reduction occurred at any time, this analysis estimates the time to first complete discontinuation of triple therapy.

Kaplan–Meier curve showing the proportion of patients remaining on triple therapy (ICS/LABA/LAMA) over 5 years among those receiving triple therapy at baseline. Discontinuation was defined as the first recorded absence of triple therapy during follow-up. Patients were censored at the time of last available follow-up. Numbers at risk are shown below the x-axis. Approximately 25% of patients discontinued triple therapy by 5 years. The slightly higher cumulative incidence compared with the crude proportion reflects adjustment for censoring and the time-to-event framework.

Figure 18: Time to Discontinuation of Triple Therapy Following Biologic Initiation



Treatment pathways following triple therapy discontinuation

Analysis was undertaken using the OPCRD cohort (n= 1,610) to determine treatment pathways following triple therapy discontinuation. 960 (60%) were receiving triple therapy at baseline, during 5 years of follow-up, 161 (17%) discontinued triple therapy.

Among these patients, the majority (78.3%, n=126) transitioned to ICS/LABA monotherapy, indicating removal of both ICS and LABA components. Relatively few stepped down to single therapy regimens, including LAMA (6.2%, n=10) or ICS (3.7%, n=6) (Figure 19).

Figure 19: Treatment Pathways Following Discontinuation of Triple Therapy

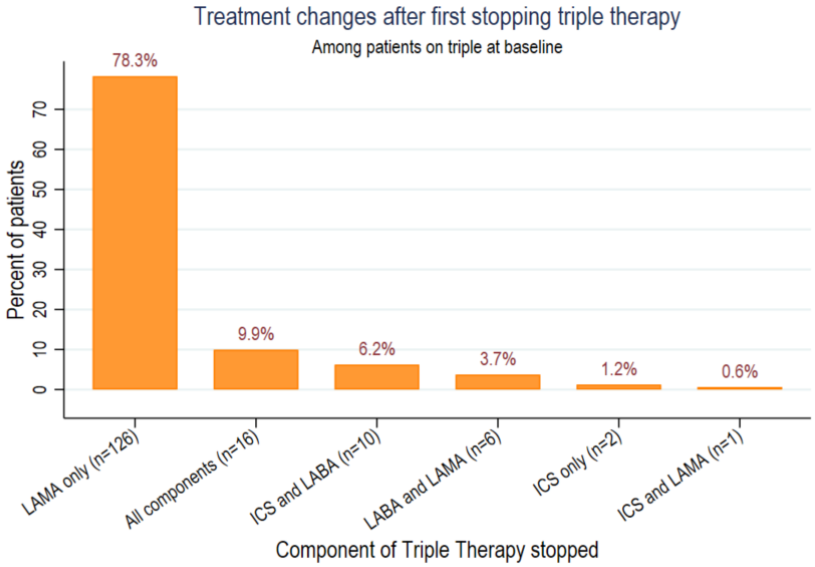
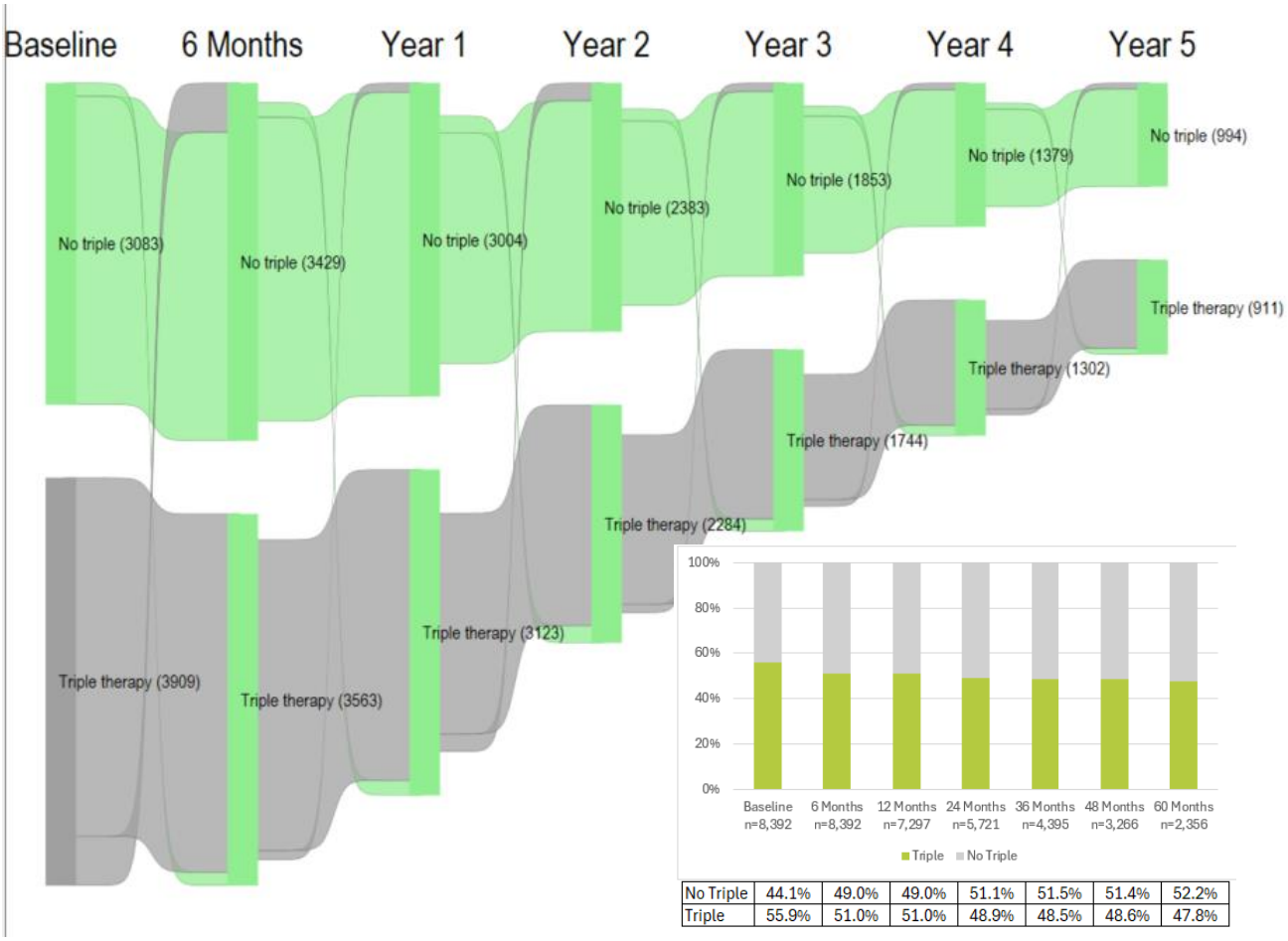


Figure 20 illustrates transitions in treatment status (triple therapy vs no triple therapy) from baseline to 5 years among patients receiving triple therapy at baseline. Over time, an increasing proportion transitioned to no triple therapy, with corresponding declines in the number remaining on triple therapy. However, the diagram also demonstrates bidirectional movement between states, indicating that some patients who discontinued triple therapy subsequently re-initiated treatment at later timepoints.

The accompanying stacked bar chart shows the overall proportion of patients receiving triple therapy and no triple therapy at each timepoint. Triple therapy use declined from 54.7% at baseline to 46.2% at 5 years, with a corresponding increase in patients not receiving triple therapy.

Overall, these findings highlight that while treatment reduction occurs in a subset of patients, changes are dynamic, with both de-escalation and re-escalation observed over time. This helps explain the modest net reduction in triple therapy prevalence at 5 years despite a greater proportion of patients experiencing a reduction at some point during follow-up.

Figure 20: River plot - how Triple therapy use changed over the 5-year follow-up



No Triple	44.1%	49.0%	49.0%	51.1%	51.5%	51.4%	52.2%
Triple	55.9%	51.0%	51.0%	48.9%	48.5%	48.6%	47.8%

7.3 Objective 2

We conducted multivariate analysis to investigate patient characteristics which are associated with ICS, SABA, and Triple Therapy reductions.

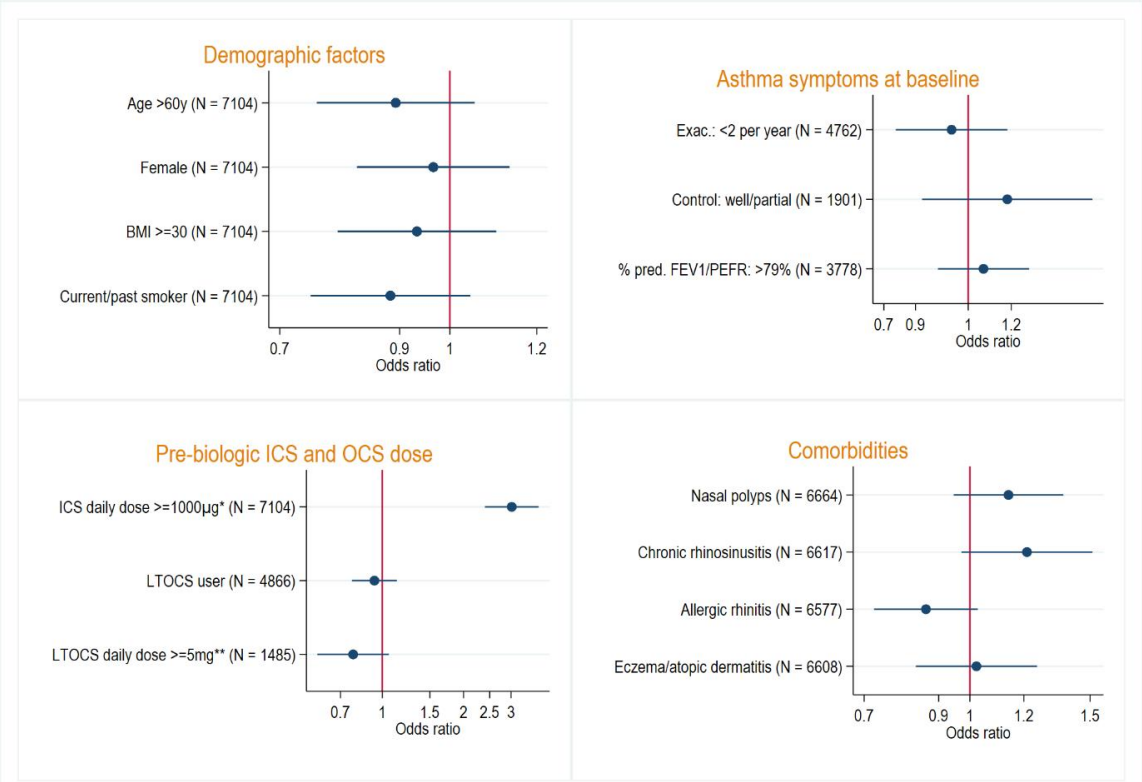
Logistic regression models were used to assess associations between baseline characteristics and reduction status at 1 and 2 years following biologic initiation.
Additional time-to-event analyses using Cox proportional hazards regression were performed for ICS reduction to evaluate (i) duration of ICS 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.

ICS Reduction and patient characteristics

At 1 year of follow-up, multivariable-adjusted analyses demonstrated that most covariates were not significantly associated with reduction in ICS. After adjustment for index year, age, sex, body mass index, smoking status, and pre-biologic inhaled corticosteroid use, older age (>=60 years) was not significantly associated with the outcome (adjusted OR ≈ 0.89, 95% CI 0.78-1.05, p = 0.179). Gender also showed no significant association at 1 year (adjusted OR ≈ 0.97, p = 0.671). Across the remaining predictors, adjusted odds ratios were generally close to unity and confidence intervals frequently included 1.0, indicating no strong independent associations at the 1-year time point. The only significant predictor was being on high dose ICS in the year prior (adjusted OR 3.017, 95% CI 2.398-3.796, p >0.001) (Figure 21).

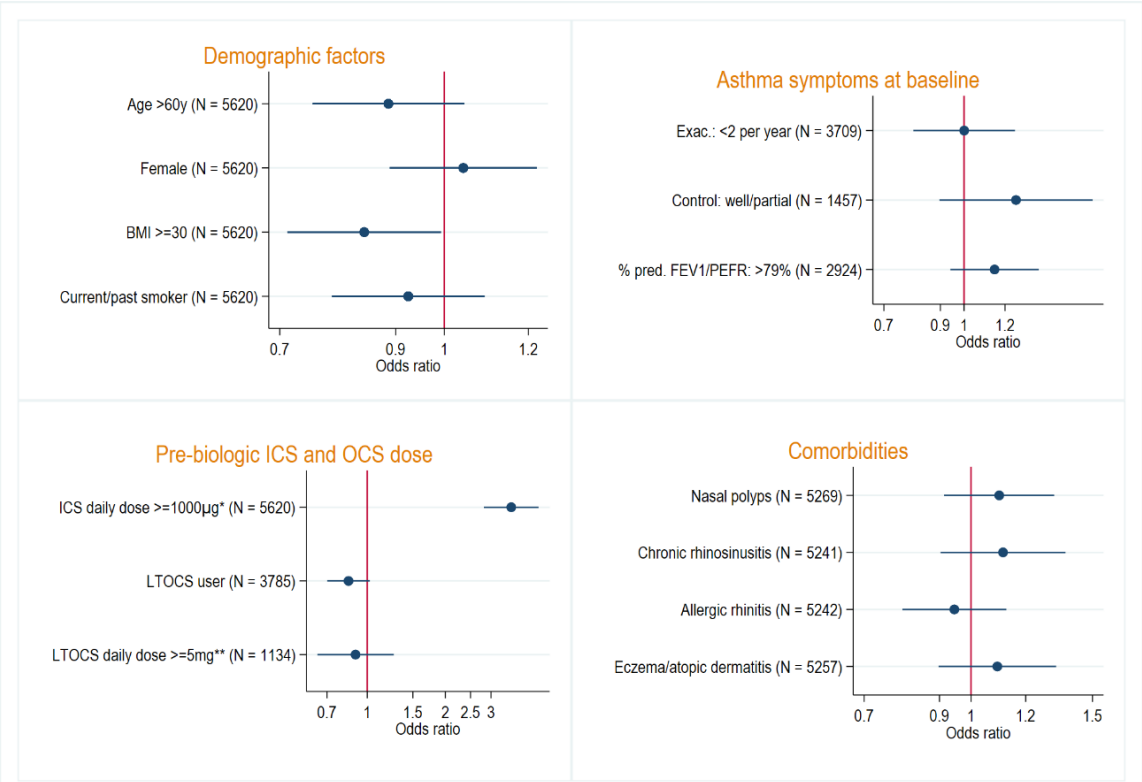
At 2 years of follow-up, results were largely consistent with those observed at 1 year. Older age (>=60 years) was again not significantly associated with the outcome (adjusted OR ≈ 0.89, 95% CI 0.752-1.0441, p = 0.149). For most covariates, adjusted odds ratios remained near 1.0, with confidence intervals spanning unity, indicating no clear independent predictors of the outcome at 2 years. As with the 1-year analyses, only high dose ICS in the year prior was significant (adjusted OR = 3.591 , 95% CI 2.816 - 4.578 p<0.001 (Figure 22).

Figure 21: Association of covariates with reduced ICS at 1 year



Source: *Adjusted for index year, age, gender, bmi, smoking status, and baseline ICS category*

Figure 22: Association of year of initiation with reduced ICS at 2 years

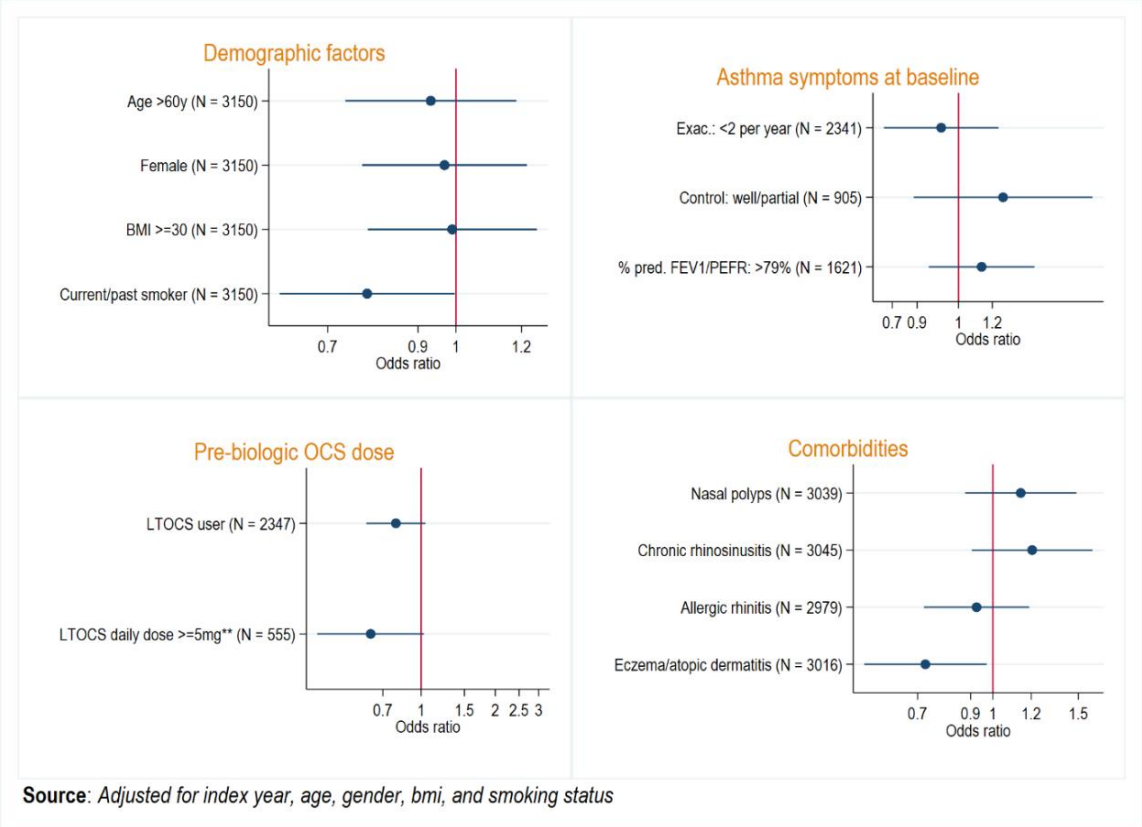


Source: *Adjusted for index year, age, gender, bmi, smoking status, and baseline ICS category*

To further explore this finding, a subgroup analysis restricted to patients receiving high-dose ICS at baseline was conducted.

In this subgroup (n=3,565), no covariates were significantly associated with ICS reduction at either 1 or 2 years. Adjusted odds ratios were close to unity, with confidence intervals crossing 1.0, indicating no clear independent predictors (Figure 23).

Figure 23: Association of covariates with reduced ICS at 1 year for patients with a high-dose ICS at baseline



Source: *Adjusted for index year, age, gender, bmi, and smoking status*

Comparison between full cohort and subgroup analyses

In the full cohort, most covariates were not significantly associated with ICS reduction at either time point; however, high-dose ICS use in the year prior was a strong and consistent predictor (OR ≈ 3.0 at 1 year; OR ≈ 3.6 at 2 years).

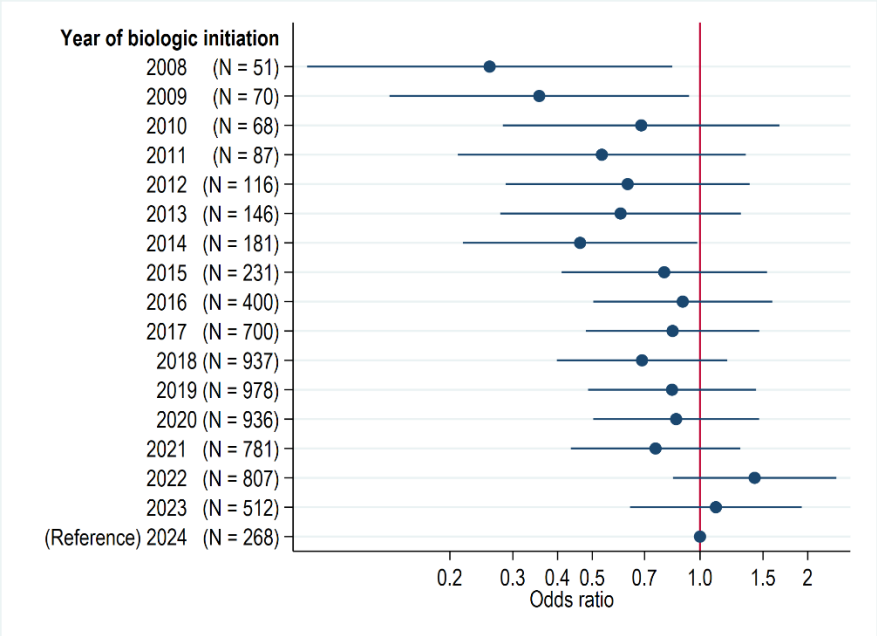
In contrast, within the high-dose ICS subgroup, no covariates were significantly associated with ICS reduction, with effect estimates close to unity.

Year of initiation and reduced ICS at 1 year

Multivariable logistic regression models were used to evaluate the association between year of initiation and the reduction in ICS dose at 1 year, adjusted for index year, age, sex, body mass index, smoking status, and pre-biologic inhaled corticosteroid use between 2008 and 2022 inclusive (Figure 24).

Compared with patients initiating biologic therapy in 2024, those treated in earlier years (2008–2014) had significantly lower odds of achieving ICS reduction, while patients initiating treatment from approximately 2018 onward demonstrated similar odds of ICS reduction, reflecting a progressive improvement in steroid-sparing effectiveness over time.

Figure 24: Association of year of initiation with reduced ICS at 1 year

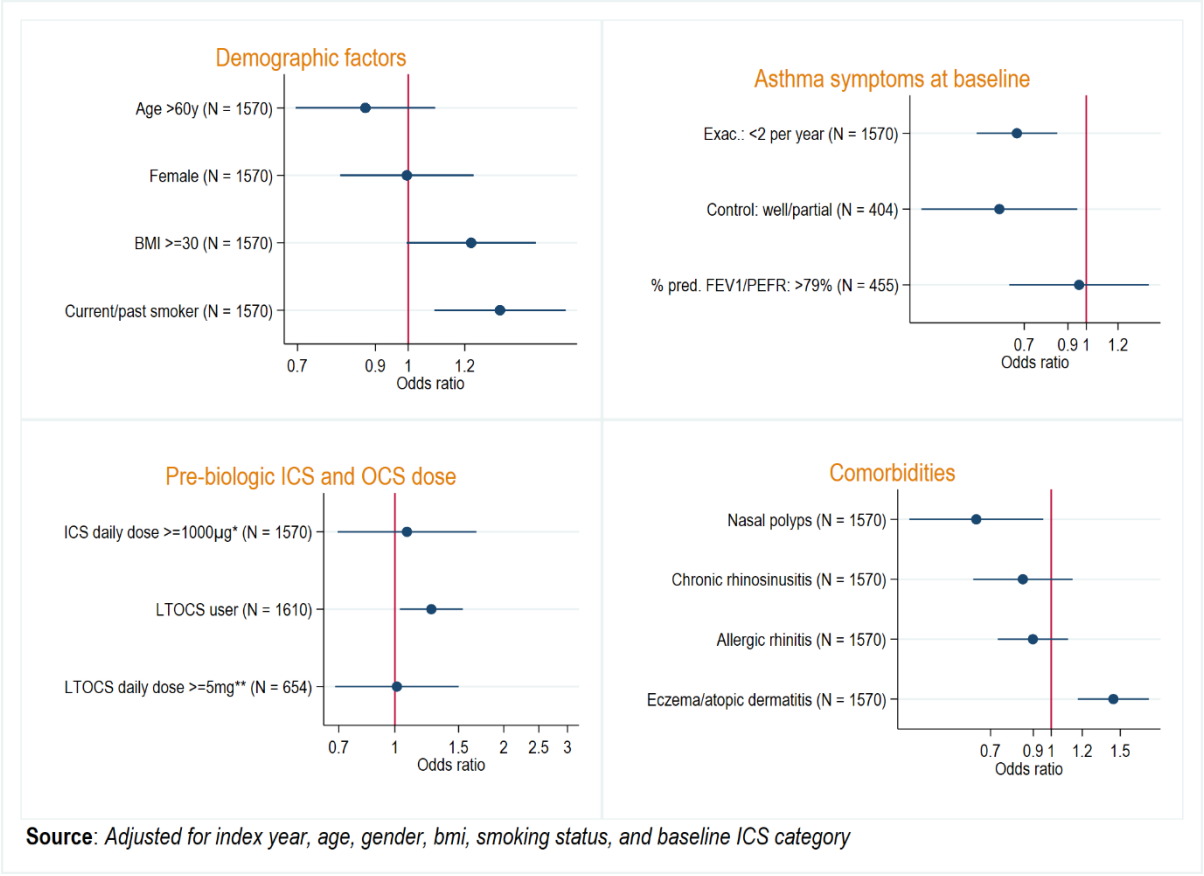


SABA and patient characteristics

Fewer than two exacerbations per year, better asthma control (well/partial control), and current or past smoking were associated with an increased likelihood of SABA reduction. In contrast, eczema/atopic dermatitis was associated with a reduced likelihood of SABA reduction (Figure 25)

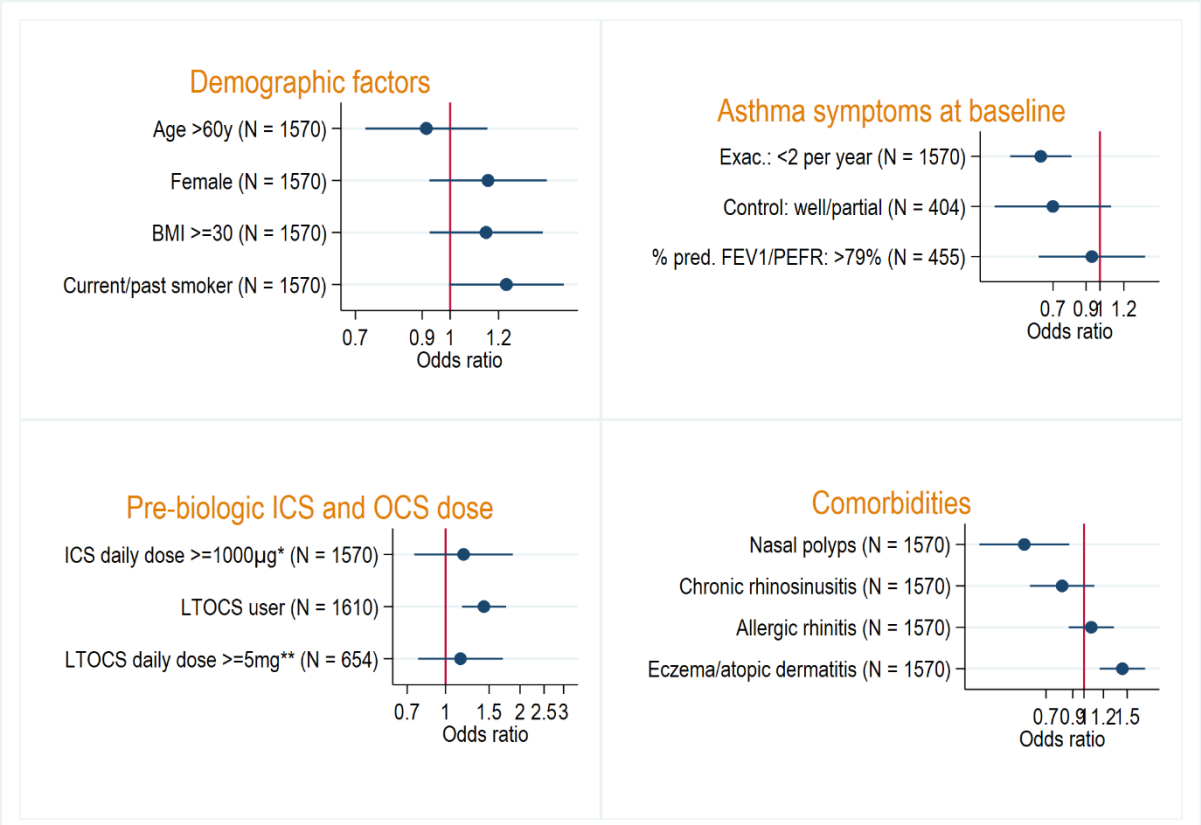
At 2 years following biologic initiation, current or past smoking and asthma control were no longer significantly associated with SABA reduction. Fewer than two exacerbations per year remained associated with an increased likelihood of SABA reduction, while long-term OCS use remained associated with a reduced likelihood of SABA reduction. Other variables were not significantly associated with SABA reduction (Figure 26).

Figure 25: Association of covariates with reduced SABA at 1 year



Source: *Adjusted for index year, age, gender, bmi, smoking status, and baseline ICS category*

Figure 26: Association of covariates with reduced SABA at 2 years

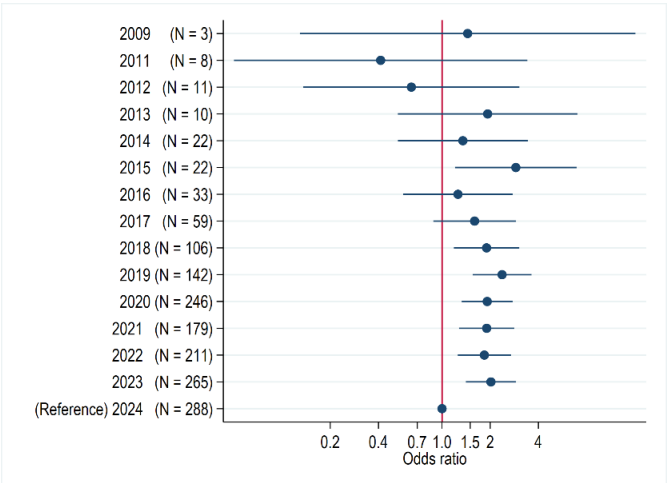


Source: *Adjusted for index year, age, gender, bmi, smoking status, and baseline ICS category*

Year of initiation and reduced SABA at 1 year

Using 2024 as a reference point the probability of achieving a reduction in SABA has not changed markedly by year of initiation of biologic. 2009 to 2017 there was no significant difference compared to 2024. 2018 to 2020 showed a significant increased likelihood of patients reducing their SABA use (Figure 27).

Figure 27: Association of year of initiation with reduced SABA at 1 year



Triple Therapy

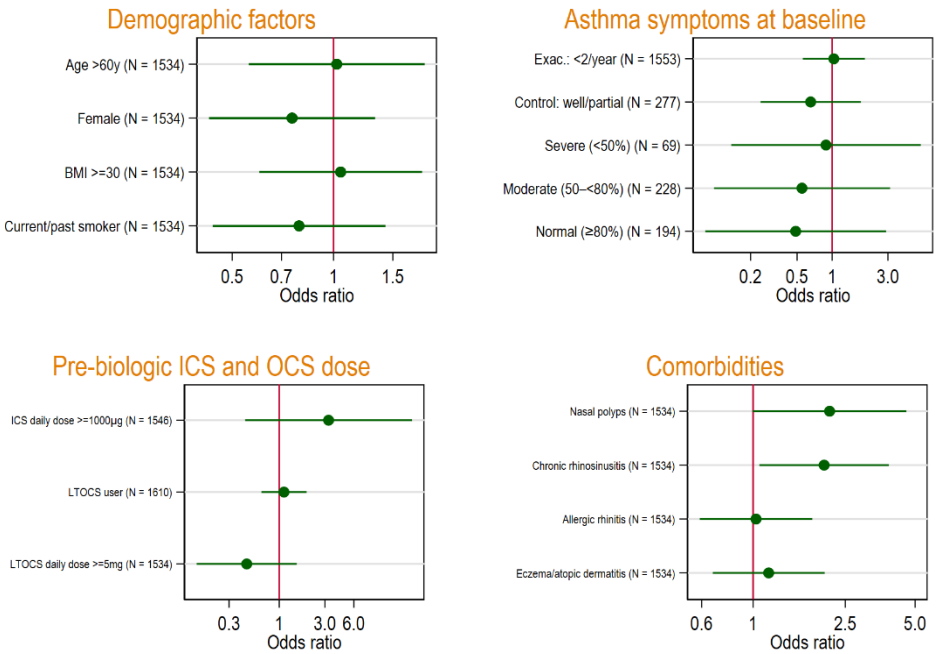
At 1 year, multivariable-adjusted analyses identified several factors associated with reduction in triple therapy use (Figure 28). High-dose ICS use at baseline was associated with an increased likelihood of stepping down from triple therapy. Better asthma control and higher percent predicted lung function categories (severe, moderate, and normal) were associated with numerically higher odds of reduction, but these were not statistically significant, and no clear gradient was observed across lung function categories.

At 2 years, findings were consistent with those observed at 1 year (Figure 29) although the association with high-dose ICS was attenuated and estimates for other treatment-related variables appeared more prominent. Clinical status measures remained non-significant.

Analysis by year of biologic initiation showed no clear temporal trend (Figure 30).

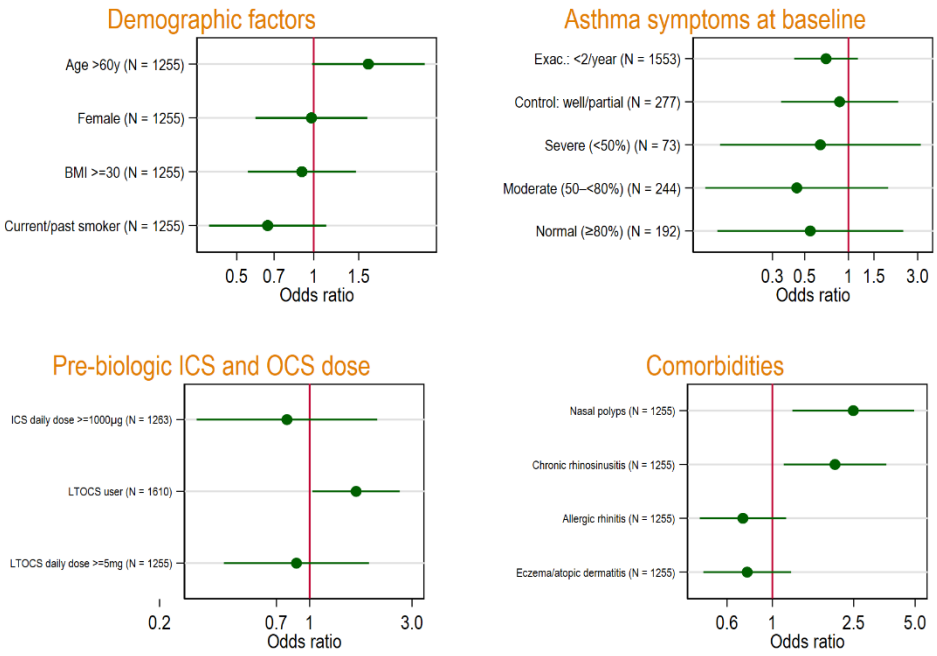
Overall, these findings suggest that triple therapy may be more strongly associated with higher baseline inhaled treatment intensity, with limited and associations observed for clinical status measures such as asthma control and lung function. Most demographic and comorbidity factors showed no significant association.

Figure 28: Association of covariates with reduced Triple Therapy at 1 year.



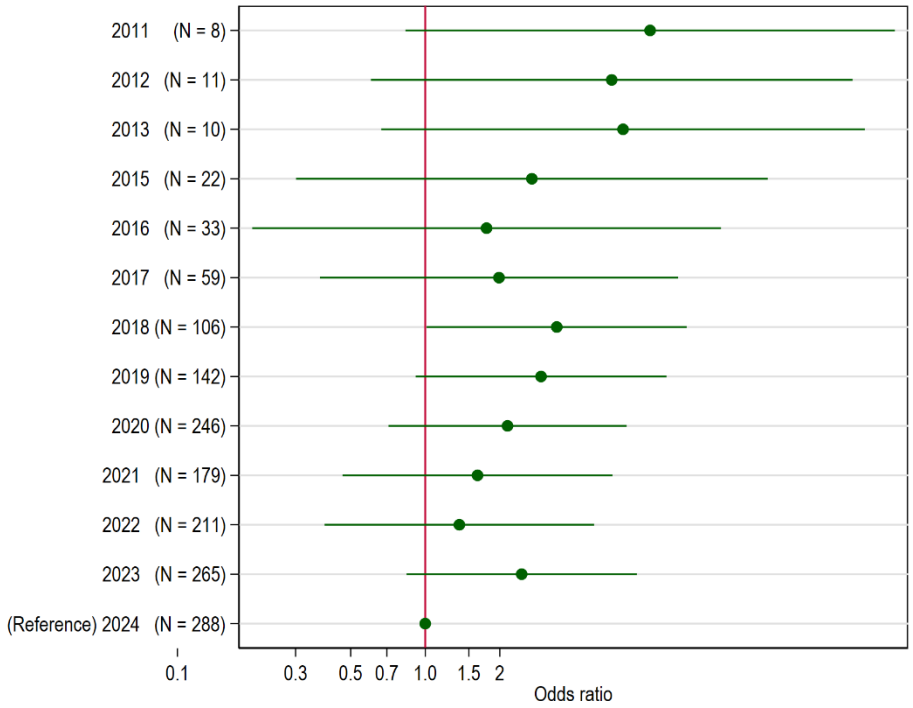
Source: *Adjusted for index year, age, gender, bmi, smoking status, and baseline ICS category*

Figure 29: Association of covariates with reduced Triple Therapy at 2 years.



Source: *Adjusted for index year, age, gender, bmi, smoking status, and baseline ICS category*

Figure 30: Association of year of initiation with reduced Triple therapy at 1 year



Cox Regression Models

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 (n=900), and (ii) time until reduction is first observed in non-reducers in the first year (n=7,492).

ICS Reducers in the first year

Of the 8,392 patients in the study 900 (10.7%) patients had a reduction in the first year, of these 31 patients subsequently increased their ICS versus baseline, a small number indicating that once reduced the population was then stable. Failure event defined as return to baseline or higher ICS dose following initial reduction. Patients without the event were right censored at last available follow-up.

Of the 900 patients who achieved ICS reduction in the first year, 887 with complete covariate data were included in the Cox regression analysis. Cox regression analysis found no significant association with age, gender, smoking status, BMI (Figure 31).

Figure 31: Cox regression ICS reducers in the first 1-year a) predictors, b) survival curve

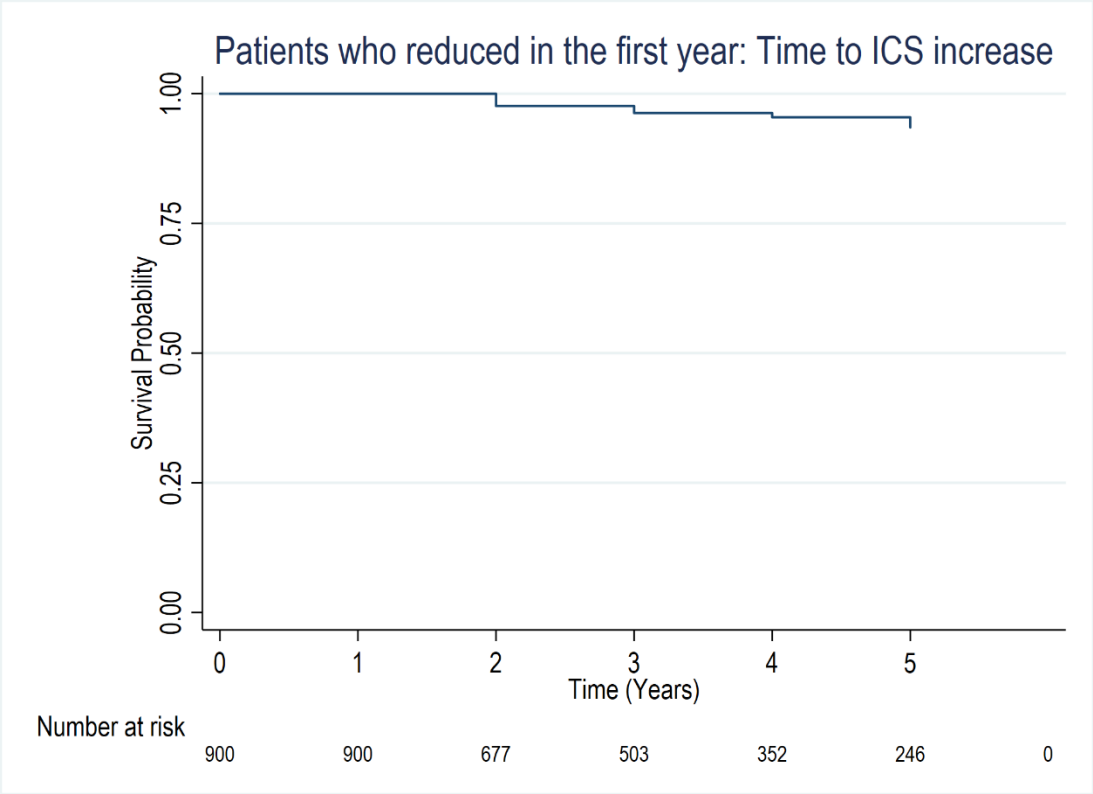
a) Predictors

No. of subjects = 887
No. of failures = 30
Time at risk = 2653

LR chi2(8) = 32.38
Prob > chi2 = 0.0001

	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Index Year	-0.062	0.060	-1.03	0.301	-0.18	0.06
Age	-0.009	0.013	-0.69	0.491	-0.03	0.02
Gender						
Female	0.329	0.407	0.81	0.419	-0.47	1.13
Smoking						
Ex-smoker	0.459	0.398	1.15	0.249	-0.32	1.24
Non-smoker	0.499	0.642	0.78	0.437	-0.76	1.76
BMI	-0.001	0.025	-0.02	0.983	-0.05	0.05
pre_biologic_ics	-0.001	0.000	-3.6	0	0.00	0.00

b) Survival curve by baseline ICS



Non-ICS Reducers in the first year

Of the 7,492 patients who did not decrease in the first 1 year 721 (6.6%) patients had a reduction between 1 and 5 years. Cox regression analysis found that for patient reducing after the first year no significant association with age, gender, and bmi. Non-smokers were more likely to show a subsequent reduction (Figure 32).

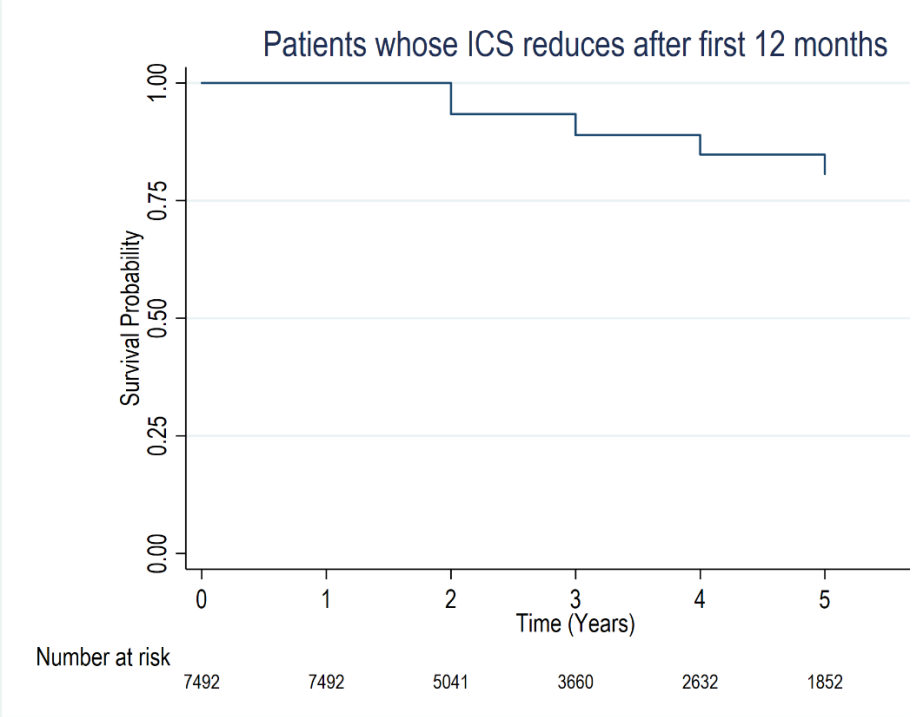
Figure 32: Cox regression ICS reducers <u>after</u> 1 year a) predictors, b) survival curve

a) Predictors

No. of subjects =	7,285	LR chi2(8) =	73.56
No. of failures =	717	Prob > chi2 =	0.0000
Time at risk =	20253		

	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
Index Year	0.088	0.014	6.35	0	0.06	0.12
Age	0.002	0.003	0.88	0.381	0.00	0.01
Gender						
Female	0.036	0.078	0.46	0.648	-0.12	0.19
Smoking						
Ex-smoker	-0.047	0.087	-0.54	0.588	-0.22	0.12
Non-smoker	-0.333	0.117	-2.84	0.004	-0.56	-0.10
BMI	-0.007	0.005	-1.34	0.181	-0.02	0.00
pre_biologic_ics	0.000	0.000	5.6	0	0.00	0.00

b) Survival curve by baseline ICS



Association between 12m and 24m reduction status

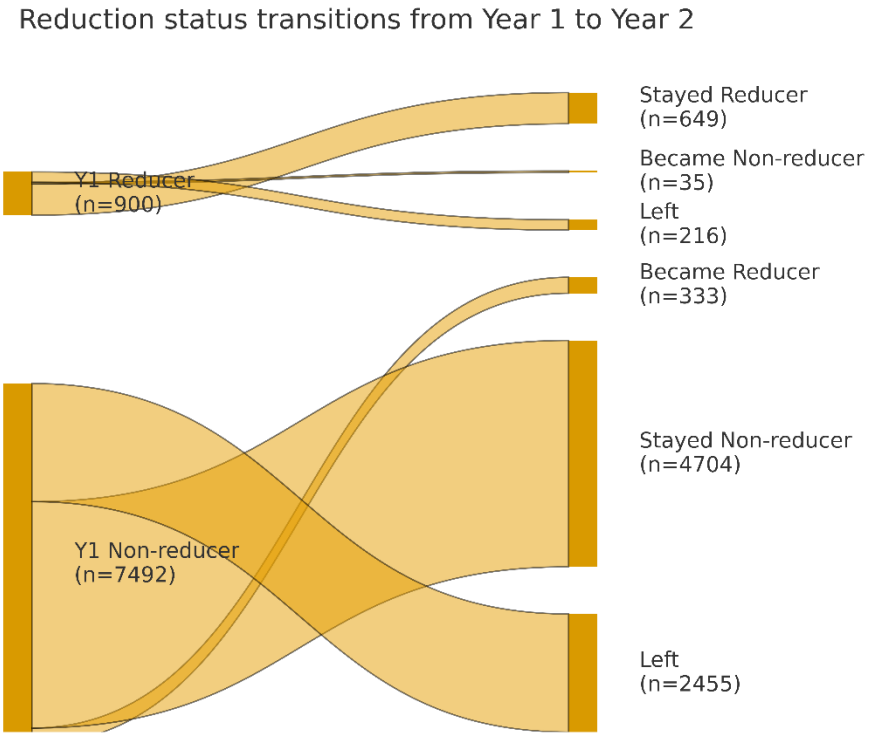
Across the cohort, 900 patients achieved a reduction at Year 1. Patients recorded as “Left” or “Leavers” represent censored observations due to loss to follow-up or end of available follow-up during the interval. Of these, the majority (649 of 684; 95%) maintained reduction at Year 2, while 35 patients (5%) no longer demonstrated reduction. Among the 5,037 at the end of year 2 follow-up, 333 patients (6.6%) had a reduction in year 2 and 4,704 (93%) continued to show no. Overall, patients who achieved reduction at Year 1 were substantially more likely to maintain this status at Year 2 than Year-1 non-reducers were to improve, indicating that early

reduction is a strong predictor of sustained improvement over time. (Table 13). This is also shown as a river plot (Figure 33).

Table 13: Number of patients with ICS reduction at 1 year vs at 2 years.

Year 1 vs. Baseline		Year 2 vs. Baseline			Total
		Reduction	Non Reduction	Leavers	
	Reduction	649	35	216	900
	Non Reduction	333	4,704	2,455	7,492
	Total	982	4,739	2,671	

Figure 33: Showing how patients that reduced in year 1 change state in year 2

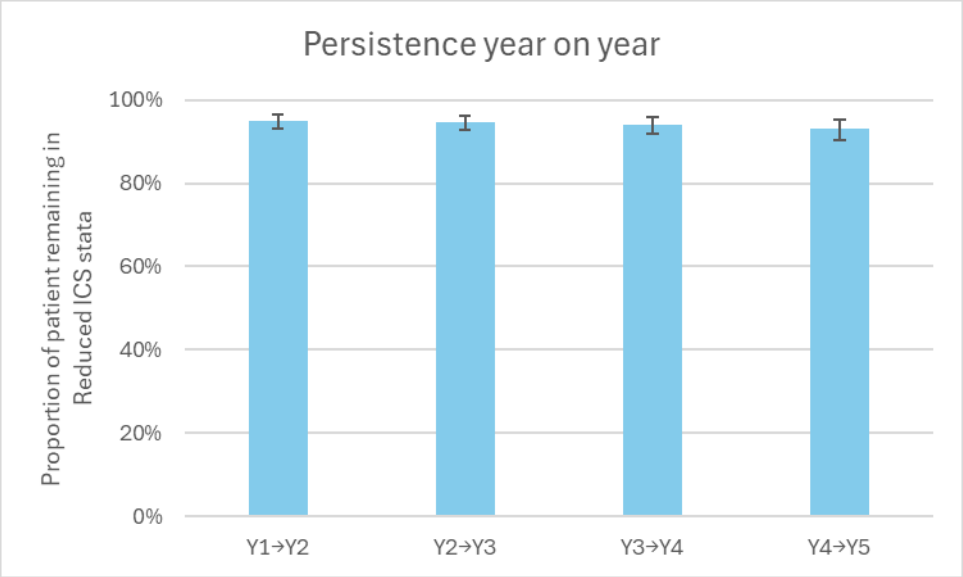


McNemar's test indicated that this difference was highly statistically significant ($\chi^2(1) = 241.32$, $p < 0.001$). The exact odds ratio suggested a markedly elevated likelihood of having a reduced ICS in the second year if it was reduced in the first (OR ≈ 0.11; exact 95% CI: 0.07–0.15).

Do the reducers in the first 1 year remain reduced?

Figure 29 illustrates the year-on-year persistence of being reduced within the first year, defined as the probability that a patient who is in reduced in the first year *t*remains a reducer. Persistence is high and decreases only slightly, from 95% in the transition from Year 1 to Year 2 to 93% from Year 4 to Year 5. The graph shows that the initial reduction is highly persistent over time (Figure 34).

Figure 34: Showing Likelihood of patients to remain in reduced ICS state



8.0 Summary and Discussion

In this large, multinational real-world cohort of adults with severe asthma initiating biologic therapy, we observed modest but progressive reductions in inhaled corticosteroid (ICS) dose, small decreases in short-acting β-agonist (SABA) exposure, and a clear downward trend in triple-therapy use over up to five years of follow-up. These findings provide important empirical evidence regarding the evolution of background inhaled therapy following biologic initiation in routine clinical practice—an area where guideline recommendations exist, but real-world data have remained limited.

Importantly, these findings also highlight substantial heterogeneity in treatment de-escalation across settings, suggesting that real-world implementation of guideline-recommended step-down strategies remains variable.

ICS use demonstrated the most nuanced pattern. Although the majority of patients remained on their baseline ICS dose, particularly those starting at a high dose, a meaningful minority achieved reductions over time. The proportion of patients showing any ICS reduction increased from 10% at 6 months to 22% by Year 5 Among patients who reduced treatment, the magnitude of reduction was substantial and clinically meaningful, with a median decrease of 800–1,000 µg However, these reductions were often not sufficient to result in a change in dose category, reflecting the relatively broad thresholds used to define low-, medium-, and high-dose ICS. Most first ICS reductions occurred within the first 1 to 2 years of biologic initiation, suggesting that inhaled therapy de-escalation typically occurs early once clinicians elect to taper treatment.

While patients who reduced ICS demonstrated numerically greater improvements in lung function compared with non-reducers, the magnitude of these differences was small and unlikely to be clinically meaningful at the population level.

However, given the observational design, this association is unlikely to reflect a causal effect of dose reduction itself and more likely reflects that patients with better underlying clinical response were preferentially selected for treatment de-escalation.

Among patients with available Year-2 follow-up data, 95% maintained ICS reduction between Years 1 and 2, indicating high persistence of reduction once achieved (Figure 31). When the full Year-1 reducer cohort was considered, including patients lost to follow-up or censored before Year 2, 72% remained reduced at Year 2 (Table 13; Figures 30 and 31).

Moreover, McNemar's analysis showed significantly more patients gained reduction status between Years 1 and 2 than lost it, suggesting a slow but consistent net movement toward lower ICS exposure. These observations support the feasibility and durability of ICS de-escalation in appropriately selected patients, with early reduction appearing to be a strong predictor of sustained long-term reduction.

Exploratory analyses stratified by biologic treatment pathway suggested that ICS reduction was more frequently observed among patients who remained on biologic therapy throughout follow-up, particularly those who switched biologic treatment. This likely reflects clinical optimisation among patients requiring biologic adjustment rather than a direct effect of switching itself and should be interpreted cautiously given the observational nature of the analysis.

Notably, the timing of treatment de-escalation differed across therapy types. ICS reductions were concentrated within the first 1-2 years following biologic initiation, whereas reductions in triple therapy occurred more gradually over time without a clear early peak, suggesting differing clinical drivers and decision-making processes for these treatment components.

In contrast, SABA use exhibited substantial state stability. Although prescribing declined modestly over time, SABA use remained highly prevalent, with persistent upper-range use in a substantial proportion of patients. This suggests that despite biologic initiation and improvements in disease control, reliance on reliever therapy remains entrenched in routine clinical practice, highlighting a potential gap in optimisation of asthma management.

Transition plots showed that most SABA users remained users, and most non-users remained non-users, across follow-up. This stability may reflect the entrenched patterns of reliever inhaler use in clinical practice.

Triple therapy (ICS/LABA/LAMA) use showed a modest overall reduction following biologic initiation. The proportion receiving triple therapy decreased from 56% at baseline to 48% at 5 years, representing a reduction of approximately 8.5 percentage points. While some patients stepped down therapy, the majority remained on triple therapy throughout follow-up, indicating persistence of inhaled treatment despite biologic use.

Treatment pathways following biologic initiation were dynamic, with approximately one-fifth of patients switching biologic therapy during follow-up. ICS reduction was more frequently observed among patients who switched or remained on biologic therapy, suggesting ongoing treatment optimisation in clinical practice. In addition, among patients discontinuing triple therapy, most transitioned to simpler regimens such as LAMA monotherapy, indicating that step-down strategies often involve substantial simplification of inhaled treatment rather than incremental reduction alone.

At the individual level, approximately 24% of patients receiving triple therapy at baseline experienced at least one reduction during follow-up, indicating that treatment de-escalation was relatively common, resulting in only a modest net reduction at the population level, reflecting both de-escalation and re-escalation over time. However, time-to-event analysis demonstrated that reductions occurred gradually over time, without a clear early peak, indicating that de-escalation of triple therapy is not concentrated in the initial period following biologic initiation.

There was also marked heterogeneity between countries, with some settings achieving substantially higher rates of treatment reduction (exceeding 40%), while others showed minimal or no reduction. This variation likely reflects differences in clinical practice, healthcare systems, and prescribing behaviours, and suggests that greater reductions in inhaled therapy may be achievable in many settings.

Taken together, these findings indicate that while a substantial proportion of patients undergo an initial reduction in triple therapy, these changes are not consistently sustained, resulting in only a modest overall reduction at the population level over 5 years.

Across all therapy domains, multivariable analyses identified few strong independent predictors of inhaled therapy reduction. For ICS dose reductions at both 1-2 years, most demographic, clinical, lung function, and biomarker variables did not show significant associations. The only consistent predictor of reduction was higher pre-biologic ICS dose, which likely reflects clinician willingness to taper from very high baseline exposures. Similarly, for SABA and triple therapy, only limited associations emerged—patients with better asthma control and fewer exacerbations were more likely to reduce SABA, whereas older age and high-dose ICS use predicted lower likelihood of triple-therapy step-down. The generally weak predictive signal across variables indicates that opportunities for inhaled

therapy de-escalation are broadly distributed across the severe asthma population rather than restricted to narrow phenotypic subgroups.

This analysis considered only pre-biologic initiation characteristics; factors emerging after treatment initiation, such as improvements in asthma control, may play a key role in guiding treatment down-titration.

Collectively, these findings offer several important insights. First, they highlight a measurable—but not universal—shift toward reduced inhaled therapy intensity following biologic initiation. This aligns with guideline recommendations encouraging cautious ICS down-titration after sustained disease control, yet the modest overall rates of reduction suggest that de-escalation remains under-utilised in practice. Potential barriers include clinician caution, reimbursement constraints, concern regarding symptom relapse, and limited visibility of down-titration pathways. Second, when reductions do occur, they appear clinically stable, with strong year-on-year persistence. This supports the safety of structured ICS tapering in patients whose disease stabilises on biologics. Third, the lack of clear baseline predictors underscores the need for dynamic, response-guided step-down approaches rather than reliance on static pre-treatment characteristics.

Strengths of this study include its global scope, large sample size, and extended follow-up, spanning up to five years after biologic initiation. The integration of ISAR and OPCRD data provides both international generalisability and the granular prescribing detail needed to evaluate therapy trajectories. Limitations include potential variation in prescribing cultures across countries, incomplete data capture and attrition over long follow-up windows. Additionally, as this was an observational study, causality between biologic therapy and inhaled therapy reduction cannot be inferred. It is also worth noting that much of the data collected in this study was prior to SHAMAL and it is possible that current medication use patterns are different.

Observed differences in ICS reduction across countries may partly reflect variation in biologic continuation criteria. In some healthcare systems, ongoing access to biologic therapy is contingent on maintaining high-dose ICS or meeting specific prescribing thresholds, which may limit opportunities for ICS down-titration and result in apparent underestimation of treatment de-escalation.

Although exploratory analyses stratified by biologic treatment pathway were undertaken, eligibility remained based on biologic initiation rather than sustained biologic exposure throughout follow-up. Consequently, some observed ICS changes may still reflect treatment discontinuation or switching during follow-up rather than the effects of continuous biologic therapy alone.

In summary, biologic therapy was associated with gradual but durable reductions in ICS dose, modest decreases in SABA exposure, and consistent step-down from triple therapy in real-world severe asthma care. These findings support the feasibility of inhaled therapy de-escalation in selected patients and underscore the need for clearer, evidence-based step-down strategies to reduce treatment burden and minimise corticosteroid-related adverse effects.

9.0 Conclusion

In this large, multinational real-world study of patients with severe asthma, initiation of biologic therapy was associated with gradual but durable reductions in inhaled corticosteroid dose, modest decreases in SABA use, and limited but measurable step-down from triple therapy over five years of follow-up.

Although most patients remained on their baseline inhaled therapy intensity, a meaningful minority achieved clinically relevant and durable reductions, with strong year-on-year persistence once down-titration occurred.

Marked variation between countries suggests that the extent of inhaled therapy reduction is influenced by local clinical practice and healthcare systems, and that greater de-escalation may be achievable in some settings. Predictors of reduction were few, indicating that opportunities for safe inhaled-therapy de-escalation extend across a broad patient population rather than being limited to specific phenotypes.

These findings provide robust global evidence (noting the observational nature of the data) that biologics can support inhaled therapy optimisation in routine clinical practice, reinforcing guideline recommendations to consider ICS tapering once asthma control is achieved.

Future work should focus on defining structured, evidence-informed pathways for step-down and evaluating clinical outcomes associated with inhaler de-escalation to further support personalised, corticosteroid-sparing care.

10.0 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, have formed the Advisory Group.

Table 14: Members of the advisory group.

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1	Jorge Máspero	Argentina
2	Olivier Chambenoit	AstraZeneca
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25	Enrico Heffler	Italy
26	Takashi Iwanaga	Japan
27	Mona Al-Ahmad	Kuwait
28	Désirée Larenas-Linnemann	Mexico
29	Job F.M. van Boven	Netherlands
30	Sverre Lehmann	Norway
31	Aaron Beastall	OPC
32	Lakmini Bulathsinhala	OPC
33	John Busby	OPC
34	Heath Heatley	OPC
35	Ruth B. Murray	OPC

No	Name	Country / Institution
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37	Ghislaine Scelo	OPC
38	John Townend	OPC
39	Piotr Kuna	Poland
40	Francisco Viana Machado	Portugal
41	Riyad Al-Lehebi	Saudi Arabia
42	Mei Fong Liew	Singapore
43	Chin Kook Rhee	South Korea
44	Borja G. Cosio	Spain
45	Luis Perez-de-Llano	Spain
46	Diahn-Warng Perng	Taiwan
47	Bassam Mahboub	United Arab Emirates
48	Liam G. Heaney	United Kingdom
49	David J. Jackson	United Kingdom
50	Paul E. Pfeffer	United Kingdom
51	Pujan H. Patel	United Kingdom / AZ
52	Rohit K. Katial	United States / National Jewish Health
53	Eileen Wang	United States / National Jewish Health
54	Michael E. Wechsler	United States / National Jewish Health
55	Anna Y. Qiu	United States / University of Michigan
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13.0 List of Tables and Figures

Figure 34: Showing Likelihood of patients to remain in reduced ICS state

14.0 Appendices

14.1 Appendix 1: Numbers of patients by country

UK OPCRD	1,610	19%
USA	1,533	18%
Italy	1,416	17%
Denmark	789	9%
Spain	717	9%
UK	552	7%
Canada	377	4%
Poland	289	3%
Kuwait	212	3%
Colombia	210	3%
Mexico	210	3%
Belgium	164	2%
Saudi Arabia	128	2%
Portugal	112	1%
Japan	91	1%
Norway	81	1%
Taiwan	80	1%
Greece	71	1%
Brazil	61	1%
Singapore	52	1%
UAE/Dubai	50	1%
Argentina	35	0%
South Korea	32	0%
Bulgaria	31	0%
Estonia	24	0%
Ireland	16	0%
India	1	0%

14.2 Appendix 2: Showing time periods 6 months, and yearly time points for 1-5 years.

			Number	OR	L 95%	U 95%	p value
Asthma Symptoms	Exacerbation (<2 p/y)	6 Months	5,624	0.898	0.713	1.13	0.359
		1 Year	4,879	0.894	0.708	1.128	0.344
		2 Year's	3,768	0.976	0.781	1.22	0.829
		3 Years	2,808	0.97	0.762	1.235	0.806
		4 Year's	2,031	1.066	0.811	1.401	0.647
		5 Year's	1,402	0.925	0.665	1.286	0.642
	Asthma Control	6 Months	2,272	1.422	0.993	2.035	0.055
		1 Year	1,943	1.232	0.862	1.761	0.251
		2 Year's	1,473	1.285	0.916	1.803	0.147
		3 Years	1,161	1.668	1.157	2.405	0.006
		4 Year's	899	1.508	1.007	2.26	0.046
		5 Year's	643	1.534	0.95	2.475	0.08
	FEV % predicted (>=80%)	6 Months	4,450	0.883	0.727	1.073	0.212
		1 Year	3,800	1.089	0.899	1.32	0.382
		2 Year's	2,939	1.147	0.943	1.395	0.17
		3 Years	2,199	1.112	0.892	1.388	0.344
		4 Year's	1,651	1.152	0.898	1.479	0.267
		5 Year's	1,181	1.031	0.768	1.383	0.84
			Number	OR	L 95%	U 95%	p value
Comorbidity	Nasal Polyps	6 Months	7,716	1.299	1.078	1.567	0.006
		1 Year	6,823	1.15	0.957	1.38	0.135
		2 Year's	5,360	1.123	0.936	1.347	0.214
		3 Years	4,130	1.15	0.941	1.406	0.172
		4 Year's	3,067	1.108	0.884	1.389	0.375
		5 Year's	2,222	0.965	0.738	1.264	0.798
	CRS	6 Months	7,634	1.236	0.981	1.557	0.072
		1 Year	6,776	1.232	0.991	1.532	0.061
		2 Year's	5,333	1.128	0.918	1.387	0.252
		3 Years	4,104	1.255	1	1.575	0.05
		4 Year's	3,074	1.214	0.942	1.563	0.133
		5 Year's	2,220	1.091	0.808	1.474	0.568
	Allergic Rhinitis	6 Months	7,617	1.06	0.888	1.264	0.519
		1 Year	6,728	0.871	0.732	1.036	0.12
		2 Year's	5,328	0.949	0.799	1.128	0.555
		3 Years	4,088	0.876	0.724	1.06	0.172
		4 Year's	3,047	0.92	0.743	1.141	0.448
		5 Year's	2,217	0.966	0.746	1.251	0.793
	Eczema/atopic dermatitis	6 Months	7,621	1.021	0.831	1.255	0.843
		1 Year	6,767	1.028	0.839	1.259	0.792
		2 Year's	5,349	1.065	0.875	1.295	0.53
		3 Years	4,104	0.933	0.75	1.159	0.529
		4 Year's	3,053	0.894	0.699	1.142	0.369
		5 Year's	2,213	0.947	0.706	1.268	0.713

			Number	OR	L 95%	U 95%	p value
Demographic Factors	Age >60	6 Months	8,371	0.978	0.834	1.148	0.787
		1 Year	7,276	0.89	0.758	1.045	0.155
		2 Year's	5,718	0.888	0.757	1.041	0.143
		3 Years	4,392	0.926	0.776	1.105	0.395
		4 Year's	3,265	1.051	0.861	1.282	0.626
		5 Year's	2,355	1.182	0.935	1.495	0.161
	Gender	6 Months	8,367	0.986	0.843	1.153	0.860
		1 Year	7,273	0.974	0.834	1.136	0.734
		2 Year's	5,717	1.01	0.866	1.179	0.894
		3 Years	4,391	1.057	0.892	1.253	0.524
		4 Year's	3,264	0.985	0.814	1.191	0.874
		5 Year's	2,354	1	0.798	1.253	0.998
	BMI >=30	6 Months	8,224	0.97	0.825	1.14	0.711
		1 Year	7,164	0.968	0.824	1.137	0.690
		2 Year's	5,659	0.871	0.742	1.023	0.092
		3 Years	4,358	0.965	0.809	1.15	0.689
		4 Year's	3,237	0.966	0.793	1.177	0.731
		5 Year's	2,339	0.927	0.734	1.17	0.522
	Smoking (ever)	6 Months	8,304	0.868	0.639	1.179	0.364
		1 Year	7,217	0.97	0.714	1.317	0.844
		2 Year's	5,681	1.104	0.831	1.468	0.494
		3 Years	4,367	1.026	0.752	1.401	0.870
		4 Year's	3,249	1.16	0.817	1.648	0.406
		5 Year's	2,344	1.439	0.936	2.211	0.097
			Number	OR	L 95%	U 95%	p value
Medication	ICS High Dose (>= 100mcgs)	6 Months	8,367	2.84	2.257	3.573	0.000
		1 Year	7,273	2.995	2.384	3.763	0.000
		2 Year's	5,717	3.595	2.821	4.581	0.000
		3 Years	4,391	3.979	3.045	5.201	0.000
		4 Year's	3,264	4.13	3.053	5.586	0.000
		5 Year's	2,354	4.749	3.34	6.753	0.000
	LTOCs	6 Months	5,645	0.968	0.801	1.17	0.735
		1 Year	4,866	0.935	0.772	1.132	0.489
		2 Year's	3,785	0.847	0.701	1.024	0.086
		3 Years	2,872	0.858	0.697	1.057	0.151
		4 Year's	2,099	0.788	0.619	1.002	0.052
		5 Year's	1,465	0.872	0.653	1.163	0.351
	LTOCS >=5mg	6 Months	1,818	0.885	0.665	1.177	0.400
		1 Year	1,512	0.804	0.598	1.08	0.147
		2 Year's	1,162	0.952	0.688	1.317	0.765
		3 Years	899	1.069	0.742	1.539	0.721
		4 Year's	678	0.94	0.62	1.423	0.769
		5 Year's	475	0.696	0.413	1.173	0.173

			Number	OR	L 95%	U 95%	p value
Year of initiation	2008		52	0.232	0.077	0.698	0.009
	2009		72	0.319	0.133	0.764	0.010
	2010		71	0.614	0.278	1.359	0.229
	2011		89	0.477	0.207	1.1	0.083
	2012		124	0.563	0.287	1.104	0.094
	2013		152	0.538	0.278	1.044	0.067
	2014		195	0.415	0.219	0.786	0.007
	2015		251	0.713	0.422	1.206	0.207
	2016		435	0.802	0.531	1.21	0.293
	2017		746	0.751	0.51	1.106	0.147
	2018		1,031	0.617	0.425	0.897	0.011
	2019		1,090	0.75	0.521	1.08	0.122
	2020		1,029	0.772	0.539	1.105	0.157
	2021		904	0.674	0.465	0.979	0.038
	2022		969	1.276	0.902	1.807	0.169