Study Report

# CLinical oUtcomes before and after biologic treatMent by bIologic class, by iNdividuAl biologic, and by subgroups of baseliNe characTeristics – (LUMINANT)

*Descriptive analysis and characterization of clinical outcomes of patients with severe asthma before and after biologic treatment overall, per class of biologic, and subgroup of patients' baseline characteristics*

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| **TITLE** | **Clinical outcomes before and after biologic treatment by biologic class, by individual biologic, and by subgroups of baseline characteristics (LUMINANT)** |
| Subtitle | Descriptive analysis and characterization of clinical outcomes in patients with severe asthma before and after biologic treatment overall, per class of biologic, and subgroup of patients' baseline characteristics |
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| Study aims and objectives | 1. Description of baseline characteristics of patients with severe asthma before biologic treatment initiation<br>a. Overall<br>b. By class of biologics<br>2. Descriptive analysis of clinical response for patients with severe asthma after biologic treatment initiation<br>a. Overall<br>b. By class of biologics<br>c. By eligibility to randomized control trial<br>3. Comparison of those who responded to those who did not respond and to the ISAR cohort who did not initiate biologics<br>4. Describe the overlap of response in different domains<br>5. Describe the frequency super-responders<br>6. Identify independent factors associated with response to biologics in the asthma outcome domains of exacerbations, $FEV_1$ and oral corticosteroid burden |
| Countries of study | United States, United Kingdom, Taiwan, Kuwait, Italy, Austria, Spain, Bulgaria, Argentina, Mexico, Korea, Japan, Canada, Colombia, Greece, Saudi Arabia, UAE, Denmark, Portugal, Ireland |
| Data source | International Severe Asthma Registry |

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|---|---|
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# LIST OF ABBREVIATIONS

| Abbreviation | Explanation |
|---|---|
| ACQ | Asthma Control Questionnaire |
| ACT | Asthma Control Test |
| ADEPT | Anonymised Data Ethics & Protocol Transparency |
| ANOVA | Analysis of variance |
| ATS | American Thoracic Society |
| BEC | Blood eosinophil count |
| BMI | Body mass index |
| ERS | European Respiratory Society |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FVC | Forced vital capacity |
| GINA | Global Initiative for Asthma |
| HDM | House dust mite |
| ICS | Inhaled corticosteroids |
| ICU | Intensive care unit |
| IgE | Immunoglobulin G |
| IL | Interleukin |
| ISAR | International Severe Asthma Registry |
| ISC | ISAR Steering Committee |
| LABA | Long-acting $\beta_2$-agonist |
| LAMA | Long-acting muscarinic antagonist |
| LTOCS | Long term oral corticosteroids |
| LTRA | Leukotriene receptor antagonist |
| MCID | Minimal clinically important difference |
| NA | Not applicable |
| OCS | Oral corticosteroids |
| OPC | Optimum Patient Care |
| OPRI | Observational and Pragmatic Research Institute |
| QoL | Quality of life |
| RCT | Randomised control trial |
| REG | Respiratory effectiveness group |
| ROC | Receiver operating characteristic |
| SAT | Serum allergen test |
| SPT | Skin prick test |

| | |
|---|---|
| SCS | Systemic corticosteroid |
| TBD | To be defined |
| T2 | Type 2 |

# 1.0 Executive Summary

Monoclonal biologic medications have been domonstrated to improve exacerbations, asthma control and lung function in those with severe asthma and elevated type 2 (T2) inflammatory biomarkers in a clinical trial setting. Less is known about response to these medications in a real-world setting. This study aimed to describe the population initiating monoconal biologic medications, and examine response and report the frequency of super-reponse to biologic medications in a large, international real-world population in the outcome domains of lung function, asthma exacerbations, asthma control and oral corticosteroid burden in comparison to those who did not initiate biologic medications. We also aimed to examine response in the subgroups of presence of lung function reversibility, T2 gradient, and randomised control trial (RCT) eligibility. Finally, we aimed to describe the baseline characteristics of those initiating different biologic classes and describe the frequency of response and super-response in the four outcomes (lung function, exacerbations, asthma control and oral corticosteroid burden) by biologic class.

This, registry-based cohort study using data from the International Severe Asthma Registry (ISAR) included data from 20 countries which shared data with ISAR between 2017 - 2021. At follow-up, mean 617 days for those initiating biologics and 319 days for those not, four outcomes were examined to define response: improved asthma control, FEV1 improvement ≥100mLs, reduction in annualised exacerbations ≥50%, and reduced long-term oral corticosteroid (LTOCS) dose. Response to these four clinical outcomes were studied in biologic patients and each biologic class (Anti-IgE, Anti-IL5/5R and Anti-IL4/13), as well as in non-biologic patients. Corresponding super-response cut-offs were: new well-controlled asthma, FEV1 improvement ≥500mLs, no annualised exacerbations, and LTOCS cessation (or weaning to adrenal insufficiency dosing of <5 mg). For subgroup analysis, the following definitions were applied: T2 gradient was assessed via applying the eosinophilic gradient algorithm as per Heaney et al[1] excluding the biologic criteria; reversibility was defined as the presence at baseline of improvement in FEV1 of ≥200mL and ≥12% following bronchodilator; RCT eligibility was assessed as per common eligibility criteria. Logistic regression was applied to assess independent factors of response (domains of exacerbations, pre-bronchodilator FEV1, and LTOCS) after initiation of a biologic.

There were 2116 patients that initiated a biologic after the baseline visit and had a follow up visit (visit at 12 months or closest to 12 months was used) and 6335 patients met inclusion criteria for the comparison group who did not initiate biologics in the follow up period. Severe asthma patients who initiated biologics differ socially and in severity to those who did not

initiate biologics, but not with regard to biomarkers, reflecting possible prescribing bias. To clarify, those who initiated biologics were significantly younger, had earlier asthma onset, a higher proportion of never smokers, and worse baseline asthma status across all four outcomes domains (lung function, asthma exacerbations, asthma control and oral corticosteroid burden).

For each outcome, there were more responders and super responders (as per single domain critiera mentioned above) among patients who initiated biologics than those who did not ($p< 0.001$ for all outcomes).The magnitude of improvement is similar to that seen in clinical trials. There was a dispersion of response across each domain between biologic patients and non-biologic patients, and by biologic class. In biologic vs non-biologic patients, exacerbation reduction of ≥50% was observed in 59% vs 43% (n=1212); $FEV_1$ improvement of ≥100mL was observed in 54% vs 42% (n=1068); asthma control improvement was observed in 49% vs 42% (n=862); LTOCS dose improvement was observed in 49% vs 33% (n=296). Anti-IL5/5R patients showed more likelihood of exacerbation reduction, FEV1 improvement, and LTOCS reduction than Anti-IgE patients. Among biologic patients, about one-fifth of patients experienced super-response in $FEV_1$ (n=323), about one quarter in asthma control (n=514), about one third in exacerbations (n=706) and about 40% in LTOCS (n=233). A smaller proportion of non-biologic patients attained super-response in these domains. This suggests the need for multidimentional assessments that can uncover treatable traits to facilitate personalized medicine. This study was not able to examine overlap of response due to lack of data completeness for all four outcomes, which may be due to regional inconsistencies of record keeping.

The presence of lung function reversibility at baseline was associated with response and super-response to biologic medications in the domains of FEV1 but not exacerbations or OCS on univariate analysis. Across the whole cohort (those who initiated biologics and who did not), the Grade 3 eosinophilic phenotype (highest T2 Gradient) was associated with a longitudinal exacerbation improvement and showed absolute improvements in FEV1 and LTOCS burden. Response as per RCT eligibility was not completed as only 2.5% (n=211) of the total cohort were eligible. This highlights the difference between RCTs and real-life data; the latter benefits from generalizability to broad patient populations. Anti-IL5/5R therapy, BMI and baseline exacerbations showed exacerbation response. Sex, baseline FEV1 and baseline exacerbations showed FEV1 response. Anti-IL5/5R showed LTOCS reduction response.

## 2.0 Background

Asthma is a heterogeneous disease, characterized by airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and

cough that vary over time and in intensity, together with variable expiratory airflow limitation[1]. There is more than 300 million people suffering from asthma and almost 0.5 million annual deaths worldwide[2]. An estimated 3 to 10% of asthmatic patients suffer from severe asthma, defined by the Global Initiative for Asthma (GINA) as asthma which is uncontrolled despite adherence with maximal optimized Step 4 or Step 5 therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased[1]. Severe asthma is associated with an increased risk of mortality and hospitalization, a reduced quality of life (QoL), and increased health care costs. While being a small proportion of the asthmatic population, patients with severe asthma contribute as much as 60% of the healthcare cost, representing a large economic burden on health system and society, and a high burden on patients and their family[3–5].

In the last decade, new innovative therapies targeting different aspects of asthma inflammatory pathways have been discovered and licensed[1]. While these biologic therapies have brought huge improvements to the treatment of people with severe asthma, significant knowledge gaps that could improve the real-world implementation and impact on patient care pathway remain. Indeed, the larger part of the body of evidence on efficacy and safety of these new drugs rely on randomised control trials (RCT). While being the gold standard in biological evidence and a pillar in the licensing process, RCT results are conducted on highly selected population under strict control conditions that may not be representative of patients behaviour in real life and of the population that could benefit from new treatments assessed[6–8]. In addition, multiple outcomes have been used to assess treatment efficacy, adding to the complexity of capturing the broad benefits treatments for different types of severe asthma patients[9].

Disease control in severe asthma is difficult to maintain and complex to assess. It is key to predict or understand very early which patients can benefit from available treatments[10]. It requires regular patient review by physicians to ensure accurate recording of asthma outcomes including assessment of symptoms, exacerbations, lung function, quality of life and other measures of control and future risk[11]. The measures of asthma control are wide-ranging and include objective measures such as lung function, biomarkers, and subjective measures reported by patients such as asthma symptoms and health-related quality of life[11,12]. Routine assessment represents an important source of information, especially for disabling conditions requiring individualised therapies such as severe asthma. As such, participation in a registry or clinical trial are advocated for patients in international guidelines[11]. Registries are useful for investigating knowledge gaps in heterogeneous and rare diseases for which clinical trials can provide limited data, and are very important in assessing the real world value of novel (and

often expensive) therapies. In particular, pooling larger and broader populations than seen in randomised controlled trials, registries can identify subgroups who do well or do not respond and to monitor safety especially for rare adverse events. Registries may capture epidemiologic characteristics of real world patients' populations, and allow hypothesis generation, formation of new evidence as well as capture of unmet needs[13].

Therefore, the aim of this study is to characterize the population of patients with severe asthma who has access to biologic treatment at baseline and after initiation of biologic therapies, and to identify those who are benefitting from them and factors that are associated with improvements in asthma-specific outcomes after biologic initiation. Using the International Severe Asthma Registry (ISAR) cohort, we will get information about real life practices and study factors determining clinical outcome improvement in patients with severe asthma receiving add-on biologics treatment. The ISAR cohort is the largest and only international registry with patient level data on adults with severe asthma available globally[14].

# 3.0 Study Aims and Objectives

## 3.1 Study Aims

To describe the ISAR cohort who initiate biologic treatment and examine clinical outcomes at follow up by biologic class, and subgroups of patients, and compare these to those not initiated on biologic medications.

## 3.2 Study Objectives

**Objective 1**: Describe baseline characteristics of patients with severe asthma before biologic treatment initiation including demographics, asthma characteristics, medications, and asthma outcomes.

a) Overall
b) By class of biologics
c) Compared to the baseline demographics of the rest of the ISAR cohort who did not initiate a biologic

**Objective 2**: Describe the proportion and clinical characteristics of severe asthma patients who improve in each domain of asthma-specific outcomes as close to 12 months after biologic initiation as possible (a minimum of 24 weeks). Examine subgroups: class of biologics and population eligible for RCT. Domains of asthma-specific outcomes below:

a) Asthma control as measured by validated asthma-control questionnaire as controlled, partially controlled, or uncontrolled to be dichotomised into controlled and partially controlled versus uncontrolled, note: excluded from this analysis if has well controlled asthma at baseline.
b) Forced expiratory volume in 1 second ($FEV_1$) pre-bronchodilator (measured in litres) improvement ≥100mL or not
c) Reduced annualized rate of exacerbations, note: if initial annualised rate of exacerbations zero then excluded from this analysis
d) Reduced dose of long-term oral corticosteroids (LTOCS), note: excluded from this analysis if not on LTOCS at baseline

**Objective 3**: Compare the responders to the non-responders and to the ISAR cohort who did not initiate biologics including by presence of $FEV_1$ reversibility and T2 biomarker gradient.

**Objective 4**: Describe the overlap of response to each domain (*Figure 1*).

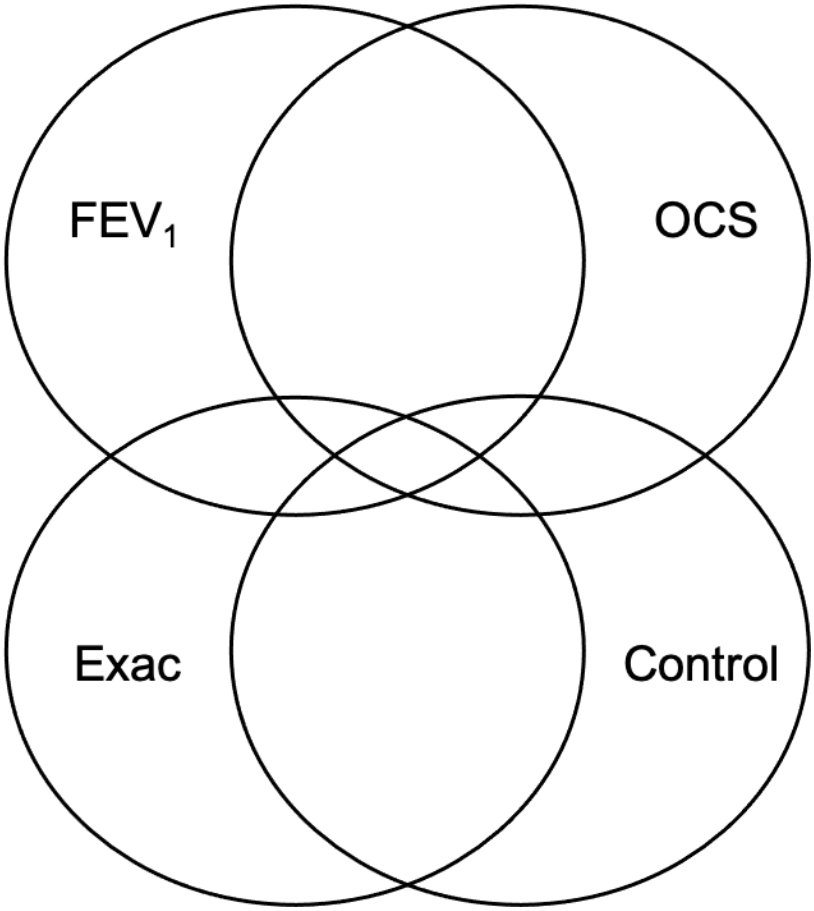



**Figure 1:** Overlap of response in each asthma-specific domain

**Objective 5**: Describe proportion of super-responders in each outcome

**Objective 6**: Identification of factors independently associated with response in patients with severe asthma receiving biologic treatment in asthma-specific outcomes:

a) $FEV_1$ pre-bronchodilator (measured in litres) change >100mL
b) Reduced annualized rate of exacerbations
c) Reduced dose of LTOCS

# 4.0 Materials and Methods

## 4.1 Overall Study Design

This is a registry-based longitudinal cohort study using a prospective international cohort of adult patients with severe asthma to characterize a real-world population treated with add-on biologic therapy and explore frequency of clinical response in four outcome domains, and factors determining clinical response. This was a pragmatic, inclusive study design that included all ISAR participants who met study criteria and aimed to describe the real-world population initiating biologics in the context of those who did not initiate biologics without matching participants.

The index date is the date of biologic initiation for those initiating biologics and the date of ISAR enrolment for those not initiating biologics. Demographic and clinical characteristics are described at or 12 months pre-biologic initiation for biologic patients, and at 12 months pre-index period for non-biologic individuals. Post-biologic initiation (≥24 weeks and closest to 1 year post-index date), the clinical domains of annualised exacerbation rate, long-term OCS, asthma control and lung function are described (*Figure 2*).

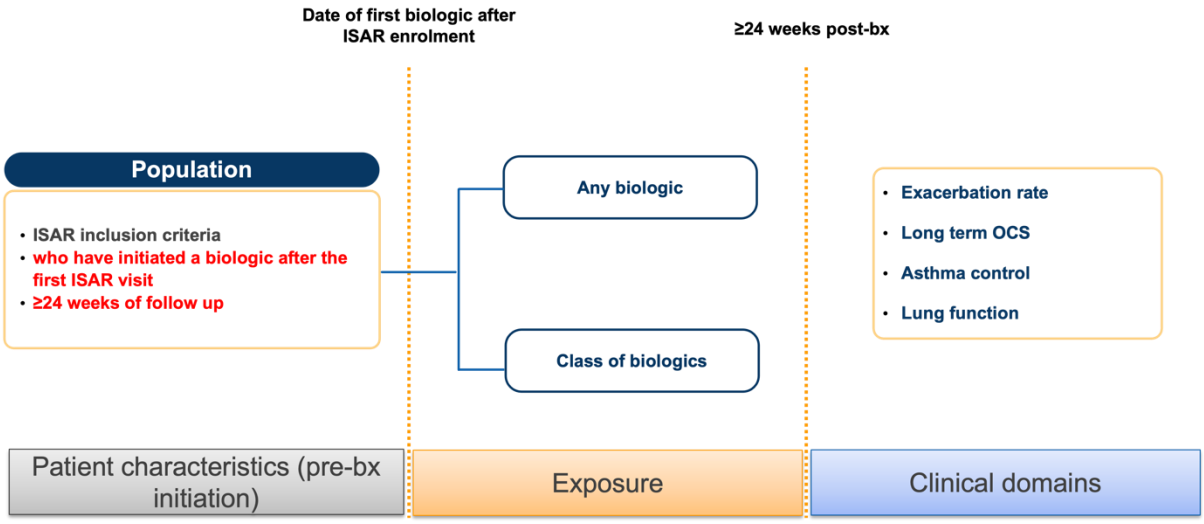



**Figure 2:** Overview of LUMINANT study design

## 4.2 Study Population and Data Source(s)

The data source is the ISAR registry[14], which is a multi-country, multi-centre, observational epidemiologic data repository, with retrospective and prospective data from >14,000 severe asthma patients. The key feature of the registry is its standardised data fields irrespective of

data source. ISAR includes patient-level data from a combination of existing and new severe asthma registries, where primary data collection is mostly performed via eCRFs on a web-based platform. Registry data collection started in 2017 and is expected to continue up to December 2023 and beyond. Ethical governance for ISAR is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[15]. Anonymised person-level data from countries contributing data currently will be used for this analysis, as defined by the inclusion criteria in section 4.3.

The study population include a subset of the ISAR population. Details of the ISAR registry have been published previously[16].

## 4.3 Inclusion and Exclusion Criteria

**Inclusion Criteria**

Eligible subjects are adults (≥18 years old) with severe asthma, defined as patients with uncontrolled asthma at GINA 2018 Step 4 or undergoing GINA 2018 Step 5 treatment at baseline, who have initiated a biologic after enrolment in ISAR, with at least 2 visits recorded, including a visit pre or at biologic initiation and 1 follow up visit post biologic treatment initiation (visit ≥24 weeks and closest to 1 year to be selected) in addition to ISAR registry inclusion criteria (Table 1).

*Table 1: ISAR patient inclusion and exclusion criteria*

| Inclusion | Exclusion |
|---|---|
| Adult (≥18 years old) patients with severe asthma<br>Undergoing GINA 2018 Step 5 treatment[a1] or<br>Uncontrolled on GINA 2018 Step 4 treatment[1]<br>Uncontrolled defined as at least one of the following (per American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines[17]):<br>• Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, or Asthma Control Test (ACT) <20 (or 'not well controlled')[1] | Lack of informed consent for participation |

| Inclusion | Exclusion |
|---|---|
| • Airflow limitation: Pre-bronchodilator $FEV_1$< 80% predicted, with reduced $FEV_1$/forced vital capacity (FVC) (defined as less than the lower limit of normal)<br>• Serious exacerbations: ≥1 hospitalisation, intensive care unit (ICU) stay or mechanical ventilation in the previous year<br>• Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids with each course >3 days in the previous year | |

[a]Asthma controlled on high-dose inhaled corticosteroids (ICS)/long-acting β2-agonist (LABA) treatment was not part of the current inclusion for ISAR

ACQ*:* Asthma Control Questionnaire; ACT*:* Asthma Control Test; ATS*:* American Thoracic Society; ERS*:* European Respiratory Society; $FEV_1$: forced expiratory volume in 1 second; FVC*:* forced vital capacity; GINA*:* Global Initiative for Asthma; ICS*:* inhaled corticosteroids; ICU*:* intensive care unit; ISAR*:* International Severe Asthma Registry; LABA*:* long-acting $\beta_2$-agonist

**Exclusion Criteria**

Within ISAR patient population, the following patients will be excluded:

- Patients who stopped biologic treatment before 24 weeks post initiation
- Patients with less than 24 weeks of follow-up time between biologic initiation and follow up visits
- Patients on a biologic at the baseline visit

Patients who meet the inclusion criteria but did not initiate a biologic after the baseline visit will be described to provide context to the results for the main study group.

# 5.0 Study Variables

## 5.1 Demographic Variables

The list of patients' variables collected in ISAR are available in Appendix 1. For this study, we will limit the analysis to the variables presented in the sections below.

## 5.2 Demographics and Clinical Characteristics

The demographic characteristics of the patients are listed in Table 2.

*Table 2: Patients' demographic variables*

| Variable Name[1] | Description |
|---|---|
| Age<br><br>Sex<br>Height<br>Weight | <br>Patient age in years<br>Gender (male or female)<br>Height measurement in metres (m)<br>Weight measurement in kilograms (kg) |
| Body Mass Index (BMI) | Defined as the ratio of weight (kg) to squared height ($m^2$) |
| Ethnicity | Caucasian, Asian, African, Latino, Mixed, Other, Unknown |
| Country | Country of enrolment of the patients |
| Smoking status | Categorised as non-smoker, current smoker, or ex-smoker |
| Pack years | Defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked |

## 5.3 Clinical Variables

The clinical characteristics of interest include usual biologics treatment criteria, asthma related outcomes, and other outcomes assessing:

- Background asthma therapy
- Lung function
- Asthma Control
- Exacerbations
- Biomarkers (FeNO, blood eosinophil count (BEC), total immunoglobulin G (IgE), measures of atopy)

The clinical characteristics (Table 3) will be described at or before biologic initiation visit (T0: within 12 months of ) and at or post biologic initiation visit (T1; ≥24 weeks and closest to 1 year post-biologic initiation).

*Table 3: Patients' clinical characteristics*

[1] All variables are measured at baseline; which will refer to the first patient visit where data is collected for ISAR

| Variable Name[2] | Description |
|---|---|
| ***ISAR Severe Asthma Criteria*** | |
| ISAR inclusion (GINA 2018[3] guidelines) | Patient on GINA Step 5 treatment<br>OR<br>Patient on GINA Step 4 treatment with<br>(a) Severe asthma symptoms<br>(b) Severe asthma exacerbations requiring systemic corticosteroids |
| ***Medical History*** | |
| Asthma duration | Whole years or months (if less than 1 year) at which first asthma diagnosis/symptoms began |
| Age of asthma onset | Age of first asthma diagnosis/symptoms |
| Annualised exacerbations | Count of exacerbations requiring rescue oral corticosteroids in the past 1 year |
| Asthma control | • Categorised as controlled, partly controlled, or uncontrolled according to the GINA Asthma Control Criteria/ACQ/ACT |
| Biologic treatment status at T1 | Stopped or ongoing or switched |
| Follow up time | Time from T0 to T1 |
| ***Biomarkers*** | |
| IgE level | Counts of IgE, measured in kilounits per litre (kU/L) or international units per litre (IU/mL) |
| BEC | Highest counts of blood eosinophils, measured in cells per litre ($10^9$/L). |
| Fractional exhaled nitric oxide (FeNO) test | Measurements of FeNO concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s |
| ***Allergy Testing*** | |

[2] All variables are measured at baseline; which will refer to the first patient visit where data is collected for ISAR
[3] Global Initiative for asthma 2018: GINA difficult-to-treat and severe asthma in adolescent and adult patients – Diagnosis and management. Available from: Link.

| | |
|---|---|
| Skin Prick Test (SPT) | House dust mite (HDM), animal dander (cat, dog), pollen (tree, grass) and moulds (*Aspergillus*).<br>• Categorised as positive reaction if ≥3 mm is wheal diameter |
| Serum Allergen Test positive allergens | Mould Mix, Dust Mite, Cat, Dog, *Aspergillus*, Animal Mix, Other<br>• Categorised as positive reaction if >0.7kU/L |
| Serum Allergen Test (SAT) | Positive/Negative/No data |
| ***Spirometry*** | |
| Pre-bronchodilator $FEV_1$ | $FEV_1$ measured in litres (L), before administering bronchodilator |
| Post-bronchodilator $FEV_1$ | $FEV_1$ measured in litres (L), after administering bronchodilator |
| $FEV_1$ reversibility | Difference between pre- and post-bronchodilator FEV1 >=12% and >=200mL |
| ***Medication***[4] | |
| Long term OCS<br>(Y/N, daily dose, duration) | Prescription of OCS for maintenance |
| Anti-IgE (Y/N, duration) | Prescription for anti-IgE: Omalizumab |
| Anti-IL5/5R/IL5R (Y/N, type, duration) | Prescription for anti-Interleukin 5 (Anti-IL5/5R): Mepolizumab, Reslizumab, Benralizumab |
| Anti-IL4Rα (Y/N, type, duration) | Prescription for anti-Interleukin 4Rα |

[4] All patients are assumed to be under ICS and LABA treatment, only additional treatments are listed

## 5.4 Primary Outcome Variables - Clinical response

In order to identify patients' characteristics associated with clinical response, relationship between patients' demographic and clinical characteristics at baseline visit pre or at biologic initiation (T0) and clinical outcomes reported at post-biologic visit (T1) will be explored. Clinical response (change from baseline) will be explored through:

1. The change from baseline in any clinical outcome meeting the definitions in Table 4 (see Table 4)[9]
    - Asthma control
    - LTOCS daily dose
    - Exacerbations
    - Lung function
2. Frequency of super-responders

Clinical response will be collected from the patients visit closest to a year post biologic initiation, with a minimum of 24-weeks of follow-up time post biologic initiation[11,26].

Clinical response from the following four categories of clinical outcomes will be explored (pending data availability) in biologic patients vs non-biologic patients at baseline and follow-up. Response and super-response for each category of following clinical outcome will be described for the overall population, and for biologic patients vs non-biologic patients:

- Asthma exacerbation, defined as:
    - Asthma-related hospital attendance/admission; AND/OR
    - Asthma-related A&E attendance; AND/OR
    - An acute oral corticosteroid course of 3 days or more
    - Separate recordings of exacerbations within 14 days of each other will be treated as the same exacerbation.
- LTOCS:
    - LTOCS dose defined prescription of daily dose for >1 month
- Asthma control, 3 categories uncontrolled, partially controlled and controlled, defined as:

- A combination of GINA, ACT and ACQ according to ISAR's site/country practices
-

- Lung function, defined as:
  - Change in pre-bronchodilator $FEV_1$

*Table 4: Clinical outcomes measure for clinical response and super-response assessment at post biologic initiation visit in patients with severe asthma*

| Variable Name[5] | Type | Excluded | Response | Super-response |
|---|---|---|---|---|
| Reduction in annual asthma exacerbations[6] | Categorical/ continuous | Those who started with no exacerbations at baseline visit | • Reduction of 50% in number of exacerbations requiring rescue steroids between biologic initiation date and T1<br>• Number of annualised exacerbations | Exacerbation elimination |
| Total dose of oral corticosteroids during follow-up[7]<br>• Long term use | Continuous/ categorical | Those not on LTOCS at baseline | • Change in daily dose for those on daily OCS (mg)<br>• Any improvement in daily dose of OCS | OCS cessation or weaning to adrenal insufficiency (<=5mg) |
| Asthma control in the past 4 weeks | Categorical | Those with well controlled asthma at baseline | • Improvement in category of asthma control on validated questionnaires<br>○ Change in category from uncontrolled to partly | • New attainment of well controlled asthma |

[5] Outcome variables are measured in the follow-up visit after biologic initiation date
[6] Total number of exacerbations will be calculated between biologic initiation date and current visit date.

| | | | | |
|---|---|---|---|---|
| | | | controlled or well controlled, or from partly controlled to well controlled | |
| Lung function | Categorical and continuous | N/A | • Increase in FEV1 pre-bronchodilator by greater than or equal to 100mL from baseline<br>• Change in FEV1 pre-bronchodilator from baseline (litres) | • Increase in ≥500mL of FEV1 from baseline to follow up |

$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

## 5.5 Subgroup of interest

The clinical characteristics will be described for patients overall, in those not initiating biologics, and per biologic class:

- Biologic class:
  - Anti-IgE
  - Anti-IL5/5R/5R
  - Anti-IL4/IL13

In addition proportion who responded in the four outcome measures will be examined in the following subgroups:

  - Presence of reversibility, defined as the presence at baseline of improvement in FEV1 of >=200mL and >=12% following bronchodilator
  - RCT eligibility as defined above
  - Modified T2 (eosinophilic) gradient, criteria as per Heaney et al[1] excluding the biologic criteria. The variables from the original algorithm (*Figure 3*) include highest BEC ever (≥300 cells/μL, ≥150-300 cells/μL, or <150 cells/μL), anti-IL-5/5 receptor treatment, long-term OCS use ever, elevated FeNO (≥ 25 parts per billion) ever, nasal polyps diagnosis ever, and adult asthma onset (≥ 18 years).

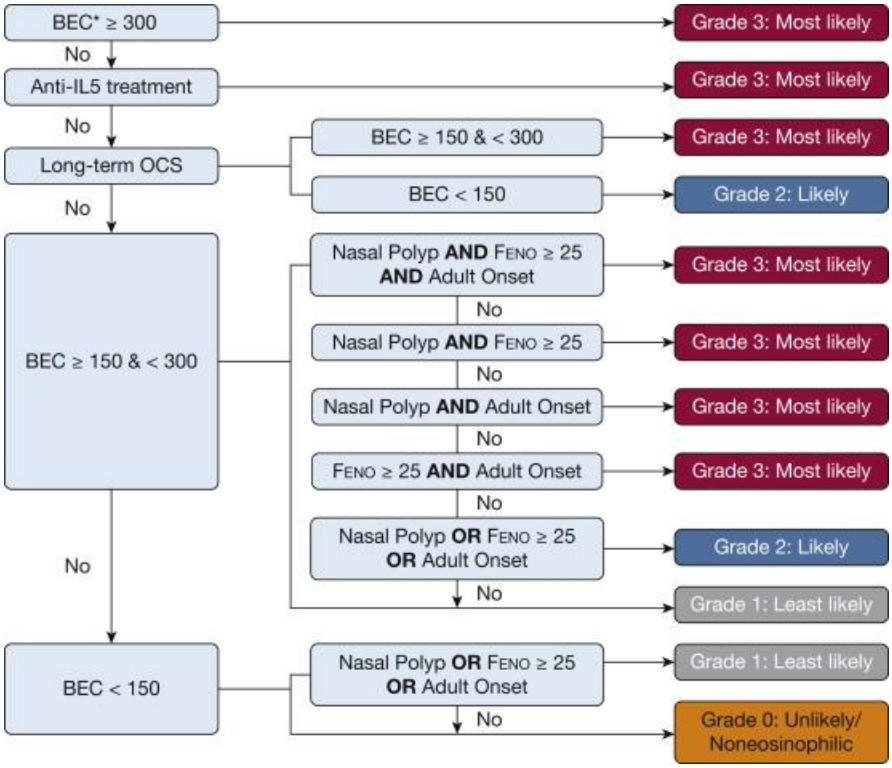



**Figure 3**: Flow chart showing the original T2 (eosinophilic) gradient algorithm (Heaney et al[1])

## 5.6 Biologic randomised clinical trial population – eligibility criteria

RCTs assessing the external validity or efficacy of severe asthma biologic therapies make the distinction between different categories of eligibility criteria: biomarker, diagnosis, and demographic. For the purpose of this study, we used simplified eligibility criteria of drug specific pivotal phase 3 trials to assess the rates of real world patients fulfilling the most common RCT eligibility criteria for their respective therapy drugs [18–22].

In the LUMINANT study, the proportion of severe asthma patients who are potentially eligible for RCTs will be examined. Simplified RCT eligibility criteria for the LUMINANT study are as follows. Participants were considered RCT eligible if they met all of the following criteria:

1. A diagnosis of severe asthma on inhaled corticosteroid dose equivalent ≥1000ug per day
2. FEV1 reversibility
3. FEV1 <80% predicted
4. Smoking history of less than 10 pack years

## 5.7 Overlap of response

In order to determine the proportion of participants who achieve a composite response to biologics – that is those who achieve an improvement across all four outcomes as per the

previous definitions – will be examined. The proportion who improve in none, one, two, three and all four domains will be described for the subgroup who have paired (baseline and follow-up) outcome data across the four outcome domains.

# 6.0 Statistical Analysis

## 6.1 Sample Size

All participants who are eligible based on pre-specified criteria will be included.

## 6.2 Main analysis

Descriptive statistics were provided for the overall population and by subgroup of interest. For variables measured on the interval or ratio scale, summary statistics produced were sample size (n), percentage non missing, mean, standard deviation, range (minimum - maximum), median, inter-quantile range (25th and 75th percentile). For categorical variables, the summary statistics were sample size (n), range (if applicable), count and percentage by category (distribution).

Comparisons between groups were presented on crosstables with Chi-squared test with the pairwise Z-test with Bonferroni correction for comparison of column proportions for categorical variables and independent t-test (for two groups) or one-way ANOVA with post-hoc Tuckey test (for greater than two groups) for continuous variables. P-values of <0.05 were deemed significant.

Evaluation of independent predictors for response in the domains of exacerbation elimination, lung function and oral corticosteroid burden was performed via binomial multivariable logistic regression after assumption testing, to determine the effect of age, sex, BMI, FEV1, annualised exacerbation rate, and biologic class on the likelihood of response in each domain. The outcome variables were binary and as defined previously for each outcome. Key baseline demographic and asthma status variables were chosen for inclusion in the regression analysis to assess the impact of these variables on the outcomes and are outlined as follows.

The results of the regression shows the effect of increasing a single unit of baseline age, BMI, FEV1 (Litres) and exacerbation rate (in the 12 months prior to ISAR baseline visit or pre-biologic initiation) or female sex compared to male sex andiologic class (anti IgE, anti-IL5/5R, anti-IL4/13) in comparison to not initiating a biologic in the follow up period.

The full LUMINANT protocol was a consensus protocol approved by all members of the working group and is available on request. Ethics approval for this project was granted by the

Anonymised Data Ethics and Protocol Transparency Committee (Reference: PROTOCOL2303.)

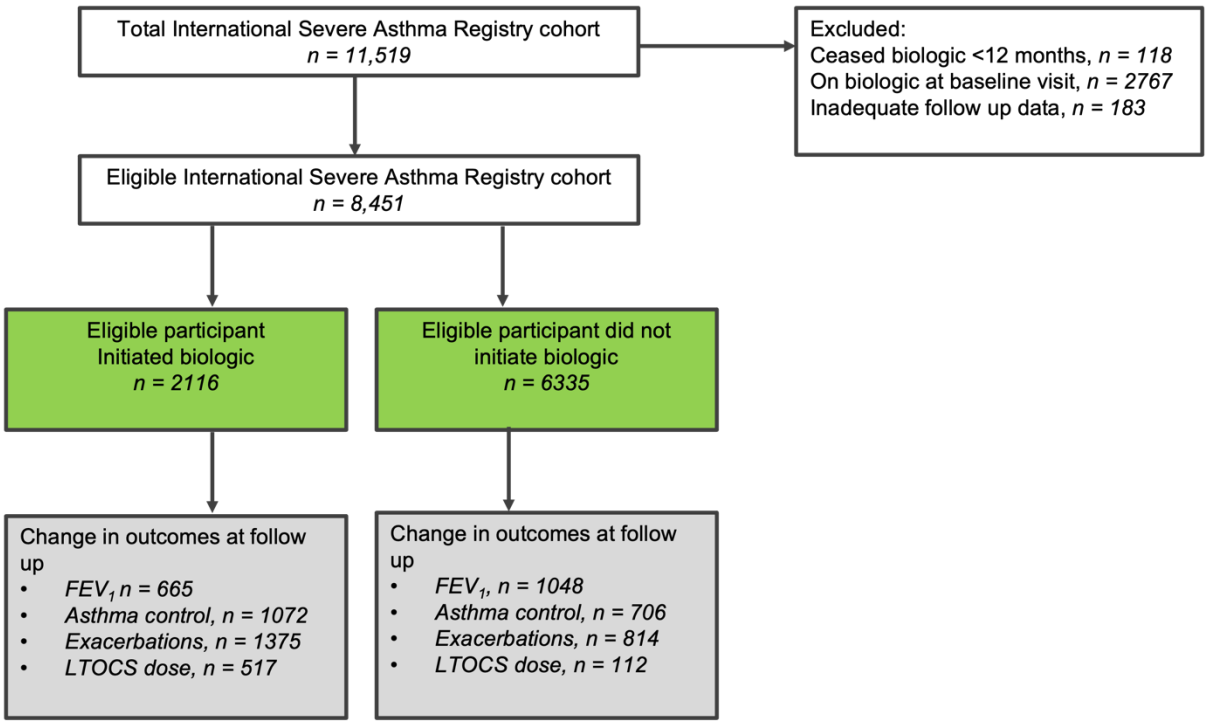
## 6.3 Software

Statistical analysis was performed with SPSS Version 24-28.

# 7.0 Results

## 7.1 Overall Patient Population/Study cohort

2116 patients initiated a biologic after the baseline visit and had a follow up visit (visit at 12 months or closest to 12 months was used) so were eligible for inclusion according to pre-defined criteria. There were 6335 who met inclusion criteria for the comparison group who did not initiate biologics in the follow up period (*Figure 4*). There were 118 patients excluded due to biologic cessation within the first 24 weeks, 2767 excluded due to being on a biologic at the baseline visit and 183 excluded due to inadequate follow up or missing data.




Measures of change in clinical outcomes ($FEV_1$, asthma control, exacerbations and LTOCS dose) are described in Table 4 of Section 5.4,
$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

**Figure 4: Summary of LUMINANT study flow.**

## 7.2 Demographic and Clinical Characteristics

Baseline characteristics of those included in the study is outlined in *Table 5*, those who initiated biologics were significantly younger, had earlier asthma onset, a higher proportion of never smokers, and worse baseline asthma status across all domains (discussed below) but there was no difference in biomarker levels contrasted to those not initiating biologics.

**Table 5: Baseline characteristics of the total LUMINANT cohort, those who were initiated on biologics and those who were not.**

| | **Biologic** ***n = 2116*** | **Non-biologic** ***n = 6330*** | **P-value** |
|---|---|---|---|
| **DEMOGRAPHICS:** | | | |
| **Sex (Female),** % (number) | 62% (1311 / 2116) | 62% (3893 / 6330) | 0.71 |
| **Ethnicity:** | | | |
| **Caucasian,** % (number) | 78% (1471 / 1876) | 79% (4380 / 5573) | |
| **Asian,** % (number) | 6% (119 / 1876) | 9% (521 / 5573) | |
| **African,** % (number) | 3% (63 / 1876) | 5% (260 / 5573) | |
| **Latin American,** % (number) | 0% (0 / 1876) | 0% (0 / 5573) | |
| **Arabic,** % (number) | 9% (173 / 1876) | 7% (388 / 5573) | |
| **Other,** % (number) | 3% (50 / 1876) | 0.4% (22 / 5573) | |
| **Age (years)**, mean ±SD | 53 ±15 (2115) | 58 ±17 (6335) | <0.001 |
| **BMI,** mean ±SD | 29.1 ±7 (1862) | 29.6 ±8 (4995) | 0.03 |
| **Smoking status:** | | | |
| **Never smoker,** % (number) | 62% (1309 / 2116) | 45% (2858 / 6330) | <0.001 |
| **Current smoker,** % (number) | 24% (504 / 2116) | 23% (1482 / 6330) | |
| **Ex-smoker,** % (number) | 3% (60 / 2116) | 6% (373 / 6330) | |
| **Other,** % (number) | 12% (243 / 2116) | 26% (1622 / 6330) | |
| **Asthma onset,** mean ±SD | 29 ±19 (1449) | 31 ±20 (2126) | <0.001 |
| | | | |
| **ASTHMA STATUS:** | | | |
| **Baseline $FEV_1$ pre,** mean ±SD | 1.9 ±0.8 (1516) | 2.1 ±0.8 (3678) | <0.001 |
| **Baseline $FEV_1$ post,** mean ±SD | 2.0 ±0.8 | 2.2 ±0.8 | <0.001 |
| **$FEV_1$ reversibility,** % (number) | 16% (178) | 12% (346) | <0.001 |
| **Poor asthma control,** % (number) | 75% (973 / 1299) | 56% (1277 / 2268) | <0.001 |
| | | | |
| **Baseline annualised exacerbations,** mean ±SD | 3.8 ±4 (1711) | 1.6 ±2 (2688) | <0.001 |
| **Baseline annualised exacerbations (categorical)** | 0 – 11%<br>1 – 3 – 48%<br>4 – 5 – 20%<br>>/=6 – 21% | 0 – 30%<br>1 – 3 – 58%<br>4 – 5 – 7%<br>>/=6 – 5% | <0.001 |
| **LTOCS,** % (number) | 43% (901 / 2116) | 14% (878 / 6335) | <0.001 |
| | | | |
| **BIOMARKERS:** | | | |
| **Blood eosinophil count,** mean ±SD | 598 ±893 (504) | 617 ±820 (954) | 0.7 |
| **FeNO (ppb),** mean ±SD | 49 ±46 (800) | 47 ±46 (1532) | 0.3 |
| **IgE,** mean ±SD | 443 ±1003 (1273) | 417 ±1306 (2441) | 0.5 |
| **Sensitised to perennial allergens,** % (number) | 39% (671 / 1724) | 44% (1844 / 4177) | 0.001 |

SD – standard deviation
BMI – body mass index
$FEV_1$ – Forced expiratory volume in one second
IgE – immunoglobulin E
FeNO – fractional exhaled nitric oxide
Ppb – parts per billion
LTOCS – long term oral corticosteroid

## 7.3 Outcome features

In biologic patients and non-biologic patients who had available outcome data at baseline and follow-up, improvements in the clinical domains of $FEV_1$, asthma exacerbations, asthma control, and long term oral corticosteroid (LTOCS) daily dose are shown in *Figure 5*.

A summary of response and super-response in the four clinical domains in biologic patients and non-biologic patients with available paired outcome data at baseline and follow-up is

outlined in *Table 8, Figure 6*. The average follow up time for those commencing biologics was 623 ±662 days and for those not commencing biologics 385 ±229 days (p<0.001).

Analysis of the time to follow up is summarised in *Figure 5* and *Table 6*. Information on number of patients available within the LUMINANT dataset relating to the LTOCS analyses are provided in *Table 7*.

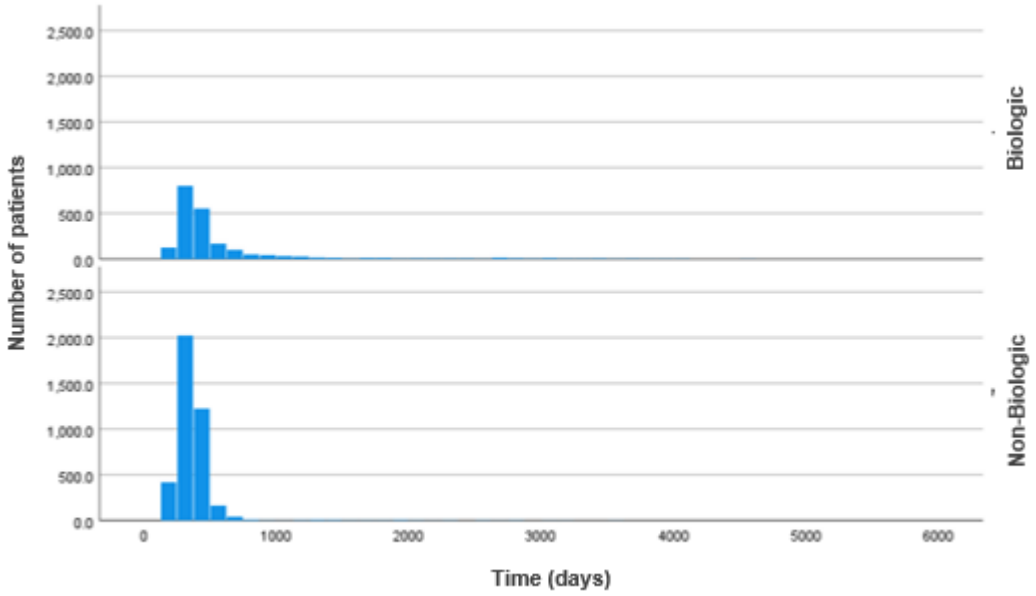


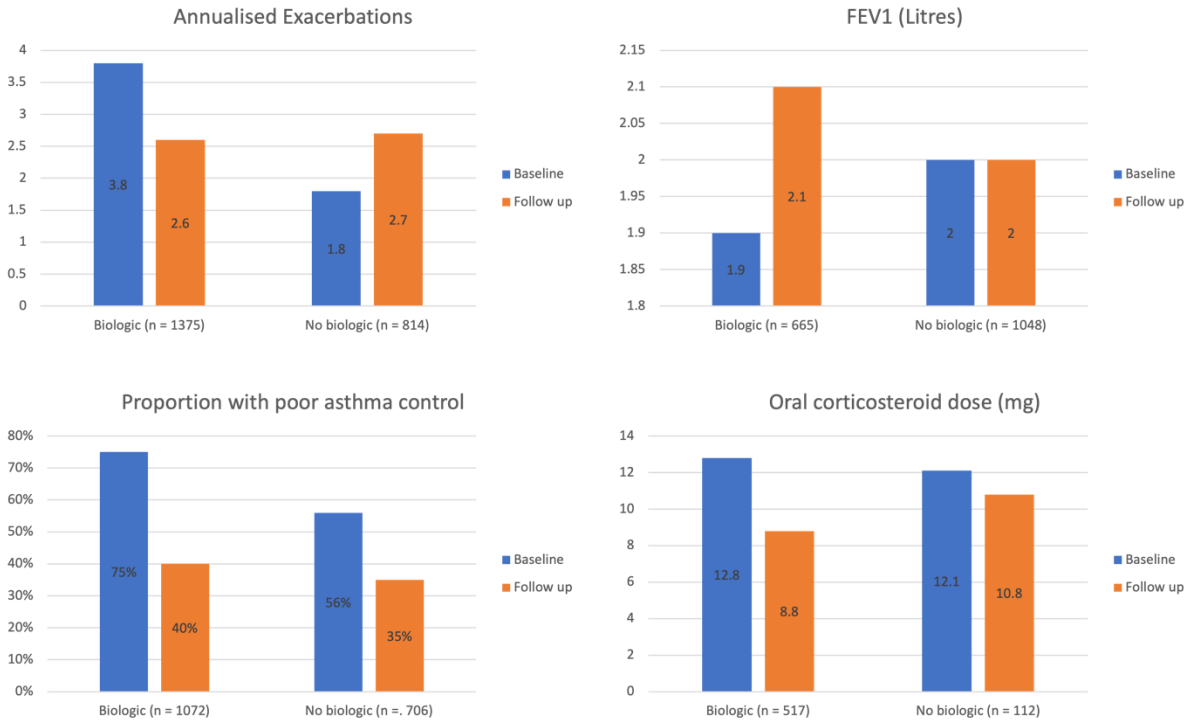

**Figure 5: Histogram of time to follow up (days) by whether a biologic was initiated or not**

**Table 6: Percentage of cohort with follow up at different time points**

| | % with follow up for at least this number of days | |
|---|---|---|
| **Follow up time** | Biologic | Non biologic |
| **6m (183 d)** | 100% | 100% |
| **8m (243 d)** | 94.4% | 90.1% |
| **10m (304 d)** | 88.3% | 79.6% |
| **11m (335 d)** | 80.7% | 70% |
| **12m (365 d)** | 62.2% | 47.3% |
| **18m (548 d)** | 25.3% | 4.9% |

**Table 7: number of patients with available data for long term oral corticosteroid calculations in the LUMINANT dataset**

| | Biologic initiators (number) | Non biologic patients (number) |
|---|---|---|
| LTOCS at baseline | 895 | 556 |
| LTOCS dose at baseline | 556 | 130 |
| LTOCS dose at follow up | 794 | 524 |
| Paired LTOCS dose at baseline and follow up | 517 | 112 |




$FEV_1$ – Forced expiratory volume in one second, OCS dose (mg) is the daily dose.

**Figure 6: Summary of response in different outcome domains in those who did and did not initiate a biologic between the baseline and follow up visit**

As shown in *Figure 6*, biologic and non-biologic patient groups differ at baseline for exacerbations, $FEV_1$ and asthma control, but were similar at baseline for LTOCS daily dose.

*Figure 6* shows that at follow-up (compared to baseline):

- Biologic patients showed a 32% decrease in annualised exacerbations, while non-biologic patients showed a 50% increase
- Biologic patients showed an 200mL increase in $FEV_1$, while non-biologic patients showed no change
- Biologic patients showed a 47% decrease in the proportion of patients with poor asthma control, while non-biologic patients showed a 37% decrease
- Biologic patients showed a 21% decrease in LTOCS daily dose, while non-biologic patients showed a 11% decrease.

**Table 8: Response and super-response in different outcome domains in those who did and did not initiate a biologic medication between the baseline and follow up visit**

| | Overall | Biologic | Non-biologic | p-value |
|---|---|---|---|---|
| **RESPONSE** | | | | |
| **Exacerbation reduced ≥50%**, % (number) | 53% (1165 / 2189) | 59% (806 / 1375) | 44% (359 / 814) | <0.001 |
| **$FEV_1$ improved ≥100mL**, % (number) | 42% (712 / 1713) | 54% (358 / 665) | 34% (354 / 1048) | <0.001 |
| **Asthma control improved**, % (number) | 46% (823 / 1778) | 49% (524 / 1072) | 42% (299 / 706) | 0.007 |
| **LTOCS dose improved**, % (number) | 46% (287 / 629) | 49% (255 / 517) | 28% (32 / 112) | <0.001 |
| | | | | |
| **SUPER RESPONSE** | | | | |
| **Exacerbation elimination**, % (number) | 19% (684 / 3587) | 27% (442 / 1620) | 12% (242 / 1967) | <0.001 |
| **$FEV_1$ improved >=500mL**, % (number) | 12% (210 / 1713) | 19% (124 / 665) | 8% (86 / 1048) | <0.001 |
| **New good asthma control**, % (number) | 27% (514 / 1778) | 30% (318 1072) | 25% (196 / 706) | 0.016 |
| **LTOCS super-response**, % (number) | 36% (225 / 629) | 39% (200 / 517) | 22% (25 / 112) | <0.001 |

$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

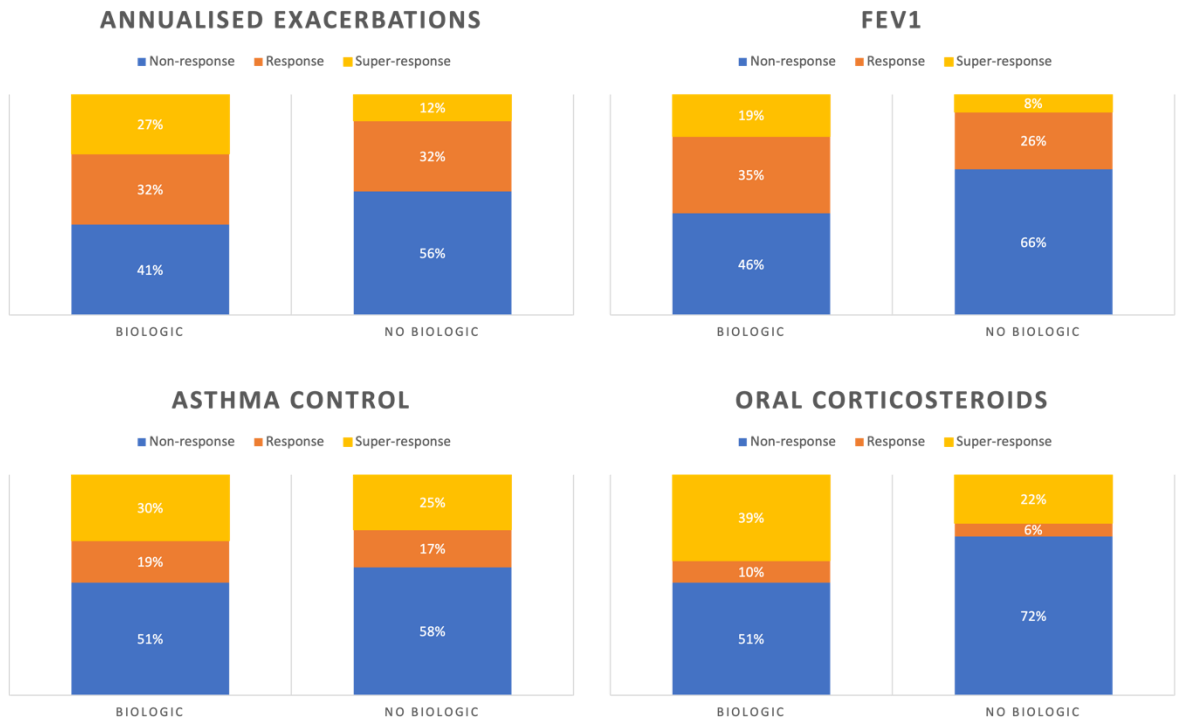
*Lung function*
Baseline pre-bronchodilator $FEV_1$ was significantly worse in those who initiated biologic medications compared to those who did not (1.9 ±0.8 litres versus 2 ±0.8 litres, p <0.001). Of those who initiated a biologic 54% (mean $FEV_1$ 2.1±0.8 litres) had an improvement in $FEV_1$ of >=100mL and 34% (mean $FEV_1$ 2±0.8 litres) who did not initiate a biologic (p <0.001).

*Asthma exacerbations*
Baseline (pre-biologic or first ISAR visit) annualised exacerbation rate was significantly worse in those who initiated biologic medications compared to those who did not (3.8±4 versus 1.6±2, p<0.001). 59% of biologic patients vs 44% of non-biologic patients had ≥50% reduction in exacerbation at follow-up (p <0.001).

*Asthma control*
A greater proportion of those who initiated biologics had poor control at baseline (pre-biologic or first ISAR visit) (75% versus 56%, p<0.001) and they had a higher proportion of those that experienced improvement in asthma control at follow up (49% versus 42%, p<0.007.)

*Long term oral corticosteroid burden*
There was a greater proportion of patients on LTOCS in those who initiated biologics (43% versus 14%, p<0.001).

*Super-responders*
There were a greater proportion of those who met criteria for super-response in each asthma outcome domain in those who initiated biologics compared to those who did not (*Table 8, Figure 7*).




$FEV_1$ – Forced expiratory volume in one second

**Figure 7: Proportion of responders, super-responders and non-responders in those initiated on biologic and those who were not initiated on biologics.**

*Subgroups of response*
The presence of lung function reversibility at baseline showed response and super-response to biologic medications in the domains of FEV1 but not exacerbations or OCS (*Table 9*).

**Table 9: Response in different domains as per the presence of reversibility**

| Outcome | Reversibility Present (99) | Reversibility Absent (463) | p-value |
|---|---|---|---|
| $FEV_1$ response | 72% | 52% | <0.001 |
| $FEV_1$ super-response | 37% | 16% | <0.001 |
| Annualised exacerbations reduced by >=50% | 56% | 61% | NS |
| Control improved | 48% | 45% | NS |
| LTOCS improved | 14% | 43% | |

$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

Across the whole cohort (those who initiated biologics and who did not) Grade 3 (highest T2 Gradient) was associated with a longitudinal exacerbation improvement (Table 10). For the

domains of $FEV_1$ and LTOCS burden, greater absolute improvements were observed in patients with the Grade 3 eosinophilic phenotype versus those with Grades 0 to 2 eosinophilic phenotypes. (Table 10).

**Table 10: Response as per presence of T2 gradient (whole cohort)**

| T2 Gradient | 0 (84) | 1 (195) | 2 (76) | 3 (2050) | p-value |
|---|---|---|---|---|---|
| $FEV_1$ response | 43% | 44% | 37% | 53% | NS |
| Annualised exacerbations reduced >=50% | 26% | 33% | 44% | 58% | <0.001 |
| Exacerbation elimination | 10% | 12% | 15% | 25% | <0.001 |
| LTOCS improved | 33% | 33% | 29% | 49% | NS |

$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

There were 4001 patients with adequate data to assess potential RCT eligibility based on simplified criteria of presence of $FEV_1$ reversibility, $FEV_1$ <80% and smoking history of <10 pack years. Of these 5.3% (211) met these criteria, this was 2.5% of the total cohort. Paired outcome data was limited for this small cohort and so further analyses were not performed.

*Independent factors determining response*

Logistic regression was performed to determine the effect of age, sex, BMI, $FEV_1$, annualised exacerbation rate, and biologic class on the likelihood that participants attained a response in the domains of exacerbations, pre-bronchodilator $FEV_1$, and LTOCS after initiation of a biologic. In these analyses <10% of variance was explained by baseline factors mentioned above. The independent factors determining response in different domains are outlined in Table 11.

**Table 11: Independent factors determining response in different asthma outcome domains**

| | Variable | Odds ratio | p-value |
|---|---|---|---|
| **Exacerbations** | Body mass index | 1.02 | 0.006 |
| | Baseline annualised exacerbations | 0.9 | <0.001 |
| | Anti-IL5/5R | 0.57 | <0.001 |
| **$FEV_1$** | Female sex | 1.3 | 0.04 |
| | Baseline annualised exacerbations | 1.1 | <0.001 |
| | Baseline $FEV_1$ | 1.4 | <0.001 |
| **LTOCS** | Anti-IL5/5R | 0.4 | 0.002 |

IL5 – interleukin 5
$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

*Response according to biologic class*

Baseline characteristics according to biologic class revealed that there was significant differences in age, BMI, smoking status, asthma onset, and baseline asthma status but not biomarker levels between those going onto different biologic classes (*Table 12*).

**Table 12: Baseline characteristics according to biologic class**

| | **Anti IgE** ***n = 809*** | **Anti-IL5/5R** ***n = 1242*** | **Anti-IL4/13** ***n = 63*** | **Non-biologic** ***n = 6330*** | **P-value** |
|---|---|---|---|---|---|
| **DEMOGRAPHICS:** | | | | | |
| **Sex (Female)**, % (number) | 66% (531)* | 59% (736)* | 70% (44) | 62% (3893) | <0.001 |
| **Caucasian**, % (number) | 76% (548) | 80% (878) | 87% (45) | 79% (4380) | |
| **Age (years)**, mean ±SD | 50 ±15*# | 55 ±14*^~ | 49 ±16^' | 58 ±17#~' | <0.001 |
| **BMI**, mean ±SD | 30 ±7* | 28.6 ±7*# | 29.3 ±8 | 29.6 ±8# | <0.001 |
| **Never smoker**, % (number) | 63% (510)* | 61% (762)# | 59% (37) | 45% (2858)*# | <0.001 |
| **Asthma onset**, mean ±SD | 25 ±18*# | 31 ±19* | 28 ±21 | 31 ±20# | <0.001 |
| **Asthma duration**, mean ±SD | 24 ±16 | 23 ±17 | 22 ±14 | 23 ±17 | NS |
| | | | | | |
| **ASTHMA STATUS:** | | | | | |
| **Baseline $FEV_1$ pre**, mean ±SD | 1.9 ±0.8*# | 1.9±0.8*^ | 1.8 ±0.7 | 2.1 ±0.8#^ | <0.001 |
| **Baseline $FEV_1$ post**, mean ±SD | 2 ±0.8* | 2 ±0.8# | 2 ±0.7 | 2.2 ±0.8*# | <0.001 |
| **Baseline reversibility**, % (number) | 17% (71) | 16% (104)* | 11% (3) | 12% (346)* | 0.008 |
| **Poor asthma control**, % (number) | 76% (402)* | 75% (556)#^ | 48% (15)# | 56% (1277)*^ | <0.001 |
| **Baseline annualised exacerbations**, mean ±SD | 3.4±3*#^ | 4.1±4*~' | 2.1±2#~ | 1.6 ±2^' | <0.001 |
| **LTOCS**, % (number) | 24% (197) *# | 35% (440)*^~ | 19% (12)^ | 18% (1130)#~ | <0.001 |
| **Steroid dose (mg)**, mean ±SD | 12±10 | 13±10 | 15±8 | 12 ±12 | NS |
| | | | | | |
| **BIOMARKERS:** | | | | | |
| **IgE**, mean ±SD | 517 ±1304 | 387 ±736 | 515 ±548 | 417 ±1306 | NS |
| **Blood eosinophil count**, mean ±SD | 596 ±584 | 605 ±962 | 505 ±428 | 617 ±820 | NS |
| **FeNO (ppb)** , mean ±SD | 49 ±46 | 49 ±47 | 23 ±12 | 47 ±46 | NS |
| **Sensitised to perennial allergens**, % (number) | 40% (267) | 38% (380)* | 47% (24) | 44% (1844)* | 0.001 |

*#^~p<0.05

SD – standard deviation
BMI – body mass index
$FEV_1$ – Forced expiratory volume in one second
IgE – immunoglobulin E
FeNO – fractional exhaled nitric oxide
Ppb – parts per billion
LTOCS – long term oral corticosteroid

Response across different outcome domains is shown in the areas of exacerbation reduction, lung function improvement, asthma control and LTOCS cessation (*Figure 8, Table 13*).

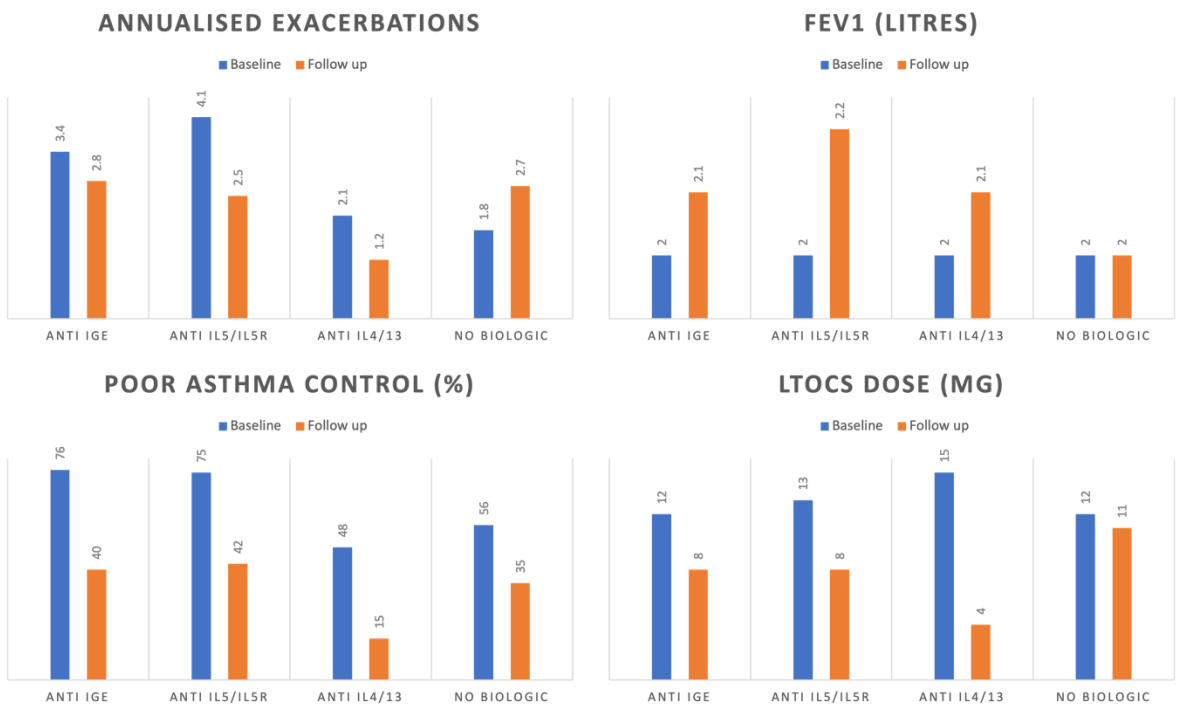



**Figure 8: Domains of response according to biologic class at baseline and follow up.**

IgE – Immunoglobulin E
IL5/IL5R – interleukin 5
IL4/13 – interleukin 4/13
$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

*Annualised exacerbations*
At follow-up (compared to baseline), Anti-IgE patients experienced an 18% decrease in annualised exacerbations, Anti-IL5/5R patients experienced a 39% decrease, and Anti-IL4/13 patients experienced a 43% decrease. While all biologic classes showed reductions in annualised exacerbations, non-biologic patients showed an 50% increase in annualised exacerbations.

*Poor asthma control*
At follow-up (compared to baseline), the proportion of Anti-IgE patients with poor asthma control decreased by 47%, that of Anti-IL5/5R patients decreased by 44%, and that of Anti-IL4/13 patients by 69%. The proportion of non-biologic patients with poor asthma control decreased by 37%.

*$FEV_1$*
At follow-up (compared to baseline), $FEV_1$ increased by 5% in Anti-IgE patients, 10% in Anti-IL5/5R patients, and 5% in Anti-IL4/13 patients. While all biologic classes showed an increase in $FEV_1$, non-biologic patients showed no change in $FEV_1$.

*LTOCS dose*
At follow-up (compared to baseline), LTOCS decreased by 33% in Anti-IgE patients, 38% in Anti-IL5/5R patients, and 73% in Anti-IL4/13 patients. Non-biologic patients showed a 11% decrease in LTOCS dose.

**Table 13: Baseline and follow up response according to biologic class**

| | **Anti IgE** ***n = 809*** | **Anti IL5** ***n = 1244*** | **Anti IL4/13** ***n = 63*** | **No biologic** ***n = 6330*** | P-value |
|---|---|---|---|---|---|
| **RESPONSE** | | | | | |
| **Exacerbation reduced >=50%**, % (number) | 52% (253/489)*# | 62% (542874)*^ | 69% (18/26)~ | 44% (359/814)#^~ | <0.001 |
| **$FEV_1$ pre improved >= 100mL**, % (number) | 49% (144/292) | 58% (212/369)* | 67% (10/15) | 34% (354/1048)* | <0.001 |
| **Asthma control improved**, % (number) | 49% (215/437) | 48% (293/616) | 75% (18/24)* | 42% (299/706)* | 0.001 |
| **LTOCS dose improved**, % (number) | 40% (37) | 52% (125)* | 50% (2) | 28% (32/112)* | <0.001 |
| **SUPER-RESPONSE** | | | | | |
| **Exacerbation elimination**, % (number) | 22% (134/618)*# | 31% (303/987)*^ | 32% (10/31)~ | 12% (242/1967)#^~ | <0.001 |
| **$FEV_1$ pre improved >= 500mL**, % (number) | 15% (44/292) | 22% (80/369)* | 27% (4/15) | 8% (86/1048)* | <0.001 |
| **New good asthma control**, % (number) | 27% (116/430)* | 31% (188/606)^ | 58% (14/24)*^# | 25% (196/706)# | <0.001 |
| **LTOCS super-responder**, % (number) | 34% (31/91) | 43% (103/240)* | 25% (1/4) | 22% (25/112)* | <0.001 |

* # ^ ~ denote columns with significant difference on post-hoc testing (p<0.05)

SD – standard deviation
$FEV_1$ – Forced expiratory volume in one second
LTOCS – long term oral corticosteroid

*Overlap of response*

The overlap of response could not be determined due to the small proportion of paired data (presence of baseline and follow-up data) collected across all four domains of response (Figure 9.) The total sample size was n = 8451, there were 3472 with missing paired data for all four outcomes (41%).

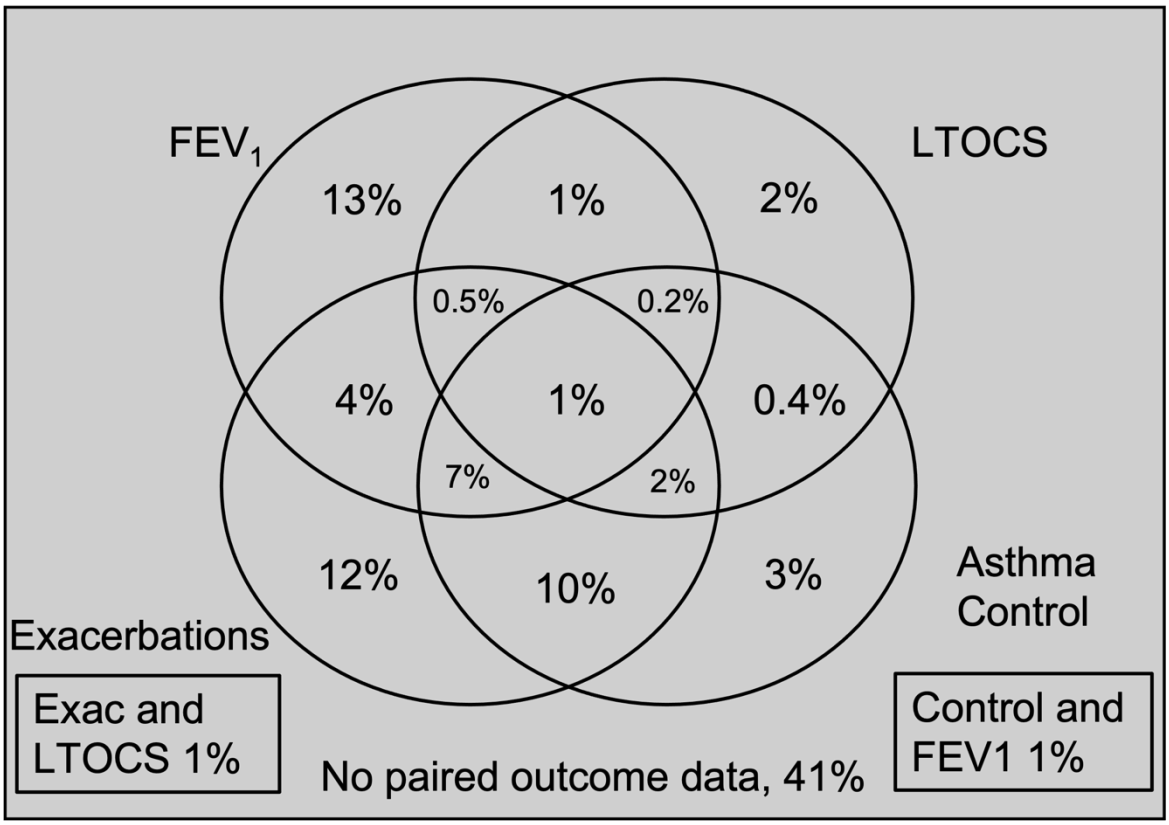



**Figure 9: Overlap of percentage of total cohort who had paired data collected on each outcome (*n = 8451*).**

# 8.0 Summary and Discussion

In a real world population comparison of severe asthma patients who initiated biologics and those who did not revealed that these two groups are significantly different at baseline with biologic initiators having poorer asthma status characterised by a higher exacerbation rate, lower lung function, worse asthma control and higher oral corticosteroid burden. This suggests that even within a population who meet ATS/ERS criteria for severe asthma there is a range of severities, underlining the heterogeneity within a severe asthma cohort. Further to this, there were demographic differences too - those who initiated biologics were significantly younger, with earlier asthma onset and more never smokers (despite having no difference in asthma biomarkers) highlighting possible selection bias amongst prescribers against older, ex- or current smokers.

The aggregate responses to biologics in this real-world severe asthma population are similar to the magnitude of response seen in randomised controlled trial populations with regards to asthma exacerbations, lung function, asthma control and long term oral corticosteroid burden.[2-10] In these outcome domains those who were treated with biologics improved to a greater extent than those who did not initiate biologics. What was interesting was that different responses to clinical domains were observed in different patient subgroups (presence of lung function reversibility, T2 gradient, and RCT eligibility). $FEV_1$ response was associated with the presence of lung function reversibility, but reversibility was not associated with other asthma outcomes such as exacerbations. Different factors were independently associated with response in different outcomes; determinants of $FEV_1$ response included baseline lung function but not biologic class; exacerbation response was associated with T2 Gradient, baseline exacerbations and Anti-IL5/5R, whilst LTOCS response was showed only in the presence of Anti-IL5/5R.

Some severe asthma patients do not have the capacity to respond in certain outcomes measures. There also appears to be different baseline variables associated with improvement in each outcome measure. These data highlight the need for standardised collection of paired outcome measures across multiple domains in severe asthma as our current approach to outcome data collection is driven largely by region-specific prescribing criteria (for example exacerbation frequency in the UK, and symptom control scores in Australia.) This is further underlined by our finding that even in a well characterised severe asthma registry population few had paired data available across any of these outcomes. Severe asthma patients require standardised evaluation, not in a way that reflects region-specific economics related to biologic prescribing.

There was heterogeneity in severe asthma response to biologics across different outcome measures. Within each biologic class and the non-biologic group there was a spread of responses in each outcome; there were some who improved (had a clinically significant response ora super-response) and some who did not. Findings also suggest the greater response in each domain between the biologic versus non-biologic patients Specifically, exacerbation reduction of ≥50% was observed in 59% of biologic patients and 43% of non-biologic patients; $FEV_1$ improvement of ≥100mL was observed in 54% of biologic patients and 42% of non-biologic patients; asthma control improvement was observed in 49% of biologic patients and 42% of non-biologic patients; LTOCS dose improvement was observed in 49% of biologic patients and 33% of non-biologic patients. These findings suggest an ongoing role for multidimensional assessment in severe asthma, particularly those who fail to improve or who worsen despite biologics.[11] As was suggested in the pivotal paper by Pavord et al, a personalised medicine approach addressing multiple treatable traits relevant to the patient – not just inflammatory traits – should be adopted.[12] The non-responders raise the question about whether clinicians should be switching biologics earlier and more frequently when optimal response has not been achieved across outcome domains.[13,14]

These data highlight the heterogeneity in severe asthma response, but also in severe asthma baseline status. It may be surprising that approximately 10% of those starting biologics and 30% of those who did not start biologics had no exacerbations at baseline (and no capacity to "respond" in this domain). This group met ATS/ERS criteria for severe asthma based on other criteria but are not well represented in randomised trials that tend to enrich for frequent exacerbators. Only 5.3% would have met simplified criteria for randomised trials in a small subset with adequate data for assessment. Frequent exacerbators have been shown to have poorer asthma control, higher burden of inhaled and oral corticosteroids, poorer quality of life, and a faster decline in lung function than those who do not exacerbate.[15] Less is known about the natural history and characteristics of severe asthma patients who do not exacerbate.

LTOCS burden is one of the most important outcome measures in severe asthma due to the high burden of toxicity associated with the use of LTOCS.[16] Long term oral steroids, and their toxicities, remain an issue in severe asthma with 31% of those initiating biologics and 18% of those not initiating biologics on these medications. Just under half of those initiating biologics had a reduced dose of oral corticosteroids at 12 months and 40% were able to cease these medications (or wean to <=5mg) and only 25% of those not starting biologics were able to reduce LTOCS to <=5mg, even fewer were able to cease completely. Recently a protocolised steroid reduction program has been shown to be effective in LTOCS cessation (or weaning to adrenal dosing) in >80% of those being initiated on benralizumab.[17] In light of these data more aggressive approach to corticosteroid weaning for severe asthma patients should be encouraged.

Differential response to biologic classes in some outcome domains was observed. In the domain of asthma exacerbations there was a significantly greater proportion of those started on Anti-IL5/5R improving compared to those initiating anti-IgE therapy and significantly more attained a super-response with elimination of exacerbations. Although limited by the observational nature of these data this is important information in the context of a lack of head-to-head trial information to inform treatment decisions for patients who may be eligible for multiple biologics. In the domain of lung function there was a larger proportion with a $FEV_1$ reponse in those who initiated Anti-IL5/5R compared to those who initiated anti-IgE. Anti-IL5/5R patients attained a significantly greater improvement in $FEV_1$ compared to anti-IgE (anti-IL4/13 had low numbers and conclusions could not be drawn), and significantly more $FEV_1$ super-responders than the non-biologic group. There was also a significantly greater proportion who were LTOCS super-responders in the Anti-IL5/5R group compared to the anti-IgE group, a finding that is consistent with previous systematic review data that has not shown that anti-IgE significantly reduced the LTOCS burden compared to placebo.[2]

More recently asthma physicians have asked whether we should be striving for more for our asthma patients?[18] Could we hope to normalise the lives of severe asthma patients or, in the future, even cure the disease? From this the concept of biologic super-responders has emerged – those who attain normalisation of lung function and freedom from asthma symptoms, exacerbations and corticosteroids.[19] Our study showed that after treatment with a biologic one-fifth of patients experience an super-response in $FEV_1$ (although we did not measure normalisation of lung function), one quarter in asthma control, one third in exacerbations and about 40% in LTOCS. A smaller proportion attain a super-response in these domains without the use of biologics. This study was not able to examine overlap of response – how many patients experience normalisation across outcome measures – due to regional inconsistencies in outcome recording. We suggest that it should be the standard of care to record baseline and follow up outcome measures for all severe asthma patients across a minimum of four outcome measures. It is only then that we will be able to accurately assess the prevalence of severe asthma remission with treatment.

# 9.0 Limitation(s)

Limitations to this study include the potential for selection bias and unadjusted confounders to affect results, a limitation common to all uncontrolled, observational studies. There is heterogeneity in biologic prescribing and from different countries. Not all datapoints were available for all participants and so outcomes were examined on subgroups with availability of paired data which may introduce bias. This highlights the need for consistency in the recording of outcomes across multiple domains in severe asthma.

## 10.0 Conclusion

Severe asthma patients who initiate biologics differ socially and in severity to those who do not initiate biologics, but not with regard to biomarkers, reflecting possible prescribing bias. The magnitude of improvement is similar to that seen in clinical trials. There is heterogeneity in biologic response across outcome domains and different baseline factors show response in different domains. Those initiating Anti-IL5/5R are more severe at baseline and show greater improvement across multiple domains than those initiating anti-IgE. Our data has shown that clinician discretion results in only one in ten patients ceasing oral steroids for severe asthma after biologic initiation and that protocolised weaning is needed. Measurement of severe asthma outcomes is suboptimal and it is time that severe asthma patients had standardised longitudinal evaluation, not in a way that reflects region-specific economics related to biologic prescribing.

## 11.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other academic collaborators of ISAR, including the ISC, as listed in the *ISAR Research Woking Group smart sheet (rows 457-544),* will form the Advisory Group. Please notify the senior researcher (lakmini@opri.sg), if you need access to the smart sheet.

## 12.0 Research Team

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