OPC Global
Study Report

Study report

Demographic and Clinical Characteristics of Severe Asthma Patients Worldwide

Describing the demographic and clinical characteristics of an international cohort of adult severe asthma patients.

Date:10 October 2018

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Title	Demographic and Clinical Characteristics of Severe Asthma Patients Worldwide
Subtitle	Describing the demographic and clinical characteristics of an international cohort of adult severe asthma patients
Report version	0.2
EU PAS registration number	EUPAS25489
Country of study	Singapore, United Kingdom
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List of abbreviations

ATS	American Thoracic Society
BMI	Body Mass Index
CPRD	Clinical Practice Research Datalink
ENCePP	European Network Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide test

GINA	Global Initiative for asthma
IgE	Immunoglobulin E level
ICS	Inhaled Corticosteroid
ISAR	International Severe Asthma Registry
KAAACI	The Korean Academy of Asthma, Allergy and Clinical Immunology (South Korea Severe Asthma Registry)
LABA	Long-Acting β-adrenoreceptor
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
REG	Respiratory Effectiveness Group
SAWD	Severe Asthma Web-based Database
SANI	Severe Asthma Network Italy

1.0 Executive Summary

Introduction

Asthma is a chronic disease of the airways, which can vary in severity from mild to very severe and is rapidly becoming a significant source of morbidity and mortality worldwide. Although severe asthma patients are estimated to represent 5-10% of the total asthmatic population, their use of health resources are disproportionately high. Severe asthma is currently defined as “asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy” by the European Respiratory Society (ERS) and American Thoracic Society (ATS) severe asthma guidelines. Lack of a universally-accepted definition of asthma is a major challenge when determining the exact prevalence and phenotypes of severe disease. National prevalence estimates are reflective of their national clinical guidelines and previous reflect national- or region-specific demographic and clinical attributes of severe asthma. The International Severe Asthma Registry (ISAR) was created by leading asthma experts around the world as a global effort to capture information on severe asthma using standardized variables with the aim of pooling data on patients with severe asthma globally.

Study aims and objectives

Study aim:

- To inform the asthma scientific community of the demographic and clinical characteristics of severe asthma patients across the globe.
- The findings of this study will drive the next key research questions to be answered at the national and international levels.

Primary objective:

- To describe the demographic and clinical characteristics of the severe asthma population globally.

Secondary objective

- To descriptively compare baseline demographic and clinical attributes of severe asthma population across participating countries.

Methods

This is a historical study to describe the baseline characteristics of severe asthma population, utilising data from the International Severe Asthma Registry (ISAR) to descriptively illustrate the differences and similarities of demographic and clinical attributes of severe asthma patients across five countries (i.e. Australia*, Italy, South Korea, United Kingdom and United States). The study included adult severe asthma patients receiving treatment according to the Global Initiative of Asthma (GINA) Step 5 or uncontrolled on GINA Step 4. Uncontrolled asthma is defined as having severe asthma symptoms or frequent exacerbations (based on ERS/ATS guidelines). Descriptive statistics were summarized for demographic factors and clinical characteristics, including medical history, healthcare resource utilisation, blood test measurements, fractional exhaled nitric oxide (FeNO) test, comorbidities and medication use categories. Percentage frequencies and 95% confidence intervals were reported for all categories and chi-square test-statistic was used to assess statistical significance between groups.

Results

The study sample for analysis included 4,990 severe asthma patients. A total of 65% of the patients were uncontrolled on GINA Step 4 therapy. The majority of patients from the UK and Italy were on GINA Step 5 (81.8% and 68.1%, respectively). The majority of patients from the US, South Korea and SAWD had uncontrolled asthma on GINA step 4 (77.7%, 76.7% and 62.5%, respectively). This international cohort was predominantly female (59.3%), overweight or obese (70.4%), non-smokers (60.6%) in the age-group of 55 to 79 years (52.1%). Global population had an average of 2 exacerbations in the baseline year† (mean (SD) – 1.7 (2.7). Nearly one-third of this global severe asthma patient population reported ≥4 exacerbations (32.4%), poorly controlled asthma (57.2%) and high healthcare resource utilisation (26.8% hospitalisations and 27.6%

* Severe Asthma Web-base Database (SAWD), included data from sites in Australia, Singapore and New Zealand
† Average number of exacerbations is based on the latest year of data available between January 2015 – December 2017.

emergency department visit). Allergic rhinitis (AR) was the most common respiratory comorbidity (49.3%). 43.1% of the patients had a low FeNO (<25 ppb), 30.7% had low blood eosinophil count (≤0.15 x 10^9/L) and 50.8% had low IgE concentration (<150). High health care resource utilisation and poorly controlled asthma was reported by patients on GINA step 5. There was no substantial variation in this global severe asthma population for blood eosinophil count or sputum eosinophil counts by gender when stratified by asthma severity status. Significant variation in healthcare resource utilisation between males and females was seen among GINA Step 5 (χ^2 =60.8, p-value<0.001).

Moreover, there was substantial variation in the age distribution (mean: 48.3 to 62.4 years), age of onset of asthma (mean: 22.7 to 41.0 years), blood eosinophil count distribution (20.0% to 35.7% for low eosinophil count (≤0.15 x 10^9/L)), FeNO concentration (19.8% to 45.4% for high ppb (>50)) and number of exacerbations (mean: 0.8 to 3.3). However, the prevalence of non-smokers and allergic rhinitis (AR) was similar across countries.

Conclusion

Findings from this study exemplifies the substantial variation in the clinical characteristics of patients managed within severe asthma services across countries. This may be partly due to differences in reimbursement of biologics, management, practice and/or referral patterns. This breadth of patients captures in ISAR provides an opportunity to study the heterogeneity of severe asthma.

2.0 Background

Asthma is a chronic airway disease, which can vary in severity from mild to very severe(1) and is rapidly becoming a significant source of morbidity and mortality worldwide(2). Patients who suffer from the severe form of this disease are estimated to represent 5-10% of the total asthmatic population(3-5). Although they represent a minority of patients with asthma, they present a challenge due to the extensive evaluation they require, insufficient evidence regarding personalised treatments, and their high healthcare resource burden.

Severe asthma is currently defined as “asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy” by the European Respiratory Society (ERS) and American Thoracic Society (ATS) task force(6). A lack of a universally accepted definition of the disease is a major challenge when determining the exact prevalence and phenotypes of severe asthma. Many countries have definitions that are reflective of their unique clinical guidelines. This has led to the development of discrete national and regional severe asthma registries(7-9), which collect country-specific demographic and clinical risk factors of severe asthma, including ethnicity and age of onset of asthma(10-12). However, the global severe asthma picture remains unknown partly due to lack of a standardised data collection methods across registries and lack of intra-operability between them, thus hindering cross country data comparisons and providing challenges for large scale epidemiological studies. This impediment of data sharing across registries has led to the development of the international severe asthma registry (ISAR)* which was created as a global effort by severe asthma experts around the world to capture information on severe asthma using a standardised method of data capture. ISAR has used a modified Delphi process to collect data on patient demographics, medical history, patient-reported outcomes, diagnostic information, clinical characteristics, adherence and management plan(13). It has pooled diverse data from large severe asthma registries across the globe (USA, UK, Italy, South Korea and SAWD) allowing us to ascertain precise severe asthma demographic and clinical characteristics according to a standardised globally-accepted definition of the disease. The current study is the first effort to descriptively aggregate demographic and clinical characteristics of severe asthma internationally. Findings from this study will improve our understanding of the clinical management of severe asthma patients by comparing the current prevalence and potential risk factors of severe asthma worldwide.

3.0 Study aim and objective

3.1 **Aim**

*http://isaregistries.org/

This study aims to inform the asthma scientific community on the demographic and clinical characteristics of severe asthma patients across the globe. The findings of this study will prompt further studies to answer the next key severe asthma questions at the regional, national, and international level.

3.2 Objective

The objective of this study is two-fold.

- ***Primary objective***: to describe the demographic and clinical characteristics of the global severe asthma population.
- ***Secondary objective*:** to conduct a descriptive comparison of baseline and clinical characteristics of severe asthma population across different participating countries.

4.0 Study population and data source

This is a historical study to describe the baseline characteristics of severe asthma population using ISAR data for known measures of severe asthma epidemiology. A selective list of demographic and clinical variables from the International Severe Asthma Registry (ISAR) from December 2014 to December 30th, 2017has been used to descriptively illustrate between-country differences and similarities.

5.0 Study population

The study population follows the inclusion and exclusion criteria of the ISAR.

5.1 Inclusion criteria

Table 1. ISAR patient inclusion and exclusion criteria

Inclusion criteria
• Patients 18 years or older • Patients receiving treatment according to GINA Step 5 or uncontrolled at Step 4. Uncontrolled is defined as having severe asthma symptoms* or frequent exacerbations†.
Exclusion criteria
• Lack of consent to share de-identified medical information.

5.2 Data source

The study utilized patient data from the ISAR, a multinational, multi-centre, observational epidemiologic data repository, containing data on severe asthma patients. The key feature of the registry is its standardised data fields irrespective of data source. The ISAR includes a combination of existing and new severe asthma registries, where primary data is collected via eCRFs on a web-based platform. Aggregate data was used for the current study from 4 participating countries in ISAR including the UK, Italy, South Korea and SAWD‡, and patient level data from the USA. The time frame used for analyses was from December 2014 to December 30th, 2017. This was to accommodate both existing and new registries which have various dates of registry induction (baseline data capture).

This study was designed, implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee. All data collection sites in the ISAR have obtained their regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country, and its relevant ethical boards and organisations.

*__Severe asthma symptoms (ERS/ATS Guidelines)__
(a) Poor symptom control where Asthma Control Questionnaire consistently >1.5, Asthma Control Test <20 (or "not well controlled" by NAEPP/GINA guidelines)
(b) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
(c) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year without clinical or laboratory data for concomitant respiratory infections

†__Frequent severe asthma exacerbations (ERS/ATS Guidelines):__
Two or more bursts of systemic Corticosteroids (>3 days course each) in the previous year

‡ Severe Asthma Web-base Database (SAWD), included data from sites in Australia, Singapore and New Zealand.

Furthermore, all patient-level data extracted and transferred from the USA was hashed and entered into the research database in the form of anonymised patient IDs. The data were retrieved by Optimum Patient Care (OPC) data analysts and utilised as an anonymized dataset to perform the analysis according to the protocol.

The study was performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

6.0 Study variables

The following demographic and clinical variables were summarized in this study

6.1 Demographic variables

Table 2. ISAR demographic variables

Variable Name*	Description
Age Sex Height Weight	Patient age in years (categorised: 18-34 years, 35-54 years, 55-79 years, ≥80 years), sex, height measurement in metres (m) and weight measurement in kilograms (kg)
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2). • Categorised as underweight (< 18.5 kg/m^2), normal weight (≥ 18.5 kg/m^2 and < 25 kg/m^2), overweight (≥ 25 kg/m^2 and < 30 kg/m^2) and obese (≥ 30 kg/m^2)
Smoking status	Categorised as non-smoker, current smoker or ex-smoker

6.2 Clinical variables

Table 3. ISAR clinical variables

Variable Name	Description
ISAR Severe Asthma Criteria	
ISAR inclusion (GINA† guidelines)	Patient on GINA Step 5 treatment OR Patient on GINA Step 4 treatment with (a) Severe asthma symptoms (b) Severe asthma exacerbations requiring systemic corticosteroids
Medical History	
Age of asthma onset	Patient age in whole years or months (if less than 1 year) at which asthma symptoms began
Number of exacerbations	• Count of exacerbations requiring rescue steroids in the past 1 year, **OR**

* All variables are measured at baseline; which will refer to the first patient visit where data is collected for ISAR
† Global Initiative for asthma 2017: GINA Stepwise approach for asthma control

	• Duration of oral corticosteroids (OCS) used as a proxy for exacerbation assuming 1 OCS course last for 7 days (for U.S. only) (14)
Number of invasive ventilations	Count of episodes of invasive ventilation ever prior to baseline.
Number of hospital admissions	Count of hospital admissions for asthma in the past 1 year
Number of emergency department admissions	Count of emergency department admissions for asthma in the past 1 year
Maintenance OCS	Prescription for maintenance OCS, **OR** ≥90 days of OCS exposure in the observation year
Long-term OCS burden	**Primary definition:** Prescription for maintenance OCS or ≥2 exacerbations **Sensitive definitions:** • Prescription of maintenance OCS only • Prescription of maintenance OCS or ≥4 exacerbations
Asthma control	• Categorised as controlled, partly controlled or uncontrolled according to the GINA Asthma Control Criteria*(15), **OR** • Determined using asthma control test (ACT) questionnaire(16)score categorised as well controlled (20-25), not well controlled (16-20) and very poorly controlled (5-15), **OR** • Determined using asthma control questionnaire (ACQ)(17) score categorised as well controlled (0 – 0.75), grey zone (0.75 – 1.5) or poorly controlled (>1.5)
Blood Test	
Immunoglobulin E count	Counts of immunoglobulin E, measured in international units per litre (IU/mL) • <150 IU/mL, 150-400 IU/mL, and >400 IU/mL
Blood eosinophil count	Counts of blood eosinophils, measured in cells per litre (10^9/L). • Categorised as ≤0.15, >0.15 - ≤0.3, >0.3 - ≤0.45 and >0.45
Sputum eosinophil count	Counts of sputum eosinophils, expressed as percentage (%) of the total cell count. • Categorised as eosinophilic asthma (sputum eosinophil count >3%) and non-eosinophilic asthma (sputum eosinophil count <3%)
Spirometry	

* Asthma symptom control is assessed by the following questions:
1. Daytime symptom more than twice/week
2. Any night walking due to asthma
3. Reliever needed more than twice/week
4. Any activity limitation due to asthma

Asthma is considered controlled if patients have none of these, partly-controlled if patients have 1-2 of these, and uncontrolled if patients have 3-4 of these.

Fractional exhaled nitric oxide (FeNO) test	Measurements of fractional nitric oxide concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s • Categorised as low (<25ppb), intermediate (25-50) and high FeNO(>50ppb)
Comorbidity	
Allergic rhinitis (AR)	AR diagnosis, **OR** Prescriptions for systemic and topical nasal products (for US only) (refer to Appendix 15.1)
Chronic rhinosinusitis	Chronic rhinosinusitis diagnosis
Eczema	Eczema diagnosis, **OR** Prescriptions for dermatological topical corticosteroids, antihistamines or emollients (for US only) (refer to Appendix 15.2)
Nasal polyps	Nasal polyps diagnosis
Medication Regimen	
High Dose inhaled corticosteroid	Prescription for ICS
ICS + long-acting β-adrenoceptor agonist (LABA)	Prescription for ICS+ LABA
ICS + leukotriene receptor antagonist (LTRA)	Prescription for LTRA and for ICS
ICS + LABA + LTRA	Prescription for ICS, LABA and LTRA
ICS + LABA + long-acting muscarinic antagonist (LAMA)	Prescription for ICS, LABA and LAMA
LTRA	Prescription for LTRA
Theophylline	Prescription for theophylline
Anti-immunoglobulin E (IgE)	Prescription for Anti-IgE (Omalizumab)
Anti-interlukin-5 (IL5)	Prescription for Anti-IL5
Macrolide Antibiotic	Prescription for Macrolide Antibiotic
Other Steroid Sparing Agent	Prescription for Other Steroid Sparing Agent

7.0 Statistical analysis

7.1 Software used

Stata version 14 (College Station, TX, USA) or SAS version 9.4/9.5 (Cary, NC, USA) was used to conduct all statistical analyses and data manipulations.

7.2 Baseline characterisation

Descriptive statistics were computed for all demographics and clinical variables for the patient population as categorical variables, and count and percentage of non-missing observations was reported for each category.

7.3 Significance testing

Country or region (group) comparison was examined with contingency tables. Frequencies and 95% confidence intervals were shown for each characteristic and group difference was tested for statistical significance via Chi-square test for comparison of counts. Statistical significance was defined as $p<0.05$.

7.4 Group characterisation

Demographic characteristics

Demographic characteristics of severe asthma patients (age, gender, ethnicity, smoking status and BMI) was described for the overall population as well as by country.

Clinical characteristics

Clinical characteristics of severe asthma patients reported in section 6.2 were described for overall population and by each country. Furthermore, the following clinical characteristics were stratified by severe asthma status (GINA Step 5 or uncontrolled on GINA Step 4) and gender for the overall population:

- healthcare resource utilisation
- immunoglobulin E count
- blood eosinophil count
- comorbidities

In addition, following characteristics were stratified based on data availability

- healthcare resource utilisation, asthma control and number of asthma exacerbations stratified by severe asthma status (GINA Step 5 or uncontrolled on GINA Step 4)
- asthma control stratified by severe asthma status (GINA Step 5 or uncontrolled on GINA Step 4)
- healthcare resource utilisation stratified by severe asthma status (GINA Step 5 or uncontrolled on GINA Step 4) and asthma control status for the overall population
- healthcare resource utilisation stratified by age of onset

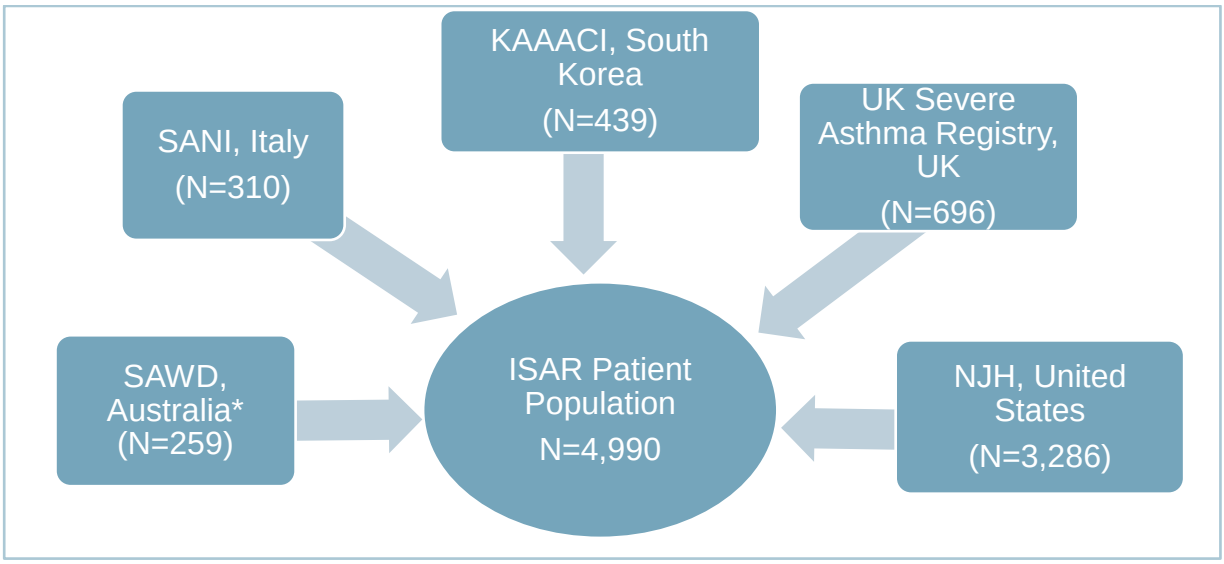
8.0 Results

8.1 Patient population

After applying the inclusion and exclusion criteria, a total of 4,990 eligible patients were included in this study from severe asthma registries and EMR databases across five countries: Severe Asthma Web-based Database (SAWD, Australia)*, Severe Asthma Network Italy (SANI, Italy),

* SAWD includes data from sites in Singapore (N=16) and New Zealand (N=18)

South Korea Severe Asthma Registry (KAAACI, South Korea), UK Severe Asthma Registry (United Kingdom) and National Jewish Health EMR Severe Asthma Cohort (NJH, United States) (Figure 1).



**includes N=16 from Singapore and N=18 from New Zealand*

Figure 1: ISAR Patient Population

Patient distribution across countries by asthma severity is shown in Figure 2. 65% of the total population was uncontrolled on a GINA step 4 treatment regimen. More severe asthma patients in the UK and Italy were GINA step 5 patients (81.8% and 68.1%, respectively) compared to other countries (between 23.3% to 37.4%, see Figure 2).

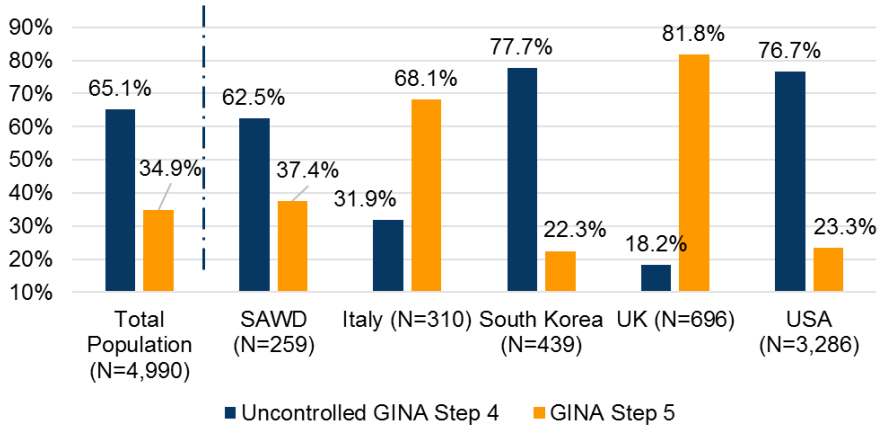


Figure 2: Population distribution across countries by severe asthma

The demographic characteristics of the study population are presented in Table 4. Patients were predominantly female (59.3%), mostly between the age of 55 and 79 years (52.1%). The majority

of the population was Caucasian (72.6%) and either overweight or obese (BMI above 24.9 kg/m^2, 70.4%). Further, the patient population was primarily never smoker (60.6%) with a much lower proportion of ex-smokers (33.4%) and current smokers (6.0%).

Table 4: Demographic characteristics

	N (%)		
Gender, n (%)			
	Overall	GINA Step 4	GINA Step 5
N (% non-missing)	4,986 (99.9)	3,246 (100.0)	1,740 (100.0)
Female	2,957(59.3)	1,924 (59.3)	1,033 (59.4)
Male	2,029(40.7)	1,322 (40.7)	707 (40.6)
Age (years), n (%)			
N (% non-missing)	4,967 (99.5)		
Mean (SD)	55.0 (15.9)		
18-34	658(13.2)		
35-54	1,510(30.4)		
55-79	2,588(52.1)		
≥80	211(4.2)		
Ethnicity, n (%)			
N (% non-missing)	4,912 (98.4)		
Caucasian	3,568(72.6)		
Asian	589(12.0)		
African	263(5.4)		
Mixed	31(0.6)		
Other	130(2.6)		
Unknown	331(6.7)		
BMI (kg/m^2), n (%)			
N (% non-missing)	4,901 (98.2)		
Underweight (<18.5)	105(2.1)		
Normal (≥18.5-<25)	1,345(27.4)		
Overweight (≥25 - <30)	1,531(31.2)		
Obese (≥30)	1,920(39.2)		
Smoking Status, n (%)			
N (% non-missing)	4.947 (99.1)		
Current smokers	294(5.9)		
Ex-smokers	1656 (33.4)		
Never-smoked	2997(60.5)		

Notes: *Gender data not available for 4 Uncontrolled GINA Step 4 patients in USA.

Clinical characteristics of global severe asthma population in the ISAR cohort is shown in Table 5. The age of asthma onset was predominantly above 12 years of age (76.5%) with nearly one-third of the patients having an age of asthma onset above 40 years of age (US not included). Almost one-third of the patients reported ≥4 exacerbations (32.4%) in the baseline period, and nearly half the population have reported no exacerbations (49%)*. More than a quarter of the population reported hospitalisation and/or emergency department visits due to asthma. The severe asthma

* Data on number of exacerbations was not available for USA, therefore, duration of OCS exposure used as a proxy for exacerbation assuming one OCS course last for 7 days. Numbers may be over-estimated due to retrospective data quality.

cohort was largely poorly controlled (57.2%); 30.7% of the patients had a low blood eosinophil count (≤0.15 x 10^9/L) and 27.6% of the patients had very high blood eosinophil counts (>0.45x 10^9/L). AR was the most common respiratory comorbidity (49.3%), followed by chronic rhinosinusitis (21.4%). The majority of the patients had low FeNO (<25 ppb) and low IgE concentrations (<150 IU/ml) (43.1% and 50.8%, respectively).

Table 5: Clinical characteristics

	N (%)
Age of asthma onset (years),* n (%)	
N (% non-missing)	1,536 (30.8)
Mean (SD)	30.7 (17.7)
<12	360(23.4)
12-40	647(42.1)
>40	529(34.4)
Exacerbations, n (%)	
N (% non-missing)	4,823 (96.6)
Mean (SD)	1.7 (2.7)
0	2,848 (59.0)
1	220 (4.6)
2	255 (5.3)
3	223 (4.6)
≥4	1,059 (21.9)
Hospital Resource Utilisation, # n (%)	
N (% non-missing)	1,704 (34.1)
hospitalization	456 (26.8)
emergency department visit	470 (27.6)
invasive ventilation	93 (5.5)
Asthma Control (ACT/ACQ), n (%)	
N (% non-missing)	2,467 (49.4)
Poorly controlled	1,412(57.2)
Not well controlled	480(19.6)
Well controlled	575(23.3)
Serum IgE Level (IU/ml), n (%)	
N (% non-missing)	2,652 (53.1)
<150	1348(50.8)
150-400	594(22.4)
>400	710(26.8)
Blood Eosinophil Count (x 10^9 cells/L), n (%)	
N (% non-missing)	3,736 (74.9)
≤0.15	1,148(30.7)
>0.15 and ≤0.3	775(20.7)
>0.3 and ≤0.45	782(20.9)
>0.45	1,031(27.6)
FeNO Level (ppb), n (%)	
N (% non-missing)	2,168 (43.4)
Low (<25)	934(43.1)
Intermediate (25-50)	547(25.2)
High (>50)	687(31.7)
Comorbidities, ~ n (%)	
N (% non-missing)	4,294 (86.1)
Allergic rhinitis	2118 (49.3)
Chronic rhinosinusitis	921 (21.4)
Eczema	412 ((9.6)

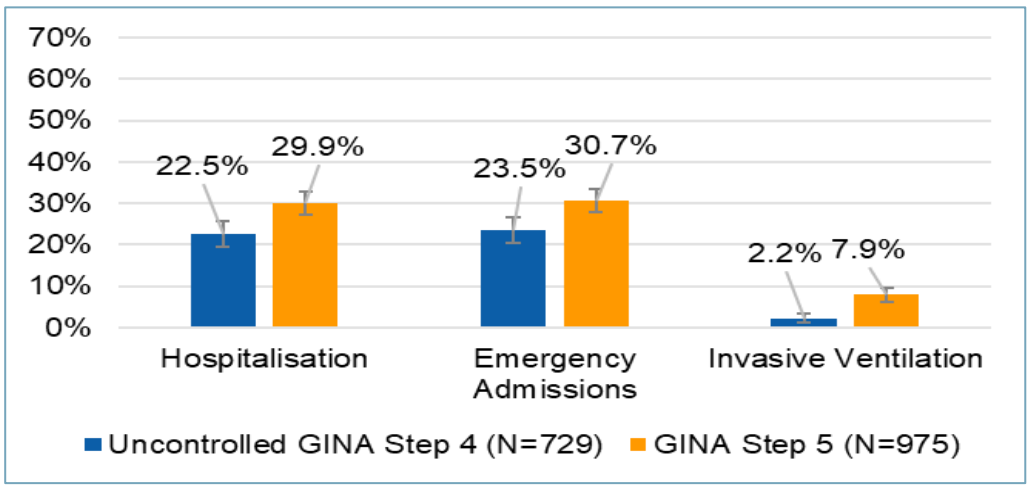
	N (%)
Nasal polyps	323 (7.5)
Medications, n(%)	
	Uncontrolled GINA Step 4
N (% non-missing)	3,250 (100.0)
ICS + LABA	2,118 (65.2)
Add-on therapies	
LAMA^	515 (16.7)
LTRA^	774 (25.1)
Theophylline	266 (8.2%)
	GINA Step 5
N (% non-missing)	1,740 (100.0)
Maintenance OCS	820 (48.8)
Anti-IgE	639 (36.7)
Anti-IL5^	629 (36.1)
Macrolide Antibiotics^	151 (9.2)
Other steroid sparing agent^	56 (3.4)

Notes: * US data not available for age of asthma onset
US data not available for healthcare resource utilisation
¯ UK data not available for comorbidities
^SAWD data not available

8.2 Clinical characteristics of the global severe asthma population stratified by severe asthma status

- **Health care resource utilisation (N=1,704)***

Patients on GINA Step 5 reported higher health care resource utilisation compared to patients on uncontrolled Step 4 therapy (Figure 3).



** USA data not available*

Figure 3: Health care resource utilisation by asthma severity

- **Asthma Control (N=1,916)**

Level of asthma control was not much different between patients on uncontrolled GINA step 4 and step 5 (Figure 4).

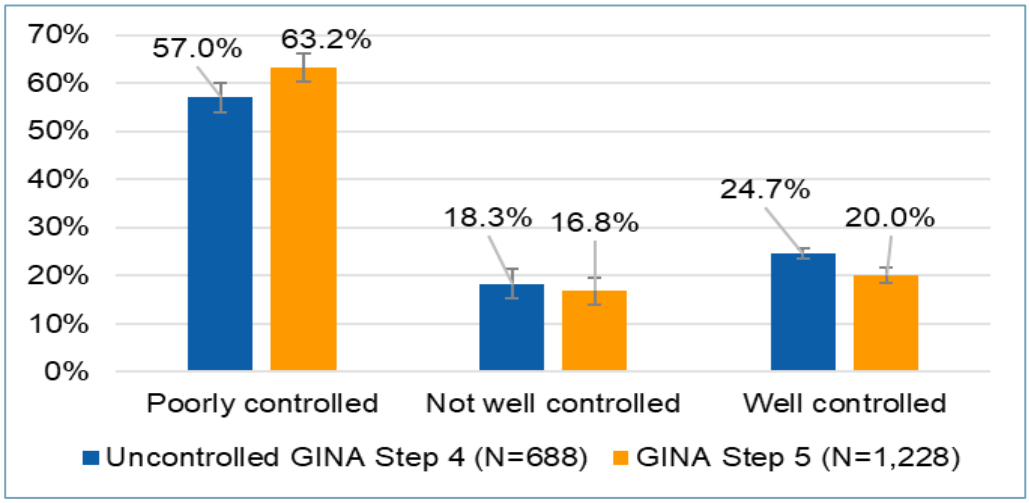


Figure 4:Asthma control by asthma severity

- **Numbers of Asthma exacerbation (N=4,823)**

Majority of GINA step 4 patients reported zero exacerbations and patients on GINA step 5 reported at least 4 exacerbations (Figure 5).

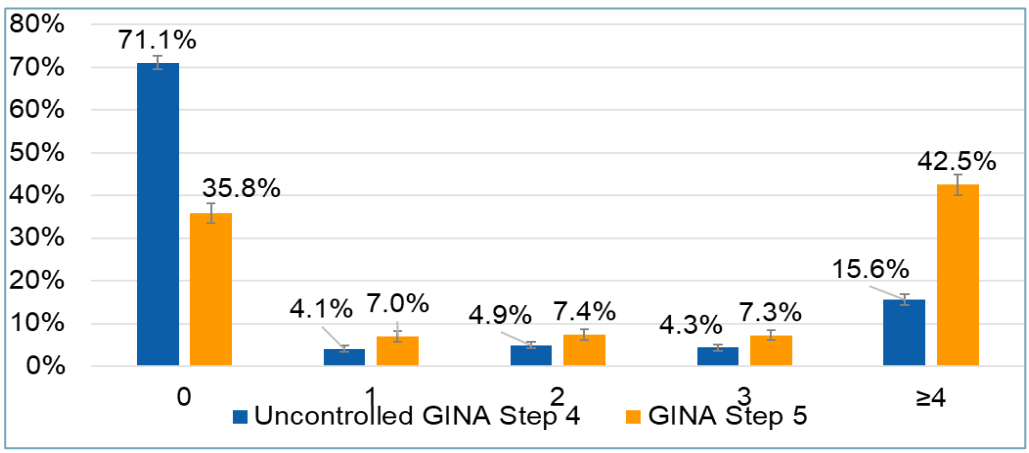


Figure 5: Number of asthma exacerbations by asthma severity

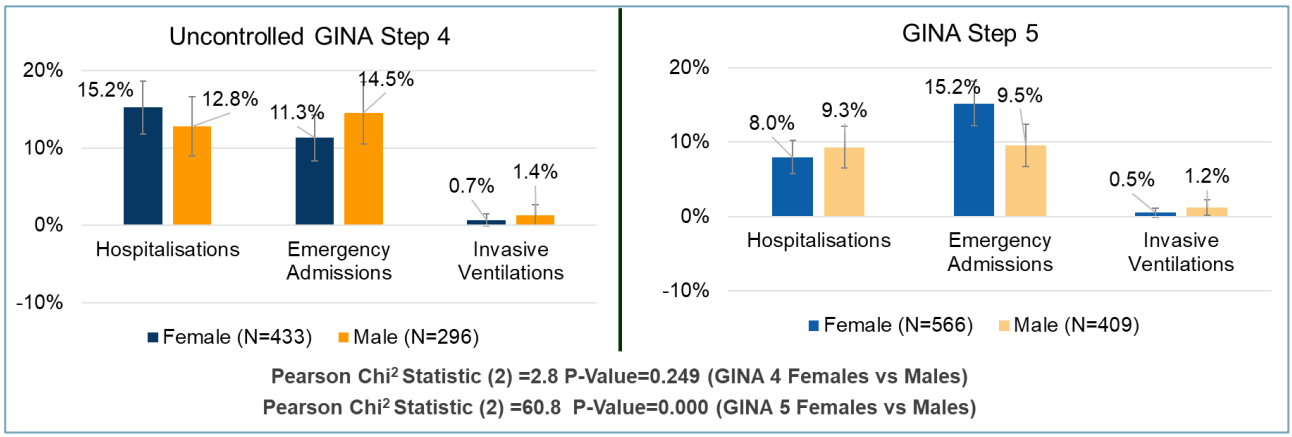
8.3 Clinical characteristics of the global severe asthma population stratified by severe asthma status and gender*†

- **Health care resource utilisation (N=1,704)***

Females on uncontrolled GINA step 4 reported higher hospitalisation compared to those on GINA step 5 (15.2% vs 8.0%). Females on GINA Step 5 had higher emergency admissions compared to

*Numbers do not match for overall population as data was lost or missing due to further stratification by severe asthma status and/or gender
†All clinical characteristics stratified by severe asthma status and gender are shown in Appendix 15.3 to 15.8.

males (15.2% vs 9.5%) (χ^2 =60.8, p-value=0.000) (Figure 6).



**USA data not available*

Figure 6: Healthcare resource utilisation by severe asthma status and gender

A potential relationship between health care resource utilisation and age of onset of asthma stratified by asthma severity showed that the pattern of hospitalisation and emergency department visits did not differ by age of onset (see Appendix 15.5). Healthcare utilisation did not differ by asthma control groups as well (see Appendix 15.6).

- **Immunoglobulin E level (N=3,400)**

The serum immunoglobulin E levels significantly differed by gender for both GINA Step 4 and Step 5 (Figure 7).

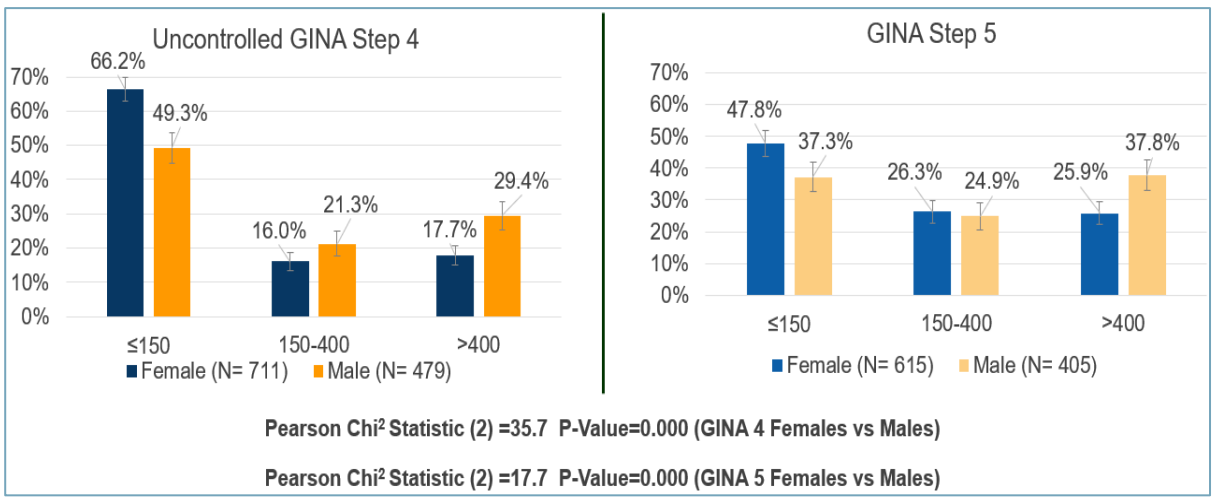


Figure 7: Immunoglobulin E levels by severe asthma status and gender

- **Blood eosinophil count (N=2,974)**

Blood eosinophil count distribution did not differ by gender for patients with uncontrolled asthma on GINA Step 4 or GINA Step 5 patients (Figure 8).

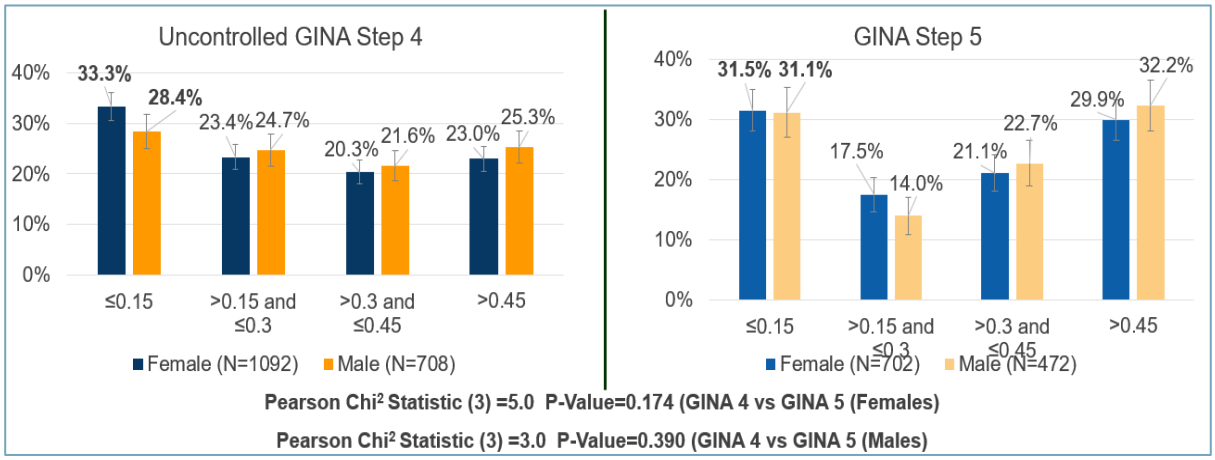
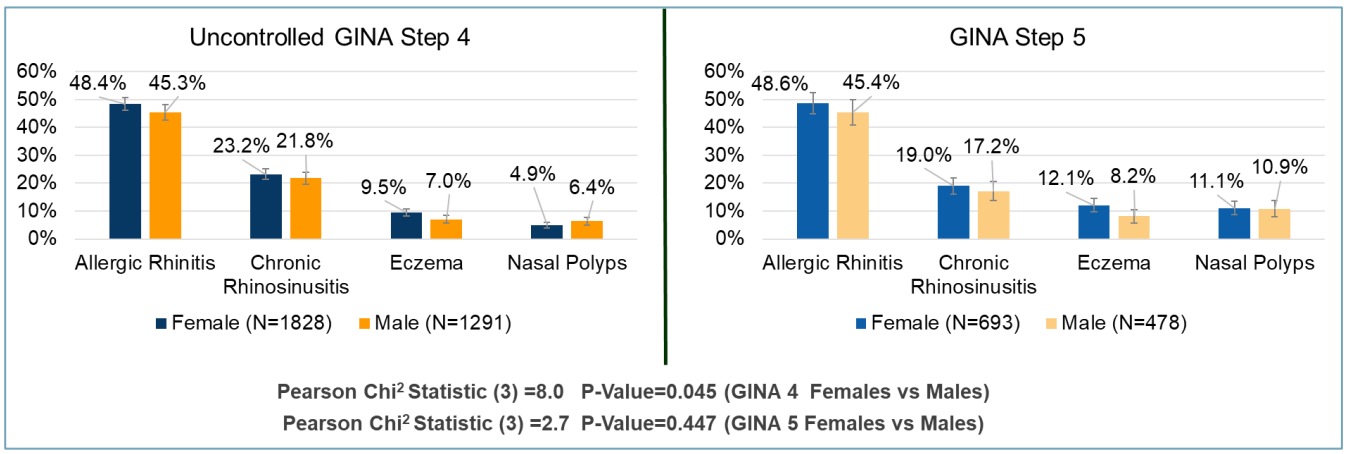


Figure 8: Blood eosinophil count distribution by severe asthma status and gender

- **Comorbidities (N=4,290)***

Comorbidity prevalence was not significantly different by gender for patients on GINA 5. Allergic rhinitis was the most prevalent comorbidity among severe asthma patients followed by chronic rhinosinusitis (Figure 9).



**UK data not available*

Figure 9: Comorbidities by severe asthma status and gender

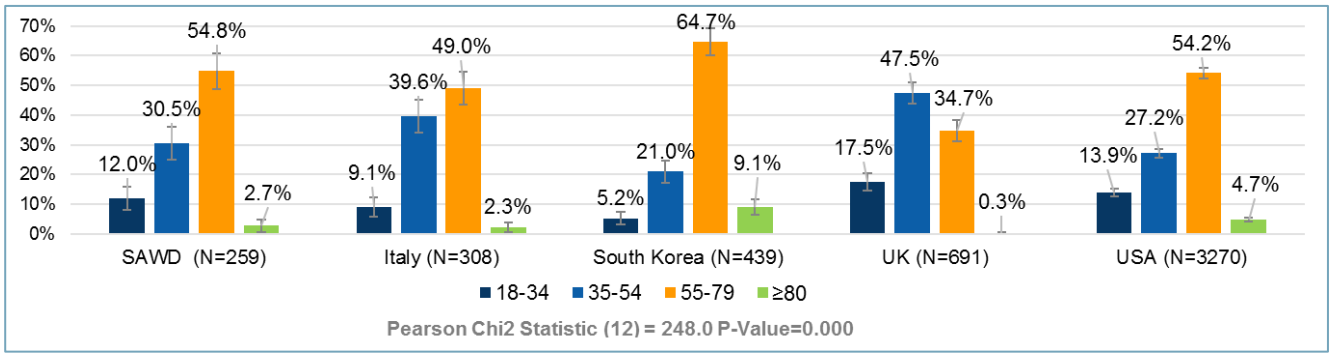
8.4 Demographic characteristics stratified by country*

- **Age (N=4,967)**

The age distribution of the severe asthma study population was significantly different (χ^2= 248, p-value=0.000) among all countries as shown in Figure 10. UK represented a younger cohort of severe asthma patients (mean (SD): 48.3 (14.1) years) compared to South Korea with older cohort

*All country level frequencies and summary statistics are provided in the appendix 15.9 to 15.11

of patients (mean (SD): 62.4 (14.1) years). Most patients were aged between 55 and 79 years, except in the UK where the highest proportion of patients with severe asthma were 35-54 years age group (47.5%).



Patient age	SAWD	Italy	South Korea	UK	USA
Mean (SD)	55.1 (15.3)	54.5 (13.8)	62.4 (14.1)	48.3 (14.1)	55.5 (16.7)

Figure 10: Age distribution by country

- **Body Mass Index (N=4,901)**

Approximately half of the severe asthma patients in UK (47.9%), USA (42.9%), SAWD (49.2%) were obese. A majority of patients in Italy (43.7%) and South Korea (59.1%) had a normal BMI (Figure 11).

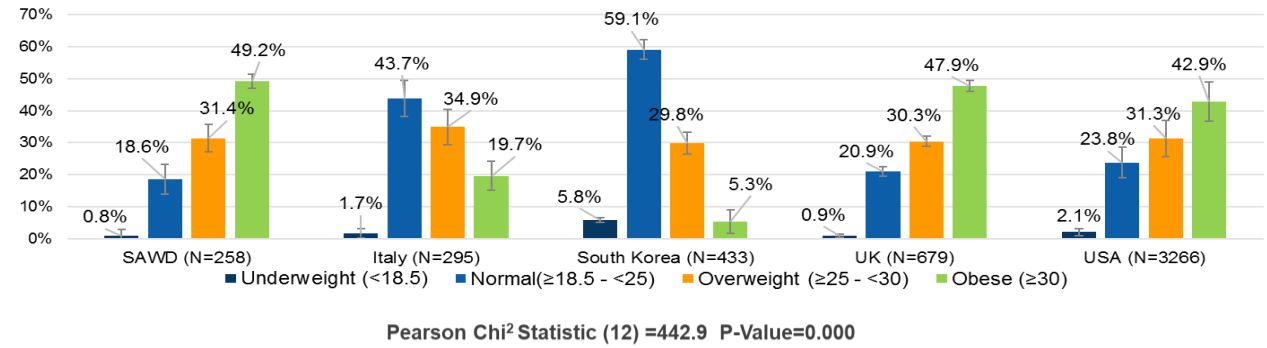


Figure 11: BMI by country

- **Smoking Status (N=4,923)**

More than half of the severe asthma population across all five countries consist of non-smokers, and slightly higher, nearly three quarters of patients, in Italy and UK (76.8% and 72.1%, respectively). Close to one-third of the patients in South Korea and USA were ex-smokers (33.9%

and 36.8%, respectively). The highest proportion of current smokers was in South Korea (12.1%; Figure 12).

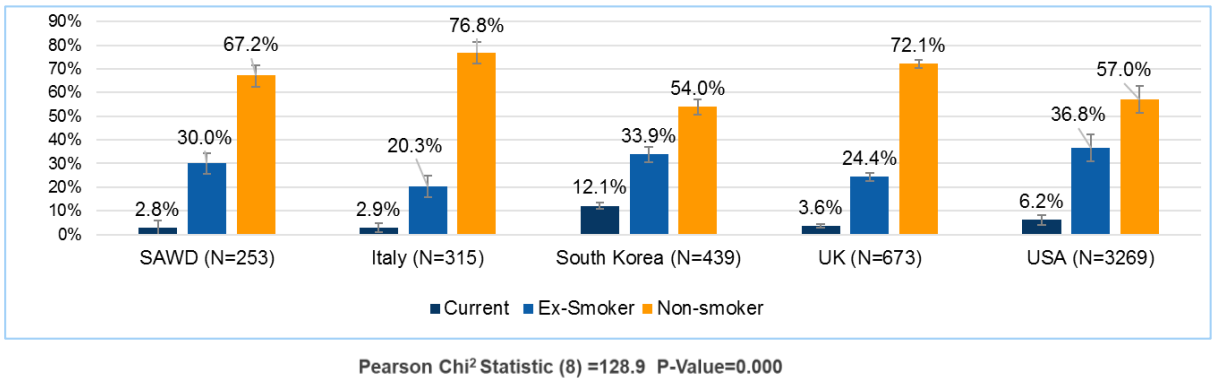
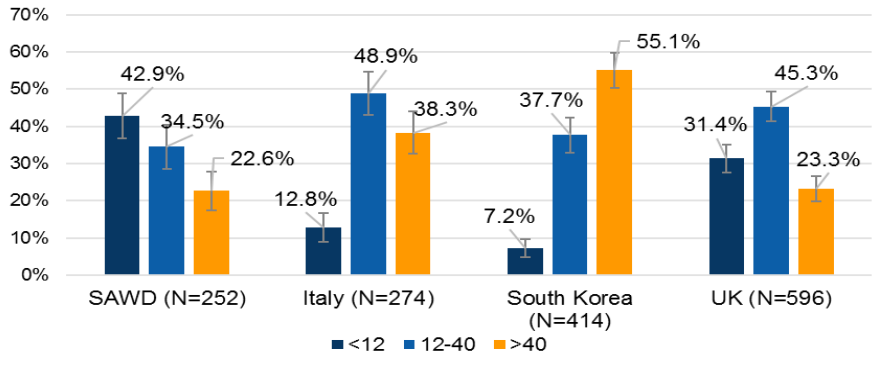


Figure 12: Smoking status by country

8.5 Clinical characteristics stratified by country

- **Age of asthma onset (N=1,536) ***

Average age of asthma onset was predominantly between 12 to 40 years for Italy (48.9%) and UK (45.3%) (Figure 13). The average age of asthma onset was lower (<12 years) in SAWD (42.9%). The South Korean cohort had the latest onset of asthma (mean age 41.0 year), with 55% of the population having asthma onset at aged 40 years or older.



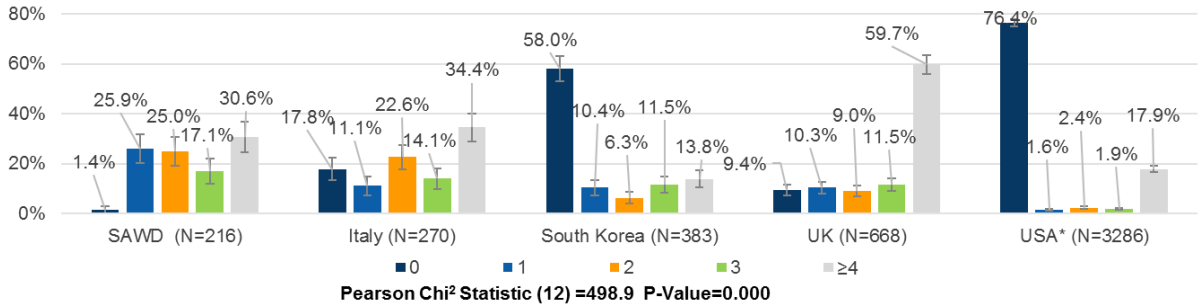
Age of asthma onset	SAWD	Italy	South Korea	UK
Mean (SD)	22.7 (17.1)	34.4 (17.1)	41.0 (17.1)	25.4 (18.7)

**USA data not available*

Figure 13: Age of asthma onset by country

- **Numbers of Asthma exacerbation (N=4,823)**

More patients in the UK (59.7%) reported 4 or more exacerbations (between 2015 and 2017) than any of the other countries (mean (SD):5.0 (4.0)). Next came Italy, with 34.4% reporting ≥ 4 exacerbations, followed by SAWD (30.6%). Conversely, 62.4% of the patients in the US* and 58% patients in South Korea reported zero exacerbations in the same time period (Figure 14).



No. of exacerbations	SAWD	Italy	South Korea	UK	USA
Mean (SD)	3.3 (2.9)	3.7 (7.2)	1.1 (1.5)	5.0 (4.0)	0.8 (1.6)

Figure 14: Number of severe asthma exacerbations by country

- **Long-term OCS Burden†(N=4,823)**

Long-term OCS burden is described for countries in Figure 15. UK, Italy and SAWD had a high burden of long-term OCS (as defined in Table 3) use (more than 85% of population)‡. The US and South Korea had relatively lower long-term OCS burden (26.8% and 48.3%, respectively).

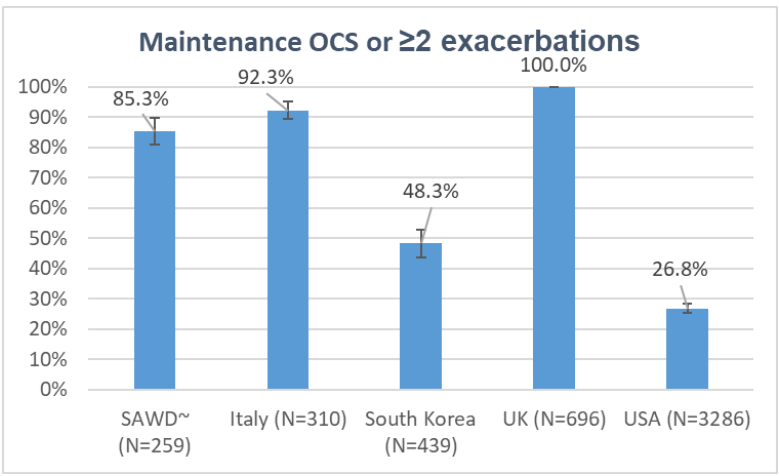


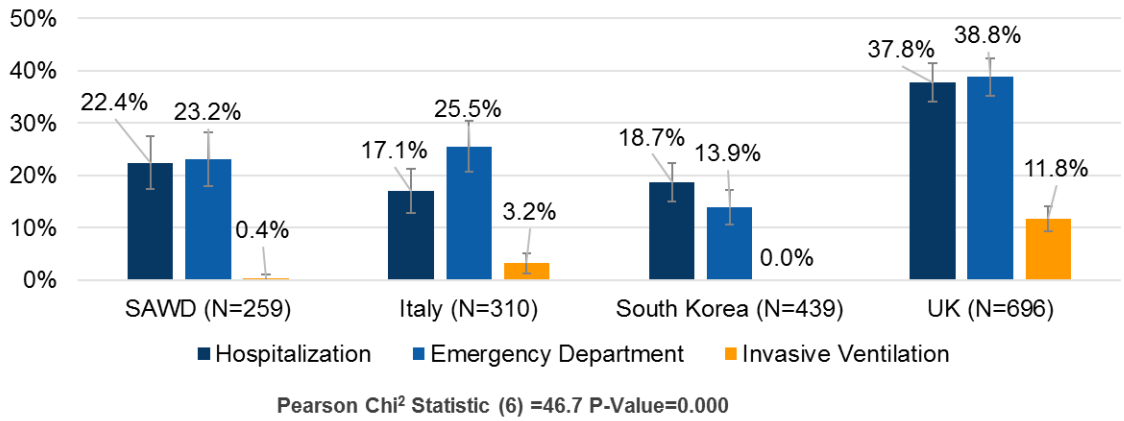
Figure 15: Long-term OCS burden by country

Long-term OCS burden was also assessed using a sensitive definition§ see Appendix 15.12.

*Duration of OCS exposure used as a proxy for asthma exacerbation for USA assuming 1 course last for 7 days. Numbers may be over-estimated due to retrospective data quality.
† Primary definition of long-term OCS burden - prescription for maintenance OCS or ≥2 exacerbations
‡Numbers may be over-estimated since patients may have over-lapping acute and maintenance oral corticosteroid use.
§Applied two definitions for sensitivity – 1) Prescription of maintenance OCS only; 2) Prescription of maintenance OCS or ≥4exacerbations requiring oral corticosteroids

- **Healthcare Resource Utilisation (N=1,704) ***

Health care resource utilisation was considerable across all five countries with UK patients reporting the highest number of hospitalisation, emergency department visits and/or invasive ventilation episodes in the baseline period. Nearly a quarter of patients in Italy had emergency department admissions (25.5%) followed by SAWD (23.2%). South Korea had the lowest reported health care resource utilisation (Figure 16).



**USA data is not available*

Figure 16: Resource Utilisation by country

- **Asthma Control (N=2,467)**

Asthma control was measured using the Asthma Control Test (ACT) for South Korea, Italy and USA and the Asthma Control Questionnaire (ACQ) for the UK and SAWD. The severe asthma cohort of all countries had a predominance of poor or not well-controlled asthma. The UK reported the highest proportion of poorly controlled severe asthma patients (87.6%), followed by SAWD (62%) and USA (48.3%). Italy reported the highest proportion of patients with well controlled asthma (43.6%), followed by South Korea (35.1%) (Figure 17).

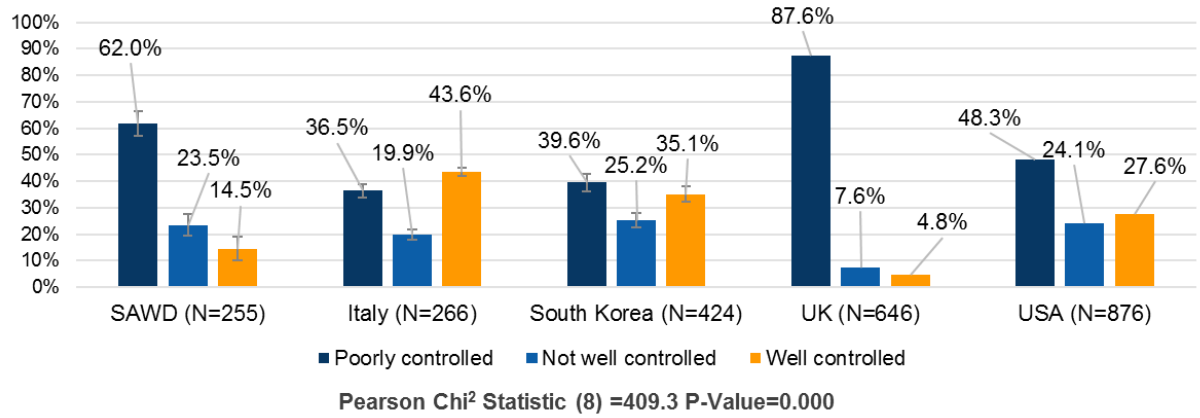


Figure 17: Asthma control by country

- **Blood eosinophil count (N=3,736)**

Italy (38.3%) and the UK (37.6%) had the highest proportion of severe asthma patients with very high blood eosinophil counts (>0.45 x 10^9/L). Conversely, approximately one-third of the population in South Korea (35.7%), USA (33.4%), and SAWD (31.0%) had low blood eosinophil counts (≤0.15 x 10^9/L) (Figure 18).

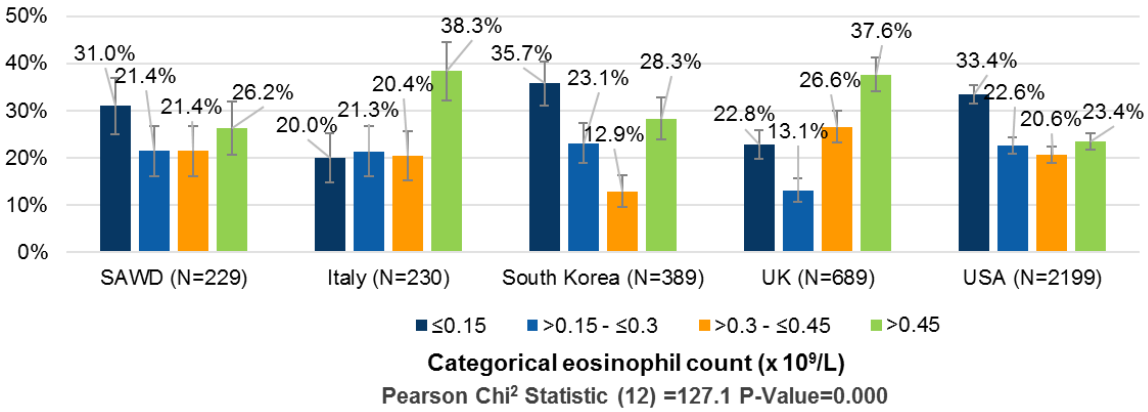


Figure 18: Distribution of blood eosinophil count by country

- **Immunoglobulin E level (N=2,652)**

Most severe asthma patients had a low serum IgE concentration (<150 IU/mL) in the USA (57.8%), the UK (47.0%), South Korea (45.3%) and SAWD (48.5%). Italy had a similar distribution of IgE level across the three-categories (low, moderate and high IgE) (Figure 19).

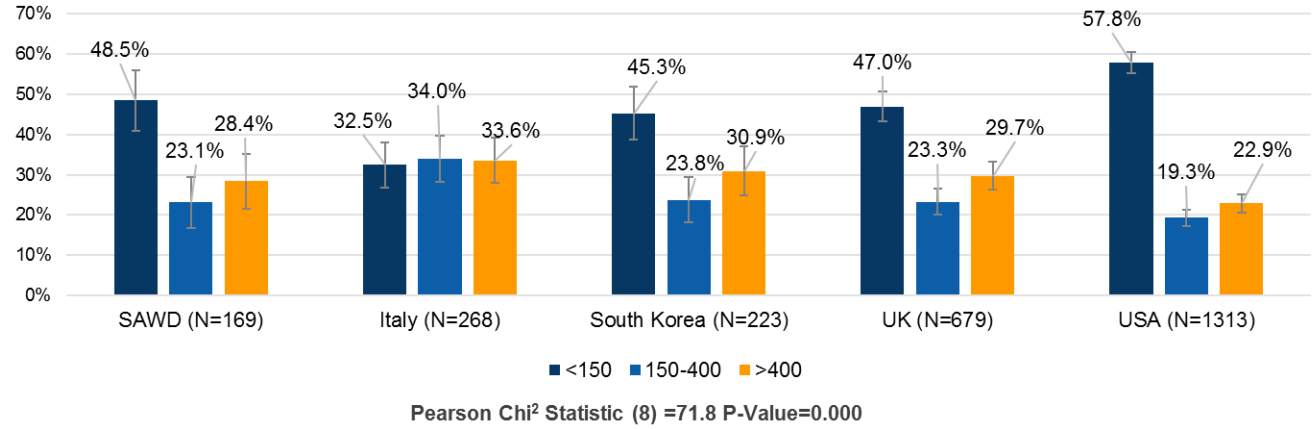


Figure 19: Serum IgE by country

- **FeNO concentration (N=2,168)**

Low FeNO concentrations (<25 ppb) were reported for the majority of patients in SAWD (60.5%) and predominate for patients in the USA (49.1%) and Italy (40.9%). Most patients in South Korea (42.5%) had intermediate FeNO concentrations(25-50 ppb), whereas most patients in the UK had high FeNO concentrations (>50 ppb) (45.4%) (Figure 20).

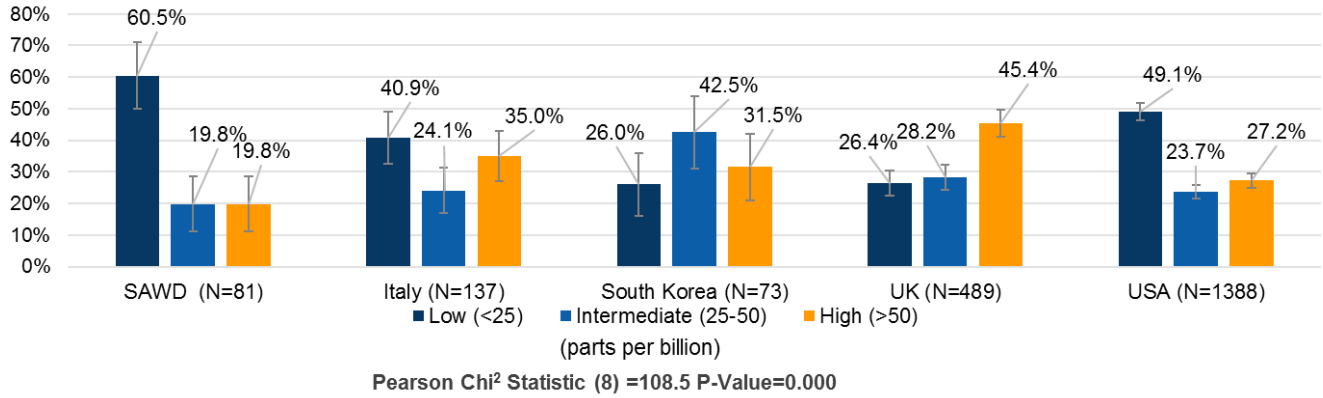
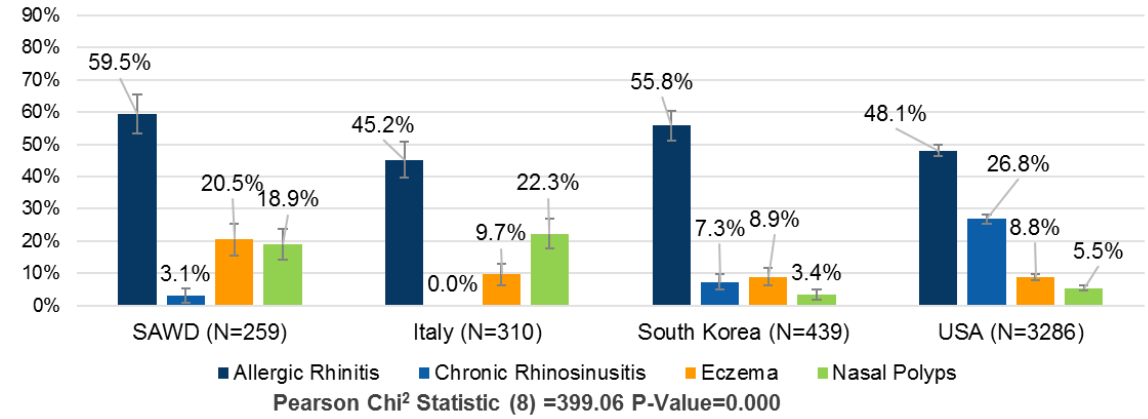


Figure 20: FeNO concentration by country

- **Comorbidities (N=4,294) ***

The majority of the severe asthma population had Allergic Rhinitis in US (48.1%), SAWD (59.5%), Italy (45.2%), and South Korea (55.8%). Also, 22.3% of patients in Italy had nasal polyps. More than a quarter of the US population had chronic rhinosinusitis (26.8%). One-fourth of the population in SAWD had eczema (20.5%) (Figure 21).



**UK data not available*

Figure 21: Comorbidities by country

- **Medication Regimen for Patients on GINA Step 5 (N=1,740)[*]**

Maintenance OCS were predominantly prescribed for GINA Step 5 patients in South Korea (92.9%), UK (72.9%), SAWD (66.0%) and Italy (61,4%). Biologics (were predominantly prescribed for GINA 5 severe asthma patients in UK (Anti-IL5) (61.0%) and Italy (Anti-IgE) (85.3%) (Figure 22). The USA reported the highest macrolide (13.2%), which was negligible or 0% in the other countries.

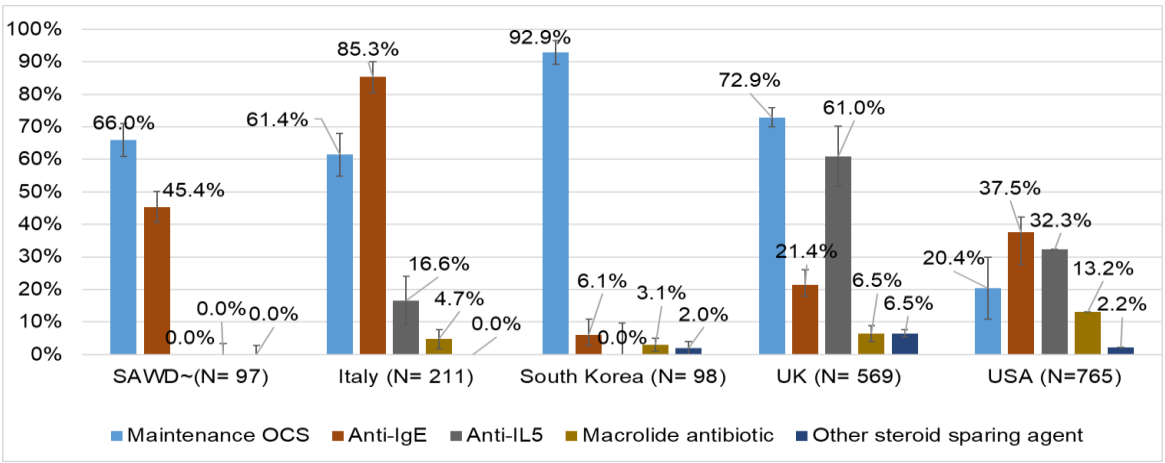


Figure 22: Medication Regimen for patients on GINA Step 5

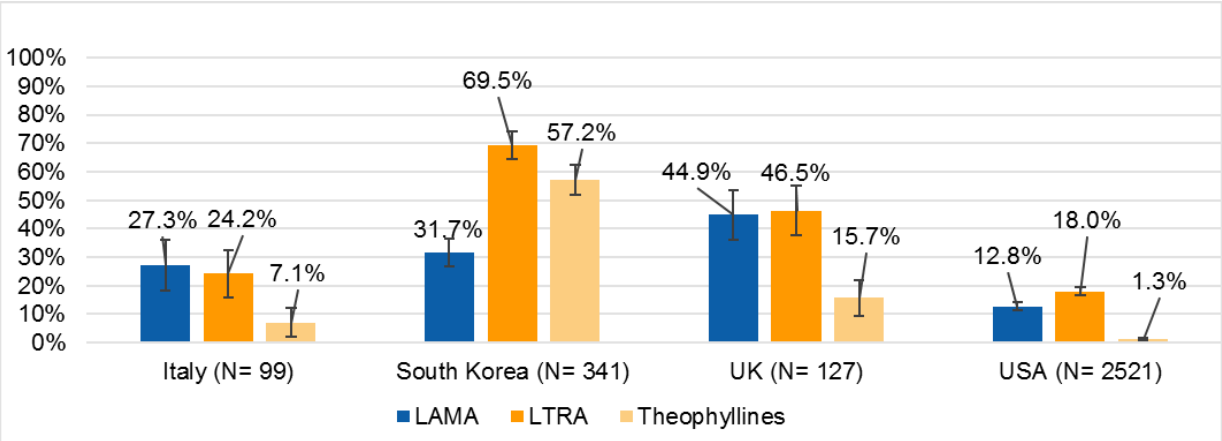
- **Medication Regimen for Patients on Uncontrolled GINA Step 4 (N=3,088)[†]**

Per GINA guidelines, assuming all patients on GINA Step 4 are taking ICS+LABA, the add-on treatment regimens are depicted in Figure 23. The use of add-on therapy LTRA was the highest in

[*]A patient can be represented in more than one treatment group, e.g. OCS and biologics (Anti-IgE) or Anti-IL5

[†] A patient can be represented in more than one treatment group, e.g. ICS+LABA and ICS + LABA + LAMA

South Korea (69.5%) followed by UK (46.5%). Theophylline use was the highest in South Korea (57.2%). Also, UK had the highest proportion (44.9%) of patients on add-on therapy LAMA compared to other countries for patients on GINA Step 4.



**SAWD not reported due to data completion*

Figure 23: Medication Regimen for Uncontrolled Patients on GINA Step 4 – ICS+LABA Add-on Therapies

9.0 Discussion

This report highlights the variation of demographic and clinical attributes of the severe asthma population globally. Certain clinical patterns may be reflective of the health system. For example, the high number of exacerbations in the UK may represent national guideline of four or more exacerbation for referral to a specialist centre. Also, high level of asthma control in South Korea may represent ease of access to care of an open health care system. Late onset of asthma in South Korea may represent a phenotype of patients with asthma COPD overlap (ACO). Moreover, the high prevalence of obesity seen only in the UK, USA and SAWD may reflect lifestyle differences from Italy. Comparing BMI categories between Asian countries and Western countries should be taken cautiously as South Korea uses a different definition to interpret body mass index that is more appropriate for that society(18). Medication regimen differences, such as high prescription of Macrolides in the US, need to be substantiated with national guidelines and accessibility to medication. Biologics are highly prescribed in UK since such patients are the ones referred to a specialist centre. Patients in South Korea have negligible biologic prescriptions since the therapy is not reimbursed under the national insurance system; in contrast these patients have

high use of oral medication, such as theophylline, LTRA and maintenance OCS as they are less costly and covered under their insurance plan(19). SAWD patients have no prescriptions for Anti-IL5 because biologics, such as Mepolizumab were only available in Australia since 2017.

Our results are similar to previous results reported by the UK, Italy, South Korea, Australia and US (7, 9, 20, 21). For example, our results for UK were similar to the distribution of gender, BMI and age reported in a UK cohort study of an adult severe uncontrolled eosinophilic asthma (SUEA) population using primary care data from OPCRD and CPRD(22). However, for Italy, long-term OCS burden use reported by ISAR differed from a previous report. An observational study on severe refractory asthma patients in Italy showed that nearly 80% of the patients were treated with Prednisone (23), which is in contrast to our finding of 5.2% long-term OCS burden for Italy. This may be due to differences of the broader inclusion criteria for the national registries versus ISAR.

10.0 Limitation

The study comprised of data collected for routine clinical care and research purposes. For example, proxies were used to estimate clinical characteristics, such as exacerbations, long term OCS burden and prevalence of comorbidities (allergic rhinitis and eczema) and applied to the electronic medical records received from USA. These proxies have not been validated and may present skewed estimations. Moreover, asthma control in UK represents baseline assessment but it was the latest assessment available for patients in other countries and therefore may represent some inconsistency when comparing results across countries. In addition, the validity and completeness of variables may vary across countries. The use of summary statistics limited the freedom to conduct post-hoc analyses, such as stratifications.

11.0 Conclusion

Findings from this study exemplifies the substantial variation in the clinical characteristics of patients managed within severe asthma services across countries. This may be partly due to differences in reimbursement of biologics, management, practice and/or referral patterns. This breadth of patients captures in ISAR provides an opportunity to study the heterogeneity of severe

asthma. Contextualising results with the country-specific health system and comparing results of those with similar health systems is recommended as a next step.

12.0 Advisory group

ISAR Steering Committee Members	Country
Liam Heaney Andrew Menzies-Gow	United Kingdom
Giorgio Walter Canonica Enrico Heffler	Italy
Richard Costello	Ireland
Nikos Papadopoulos	Greece
Arnaud Bourdin Camille Taille	France
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15.0 Appendix

15.1 Prescription for allergic rhinitis (US only)

Medication Therapy Class	Medication Therapy Subclass	Medication
Systemic and Topical Nasal Products	Nasal Antiallergy	Astelin 137 MCG/SPRAY SOLN Astelin SOLN Astepro 0.15 % Nasal Solution Astepro 137 MCG/SPRAY SOLN Astepro SOLN Azelastine HCl - 0.1 % Nasal Solution Azelastine HCl - 0.15 % Nasal Solution Azelastine HCl - 137 MCG/SPRAY Nasal Solution Cromolyn Sodium 5.2 MG/ACT Nasal Aerosol Solution Cromolyn Sodium AERS Nasal Allergy AERS NasalCrom 5.2 MG/ACT Nasal Aerosol Solution NasalCrom AERS Olopatadine HCl - 0.6 % Nasal Solution Olopatadine HCl SOLN Patanase 0.6 % Nasal Solution Patanase SOLN
	Nasal Anticholinergics	Atrovent 0.03 % SOLN Atrovent 0.06 % SOLN Atrovent SOLN Ipratropium Bromide 0.03 % Nasal Solution Ipratropium Bromide 0.06 % Nasal Solution Ipratropium Bromide SOLN
	Nasal Combinations	DermacinRx Azenase Pak 137 & 50 MCG/ACT Nasal Therapy Pack Dymista 137-50 MCG/ACT Nasal Suspension Dymista SUSP
	Nasal Steroids	Beconase AERS Beconase AQ 42 MCG/SPRAY Nasal Suspension Beconase AQ INHA Budesonide 32 MCG/ACT Nasal Suspension CVS Budesonide SUSP CVS Fluticasone Propionate 50 MCG/ACT Nasal Suspension ClariSpray SUSP EQ Nasal Allergy 55 MCG/ACT Nasal Aerosol EQL Fluticasone Childrens 50 MCG/ACT Nasal Suspension EQL Fluticasone Propionate 50 MCG/ACT Nasal Suspension Flonase 50 MCG/ACT SUSP Flonase 50 MCG/DOSE INHA Flonase Allergy Relief 50 MCG/ACT Nasal Suspension Flonase Allergy Relief SUSP Flonase SUSP Flonase Sensimist 27.5 MCG/SPRAY Nasal Suspension Flunisolide 25 MCG/ACT (0.025%) Nasal Solution Flunisolide 29 MCG/ACT (0.025%) SOLN Flunisolide SOLN Fluticasone Propionate 50 MCG/ACT Nasal Suspension Fluticasone Propionate SUSP GNP Fluticasone Propionate 50 MCG/ACT Nasal Suspension KLS Aller-Flo 50 MCG/ACT Nasal Suspension KP Fluticasone Propionate 50 MCG/ACT Nasal Suspension Mometasone Furoate 50 MCG/ACT Nasal Suspension

		Mometasone Furoate SUSP Nasacort 55 MCG/ACT AERS Nasacort AERS Nasacort AQ 55 MCG/ACT AERO Nasacort AQ 55 MCG/ACT AERS Nasacort AQ AERO Nasacort AQ AERS Nasacort Allergy 24HR 55 MCG/ACT Nasal Aerosol Nasacort Allergy 24HR AERO Nasacort Allergy 24HR Children 55 MCG/ACT Nasal Aerosol Nasal Allergy 24 Hour 55 MCG/ACT Nasal Aerosol Nasarel 29 MCG/ACT SOLN Nasarel SOLN Nasonex 50 MCG/ACT Nasal Suspension Nasonex SUSP Omnaris 50 MCG/ACT Nasal Suspension Omnaris SUSP Qnasl 80 MCG/ACT Nasal Aerosol Solution Qnasl AERS Qnasl Childrens 40 MCG/ACT Nasal Aerosol Solution RA Budesonide 32 MCG/ACT Nasal Suspension Rhinocort 32 MCG/ACT AERO Rhinocort AERO Rhinocort Allergy 32 MCG/ACT Nasal Suspension Rhinocort Allergy SUSP Rhinocort Aqua 32 MCG/ACT SUSP Rhinocort Aqua SUSP Triamcinolone Acetonide 55 MCG/ACT INHA Triamcinolone Acetonide 55 MCG/ACT Nasal Aerosol Triamcinolone Acetonide INHA Veramyst 27.5 MCG/SPRAY SUSP Veramyst SUSP Zetonna 37 MCG/ACT Nasal Aerosol Solution Zetonna AERS
	Sympathomimetic Decongestants	12 Hour Cold TB12 12 Hour Nasal Relief Spray 0.05 % Nasal Solution Afrin 12 Hour 0.05 % Nasal Solution Afrin 12 Hour SOLN Afrin Allergy SOLN Afrin Nasal Spray 0.05 % Nasal Solution Afrin Nasal Spray SOLN Afrin NoDrip Extra Moisture 0.05 % Nasal Solution Afrin Sinus 0.05 % Nasal Solution Afrin Sinus SOLN Benzedrex Nasal Inhaler Decongestant TABS MP 12HR Nasal Spray SOLN Mucinex Nasal Spray Full Force SOLN Nasal Decongestant 30 MG Oral Tablet Nasal Decongestant PE TABS Nasal Decongestant TABS Nasal Four 1 % Nasal Solution Nasal Spray Moisturizing 12 HR 0.05 % Nasal Solution Nasal Spray SOLN Nasal Spray Sinus SOLN Neo-Synephrine 0.5 % SOLN Osco Pseudoephedrine HCl 30 MG TABS Osco Pseudoephedrine HCl TABS Oxymetazoline HCl 0.05 % SOLN PX Nasal Spray Moisturizing 0.05 % Nasal Solution Phenylephrine HCl 10 MG TABS Phenylephrine HCl TABS Pseudoephedrine 30 MG TABS Pseudoephedrine HCl - 30 MG Oral Tablet Pseudoephedrine HCl - 60 MG Oral Tablet Pseudoephedrine HCl ER 120 MG Oral Tablet Extended Release 12 Hour Pseudoephedrine HCl TABS Pseudoephedrine TABS Pseudofed 30 MG TABS Pseudofed TABS SM Suphedrine 30 MG TABS SM Suphedrine TABS Sudafed 12 Hour 120 MG Oral Tablet Extended Release 12 Hour Sudafed 12 Hour TB12 Sudafed 12 Hour TBCR Sudafed 24 Hour 240 MG Oral Tablet Extended Release 24 Hour

		Sudafed 30 MG Oral Tablet Sudafed 60 MG TABS Sudafed Childrens LIQD Sudafed PE Maximum Strength TABS Sudafed TABS SudoGest 30 MG Oral Tablet SudoGest TABS Sudodrine 30 MG TABS Suphedrin 30 MG TABS Suphedrine TABS Vicks Sinex 12 Hour Decongest 0.05 % Nasal Solution Vicks Sinex SOLN Wal-phed 30 MG Oral Tablet
	Miscellaneous Nasal Preparations	Afrin Saline Nasal Mist SOLN Alkalol Nasal Solution Alkalol SOLN Ayr 0.65 % Nasal Solution Ayr Nasal Mist Allergy/Sinus 2.65 % Nasal Solution Ayr Nasal Mist Allergy/Sinus SOLN Ayr SOLN Ayr Saline Nasal GEL Ayr Saline Nasal Nasal Gel Ayr Saline Nasal No-Drip GEL Ayr Saline Nasal No-Drip Nasal Gel Deep Sea Nasal Spray 0.65 % Nasal Solution Deep Sea Nasal Spray SOLN HCA Saline Nasal SOLN HM Saline Nasal Spray SOLN NasaFlo Neti Pot Nasal Wash Nasal Packet Nasal 0.65 % SOLN Nasal Moist 0.65 % Nasal Solution Nasal SOLN Nasal Saline SOLN Nasal Saline Spray SOLN Nasal Spray Saline SOLN NasalCare Nasal Packet Neti Pot Sinus Wash 2300-700 MG Nasal Kit Neti Pot Sinus Wash KIT Ocean Nasal Mist 0.65 % SOLN Ocean Nasal Spray 0.65 % Nasal Solution Ocean Nasal Spray SOLN Ocean Ultra Saline Mist Nasal Solution Ocean Ultra Saline Mist SOLN Ocean for Kids 0.65 % Nasal Solution SB Saline Nose 0.65 % Nasal Solution SG Saline Nasal SOLN SM Nasal Spray Saline SOLN SM Sinus Wash Neti Pot 2300-700 MG Nasal Kit Saline Mist Spray 0.65 % Nasal Solution Saline Mist Spray SOLN Saline Nasal Mist 0.65 % SOLN Saline Nasal Mist SOLN Saline Nasal Spray 0.65 % Nasal Solution Saline Nasal Spray SOLN Salinex SOLN Simply Saline 0.9 % Nasal Aerosol Solution Simply Saline AERS SinuFlo ReadyRinse Nasal Kit Sinus Rinse Bottle Kit Nasal Packet Sinus Rinse Bottle Kit PACK Sinus Rinse Kit Nasal Packet Sinus Rinse Kit PACK Sinus Rinse Nasal Packet Sinus Rinse PACK Sinus Rinse Refill Nasal Packet Sinus Wash Salt Nasal Crystals Sinus Wash Squeeze Bottle 2300-700 MG Nasal Kit Sodium Chloride 0.65 % SOLN Sodium Chloride Nasal Spray 0.65 % SOLN Sodium Chloride SOLN Squeeze Bottle Sinus Wash 2300-700 MG Nasal Kit

15.2 Prescriptions for eczema (US only)

Medication Therapy Class	Medication Therapy Subclass	Medication
Dermatological	Antihistamines-Topical	Anti-Itch 2-0.1 % External Cream Diphenhydramine-Zinc Acetate 2-0.1 % External Cream
	Corticosteroids-Topical	Alclometasone Dipropionate 0.05 % External Cream Alclometasone Dipropionate 0.05 % External Ointment Anusol-HC 2.5 % CREA ApexiCon E CREA Aristocort A 0.5 % CREA Betamethasone Dipropionate 0.05 % External Cream Betamethasone Dipropionate 0.05 % External Lotion Betamethasone Dipropionate 0.05 % External Ointment Betamethasone Dipropionate Aug 0.05 % External Cream Betamethasone Dipropionate Aug 0.05 % External Gel Betamethasone Dipropionate Aug 0.05 % External Lotion Betamethasone Dipropionate Aug CREA Betamethasone Dipropionate CREA Betamethasone Dipropionate LOTN Betamethasone Dipropionate OINT Betamethasone Valerate 0.01 % CREA Betamethasone Valerate 0.1 % External Cream Betamethasone Valerate 0.1 % External Lotion Betamethasone Valerate CREA Clobetasol Prop Emollient Base CREA Clobetasol Propionate 0.05 % External Cream Clobetasol Propionate 0.05 % External Foam Clobetasol Propionate 0.05 % External Gel Clobetasol Propionate 0.05 % External Lotion Clobetasol Propionate 0.05 % External Ointment Clobetasol Propionate 0.05 % External Shampoo Clobetasol Propionate 0.05 % External Solution Clobetasol Propionate CREA Clobetasol Propionate E 0.05 % External Cream Clobetasol Propionate E CREA Clobetasol Propionate OINT Clobetasol Propionate POWD Clobetasol Propionate SHAM Clobex Spray 0.05 % External Liquid Cordran 0.05 % External Lotion Corticaine CREA Cortizone-10 CREA Cortizone-10 OINT Cutivate 0.005 % OINT Derma-Smooth FS 0.01 % OIL Derma-Smoothe/FS Scalp 0.01 % External Oil Desonate 0.05 % External Gel Desonide 0.05 % External Cream Desonide 0.05 % External Lotion Desonide 0.05 % External Ointment Desonide CREA Desoximetasone 0.05 % External Ointment Desoximetasone 0.25 % External Cream Desoximetasone 0.25 % External Ointment Diflorasone Diacetate 0.05 % External Cream Diflorasone Diacetate 0.05 % External Ointment Diprolene AF 0.05 % External Cream Diprolene AF CREA Diprosone CREA Epifoam FOAM Fluocinolone Acetonide 0.01 % External Cream Fluocinolone Acetonide 0.025 % External Cream Fluocinolone Acetonide 0.025 % External Ointment Fluocinolone Acetonide Body 0.01 % External Oil Fluocinolone Acetonide Body OIL Fluocinolone Acetonide Scalp 0.01 % External Oil Fluocinonide 0.05 % External Cream Fluocinonide 0.05 % External Gel Fluocinonide 0.05 % External Ointment Fluocinonide 0.05 % External Solution Fluocinonide 0.1 % External Cream Fluocinonide CREA Fluocinonide OINT Fluocinonide-E 0.05 % CREA Fluocinonide-E CREA Fluticasone Propionate 0.005 % External Ointment Fluticasone Propionate 0.05 % External Cream Fluticasone Propionate CREA

		Halog 0.1 % External Cream Hydrocortisone 0.5 % External Cream Hydrocortisone 1 % External Cream Hydrocortisone 1 % External Ointment Hydrocortisone 2.5 % External Cream Hydrocortisone 2.5 % External Lotion Hydrocortisone 2.5 % External Ointment Hydrocortisone Ace-Pramoxine 2.5-1 % External Cream Hydrocortisone Acetate 1 % CREA Hydrocortisone Acetate 1-1 % OINT Hydrocortisone Acetate 2 % LOTN Hydrocortisone Valerate 0.2 % External Cream Hydrocortisone Valerate 0.2 % External Ointment Kenalog 0.1 % CREA Kenalog 0.147 MG/GM External Aerosol Solution Kenalog 0.5 % CREA Kenalog AERS Kenalog CREA Kenalog LOTN Kenalog OINT Lidex 0.05 % CREA Locoid Lipocream CREA Mometasone Furoate 0.1 % External Cream Mometasone Furoate 0.1 % External Ointment Mometasone Furoate 0.1 % External Solution Mometasone Furoate SOLN Olux Olux-E Complete Pack MISC Pramoxine-HC OINT Proctosol HC 2.5 % CREA Proctozone-HC 2.5 % CREA Synalar 0.025 % External Ointment Temovate E 0.05 % CREA Temovate OINT Triamcinolone Acetonide 0.025 % External Cream Triamcinolone Acetonide 0.025 % External Ointment Triamcinolone Acetonide 0.1 % External Cream Triamcinolone Acetonide 0.1 % External Lotion Triamcinolone Acetonide 0.1 % External Ointment Triamcinolone Acetonide 0.5 % External Cream Triamcinolone Acetonide 0.5 % External Ointment Triamcinolone Acetonide CREA Triamcinolone Acetonide LOTN Triamcinolone Acetonide OINT Westcort 0.2 % CREA
	Eczema Agents	Dupixent 300 MG/2ML Subcutaneous Solution Prefilled Syringe
	Emollients	AmLactin 12 % CREA AmLactin 12 % External Lotion Ammonium Lactate 12 % External Cream Ammonium Lactate 12 % External Lotion Ammonium Lactate LOTN Aquaphilic OINT Aquaphor External Ointment Aquaphor OINT Cetaphil CREA DerMend Bruise Formula CREA DHEA 1 % External Cream DHEA CREA Eucerin LOTN Eucerin Plus Intensive Repair 2.5-10 % CREA Hylatopic Plus External Cream Lac-Hydrin 12 % External Cream Lac-Hydrin 12 % LOTN LubriSoft LOTN RisaBal-pH External Cream Vanicream CREA Vanicream External Cream Vitamin A & D OINT
	Immunosuppresive Agents- Topical	Elidel 1 % External Cream Elidel CREA Protopic 0.03 % External Ointment Protopic 0.1 % External Ointment Protopic OINT Tacrolimus 0.03 % External Ointment Tacrolimus 0.1 % External Ointment
	Miscellaneous Dermatological Products	Aurstat Anti-Itch Hydrogel GEL Aurstat Anti-Itch Hydrogel KIT EpiCeram EMUL

	Miscellaneous Topical	Hydrocerin CREAM Vanicream External Bar Vaniply 1 % External Ointment

15.3 Healthcare resource utilisation and asthma control by severe asthma status

Healthcare Resource Utilisation, n(%)	GINA Step 4: Uncontrolled (N=729)	GINA Step 5 (N=975)
Hospitalisations	164 (22.50%)	292 (29.95%)
Emergency Admissions	171 (23.46%)	299 (30.67%)
Invasive Ventilations	16 (2.19%)	77 (7.9%)
Asthma Control Status, n(%)	GINA Step 4: Uncontrolled (N=688)	GINA Step 5 (N=1,228)
Poorly controlled	392 (56.98%)	776 (63.19%)
Not well controlled	126 (18.31%)	206 (16.78%)
Well controlled	170 (24.71%)	246 (20.03%)

*US data not available

15.4 Healthcare resource utilisation by severe asthma status and gender

Healthcare Resource Utilisation, n (%)	GINA Step 4: Uncontrolled		GINA Step 5	
	Female (N=433)	Male (N=296)	Female (N=566)	Male (N=409)
Hospitalisations	66(15.24%)	38(12.83%)	45(7.95%)	38(9.29%)
Emergency Admissions	49(11.31%)	43(14.52%)	86(15.19%)	39(9.53%)
Invasive Ventilations	3(0.69%)	4(1.35%)	3(0.53%)	5(1.22%)

*US data not available

15.5 Healthcare resource utilisation by asthma severity and age of onset*

Healthcare Resource Utilisation, n (%)	GINA Step 4: Uncontrolled			GINA Step 5		
	Age of Onset			Age of Onset		
	<12 (N=146)	12-40 (N=260)	>40 (N=288)	<12 (N=214)	12-40 (N=387)	>40 (N=241)
Hospitalisations	14(9.58%)	41(15.76%)	42(14.58%)	20(9.34%)	33(8.52%)	20(8.29%)
Emergency Admissions	17(11.64%)	28(10.76%)	41(14.23%)	27(12.61%)	53(13.69%)	23(9.54%)
Invasive Ventilations	1(0.68%)	5(1.92%)	1(0.34%)	1(0.46%)	2(0.51%)	0(0%)

*US data not available

15.6 Healthcare resource utilisation by asthma severity and asthma control*

Asthma Control Status	GINA Step 4: Uncontrolled			GINA Step 5		
	Hospitalization	Emergency admission	Invasive ventilation	Hospitalization	Emergency admission	Invasive ventilation
GINA	n=90	n=79	n=7	n=50	n=74	n=7
Uncontrolled	53(58.88%)	51(64.55%)	4(57.14%)	25(50%)	32(43.24%)	4(57.14%)
Partly controlled	30(33.33%)	23(29.11%)	2(28.57%)	17(34%)	30(40.54%)	2(28.57%)
Controlled	7(7.77%)	5(6.32%)	1(14.28%)	8(16%)	12(16.21%)	1(14.28%)
ACQ	n=29	n=32	n=3	n=54	n=87	n=3
Poorly Controlled (Score >1.5)	23(79.31%)	27(84.37%)	2(66.66%)	45(83.33%)	77(88.5%)	3(100%)
Grey Zone (Score 0.75–1.5)	4(13.79%)	4(12.5%)	1(33.33%)	6(11.11%)	9(10.34%)	0(0%)
Well Controlled (Score 0.0–0.75)	2(6.89%)	1(3.12%)	0(0%)	3(5.55%)	1(1.14%)	0(0%)
ACT	n=77	n=57	n=4	n=43	n=63	n=6
Very Poorly Controlled (Score 5–15)	37(48.05%)	29(50.87%)	2(50%)	22(51.16%)	32(50.79%)	3(50%)
Not Well Controlled (Score 16–20)	19(24.67%)	14(24.56%)	1(25%)	10(23.25%)	15(23.8%)	0(0%)
Well Controlled (Score 20–25)	21(27.27%)	14(24.56%)	1(25%)	11(25.58%)	16(25.39%)	3(50%)
*US data not available						

15.7 Blood test measurements by severe asthma status and gender

Serum IgE Level (IU/ml), n (%)	GINA Step 4: Uncontrolled		GINA Step 5	
	Female (N=711)	Male (N=479)	Female (N=615)	Male (N=405)
≤150	471(66.24%)	236(49.26%)	294(47.8%)	151(37.28%)
150-400	114(16.03%)	102(21.29%)	162(26.34%)	101(24.93%)
>400	126(17.72%)	141(29.43%)	159(25.85%)	153(37.77%)
Blood Eosinophil Count (× 10^9/L), n (%)	GINA Step 4: Uncontrolled		GINA Step 5	
	Female (N=1092)	Male (N=708)	Female (N=702)	Male (N=472)
≤0.15	364(33.33%)	201(28.38%)	221(31.48%)	147(31.14%)
>0.15 and ≤0.3	255(23.35%)	175(24.71%)	123(17.52%)	66(13.98%)
>0.3 and ≤0.45	222(20.32%)	153(21.61%)	148(21.08%)	107(22.66%)
>0.45	251(22.98%)	179(25.28%)	210(29.91%)	152(32.2%)
Sputum Eosinophil Count (%), N (%)*	GINA Step 4: Uncontrolled		GINA Step 5	
	Female (N=150)	Male (N=172)	Female (N=131)	Male (N=141)
<3	107(71.33%)	113(65.69%)	93(70.99%)	87(61.7%)
>3	43(28.66%)	59(34.3%)	38(29%)	54(38.29%)

*UK data not available

15.8 Comorbidities by severe asthma status and gender

Comorbidities, n (%)	GINA Step 4: Uncontrolled		GINA Step 5	
	Female (N=1828)	Male (N=1291)	Female (N=693)	Male (N=478)
Eczema	174(9.51%)	91(7.04%)	84(12.12%)	39(8.15%)
Allergic Rhinitis	885(48.41%)	585(45.31%)	337(48.62%)	217(45.39%)
Chronic Rhinosinusitis	425(23.24%)	281(21.76%)	132(19.04%)	82(17.15%)
Nasal Polyps	89(4.86%)	82(6.35%)	77(11.11%)	52(10.87%)

*UK data not available

15.9 Demographic characteristics of severe asthma population by country

ISAR Severe Asthma Population*					
Countries	**South Korea**	**Italy**	**UK**	**USA**	**SAWD**
Gender, n (%)	**N=439**	**N=310**	**N=696**	**N=3282**	**N=259**
Female	238(54.2%)	174(56.1%)	436(62.6%)	1958(59.7%)	151(58.3%)
Male	201(45.8%)	136(43.9%)	260(37.4%)	1324(40.3%)	108(41.7%)
Ethnicity, n (%)	**N=439**	**N=310**	**N=681**	**N=3265**	**N=217**
Caucasian	N/A	310(100%)	480(70.5%)	2606(79.8%)	172(79.3%)
Asian	439(100%)	N/A	60(8.8%)	59(1.8%)	31(14.3%)
African	N/A	N/A	40(5.9%)	223(6.8%)	0(0%)
Mixed	N/A	N/A	10(1.5%)	21(0.6%)	0(0%)
Other	N/A	N/A	91(13.4%)	25(0.8%)	14(6.5%)
Unknown	N/A	N/A	0(0%)	331(10.1%)	0(0%)
Age (years), n (%)	**N=439**	**N=308**	**N=691**	**N=3270**	**N=259**
18-34	23(5.2%)	28(9.1%)	121(17.5%)	455(13.9%)	31(12.0%)
35-54	92(21.0%)	122(39.6%)	328(47.5%)	889(27.2%)	79(30.5%)
55-79	284(64.7%)	151(49.0%)	240(34.7%)	1771(54.2%)	142(54.8%)
≥80	40(9.1%)	7(2.3%)	2(0.3%)	155(4.7%)	7(2.7%)
BMI (kg/m^2), n (%)	**N=433**	**N=295**	**N=679**	**N=3236**	**N=258**
<18.5	25(5.8%)	5(1.7%)	6(0.9%)	67(2.1%)	2(0.8%)
18.5-24.9	256(59.1%)	129(43.7%)	142(20.9%)	770(23.8%)	48(18.6%)
25-29.9	129(29.8%)	103(34.9%)	206(30.3%)	1012(31.3%)	81(31.4%)
≥30	23(5.3%)	58(19.7%)	325(47.9%)	1387(42.9%)	127(49.2%)
Smoking Status, n (%)	**N=437**	**N=315**	**N=673**	**N=3269**	**N=253**
Current smokers	53(12.1%)	9(2.9%)	24(3.6%)	201(6.2%)	7(2.8%)
Ex-smokers	148(33.9%)	64(20.3%)	164(24.4%)	1204(36.8%)	76(30.0%)
Never-smoked	236(54.0%)	242(76.8%)	485(72.1%)	1864(57.0%)	170(67.2%)

15.10 Clinical characteristics of severe asthma population by country

ISAR Severe Asthma Population*					
Countries	**South Korea**	**Italy**	**UK**	**USA**	**SAWD**
Age of asthma onset, * n (%)	**N=414**	**N=274**	**N=596**	**N=0**	**N=252**
<12	30(7.2%)	35(12.8%)	187(31.4%)	N/A	108(42.9%)

12-40	156(37.7%)	134(48.9%)	270(45.3%)	N/A	87(34.5%)
>40	228(55.1%)	105(38.3%)	139(23.3%)	N/A	57(22.6%)
Asthma Control (ACT/ACQ), n (%)	**N=424**	**N=266**	**N=646**	**N=876**	**N=255**
Poorly controlled	168(39.6%)	97(36.5%)	566(87.6%)	423(48.3%)	158(62.0%)
Not well controlled	107(25.2%)	53(19.9%)	49(7.6%)	211(24.1%)	60(1.6%)
Well controlled	149(35.1%)	116(43.6%)	31(4.8%)	242(27.6%)	37(3.4%)
Exacerbations, n (%)	**N=383**	**N=270**	**N=668**	**N=3,286**	**N=216**
Mean (SD)	**1.1 (1.5)**	**3.7 (7.2)**	**5.0 (4.0)**	**0.83 (1.6)**	**2.5 (1.2)**
0	222(58.0%)	48(17.8%)	63 (9.4%)	2509 (76.35%)	3(1.4%)
1	40(10.4%)	30(11.1%)	69 (10.3%)	51 (1.55%)	56(25.9%)
2	24(6.3%)	61(22.6%)	60 (9.0%)	78 (2.37%)	54(25.0%)
3	44(11.5%)	38(14.1%)	77 (11.5%)	61 (1.86%)	37(17.1%)
≥4	53(13.8%)	93(34.4%)	399 (59.7%)	587 (17.86%)	66(30.6%)
Comorbidities, n (%) ˜	**N=439**	**N=310**	**N=0**	**N=3286**	**N=259**
Allergic rhinitis	245(55.8%)	140(45.16%)	N/A	1579 (48.1)	154(59.45%)
Chronic rhinosinusitis	32(7.28%)	0(0%)	N/A	881 (26.8)	8(3.08%)
Eczema	39(8.88%)	30(9.67%)	N/A	290 (8.83)	53(20.46%)
Nasal polyps	15(3.41%)	69(22.25%)	N/A	179 (5.45)	49(18.91%)
Blood Eosinophil Count ($x\ 10^9$), n (%)	**N=389**	**N=230**	**N=689**	**N=2199**	**N=229**
≤0.15	139(35.7%)	46(20.0%)	157(22.8%)	735(33.4%)	71(31.0%)
>0.15 and ≤0.3	90(23.1%)	49(21.3%)	90(13.1%)	497(22.6%)	49(21.4%)
>0.3 and ≤0.45	50(12.6%)	47(20.4%)	183(26.6%)	453(20.6%)	49(21.4%)
>0.45	110(28.3%)	88(38.3%)	259(37.6%)	514(23.4%)	60(26.2%)
Serum IgE Level (IU/ml), n (%)	**N=223**	**N=268**	**N=679**	**N=1313**	**N=169**
<150	101(45.3%)	87(32.5%)	319(47.0%)	759(57.8%)	82(48.5%)
150-400	53(23.8%)	91(34.0%)	158(23.3%)	253(19.3%)	39(23.1%)
>400	69(30.9%)	90(33.6%)	202(29.7%)	301(22.9%)	48(28.4%)
FeNO Level (ppb), n (%)	**N=73**	**N=137**	**N=489**	**N=1388**	**N=81**
Low (<25)	19(26.0%)	56(40.9%)	129(26.4%)	681(49.1%)	49(60.5%)
Intermediate (25-50)	31(42.5%)	33(24.1%)	138(28.2%)	329(23.7%)	16(19.8%)
High (>50)	23(31.5%)	48(35.0%)	222(45.4%)	378(27.2%)	16(19.8%)
HRU, n (%)#	**N=439**	**N=310**	**N=696**	**N/A**	**N=259**
hospitalization	82(18.7%)	53(17.1%)	263(37.8%)	N/A	58(22.4%)
emergency department visit	61(13.9%)	79(25.5%)	270(38.8%)	N/A	60(23.2%)
invasive ventilation	0(0.0%)	10(3.2%)	82(11.8%)	N/A	1(0.4%)

* US data not available for age of asthma onset
# US data not available for healthcare resource utilisation
˜ UK data not available for comorbidities

15.11 Medication regimen of severe asthma population by country

Medication	South Korea (N=439)	Italy (N=310)	UK (N=696)	USA (N=3286)	SAWD (N=259)
Maintenance oral steroid	91(20.72%)	94(37.3%)	415(59.62%)	765(23.28%)	64(24.71%)
ICS (high dose ICS only)	6(1.36%)	N/A	41(5.89%)	980(29.82%)	84(32.43%)
ICS + LABA	280(63.78%)	123(39.67%)	616(88.5%)	2154(65.55 %)	231(89.18%)
ICS + LABA + LAMA	129(29.38%)	49(15.8%)	330(47.41%)	523(15.91%)	N/A

ICS + LABA + LTRA	302(68.79%)	85(27.41%)	265(38.07%)	691(21.02%)	N/A
Theophyllines	255(58.08%)	11(3.54%)	166(23.85%)	58(1.76%)	19(7.33%)
Leukotriene receptor antagonist	309(70.38%)	143(46.12%)	287(41.23%)	1028(31.28 %)	42(16.21%)
Anti-IgE (Omalizumab)	6 (1.37%)	180(58.06%)	122 (17.5%)	287(8.73%)	44(16.98%)
Anti-IL5	N/A	35(11.29%)	347 (49.8%)	247(7.51%)	N/A
Macrolide antibiotic	29(6.6%)	26(8.38%)	41(5.89%)	280(8.52%)	N/A
Other steroid sparing agent	2(0.45%)	N/A	40(5.74%)	17(0.51%)	N/A

15.12 Long-term OCS burden (sensitive definition)*

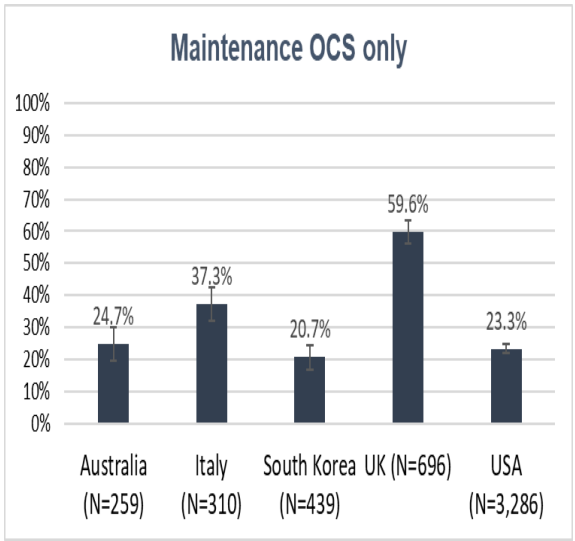

Fig. A: Patients on maintenance OCS only

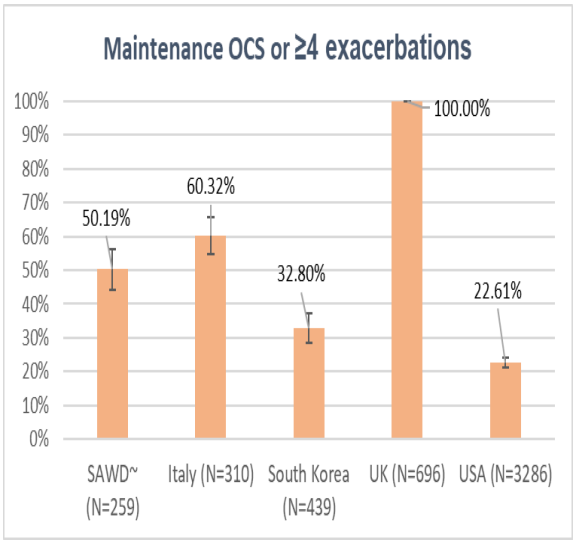

Fig. B: Patients on maintenance OCS or with ≥4 exacerbations

*Sensitive definition 1: maintenance OCS only; 2: maintenance OCS or ≥4 exacerbations requiring rescue steroids