

Real World Biologic Use and Switch Patterns in Severe Asthma: Data from the International Severe Asthma Registry and the US CHRONICLE Study

Andrew N Menzies-Gow,¹ Claire McBrien,² Bindhu Unni,³ Celeste M Porsbjerg,⁴ Mona Al-Ahmad,⁵ Christopher S Ambrose,⁶ Karin Dahl Assing,⁷ Anna von Bülow,⁴ John Busby,⁸ Borja G Cosio,⁹ J Mark FitzGerald,¹⁰ Esther Garcia Gil,¹¹ Susanne Hansen,¹² Liam G aHeaney,⁸ Mark Hew,^{13,14} David J Jackson,^{15,16} Maria Kallieri,¹⁷ Stelios Loukides,¹⁷ Njira L Lugogo,¹⁸ Andriana I Papaioannou,¹⁹ Désirée Larenas-Linnemann,¹⁹ Wendy C Moore,²⁰ Luis A Perez-de-Llano,²¹ Linda M Rasmussen,²² Johannes M Schmid,²³ Salman Siddiqui,²⁴ Marianna Alacqua,²⁵ Trung N Tran,⁶ Charlotte Suppli Ulrik,²⁶ John W Upham,²⁷ Eileen Wang,^{28,29} Lakmini Bulathsinhala,^{3,30} Victoria A Carter,^{3,30} Isha Chaudhry,^{3,30} Neva Eleangovan,^{3,30} Ruth B Murray,^{3,30} Chris A Price,^{3,30} David B Price,^{3,30,31}

¹UK Severe Asthma Network and National Registry, Royal Brompton & Harefield Hospitals, London, UK; ²Kingston Hospital, London, UK; ³Observational and Pragmatic Research Institute, Singapore, Singapore; ⁴Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark; ⁵Al-Rashed Allergy Center, Ministry of Health, Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait, Kuwait; ⁶AstraZeneca, Gaithersburg, MD, USA; ⁷Department of Respiratory Medicine, Aalborg University Hospital, Aalborg, Denmark; ⁸UK Severe Asthma Network and National Registry, Queen's University Belfast, Belfast, Northern Ireland; ⁹Son Espases University Hospital-IdISBa-Ciberes, Mallorca, Spain; ¹⁰The Centre for Lung Health, Vancouver Coastal Health Research Institute, UBC, Vancouver, Canada; ¹¹AstraZeneca, Barcelona, Spain; ¹²Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; ¹³Allergy, Asthma & Clinical Immunology Service, Alfred Health, Melbourne, Australia; ¹⁴Public Health and Preventive Medicine, Monash University, Melbourne, Australia; ¹⁵UK Severe Asthma Network and

Introduction: International registries provide opportunities to describe use of biologics for treating severe asthma in current clinical practice. Our aims were to describe real-life global patterns of biologic use (continuation, switches, and discontinuations) for severe asthma, elucidate reasons underlying these patterns, and examine associated patient-level factors.

Methods: This was a historical cohort study including adults with severe asthma enrolled into the International Severe Asthma Registry (ISAR; <http://isaregistries.org>, 2015–2020) or the CHRONICLE Study (2018–2020) and treated with a biologic. Eleven countries were included (Bulgaria, Canada, Denmark, Greece, Italy, Japan, Kuwait, South Korea, Spain, UK, and USA). Biologic utilization patterns were defined: 1) continuing initial biologic; 2) stopping biologic treatment; or 3) switching to another biologic. Reasons for discontinuation/switching were recorded and comparisons drawn between groups.

Results: A total of 3531 patients were included. Omalizumab was the most common initial biologic in 2015 (88.2%) and benralizumab in 2019 (29.6%). Most patients (79%; 2791/3531) continued their first biologic; 10.2% (356/3531) stopped; 10.8% (384/3531) switched. The most frequent first switch was from omalizumab to an anti-IL-5/5R (49.6%; 187/377). The most common subsequent switch was from one anti-IL-5/5R to another (44.4%; 20/45). Insufficient efficacy and/or adverse effects were the most frequent reasons for stopping/switching. Patients who stopped/switched were more likely to have a higher baseline blood eosinophil count and exacerbation rate, lower lung function, and greater health care resource utilization.

Conclusion: The description of real-life patterns of continuing, stopping, or switching biologics enhances our understanding of global biologic use. Prospective studies involving structured switching criteria could ascertain optimal strategies to identify patients who may benefit from switching.

Keywords: severe asthma, biologics, prescribing, cohort study, management, international

Introduction

With the advent of personalized medicine, biologic therapy is becoming more widely used for a number of diseases, including severe asthma.¹ However, there is a paucity of literature on both the frequency and patterns of biologic use in severe asthma, as well as the characterization of pre-biologic patient factors associated with stopping or switching versus continuation of the initial biologic.

Omalizumab was the first available biologic therapy for severe asthma, targeting immunoglobulin E (IgE) and therefore the allergic asthma phenotype. In recent years, four more monoclonal antibodies have been added to the biologic repertoire. For the eosinophilic phenotype, there are three available biologic agents.

National Registry, Guy's and St Thomas' NHS Trust, London, UK; ¹⁸School of Immunology & Microbial Sciences, King's College London, London, UK; ¹⁷2nd Respiratory Medicine Department, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece; ¹⁸Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA; ¹⁹Directora Centro de Excelencia en Asma y Alergia, Hospital Médica Sur, Ciudad de México, Mexico; ²⁰Pulmonary, Critical Care, Allergy, and Immunologic Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA; ²¹Department of Respiratory Medicine, Hospital Universitario Lucus Augusti, Lugo, Spain; ²²Allergy Clinic, Department of Dermato-Allergology, Gentofte Hospital, Copenhagen, Denmark; ²³University Hospital of Aarhus, Aarhus, Denmark; ²⁴University of Leicester, Department of Respiratory Sciences & NIHR Leicester Biomedical Research Centre (Respiratory Theme), Leicester, UK; ²⁵AstraZeneca, Cambridge, UK; ²⁶Department of Respiratory Medicine, Copenhagen University Hospital-Hvidovre, Hvidovre, Denmark; ²⁷Diamantina Institute & PA-Southside Clinical Unit, The University of Queensland, Brisbane, Australia; ²⁸Division of Allergy & Clinical Immunology, Department of Medicine, National Jewish Health, Denver, CO, USA; ²⁹Division of Allergy & Clinical Immunology, Department of Internal Medicine, University of Colorado School of Medicine, Aurora, CO, USA; ³⁰Optimum Patient Care, Cambridge, UK; ³¹Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

Mepolizumab and reslizumab both target interleukin-5 (IL-5), whereas benralizumab binds to the alpha subunit of the IL-5 receptor.² The most recently-approved biologic, dupilumab, inhibits both IL-4 and IL-13 pathways by binding to the alpha subunit of the IL-4 receptor.³ Due to the different mechanisms of action, selection of the optimal initial biologic for each individual depends on accurate phenotyping using clinical characteristics (age of onset, allergy-related symptoms) and appropriate biomarkers such as blood eosinophil count (BEC) and Fractional exhaled Nitric Oxide (FeNO).⁴⁻⁷ Other considerations include: 1) route of delivery (reslizumab is intravenous whereas all the other biologics are administered subcutaneously); 2) frequency of administration (which, during the maintenance phase, varies between every two weeks and every eight weeks); 3) adverse effect profile; 4) patient preferences; and 5) comorbidities, such as atopic dermatitis and nasal polyposis. Prescribers are also constrained by licensing and availability of biologics and influenced by prescribing and reimbursement guidelines issued at international, national and/ or local levels. In general, biologics are indicated for individuals with severe asthma, who experience uncontrolled disease despite optimized standard medical care and for whom other factors that could contribute to the lack of asthma control (including comorbidities, incorrect inhalation technique and non-adherence) have been ruled out or appropriately optimized. In appropriately selected patients, biologics can result in a significant reduction in annualized exacerbation frequency.⁸ Additional benefits can include reduced exposure to systemic corticosteroids and improvements in lung function and quality of life/symptom control.⁹ Reduced exposure to systemic corticosteroids is particularly desirable due to their numerous short- and long-term adverse effects, including increased risk of diabetes mellitus, infections and osteoporosis.¹⁰

Despite a growing body of evidence with regards to the efficacy of biologics in asthma management, detailed knowledge of how biologics are actually used in real life is lacking. In particular, it is important to understand what proportion of patients continue, stop and switch from their initial biologic and the patient factors associated with biologic stopping or switching versus continuation.

Until recently we were unable to answer these questions. Small national and regional severe asthma registries did exist, but they were discrete and did not share information between them. The situation has now changed with the availability of data from two large databases, the International Severe Asthma Registry (ISAR; <http://isaregistries.org/>) and the CHRONICLE study (USA). ISAR, the largest adult severe asthma registry in the world, retrospectively and prospectively collects patient level, standardized variables from 29 countries around the world;¹¹⁻¹⁴ at the time of writing it included >11,500 patients and covers diverse health care systems. It, therefore, has sufficient power to investigate, quantify, and describe biologic patterns of use, facilitating the generalizability of findings to the wider severe asthma population. Patients entered into the ISAR database represent, in the UK: a convenience sample from the UK Severe Asthma Registry, and in all other countries: all patients in severe asthma centres. The CHRONICLE study (ClinicalTrials.gov: NCT03373045) is a real-world, prospective, non-interventional cohort study of US specialist-treated patients with severe asthma that is aligned with ISAR and collects primary health care provider-reported and patient-reported data on patient characteristics, comorbidities, laboratory and imaging assessments, medical treatments, health care utilization (HCRU), and health outcomes from a

Correspondence: David B Price
Observational and Pragmatic Research
Institute, 22 Sin Ming Lane, #06 Midview
City, Singapore, 573969
Tel +65 3105 1489
Email dprice@opri.sg

large, geographically diverse cohort of US patients and providers.^{15,16} Per protocol, sites approach all eligible patients for enrollment. Although ISAR has a US site, there is no expected overlap between ISAR and CHRONICLE as the ISAR site is not included in CHRONICLE.

This study sought to describe biologic treatment frequency, patterns of use and reasons for biologic treatment discontinuation and switching in a real-life severe asthma cohort. Patient demographic and clinical characteristics (prior to initial biologic prescription) were also captured according to patterns of biologic use to identify individual patient-level factors associated with biologic stopping or switching versus continuation.

Materials and Methods

Study Design and Data Source

This was a historical cohort study using data from patients enrolled into ISAR (2015–2020) or CHRONICLE (2018–2020). Eleven countries had at least two biologics available (Bulgaria, Canada, Denmark, Greece, Italy, Japan, Kuwait, South Korea, Spain, UK, and the USA). Longitudinal de-identified patient data relating to these countries were extracted from CHRONICLE (USA) and ISAR Italy in February 2020, from ISAR UK in December 2019; and from the other ISAR countries included in the analysis in September 2019.

Patients

Patients were required to be aged ≥ 18 years old at the date of biologic initiation, have severe asthma (ie receiving treatment at Global Initiative for Asthma [GINA] 2018 Step 5 or with uncontrolled asthma at GINA Step 4)¹⁷ and treated with a biologic (ie omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab). Patients were required to have a minimum of six months of follow-up after biologic initiation.

The majority of countries included had at least two biologics available by 2018. With regard to patterns of biologic use after initiation, information regarding subjects who stopped or switched in 2018 or later was assessed. All subjects included in these analyses were treated in countries that, in 2018, had access to at least two biologics, therefore each of the possible patterns of biologic use (continuation, stopping, or switching) was feasible.

Outcomes (Definition of Biologic Continuation/Switching/Stopping)

Information on biologic use (availability, frequency, and duration of biologic use as well as reasons for switching/stopping) were collected. The percentages of patients who continued, stopped, or switched their first biologic were calculated overall and by country. “Continued biologic” was defined as the ongoing use of one biologic for at least 6 months at the time of data extraction without data indicating switching to another biologic. “Switched biologic” indicated those who received >1 biologic during follow-up; there was no restriction on how much time elapsed between the different biologics. “Stopped biologic” referred to individuals who received one biologic, stopped and did not commence another biologic during their follow-up period. Patients with ongoing biologic use of <6 months at the time of data extraction were excluded, as they would not meet the criteria for Continued, Switched, or Stopped.

Demographic and Clinical Characteristics Pre-First Biologic Treatment

A full description of pre-biologic demographic and clinical variables collected is provided in [Table E1](#) including details on asthma exacerbations, hospitalizations and emergency visits, presence of comorbidities, test results (eg IgE, BEC, and FeNO), and treatment regimen (eg long-term oral corticosteroid (OCS) use and other add-on therapies to inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA)).

Analyses

Patterns of Biologic Use

The time to cessation of first biologic after initiation (for those that stopped or switched in 2018 or later) was assessed. Patterns of biologic use were established for the total population and by country. Switch patterns (aggregated by biologic class) were analysed for all switched patients, including those who switched once and more than once. Additionally, first switch patterns were analyzed by age, long-term OCS use, age of asthma onset and presence of nasal polyps, factors which were identified as likely to affect outcomes. Demographic and clinical features stratified by patterns of biologic use were explored. Patients who switched or stopped were compared to patients who continued using univariate chi-square tests. Data from the closest preceding visit of the

initial biologic start date were used. For emergency visits, hospitalization, BEC, and other asthma therapy, data within the 12 months preceding first biologic initiation were analyzed to align data collection methods from both ISAR and CHRONICLE.

Sensitivity Analyses

Analyses were repeated for three subpopulations within the larger cohort: 1) Prospective population (all countries, n=2656) assessed to ensure only patients with active data collection were used (to minimize information bias); 2) US only (n=2127 – predominantly prospective) as these patients made up a large proportion of the dataset (60%), and the US had the largest deviation from other countries included in the study; 3) Non-US (n=1404, prospective).

Results

Patients

A total of 3531 patients with severe asthma were included, 2295 from ISAR and 1236 from CHRONICLE (Figure 1). The three sub-populations each contained >1000 patients: 1) Prospective population (n=2656) (Figure E1); 2) US populations (n=2127); 3) Non-US (n=1404) (Figure E2).

Biologic Availability and Overall Utilization

Biologic availability increased over time from 2015 to 2019 (Figure E3). All countries had ≥2 biologics available as of May 2019 (Table E2; Figure E3). Omalizumab and mepolizumab were available in all 11 countries. Benralizumab, reslizumab and dupilumab were available in 82% (9/11), 64% (7/11), and 55% (6/11) of countries, respectively. Most countries (8/11) recommended assessment of biologic efficacy at 4–12 months after patient initiation.

Omalizumab was used by 96.4% (n=756/784) of patients in 2015; its proportional use steadily declining to 45.5% (n=1510/3319) of users by 2019 (Figure E4). During the same time frame the proportion of patients prescribed mepolizumab increased from 3.6% (n=28/784) to 35.4% (n=1174/3319), whilst use of benralizumab increased from 0.9% (n=22/2266) of patients in 2017 to 12.8% (n=423/3319) in 2019. Reslizumab use stayed <3% throughout 2017–2019, whereas dupilumab was prescribed to 354/3272 patients (10.8%) in 2018, increasing to 425/3319 patients (12.8%) in 2019 (Figure E4).

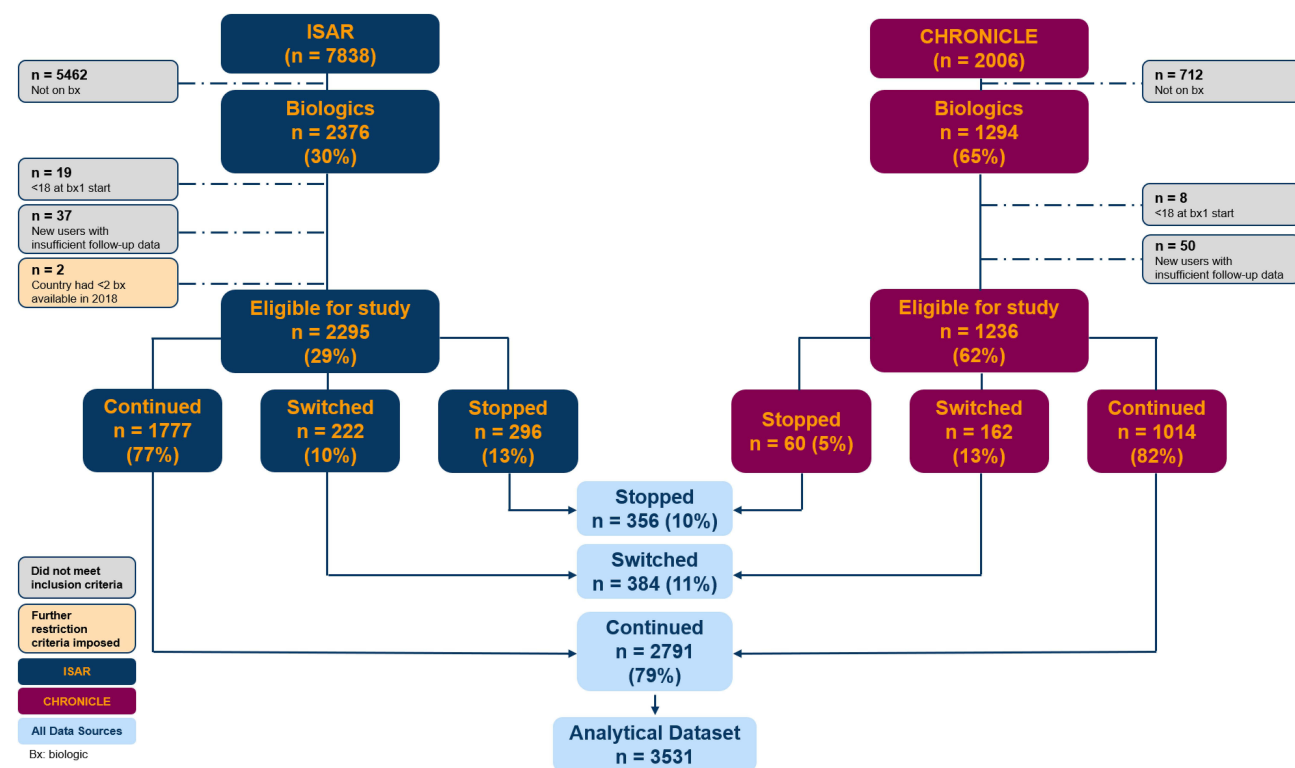


Figure 1 Subject disposition and pattern of biologic use of patients enrolled into ISAR or CHRONICLE. **Abbreviations:** ISAR, International Severe Asthma Registry; Bx, biologic.

First Biologic

Of the 229 patients who newly started a biologic in 2015, the majority commenced omalizumab (88.2%; n=202/229). However, as the number of available biologics increased, so too did the proportion of patients starting on an anti-IL-5/5R; by 2019, most patients started with an anti-IL-5/5R (56.9%; n=202/356) (Figure 2). By 2019, the highest proportion of patients (29.6%; n=105/356) started with benralizumab, followed by mepolizumab (24.5%; n=87/356) and dupilumab (23.1%; n=82/356). Meanwhile, the proportion of patients starting on omalizumab declined to 20% (71/356). A similar pattern of first biologic prescription was noted for the prospective and non-US populations (ie decreasing first prescription of omalizumab and increasing prescription of anti-IL-5/5R over time), but in the case of the non-US population, a much higher proportion of patients started with anti-IL-5/5R (83.6%; n=61/73) by 2019 as dupilumab was not yet available for many of these countries (ie UK, Spain, Bulgaria, South Korea, and Greece) (Figure E5).

Patterns of Biologic Use

Most patients included in the overall analysis continued their first biologic for at least 6 months (79%; n=2791/3531), whereas a small proportion stopped (10.2%; n=356/3531) or switched (10.8%; n=384/3531) during the course of follow up (Figure 1; Table 1). A numerically higher

proportion of patients in the US cohort proceeded to stop biologic treatment than patients from the other cohorts (% who stopped - prospective: 5.3% [n=139/2656]; US: 13.1% [n=279/2127]; non-US: 5.5% [n=77/1404]) (Table 1).

Duration of Biologic Use in Stoppers and Switchers

Most patients who initiated biologic therapy in 2018 and subsequently stopped or switched (n=117), stopped their first biologic within 12 months (Figure 3). This was true for 85% of omalizumab (n=29/34) and mepolizumab (n=34/40) recipients and 91% (n=39/43) of benralizumab recipients. Among those who switched, the time for which patients received their initial biologic varied numerically between drugs, with median durations of 6.8 months for omalizumab, 4.3 months for mepolizumab, and 6.0 months for benralizumab.

Japan and the US had numerically the highest proportions of users in whom biologic treatment was stopped (17.7% and 13.1% respectively) (Table 1). The US, UK, and Spain had higher proportions of patients stopping biologics versus switching; Kuwait, Bulgaria, Canada, Denmark, South Korea, Italy, and Greece had higher proportions switching biologic versus stopping; Japan had an equal proportion of patients stopping and switching.

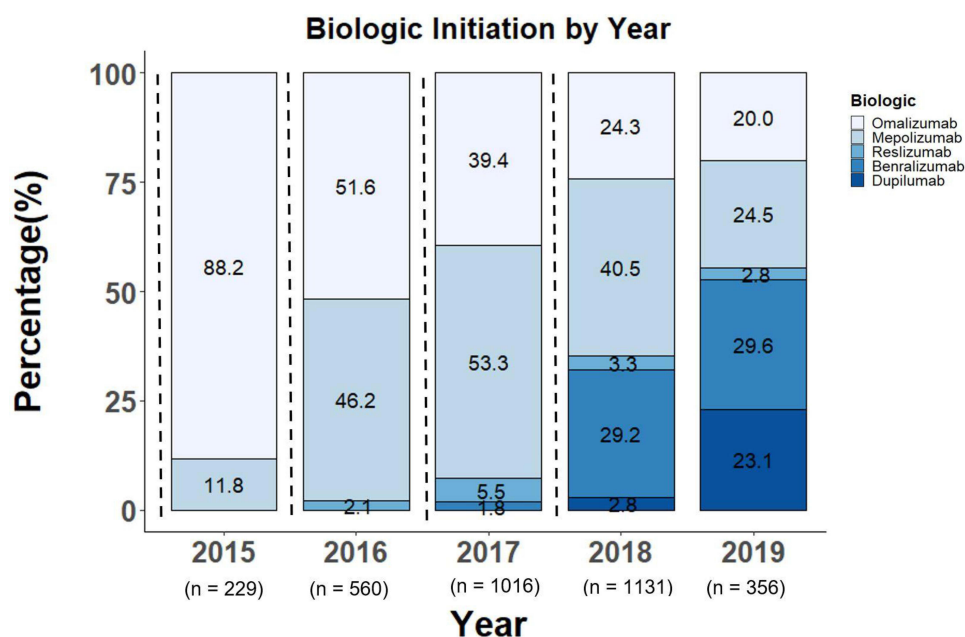


Figure 2 Proportion of patients with severe asthma enrolled into ISAR or CHRONICLE (n= 3531) on each biologic (first use) by year.

Abbreviation: ISAR, International Severe Asthma Registry.

Table 1 Pattern of Biologic Use Overall and by Country for Patients with Severe Asthma Enrolled into ISAR and CHRONICLE

Year in Which ≥ 2 Biologics Became Available	Population or Country	Continued n (%)	Stopped n (%)	Switched n (%)
Overall	Total (n=3531)	2791 (79.0)	356 (10.2)	384 (10.8)
	eCRF (n=2656)	2237 (84.2)	139 (5.3)	280 (10.5)
	USA only (n=2127)	1575 (74.1)	279 (13.1)	273 (12.8)
	Non-USA (n=1404)	1216 (86.6)	77 (5.5)	111 (7.9)
Total population (n=3531)				
2018	Japan (n=17)	11 (64.7)	3 (17.7)	3 (17.7)
2017	Kuwait (n=139)	119 (85.6)	2 (1.4)	18 (13.0)
2016	Bulgaria (n=30)	27 (90.0)	1 (3.3)	2 (6.7)
	Canada (n = 57)	46 (80.7)	3 (5.3)	8 (14.0)
	Denmark (n=132)	112 (84.9)	0 (0.0)	20 (15.2)
	2016 Strata (n=219)	185 (84.5)	4 (1.8)	30 (13.7)
2015	Italy (n=523)	492 (94.1)	11 (2.1)	20 (3.8)
	South Korea (n=5)	3 (60.0)	0 (0.0)	2 (40.0)
	Spain (n=188)	161 (85.6)	22 (11.7)	5 (2.7)
	Greece (n=10)	9 (90.0)	0 (0.0)	1 (10.0)
	UK (n=303)	236 (77.9%)	35 (11.6)	32 (10.6)
	USA (n=2127)	1575 (74.1)	279 (13.1)	273 (12.8)
	2015 Strata (n=3156)	2476 (78.5)	347 (11.0)	333 (10.6)

Abbreviations: eCRF, electronic case report form; ISAR, International Severe Asthma Registry.

Patterns of Switching

First Switch

Of those patients who stopped or switched their first biologic, the most common first switch was from omalizumab to (or, rarely, combined with) an anti-IL-5/5R (49.6%; n=187/377); (Figure 4). The second most common switch was within class, adding or switching from one anti-IL-5/5R to another (30.8%; n=116/377). A similar first switch pattern was noted for the prospective, US only and non-US cohorts (Figure E6).

Figure E7 describes the variability in switch patterns between the different biologic classes. For example, the cohort of subjects who switched from anti-IL-5-IL5/5R to anti-IL-4-IL4 contained a numerically higher proportion of patients taking long-term OCS, compared to other switch patterns.

Subsequent Switch

For the 45 patients who switched more than once, the most common subsequent biologic switch was from one anti-

IL-5/5R to another (44.4%; n=20/45); (Figure E8). The next most common second switch was from an anti-IL-5/5R to (or combined with) an anti-IL-4 (22.4%; n=11/45). 17.5% of these patients (n=8/45) switched more than twice.

Description of Those Who Switched or Stopped Their First Prescribed Biologic

Comparing the pre-biologic characteristics of individuals who continued their first prescribed biologic to those who switched (Table 2), switchers had a numerically higher BEC (both on and off long-term OCS). Switchers also had a higher FeNO than continuers (p=0.007) and were more likely to be using theophylline as add-on therapy (3.8% vs 1.3%, p=0.003). In patients not on long-term OCS, switchers had more exacerbations than continuers (p=0.004). Switchers were numerically more likely than continuers to have used more healthcare resources: more invasive ventilation episodes (p=0.079), emergency visits

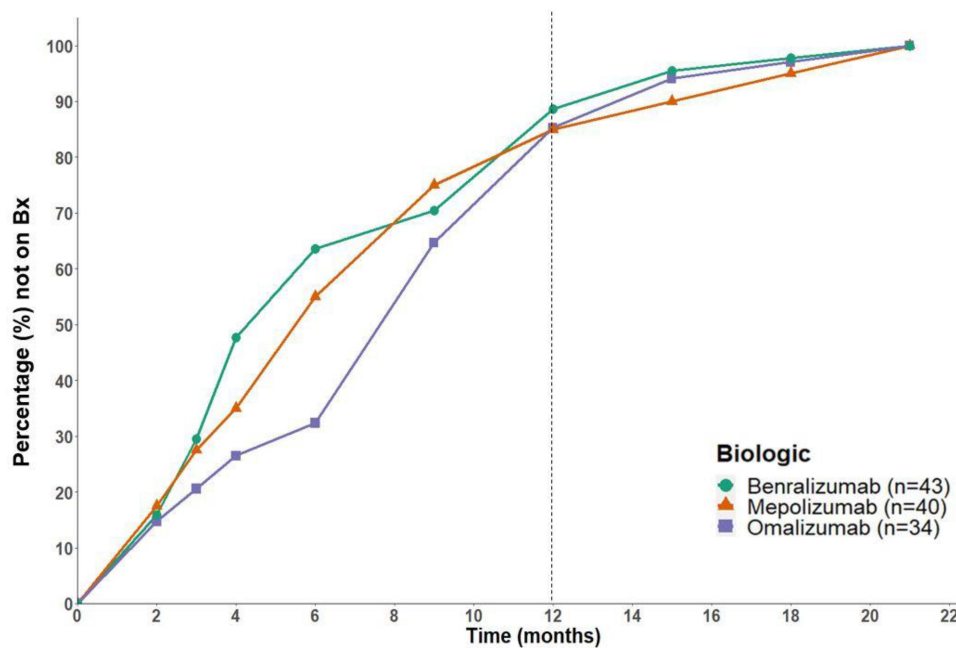


Figure 3 Time to biologic cessation for patients with severe asthma enrolled into ISAR or CHRONICLE who stopped or switched biologic (from 2018 onwards). **Abbreviation:** ISAR, International Severe Asthma Registry.

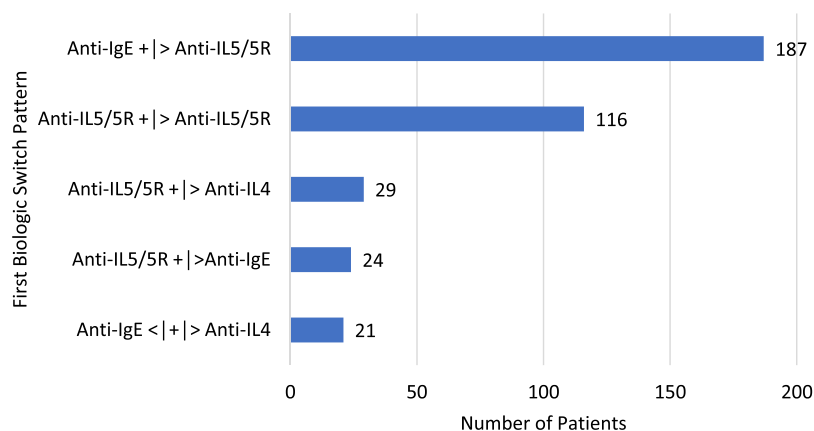


Figure 4 Pattern of biologic switch for patients with severe asthma enrolled into ISAR or CHRONICLE those who switched once (n=377). Patterns are mutually exclusive; | : or, <, >: sequence of switch; +: add-on use.

Abbreviations: IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; IL, interleukin.

($p=0.010$), and hospitalizations ($p<0.001$) Switchers also showed a higher proportion of patients with eosinophilic chronic rhinosinusitis (19.8%) than continuers (11.0%) ($p=0.020$).

Comparing the pre-biologic characteristics of individuals who continued their first prescribed biologic to those who stopped biologic therapy (Table 2), stoppers were numerically less likely to be on long-term OCS ($p=0.007$) and to be using LTRA as add-on therapy ($p=0.005$). In patients not on long-term OCS, switchers

had more exacerbations than continuers ($p=0.002$). Similar to switchers, stoppers tended to have used more healthcare resources than continuers: more invasive ventilation episodes ($p=0.002$), emergency visits ($p=0.142$), and hospitalizations ($p=0.004$). Although the proportion of patients with chronic rhinosinusitis was higher in stoppers (93.2%) than in continuers (75.0%), the proportion of patients who had chronic rhinosinusitis with nasal polyps was higher in continuers (60.1%) than in stoppers (38.4%) ($p<0.001$).

Table 2 Demographic and Clinical Characteristics of Patients with Severe Asthma Enrolled into ISAR or CHRONICLE, Prior to First Biologic, According to Pattern of First Biologic Use

Biologic Utilisation Group	Continued 2791	Stopped 356	Switched 384	Stoppers vs Continuers: P-value ^a	Switchers vs Continuers: P-values ^a
Demographics					
Age categories, years	2776	350	379	0.086	0.065
18–34, n (%)	312 (11.2)	54 (15.4)	50 (13.2)		
35–54, n (%)	1054 (38.0)	121 (34.6)	164 (43.3)		
55–79, n (%)	1352 (48.7)	165 (47.1)	157 (41.4)		
≥80, n (%)	58 (2.1)	10 (2.9)	8 (2.1)		
Sex	2787	356	383	0.916	0.154
Male	1002 (36.0)	129 (36.2)	152 (39.7)		
Female	1785 (64.0)	227 (63.8)	231 (60.3)		
Ethnicity	2724	355	378	0.701	0.310
Caucasian, n (%)	2147 (78.8)	280 (78.9)	283 (74.9)		
Asian, n (%)	73 (2.7)	9 (2.5)	13 (3.4)		
African, n (%)	221 (8.1)	34 (9.6)	39 (10.3)		
Mixed/Other/Unknown, n (%)	283 (10.4)	32 (9.0)	43 (11.4)		
Smoking status	1292	240	172	0.804	0.876
Current smoker, n (%)	24 (1.9)	6 (2.5)	4 (2.3)		
Ex-smoker, n (%)	356 (27.6)	66 (27.5)	49 (28.5)		
Never Smoked, n (%)	912 (70.6)	168 (70.0)	119 (69.2)		
Age of asthma onset, years	2057	125	261	0.560	0.959
<12, n (%)	521 (25.3)	37 (29.6)	64 (24.5)		
≥12–29, n (%)	510 (24.8)	30 (24.0)	65 (24.9)		
≥30, n (%)	1026 (49.9)	58 (46.4)	132 (50.6)		
BMI Category	1306	261	188	0.295	0.590
Underweight, n (%)	25 (1.9)	6 (2.3)	3 (1.6)		
Normal weight, n (%)	368 (28.2)	68 (26.1)	48 (25.5)		
Overweight, n (%)	425 (32.5)	74 (28.4)	57 (30.3)		
Obese, n (%)	488 (37.4)	113 (43.3)	80 (42.6)		
Comorbidities					
Allergic Rhinitis	514	109	77	0.026	1.000
Ever, n (%)	467 (90.9)	106 (97.2)	70 (90.9)		
Eczema	676	55	67	0.608	0.493
Ever, n (%)	32 (4.7)	4 (7.3)	5 (7.5)		

(Continued)

Table 2 (Continued).

Biologic Utilisation Group	Continued 2791	Stopped 356	Switched 384	Stoppers vs Continuers: P-value ^a	Switchers vs Continuers: P-values ^a
CRS and NP	684	73	101	<0.001	0.020
CRSwNP, n (%)	411 (60.1)	28 (38.4)	63 (62.4)		
eCRS, n (%)	75 (11.0)	28 (38.4)	20 (19.8)		
CRSsNP, n (%)	27 (3.9)	12 (16.4)	3 (3.0)		
None	171 (25.0)	5 (6.8)	15 (14.9)		
Biomarkers					
BEC (cells/μL)[#]	865	166	153		
Not on long-term OCS	771	150	134	0.411	0.011
<300, n (%)	326 (42.3)	58 (38.7)	41 (31.1)		
\geq 300, n (%)	445 (57.7)	92 (61.3)	93 (68.9)		
On long-term OCS	94	16	18	0.064	0.083
<300, n (%)	47 (50.0)	4 (25.0)	5 (27.8)		
\geq 300, n (%)	47 (50.0)	12 (75.0)	13 (72.2)		
FeNO (ppb)	795	126	94	0.663	0.007
0-<25, n (%)	357 (44.9)	62 (49.2)	28 (29.8)		
\geq 25 - <50, n (%)	250 (31.4)	37 (29.4)	32 (34.0)		
\geq 50, n (%)	188 (23.6)	27 (21.4)	34 (36.2)		
IgE Concentration (IU/mL)	1417	207	209	0.158	0.462
<150, n (%)	601 (42.4)	80 (38.6)	83 (39.7)		
\geq 150 - <400, n (%)	388 (27.4)	70 (33.8)	54 (25.8)		
\geq 400, n (%)	428 (30.2)	57 (27.5)	72 (34.4)		
Medication					
Long-term OCS[#]	1950	307	260	0.007	0.516
Use, n (%)	228 (11.7)	20 (6.5)	34 (13.1)		
Add on therapy[#]	1950	307	260		
LAMA, n (%)	326 (16.7)	38 (12.4)	33 (12.7)	0.055	0.098
Theophylline, n (%)	26 (1.3)	6 (2.0)	10 (3.8)	0.392	0.003
LTRA, n (%)	224 (11.5)	19 (6.2)	24 (9.2)	0.005	0.279
Exacerbations[#]					
	728	46	73		
Not on long-term OCS, n (%)	503 (69.1)	39 (84.8)	62 (84.9)	0.002	0.004
Median (IQR)	4.0 (2, 6)	5.0 (4, 8)	4.5 (3, 8)		

(Continued)

Table 2 (Continued).

Biologic Utilisation Group	Continued 2791	Stopped 356	Switched 384	Stoppers vs Continuers: P-value ^a	Switchers vs Continuers: P-values ^a
On long-term OCS, n (%)	101 (13.9)	0 (0.0)	8 (11.0)	Nc	0.802
Median (IQR)	2.0 (2, 4)	-	2.5 (2, 6)		
Healthcare resource utilization					
Invasive Ventilation Episodes	715	42	67	0.002	0.079
≥1, n (%)	45 (6.3)	8 (19.0)	8 (11.9)		
Emergency Visits [#]	450	47	65	0.142	0.010
≥1, n (%)	180 (40.0)	24 (51.1)	37 (56.9)		
Hospitalizations [#]	639	45	63	0.004	<0.001
≥1, n (%)	136 (21.3)	18 (40.0)	29 (46.0)		
Lung function					
Post-bronchodilator percentage predicted FEV ₁	1247	220	191	0.733	0.794
<80%, n (%)	659 (52.8)	119 (54.1)	99 (51.8)		
≥80%, n (%)	588 (47.2)	101 (45.9)	92 (48.2)		
Post-bronchodilator FEV ₁ :FVC	1260	219	194	0.064	0.116
<0.7, n (%)	503 (39.9)	102 (46.6)	89 (45.9)		
≥0.7, n (%)	757 (60.1)	117 (53.4)	105 (54.1)		

Notes: [#]Variable that was further restricted to data ONLY within the 12 months preceding biologic therapy. ^aP-values from Pearson chi-square tests, applying Yates correction when the expected frequency was less than 5 in more than 20% of the sub-categories, for all variables except for exacerbation counts which were compared using the Wilcoxon score test.

Abbreviations: BEC, blood eosinophil count; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; eCRS, eosinophilic chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; IgE, Immunoglobulin E; IQR, inter-quartile range; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; NC, Not calculated (no patients on long-term OCS stopped their initial biologic).

Reasons for Stop or Switch

The most commonly cited reason for stopping or switching a biologic was due to insufficient clinical efficacy (72 of 113 stopped patients [63.7%] and (158 of 183 switched patients [86.3%], %) respectively. The presence of adverse outcomes potentially caused by biologic was also cited by approximately 15.9% (n=18) and 7.7% (n=14) of all stopped and switched individuals, respectively (Table 3).

Discussion

The severe asthma biologic landscape is becoming increasingly complex due to the array of monoclonal antibodies available to prescribers and the lack of head-to-head studies to inform clinical decision-making when an individual patient qualifies for more than one

biologic option. To our knowledge, this is the largest study to investigate biologic treatment patterns for severe asthma in real-life, spanning 11 countries and 3 continents. Within this cohort, we have assessed both initial biologic treatment choice and subsequent prescribing patterns. When analyzed globally and at the country level, a low rate of biologic switching is a consistent finding, albeit with some inter-country variability. The data set provided sufficient depth of information to investigate first and subsequent switch patterns at the biologic class level, to describe reasons for this behavior and to assess the spread of baseline clinical factors (eg presence of nasal polyps, age of asthma onset, and long-term OCS use) across subjects undergoing different biologic utilization patterns.

Table 3 Reasons Why eCRF Patients with Severe Asthma Enrolled into ISAR or CHRONICLE Stopped or Switched Their First Prescribed Biologic

Reason	Stopped (n=139)	Switched (n=280)
Reason available n (%)	113	183
Insufficient Clinical Efficacy	72 (63.7)	158 (86.3)
Potential adverse outcomes	18 (15.9)	14 (7.7)
Biologic Access Restriction	8 (7.1)	5 (2.7)
Patient Preference	4 (3.5)	3 (1.6)
Other	12 (10.6)	11 (6.0)

Abbreviations: eCRF, electronic case report form; ISAR, International Severe Asthma Registry.

Other studies have attempted to elucidate real-world biologic prescribing patterns. For example, a survey performed among allergists using a semi-structured 10-item self-administered web-based questionnaire, published in 2020, found that omalizumab was the most commonly-prescribed biologic for asthma (98%), and that “uncontrolled asthma despite adherence to controller medication” was the most common indication.¹⁸ The selection bias in this study, favouring omalizumab over alternative biologic agents, was considerable, given that the questionnaire was directed toward allergists. A cross-sectional observational study including six countries analysed a cohort of 670 patients with severe asthma, recruited between December 2014 and May 2015. Biologic eligibility was 31–41% for omalizumab, 20% for mepolizumab, and 5% for reslizumab. Substantial overlap was noted between groups; for example, out of 101 patients who were eligible for mepolizumab (and not currently receiving omalizumab), 27–37% were also eligible for omalizumab.¹⁹ A separate retrospective cohort study investigated the characteristics of 1834 individuals who commenced treatment with either omalizumab or mepolizumab between November 2015 and March 2017. Compared to patients prescribed omalizumab, those prescribed mepolizumab were more likely to have experienced an exacerbation in the 12 months leading up to biologic initiation (81.4% vs 57.5%) and were more likely to have conditions such as sinusitis (35.4% vs 26.3%) and nasal polyps (19.1% vs 6.9%) but less likely to have allergic rhinitis (69.7% vs 77%), atopic dermatitis

(2.2% vs 8.1%), or chronic idiopathic urticaria (0.5% vs 21.2%).²⁰

Despite a rapid increase in the availability of biologic therapies for asthma with different mechanisms of action, 79% of subjects in this study remained on the first biologic that they were prescribed (biologic 1). Overall, the percentage of patients who switched to another biologic was low. These findings naturally trigger the question: “Is the first biologic prescribed to a patient usually the best one for that individual, or are we under-switching?” Although in many cases, continuation of the first biologic may reflect appropriate biomarker-guided biologic selection and good clinical efficacy of the initial biologic, a substantial proportion of patients qualify for one or more alternative biologic agents. The response to the un-tried agent(s) is unknown and perhaps a subset would be better served by switching biologics.

It may be that the careful selection of an appropriate first biologic based on clinical characteristics and biomarkers resulted in adequate clinical efficacy in the majority of patients. It is, however, possible to speculate on other reasons for the evident low rate of switching once a patient is established on the initial agent, with possibilities including: 1) a high initial logistical hurdle to biologic prescription that may lead individuals to persist with the first biologic, rather than invest further time and effort in pursuing an alternative agent; 2) conservative thresholds for response, eg, a 50% reduction in exacerbation rate and /or maintenance oral corticosteroid dose in the UK for anti-IL-5/5R: although an individual’s response to their initial biologic may not be transformative, if it is better than their previous treatment they may be unwilling to change treatment, due to underestimation of the effect which may be achieved with a different biologic and fear of losing the marginal improvement seen with the first choice of biologic and; 3) there is currently limited evidence with regards to the potential benefits of switching biologic. All of these reasons underscore the need for further research into which patients respond best to the available biologics.

It is important to note that within this study most switches occurred within 12 months of initial biologic prescription. This is likely related to GINA and national payer recommendations to review biologic response within 4–12 months after initiation. In contrast, the UK’s National Institute for Health and Care Excellence (NICE) recommendation to review at 12 months is often misinterpreted as “must treat for 12 months”, a phenomenon that may in some instances provide another explanation for the low

rates of switching. International variation in practice was observed. We saw more switchers in South Korea (although based on low numbers), Japan, and Denmark, and a low prevalence of switchers in Spain and Bulgaria. We also saw the highest proportion of stoppers in Japan and the US, perhaps due to higher patient co-pay practices in both healthcare systems. Regional or national prescribing restrictions and local policies with regard to biologic initiation and switching are other important factors. Full exploration of these factors are beyond the scope of this study.

Some switch patterns are associated with different comorbidities. For example, individuals with chronic rhinosinusitis with nasal polyposis (CRSwNP) had the highest likelihood of switching to an anti-IL-4R agent, possibly due to early evidence that anti-IL-4R may treat CRSwNP.²¹ Additionally, switchers were more likely to have more severe disease (shown by more exacerbations and greater healthcare resource utilization [HCRU] pre-biologic) and evidence of eosinophilic disease (ie high BEC and FeNO). These individuals were likely switching from an anti-IgE to an anti-IL-5/5R or anti-IL-4R in an effort to personalize their medicine and specifically target the underlying drivers of their severe asthma.

Clinicians should be alert to factors present at baseline that are predictive of a subsequent decision to switch biologics, such as a high BEC, high exacerbation rate and high HCRU. These factors may be associated with biologic switching simply because such patients are likely to qualify for more than one drug, eg subjects commencing omalizumab who are known to have a high BEC will have the option to switch to anti-IL-5/5R therapy, and within the eosinophilic phenotype, there is scope to switch between different anti-IL-5/5R agents. Patients with one or more of these characteristics may benefit from tailored pre-biologic counselling regarding the decision to stop or switch drug, a decision which is often due to perceived insufficient clinical efficacy. Conversely, patients who were found in this study to be less likely to stop or switch biologic may benefit from increased scrutiny with regards to the clinical efficacy of their initial biologic. For example, patients are more likely to continue on their initial biologic if they have a low baseline exacerbation rate. Such individuals may not be flagged as experiencing insufficient clinical efficacy due to an ongoing low exacerbation rate following initiation of biologic therapy. This, however, does not guarantee that their initial biologic choice is the best available option for them; there is a risk of

accepting mediocre improvement when a better outcome is possible. A “treat-to-target” approach may be beneficial. In such a treatment paradigm, patients who do not reach a predefined threshold of ‘success’ (prospectively agreed between the clinician and the patient) after an appropriate trial period and who qualify for one or more alternative biologic agents, should be offered the opportunity to switch biologic. As treatment for severe asthma continues to improve, clinical remission on treatment is an aggressive treatment target that may help guide clinical decision-making.²²

The data collected in this study carry some inherent limitations. The clinical profile of ISAR patients in the intervening time between switches cannot be ascertained as patients are followed up annually, and most switches occur during the course of the first year. As such, data on clinical outcomes is limited. Further real-world studies examining clinical outcomes (eg, exacerbation rates) before and after switching from one biologic to another could potentially provide valuable information regarding any potential benefits that switching biologics may yield for individuals. The criteria used to define stopping and switching were somewhat arbitrary but we do not expect this to negatively influence the results. Future studies using time-to-event analysis might help further refine the patterns that we observed in this descriptive study.

By combining data from two sizeable registries, the large sample size and broad international representation within this study is a significant strength. Some differences between subpopulations were noted, in particular between US and non-US populations, which were likely due to differences in biologic availability and healthcare structure. Additionally, only countries with at least two biologics available as of 2018 were included in this study, to reduce the magnitude of confounding from limited biologic access. To describe the duration of use of a biologic, only biologic initiations from 2018 and after were included as all 11 countries had at least two biologics available for the treatment of severe asthma. Further studies will be needed to assess the independent impact of country of residence, healthcare structure, and biologic accessibility on varying biologic use patterns.

Conclusions

This study illustrates that the majority of patients with severe asthma continue treatment with their initial biologic. In the era of precision medicine, it is important that

we direct our most targeted therapies (ie, biologics) to the right patients, thereby ensuring the greatest possible benefits with respect to clinical and healthcare economic outcomes. Further research is needed to investigate in more detail the reasons for biologic stopping and switching and to more accurately predict those most likely to stop or switch and conversely those most likely to benefit from continuing each biologic. Additionally, real-world longitudinal evidence of outcomes following various switch patterns would help to inform appropriate clinical decisions regarding if and when to switch biologics, with the ultimate aim of ensuring that every individual receives the best available treatment at the earliest opportunity.

Abbreviations

BEC, blood eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyposis; FeNO, Fractional exhaled Nitric Oxide; GINA, Global Initiative for Asthma; HCRU, health care utilization; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-4, interleukin-4; IL4R, interleukin 4 receptor; IL-5, interleukin-5; IL5/5R, interleukin 5/5 receptor; IL-13, interleukin-13; ISAR, International Severe Asthma Registry; LABA, long-acting β 2-agonist; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid.

Data Sharing Statement

In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR steering committee (ISC) members in accordance with patient consent, patient confidentiality and ethical considerations. The study documents (protocol, statistical analysis plan, clinical study report) will be made available in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance ([EUPAS32724]). Proposals should be directed to info@isaregistries.org; to gain access, if approved by the regulatory boards data requestors will need to sign a data access agreement. Specific approval for this research study was granted by the Anonymised Data Ethics Protocols and Transparency committee (ADEPT approval reference: ADEPT1119).

Ethics Approval and Informed Consent

This study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of

Conduct (EMA 2014; EUPAS32724) and with all applicable local and international laws and regulation. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). Governance was provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (registration number: ADEPT1119). All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.

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Disclosure

Andrew N. Menzies-Gow has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis, Roche, Sanofi and Teva, and has received speaker fees from AstraZeneca, Novartis, Teva, and Sanofi. He has participated in research with AstraZeneca for which his institution has been remunerated and has attended international conferences with Teva. He has had consultancy agreements with AstraZeneca and Sanofi. Claire McBrien has attended an international conference with Boehringer Ingelheim and a national meeting with TEVA. Celeste M. Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline;

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