Pragmatic and Observational Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Real-World Biologic Use Patterns in Severe Asthma, 2015–2021: The CLEAR Study

Trung N Tran[1], Stephanie Chen[1], Benjamin Emmanuel[1], Alan Altraja[2,3], Arnaud Bourdin[4,5], Chau-Chyun Sheu[6,7], Ming-Ju Tsai[6,7], Flavia CL Hoyte[8], Anna Quinton[9], Bill Cook[1], Lakmini Bulathsinhala[10], William Henley[10,11], Celine Yun Yi Goh[10,12], Yang Liu[10], Cono Ariti[10,12], Victoria Carter[10,12], David B Price[10,12,13] On behalf of the CLEAR Study Working Group

[1]Respiratory and Immunology, BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [2]Department of Pulmonary Medicine, University of Tartu, Tartu, Estonia; [3]Lung Clinic, Tartu University Hospital, Tartu, Estonia; [4]Phymedexp, CNRS, INSERM, University of Montpellier, Montpellier, France; [5]Department of Pulmonology and Addiction, University Hospital of Montpellier, Montpellier, France; [6]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [7]Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [8]Division of Allergy and Immunology, National Jewish Health, Denver, CO, USA; [9]BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; [10]Observational and Pragmatic Research Institute, Singapore; [11]Department of Health and Community Sciences, University of Exeter Medical School, Exeter, UK; [12]Optimum Patient Care Global, Cambridge, UK; [13]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

Correspondence: David B Price, Observational and Pragmatic Research Institute, 22 Sin Ming Lane, #06 Midview City, Singapore, 573969, Tel +6531051489, Email dprice@opri.sg

**Background:** Biologics targeting immunoglobulin E, interleukin (IL)-4/IL-13 or IL-5 signaling are effective at treating severe asthma; however, individual patients' responses may be suboptimal, leading to therapy switching or stopping. The CLEAR study aimed to assess real-world biologic use patterns and associated clinical outcomes in patients receiving care for severe asthma.

**Methods:** CLEAR was a multicenter, observational study that included adults (≥18 years old) from 23 countries enrolled in the International Severe Asthma Registry between December 2015 and August 2021. Patients who initiated biologic therapy were categorized as continuing the initial biologic for 6 months, switching to another biologic within 6 months or stopping biologic treatment within 6 months. Outcomes were assessed using the closest available data to 12 months after biologic initiation, using propensity score-weighted multivariable regression models.

**Results:** Among 1,859 patients who initiated biologic therapy, 1,116 (60.0%) continued, 474 (25.5%) switched and 269 (14.5%) stopped treatment. Patients who switched or stopped therapy had a higher annualized asthma exacerbation rate post-initiation than those who continued (adjusted incidence rate ratio [aIRR] [95% confidence interval]: switched, 1.83 [1.51, 2.22]; stopped, 1.53 [1.19, 1.95]) and were more likely to have uncontrolled asthma at last assessment (adjusted odds ratio: switched, 5.40 [3.12, 9.33]; stopped, 4.02 [2.32, 6.98]). Compared with those who continued therapy, patients who switched had a higher long-term daily oral corticosteroid dose (adjusted β: 3.77 [1.71, 4.37] mg) and higher rates of hospitalizations (aIRR: 2.58 [1.52, 4.37]) and emergency room visits (aIRR: 2.12 [1.39, 3.24]).

**Conclusion:** Switching or stopping biologic therapy was associated with worse clinical outcomes than continuing the initial therapy.

**Keywords:** biologics, effectiveness, ISAR, real-world, severe asthma

## Introduction

Despite the availability of inhaled medications, biologic therapies and oral corticosteroids (OCS), severe asthma remains poorly controlled in many patients.[1] Patients with severe asthma tend to exhibit substantial bronchoconstriction with variable post-bronchodilator improvement, especially those patients with elevated biomarkers of type 2 inflammation,[2,3] and continued exacerbations contribute to lung function decline.[4] These exacerbations can be life-threatening and require substantial healthcare resource utilization (HCRU), resulting in considerable clinical, humanistic and economic burdens.[5] Additionally, even short-term use of OCS is associated with potentially life-changing adverse events (AEs) and increased HCRU.[6–9] Therefore, there is a clear unmet need for improved patient management and therapy in severe asthma.

Received: 19 September 2024
Accepted: 22 February 2025
Published: 18 March 2025

Biologics are an effective add-on treatment in many patients with severe asthma and reduce exacerbations and the need for long-term OCS (LTOCS) while improving symptom control and lung function in a real-world setting.[10–12] Most of the currently available biologics for severe asthma target specific type 2 inflammatory pathways: immunoglobulin E (IgE) with omalizumab (anti-IgE), interleukin (IL)-5 with mepolizumab, reslizumab (both anti-IL-5) or benralizumab (anti-IL-5 receptor α), or IL-4 and IL-13 with dupilumab (anti-IL-4 receptor α).[13–17] Eligibility for these therapies is based on assessment of asthma phenotype/endotype (ie, allergic or eosinophilic asthma). One exception is the anti-thymic stromal lymphopoietin biologic tezepelumab,[18] which is approved in some countries for the treatment of severe asthma without biomarker or phenotypic restrictions.[19]

It is important to direct targeted therapies, including biologics, to the patients who can benefit from them most, and a change to an alternative treatment should be considered in cases of suboptimal response to therapy.[20] Reasons for switching or stopping biologic therapy can include insufficient efficacy in terms of symptoms and/or exacerbations, the incidence of AEs, the presence of comorbidities, and economic and lifestyle factors.[21–24] An early analysis of data from the International Severe Asthma Registry (ISAR), an international registry of patients with severe asthma,[25] found that 23% of patients receiving biologics switched or stopped therapy within 6 months of initiation.[26] The most commonly reported reasons for switching/stopping therapy were lack of clinical effectiveness and AEs.[26]

Understanding the differences in clinical outcomes between patients who initiate or do not initiate biologic therapy and, among the initiators, those who subsequently continue, switch or stop their therapy, may help to guide treatment selection and ensure that every individual receives the best available treatment at the earliest opportunity.[26] To achieve this understanding, the CLEAR study was designed to build on early ISAR findings using a larger cohort of patients with recent data from more countries. CLEAR aimed to: evaluate the extent of initiating and then continuing, switching or stopping biologics among patients receiving care for severe asthma; identify any differences in patient populations associated with these patterns of biologic use (initiators; non-initiators; and initiators continuing, switching or stopping); and assess patients' experiences regarding clinical outcomes and HCRU across patterns of biologic use, from the date of biologic initiation onwards.

# Methods

## Study Design and Data Source

CLEAR was a multicenter, observational study of adults receiving treatment for severe asthma from 23 countries enrolled in ISAR between December 2015 and August 2021, with the final data extraction taking place on August 19, 2021. The ISAR aggregates and standardizes data from severe asthma registries worldwide, as described previously.[1] Only data from countries with at least two biologics licensed for the treatment of severe asthma during the study period were included in CLEAR. Tezepelumab was not included because it was not licensed at the time of data extraction.

The study was designed, implemented and reported in accordance with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance requirements (registration number EUPAS49548). Ethical governance for ISAR was provided by the Anonymised Data Ethics Protocols & Transparency Committee (approval reference number ADEPT-1021).[27] The CLEAR Study Working Group members are listed in eTable 1.

## Study Cohort

Included patients were 18 years of age or older with a diagnosis of severe asthma requiring Global Initiative for Asthma (GINA) 2018 step 5 treatment,[28] or were receiving step 4 treatment but still had uncontrolled asthma per GINA 2018 or European Respiratory Society (ERS)/ American Thoracic Society (ATS) guidelines.[29] Patients who had received bronchial thermoplasty or who were participating in a clinical trial involving an intervention were excluded. Patients must have had registry data available for at least one of the outcomes of interest for at least 12 months before the index date and for at least 6 months after the index date; the index date was the date of biologic initiation for initiators and ISAR enrollment for non-initiators.

## Assessment of Biologic Initiation and Eligibility

All included patients who had prescriptions for biologic therapies during the study period were categorized as initiators, whereas other patients were categorized as non-initiators. Non-initiators' eligibility for biologic therapy was determined according to the criteria detailed in eMethods 1.

## Assessment of Biologic Continuation, Switching and Stopping

Among initiators, treatment patterns in the 6 months after the index date were used to categorize patients into three subgroups: 'continuers', 'switchers' and 'stoppers'. Continuers were defined as those who used (ie, had prescriptions for) the initial biologic for at least 6 months without stopping or switching to a different biologic. Patients who discontinued the initial biologic temporarily and restarted within the 6-month period were categorized as continuers, regardless of the time that elapsed between stopping and restarting. Switchers were defined as those who stopped the initial biologic within 6 months of initiation and received at least one prescription for a different biologic within the 6 months. There was no restriction on the length of time that elapsed between stopping the initial biologic and starting the different biologic. Patients were still categorized as switchers if they discontinued a biologic to which they had switched in the 6 months. Stoppers were defined as those who stopped the initial biologic within 6 months of initiation and did not receive a different biologic within the 6 months.

The 6-month window for assessment of biologic response was in alignment with ERS/ATS and GINA 2021 guideline recommendations that biologics be trialed for at least 4 months.[29,30]

## Outcomes

The primary outcome was the annualized asthma exacerbation rate (AAER); time to first exacerbation was also assessed. Secondary outcomes were asthma control (controlled, partly controlled or uncontrolled according to the GINA 2018 asthma control criteria, Asthma Control Questionnaire-6 or Asthma Control Test), change in daily LTOCS dose (assessed from patients' cumulative total dose of OCS, calculated as label dose × frequency per day × duration of use; minimum 3 months' consecutive daily use at any dose) and emergency HCRU (annualized numbers of hospitalizations and emergency room [ER] visits). Further details of variable definitions are provided in eTables 2 and 3.

Outcomes were assessed at baseline (ie, before biologic therapy for initiators) using data taken from the 12-month period before the index date, and were assessed at follow-up (ie, after biologic initiation for initiators [including continuers, switchers and stoppers]) using the closest available data to 12 months after the index date. The data entries analyzed corresponded to whichever visits the individual patients had made; other than a minimum follow-up of 6 months, there was no requirement for a number or frequency of visits after the index date. Depending upon the visit dates, the duration of follow-up varied between individual patients, as did the duration of time between stopping or switching and follow-up outcome assessment; follow-up outcomes could be assessed both before and after the date of switching/stopping.

## Statistical Analyses

Comparisons of baseline characteristics and of outcomes during follow-up were performed between initiators and non-initiators and between continuers, switchers and stoppers. Before assessment of follow-up outcomes, inverse probability of treatment weighting (IPTW) using the propensity score was used to correct for baseline imbalances between initiators and non-initiators, as well as between continuers, switchers and stoppers. The factors included in the propensity score model for IPTW were sex, age at index date, LTOCS use, body mass index at index date, asthma control at index date, age of asthma onset, smoking status, pre-index date asthma exacerbations and pre-index date values of the other outcomes considered; inclusion of age at index date and age at asthma onset as factors in the model allowed differences in cohort index dates between initiators and non-initiators to be accounted for. A doubly robust approach to controlling for confounding was used when assessing outcome comparisons, in which IPTW was augmented with multivariable adjustment of the regression models for baseline levels of the outcome and other confounders. A sensitivity analysis of the outcome estimates was performed to account for clustering by country. Further details of the statistical methods used are provided in eMethods 2.

# Results

## Patients and Patterns of Biologic Use

In total, 3,404 patients were eligible for CLEAR, of whom 1,859 (54.6%) initiated biologic therapy (Figure 1). Among the initiators, 1,116 (60.0%), 474 (25.5%) and 269 (14.5%) continued, switched and stopped treatment, respectively. Approximately half of biologic initiators in CLEAR were from the UK (24.4%) and USA (24.3%); in the USA, biologic stopping and switching

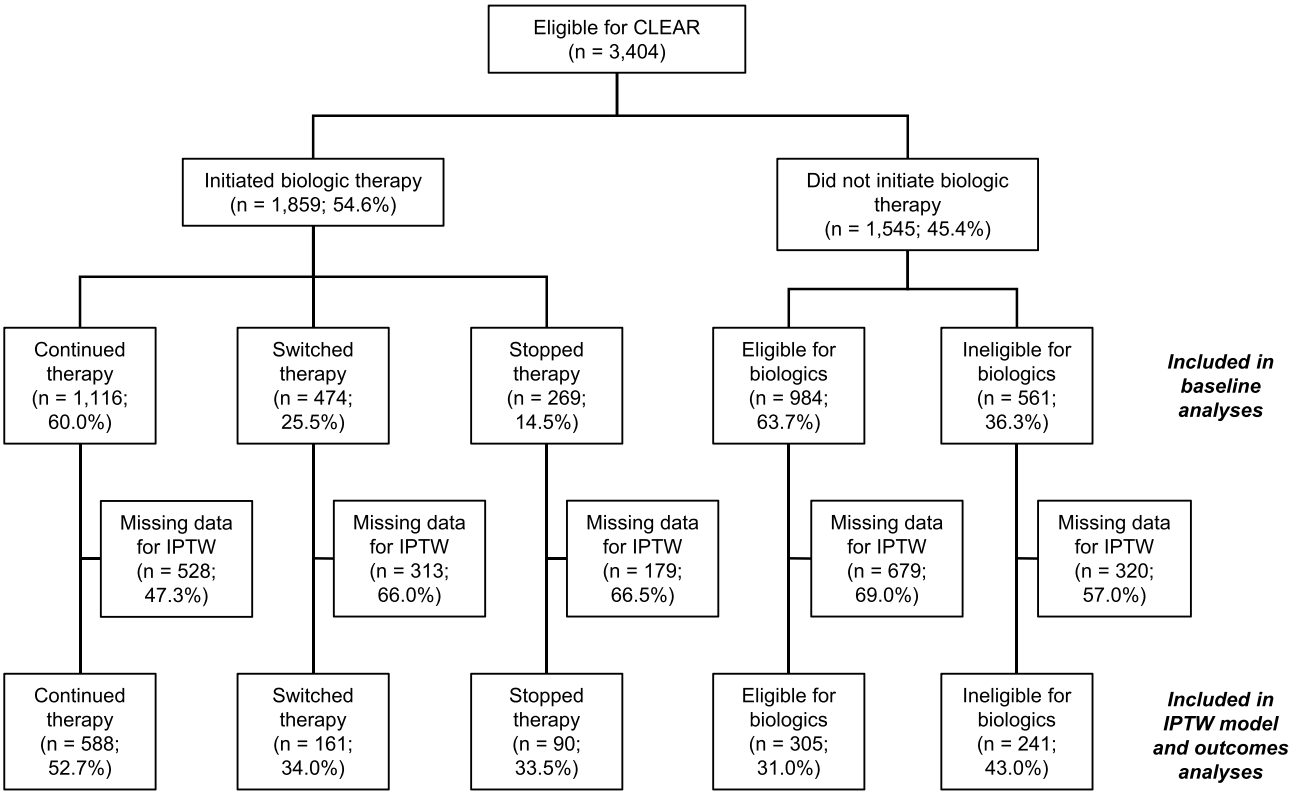


**Figure 1** Study population and subgroups included in the baseline analyses (before IPTW) and outcomes analyses (after IPTW).
**Abbreviation**: IPTW, inverse probability of treatment weighting.

were more common than continuing (in contrast to most other countries; eTable 4). Among the 1,545 non-initiators, 984 (63.7%) were considered eligible for therapy with the included biologics (Figure 1). Approximately half to two-thirds (47.3–69.0%) of patients across subgroups were missing the necessary data to be included in the IPTW model and outcomes analyses (Figure 1). The median duration of follow-up (approximately 1 year) was similar across all subgroups (Table 1).

**Table 1** Baseline Demographics and Characteristics of Biologic Use Subgroups Before IPTW

| Demographic/Characteristic | Initiators (N = 1,859) | Non-Initiators (N = 1,545) | *P* value† | Continuers (N = 1,116) | Switchers (N = 474) | Stoppers (N = 269) | *P* value‡ |
|---|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | | |
| N | 1,859 | 1,545 | 0.001 | 1,116 | 474 | 269 | 0.297 |
| Female | 1,122 (60.4) | 1,018 (65.9) | | 687 (61.6) | 272 (57.4) | 163 (60.6) | |
| Age at index date,* years, n (%) | | | | | | | |
| N | 1,859 | 1,545 | < 0.001 | 1,116 | 474 | 269 | 0.088 |
| 18–45 | 527 (28.3) | 367 (23.8) | | 286 (25.6) | 155 (32.7) | 86 (32.0) | |
| 46–55 | 502 (27.0) | 308 (19.9) | | 315 (28.2) | 118 (24.9) | 69 (25.7) | |
| 56–65 | 479 (25.8) | 411 (26.6) | | 292 (26.2) | 121 (25.5) | 66 (24.5) | |
| >65 | 351 (18.9) | 459 (29.7) | | 223 (20.0) | 80 (16.9) | 48 (17.8) | |
| Age at onset of asthma, years | | | | | | | |
| N | 1,246 | 610 | 0.108 | 866 | 275 | 105 | 0.135 |
| Mean ± SD | 28.5 ± 18.8 | 30.1 ± 21.1 | | 29.4 ± 18.4 | 25.8 ± 18.6 | 28.7 ± 21.2 | |

(*Continued*)

**Table 1** (Continued).

| Demographic/Characteristic | Initiators (N = 1,859) | Non-Initiators (N = 1,545) | *P* value† | Continuers (N = 1,116) | Switchers (N = 474) | Stoppers (N = 269) | *P* value‡ |
|---|---|---|---|---|---|---|---|
| BMI at index date,* kg/m$^2$ | | | | | | | |
| N | 1,671 | 1,474 | 0.03 | 992 | 416 | 263 | 0.297 |
| Mean ± SD | 29.1 ± 6.6 | 29.6 ± 7.2 | | 28.9 ± 6.6 | 29.1 ± 6.3 | 30.0 ± 7.3 | |
| Asthma control at index date,* n (%) | | | | | | | |
| N | 1,199 | 1,452 | < 0.001 | 789 | 251 | 159 | < 0.001 |
| Uncontrolled | 808 (67.4) | 434 (29.9) | | 533 (70.1) | 168 (66.9) | 87 (54.7) | |
| Partially controlled | 164 (13.7) | 221 (15.2) | | 131 (16.6) | 22 (8.8) | 11 (6.9) | |
| Well controlled | 227 (18.9) | 797 (54.9) | | 105 (13.3) | 61 (24.3) | 61 (38.4) | |
| Smoking status, n (%) | | | | | | | |
| N | 1,609 | 1,395 | < 0.001 | 979 | 382 | 248 | 0.098 |
| Current smoker | 39 (2.4) | 85 (6.1) | | 17 (1.7) | 15 (3.9) | 7 (2.8) | |
| Ex-smoker | 436 (27.1) | 492 (35.3) | | 271 (27.7) | 107 (28.0) | 58 (23.4) | |
| Non-smoker | 1,134 (70.5) | 818 (58.6) | | 691 (70.6) | 260 (68.1) | 183 (73.8) | |
| Asthma exacerbations in the Previous 12 months, n (%) | | | | | | | |
| N | 1,341 | 621 | < 0.001 | 938 | 297 | 106 | 0.374 |
| 0 | 158 (11.8) | 114 (18.4) | | 116 (12.4) | 31 (10.4) | 11 (10.4) | |
| 1 | 185 (13.8) | 194 (31.2) | | 127 (13.5) | 46 (15.5) | 12 (11.3) | |
| 2 | 167 (12.5) | 70 (11.3) | | 126 (13.4) | 34 (11.5) | 7 (6.6) | |
| 3 | 174 (13.0) | 72 (11.6) | | 123 (13.1) | 39 (13.1) | 12 (11.3) | |
| 4 | 149 (11.1) | 57 (9.2) | | 107 (11.4) | 29 (9.8) | 13 (12.3) | |
| ≥5 | 508 (37.9) | 114 (18.4) | | 339 (36.1) | 118 (39.7) | 51 (48.1) | |
| Receiving LTOCS | | | | | | | |
| N | 1,859 | 1,537 | 0.176 | 938 | 297 | 106 | < 0.001 |
| n (%) | 890 (47.9) | 701 (45.6) | | 538 (57.4) | 104 (35.0) | 57 (53.8) | |
| Duration of follow-up, days, median (IQR) | 370 (173) | 365 (2) | < 0.001 | 378 (231) | 371 (138) | 365 (55) | 0.403 |
| Blood eosinophil count, cells/μL | | | | | | | |
| N | 1,671 | 1,216 | < 0.001 | 1,005 | 433 | 233 | 0.007 |
| Median (IQR) | 300 (480) | 200 (260) | | 340 (480) | 300 (510) | 300 (400) | |
| FeNO, ppb | | | | | | | |
| N | 1,159 | 544 | < 0.001 | 691 | 313 | 155 | 0.001 |
| Median (IQR) | 35 (49) | 22 (32) | | 33 (44) | 42 (53) | 30 (53) | |
| Serum total IgE, IU/mL | | | | | | | |
| N | 1,476 | 893 | < 0.001 | 904 | 367 | 205 | 0.105 |
| Median (IQR) | 191 (428) | 63 (229) | | 185 (411) | 197 (519) | 238 (390) | |

**Notes**: *For initiators, this was biologic initiation; for non-initiators, this was at the time of study enrollment. †Comparing initiators and non-initiators. ‡Comparing continuers, switchers and stoppers.

**Abbreviation**: BMI, body mass index; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LTOCS, long-term oral corticosteroids; SD, standard deviation.

## Baseline Demographics and Characteristics According to Patterns of Biologic Use

At baseline, biologic initiators were more likely than non-initiators to have uncontrolled asthma ($P < 0.001$) and were less likely to be current or ex-smokers ($P < 0.001$; Table 1). Initiators were also younger ($P < 0.001$) and had more exacerbations in the previous 12 months ($P < 0.001$) than non-initiators. Furthermore, initiators had higher baseline blood eosinophil counts ($P < 0.001$), fractional exhaled nitric oxide (FeNO) levels ($P < 0.001$) and serum total IgE levels ($P < 0.001$) than non-initiators.

Among biologic initiators, continuers were more likely than switchers or stoppers to have uncontrolled or partially controlled asthma at baseline ($P < 0.001$ for both comparisons; Table 1). Compared with switchers, continuers were less likely to have had a hospital admission ($P < 0.001$). Compared with stoppers, continuers were more likely to have negative allergen tests ($P < 0.001$), to have made ER visits ($P < 0.001$) and to have had hospital admissions ($P < 0.001$) and were less likely to be obese (BMI ≥30 kg/m$^2$; $P < 0.001$). Switchers had higher FeNO levels at baseline than continuers or stoppers ($P = 0.001$) and were less likely to be receiving LTOCS ($P < 0.001$; Table 1).

Before analyzing patient outcomes, IPTW was performed separately for the comparison of initiators and non-initiators and for the comparison of continuers, switchers and stoppers, resulting in more balanced baseline demographics and clinical characteristics (Table 2). After IPTW, all standardized mean differences between these variables were found to be less than 10% for initiators versus non-initiators, for continuers versus switchers and for continuers versus stoppers (eTables 5 and 6).

**Table 2** Baseline Demographics and Characteristics of Biologic Use Subgroups After IPTW

| Demographic/Characteristic | Initiators (N = 683) | Non-Initiators (N = 703) | *P* value† | Continuers (N = 283) | Switchers (N = 254) | Stoppers (N = 303) | *P* value‡ |
|---|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | | |
| Female | 445 (65.2) | 462 (65.7) | 0.856 | 185 (65.5) | 162 (63.8) | 192 (63.3) | 0.904 |
| Age at index date,* years, n (%) | | | | | | | |
| 18–45 | 191 (28.0) | 240 (34.2) | 0.119 | 91 (32.3) | 85 (33.6) | 90 (29.8) | 0.621 |
| 46–55 | 195 (28.6) | 165 (23.5) | | 88 (31.2) | 74 (29.3) | 106 (34.9) | |
| 56–65 | 175 (25.7) | 170 (24.1) | | 66 (23.2) | 76 (30.0) | 73 (24.0) | |
| >65 | 120 (17.7) | 128 (18.2) | | 38 (13.3) | 18 (7.1) | 34 (11.4) | |
| Age at onset of asthma, years, mean ± SD | 29.6 ± 20.3 | 28.1 ± 17.6 | 0.205 | 28.1 ± 25.1 | 26.3 ± 14.2 | 29.5 ± 11.6 | 0.510 |
| BMI at index date,* mean ± SD | 29.3 ± 7.4 | 29.8 ± 6.4 | 0.316 | 29.8 ± 10.1 | 29.5 ± 5.1 | 30.1 ± 3.3 | 0.772 |
| Asthma control at index date,* n (%) | | | | | | | |
| Uncontrolled | 460 (67.4) | 496 (70.6) | 0.508 | 218 (76.9) | 211 (83.3) | 213 (70.2) | 0.152 |
| Partially controlled | 147 (21.6) | 136 (19.3) | | 43 (15.2) | 26 (10.1) | 39 (13.0) | |
| Well controlled | 75 (11.0) | 71 (10.1) | | 22 (7.9) | 17 (6.6) | 51 (16.8) | |
| Smoking status, n (%) | | | | | | | |
| Current smoker | 20 (2.9) | 31 (4.4) | 0.105 | 5 (1.6) | 7 (2.6) | 20 (6.6) | 0.369 |
| Ex-smoker | 194 (28.4) | 164 (23.3) | | 68 (23.9) | 56 (22.3) | 55 (16.7) | |
| Non-smoker | 468 (68.7) | 508 (72.3) | | 211 (74.5) | 190 (75.1) | 228 (75.4) | |
| Asthma exacerbations in the previous 12 months, n (%) | | | | | | | |
| 0 | 114 (16.7) | 69 (9.9) | 0.012 | 31 (11.0) | 22 (8.7) | 47 (15.7) | 0.219 |
| 1 | 112 (16.4) | 145 (20.6) | | 35 (12.3) | 27 (10.5) | 64 (21.1) | |
| 2 | 74 (10.8) | 73 (10.4) | | 27 (9.4) | 21 (8.3) | 10 (3.1) | |
| 3 | 81 (11.9) | 90 (12.8) | | 33 (11.8) | 38 (15.1) | 33 (11.0) | |
| 4 | 69 (10.1) | 92 (13.2) | | 33 (11.6) | 30 (11.7) | 30 (9.8) | |
| ≥5 | 233 (34.2) | 234 (33.2) | | 124 (43.9) | 116 (45.8) | 119 (39.4) | |
| Receiving LTOCS, n (%) | 402 (58.9) | 439 (62.4) | 0.293 | 143 (50.4) | 128 (50.5) | 173 (57.2) | 0.455 |

**Notes**: IPTW weights were scaled to give the overall total number of patients after excluding those with missing data for IPTW propensity score modeling; the IPTW approach creates a pseudo-population that does not constrain the relative sample sizes of the subgroups to match their equivalents before IPTW. *For initiators, this was biologic initiation; for non-initiators, this was at the time of study enrollment. †Comparing initiators and non-initiators. ‡Comparing continuers, switchers and stoppers.
**Abbreviations**: BMI, body mass index; IPTW, inverse probability of treatment weighting; LTOCS, long-term oral corticosteroids; SD, standard deviation.

## Outcomes Among Biologic Initiators and Non-Initiators

### Asthma Exacerbations

Initiators had a lower AAER during the follow-up period than non-initiators (adjusted incidence rate ratio [IRR]: 0.76 [95% confidence interval (CI): 0.65, 0.88]; Table 3), with a mean (standard deviation [SD]) AAER of 1.6 (2.9) for initiators and 2.1 (3.5) for non-initiators (eTable 7; see eTables 8 and 9 for the full multivariable model results of this analysis). The proportion of patients who experienced at least one exacerbation (annualized count) during the follow-up period was 54.1% for initiators and 66.5% for non-initiators (Figure 2A; baseline period data are shown in eFigure 1). Biologic initiators had a longer time to first exacerbation than non-initiators (hazard ratio [HR]: 0.39 [95% CI: 0.33, 0.47]; Table 3).

### Asthma Control

Initiators were less likely to have uncontrolled asthma during the follow-up period than non-initiators (adjusted odds ratio: 0.76 [95% CI: 0.55, 1.06]; Table 3). The proportion of patients with uncontrolled asthma at last assessment during follow-up was 35.6% for initiators and 41.0% for non-initiators (Figure 2B).

### LTOCS Dose

The mean (SD) daily LTOCS dose during the follow-up period was 7.8 (10.0) mg for initiators and 9.5 (8.8) mg for non-initiators (baseline: initiators, 13.0 (9.8) mg; non-initiators, 11.6 (7.2) mg; eTable 7). Initiators had a greater reduction in daily LTOCS dose between baseline and follow-up than non-initiators (adjusted β: −2.73 mg [95% CI: −4.77, −0.68]; Table 3).

### HCRU

There were no substantive differences between initiators and non-initiators in rates of hospitalizations (adjusted IRR: 0.81 [95% CI: 0.51, 1.28]) or ER visits (adjusted IRR: 1.19 [95% CI: 0.82, 1.61]) during the follow-up period (Table 3). The annualized mean (SD) number of hospitalizations was 0.2 (0.9) for initiators and 0.2 (0.6) for non-initiators, whereas for ER visits this was 0.4 (2.1) for initiators and 0.3 (1.2) for non-initiators (eTable 7). In total, 8.6% of initiators and 11.7% of non-initiators

**Table 3** Clinical Outcomes (Crude and Adjusted) During the Follow-up Period of Biologic Use Subgroups After IPTW

| Outcome | Initiators vs Non-Initiators | | Switchers vs Continuers | | Stoppers vs Continuers | |
|---|---|---|---|---|---|---|
| | Crude | Adjusted | Crude | Adjusted | Crude | Adjusted |
| AAER | IRR: 0.99 (0.86, 1.13) | aIRR: 0.76 (0.65, 0.88) | IRR: 2.29 (1.86, 2.81) | aIRR: 1.83 (1.51, 2.22) | IRR: 1.64 (1.24, 2.17) | aIRR: 1.53 (1.19, 1.95) |
| Time to first asthma exacerbation* | HR: 0.69 (0.62, 0.76) | HR: 0.39 (0.33, 0.47) | HR: 1.69 (1.46, 1.96) | HR: 1.68 (1.34, 2.10) | HR: 1.76 (1.47, 2.12) | HR: 1.52 (1.13, 2.03) |
| Asthma control (uncontrolled asthma)† | OR: 2.46 (2.05, 2.95) | aOR: 0.76 (0.55, 1.06) | OR: 3.10 (2.23, 4.09) | aOR: 5.40 (3.12, 9.33) | OR: 1.50 (1.05, 2.15) | aOR: 4.02 (2.32, 6.98) |
| Change in daily LTOCS dose between baseline and follow-up, mg‡ | β: −5.21 (−6.95, −3.97) | aβ: −2.73 (−4.77, −0.68) | β: 1.96 (−0.25, 4.17) | aβ: 3.77 (1.71, 4.37) | β: −2.12 (−5.02, 0.78) | aβ: 3.09 (−0.27, 6.45) |
| Number of hospitalizations (annualized) | IRR: 1.11 (0.75, 1.62) | aIRR: 0.81 (0.51, 1.28) | IRR: 3.33 (2.09, 5.29) | aIRR: 2.58 (1.52, 4.37) | IRR: 2.81 (1.36, 5.78) | aIRR: 1.20 (0.59, 2.42) |
| Number of ER visits (annualized) | IRR: 1.42 (1.01, 2.01) | aIRR: 1.19 (0.82, 1.61) | IRR: 2.48 (1.65, 3.72) | aIRR: 2.12 (1.39, 3.24) | IRR: 1.97 (1.03, 3.77) | aIRR: 1.10 (0.60, 2.01) |

**Notes**: All outcome values are accompanied by 95% confidence intervals in parentheses. In the adjusted analyses, additional covariates were included (details in the Online Supplement). *An HR of less than 1 indicates a longer time to first exacerbation (and *vice versa*). †Asthma control (according to the GINA 2018 asthma control criteria, Asthma Control Questionnaire-6 or Asthma Control Test) at the last available assessment; the OR is for having uncontrolled asthma. ‡Assessed from patients' cumulative total dose of OCS, calculated as label dose × frequency per day × duration of use; minimum of 3 months' consecutive daily OCS use (any dose); β is the difference between groups in change in daily LTOCS dose.

**Abbreviations**: AAER, annualized asthma exacerbation rate; β, beta coefficient; aβ, adjusted beta coefficient; aIRR, adjusted incidence rate ratio; aOR, adjusted odds ratio; ER, emergency room; GINA, Global Initiative for Asthma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; LTOCS, long-term oral corticosteroid; OR, odds ratio.

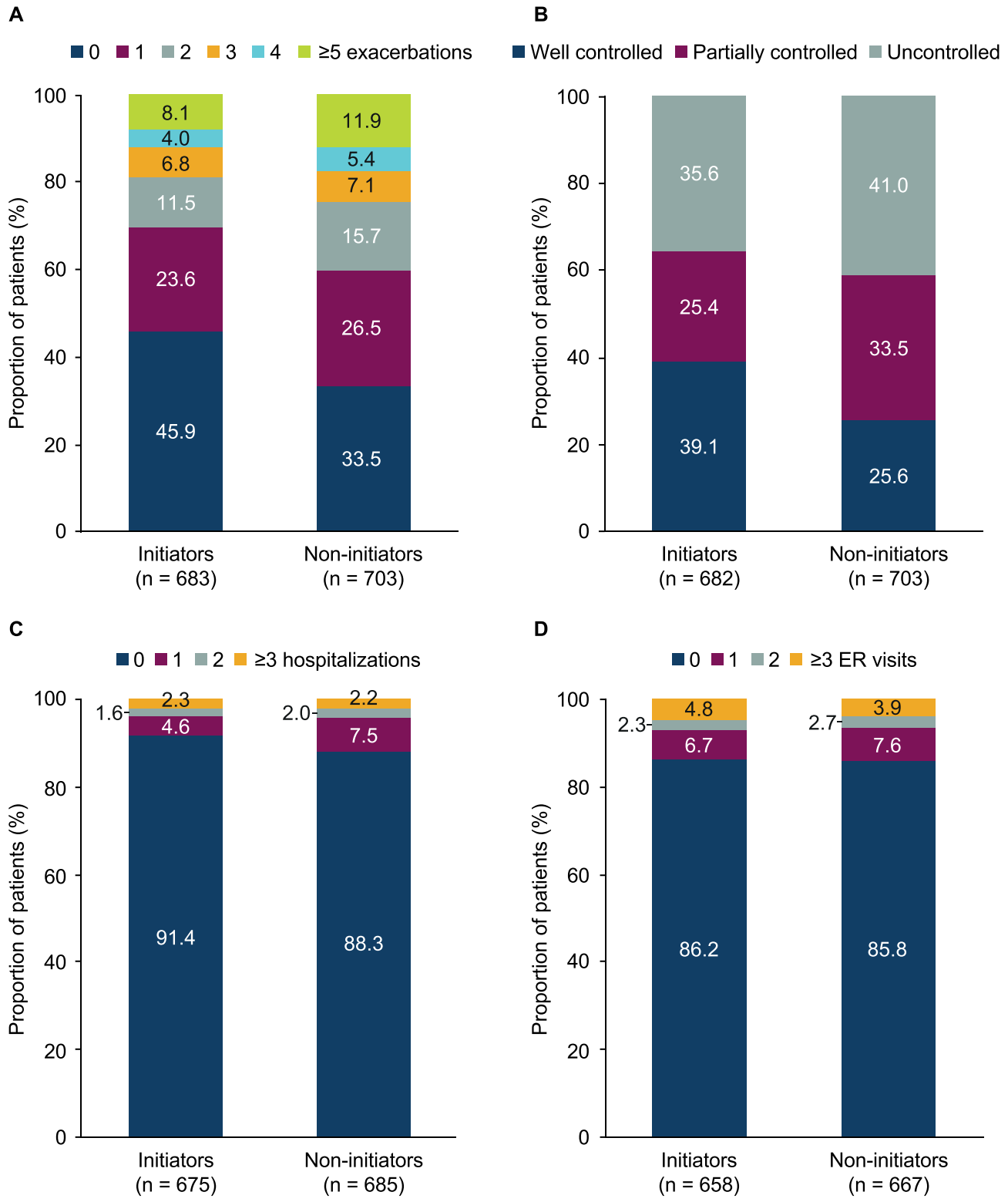


**Figure 2** Exacerbations (**A**), asthma control (**B**), hospitalizations (**C**) and ER visits (**D**) during the follow-up period among biologic initiators and non-initiators after IPTW. Exacerbations, hospitalizations and ER visits are annualized numbers. Asthma control is last available assessment.
**Abbreviations**: ER, emergency room; IPTW, inverse probability of treatment weighting.


https://doi.org/10.2147/POR.S497033

experienced at least one hospitalization (annualized count) during the follow-up period (Figure 2C), whereas 13.8% of initiators and 14.2% of non-initiators experienced at least one ER visit (annualized count; Figure 2D).

## Outcomes Among Biologic Initiators Who Continued, Switched or Stopped Therapy

### Asthma Exacerbations

Patients who switched or stopped biologic therapy had a higher AAER during the follow-up period than those who continued therapy (adjusted IRR of 1.83 [95% CI: 1.51, 2.22] for switchers relative to continuers and 1.53 [95% CI: 1.19, 1.95] for stoppers relative to continuers; Table 3). The mean (SD) AAER during follow-up was 1.4 (2.7) for continuers, 2.5 (2.9) for switchers and 2.0 (2.4) for stoppers (eTable 7). The proportion of patients who experienced at least one exacerbation during the follow-up period was 52.7% for continuers, 84.0% for switchers and 61.4% for stoppers (Figure 3A; baseline period data are shown in eFigure 2). Compared with continuers, both switchers (HR: 2.59 [95% CI: 1.57, 4.27]) and stoppers (HR: 2.12 [95% CI: 1.11, 4.04]) had a shorter time to first exacerbation (Table 3).

### Asthma Control

Switchers and stoppers were more likely to have uncontrolled asthma after therapy initiation than continuers (switchers versus continuers adjusted OR: 5.40 [95% CI: 3.12, 9.33]; stoppers versus continuers adjusted OR: 4.02 [95% CI: 2.32, 6.98]; Table 3). The proportion of patients with uncontrolled asthma at last assessment during the follow-up period was 33.3% for continuers, 67.1% for switchers and 50.1% for stoppers (Figure 3B).

### LTOCS Dose

The mean (SD) daily LTOCS dose during the follow-up period was 6.2 (8.7) mg for continuers, 11.1 (11.4) mg for switchers and 10.8 (12.5) mg for stoppers (baseline: continuers, 12.2 (8.4) mg; switchers, 14.4 (10.8) mg; stoppers, 15.0 (13.1) mg; eTable 7). The reduction in daily LTOCS dose between baseline and follow-up was smaller for switchers and stoppers than for continuers (adjusted β: 3.77 mg [95% CI: 1.71, 4.37] and 3.09 mg [95% CI: −0.27, 6.45] for switchers and stoppers, respectively, versus continuers; Table 3). The proportion of patients whose daily LTOCS dose was 5 mg or less during follow-up was highest in continuers. Continuers and stoppers were more likely than switchers to halt OCS treatment (eTable 7).

### HCRU

Switchers had a higher rate of hospitalizations and ER visits during the follow-up period than continuers (adjusted IRR [95% CI]: hospitalizations, 2.58 [1.52, 4.37]; ER visits, 2.12 [1.39, 3.24]); there was no substantive difference between stoppers and continuers (adjusted IRR [95% CI]: hospitalizations, 1.20 [0.59, 2.42]; ER visits, 1.10 [0.60, 2.01]; Table 3). The annualized mean (SD) number of hospitalizations during the follow-up period was 0.1 (0.5) for continuers, 0.5 (1.6) for switchers and 0.3 (1.1) for stoppers, whereas for ER visits this was 0.3 (1.1) for continuers, 1.3 (3.9) for switchers and 0.4 (1.7) for stoppers (eTable 7). In total, 7.5% of continuers, 18.8% of switchers and 12.2% of stoppers experienced at least one hospitalization (annualized count) during the follow-up period (Figure 3C), whereas 11.9% of continuers, 28.3% of switchers and 17.2% of stoppers experienced at least one ER visit (annualized count; Figure 3D).

## Sensitivity Analysis

Accounting for clustering by country did not lead to substantive changes in the comparisons of outcomes for biologic continuers, stoppers and switchers (eTable 10).

# Discussion

During the CLEAR study period, just over half of patients receiving care for severe asthma initiated biologic therapy targeting IgE, IL-5 or IL-4/IL-13 signaling; these patients had fewer exacerbations and lower LTOCS use during follow-up than non-initiators and were less likely to have uncontrolled asthma. Approximately two-thirds of non-initiators in CLEAR were eligible for biologic therapy. Among biologic initiators, 40% switched or stopped treatment during the first 6 months, whereas 60% continued using the same biologic for at least 6 months. At baseline, continuers had lower asthma control than stoppers or switchers, higher rates of HCRU than stoppers and were more likely to be receiving LTOCS than switchers. After biologic initiation, continuers had fewer exacerbations, lower LTOCS use and were less

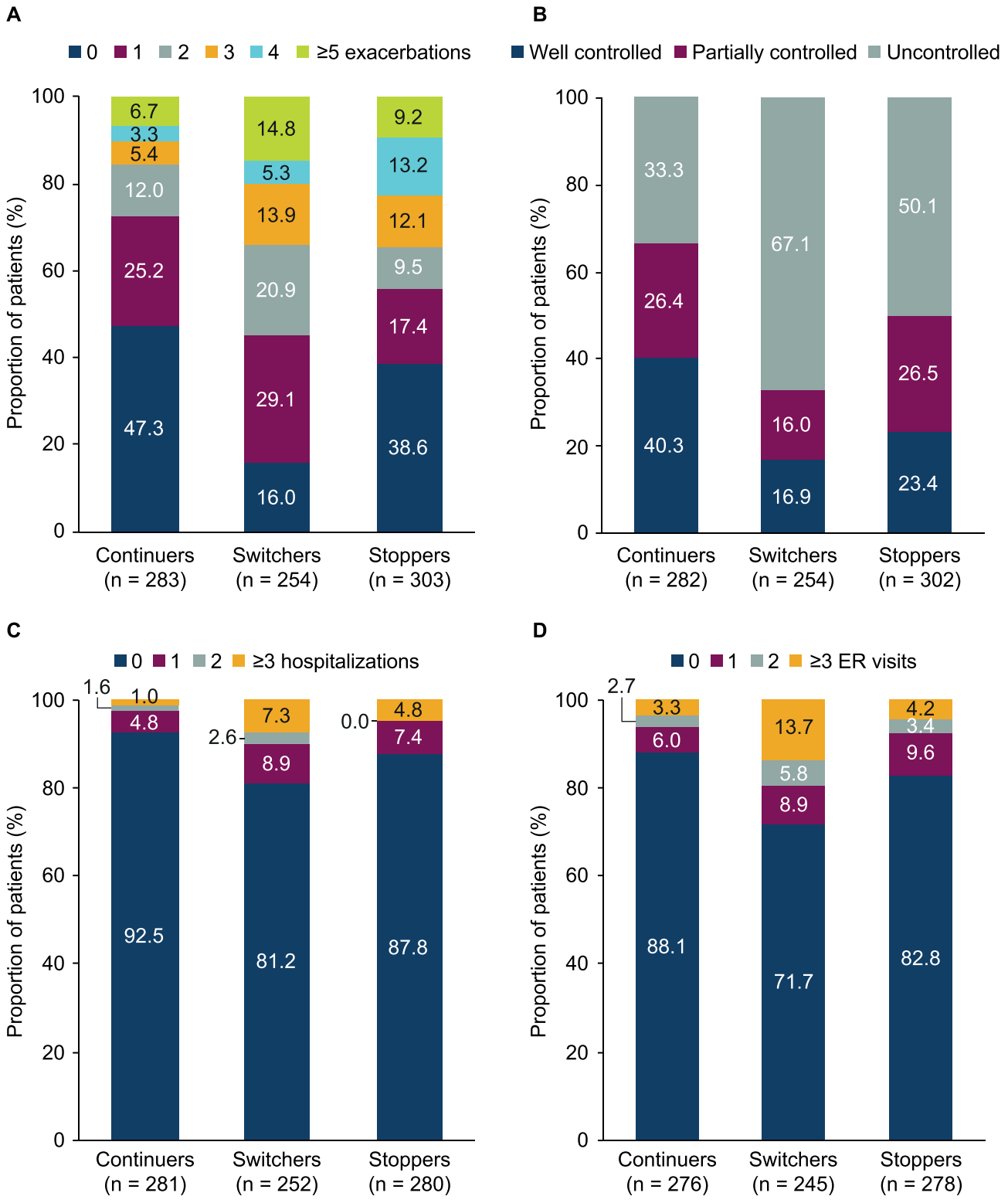


**Figure 3** Exacerbations (**A**), asthma control (**B**), hospitalizations (**C**) and ER visits (**D**) during the follow-up period among biologic continuers, switchers and stoppers after IPTW. Exacerbations, hospitalizations and ER visits are annualized numbers. Asthma control is last available assessment.
**Abbreviations**: ER, emergency room; IPTW, inverse probability of treatment weighting.


https://doi.org/10.2147/POR.S497033

likely to have uncontrolled asthma than switchers or stoppers; continuers also had lower rates of HCRU than switchers. However, there was considerable remaining unmet need in all patient subgroups.

The improved clinical outcomes in biologic initiators compared with non-initiators observed in this study provides further evidence of the real-life effectiveness of biologic treatment and suggests that patients who qualify for but are not currently receiving biologics could benefit from these therapies. However, as shown here and previously,[11,31–33] a significant proportion of patients who meet the respective biologic eligibility criteria do not receive these treatments. Research has shown that key patient-reported barriers to initiating biologic therapy are the potential for side-effects and the mode of administration (eg receiving an injection), as well as cost, time commitment, scheduling inconvenience and delayed onset of therapeutic effect.[34] Reimbursement criteria may hinder access to biologic therapy, causing patients to delay initiation or cease therapy.[35] Clinical factors, including the lack of biomarker test availability to assess eligibility and the administrative burden of obtaining insurance approval, can also affect access to biologic therapy.[34] These factors may have influenced the results of CLEAR, given that the mean age of patients initiating treatment was approximately 50 years old. There is some evidence that the effect of biologics is weaker for patients who have a longer duration of asthma,[36] suggesting that delaying initiation may have long-term detrimental effects on airway remodeling and lung function, emphasizing the need for prompt access to these therapies.

The proportions of patients who continued, switched and stopped biologic therapy in CLEAR were largely consistent with the earlier SUNNIE real-world study of patients with severe asthma in the ISAR and CHRONICLE databases.[26] In SUNNIE, 79% of patients with severe asthma continued biologic therapy, whereas 11% switched and 10% stopped within 6 months of initiation.[26] The proportion of switchers and stoppers in CLEAR was higher, particularly in the USA (switchers, 39.2%; stoppers, 36.1%), which may reflect recent practice changes and greater access to recently approved biologics leading to more treatment options. This may also reflect patients who were prescribed a biologic which was not covered by their insurance plan, so were subsequently prescribed a different biologic or not prescribed any further biologics. Given a longer duration of follow-up the proportion of switchers may well have been higher, as seen in a real-world German study evaluating data from 2010–2021 in which 44% of patients switched biologic at least once during the study period.[22] Switch patterns between/within individual biologic classes were not assessed here, but in the SUNNIE study the most common first switch was from omalizumab to (or, rarely, combined with) an anti–IL-5/5R (49.6%) and the second most common was within class, adding or switching from one anti–IL-5/5R to another (30.8%).[26] In both CLEAR and SUNNIE, participants who switched biologic had higher FeNO levels at baseline than those who continued on their original biologic. This may indicate that the airway inflammation of switchers was driven relatively more by IL-13 signaling than continuers, so these patients were more likely to have a weaker response to anti-IL-5/5R/IgE (if this was their initial biologic) and so need to switch therapy. Higher FeNO levels would also suggest that switchers were more likely to be eligible for anti-IL-4/13 than continuers, providing more switching options.

Among CLEAR participants, continuing the initial biologic treatment was associated with improvements in several clinical outcomes compared with switching or stopping, with continuers having fewer exacerbations, longer time to first exacerbation, better asthma control and lower LTOCS use than switchers and stoppers. It is likely that patients with better asthma control did not see a need to switch or stop, and the patients who switched or stopped self-selected the decision due to unsatisfactory disease control. Furthermore, because continuers had lower asthma control than stoppers or switchers at baseline, continuers may have had greater room for improvement and therefore a greater likelihood of response to biologic treatment (at least regarding asthma control).[37] Outcomes also appeared to be improved in stoppers compared with switchers, potentially reflecting those patients whose disease improved following biologic therapy initiation and so were later able to cease therapy compared with those whose disease did not respond well to the initial biologic and had to switch. It should be noted that CLEAR assessed outcomes from the point of biologic initiation onwards rather than from the point of switching or stopping. Evidence from other studies suggests that asthma control and other outcomes can improve after switching biologic therapy.[21–24] Biologic discontinuation may be associated with worsening outcomes but can be considered in certain scenarios.[23,24,38]

Factors that may have limited treatment effectiveness and led patients to switch or stop therapy could include incorrect phenotyping, comorbidities (despite clinicians' efforts to control them) such as sleep apnea, obesity, gastro-esophageal reflux disease, chronic rhinosinusitis with nasal polyps or intermittent laryngeal obstruction, psychological

factors, and poor adherence.[39] The reasons for switching or stopping therapy in CLEAR were not assessed, but the most commonly reported reasons in the SUNNIE study were lack of clinical effectiveness (86.3% and 63.7% of patients who switched and stopped, respectively) and AEs (7.7% and 15.9% of patients who switched and stopped, respectively).[26] Similarly, the most common reasons for the initial biologic switch in the German study noted above were insufficient efficacy (57%), AEs (20%) and comorbidity treatment (17%).[22] Further reasons for switching in CLEAR could include ambiguous patient phenotype leading to suboptimal initial biologic choice; physician decision based on experience; changes in treatment access criteria; limited biologic options; or changes in or access to biomarker tests or other means of assessment.[40] Although switching biologics should be considered if clinical outcomes are not optimal,[20] the optimal time to switch biologic therapy and the treatment period to determine effectiveness are unknown.[41,42]

Despite at least 6 months' continuous therapy, there was considerable remaining unmet need among the biologic continuers, with over half experiencing at least one exacerbation during approximately 12 months follow-up after starting biologic therapy and one-third still having uncontrolled asthma at the end of that timeframe. This suggests that some patients may not have been prescribed the optimal therapy, and switching may have been worthwhile, or that earlier initiation of therapy would have been more beneficial; however, it is also possible that these patients would not have responded to any of the biologics studied here. The heterogeneity of severe asthma results in many patients having disease mechanisms that are not well-treated by currently available biologics. Furthermore, comorbidities that influence symptoms and signs shared by asthma could limit the effectiveness of asthma treatment.[39]

Biologic therapy selection should be personalized for each patient to improve outcomes and reduce costs,[40] but the lack of comparative studies between biologics (despite one exception)[12] means there is no fully clear guidance on which biologic to use in which patient. Most biologic therapies require accurate phenotyping of patients based on biomarkers. However, phenotyping is complicated by the uncertain stability of biomarker measurements over time[43] and the considerable overlap in positivity for inflammatory biomarkers in patients with severe asthma, resulting in eligibility for multiple biologics.[44] Further research is required to determine how to adequately predict and assess patient response to biologic treatment.[36] Appropriate biologic selection is also confounded by variations in licensed indications and reimbursement policies between countries.[35] The introduction of biologics with less restrictive eligibility criteria (such as tezepelumab) may help to simplify the treatment decision and reduce the need for future switching between therapies.

The CLEAR study was strengthened by its large patient population and broad international representation through use of the ISAR database. Furthermore, real-world studies capture patient profiles and outcomes that may not be represented in randomized clinical trials. However, the study did have limitations, including the need to generalize findings between countries with different healthcare systems (particularly regarding differences in biologic accessibility); related to this, study sites contributing small numbers of patients to this analysis may have different criteria for prescribing a biologic from sites with large patient numbers. Although the sensitivity analysis did not show substantive variations in the group comparisons when adjusting for country differences, this did not fully address the issue of differences in biologic accessibility between sites. A further study limitation is that switching/stopping was assessed within 6 months of biologic initiation, in line with clinical guidelines,[29,30] but 6 months may be too short a period to accurately evaluate biologic effectiveness; consequently, some continuers may subsequently have switched therapy later in the follow-up period (outcomes were assessed using the closest available data to 12 months after biologic initiation). Moreover, in switchers and stoppers, the analysis of outcomes after biologic initiation did not consider exactly when patients switched/stopped therapy. The lack of assessment of the reasons for not initiating biologic therapy, or for switching or stopping treatment, was a further limitation (though this has been assessed previously in a similar cohort in the SUNNIE study[26]). The use of prescriptions as a surrogate for receiving biologic therapy was another limitation, because patients may be prescribed biologics but not receive them owing to a lack of cover by their health insurance. Lastly, a substantial number of patients included in the baseline analyses were missing the necessary data to be included in the IPTW model and so were excluded from the outcomes analyses – missing data is an inherent challenge in real-world studies.

## Conclusions

In this real-world study of patients receiving care for severe asthma, initiation of biologic therapy was associated with improved clinical outcomes compared with non-initiation in terms of exacerbations, LTOCS use, and asthma control.

Two-thirds of non-initiators were eligible for the biologics studied here. Among initiators, 40% switched or stopped within the first 6 months of therapy; these patients had unmet need and may have benefited from alternative treatment options to their initial biologic. The 60% of initiators who continued biologic therapy for at least 6 months had improved clinical outcomes during the 12 months after biologic initiation in terms of exacerbations, LTOCS use, and asthma control when compared with those who switched or stopped; however, there was considerable remaining unmet need among continuers, suggesting that earlier initiation of biologic therapy or alternative treatments may have been beneficial. Further research regarding how to predict patient response to biologic treatment is required.

## Data Sharing Statement

The dataset supporting the conclusions of this article was derived from the International Severe Asthma Registry (ISAR). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for ISAR. The authors do not have permission to give public access to the study dataset; researchers may request access to ISAR data for their own purposes. ISAR research requests and proposals can be made via the ISAR website (https://isaregistries.org/research-proposal-requests/) or via the enquiries Email to info@isaregistries.org. In line with ISAR governance restrictions, sharing individual deidentified participant data is subject to the consent of the ISAR steering committee 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 (EUPAS38128). 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.

## Ethical Approval and Informed Consent

The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (registration number: EUPAS106967) and with all applicable local and international laws and regulations. Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). Ethical governance for ISAR was provided by ADEPT (approval reference number: ADEPT-1021). All data collection sites in ISAR have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations. The study was approved by the ISAR International Steering Committee and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All participating patients provided informed consent, and their data were anonymized.

## Acknowledgments

We thank all members of the CLEAR Study Working Group (full details in eTable 1). We also thank Nasloon Ali, formerly of Observational and Pragmatic Research Institute, Singapore, for their contributions to the design and conduct of the study. Medical writing support was provided by Richard Claes, PhD, of PharmaGenesis London, London, UK, with funding from AstraZeneca.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was funded by AstraZeneca. The International Severe Asthma Registry is jointly funded by Optimum Patient Care Global and AstraZeneca.

## Disclosure

**Trung N. Tran, Stephanie Chen, Benjamin Emmanuel, Anna Quinton** and **Bill Cook** are employees of AstraZeneca and may own stock or stock options in AstraZeneca. **Alan Altraja** has received lecture fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CSL Behring, Chiesi, GSK, MSD, Norameda, Novartis, Orion, Sanofi, Teva Pharmaceuticals and Zentiva; has received sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, Chiesi, GSK, MSD, Norameda, Novartis, Sanofi and Teva Pharmaceuticals; and has been a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi and Teva Pharmaceuticals. **Arnaud Bourdin** has received grants from AstraZeneca, Boehringer Ingelheim, Cephalon-Teva, GSK, Novartis and Sanofi-Regeneron; has received consultancy fees from Actelion, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, MedinCell, Merck, Novartis, Roche and Sanofi-Regeneron; and has acted as an investigator or co-investigator for trials sponsored by Actelion, AstraZeneca, Boehringer Ingelheim, Chiesi, Galapagos, GSK, Merck, Novartis, Roche, Sanofi-Regeneron and Vertex Pharmaceuticals. **Chau-Chyun Sheu** has received speaker fees from AstraZeneca, Boehringer Ingelheim, GSK, Novartis and Pfizer, and has acted as an investigator for trials sponsored by Aridis Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Galapagos, Horizon Therapeutics, Insmed, Novartis, Roche, Sanofi-Regeneron and Shionogi. **Ming-Ju Tsai** has received sponsorship to attend or speak at conferences, honoraria for lecturing or attending advisory boards, and research grants from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Orient EuroPharma, Pfizer and Shionogi. **Flavia C. L. Hoyte** has received honoraria from AstraZeneca, Genentech, Sanofi and Teva Pharmaceuticals for serving on advisory boards; has received speaker fees from AstraZeneca and Genentech; has participated in research with Genentech, GSK and Sanofi, for which her institution has been remunerated; and her family owns stock in Amgen, Johnson & Johnson, Merck and Pfizer. **Lakmini Bulathsinhala** and **William Henley** are employees of Observational and Pragmatic Research Institute, which conducted this study in collaboration with Optimum Patient Care Global and AstraZeneca. **Celine Yun Yi Goh** and **Victoria Carter** are employees of Optimum Patient Care Global, a co-funder of the International Severe Asthma Registry. **Yang Liu** was an employee of Optimum Patient Care Global at the time that this study was conducted. **Cono Ariti** was an employee of Observational and Pragmatic Research Institute at the time that this study was conducted. **David B. Price** has advisory board memberships with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mundipharma, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals and Thermofisher; has consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Mylan, Novartis, Pfizer, Teva Pharmaceuticals and Theravance; has received grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Medscape, Mundipharma, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, the UK National Health Service and Viatris; has received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Inside Practice, GSK, Kyorin, Mundipharma, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme and Teva Pharmaceuticals; has received payment for the development of educational materials from Mundipharma and Novartis; has received payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis and Thermofisher; has received funding for patient enrollment or completion of research from Novartis; owns stock/stock options from AKL Research and Development, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care (Australia and UK) and 74% of Observational and Pragmatic Research Institute (Singapore); owns 5% of Timestamp, which develops adherence monitoring technology; is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme and Health Technology Assessment; and was an expert witness for GSK. The authors report no other conflicts of interest in this work.

## References

1. Wang E, Wechsler ME, Tran TN, et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. *Chest*. 2020;157(4):790–804. doi:10.1016/j.chest.2019.10.053
2. Fitzpatrick AM, Moore WC. Severe asthma phenotypes - how should they guide evaluation and treatment? *J Allergy Clin Immunol Pract*. 2017;5(4):901–908. doi:10.1016/j.jaip.2017.05.015

3. Porsbjerg CM, Townend J, Bergeron C, et al. Association between pre-biologic T2-biomarker combinations and response to biologics in patients with severe asthma. *Front Immunol*. 2024;15:1361891. doi:10.3389/fimmu.2024.1361891
4. Soremekun S, Heaney LG, Skinner D, et al. Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax*. 2023;78(7):643–652. doi:10.1136/thorax-2021-217032
5. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA steps 4 or 5 treatment. *Curr Med Res Opin*. 2018;34(12):2075–2088. doi:10.1080/03007995.2018.1505352
6. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med*. 2020;201(3):276–293. doi:10.1164/rccm.201904-0903SO
7. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193–204. doi:10.2147/JAA.S176026
8. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. 2017; 357:j1415.
9. Heatley H, Tran TN, Bourdin A, et al. Observational UK cohort study to describe intermittent oral corticosteroid prescribing patterns and their association with adverse outcomes in asthma. *Thorax*. 2023;78(9):860–867. doi:10.1136/thorax-2022-219642
10. Abbas F, Georas S, Cai X, Khurana S. Asthma biologics: real-world effectiveness, impact of switching biologics, and predictors of response. *Ann Allergy Asthma Immunol*. 2021;127(6):655–660e651. doi:10.1016/j.anai.2021.08.416
11. Chen W, Sadatsafavi M, Tran TN, et al. Characterization of patients in the international severe asthma registry with high steroid exposure who did or did not initiate biologic therapy. *J Asthma Allergy*. 2022;15:1491–1510. doi:10.2147/JAA.S377174
12. Pfeffer PE, Ali N, Murray R, et al. Comparative effectiveness of anti-IL5 and anti-IgE biologic classes in patients with severe asthma eligible for both. *Allergy*. 2023;78(7):1934–1948. doi:10.1111/all.15711
13. US Food & Drug Administration. NUCALA (mepolizumab) Prescribing Information. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Accessed February 22, 2024.
14. US Food & Drug Administration. CINQAIR (reslizumab) prescribing information. 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed February 22, 2024.
15. US Food & Drug Administration. Dupixent (dupilumab) Prescribing Information. 2017; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf. Accessed February 22, 2024.
16. US Food & Drug Administration. FASENRA (benralizumab) Prescribing Information. 2017; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Accessed February 22, 2024.
17. US Food & Drug Administration. XOLAIR (omalizumab) prescribing information. 2021; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf. Accessed February 22, 2024.
18. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets*. 2020;24(8):777–792. doi:10.1080/14728222.2020.1783242
19. US Food & Drug Administration. TEZSPIRE (tezepelumab) Prescribing Information. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761224s001lbl.pdf. Accessed February 22, 2024.
20. Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. Version 2.0. 2019. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf. Accessed February 15, 2024.
21. Dragonieri S, Portacci A, Quaranta VN, Carpagnano GE. Advancing care in severe asthma: the art of switching biologics. *Adv Respir Med*. 2024;92(2):110–122. doi:10.3390/arm92020014
22. Kayser MZ, Julicher BL, Welte T, Fuge J, Suhling H. Retrospective assessment and biologic asthma response score reveal roadmap for switching biologics in severe asthma. *Ann Allergy Asthma Immunol*. 2024;132(1):91–93. doi:10.1016/j.anai.2023.08.006
23. Nagase H, Suzukawa M, Oishi K, Matsunaga K. Biologics for severe asthma: the real-world evidence, effectiveness of switching, and prediction factors for the efficacy. *Allergol Int*. 2023;72(1):11–23. doi:10.1016/j.alit.2022.11.008
24. Mohan A, Qiu AY, Lugogo N. Long-term safety, durability of response, cessation and switching of biologics. *Curr Opin Pulm Med*. 2024;30(3):303–312. doi:10.1097/MCP.0000000000001067
25. FitzGerald JM, Tran TN, Alacqua M, et al. International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol*. 2020;20(1):212. doi:10.1186/s12874-020-01065-0
26. Menzies-Gow AN, McBrien C, Unni B, et al. Real world biologic use and switch patterns in severe asthma: data from the international severe asthma registry and the US CHRONICLE study. *J Asthma Allergy*. 2022;15:63–78. doi:10.2147/JAA.S328653
27. Respiratory Effectiveness Group. ADEPT (anonymised data ethics and protocol transparency) committee. Available from: https://www.regresearchnetwork.org/adept-committee/. Accessed February 15, 2024.
28. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2018. Available from: https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf. Accessed February 15, 2024.
29. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–373. doi:10.1183/09031936.00202013
30. Global Initative for Asthma. Global strategy for asthma management and prevention. 2021. Available from: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Accessed February 15, 2024.
31. Marques Mello L, Viana KP, Dos Santos F M, et al. Severe asthma and eligibility for biologics in a Brazilian cohort. *J Asthma*. 2021;58(7):958–966. doi:10.1080/02770903.2020.1748049
32. Akenroye AT, Heyward J, Keet C, Alexander GC. Lower use of biologics for the treatment of asthma in publicly insured individuals. *J Allergy Clin Immunol Pract*. 2021;9(11):3969–3976. doi:10.1016/j.jaip.2021.01.039
33. Inselman JW, Jeffery MM, Maddux JT, Shah ND, Rank MA. Trends and disparities in asthma biologic use in the United States. *J Allergy Clin Immunol Pract*. 2020;8(2):549–554e541. doi:10.1016/j.jaip.2019.08.024
34. Gelhorn HL, Balantac Z, Ambrose CS, Chung YN, Stone B. Patient and physician preferences for attributes of biologic medications for severe asthma. *Patient Prefer Adherence*. 2019;13:1253–1268. doi:10.2147/PPA.S198953
35. Porsbjerg CM, Menzies-Gow AN, Tran TN, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract*. 2022;10(5):1202–1216e1223. doi:10.1016/j.jaip.2021.12.027

36. Kroes JA, Zielhuis SW, van Roon EN, Ten Brinke A. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. *Biochem Pharmacol*. 2020;179:113978. doi:10.1016/j.bcp.2020.113978
37. Scelo G, Tran TN, Le TT, et al. Exploring definitions and predictors of response to biologics for severe asthma. *J Allergy Clin Immunol Pract*. 2024;12(9):2347–2361. doi:10.1016/j.jaip.2024.05.016
38. Hamada K, Oishi K, Murata Y, Hirano T, Matsunaga K. Feasibility of discontinuing biologics in severe asthma: an algorithmic approach. *J Asthma Allergy*. 2021;14:1463–1471. doi:10.2147/JAA.S340684
39. Scelo G, Torres-Duque CA, Maspero J, et al. Analysis of comorbidities and multimorbidity in adult patients in the international severe asthma registry. *Ann Allergy Asthma Immunol*. 2024;132(1):42–53. doi:10.1016/j.anai.2023.08.021
40. Bakakos A, Loukides S, Usmani OS, Bakakos P. Biologics in severe asthma: the overlap endotype - opportunities and challenges. *Expert Opin Biol Ther*. 2020;20(12):1427–1434. doi:10.1080/14712598.2020.1809651
41. Dragonieri S, Carpagnano GE. Biological therapy for severe asthma. *Asthma Res Pract*. 2021;7(1):12. doi:10.1186/s40733-021-00078-w
42. Rogliani P, Calzetta L, Matera MG, et al. Severe asthma and biological therapy: when, which, and for whom. *Pulm Ther*. 2020;6(1):47–66. doi:10.1007/s41030-019-00109-1
43. Zaihra T, Walsh CJ, Ahmed S, et al. Phenotyping of difficult asthma using longitudinal physiological and biomarker measurements reveals significant differences in stability between clusters. *BMC Pulm Med*. 2016;16(1):74. doi:10.1186/s12890-016-0232-2
44. Denton E, Price DB, Tran TN, et al. Cluster analysis of inflammatory biomarker expression in the international severe asthma registry. *J Allergy Clin Immunol Pract*. 2021;9(7):2680–2688e2687. doi:10.1016/j.jaip.2021.02.059