

The CHRONICLE Study of US Adults with Subspecialist-Treated Severe Asthma: Objectives, Design, and Initial Results

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Background: Approximately 5–10% of patients with asthma have severe disease. High-quality real-world studies are needed to identify areas for improved management.

Objective: Aligned with the International Severe Asthma Registry, the CHRONICLE study (ClinicalTrials.gov: NCT03373045) was developed to address this need in the US.

Study Design: Learnings from prior studies were applied to develop a real-world, prospective, noninterventional study of US patients with confirmed severe asthma who are treated by subspecialist physicians and require biologic or maintenance systemic immunosuppressant therapy or who are uncontrolled by high-dosage inhaled corticosteroids and additional controllers. Target enrollment is 4000 patients, with patient observation for ≥ 3 years. A geographically diverse sample of allergist/immunologist and pulmonologist sites approach all eligible patients under their care and report patient characteristics, treatment, and health outcomes every 6 months. Patients complete online surveys every 1–6 months.

Initial Results: From February 2018 to February 2019, 102 sites screened 1428 eligible patients; 936 patients enrolled. Study sites (40% allergist/immunologist, 42% pulmonologist, 18% both) were similar to other US asthma subspecialist samples. Enrolled patients were 67% female with median ages at enrollment and diagnosis of 55 (range: 18–89) and 26 (0–80) years, respectively. Median body mass index was 31 kg/m²; 3% and 29% were current or former smokers, respectively, and >60% reported ≥ 1 exacerbation in the prior year and suboptimal symptom control.

Conclusion: CHRONICLE will provide high-quality provider- and patient-reported data from a large, real-world cohort of US adults with subspecialist-treated severe asthma.

Keywords: asthma exacerbations, longitudinal studies, allergists, pulmonologists, biologic therapy

Introduction

Asthma is a heterogeneous disease characterized by variable phenotypes of airway inflammation, reversible airflow obstruction, and airway hyperresponsiveness.¹ Approximately 5% to 10% of patients with asthma have severe disease, defined by the American Thoracic Society and European Respiratory Society (ATS/ERS) as needing high-dosage inhaled corticosteroids (ICS) plus additional controllers to maintain control, remaining uncontrolled even when using these treatments, or requiring systemic corticosteroids for $\geq 50\%$ of the previous year to maintain control.^{2,3} Control of asthma is independent of severity, but patients with severe asthma are at higher risk for poor control, resulting in severe exacerbations,

emergency department visits, hospitalizations, lost productivity, and reduced quality of life compared with patients with nonsevere asthma.^{4–8} Although severe asthma affects only a small percentage of patients, it is a major contributor to the overall societal and economic burden of the disease.^{9,10}

Statements from the ATS/ERS² and the Global Initiative for Asthma (GINA)³ support the proper management of severe asthma; however, the level of adoption of these guidelines is unknown and likely incomplete. Additionally, newer treatment approaches need to be understood in real-world samples to inform future guidelines and recommendations. In particular, several monoclonal antibody therapies have been approved for the treatment of severe asthma;⁹ however, few high-quality data are available to describe the real-world use of and outcomes associated with these agents.

There is a clear need to enhance our understanding of severe asthma with contemporary data from large, real-world, longitudinal, observational studies. Global randomized controlled trials (RCTs) are the gold standard for establishing treatment safety and efficacy, but RCTs in severe asthma do not represent the overall patient population due to study inclusion/exclusion criteria and limited country-specific samples.¹¹ Analyses of secondary data sources (eg, health care utilization records or insurance claims) may not allow for accurate identification and characterization of patients with severe asthma due to incomplete data, inaccuracies in data entry, and an inability to document subspecialist (allergist/immunologist [AI] or pulmonologist [P]) confirmation of a severe asthma diagnosis. These data sources also often lack data on environmental and social risk factors, laboratory testing, pulmonary function, and subjective assessments by health care providers (HCPs) and patients. In contrast, standardized, longitudinal, observational registry studies are an ideal approach to better understand real-world national and regional variations in the care of patients with severe asthma¹² and to address challenges in clinical trial design and patient selection, particularly given the variable nature of asthma.^{11,12}

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, initiated in 2001, was a real-world, 3-year, multicenter, prospective cohort study of 4756 patients aged ≥ 6 years with severe (48% of patients) or difficult-to-treat (96% of patients) asthma. The TENOR study provided valuable insights into the natural history and medical management

of severe or difficult-to-treat asthma in the United States at that time.^{13,14} Despite substantial changes to the treatment landscape in recent years, no large, real-world, observational study of US patients with severe asthma has been undertaken since the TENOR study.

The International Severe Asthma Registry (ISAR) was initiated in 2017 to address this need at the global level by combining retrospective and prospective data from existing national severe asthma registries (and supporting the development of new national severe asthma registries) in more than 14 countries.¹⁵ A panel of 27 international asthma experts used a modified Delphi process to reach a consensus on a common set of 95 core variables for standardized collection across all participating countries.¹⁶ ISAR chose to focus on the population of adult patients receiving monoclonal antibody or maintenance systemic corticosteroid treatment, or those uncontrolled while receiving high-dosage ICS with additional controllers. At present, only a single US site is involved in ISAR.

The CHRONICLE study was developed to align with ISAR and provide contemporary real-world data describing a large, geographically diverse cohort of US adults with subspecialist-treated severe asthma that is not controlled by high-dosage inhaled therapies. The ultimate goal is to help improve the US standard of care for severe asthma, including optimal use of monoclonal antibody therapies recently approved by the US Food and Drug Administration (FDA), by better characterizing the disease burden and treatment gaps associated with US severe asthma care. The goal of this manuscript is to describe the CHRONICLE study design and present initial observations from the first year of the study, which demonstrate that the study has been effective in enrolling a diverse, real-world sample of US patients with severe asthma treated by subspecialists.

Patients and Methods

Study Design

The CHRONICLE study is designed to be a real-world, prospective, noninterventional cohort study that collects primary HCP-reported and patient-reported data on patient characteristics, comorbidities, laboratory and imaging assessments, medical treatments, health care utilization, and health outcomes from a large, geographically diverse cohort of US patients and providers. The study is sponsored by AstraZeneca and led by AstraZeneca staff and a scientific advisory committee composed of 8 US clinical

experts in severe asthma care and research (authors WWC, BEC, DKL, NL, WCM, RAP, WS, JT). This committee provides scientific leadership of the study objectives, protocol, conduct, and analysis.

Study Participants

Inclusion and exclusion criteria are outlined in Table 1. To enable pooled analyses of CHRONICLE and ISAR data, it was essential to align the patient population with that of ISAR; specifically, patients receiving subspecialist care who are either not controlled on high-dosage ICS with additional controllers and/or require monoclonal antibody or maintenance systemic corticosteroid (mSCS)/immunosuppressant therapy.

Confirmation of severe asthma by subspecialists was considered essential given the high prevalence of conditions that mimic severe asthma.^{17–19} To ensure accuracy of diagnosis, patients are required to have a diagnosis of severe asthma for ≥ 12 months prior to enrollment. To ensure accurate data collection and enable capture of the provider's subjective assessments of the patient's disease, enrollment is limited to patients currently receiving care from subspecialist physicians at the investigator's site.

The study is designed to minimize participation bias. The protocol requires sites to approach every eligible patient (defined as patients meeting all inclusion criteria) under their care, with only 1 exception. When the original

Table 1 Patient Inclusion and Exclusion Criteria in the CHRONICLE Study

| Inclusion criteria | Exclusion criteria |
|---|---|
| <ol style="list-style-type: none"> 1. Diagnosis of severe asthma, per ERS/ATS guidelines,² for ≥ 12 months prior to enrollment, with investigator confirmation that severe asthma symptoms are not due to an alternative diagnosis 2. Currently receiving care from specialist physicians (eg, AI) at the investigator's or sub-investigator's site 3. Age ≥ 18 years 4. Meeting ≥ 1 of the following criteria: <ol style="list-style-type: none"> a. Uncontrolled on asthma treatment consistent with GINA Step 4 or 5, receiving high-dosage ICS with additional controllers <ol style="list-style-type: none"> i. Uncontrolled is defined by meeting ≥ 1 of the following (as outlined by ATS/ERS guidelines): <ol style="list-style-type: none"> 1. Poor symptom control: Asthma Control Questionnaire consistently > 1.5, ACT < 20 (or "not well controlled" by NAEPP/GINA guidelines) 2. Frequent severe exacerbations: ≥ 2 bursts of systemic corticosteroids (> 3 days each) in the previous 12 months 3. Serious exacerbations: ≥ 1 hospitalization, ICU stay, or mechanical ventilation in the last 12 months 4. Airflow limitation: after appropriate bronchodilator withheld $FEV_1 < 80\%$ predicted (in the face of reduced FEV_1/FVC defined as less than the LLN) ii. For the purposes of this study, high-dosage ICS will be defined as: <ol style="list-style-type: none"> 1. ICS at a cumulative dosage of > 500 μg fluticasone propionate equivalents daily, or 2. Highest labeled dosage of a combination of ICS/LABA b. Current use of an FDA-approved monoclonal antibody agent for treatment of severe asthma (with use not primarily for an alternative condition) c. Use of systemic corticosteroids or other systemic immunosuppressants (any dosage level) for $\geq 50\%$ of the prior 12 months for treatment of severe asthma (with use not primarily for an alternative condition) | <ul style="list-style-type: none"> • Not willing and able to sign written informed consent • Not fluent in English or Spanish • Unable to complete study follow-up or web-based PROs • Received an investigational therapy for asthma, allergy, atopic disease, or eosinophilic disease as part of a clinical trial during the 6 months prior to enrollment • Once enrolled in CHRONICLE, patients can enroll in trials of investigational therapies (as well as other noninterventional studies) as long as they continue to complete study follow-up. If a patient enrolls in a trial of investigational therapy, the identity (NCT number) of the study and dates of the first and last investigational therapy administration will be collected. If the patient receives blinded therapy in a trial, the investigator will request the identity of that therapy at trial conclusion so that treatment information collected for the current study may be updated accordingly |

Abbreviations: ACT, Asthma Control Test; AI, allergist/immunologist; ATS, American Thoracic Society; ERS, European Respiratory Society; FDA, US Food and Drug Administration; FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; ICU, intensive care unit; LABA, long-acting beta-agonist; LLN, lower limit of normal; NAEPP, National Asthma Education and Prevention Program; NCT, National Clinical Trial; PRO, patient-reported outcome.

protocol was written, there was concern that the number of patients qualifying under inclusion criterion 4a (uncontrolled severe asthma treated with high-dosage ICS with additional controllers; Table 1) would greatly exceed those qualifying under 4b or 4c (use of monoclonal agents or systemic corticosteroids/immunosuppressants, respectively). As a result, the CHRONICLE protocol directed sites to approach only every third patient who was eligible for enrollment according to inclusion criterion 4a but did not qualify under 4b or 4c. Following the first year of enrollment, it was clear that the restricted enrollment of these patients was not necessary. As a result, this “every third” enrollment restriction for patients meeting only inclusion criterion 4a was eliminated in February 2019.

Among all study-eligible patients, basic de-identified characteristics are collected on all patients, including those not approached, those approached but not enrolled, and those enrolled, to enable a direct assessment of any participation biases. A signed informed consent form is obtained at enrollment for study participation and to acquire medical records from other providers, including pharmacy records. Once consented and enrolled, patients are followed until study discontinuation, withdrawal, or death. As with ISAR, there is no required testing or imaging, as all data collection is meant to observe real-life clinical practices, and required testing, imaging, or other intervention could alter provider behavior and/or patient treatment. Moreover, no study visits are required following the initial enrollment. Patients are expected to continue follow-up for ≥ 3 years. A study termination date has not yet been determined.

Study Conduct

The CHRONICLE study is being performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practices, Good Pharmacoepidemiology Practices, the Health Insurance Portability and Accountability Act (HIPAA), and applicable legislation for observational studies. HCP-reported data and patient-reported outcomes (PROs) recorded from the date of enrollment are summarized in Table 2. Upon enrollment, HCPs document patient information such as demographic characteristics and asthma history. They further document the patient’s environmental and social milieu, health care insurance status, smoking history, asthma events, treatment characteristics,

health care utilization, comorbidities, major medical events, and HCP assessments of patient status; these data are updated every 6 months. A variety of PROs are recorded at enrollment. Of these, asthma symptom control, exacerbations, and adherence are assessed monthly; asthma-related health care resource utilization, work productivity, and treatment effectiveness are evaluated every 3 months; and information regarding health-related quality of life, prescription medication source(s), and presence of an asthma treatment plan are collected every 6 months. This schedule was selected based on the relevant time periods for validated surveys and to reduce patient survey burden.

CHRONICLE data collection was aligned with ISAR core data collection¹⁶ to capture core asthma-related variables and ensure that ISAR and CHRONICLE data can be merged to create a larger global dataset. However, additional data elements collected in CHRONICLE enable a more complete characterization of HCPs and patients, including information on important potential confounders of patient health outcomes. These include social and environmental risk factors (eg, marital status, education level, employment, potential air quality risk), comorbidities and major medical events that can impact a patient’s overall health status, relevant nonasthma treatments, and adverse conditions associated with systemic corticosteroid therapy (see Table 2).

Because there are no specified study visits following the enrollment visit, longitudinal collection of HCP-reported information occurs with the extraction of information from medical records and investigator assessments every 6 months. Data quality is optimized through programmed data quality checks that automatically detect anomalous data, as well as a data management team that routinely reviews site-entered data and issues additional queries as necessary. In order to collect patient-reported data, patients are sent online surveys via email for completion outside of the study site, which minimizes influence from HCP opinions. To optimize data accuracy and limit missing data, data collection from HCPs is limited to the 12 months prior to enrollment for most items. However, the surveillance period prior to enrollment was extended up to 3 years for prior laboratory and pulmonary function testing, and to any time prior to enrollment for more serious or rare events (eg, asthma hospitalizations, prior monoclonal or systemic immunosuppressant therapy, diagnosed malignancies). For all data elements, dates of events and changes in patient status are recorded. As a result, sites provide updates to each patient’s data on a feasible schedule of every 6 months, but

Table 2 Data Collection in the CHRONICLE Study

| HCP-reported data | Patient-reported outcomes |
|---|---|
| <p>Enrollment</p> <ul style="list-style-type: none"> ● Patient characteristics <ul style="list-style-type: none"> ○ Eligibility criteria and demography ○ Asthma history <p>Enrollment + every 6 months:</p> <ul style="list-style-type: none"> ● Patient characteristics <ul style="list-style-type: none"> ○ Social,^a environmental,^a and smoking history/status ○ Respiratory and nonrespiratory comorbidities ○ Major medical events and procedures^a ● Treatment characteristics <ul style="list-style-type: none"> ○ Current asthma treatment and select other treatments ○ If asthma treatment changed, reason for change ● Health outcomes^b <ul style="list-style-type: none"> ○ Vital signs^a and physical exam^a ○ Asthma exacerbations and hospitalizations ○ Nonasthma hospitalizations^a ○ Most recent imaging, FeNO, spirometry, PFTs ○ BAL/sputum testing (all) ○ CBC with differential (all)^a ○ Most recent other lab tests^a ○ Diagnosed malignancies, serious infections, anaphylaxis ○ Clinical trial participation^a ○ Assessment of overall patient and treatment status | <p>Enrollment only</p> <ul style="list-style-type: none"> ● Health literacy^a <p>Enrollment + monthly</p> <ul style="list-style-type: none"> ● Medication adherence^a ● Asthma exacerbations^a ● ACT^a <p>Enrollment + every 3 months</p> <ul style="list-style-type: none"> ● Asthma-related HCRU^a ● Work productivity (WPAl-Asthma)^a ● Assessment of treatment effectiveness^a <p>Enrollment + every 6 months</p> <ul style="list-style-type: none"> ● Quality of life: SGRQ^a ● Source of prescription medications^a ● Presence of asthma treatment plan^a |

Notes: ^aVariables not assessed in ISAR. ^bBone densitometry data obtained using dual-energy x-ray absorptiometry (DEXA) are collected in ISAR but not the CHRONICLE study.

Abbreviations: ACT, Asthma Control Test; BAL, bronchoalveolar lavage; CBC, complete blood count; FeNO, fractional exhaled nitric oxide; HCP, health care provider; HCRU, health care resource utilization; ISAR, International Severe Asthma Registry; PFT, pulmonary function test; SGRQ, St. George’s Respiratory Questionnaire; WPAl-Asthma, Work Productivity and Activity Impairment Asthma questionnaire.

a comprehensive longitudinal record of the patient’s medical history is constructed.

Because the CHRONICLE study is not designed to test a specific hypothesis, the target study population size was not determined by statistical power calculations. The initial target sample size of ≥1500 patients was increased to 4000 patients based on the sample deemed necessary to enable robust subgroup analyses, similar to that achieved by the TENOR study.²⁰ Site feasibility survey results suggested that enrollment of 4000 patients would require 125 study sites enrolling subjects for approximately 3 years. Study sites were selected to represent a geographically diverse mix of academic and community-based medical centers, as well as hospital-based and office-based sites. The only site selection criteria were requirements that the HCP(s) be a relevant US subspecialist (AI and/or P who treats severe asthma), that the site was able to complete the study procedures, and that the overall site sample was geographically dispersed across the United States.

Data Analysis

The study uses a hypothesis-free approach. Hypothesis-testing analyses may be conducted following initial descriptive results. All data will be reported in a manner aligned with Good Publication Practice (GPP3) guidelines,²¹ recommendations of the International Committee of Medical Journal Editors,²² the STrengthening the Reporting of OBServational studies in Epidemiology Initiative checklist for cohort studies (STROBE 2012),²³ and study sponsor (AstraZeneca) policies. Annual descriptive analyses of eligible and enrolled patients are planned. The current manuscript presents baseline site and patient characteristics from the first year of data collection. More detailed analyses will be shared in future publications.

Initial Results

A comparison of the CHRONICLE study and other severe asthma registry-style cohort studies is presented in Table 3. Compared with the TENOR study, CHRONICLE has fewer sites but a similar number of treating physicians, focuses

Table 3 Comparison of Asthma Registries: TENOR, ISAR, and CHRONICLE

| Characteristic | TENOR study ²⁰ | ISAR ^{15,20} | CHRONICLE study |
|--|---|---|---|
| Age range, years | ≥6 | ≥18 | ≥18 |
| Type of asthma | Severe or difficult-to-treat | Severe | Severe |
| Study period | 2001–2004 | Initiated in 2018, no end date | Initiated in 2018, no end date |
| Patients, n | 4756 | >10,000 (currently >5000) | 4000 |
| Sites, n | 283 | TBD | 102 as of February 2019; targeting 125 |
| Country | USA | >14; one site in USA | USA |
| Physicians, n | >400 | TBD | 423 (at 102 sites) |
| Specialty of physicians at enrolling sites | Als (54%), pulmonologists (41%) | Als, pulmonologists | Als (40%), pulmonologists (42%), both (18%) |
| Duration of follow-up, years | 3 | Indefinite | Indefinite; target average of 5 |
| Data collected | Natural history of disease, treatments, outcomes, comorbidities, IgE levels | Patient demographics and medical history, outcomes, diagnostic information, clinical characteristics, treatments | Patient demographics and medical history, outcomes, diagnostic information, clinical characteristics, treatments, PROs |
| Fixed mandatory study visit(s) | Baseline and every 6 months | Baseline, with no mandatory follow-up visit. Informed consent addressed per local requirements and existing registry structure. Data are collected at subsequent patient visits as they occur | Baseline only; no mandated study visits; however, data are routinely collected from medical records every 6 months |
| PROs | Every 6 months: ATAQ Every 12 months: WPAL-Asthma, AQLQ | None; HCP-reported GINA control questions at every visit | Every month: ACT, treatment adherence, exacerbations Every 3 months: WPAL-Asthma, HCRU; GETE Every 6 months: SGRQ, asthma treatment plan, prescription medication source HCP-reported GINA control questions also collected every 6 months |

Abbreviations: ACT, Asthma Control Test; AI, allergist/immunologist; AQLQ, Asthma Quality of Life Questionnaire; ATAQ, Asthma Therapy Assessment Questionnaire; GETE, Global Evaluation of Treatment Effectiveness; GINA, Global Initiative for Asthma; HCP, health care provider; HCRU, health care resource utilization; IgE, immunoglobulin E; ISAR, International Severe Asthma Registry; PRO, patient-reported outcome; SGRQ, St. George's Respiratory Questionnaire; TBD, to be determined; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; WPAL-Asthma, Work Productivity and Activity Impairment Asthma questionnaire.

exclusively on adults with severe asthma, has a longer duration of follow-up planned, and assesses more patient-reported data, which are collected more frequently.²⁰ By design, the characteristics of ISAR and CHRONICLE are similar. Two primary differences are that CHRONICLE has a robust set of PROs collected every 1 to 6 months and that HCP-reported data collection in CHRONICLE occurs every 6 months based on site medical records to provide a comprehensive longitudinal record for each patient. In ISAR, longitudinal data collection is intermittent, as it is driven by the timing of patient visits to specialist centers.

In the sections below, we present baseline characteristics for the study sites and patients in CHRONICLE. These initial observations are included to show that the study design has effectively enrolled a diverse sample of patients with severe asthma treated by US subspecialists; detailed results from the first interim analysis will be presented in a subsequent report.

CHRONICLE Study Sites

As of February 2019, a total of 102 sites were active in CHRONICLE; characteristics of included study sites are summarized in Table 4. Among the first 102 sites, 40% were AI

Table 4 CHRONICLE Study Site Characteristics

| Characteristic of site or principal treating physician | Site count (%) or median (range) (N=102) |
|--|--|
| Site subspecialty | |
| AI | 41 (40%) |
| Pulmonologist | 43 (42%) |
| AI and pulmonologist | 18 (18%) |
| Board certification of principal treating physician | 99 (97%) board-certified; 2 previous but not current; 1 NR |
| Principal treating physician sex | 1 NR |
| Female | 16 (16%) |
| Male | 85 (83%) |
| Principal treating physician age, years, median (range) | 54 (35–78) |
| Years practicing in specialty, median (range) | 22 (3–43) |
| Practice type | |
| Single specialty | 65 (64%) |
| Multiple specialty | 37 (36%) |
| Practice setting | |
| Private (nonhospital) | 85 (83%) |
| University hospital | 14 (14%) |
| Nonuniversity hospital | 3 (3%) |
| Geographic setting | 1 NR |
| Urban | 50 (49%) |
| Suburban | 45 (44%) |
| Rural | 6 (6%) |
| Presence of severe asthma clinic | |
| Yes, practice is a dedicated severe asthma clinic | 9 (9%) |
| Yes, practice includes a severe asthma clinic | 29 (28%) |
| No | 64 (63%) |
| Biologic therapies administered onsite | 90 (88%) ^a |
| Number of physicians treating severe asthma | |
| 1 | 34 (33%) |
| 2 | 18 (18%) |
| 3 | 13 (13%) |
| 4 | 5 (5%) |
| 5 | 4 (4%) |
| ≥6 | 28 (28%) |
| Median (range) | 2 (1–31) |
| Number of nonphysician HCPs treating severe asthma, median (range) | 2 (0–64) |
| Estimated number of severe asthma patients treated at site in a year, median (range) | 200 (7–6000) |

Notes: ^aAll biologic nonadministering sites were those of pulmonologists.

Abbreviations: HCP, health care provider; NR, not reported.

practices, 42% were P practices, and 18% reported having both AIs and Ps in their severe asthma practice. Principal treating physicians were predominantly male (83%), had practiced in the specialty for a median of 22 years (range: 3–43), were in single-specialty practices (64%) with a median of 2 physicians and 2 nonphysicians treating severe asthma, and were in non-hospital (83%) and urban/suburban (49%/44%) settings. Practices reported treating a median of 200 patients per year with severe asthma, ranging from 7 to 6000. The presence of a severe asthma clinic was reported by 37% of sites, and 88% reported administering biologics onsite. Overall, the physician characteristics of the first 102 sites in CHRONICLE were similar to those of asthma specialists in the Centers for Disease Control and Prevention National Asthma Survey of Physicians (CDC NAS)²⁴ and AIs and Ps overall in the American Medical Association (AMA) subspecialist characteristics (Table 5).²⁵ Additionally, the geographic distribution of CHRONICLE sites was generally aligned with that of the CDC NAS and AMA subspecialist characteristics, but with moderate underrepresentation of providers in the Midwest and Pacific regions.

Eligible and Enrolled Patient Characteristics

Between February 2018 and February 2019, a total of 1428 eligible patients were screened for enrollment in CHRONICLE, and 936 patients had enrolled, of whom 796 had all baseline forms completed (see Figure E1 in the Online Repository). Table 6 summarizes the general patient characteristics of the eligible and enrolled patient populations. Eligible patients had median ages at enrollment and diagnosis of 56 and 27 years, respectively; 68% were female, and 60% had commercial health care insurance. By asthma treatment category, 58% of all eligible patients were receiving biologics, 12% were receiving mSCS therapy, and 37% were receiving high-dosage ICS therapy with additional controllers without biologics or mSCS. Asthma exacerbations were common, with 61% reporting ≥1 exacerbation in the 12 months prior to screening, for an overall mean of 1.9 exacerbations in the prior year. Characteristics of the enrolled population were similar, with the exception of the expected underrepresentation of patients receiving high-dosage ICS therapy with additional controllers without biologics or mSCS (due to the protocol-mandated “every-third” enrollment scheme). Additional data collected from enrolled patients demonstrated a median body mass index of 31 kg/m²; most patients were non-Hispanic White (71%) and 50% lived in

Table 5 Site-Level Characteristics in the CHRONICLE Study Compared with the CDC NAS and AMA Subspecialist Data

| Site characteristic | CHRONICLE | CDC NAS ^{a,24} | AMA ²⁵ | |
|---|---|--|---------------------|---------------------|
| | | | Als | Ps |
| Number of physicians | 423 severe asthma subspecialist physicians at first 102 sites | 233 asthma subspecialist physicians ^b | 4561 physicians | 12,564 physicians |
| Board certification | 97% board-certified | NR | 89% board-certified | 93% board-certified |
| Principal treating physician sex, % | | | | |
| Female | 16% (AI: 20%; P: 12%; AI/P: 17%) | 16% | 35% | 19% |
| Male | 83% (AI: 81%; P: 86%; AI/P: 83%) | 84% | 65% | 81% |
| Principal treating physician age, years | Median (range): 54 (35-78) | <40: 9.5% 40-59: 54.0% ≥60: 36.5% | Mean: 66 | Mean: 59 |
| Practice type | | | | |
| Private office (nonhospital) | 83% (AI: 93%; P: 74%; AI/P: 83%) | 84% | 87% | 76% |
| Hospital-based | 17% (AI: 7%; P: 26%; AI/P: 17%) | 12% (HMO, academic, other) | 13% | 24% |
| Other or NR | NA | 4% | | |
| Geographic distribution, % ^c | | | | |
| Northeast | 26% | 21% | 23% | 25% |
| New England | 4% | | 7% | 8% |
| Middle Atlantic | 22% | | 16% | 17% |
| Midwest | 13% | 18% | 20% | 20% |
| East North Central | 10% | | 14% | 14% |
| West North Central | 3% | | 6% | 6% |
| South | 44% | 38% | 36% | 35% |
| South Atlantic | 25% | | 20% | 20% |
| East South Central | 6% | | 5% | 6% |
| West South Central | 14% | | 11% | 9% |
| West | 17% | 23% | 21% | 21% |
| Mountain | 6% | | 5% | 6% |
| Pacific | 11% | | 16% | 15% |

Notes: ^aData presented as weighted %. ^bIn the CDC NAS analysis, Als and Ps were oversampled to target asthma treatment specialists. ^cTotals may not equal 100% due to rounding. New England: CT, ME, MA, NH, RI, VT; Middle Atlantic: NJ, NY, PA; East North Central: IL, IN, MI, OH, WI; West North Central: IA, KS, MN, NE, ND, SD; South Atlantic: DE, DC, FL, GA, MD, NC, SC, VA, WV; East South Central: AL, KY, MI, TN; West South Central: AR, MS, LA, OK, TX; Mountain: AZ, CO, ID, MT, NV, NM, UT, WY; Pacific: CA, OR, WA, AK, HI. For reference, the distribution of the US population in the 2010 census was 18% Northeast, 39% South, 20% Midwest, and 24% West (<https://www.census.gov/data/tables/2010/dec/density-data-text.html>).

Abbreviations: AI, allergist/immunologist; AMA, American Medical Association; CDC NAS, Centers for Disease Control and Prevention National Asthma Survey of Physicians; HMO, health maintenance organization; NR, not reported; P, pulmonologist.

a suburban setting; and 3% and 29% were current or former smokers with median pack-year histories of 7.5 and 6.8 pack-years, respectively. As of enrollment, patients first received subspecialty care for asthma a median of 12.2 years previously, with a median of 4.6 years since the first visit with their current subspecialist. Among those receiving ongoing therapy with biologics, 54% were receiving omalizumab, 24% mepolizumab, 18% benralizumab,

5% reslizumab, and 1% dupilumab. Based on HCP report and as of their most recent visit prior to enrollment, ≥50% of all enrolled patients had suboptimal asthma symptom control based on daytime symptoms, asthma reliever use, and activity limitation, with 40% reporting nocturnal asthma awakenings/symptoms and 12% reporting an asthma hospitalization in the prior 12 months. Spirometry or complete pulmonary function testing was reported for 88% of

Table 6 Characteristics of the Initial Eligible and Enrolled Patients

| Patient characteristic | All eligible (N=1428) | Enrolled with baseline forms complete (N=796) |
|---|-----------------------|---|
| Age at screening/enrollment, years | | |
| Mean (SD) | 54 (15) | 54 (14) |
| Median (range) | 56 (18–90) | 55 (18–89) |
| 18–29, % | 7% | 7% |
| 30–39, % | 10% | 9% |
| 40–49, % | 17% | 18% |
| 50–59, % | 26% | 29% |
| 60–69, % | 25% | 24% |
| 70–79, % | 13% | 12% |
| ≥80, % | 2% | 1% |
| Age at asthma diagnosis, years | | |
| Mean (SD) | 29 (21) | 28 (21) |
| Median (range) | 27 (0–80) | 26 (0–80) |
| <12, % | 27% | 32% |
| 12–20, % | 12% | 10% |
| >20, % | 52% | 56% |
| NR | 9% | 2% |
| Duration of subspecialty care for asthma, years | | |
| Time since first subspecialist visit for asthma | | |
| Mean (SD) | NA | 18.5 (17.8) |
| Median (range) | | 12.2 (0–87) |
| Time since first visit with current subspecialist | | |
| Mean (SD) | NA | 7.2 (7.9) |
| Median (range) | | 4.6 (0–58) |
| Female sex, % | 68% | 67% |
| Race/ethnicity, % | | |
| Non-Hispanic White | NA | 71% |
| Non-Hispanic Black | | 16% |
| Hispanic | | 8% |
| Asian | | 2% |
| American Indian or Alaska Native | | 1% |
| Other | | 2% |
| NR | | 3% |
| BMI (kg/m²) | | |
| Mean (SD) | NA | 33 (8) |
| Median (range) | | 31 (16–70) |
| Regularly exposed to allergens known to exacerbate asthma, %^a | | |
| Yes | NA | 62% |
| No | | 31% |
| Unknown | | 6% |
| Smoking status | | |
| Current smoker, % | NA | 3% |
| Pack-year history for current smokers, mean, median | | 12.7, 7.5 |

(Continued)

Table 6 (Continued).

| Patient characteristic | All eligible (N=1428) | Enrolled with baseline forms complete (N=796) |
|---|-----------------------|---|
| Former smoker, % | NA | 29% |
| Pack-year history for former smokers, mean, median | | 12.3, 6.8 |
| Residential setting, % | | |
| Rural | NA | 22% |
| Suburban | | 50% |
| Urban | | 26% |
| Not reported | | 2% |
| Insurance status, %^b | | |
| Commercial: No PCP referral required | 46% | 48% |
| Commercial: PCP referral required | 14% | 16% |
| Medicare | 23% | 22% |
| Medicaid | 10% | 9% |
| Other government insurance (eg, Tricare, VA, etc.) | 1% | 2% |
| Other | 4% | 3% |
| Uninsured | 2% | 1% |
| First degree relative with asthma, % | NA | 45% |
| Asthma treatment category^b | | |
| High-dosage ICS with additional controllers, no biologics or mSCS | 37% | 19% ^c |
| Biologics, no mSCS | 51% | 67% |
| Biologics and mSCS | 7% | 9% |
| mSCS, no biologics | 5% | 4% |
| Biologics used among those receiving biologics, %^b | | |
| Omalizumab | NA | 54% |
| Mepolizumab | NA | 24% |
| Benralizumab | NA | 18% |
| Reslizumab | NA | 5% |
| Dupilumab | NA | 1% |
| Exacerbations^d in the 12 months prior to enrollment | | |
| ≥1 exacerbation, % | 61% | 65% |
| ≥1 exacerbation resulting in hospitalization, % | NA | 12% |
| Mean overall, n | 1.9 | 2.0 |
| Mean among those with any exacerbation, n | 3.0 | 3.2 |
| Provider-reported GINA asthma symptom control assessment as of last visit prior to enrollment, %^e | | |
| Daytime symptoms more than twice per week | NA | 54% |
| Nocturnal awakening/symptoms | NA | 40% |
| Asthma reliever use more than twice per week | NA | 55% |
| Activity limitation due to asthma | NA | 55% |

(Continued)

Table 6 (Continued).

| Patient characteristic | All eligible (N=1428) | Enrolled with baseline forms complete (N=796) |
|---|-----------------------|---|
| Most recent pulmonary function testing, median percent predicted FEV₁ / FVC | | |
| Regardless of bronchodilator withhold (n=697 / n=699) | NA | 75% / 79% |
| With bronchodilator withhold (n=238 / n=238) | NA | 70% / 78% |
| Without bronchodilator withhold (n=92 / n=93) ^f | NA | 78% / 81% |
| Most recent laboratory results for relevant biomarkers | | |
| Mean / median blood eosinophil count (per μ L) from CBC (n=359) | NA | 287 / 152 |
| Mean / median total immunoglobulin E (IU/mL) (n=360) | NA | 580 / 202 |
| Mean / median fractional exhaled nitric oxide (ppb) (n=244) | NA | 36 / 25 |

Notes: Fields marked NA represent data that were not collected for nonenrolled patients. ^an=10 (1.3%) patients had missing values. ^bPercentages may not total 100.0% due to rounding. ^cPer protocol, there was systematic undersampling of this population; sites approached every third patient in this category due to anticipated greater prevalence. ^dAggregate count reported at screening. An exacerbation was defined as a worsening of asthma that required systemic corticosteroids for ≥ 3 days (or a single depo-injectable dose), an urgent care or emergency room visit requiring systemic corticosteroids due to asthma, or an inpatient hospitalization due to asthma. Ten or more exacerbations were counted as 10 for calculation of mean. ^eSites described symptoms as of the patient's most recent visit. Additionally, 7–17% of patients had "unknown" as a reported value and were excluded from the reported percentages. ^fn=366 and n=367 patients had unknown status regarding bronchodilator withhold for % predicted FEV₁ and FVC, respectively. These patients are included in the "regardless of bronchodilator withhold" population but excluded from the subgroups with known status for bronchodilator withhold.

Abbreviations: BMI, body mass index; CBC, complete blood count; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; mSCS, maintenance systemic corticosteroids; NR, not reported; PCP, primary care physician; ppb, parts per billion; SD, standard deviation; VA, Veterans Affairs.

enrolled patients. For the subset with confirmed bronchodilator withhold, median FEV₁ and FVC were 70% and 78% predicted, respectively. Mean and median blood eosinophil counts were 287 and 152 cells/ μ L, which varied significantly by treatment group: 370 and 263 cells/ μ L for those receiving high-dosage ICS with additional controllers without biologic or mSCS use, 236 and 106 cells/ μ L for those receiving biologics, and 206 and 74 cells/ μ L for those receiving mSCS.

Discussion

The CHRONICLE study will provide high-quality, longitudinal, real-world data regarding US adult patients with severe asthma treated by subspecialists. The noninterventional design has no mandated study visits following

enrollment so as not to affect the natural history of the disease or treatment. Several strategies to minimize bias have been incorporated into the study design, including systematic enrollment, minimal exclusion criteria for sites and patients, standardization of data collection at the study sites with routine monitoring of data entry, and PROs collected directly from patients using a web-based interface on a regular schedule and not during HCP visits. Study sites represent a geographically diverse mix of US academic and community-based medical centers, with both hospital-based and office-based sites. Characteristics of the first 102 study sites are similar to other samples and suggest that there is no significant bias with site selection. Additionally, a comparison of the characteristics of the initial eligible and enrolled patients demonstrate no substantial recruitment or enrollment biases, other than the protocol-mandated under-enrollment of patients not on biologics or mSCS therapy, which has been eliminated as of February 2019.

After 1 year of operation, the CHRONICLE study has provided novel insights into the characteristics of US adults who suffer from severe asthma as well as the subspecialist physicians and HCPs who care for them. Despite subspecialist assessment and treatment for a median of 12 years, >60% of patients reported ≥ 1 exacerbation within the past year and suboptimal asthma symptom control, and approximately 1 in 8 patients were receiving mSCS therapy, which can have significant associated toxicity^{26,27} and indirect cost.^{27,ccc28} These observations underscore the need for novel therapies and further improvements in the standard of care for this population. Additionally, the initial observations demonstrate that one-third of patients with severe asthma in the United States are current or former smokers, many with a significant pack-year history, which is a population rarely studied in randomized controlled trials for severe asthma treatments.¹¹ With regard to the ongoing use of biologics, newer anti-interleukin (IL)-5/IL-5 receptor therapies had a cumulative prevalence similar to anti-immunoglobulin E therapy (omalizumab), which demonstrates a significant shift in US severe asthma biologic therapy following the approvals of mepolizumab, reslizumab, and benralizumab. Dupilumab received FDA approval for moderate to severe asthma in October 2018; as a result, its use was limited in this analysis of patients enrolled between February 2018 and February 2019. Future analyses of CHRONICLE will provide insights into the evolving use of biologics among US subspecialists.

The first-year patient cohort from the CHRONICLE study already represents the largest real-world study population of US patients with subspecialist-confirmed severe asthma since the TENOR study. Future analyses and long-term follow-up will greatly improve our understanding of severe asthma in the United States and potentially enable improvements in the standard of care. The CHRONICLE study cohort is particularly important given the decentralized nature of severe asthma management by US subspecialists. With the potential to integrate data from CHRONICLE and ISAR,^{15,16} US subspecialist patients with severe asthma will be better represented in a large global sample of patients with severe asthma. Potential benefits of pooling data across multiple national registries include enhanced accuracy of epidemiologic estimates, improved recognition of rare events, and greater ability to examine possible drug-demographic, drug-disease, and drug-drug interactions in various subpopulations.¹⁶

Despite the strengths of the CHRONICLE study, there are several potential limitations. First, patient recall bias and missing data from medical records could limit the utility of the results. To address this issue, study sites routinely request supplementary information regarding each patient's health care utilization from the patient's primary care physician; additionally, acquisition of pharmacy claims information is planned. However, information regarding actual treatment costs from patient, insurer, and societal perspectives are not collected, as providers and patients have limited access to accurate payment data. The study collects some information about financial decisions (eg, missed medication doses due to cost, declination of biologic therapy due to cost, etc.), but a complete assessment of financial decision-making is beyond the scope of the study. Another limitation is that laboratory testing, pulmonary function testing, and other procedures are not mandated but are performed according to standard clinical practice. As a result, not all patients will contribute data to all outcomes of interest, and those tested represent a selected sample. However, the real-world frequency of testing and procedures can be ascertained, and the available data will reflect real-world care. Despite efforts to involve a diverse mix of study sites, the site selection procedure was not random, and the precise generalizability of the study results is unknown. To address this uncertainty, the characteristics of the study cohort will continue to be compared with other cohorts described in the literature or other sources. Finally, the study does not include patients with severe asthma who were not treated by subspecialists, and children and adolescents with severe asthma are not enrolled. These were purposeful

decisions made to align with ISAR and to study adults with subspecialist-confirmed severe asthma.

Conclusions

There is an urgent need for improved management and treatment approaches for adults with severe asthma. The CHRONICLE study is a longitudinal, prospective, observational study that provides high-quality data on patient characteristics, treatment patterns, and health outcomes among a large, geographically diverse cohort of adults with severe asthma treated by US subspecialists. The study will provide a rich source of real-world data in the years ahead to expand our understanding of severe asthma and potentially improve the standard of care in the United States and globally.

Abbreviations

ACT, Asthma Control Test; AI, allergist/immunologist; AMA, American Medical Association; AQLQ, Asthma Quality of Life Questionnaire; ATAQ, Asthma Therapy Assessment Questionnaire; ATS, American Thoracic Society; BAL, bronchoalveolar lavage; BMI, body mass index; CBC, complete blood count; CDC, Centers for Disease Control and Prevention; ERS, European Respiratory Society; FDA, US Food and Drug Administration; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GETE, Global Evaluation of Treatment Effectiveness; GINA, Global Initiative for Asthma; HCP, health care provider; HCRU, health care resource utilization; HMO, health maintenance organization; ICS, inhaled corticosteroids; ICU, intensive care unit; IgE, immunoglobulin E; IL, interleukin; ISAR, International Severe Asthma Registry; LABA, long-acting beta-agonist; LLN, lower limit of normal; mSCS, maintenance systemic corticosteroids; NAEPP, National Asthma Education and Prevention Program; NAS, National Asthma Survey of Physicians; NCT, National Clinical Trial; NR, not reported; P, pulmonologist; PCP, primary care physician; PFT, pulmonary function test; ppb, parts per billion; PRO, patient-reported outcome; RCT, randomized controlled trial; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; TBD, to be determined; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; VA, Veterans Affairs; WPAI-Asthma, Work Productivity and Activity Impairment Asthma questionnaire.

Data Sharing Statement

CHRONICLE is an ongoing study; individual de-identified participant data cannot be shared until the study concludes. The full study protocol is available upon request of the corresponding author. Individuals who were or were not involved in the study may submit publication proposals to the study's Publication Steering Committee by contacting the corresponding author.

Ethics Approval and Informed Consent

The CHRONICLE study protocol received central institutional review board (Advarra, Columbia, MD) approval on November 3, 2017, and was registered on ClinicalTrials.gov on December 14, 2017 (NCT03373045).

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Author Contributions

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Christopher S. Ambrose, Frank Trudo, and Trung N. Tran are employees of AstraZeneca. Bradley E. Chipps is an advisor for, received consultancy fees from, and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron, and Sanofi Genzyme. Wendy C. Moore is on advisory boards for and reports grant and personal fees from AstraZeneca, Sanofi Regeneron, Genentech, and GlaxoSmithKline. She is also a member of the writing and steering committee for the CHRONICLE study as well as a PI of the clinical trial at Wake Forest. Weily Soong is a consultant for and reports grants from AstraZeneca, Genentech, GlaxoSmithKline, Mandala, Novartis, Regeneron, Sanofi, and Teva; and is a speaker for AstraZeneca, GlaxoSmithKline, Regeneron, Sanofi, and Optinose. Jennifer Trevor is a consultant for AstraZeneca; and is on advisory boards for AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim. Dennis K. Ledford reports research support (paid to University) from Genentech/Roche, Novartis, and AstraZeneca. He reports royalties from Wolters Kluwer Health and Taylor and Francis. He is an Editor for the American Academy of Allergy, Asthma & Immunology (AAAAI). He is also a consultant/speaker for and reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Genentech/Roche, GlaxoSmithKline, Meda, Novartis, Sanofi/Regeneron, and Teva, and fees received for legal opinions on drug allergy, metal allergy, radiocontrast reaction, and asthma death. Warner W. Carr is a speaker for

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