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Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorisation Safety Study

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PASS INFORMATION

Title	Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorisation Safety Study
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Research question and objectives	The primary objective of this study is to assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics. The secondary objective is to describe the clinical characteristics of the new malignancy cases that develop in severe asthma patients and relevant subgroups.
Countries of study	United States, Canada, United Kingdom, Spain, Italy, Denmark, Ireland, Bulgaria, South Korea, Japan, Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Singapore, Taiwan, the United Arab Emirates, Poland, and Portugal
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1. ABSTRACT

Title

Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorisation Safety Study.

Keywords

Benralizumab, Post authorisation, Active Surveillance, Malignancy, Safety

Rationale and Background

Benralizumab is an eosinophil-depleting monoclonal antibody (immunoglobulin G1 kappa). In Europe, it is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-adrenoreceptor agonists. In the United States, it is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, with an eosinophilic phenotype.

Although there is no current evidence suggesting a causal relationship between benralizumab and malignancies, malignancy is considered to be an important potential risk of eosinophil lowering therapies based on the putative effect of eosinophils in neoplastic diseases. This study intends to describe the occurrence of malignancy in patients with severe asthma receiving benralizumab compared with those receiving non-benralizumab biologics, and those receiving non-biologic treatment only. This is being accomplished through analysis of data from 2 databases which include patients with specialist-confirmed severe asthma, with confirmation of drug exposures, and detailed descriptions of characteristics of malignancy cases.

This study fulfils a Category 3 post authorisation measure to the European Medicines Agency's Pharmacovigilance Risk Assessment Committee. As more data has accrued, this third interim report builds on the evidence generated so far in the study, ie, that no increase in risk of malignancies was observed among severe asthma patients on benralizumab as compared with severe asthma patients on non-benralizumab biologics and severe asthma patients not on any biologic. Furthermore, in this interim report, more precise estimates for the incidence of malignancies in all cohorts evaluated are provided as compared with previous interim reports.

Herein we report the third of 3 annual interim analyses (IA) of this study, which precede a final report in 2024 at the end of data collection.

Research Question and Objectives

The primary objective of this study is to assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics and those not receiving biologics. The secondary objective is to describe the clinical characteristics of the new malignancy cases that develop in severe asthma patients and relevant subgroups.

Study Design

This is an ongoing real-world, observational, prospective cohort study in patients with severe asthma recruited into the International Severe Asthma Registry (ISAR) and the AZ sponsored United States Severe Asthma Study (CHRONICLE) who are followed up to assess the occurrence of new malignancies. Incidence rates per 1000 person-years (PY) were calculated for severe asthma patients receiving benralizumab and compared with patients with severe asthma receiving non-benralizumab biologics and patients with severe asthma not receiving biologics. New malignancy cases developed during the follow-up period are described with regards to history of prior malignancy, malignancy type, location, stage, and outcomes. Data from ISAR and CHRONICLE were pooled to increase the precision of the study.

Setting

ISAR is being conducted by Optimum Patient Care in collaboration with the Respiratory Effectiveness Group and AZ. CHRONICLE is an AZ sponsored study with study operations led in collaboration with Parexel, a global contract research organisation. Accrual of data to support this study is expected to be completed for ISAR by 31 October 2023 and for CHRONICLE by 31 December 2023. Longitudinal data on the occurrence of malignancy is collected from enrolled patients starting from the point of database entry. Countries not yet contributing malignancy data in the ISAR registries are excluded from the database transfer to AZ. Data from ISAR and CHRONICLE were pooled to create the analysis dataset. Interim Analysis 1 was submitted in 2021, IA2 was submitted in 2022, and IA3 is expected to be the final interim analysis before the final report in 2024. Each IA had a data lag period of one year. Therefore, IA1 for 2021 and IA2 for 2022 included data that was accrued up until 31 December 2020 and 31 December 2021, respectively, and the current IA3 for 2023, includes data that was accrued up until 31 December 2022.

Patients and Study Size, Including Cohort Attrition

The study population includes patients with severe asthma recruited into ISAR and CHRONICLE. Severe asthma patients are defined as those receiving treatment consistent with Global Initiative for Asthma (GINA) Step 5 or who are uncontrolled on GINA Step 4 treatment regimens.

Collectively, ISAR and CHRONICLE recruited 18009 patients with severe asthma from countries contributing malignancy data by the end of 2022.

The study sample size is based on expected precision around estimates at the time of the final report, not at the time of the annual IA (where the extent of follow-up and reported cases will be less).

Variables and Data Sources

The primary outcome for this study is new malignancy cases, which are ascertained by the treating physicians during office visits. Potential risk factors for malignancies as well as patient characteristics including demographics, asthma features, comorbidities, asthma treatment are collected.

This study analyses data from the ISAR and CHRONICLE databases. ISAR prospectively collects routine specialist care data on severe asthma patients from the following countries: United States, Canada, United Kingdom, Spain, Italy, Denmark, Ireland, Bulgaria, South Korea, Japan, Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Singapore, Taiwan, United Arab Emirates, Poland, and Portugal. CHRONICLE is a multi-centre, observational, prospective cohort study of adults with severe asthma in the United States that routinely collects data on malignancies.

Results and Discussion

At the time of data extraction, 18009 patients with malignancy data had been enrolled in both ISAR and CHRONICLE, and 9572 patients were included in the main analysis.

The overall PY of follow-up in the main analysis in this IA is 27090.6 as of 31 December 2022, with the follow-up for the benralizumab cohort at 4005.2 PY, the non-benralizumab biologics cohort at 13459.0 PY, and the non-biologic cohort at 9626.5 PY.

In the benralizumab cohort, 16.2% (252/1554) patients switched to the non-benralizumab biologics cohort, while 6.2% (273/4436) patients of the non-benralizumab biologics cohort switched to the benralizumab cohort. By study design, there were no switches within the non-biologic cohort, as starting of a biologic was considered a censoring criterion in this cohort.

In each cohort, most patients had at least one comorbidity at baseline: 94.2% (1464/1554) in the benralizumab cohort, 93.8% (4159/4436) in the non-benralizumab biologics cohort, and 93.9% (3788/4036) in the non-biologic cohort.

Of the asthma-related comorbidities, the most common in the benralizumab and non-benralizumab biologics cohorts, was allergic rhinitis, and the most common asthma-related comorbidity in the non-biologic cohort was atopic diseases/eczema. The

prevalence of chronic rhinosinusitis (operationally defined to exclude allergic rhinitis and nasal polyps) was higher in the benralizumab and non-benralizumab biologics cohorts, compared with the non-biologic cohort. Nasal polyps were also more commonly reported in the benralizumab and non-benralizumab biologics cohorts than the non-biologic cohort.

Obesity was the most common OCS-related comorbidity at baseline. Diabetes was the least reported OCS-related comorbidity at baseline and is similar across the cohorts.

There were differences between the cohorts in the prevalence of other baseline comorbidities, such as cardiovascular disease, hypertension, and chronic obstructive pulmonary disease. Propensity score weighting was used to adjust for the differences in baseline comorbidities and demographic characteristics.

At the time of this report, the primary analysis included a total of 48 new malignancy cases reported since index date (27 new malignancies were reported in the second IA report). Within cohorts, the crude incidence of malignancies was low and consistent: 0.5% (8/1554) in the benralizumab cohort, 0.5% (21/4436) in the non-benralizumab biologics cohort, and 0.5% (19/4036) in the non-biologic cohort.

Adjusted incidence rate per 1000 PY (95% CI) for benralizumab versus non-benralizumab biologics were 0.9 (0.51 - 1.55) and 0.9 (0.51 - 1.47), respectively, and for benralizumab versus non-biologics 1.5 (0.95 - 2.36) and 2.1 (1.33 - 3.21), respectively. There was no significant difference noted in risk between the cohorts, with the 95% CI for rate differences between benralizumab and the other 2 cohorts including zero for all calculable crude and adjusted comparisons.

In a sensitivity analysis which included patients who had used a biologic/enrolled in the registries prior to 1 November 2017, 17478 patients were included in the cohorts in the crude analyses (1950 patients contributed 5150.3 PY in the benralizumab cohort, 7808 patients contributed 39527.3 PY in the non-benralizumab biologics cohort, and 7720 contributed 43431.1 PY in the non-biologic cohort) resulting in 88108.7 PY at risk. However, some patients contributed person time to more than one cohort.

With the increase in sample size in this sensitivity analysis compared to the main analysis, there was increased precision in the incidence rates calculated, with tighter confidence intervals. Furthermore, the point estimates from this sensitivity analysis remained very similar to the point estimates from the main analysis for both the crude and adjusted incidence rates.

Conclusion

The pre-defined analyses, which included both crude and adjusted analyses, do not show evidence of a difference in the underlying risk of malignancies in patients receiving benralizumab compared to those receiving non-benralizumab biologics or non-biologic

therapy. This result builds upon results from previous interim reports with a consistent observation of an absence of increased risk among benralizumab users, in addition to more precise risk estimates for each cohort due to the increased data accrual in this report compared to previous reports. Furthermore, the observed crude and adjusted incident rates in the cohorts are consistent with the background incidence of malignancy among severe asthma patients reported in published literature.

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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AZ	AstraZeneca
BMI	body mass index
CHRONICLE	AstraZeneca sponsored United States Severe Asthma Study
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CSP	clinical study protocol
eCRF	electronic case report form
FEV_1	forced expiratory volume during 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
IA	Interim Analysis
ICD-10	International Classification of Diseases 10th Revision
ICS	inhaled corticosteroids
Ig	immunoglobulin
IgG1	immunoglobulin G1
IgE	immunoglobulin E
ISAR	International Severe Asthma Registry
LABA	Long-acting β-adrenoreceptor agonist
LAMA	Long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
MAH	Marketing Authorisation Holder
NMSC	non-melanoma skin cancer
OCS	oral corticosteroids
PASS	post authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PS	propensity scores
PY	person-years
SAP	statistical analysis plan
SAS	Statistical Analysis System
SC	subcutaneous
SD	standard deviation

Abbreviation or special term	Explanation
SMD	standardised mean difference

3. INVESTIGATORS

The details of the principal investigator are as below.

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4. OTHER RESPONSIBLE PARTIES

For the details of other responsible parties, refer to Section 3 of the CSP v5.0.

5. MILESTONES

The study is planned to run for 7 years from 2018 to 2024. Three annual interim study reports were planned for, using accrued data ending each year prior to the report, along with a final report of study results for all data accrued until the end of planned follow-up. A detailed explanation of the study milestones is summarised in Table 1.

Table 1 Milestones

Milestone	Planned date	Actual date
Start of data collection	01 January 2018	01 January 2018
End of data collection	31 December 2023	*<<To be determined>>*
Registration in the EU PAS register	November 2018	14 November 2018
Interim report 1 data cut-off	31 December 2020	31 December 2020
Interim report 1	26 September 2021	17 September 2021
Interim report 2 data cut-off	31 December 2021	31 December 2021
Interim report 2	Q4 2022	12 October 2022
Interim report 3 data cut-off	31 December 2022	31 December 2022
Interim report 3	Q4 2023	*<<To be determined>>*
Final report data cut-off	ISAR: 31 October 2023 CHRONICLE: 31 December 2023	*<<To be determined>>*
Final report of study results	Q4 2024	*<<To be determined>>*

Abbreviations: EU PAS = European Post-authorisation Study; Q4 = quarter 4.

6. RATIONALE AND BACKGROUND

Approximately 5% to 10% of asthma patients have severe asthma which can be effectively treated with available controller medications like high-dose ICS plus a second controller (most commonly LABA). However, a subset of patients do not adequately respond to current standard therapy leading to increased health care costs. Approximately 30% to 50% of severe asthma patients are reported to have severe eosinophilic asthma, a phenotype associated with increased eosinophils in the blood or sputum (Zeiger et al 2018, Wenzel 2005).

Benralizumab is an eosinophil-depleting anti-interleukin-5 receptor α binding monoclonal antibody (IgG1 kappa), indicated as an add-on maintenance treatment in adult patients (in Europe and the United States) with severe eosinophilic asthma that is inadequately controlled despite ICS and LABA treatment. It is administered as a 30 mg SC injection given every 4 weeks for the first 3 doses, followed by 30 mg SC injection every 8 weeks thereafter.

There is no current evidence suggesting a causal relationship between benralizumab and malignancies. However, malignancy is considered to be an important potential risk of eosinophil-lowering therapies based on the putative effect of eosinophils in neoplastic diseases (Samoszuk 1997, Davis and Rothenberg 2014). While eosinophils have been observed in literature in association with certain solid tumours, especially those of epithelial origin (breast and colon), the role of eosinophils in the immune response to malignant neoplasms remains unclear. Some clinical studies have suggested the presence of eosinophils may be a positive prognostic indicator of patient malignancy survival; however, a definitive link has not yet been objectively established (Lowe et al 1981; Hogan 2007).

Several observational studies have evaluated the association of asthma and malignancies, which resulted in the following two hypotheses. One hypothesis suggests a protective effect of atopy due to an enhanced surveillance by stimulated immune systems which are able to destroy malignant cells (Alderson 1974, Allegra et al 1976, Cockcroft et al 1979, Fisherman 1960). The second postulates that chronic immune stimulation due to atopy may result in mutations in stem cells which could be associated with an increased risk of malignancy (Bernard et al 1984, Gallagher et al 1983, Logan and Saker 1953).

Gonzalez-Perez et al conducted a cohort study with a nested case-control analysis using the General Practitioner Research Database in the United Kingdom. In this study, patients with asthma (129860 patients) did not exhibit an overall greater risk of malignancy compared to the general population (20000 patients) (odds ratio = 0.93, 95% CI: 0.86 - 1.00) (Gonzalez-Perez et al 2006). Long et al conducted a prospective, observational cohort, Phase IV (EXCELS) study of omalizumab-treated and non-omalizumab-treated patients (7857 patients total) enrolled from multiple United States centres and followed for up to 5 years. The results from the EXCELS study suggest that omalizumab therapy is not associated with an increased risk of malignancy (Long et al 2014).

Salameh et al conducted a single centre cohort retrospective study to investigate the role of asthma in malignancies. Patients were followed for a period of 9 years and the study suggests an association between increased severity of asthma with various cancers. However, as this study was conducted in a single centre, the generalisability of results is limited. Additional limitations include the low number of cancers and small difference in malignancy incidence in the asthma (2% [38/1868]) versus matched control (1.2% [20/1637]) cohorts (Salameh et al 2021).

This study combines the data collected from the patients enrolled in the ISAR and CHRONICLE database to investigate the risk of malignancy in patients with severe asthma, comparing the patients receiving benralizumab with the patients not receiving benralizumab.

This study fulfils the European Medicines Agency PRAC's request for a Category 3 PASS to evaluate the risk of malignancies in benralizumab users. As more data has accrued, this third interim report builds on the evidence generated so far in the study, ie, that no increase in risk of malignancies was observed with more precision in incidence rate estimates in each cohort of interest. Herein we report on the third of 3 annual IA for this study, which will be followed by a final analysis and report after data collection is completed.

7. RESEARCH QUESTION AND OBJECTIVES

The objectives of this descriptive study using data of global databases are as follows:

Primary objective: To assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics.

Secondary objective: To describe the clinical characteristics of new malignancy cases that develop in severe asthma patients and relevant subgroups.

8. AMENDMENTS AND UPDATES

For details of amendments and updates refer to Section 5 of the CSP v5.0.

9. RESEARCH METHODS

For additional details of the research methods, refer to the CSP v5.0 and the SAP v5.0.

9.1 Study Design

This is an ongoing real-world, observational, prospective cohort study in patients with severe asthma recruited into the ISAR and CHRONICLE and followed up to assess the occurrence of new malignancies. Note that all CHRONICLE sites are part of this malignancy PASS and contribute data, while in ISAR, only sites that have agreed to collect malignancy data

contribute data to this PASS (refer to list of countries in Section 9.2). Information on the occurrence, type of malignancy, location, date of diagnosis, staging, and outcome are collected at each patient's visit after the enrolment visit irrespective of the type of asthma treatment the patient is on. Data from ISAR and CHRONICLE were pooled to increase the precision of the study.

The main objective of this study is to assess the incidence rates of malignancies, event rates, and time to first malignancies across the 3 cohorts: the benralizumab, non-benralizumab biologics, and non-biologic cohorts.

9.2 Setting

Data from ISAR and CHRONICLE were pooled to create the analysis dataset from United States, Canada, United Kingdom, Spain, Italy, Denmark, South Korea, Japan, Bulgaria, Ireland, Greece, Argentina, Colombia, India, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, Taiwan, and United Arab Emirates. This interim analysis includes United States data from ISAR for the first time. Interim Analysis 1 was submitted in 2021, IA2 was submitted in 2022, and IA3 is expected to be the final interim analysis before the final report in 2024. Each IA had a data lag period of one year. Therefore, IA1 for 2021 and IA2 for 2022 included data that was accrued up until 31 December 2020 and 31 December 2021, respectively, and the current IA3 for 2023, includes data that was accrued up until 31 December 2022.

The index date for patients in the benralizumab cohort is the date of first benralizumab use on or after 01 November 2017. The index date for patients in the non-benralizumab biologics cohort is the date of the first non-benralizumab biologics use on or after 01 November 2017.

For those patients who did not receive any biologics, the index date is the date of database entry on or after 01 November 2017. A patient can contribute person-time to more than one study cohort and have multiple corresponding index dates if they switch medications. However, a patient can only contribute person-time to one cohort at any given time.

For this third IA, patients from both databases were followed up to the end of December 2022, or until patients withdrew from the database, or death, whichever occurred first.

9.3 Patients

Among ISAR and CHRONICLE patients, only those patients who met the study specific eligibility criteria were included in the analysis (refer to Table 3 and Figure 2 for a breakdown). Eligibility to participate in ISAR and CHRONICLE are provided in Table 2. Study-specific criteria are availability of data to determine malignancy outcome, enrolment during the study time period of interest (1 November 2017 to 31 December 2022) for the main analysis, and age > 18 years at enrolment.

Patients may change biologic treatment cohorts during the study. For patients who switched from the benralizumab cohort to the non-benralizumab biologics cohort, the censoring date in the primary analysis is the date of the switch. A similar approach was applied to patients who switched from the non-benralizumab biologics cohort to benralizumab cohort.

The non-biologic cohort only includes patients who have never received any biologic treatment during the study. Thus, a patient in the non-biologic cohort did not switch from or to the other 2 cohorts.

Patients were summarised in their original biologic cohort if they discontinued benralizumab or non-benralizumab biologics use and did not receive any biologic treatment after discontinuation. The definition of index dates and baseline for patients who switched treatment during the study is detailed in Section 6.3 of SAP v5.0.

The calculation of PY for patients with treatment switch is specified in Section 6.4 of SAP v5.0. Considering the possible lag period between a treatment and cancer development, a lag time sensitivity analysis was also performed (refer to Section 6.11.5 of SAP v5.0).

Table 2 Study Population (ISAR and CHRONICLE)

ISAR	CHRONICLE
Inclusion Criteria	
• Individuals, 18 years of age or older, with a diagnosis of severe asthma which requires treatment with guidelines suggested medications for GINA Step 4 (medium-high-dose ICS and LABA or leukotriene modifier/theophylline) and being uncontrolled or GINA Step 5 (maintenance systemic corticosteroid, biologics, or other immunosuppressants). • Uncontrolled [a] asthma.	• Individuals, 18 years of age and older, with a diagnosis of severe asthma for at least 12 months prior to enrolment and currently treated by specialist physicians (eg, pulmonologists and/or allergists) at the Investigator's or sub-investigators' site. • Meeting at least one of the following 3 criteria: ° Uncontrolled [a] on asthma treatment consistent with GINA Step 4 or 5, receiving high-dose ICS [b] with additional controllers. ° Current use of an FDA-approved monoclonal antibody agent for treatment of severe asthma (use is not primarily for an alternative condition). ° Use of systemic corticosteroids or other systemic immunosuppressants (any dose level) for approximately 50% or more of the prior 12 months for treatment of severe asthma (use is not primarily for an alternative condition).
Exclusion Criteria	
• Not willing and able to sign written informed consent. Consent can be obtained from having a responsible, legally authorised representative acting on patient's behalf.	• Not willing and able to sign written informed consent. Consent can be obtained from having a responsible, legally authorised representative acting on patient's behalf. • Not fluent in English or Spanish. • Inability to complete study follow-up or web-based PROs. If the patient does not have email or web access, minimal assistance from others to access the web-based PRO is permitted (ie, receiving the email and/or assisting patient in navigating to the web page); PROs must be completed by the patient. • Received an investigational therapy for asthma, allergy, atopic disease, or eosinophilic disease as part of a clinical trial during the 6 months prior to enrolment.

[a] Uncontrolled is defined by meeting at least one of the following (as outlined by American Thoracic Society/European Respiratory Society guidelines):

1) Poor symptom control: Asthma Control Questionnaire consistently > 1.5, Asthma Control Test < 20 (or "not well controlled" by National Asthma Education and Prevention Program/GINA guidelines).

2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids (> 3 days each) in the previous 12 months.
3) Serious exacerbations: at least one hospitalisation, intensive care unit stay or mechanical ventilation in the previous 12 months.
4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 < 80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal).

[b] High-dose ICS is defined as: ICS at a cumulative dose of > 500 µg fluticasone propionate equivalents daily or highest labelled dose of a combination of ICS/LABA.

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; FDA = Food and Drug Administration; FEV_1 = forced expiratory volume during 1 second; FVC = forced vital capacity; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; ISAR = International Severe Asthma Registry; LABA = long-acting β-adrenoreceptor agonists; PRO = patient reported outcome.

9.4 Variables

The new onset malignancy data were collected at the baseline visit and at follow-up visits. In the CHRONICLE study, follow-up visits are scheduled to occur every 6 months, while in ISAR, the frequency of follow-up visits was not pre-determined, and they occurred as needed.

Both ISAR and CHRONICLE collected data on demographic characteristics, relevant medical history, laboratory tests of interest, diagnostic procedures, lung function testing, presence of confirmed allergy, asthma control, asthma medications, serious infection, and anaphylaxis. For further details refer to Section 5.3 of the SAP v5.0.

9.5 Data Sources and Measurement

The study objectives were assessed using a combined dataset from ISAR and CHRONICLE.

Both ISAR and CHRONICLE recruit a similar study population of patients with severe asthma (using similar inclusion and exclusion criteria previously enumerated) and follow-up to collect data in a similar fashion.

All variables from ISAR and CHRONICLE have been mapped and their values assessed for the ability to pool results for combined analysis. No major issues were identified and all relevant variables from the domains were mapped directly. There were some challenges merging on the following fields: occupation, medication, comorbidities, and medication dose. The challenges stemmed mainly from differences in terminology across the countries. These were addressed through clinical review of these terms and harmonisation across the datasets prior to data analysis. This means that the exposure, the outcome, and all key covariates for generating the PS align between ISAR and CHRONICLE databases allowing for a smooth data pooling.

9.6 Bias

Given the nature of this observational study, patients in the 3 cohorts may differ with regard to important demographics and baseline characteristics. For the details about limitations of the research methods refer to Section 9.9 of CSP v5.0 and Section 11.2. To assess signs of potential imbalances, differences between cohorts with regard to potential risk factors of malignancy (described in Section 5.3 of SAP v5.0) were explored in the main and subpopulation analysis sets using descriptive summaries. Considering the impact of potential imbalances between study cohorts, estimates in this study were adjusted based on PS. The PS determine the probabilities of patients receiving benralizumab and were calculated using a logistic regression model. Other methods to tackle bias are discussed in Section 9.9.4 on sensitivity analyses.

9.7 Study Size

At the time of IA2, which included a total of 5324 patients contributing approximately 11949 PY in the main analysis, there were concerns from PRAC about the ability to reach the estimated total number of patients and follow-up time (14000 patients contributing 39500 PY of follow-up time) as projected in the protocol by the expected end of data collection (31 December 2023). Since then, additional measures such as ISAR's increasing collaborations with more countries and improvements in data collection to minimise the exclusion of patients, have led to substantial increase in the sample size reported in this IA3.

In this IA3, 9572 patients are included in the main analysis, which is approximately 1.8 times more than the number of patients in IA2. The overall PY of follow-up in the main analysis in this IA is 27090.6 as of 31 December 2022, which is approximately 2.3 times more than the overall PY in IA2. In the benralizumab cohort, a total of 4005.2 PY were accrued (refer to Section 10.1.1), while in the non-benralizumab biologics cohort and in the non-biologic cohort, 13459.0 PY and 9626.5 PY were accrued, respectively.

Furthermore, in the sensitivity analysis, which included patients who initiated biologics or enrolled in the registry prior to 1 November 2017, 17478 patients were included in the cohorts for the crude analysis, although patients could have contributed follow-up time to more than one cohort (Section 10.4.7.2). The overall follow-up time at risk in the crude analysis in this sensitivity analysis was 88108.7 PY, with 5150.3 PYs for the benralizumab cohort, 39527.3 PY for the non-benralizumab cohort and 43431.1 in the non-biologic cohort (Section 10.4.7.2).

The data collection and enrolment into this PASS study is ongoing and the planned date for end of data collection is 31 October 2023 for ISAR and 31 December 2023 for CHRONICLE. For a detailed explanation of the projected study sample size at the end of data collection refer to Section 9.5 of CSP v5.0 and Section 11.

9.8 Data Transformation

All the data transformation methods were followed as per CSP (refer to Section 9.6 of CSP v5.0). Data from the 2 datasets were pooled to create the analysis dataset prior to statistical analyses. Details of the collected variables are included in the CRFs for the study (a list of the CRFs is included in Annex 1 of the CSP v5.0). There was no coding system for the exposure or the covariates as information was entered directly to the clinical report form which was standard across sites and countries for ISAR and across sites for CHRONICLE.

Collected data for new malignancy cases (outcome) from both databases were reviewed for quality and then coded using international statistical classification of diseases and related health problems ICD-10 codes by an oncologist. Cases that were not reviewed by an

oncologist were excluded from this analysis. This ensures harmonisation of the outcome across databases and a seamless data merging of this key variable.

9.9 Statistical Methods

9.9.1 Main Summary Measures

All analyses are made based on the aforementioned analysis sets, including pooled data from ISAR and CHRONICLE, and separately by data source (ISAR and CHRONICLE). The main analysis was conducted on pooled data. Subpopulation analysis was performed to support the main analysis. For detailed methodology, refer to Section 6 of the SAP v5.0. Percentages for categorical data are based on the number of patients in each cohort. Statistical methods are also footnoted in the relevant results tables, and any changes to analyses from the SAP are noted and reported in their respective sections. All analyses were performed using SAS® v9.4 or higher.

9.9.2 Main Statistical Methods

9.9.2.1 Characteristics of Patients and New Malignancy Cases

Demographics and other baseline characteristics of patients, and characteristics of new malignancies developed during the follow-up were summarised using descriptive statistics.

9.9.2.2 Propensity Score

Propensity score is the probability that patients would receive a particular treatment given their baseline characteristics. In this study, an inverse probability of treatment weighting approach with PS was used to balance the 3 cohorts in terms of baseline characteristics to account for confounding. Since there was no intent to compare between the non-benralizumab biologics versus non-biologic cohort, separate sets of PS were generated for each comparison between benralizumab versus non-benralizumab biologics cohorts and between benralizumab versus non-biologic cohorts. The PS model was adjusted for the following covariates: age, sex, BMI, smoking status, comorbid conditions (allergic rhinitis, cardiovascular disease, liver disease, COPD, chronic rhinosinusitis, diabetes, and nasal polyps), asthma medications (LABA, LAMA, theophylline, LTRA, macrolide antibiotics and steroid-sparing agents), steroid use, previous serious infection, previous anaphylaxis, previous chemotherapy as well as history of malignancy.

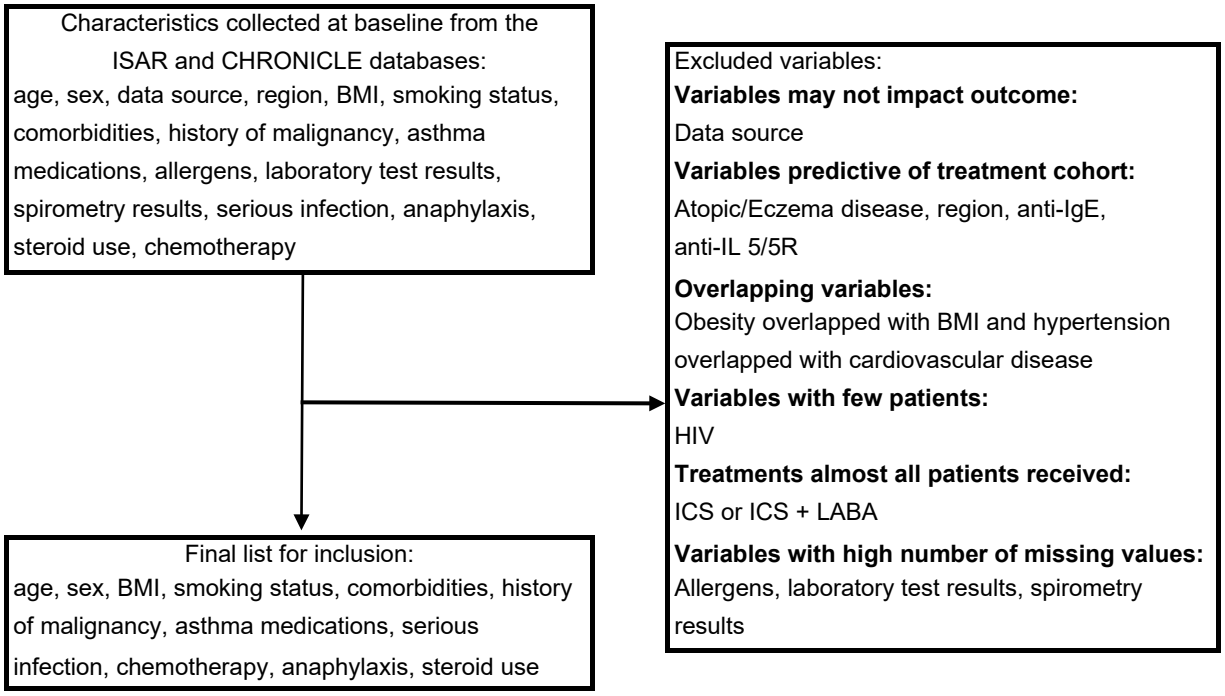
Because a patient needed to have a complete set of covariates for inclusion in weighted PS analyses, the covariates in the PS model were reduced from the original full variables list based on missingness and data quality/availability as proposed in SAP v5.0 Section 6.11.1. Laboratory results (blood eosinophil, IgE, fractional exhaled nitric oxide, allergen sensitisation) and spirometry (% FEV_1, % FVC, pre- and post-bronchodilator FEV_1 and FVC, and pre- and post-bronchodilator FEV_1/FVC) had more than 10% missing values and were thus not included in the PS model. Almost all patients in this study received ICS or

ICS + LABA treatment, thus those corresponding asthma treatment variables were excluded from the model. Region was not included in the model because the approval time of benralizumab varied across regions which might impact patients' choice of receiving the benralizumab. Hypertension was excluded from the PS model as this was included in cardiovascular disease. The flow chart states detailed reasons for excluding baseline variables in Figure 1.

A separate PS was also calculated for each subpopulation analysis set. The balance of the covariates across 3 cohorts before and after adjusting PS was examined. As previously stated in the approved SAP v5.0, patients with extreme weights (values above the 99th and below the 1st percentile) were excluded in estimating adjusted incidence rates (refer to Section 6.11.2 of SAP v5.0) and the weighted Cox-proportional hazard model (refer to Section 6.11.3 of SAP v5.0).

Stratified analysis of PS was also performed, with the number of strata limited to 5 because of a low incidence of malignancies in the data. Patients were subclassified into 5 strata based on the quintile distribution of the PS in the benralizumab cohort, and each strata cut-off value was applied to the other two cohorts. The strata reflected the probability of the patient receiving benralizumab, with the first strata indicating the lowest probability of receiving benralizumab. Side-by-side box plots of PS for each comparison within each quintile were displayed and visually compared for the balance (refer to Section 6.11.1 of SAP v5.0).

Figure 1 Variables Excluded from Propensity Score Model



Abbreviations: BMI = body mass index; CHRONICLE = AZ sponsored United States Severe Asthma Study; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; HIV = human immunodeficiency virus; ISAR = International Severe Asthma Registry; LABA = long-acting β-adrenoreceptor agonists.

9.9.2.3 Incidence Rates and Event Rates

The definition of incidence rates and event rates, and time at risk for incidence rates and event rates are described in Sections 6.11.2 and 6.4.2 of SAP v5.0, respectively. Poisson regression models were used to estimate the incidence rate, difference in incidence rate, incidence rate ratio and corresponding 95% CIs. For adjusted estimates, poison regression models controlled for cohort, age, sex, region, smoking and BMI. All incidence rates were reported as new malignancies incidence rates per 1000 PY.

9.9.2.4 Time to Event Analysis

Time from the index date (defined in Section 6.11.3 of SAP v5.0) to first new malignancy for each cohort, subgroup and data source was displayed graphically using Kaplan-Meier plots. Cox-proportional hazard models were used to estimate the hazard ratio and 95% CIs after adjusting for cohort, age, sex, region, smoking, and BMI.

9.9.3 Missing Values

The procedures for handling missing values were discussed in Section 6.6 of the SAP v5.0.

9.9.4 Sensitivity Analyses

The following sensitivity analyses were performed:

Lag Time Considerations

To explore the potential impact of the lag period on the estimation, incidence rates, event rates, and time to event were estimated after excluding patients with new malignancies developed within one year after the index dates (ie, one year after initiation of benralizumab or any non-benralizumab biologic or enrolment in the database for non-biologic patients).

For patients with treatment switch, a one-year lag period was explored as well, considering such patients as the previous cohort within one year after the switching treatment date, ie, exposure data and events diagnosed within this time should be included in their previous cohort and not in the cohort they switched to.

Alternative Definition of Index Date

Since there were many more non-benralizumab biologics users who initiated biologics before 01 November 2017, an alternative definition of the index date was used to minimise this exclusion. In this sensitivity analysis, the index dates for the benralizumab and non-benralizumab biologics cohort were defined as the first biologic use, and for the non-biologic cohort as database entry, regardless of whether these dates were before, on, or after 01 November 2017. Incidence rates, event rates, and time to event analysis were estimated using this definition.

9.9.5 Amendments to the Statistical Analysis Plan

Minor amendments were made to the SAP to include clarification of no treatment switch in the non-biologic cohort and follow-up time for patients who start biologics after registry entry. Handling of missing start/end dates for concomitant medications, death and study discontinuation dates, malignancy data and smoking status were also clarified. For further details see Amendment History in SAP v5.0

9.10 Quality Control

All patients enrolled in the ISAR and CHRONICLE databases were followed by asthma specialists who confirmed the diagnosis of severe uncontrolled asthma prior to patient enrolment. All countries participating in ISAR abide by data quality control operating procedures.

Data quality was assessed via a series of pre-programmed data quality checks that automatically detect out-of-range or anomalous data on the data collection instrument, the eCRF. To minimise data entry errors, most of the fields requested on the ISAR eCRF were numeric. Data quality was further enhanced through a series of data cleaning and validation programs by utilising robust data management programs (SAS v9.4) to detect discrepancies or implausible data. A clinical review was also performed by an independent oncologist to ensure that the data were compatible with the known clinical history of malignancy in cases

that were identified (see also Section 9.8). Sites were queried for further information and the raw data were updated by the sites prior to transmission of the data, anonymisation, merging, and subsequent analysis.

Information that remains missing or unknown after this process are identified as such in this report. For such data, the query process shall continue and improve on the data where sites provide information, with each subsequent analysis and report.

Data monitoring was accomplished largely through automated edit checks within the electronic data capture system and remote monitoring of site performance and aggregated data. In-person site monitoring may be performed if a specific cause requires investigation. All the modifications to the data were recorded in an audit trail.

10. RESULTS

The source tables and figures referenced in this report are presented in Appendix B.

10.1 Patients

10.1.1 Overall Population

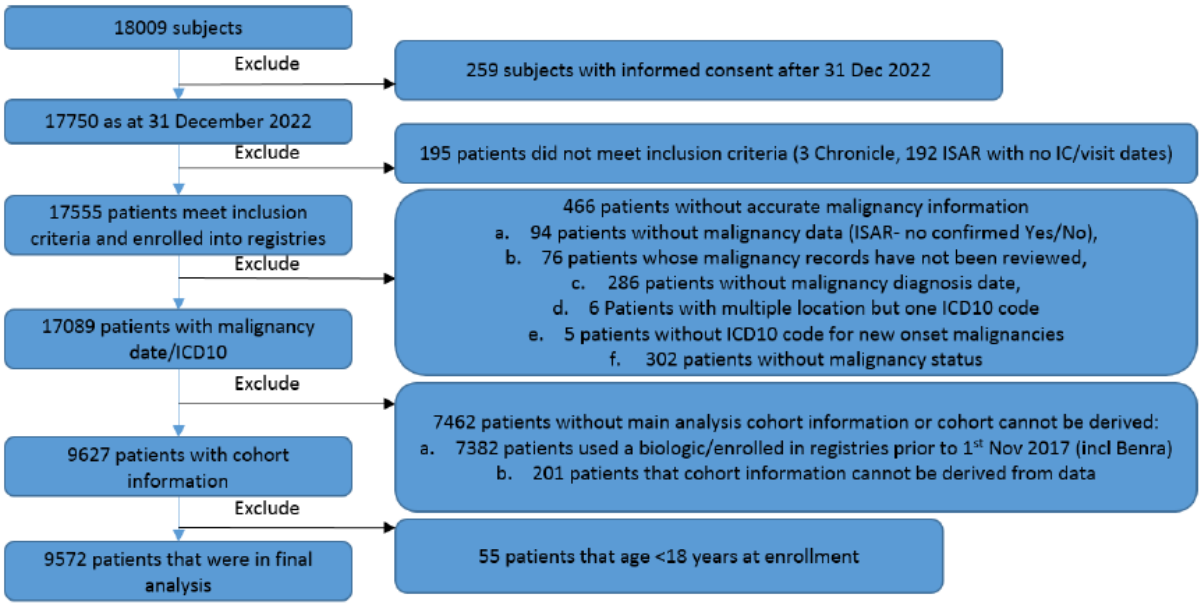
Figure 2 represents a hierarchical exclusion flow of patients. As patients might have had multiple reasons for exclusion from the analysis set, the numbers may not match the disposition numbers the footnote of in Table 14.1.1.1 which do not apply a hierarchical exclusion logic.

At the time of data extraction, 18009 patients with malignancy data had been enrolled in both ISAR and CHRONICLE. Of these patients, 259 were excluded because their enrolment date was after 31 December 2022 (which is the data cut-off point for this interim report) and 195 were excluded because they did not meet the inclusion criteria.

Of the 17555 patients with informed consent in the relevant time window, 7983 patients were further excluded for various reasons, leaving 9572 patients for the main analysis.

Of the 7983 patients excluded from the main analysis (applying the exclusion criteria in a hierarchical logic as presented in Figure 2), 7382 patients reported initial use of a biologic or enrolment in the study registry prior to 1 November 2017. Most of the patients excluded for this reason were included in a sensitivity analysis (Section 10.4.7.2).

Figure 2 Patient Disposition Exclusion Flowchart (ISAR and CHRONICLE Combined Analysis Set)



Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ICD-10 = International Classification of Diseases 10th Revision; ISAR = International Severe Asthma Registry.
Source: Figure 14.1.1.1

Patient disposition of eligible patients from ISAR and CHRONICLE are summarised in Table 3. For database-specific analysis refer to Table 14.1.1.2 (for ISAR) and Table 14.1.1.3 (for CHRONICLE). Note that the term "other-biologic cohort" is used to describe the non-benralizumab biologics cohort in the in-text and source data tables (Appendix B).

Among the 9572 patients in the main analysis, there were 1554 patients in the benralizumab cohort, 4436 patients in the non-benralizumab biologics cohort, and 4036 patients in the non-biologic cohort. The overall PY of follow-up in this IA is 27090.6 as of 31 December 2022, with the follow-up for the benralizumab cohort at 4005.2 PY, the non-benralizumab biologics cohort at 13459.0 PY, and the non-biologic cohort at 9626.5 PY.

Of the 9572 patients included in the main analysis, a total of 5.9% (562/9572) patients discontinued from the study, but since discontinuation date was not recorded for patients in the ISAR registry unless it was death caused by malignancy, serious infection, or anaphylaxis, all discontinuation data is for patients in the CHRONICLE study.

Within the cohorts, the proportion of patients who discontinued were 8.4% (130/1554) in the benralizumab cohort, 5.6% (248/4436) in the non-benralizumab biologics cohort, and 5.5% (222/4036) in the non-biologic cohort.

Of the patients included in the main analysis, 0.5% (46/9572) discontinued due to death. Within the cohorts, the proportion of patients who discontinued due to death was 0.7% (11/1554) in the benralizumab cohort, 0.5% (23/4436) in the non-benralizumab biologics cohort, and 0.3% (14/4036) in the non-biologic cohort.

In the benralizumab cohort, 16.2% (252/1554) patients switched to the non-benralizumab biologics cohort, while 6.2% (273/4436) patients of the non-benralizumab biologics cohort switched to the benralizumab cohort. By study design, there were no switches within the non-biologic cohort, as starting of a biologic was considered a censoring criterion in this cohort.

Table 3 Patient Disposition (ISAR and CHRONICLE Combined Analysis Set)

	Number (%) of patients			
	Benralizumab cohort	**Other-biologic cohort**	**Non-biologic cohort**	**Total**
Patients met inclusion criteria	1554	4436	4036	9572
Patients discontinued [a]	130 (8.4)	248 (5.6)	222 (5.5)	562 (5.9)
Patients died during follow-up	11 (0.7)	23 (0.5)	14 (0.3)	46 (0.5)
Patients discontinued without a switch [b]	92 (5.9)	210 (4.7)	222 (5.5)	524 (5.5)
Patients discontinued treatment [c]	599 (38.5)	1506 (33.9)	NA	1901 (19.9)
Patients discontinued treatment without a switch [b,c]	395 (25.4)	1302 (29.4)	NA	1697 (17.7)
Patients switched to another cohort	252 (16.2)	273 (6.2)	NA	454 (4.7)
Switch to benralizumab cohort	NA	273 (6.2)	NA	NA
Switch to other-biologic cohort	252 (16.2)	NA	NA	NA
Total follow-up time (years)				
Mean (SD)	2.5 (1.32)	3.0 (1.38)	2.4 (1.36)	2.7 (1.39)
Median	2.6	3.1	2.3	2.8
Q1, Q3	1.4, 3.6	1.9, 4.2	1.2, 3.4	1.5, 3.8
Min, Max	0.0, 5.1	0.0, 5.2	0.0, 5.2	0.0, 5.2
Total PY of follow-up (years)	4005.2	13459.0	9626.5	27090.6

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry; PY = person-years; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

[a] Discontinuation of study and death date were not collected in ISAR. Note: ISAR only recorded deaths resulting from malignancy, anaphylaxis event, and serious infection. Deaths due to other reasons were not captured. ISAR patients with deaths reported were censored at date of last visit. All other discontinuations were based on CHRONICLE data.

[b] Patients without cohort switch was defined as patients who stayed in only one cohort from the beginning of the study.

[c] Discontinuation of treatment is defined as discontinuation from either benralizumab or other-biologic without receiving any further biologic treatment in the study. Patients who discontinued still contributed person time to their respective cohort after discontinuation.

Non-biologic cohort is defined as patients who never received benralizumab or other-biologic treatment. Patients who switched cohort were counted in each of the cohort in turn, but were only counted once in the total column. The number of patients in total column may not be equal to the sum of numbers of patients in each cohort. If not stated otherwise, percentages were based on number of patients enrolled in the database. Total person-years of follow-up (years) = [(The earliest date of either; end of study, death, last visit before the loss to follow-up or date cut-off) – the index date + 1]/365.25.

Source: Table 14.1.1.1

10.2 Descriptive Data

10.2.1 Baseline Demographic Characteristics (Prior to PS Trimming)

For abbreviated patient baseline demographic characteristics of the ISAR and CHRONICLE combined analysis refer to Table 4. For complete patient baseline demographic characteristics of the ISAR and CHRONICLE combined analysis refer to Table 14.1.2.1 and for separate analysis sets refer to Table 14.1.2.2.

More than half of the study population (56% [5363/9572]) were aged 40 to < 65 years which was consistent across all cohorts. The majority of patients from the overall study population were white (61.5% [5884/9572]) and were female (64.8% [6199/9572]).

Table 4 Demographic Characteristics Prior to Propensity Score Trimming (ISAR and CHRONICLE Combined Analysis Set)

		Number (%) of patients			
Demographic characteristic	**Statistics or category**	**Benralizumab cohort (N = 1554)**	**Other-biologic cohort (N = 4436)**	**Non-biologic cohort (N = 4036)**	**Total (N = 9572)**
Age (years)	n	1551	4421	4000	9519
	Mean (SD)	54.8 (13.91)	52.4 (14.54)	53.5 (15.58)	53.2 (14.94)
	Median	56.0	54.0	55.0	54.8
Age (years) subgroups n (%)	≥ 18 to < 40	224 (14.4)	907 (20.4)	817 (20.2)	1868 (19.5)
	≥ 40 to < 65	918 (59.1)	2573 (58.0)	2152 (53.3)	5363 (56.0)
	≥ 65 to < 80	385 (24.8)	890 (20.1)	909 (22.5)	2094 (21.9)
	≥ 80	24 (1.5)	51 (1.1)	122 (3.0)	194 (2.0)
	Total	1551 (99.8)	4421 (99.7)	4000 (99.1)	9519 (99.4)
	Missing	3	15	36	53
Sex n (%)	Female	1013 (65.2)	2869 (64.7)	2616 (64.8)	6199 (64.8)
	Male	540 (34.7)	1562 (35.2)	1390 (34.4)	3337 (34.9)
	Total	1553 (99.9)	4431 (99.9)	4006 (99.3)	9536 (99.6)

		Number (%) of patients			
Demographic characteristic	**Statistics or category**	**Benralizumab cohort (N = 1554)**	**Other-biologic cohort (N = 4436)**	**Non-biologic cohort (N = 4036)**	**Total (N = 9572)**
	Missing	1	5	30	36
Data source n (%)	ISAR	1002 (64.5)	3101 (69.9)	3266 (80.9)	7122 (74.4)
	CHRONICLE	552 (35.5)	1335 (30.1)	770 (19.1)	2450 (25.6)
Race n (%)	White	1141 (73.4)	3101 (69.9)	1945 (48.2)	5884 (61.5)
	Black or African American	133 (8.6)	303 (6.8)	177 (4.4)	546 (5.7)
	Asian	92 (5.9)	277 (6.2)	814 (20.2)	1159 (12.1)
	Native Hawaiian or Other Pacific Islander	2 (0.1)	4 (0.1)	0	6 (0.1)
	American Indian or Alaska Native	2 (0.1)	8 (0.2)	1 (0.0)	11 (0.1)
	Other	67 (4.3)	256 (5.8)	617 (15.3)	921 (9.6)
	Total	1437 (92.5)	3949 (89.0)	3554 (88.1)	8527 (89.1)
	Missing	117	487	482	1045

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry; n = number of patients in analysis; N = number of patients in cohort; SD = standard deviation.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set. Patients who switched cohort were counted in each of the cohort in turn, but were only counted once in the total column. The number of patients in total column may not be equal to the sum of numbers of patients in each cohort.

Source: Table 14.1.2.1

10.2.2 Baseline Clinical Characteristics (Prior to Propensity Score Trimming)

For complete patient baseline clinical characteristics of the ISAR and CHRONICLE combined analysis set refer to Table 14.1.3.1 and for separate analysis sets refer to Table 14.1.3.2. For abbreviated patient baseline clinical characteristics of the ISAR and CHRONICLE combined analysis refer to Table 5.

At baseline, patients' asthma exacerbations, hospital admissions, emergency department visits, and invasive ventilations include events up to one year prior to index date, except for invasive ventilations reported by ISAR, which may have occurred at any time prior to index date. Serious infection, anaphylaxis, and history of malignancy at any time on or prior to index date are included in the count. Other variables were assessed at initial index date.

Less than a third (30.1% [2878/9572]) of the overall study population were either previous or current smokers. The proportion of previous and/or current smokers was comparable across the cohorts, although there was a slightly lower proportion in the non-biologic cohort. The mean (SD) age at asthma onset ranged from approximately 30 (19.55) to 33 (19.64) years across the cohorts.

Medication adherence to the prescribed asthmatic drugs across all cohorts was high, with an estimate of 74.0% (1150/1554) patients reported in the benralizumab cohort, 72.9% (3236/4436) in the non-benralizumab biologics cohort, and 84.6% (3416/4036) in the non-biologic cohort. Adherence was evaluated by the treating physician of each patient and was determined based on either clinical impression or objective measures (eg, review of prescription records).

At baseline, asthma status across cohorts was uncontrolled in 39.7% (3801/9572) of the patients. The non-biologic cohort had the greatest percentage of uncontrolled asthma status, 44.6% (1800/4036), compared to 35.7% (555/1554) for the benralizumab cohort, and 37.3% (1653/4436) for the non-benralizumab biologics cohort.

Table 5 Patient Clinical Characteristics at Baseline Prior to Propensity Score Trimming (ISAR and CHRONICLE Combined Analysis Set)

		Number (%) of patients			
Demographic characteristic	**Statistics or category**	**Benralizumab cohort (N = 1554)**	**Other-biologic cohort (N = 4436)**	**Non-biologic cohort (N = 4036)**	**Total (N = 9572)**
Body mass index (kg/m^2)	n	1462	4218	3841	9077
	Mean (SD)	30.192 (7.6513)	29.930 (7.5245)	28.821 (7.2571)	29.456 (7.4436)
Smoking status n (%)	Non-smoker	1047 (67.4)	2955 (66.6)	2793 (69.2)	6501 (67.9)
	Previous and/or current smoker	493 (31.7)	1435 (32.3)	1106 (27.4)	2878 (30.1)
	Total	1540 (99.1)	4390 (99.0)	3899 (96.6)	9379 (98.0)
	Missing	14	46	137	193
Pack years [a]	n	443	1254	1018	2576
	Mean (SD)	17.049 (18.6973)	17.712 (20.7203)	15.893 (17.4456)	16.947 (19.2358)
Age at asthma onset (years)	n	1144	3239	3459	7495
	Mean (SD)	32.632 (19.8027)	30.404 (19.5496)	32.752 (19.6447)	31.830 (19.6454)

		Number (%) of patients			
Demographic characteristic	**Statistics or category**	**Benralizumab cohort (N = 1554)**	**Other-biologic cohort (N = 4436)**	**Non-biologic cohort (N = 4036)**	**Total (N = 9572)**
Number of exacerbations [b]	n	1554	4436	4036	9572
	Mean (SD)	1.0 (1.53)	0.7 (1.33)	0.8 (1.21)	0.8 (1.29)
Number of invasive ventilations	n	1554	4436	4036	9572
	Mean (SD)	0.0 (0.13)	0.0 (0.17)	0.1 (0.66)	0.0 (0.45)
Number of hospital admissions	n	1554	4436	4036	9572
	Mean	0.2 (0.75)	0.2 (0.84)	0.2 (0.68)	0.2 (0.76)
Number of emergency department visits	n	1554	4436	4036	9572
	Mean (SD)	0.3 (1.22)	0.3 (1.56)	0.6 (1.90)	0.4 (1.67)
Medication adherence status n (%) [c]	Yes	1150 (74.0)	3236 (72.9)	3416 (84.6)	7446 (77.8)
	No	26 (1.7)	78 (1.8)	67 (1.7)	162 (1.7)
	Total	1176 (75.7)	3314 (74.7)	3483 (86.3)	7608 (79.5)
	Missing	378	1122	553	1964
Asthma control status n (%) [d]	Well controlled	280 (18.0)	769 (17.3)	517 (12.8)	1501 (15.7)
	Partially controlled	261 (16.8)	893 (20.1)	876 (21.7)	1954 (20.4)
	Not controlled	555 (35.7)	1653 (37.3)	1800 (44.6)	3801 (39.7)
	Total	1096 (70.5)	3315 (74.7)	3193 (79.1)	7256 (75.8)
	Missing	458	1121	843	2316
History of malignancy n (%)	Yes	57 (3.7)	125 (2.8)	132 (3.3)	295 (3.1)
	No	1497 (96.3)	4311 (97.2)	3904 (96.7)	9277 (96.9)
	Total	1554 (100)	4436 (100)	4036 (100)	9572 (100)

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; GINA = Global Initiative for Asthma; ISAR = International Severe Asthma Registry; n = number of patients in analysis; N = number of patients in cohort; SD = standard deviation.

[a] Number of pack years = number of years smoked × [number of cigarettes smoked per day/20] (1 pack/20 cigarettes).

[b] The number of exacerbations only counts severe asthma exacerbations, which were defined as events that require rescue steroids.

[c] The medication adherence status of asthma treatment was evaluated based on either clinical impression or objective measures (eg, review of prescription records).

[d] Categorised according to the GINA Asthma Control Criteria.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set. Baseline is defined as the last record on or prior to the index date. For patients who switched treatment, the baseline for the new cohort is the last record before the switch. Number of exacerbations, hospital admissions, emergency department admissions and invasive ventilations (except ISAR) summarise all events occurring within 12 months preceding index dates within each cohort. For ISAR, number of invasive ventilations summarise all events ever preceding index dates within each cohort. Patients who switched cohort were counted in each of the cohort in turn but were only counted once in the total column.

The number of patients in total column may not be equal to the sum of numbers of patients in each cohort. Total column summarises patient baseline characteristics for first exposure (first cohort).

Source: Table 14.1.3.1 and Table 14.1.5.1

10.2.3 Baseline Comorbidities (Prior to Propensity Score Trimming)

For complete baseline comorbidities of the ISAR and CHRONICLE combined analysis set refer to Table 14.1.4.1 and for separate analysis sets refer to Table 14.1.4.2. The baseline comorbidities from the ISAR and CHRONICLE are summarised in Table 6 with percentages below based on the total number of patients in each cohort.

In each cohort, most patients had at least one comorbidity at baseline: 94.2% (1464/1554) in the benralizumab cohort, 93.8% (4159/4436) in the other-biologic cohort, and 93.9% (3788/4036) in the non-biologic cohort.

Of the asthma-related comorbidities, the most common in the benralizumab and non-benralizumab biologics cohort, was allergic rhinitis with a prevalence of 45.5% (707/1554) and 53.3% (2363/4436), respectively. The most common asthma-related comorbidity in the non-biologic cohort was atopic diseases/eczema (68.2% [2752/4036]). The prevalence of chronic rhinosinusitis (operationally defined to exclude allergic rhinitis and nasal polyps) was higher in the benralizumab (40.9% [636/1554]) and non-benralizumab biologics (40.3% [1786/4436]) cohorts, compared with the non-biologic cohort (29.0% [1172/4036]). Nasal polyps were also more commonly reported in the benralizumab (17.8% [277/1554]) and non-benralizumab biologics (19.4% [859/4436]) cohorts than the non-biologic (13.7% [552/4036]) cohort. Chronic obstructive pulmonary disease was reported in all 3 cohorts (benralizumab cohort 10.2% [159/1554], non-benralizumab biologics cohort 8.2% [364/4436], and non-biologic cohort 3.1% [127/4036]).

Obesity was the most common OCS-related comorbidity at baseline with the benralizumab cohort reporting 40.2% [625/1554] with this comorbidity, followed by the non-benralizumab biologics cohort 39.7% [1761/4436], and the non-biologic cohort 33.1% [1337/4036]. Diabetes was the least reported OCS-related comorbidity at baseline with the benralizumab

cohort reporting 12.1% [188/1554] with this comorbidity, followed by the non-benralizumab biologics cohort 10.3% [457/4436], and the non-biologic cohort 9.4% [380/4036].

Other baseline comorbidities were not generally comparable and differences in baseline comorbidities and characteristics were adjusted across the cohorts in the analysis by means of PS weighting.

Table 6 Comorbidities at Baseline Prior to Propensity Score Trimming (ISAR and CHRONICLE Combined Analysis Set)

	Number (%) of patients		
Comorbidity term	**Benralizumab cohort (N = 1554)**	**Other-biologic cohort (N = 4436)**	**Non-biologic cohort (N = 4036)**
Patients with any comorbidities at baseline	1464 (94.2)	4159 (93.8)	3788 (93.9)
Asthma-related comorbidities			
Allergic rhinitis	707 (45.5)	2363 (53.3)	2100 (52.0)
Atopic diseases/eczema [a]	610 (39.3)	2003 (45.2)	2752 (68.2)
Chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps)	636 (40.9)	1786 (40.3)	1172 (29.0)
Nasal polyps	277 (17.8)	859 (19.4)	552 (13.7)
Oral corticosteroids-related comorbidities			
Cardiovascular disease [b]	533 (34.3)	1347 (30.4)	707 (17.5)
Diabetes	188 (12.1)	457 (10.3)	380 (9.4)
Hypertension	406 (26.1)	1034 (23.3)	527 (13.1)
Obesity	625 (40.2)	1761 (39.7)	1337 (33.1)
Other comorbidities			
Chronic obstructive pulmonary disease	159 (10.2)	364 (8.2)	127 (3.1)
Human immunodeficiency virus	0	1 (0.0)	0
Liver disease	11 (0.7)	38 (0.9)	6 (0.1)

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry; N = number of patients in cohort.

[a] Examples of atopic diseases/eczema are atopic asthma, atopic dermatitis, and eczema but excluding allergic rhinitis as this was accounted for separately.

[b] Cardiovascular disease included hypertension. Examples of cardiovascular disease are hypertension, coronary artery disease, arterial hypertension, and unspecified cardiovascular disease.

Number (%) of patients were sorted alphabetically by comorbidity term. A patient could have one or more comorbidities. Patients with multiple events in the same category were counted only once in that category.

If not stated otherwise, percentages were based upon number of patients in each cohort within the combined analysis set.

Comorbidities at baseline is defined as comorbidities that occurred within 12 months preceding the first index date or had been ongoing at the first index date. Comorbidities with missing start dates/status were considered as baseline comorbidities.

Source: Table 14.1.4.1

10.2.4 Baseline Asthma Medication (Prior to Propensity Score Trimming)

10.2.4.1 Overall Population

For the complete description of baseline asthma medications of the ISAR and CHRONICLE combined analysis set refer to Table 14.1.5.1 and for separate analysis sets refer to Table 14.1.5.2. Asthma medications at baseline for the ISAR and CHRONICLE are summarised in Table 7. Percentages below are based on the total number of patients in each cohort.

All the patients in the benralizumab and non-benralizumab biologics cohorts and 78.8% (3179/4036) of the patients in the non-biologic cohort used at least one asthma medication at baseline. The most commonly used asthma medication at baseline was ICS + LABA, with 52.1% (809/1554) in the benralizumab cohort, 46.3% (2054/4436) in non-benralizumab biologics cohort, and 48.4% (1953/4036) in the non-biologic cohort, followed by LTRA (benralizumab cohort 43.5% [676/1554], non-benralizumab biologics cohort 41.7% [1850/4436], and non-biologic cohort 34.1% [1377/4036]).

Baseline OCS use was assessed as use at any time within one year prior to index date, but baseline OCS dose was the dose at the latest record prior to index date. When comparing across the cohorts, the percentage of patients on maintenance OCS treatment at baseline was lower in the non-biologic cohort (37.3% [1506/4036]) and non-benralizumab biologics cohort (37.9% [1682/4436]) compared to the benralizumab cohort (47.0% [730/1554]) (Table 14.1.5.1).

Medication adherence to the prescribed asthmatic drugs across all cohorts was high. Adherence was evaluated by the treating physician of each patient and was determined based on either clinical impression or objective measures (refer to Section 10.2.2 for detail).

Table 7 Asthma Medication at Baseline Prior to Propensity Score Trimming (ISAR and CHRONICLE Combined Analysis Set)

Asthma medication term	Statistics or category	Benralizumab cohort (N = 1554)	Other-biologic cohort (N = 4436)	Non-biologic cohort (N = 4036)
Patients with any asthma medication		1554 (100)	4436 (100)	3179 (78.8)
Maintenance OCS	Yes	730 (47.0)	1682 (37.9)	1506 (37.3)
	No	824 (53.0)	2754 (62.1)	2530 (62.7)
	Total	1554 (100)	4436 (100)	4036 (100)
Maintenance OCS dose (mg/day)	n	625	1468	1395
	Mean (SD)	26.37 (19.039)	24.13 (18.910)	30.29 (21.842)
ICS only	Yes	546 (35.1)	1590 (35.8)	1169 (29.0)
	No	1008 (64.9)	2846 (64.2)	2867 (71.0)

Asthma medication term	Statistics or category	Benralizumab cohort (N = 1554)	Other-biologic cohort (N = 4436)	Non-biologic cohort (N = 4036)
LABA only	Yes	28 (1.8)	67 (1.5)	40 (1.0)
	No	1526 (98.2)	4369 (98.5)	3996 (99.0)
ICS + LABA	Yes	809 (52.1)	2054 (46.3)	1953 (48.4)
	No	745 (47.9)	2382 (53.7)	2083 (51.6)
LAMA	Yes	598 (38.5)	1577 (35.6)	1194 (29.6)
	No	956 (61.5)	2859 (64.4)	2842 (70.4)
Theophylline	Yes	49 (3.2)	117 (2.6)	132 (3.3)
	No	1505 (96.8)	4319 (97.4)	3904 (96.7)
LTRA	Yes	676 (43.5)	1850 (41.7)	1377 (34.1)
	No	878 (56.5)	2586 (58.3)	2659 (65.9)
Anti-IgE	Yes	76 (4.9)	1586 (35.8)	0
	No	1478 (95.1)	2850 (64.2)	4036 (100)
Anti-IL5/5R	Yes	NA	2002 (45.1)	0
	No	NA	2434 (54.9)	4036 (100)
Macrolide antibiotics	Yes	118 (7.6)	278 (6.3)	161 (4.0)
	No	1436 (92.4)	4158 (93.7)	3875 (96.0)
Steroid-sparing agents	Yes	0	2 (< 0.1)	1 (< 0.1)
	No	1554 (100)	4434 (100.0)	4035 (100.0)

Abbreviations: anti-IgE = anti-immunoglobulin E; anti-IL5/5R = anti-interleukin 5/5 receptor; CHRONICLE = AZ sponsored United States Severe Asthma Study; ICS = inhaled corticosteroids; ISAR = International Severe Asthma Registry; IVIG = intravenous gammaglobulin; LABA = long-acting β-adrenoreceptor agonists; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonist; N = number of patients in cohort; OCS = oral corticosteroids.

Patients with multiple medications were counted once for each asthma medication term.

Doses of ICS and LABA combination treatment were recorded differently in ISAR and CHRONICLE studies and were not summarised in this table.

Steroid-sparing agents included IVIG, methotrexate, and mycophenylate.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

Asthma medications at baseline is defined as asthma medications that started within 12 months preceding the index date or were ongoing at the index date. Baseline asthma medications for patients with follow-up time in more than one cohort were reported for the 12 months preceding index date for each cohort.

Source: Table 14.1.5.1

10.3 Outcome Data

No distinction was made for different types of malignancy, except NMSC. Multiple malignancy events occurring within 3 months and with the same diagnosis (ie, same location and cell type) in a patient were considered one event.

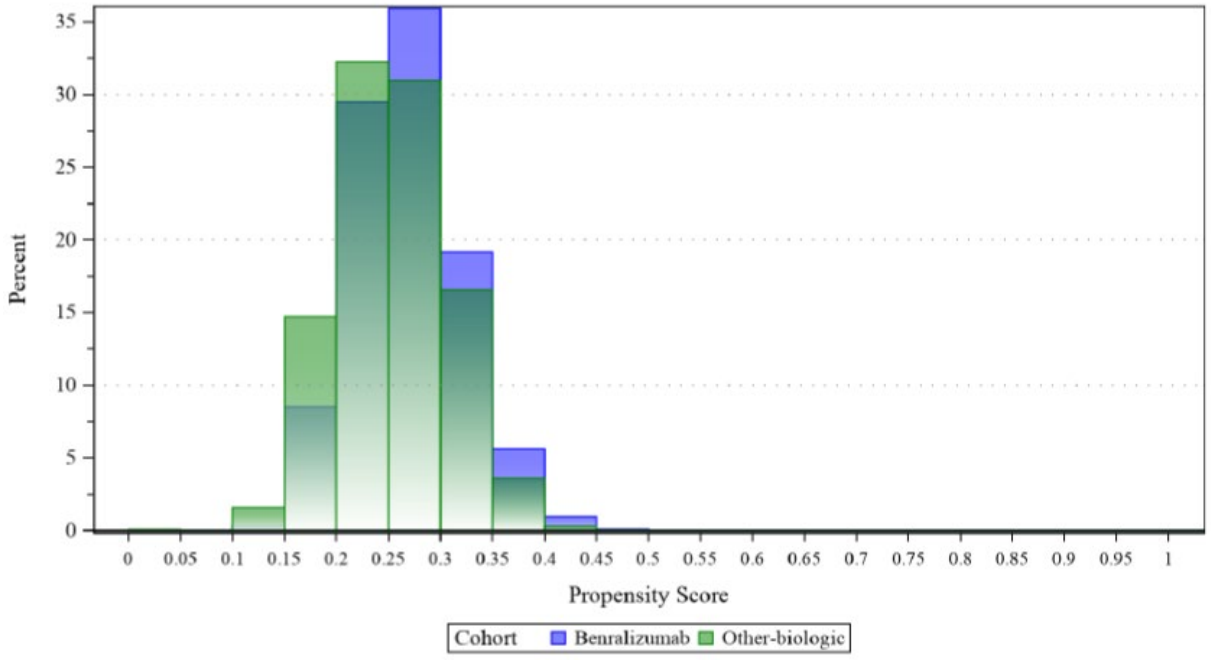
10.4 Main Results

10.4.1 Propensity Score by Cohort

Propensity scores are calculated based on baseline characteristics and indicate the probability that patients would receive benralizumab. The overlaid distribution of PS for the benralizumab cohort versus the non-benralizumab biologics cohort is provided in Figure 3 and for the non-biologic cohort is provided in Figure 4.

The balance of the covariates across 3 cohorts were examined by checking the distribution of PS (graphic approach) and SMD (tabular approach). In Figure 3, the overlapping histograms indicate that the PS model has balanced the baseline characteristics included in the model across the cohorts. In Figure 4, there is less of an overlap indicating slightly less balance between the baseline covariates in these two cohorts.

Figure 3 Overlaid Distribution of Propensity Score for the Benralizumab Cohort Versus the Non-benralizumab Biologics Cohort, Histogram (ISAR and CHRONICLE Combined Analysis Set)

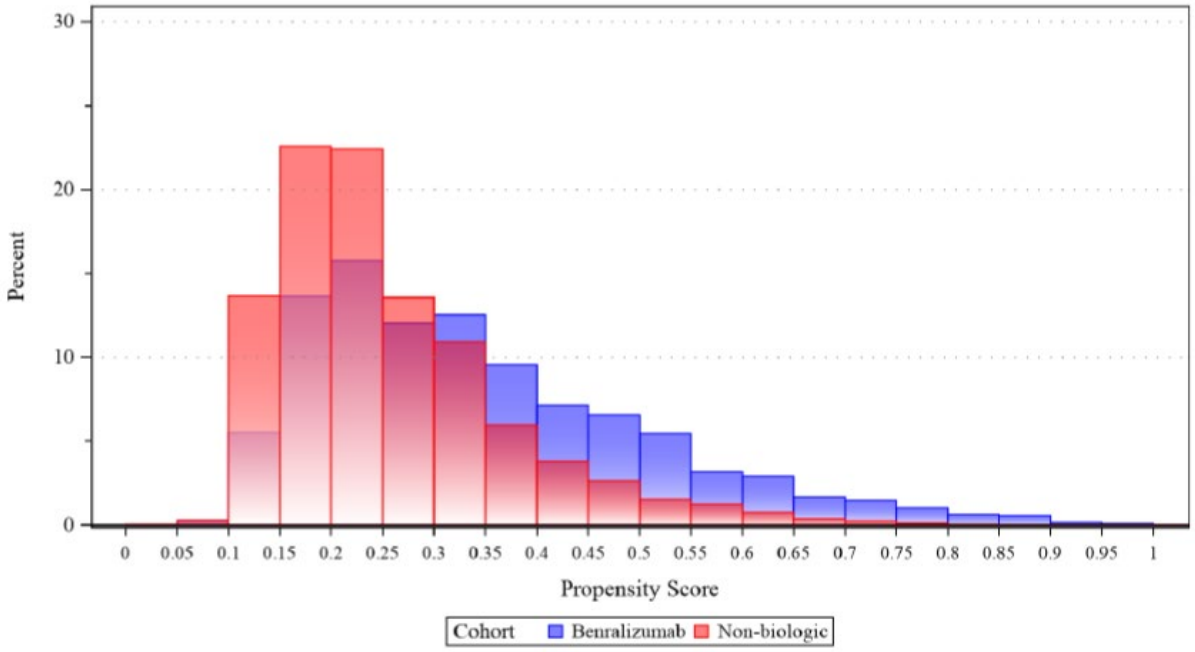


Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry.

Propensity scores were calculated based on baseline characteristics and indicate the probability that patients would receive benralizumab, given measured baseline characteristics.

Source: Figure 14.2.1.2.1

Figure 4 Overlaid Distribution of Propensity Score for the Benralizumab Cohort Versus Non-biologic Cohort, Histogram (ISAR and CHRONICLE Combined Analysis Set)



Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry.

Propensity scores were calculated based on baseline characteristics and indicate the probability that patients would receive benralizumab, given measured baseline characteristics.

Source: Figure 14.2.1.2.2

10.4.1.1 Comparison of Baseline Characteristics Before Trimming: Overall Population

Baseline characteristics are summarised in Section 10.2. Subsequent sub-sections are technical sections discussing the impact of weighting and trimming on the balance of characteristics across the cohorts.

Benralizumab Cohort Versus Non-benralizumab Biologics Cohort

Pre-weighting and post-weighting SMDs are reported in Table 8; for more details refer to Table 14.2.1.1.1. P-values testing the difference between cohorts prior to PS weighting are included, but it is noted that these do not account for multiplicity, and differences reaching nominal significance (eg, $p < 0.05$) may not represent clinically meaningful differences between cohorts.

The variables age, allergic rhinitis, atopic diseases/eczema, cardiovascular disease, hypertension, COPD, use of asthma medications (ICS + LABA, LAMA, anti-IgE, steroid use), blood eosinophil, IgE, FeNO, and allergen sensitisation were not balanced at baseline, and differences reaching nominal significance ($p < 0.05$) between the benralizumab and the non-benralizumab biologics cohort were observed for these variables. Other significant and non-significant variables are reported in Table 8.

A SMD closer to zero indicates an improved balance in that variable between cohorts. When PS weighting was applied to the data, the SMD between the cohorts for all variables included in the PS model decreased to ≤ 0.1, indicating improved balance in the baseline variables following adjustment (Table 8 for pre- and post-weighting SMDs).

Benralizumab Cohort Versus Non-biologic Cohort

Pre-weighting and post-weighting SMDs are reported in Table 8; for more details refer to Table 14.2.1.1.2. As for the previous comparison, p-values testing the difference between cohorts prior to PS weighting are included, but it is noted that these do not account for multiplicity, and differences reaching nominal significance ($p < 0.05$) may not represent clinically meaningful differences between cohorts.

The variables age, data source, region, BMI, smoking status, comorbidities, previous anaphylaxis, asthma medications (ICS only, LABA only, ICS + LABA, LAMA, LTRA, macrolide antibiotics), steroid use, blood eosinophil, IgE, FeNO, and pre- and post-bronchodilator FEV_1/FVC were imbalanced at baseline, ie, differences reaching nominal significance ($p < 0.05$) between the benralizumab cohort and the non-biologic cohort were observed.

Post-weighting absolute SMD was < 0.1 for all the variables included in the PS model, which confirmed that weighting balanced these baseline characteristics across the cohorts (Table 8 for pre- and post-weighting SMDs). Clear improvements in SMD were observed post-weighting in BMI, chronic rhinosinusitis, cardiovascular disease, COPD, and the use of LAMA and LTRA.

Table 8 Standardised Mean Difference Before Trimming

Variable	Benralizumab cohort versus other-biologic cohort		Benralizumab cohort versus non-biologic cohort	
	Pre-weighting SMD	Post-weighting SMD	Pre-weighting SMD	Post-weighting SMD
Age (years)	0.168 [a]	0.008	0.073	0.028
Sex	-0.009	0.005	0.013	-0.004
BMI (kg/m^2)	0.040	0.004	0.174 [a]	0.017
Smoking status	0.006	-0.007	-0.103	-0.013

Variable	Benralizumab cohort versus other-biologic cohort		Benralizumab cohort versus non-biologic cohort	
	Pre-weighting SMD	Post-weighting SMD	Pre-weighting SMD	Post-weighting SMD
Comorbidities				
Allergic rhinitis	0.159 [a]	0.007	0.143 [a]	-0.007
Chronic rhinosinusitis	0.001	-0.001	-0.250 [a]	0.010
Nasal polyps	0.043	0.002	-0.104 [a]	-0.013
Cardiovascular disease	-0.096	-0.003	-0.418 [a]	-0.001
Diabetes	-0.049	0.001	-0.071	0.011
COPD	-0.067	0.000	-0.297 [a]	-0.005
Liver disease	0.011	-0.007	-0.105	-0.001
History of malignancy	-0.054	-0.001	-0.024	-0.012
Previous chemotherapy	0.001	-0.009	-0.019	0.000
Previous anaphylaxis	-0.020	-0.001	-0.055	0.002
Previous serious infection	-0.012	0.001	0.014	-0.010
Asthma medication				
LABA only	-0.022	0.002	-0.076	0.009
LAMA	-0.068	-0.008	-0.180 [a]	-0.010
Theophylline	-0.032	-0.002	0.011	-0.017
LTRA	-0.041	-0.004	-0.181 [a]	-0.008
Macrolide antibiotics	-0.051	0.004	-0.156 [a]	-0.006
Steroid use	-0.112	-0.013	-0.117 [a]	-0.014

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; LABA = long-acting β-adrenoreceptor agonist; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonist; SMD = standardised mean difference.

[a] Variables with the strongest statistical evidence for differences between cohorts prior to PS weighting ($p < 0.001$) are noted to highlight the extent to which the PS weighting improves balance between cohorts.

Source: Table 14.2.1.1.1 and Table 14.2.1.1.2

10.4.1.2 Comparison of Baseline Characteristics After Trimming - Overall Population Benralizumab Cohort versus Non-benralizumab Biologics Cohort

Patients with extreme PS (< 1% and > 99%) were trimmed from the analysis set to further balance the cohorts and differences between baseline characteristics were assessed again. Pre-weighting and post-weighting SMDs are reported in Table 9; for more details refer to Table 14.2.1.3.1 and Table 14.2.1.3.2. The total number of patients (N) for baseline characteristics before and after trimming were 1554 and 1389 in the benralizumab cohort; 4436 and 4109 in the non-benralizumab biologics cohort, respectively. Here also, p-values testing the difference between cohorts prior to PS weighting are included, but these do not

account for multiplicity, and differences reaching nominal significance ($p < 0.05$) may not represent clinically meaningful differences between cohorts.

After weighting and trimming the datasets, the benralizumab and non-benralizumab biologics cohorts' baseline characteristics were comparable for the variables included in the PS, (Table 9 for pre- and post-weighting SMDs).

Benralizumab Cohort Versus Non-biologic Cohort

The total number of patients (N) for baseline characteristics before and after trimming were 1554 and 1389 in the benralizumab cohort; 4036 and 3654 in the non-biologic cohort, respectively. Pre-weighting and post-weighting SMDs are reported in Table 9; for more details refer to Table 14.2.1.3.2.

When PS weighting was applied to the data, the SMD for BMI decreased from 0.184 to 0.034 for the benralizumab versus non-biologic cohort. Similar improvements in SMD were observed post-weighting in other variables. PS weighting and trimming improved balance in baseline characteristics between the benralizumab and non-biologic cohorts (Table 9 for pre- and post-weighting SMDs).

Table 9 Standardised Mean Difference After Trimming

Variable	Benralizumab cohort versus other-biologic cohort		Benralizumab cohort versus non-biologic cohort	
	Pre-weighting SMD	Post-weighting SMD	Pre-weighting SMD	Post-weighting SMD
Age (years)	0.201 [a]	0.026	0.075	0.023
Sex	-0.012	0.006	0.009	-0.004
BMI (kg/m^2)	0.047	0.009	0.184 [a]	0.034
Smoking status	0.014	-0.005	-0.098	-0.018
Comorbidities				
Allergic rhinitis	0.188 [a]	0.022	0.172 [a]	0.020
Chronic rhinosinusitis	-0.004	-0.006	-0.272 [a]	-0.007
Nasal polyps	0.053	0.009	-0.113	-0.026
Cardiovascular disease	-0.111 [a]	-0.010	-0.435 [a]	-0.011
Diabetes	-0.059	-0.004	-0.086	0.011
COPD	-0.078	-0.006	-0.299 [a]	-0.007
Liver disease	0.024	-0.004	-0.069	0.008
History of malignancy	-0.060	-0.005	-0.027	-0.015
Previous chemotherapy	0.000	-0.012	-0.020	0.000
Previous anaphylaxis	-0.022	-0.003	-0.058	0.002
Previous serious infection	-0.016	-0.000	0.020	0.004

Variable	Benralizumab cohort versus other-biologic cohort		Benralizumab cohort versus non-biologic cohort	
	Pre-weighting SMD	Post-weighting SMD	Pre-weighting SMD	Post-weighting SMD
Asthma medication				
LABA only	-0.026	0.001	-0.080	0.009
LAMA	-0.080	-0.016	-0.196 [a]	-0.030
Theophylline	-0.037	-0.006	0.023	0.000
LTRA	-0.048	-0.009	-0.198 [a]	-0.032
Macrolide antibiotics	-0.059	0.001	-0.160 [a]	-0.008
Steroid use	-0.136 [a]	-0.029	-0.115 [a]	-0.014

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; LABA = long-acting β-adrenoreceptor agonist; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonist; SMD = standardised mean difference.

[a] Variables with the strongest statistical evidence for differences between cohorts prior to PS weighting ($p < 0.001$) are noted to highlight the extent to which the PS weighting improves balance between cohorts.

Source: Table 14.2.1.3.1 and Table 14.2.1.3.2

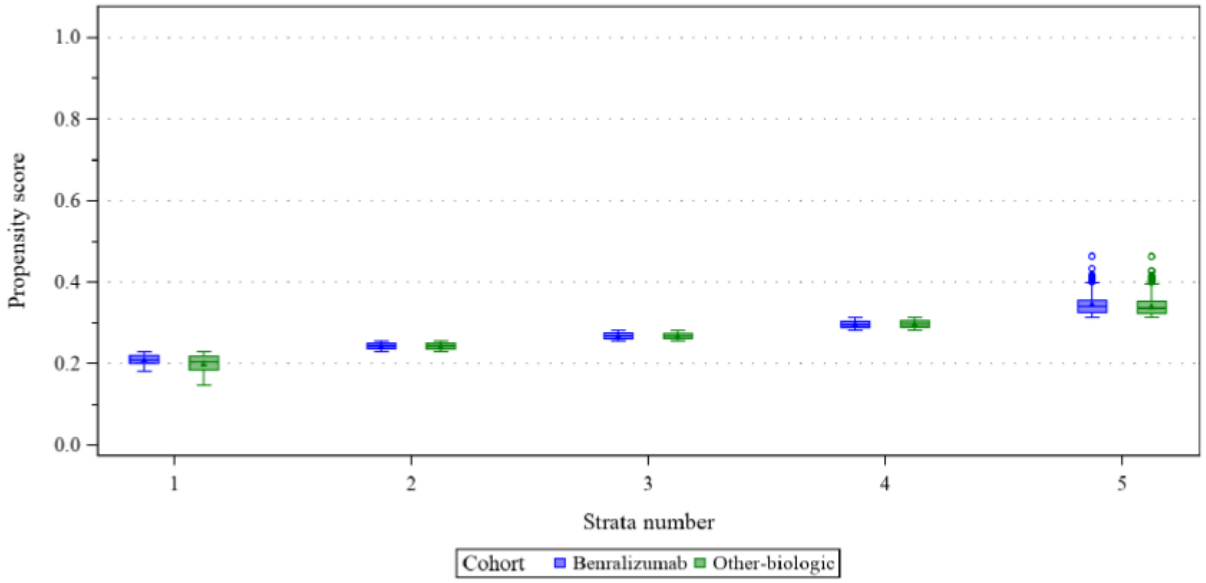
10.4.2 Stratification Analyses of Propensity Scores

Stratified analysis of PS was limited to 5 strata due to the small number of malignancies or absence of malignancies in many of the strata.

The distribution of PS within each stratum for the benralizumab cohort versus the non-benralizumab biologics cohort is provided in Figure 5 and for the non-biologic cohort is provided in Figure 6.

The PS distribution within each stratum is similar between cohorts when comparing benralizumab versus non-benralizumab biologics cohort. Similar distribution is observed when the comparison is between benralizumab versus the non-biologic cohort.

Figure 5 Distribution of Propensity Score for Benralizumab Cohort and Other-biologic Cohort Within Each Strata, Box Plot (ISAR and CHRONICLE Combined Analysis Set)



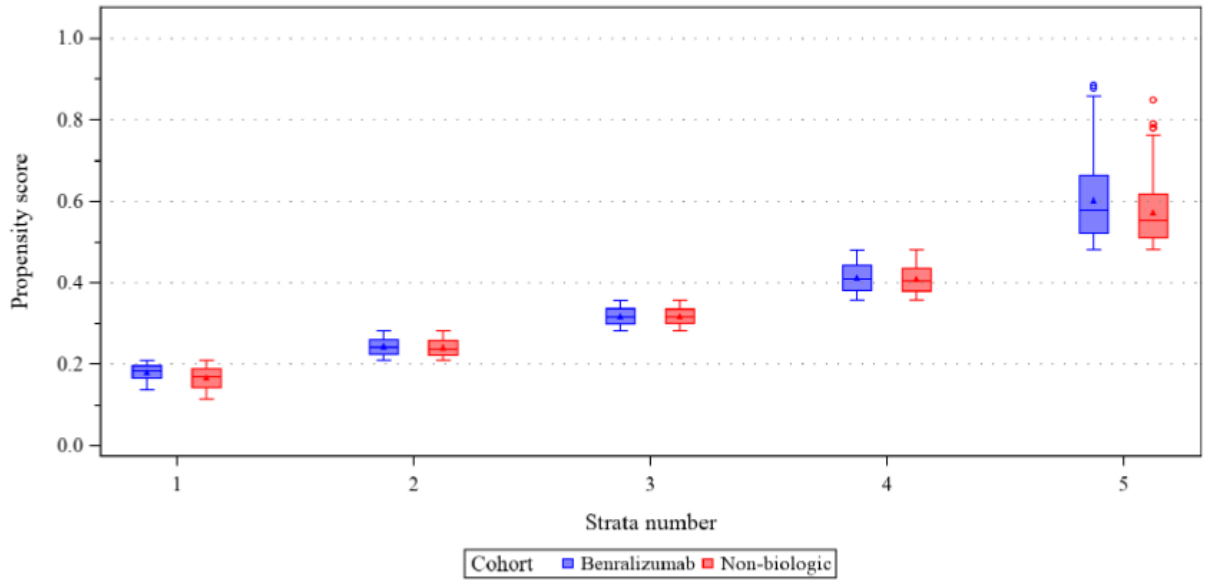
Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry.

Propensity scores were calculated based on baseline characteristics and indicate the probability that patients would receive benralizumab, given measured baseline characteristics.

Strata was decided based on the quintile distribution of the propensity scores in the benralizumab cohort. The strata reflect the probability of the patient receiving benralizumab, with the first strata indicating the lowest probability of receiving benralizumab.

Source: Figure 14.2.1.4.1

Figure 6 Distribution of Propensity Score for Benralizumab Cohort and Non-biologic Cohort Within Each Strata, Box Plot (ISAR and CHRONICLE Combined Analysis Set)



CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry.

Propensity scores were calculated based on baseline characteristics and indicate the probability that patients would receive benralizumab, given measured baseline characteristics.

Strata was decided based on the quintile distribution of the propensity scores in the benralizumab cohort. The strata reflect the probability of the patient receiving benralizumab, with the first strata indicating the lowest probability of receiving benralizumab.

Source: Figure 14.2.1.4.2

10.4.3 Crude and Adjusted Incidence Rates of New Malignancies: Overall Population

The crude and adjusted incidence rates for new malignancies are given in Table 10. Overall, the crude incidence rates were low across all populations.

A total of 48 patients reported a new malignancy during the study, 0.5% (8/1554), 0.5% (21/4436), and 0.5% (19/4036) in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively. Before PS adjustment, the crude incidence rates per 1000 PY (95% CI) in these 3 cohorts were 2.0 (1.00 – 4.01), 1.6 (1.02 – 2.40), and 2.0 (1.26 – 3.11), respectively.

After adjustment for age, sex, BMI, region, and smoking status, the number (%) of patients reporting a new malignancy, relative to the total number of patients in each cohort, remained 0.5% (19/3654) in the non-biologic cohort and decreased to 0.5% (7/1389), and 0.4% (17/4109) for the benralizumab and non-benralizumab cohorts, respectively. All

5 patients excluded from the adjusted analysis had missing baseline BMI. In the PS adjusted benralizumab and non-biologic cohort, the adjusted incidence rates per 1000 PY (95% CI) were 1.5 (0.95 – 2.36) for the benralizumab cohort, and 2.1 (1.33 – 3.21) for the non-biologic cohort. In the PS adjusted benralizumab and non-benralizumab biologics cohorts, the adjusted incidence rates per 1000 PY (95% CI) were 0.9 (0.51 – 1.55) for the benralizumab cohort, and 0.9 (0.51 – 1.47) for the non-benralizumab biologics cohort.

10.4.3.1 Subpopulation-excluding Non-melanoma Skin Cancer

Due to the multicentric/multifocal nature of NMSCs, the same NMSCs may occur at different sites with a potential to inflate incidence rates. Therefore, it was stated in the protocol and SAP v5.0 to perform sensitivity analyses excluding NMSCs.

The crude incidence rate of new malignancies after excluding patient with NMSC, is given in Table 10. Overall, the crude incidence rates were low across all populations. The number (%) of patients reporting a new malignancy, relative to the total number of patients in each cohort excluding NMSC, was 0.5% (7/1554), 0.4% (18/4436) and 0.4% (16/4036) in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively.

After adjustment for age, sex, BMI, region, and smoking status, the adjusted incidence rates per 1000 PY (95% CI) in the benralizumab cohort and non-benralizumab biologics cohort, excluding NMSC, were similar at 0.9 (0.54 – 1.64) and 0.8 (0.46 – 1.39), respectively. When comparing the benralizumab and non-biologic cohorts, the adjusted incidence rates per 1000 PY (95% CI) were 1.7 (1.09 – 2.64) and 1.9 (1.24 – 3.05), respectively.

10.4.3.2 Crude and Adjusted Incidence Rates of New Malignancies: ISAR and CHRONICLE

In the ISAR registry, there were overall 22 new malignancies reported. The number (%) of patients reporting a new malignancy, relative to the total number of patients in each cohort, was 2 (0.2%), 7 (0.2%), and 13 (0.4%) in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively. The crude incidence rates per 1000 PY (95% CI) in these 3 cohorts were 0.7 (0.19 – 2.98), 0.7 (0.34 – 1.47), and 1.7 (0.97 - 2.86), respectively. In the PS adjusted cohorts (ie, benralizumab versus non-benralizumab biologics cohort; and benralizumab versus non-biologic cohorts), the number (%) of patients in each cohort reporting a new malignancy were 0.1% (1/889), 0.1% (4/2889), and 0.4% (13/2954). Adjusted rates per 1000 PY (95% CI) for benralizumab versus non-benralizumab biologics were 0.0 and 0.0, respectively, and for benralizumab versus non-biologic 0.0 and 1.8 (0.90 – 3.61), respectively.

In CHRONICLE, there were overall 26 new malignancies reported. The number (%) of patients in each cohort reporting a new malignancy was 1.1% (6/552), 1.0% (14/1335), and 0.8% (6/770) in the benralizumab cohort, the non-benralizumab biologics cohort, and the

non-biologic cohort, respectively. Crude incidence rates per 1000 PY (95% CI) for CHRONICLE benralizumab, non-benralizumab biologics and non-biologic cohorts were 4.6 (2.07 – 10.25), 4.0 (2.39 – 6.81), and 3.4 (1.53 – 7.56), respectively. In the PS adjusted cohorts (ie, benralizumab versus non-benralizumab biologics cohort; and benralizumab versus non-biologic cohorts), the number (%) of patients with a new malignancy were 1.2% (6/501), 1.1% (13/1221), and 0.9% (6/700). Adjusted incidence rates per 1000 PY (95% CI) for benralizumab versus non-benralizumab biologics were 3.3 (1.86 – 5.78) and 3.2 (1.86 – 5.49), respectively, and for benralizumab versus non-biologic 3.1 (1.54 – 6.34) and 2.2 (0.94 – 4.92), respectively.

Table 10 Observed Crude and Adjusted Incidence Rates for New Malignancy, Poisson Regression (ISAR and CHRONICLE Combined Analysis Set)

					Rate difference	Rate ratio	
	Comparison	Number (%) of patients with a new malignancy	Total time at risk (years)	Incidence rate (per 1000 PY) (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
Crude [a]							
Overall	Benralizumab cohort (N = 1554) versus Other-biologic cohort (N = 4436)	8 (0.5) versus 21 (0.5)	3988.90 versus 13426.90	2.0 (1.00, 4.01) versus 1.6 (1.02, 2.40)	0.4 (-1.10, 1.98)	NC	NC
	Benralizumab cohort (N = 1554) versus Non-biologic cohort (N = 4036)	8 (0.5) versus 19 (0.5)	3988.90 versus 9588.18	2.0 (1.00, 4.01) versus 2.0 (1.26, 3.11)	0.0 (-1.63, 1.67)	NC	NC
Without NMSC	Benralizumab cohort (N = 1554) versus Other-biologic cohort (N = 4436)	7 (0.5) versus 18 (0.4)	3990.87 versus 13430.49	1.8 (0.84, 3.68) versus 1.3 (0.84, 2.13)	0.4 (-1.03, 1.85)	NC	NC
	Benralizumab cohort (N = 1554) versus Non-biologic cohort (N = 4036)	7 (0.5) versus 16 (0.4)	3990.87 versus 9594.66	1.8 (0.84, 3.68) versus 1.7 (1.02, 2.72)	0.1 (-1.45, 1.62)	NC	NC
Adjusted [b]							
Overall	Benralizumab cohort (N = 1389) versus Other-biologic cohort (N = 4109)	7 (0.5) versus 17 (0.4)	3521.97 versus 12381.31	0.9 (0.51, 1.55) versus 0.9 (0.51, 1.47)	0.0 (-0.48, 0.52)	1.0 (0.58, 1.80)	0.9417
	Benralizumab cohort (N = 1389) versus Non-biologic cohort (N = 3654)	7 (0.5) versus 19 (0.5)	3524.04 versus 8582.25	1.5 (0.95, 2.36) versus 2.1 (1.33, 3.21)	-0.6 (-1.50, 0.36)	0.7 (0.43, 1.21)	0.2155
Without NMSC	Benralizumab cohort (N = 1389) versus Other-biologic cohort (N = 4109)	7 (0.5) versus 15 (0.4)	3521.97 versus 12382.82	0.9 (0.54, 1.64) versus 0.8 (0.46, 1.39)	0.1 (-0.38, 0.65)	1.2 (0.65, 2.10)	0.5954

					Rate difference	Rate ratio	
	Comparison	**Number (%) of patients with a new malignancy**	**Total time at risk (years)**	**Incidence rate (per 1000 PY) (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**p-value**
	Benralizumab cohort (N = 1389) versus Non-biologic cohort (N = 3654)	7 (0.5) versus 16 (0.4)	3524.04 versus 8588.73	1.7 (1.09, 2.64) versus 1.9 (1.24, 3.05)	-0.2 (-1.22, 0.73)	0.9 (0.51, 1.49)	0.6213

Abbreviations: BMI = body mass index; CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; NC = not calculated as per statistical analysis plan; NMSC = non-melanoma skin cancer; PY = person-years.

[a] The 95% CIs for crude rates and rate differences for each comparison were estimated from a Poisson regression model. The response variable in the model is the number of patients with a new malignancy. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariate in the model includes cohort.

[b] The estimate of adjusted incidence rates, rate ratio, rate differences and corresponding 95% CIs for each comparison are calculated using a weighted Poisson regression model. The weight used in the model is the inverse propensity score (1/propensity score for benralizumab cohort, 1/(1-propensity score) for other cohorts). The response variable in the model is the number of patients with a new malignancy. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariates in the model include cohort, age, sex, region, smoking and BMI.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

For overall group, total time at risk is defined as from the index date to the date of first new malignancy or censoring due to death, loss to follow-up, switching the cohort, data cut-off or end of study, whichever comes first. For without NMSC group, total time at risk is defined as from the index date to the date of first new malignancy (excluding NMSC) or censoring due to death, loss to follow-up, switching the cohort, data cut-off or end of study, whichever comes first.

Source: Table 14.2.2.1.1

10.4.3.3 Crude and Adjusted Incidence Rates of New Malignancies: Patients with No Cohort Switch

An analysis, excluding patients with cohort switches, was performed as reported in Table 11. In this analysis, the number (%) of patients reporting a new malignancy, relative to the number of patients in the cohort, was 0.6% (7/1100) and 0.5% (19/3982) in the benralizumab cohort and the non-benralizumab biologics cohort, respectively. The crude incidence rates per 1000 PY (95% CI) in these 2 cohorts were 2.2 (1.06 – 4.65), and 1.5 (0.96 – 2.36), respectively.

After adjustment for age, sex, BMI, region, and smoking status, the incidence rates per 1000 PY (95% CI) for new malignancies were 0.8 (0.45 – 1.58) and 0.8 (0.43 – 1.36) in the benralizumab and the non-benralizumab biologics cohorts, respectively.

Table 11 Observed Crude and Adjusted Incidence Rates for New Malignancy, Patients Taken Benralizumab/Other-biologics and Without Cohort Switches, Poisson Regression (ISAR and CHRONICLE Combined Analysis Set)

					Rate difference	Rate ratio	
	Comparison	Number (%) of patients with a new malignancy	Total time at risk (years)	Incidence rate (per 1000 PY) (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
Crude [a]	Benralizumab cohort (N = 1100) versus Other-biologic cohort (N = 3982)	7 (0.6) versus 19 (0.5)	3154.83 versus 12621.35	2.2 (1.06, 4.65) versus 1.5 (0.96, 2.36)	0.7 (-1.06, 2.49)	NC	NC
Adjusted [b]	Benralizumab cohort (N = 975) versus Other-biologic cohort (N = 3676)	6 (0.6) versus 15 (0.4)	2767.74 versus 11609.82	0.8 (0.45, 1.58) versus 0.8 (0.43, 1.36)	0.1 (-0.42, 0.58)	1.1 (0.60, 2.03)	0.7552

Abbreviations: BMI = body mass index; CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; NC = not calculated as per statistical analysis plan.

[a] The 95% CIs for crude rates and rate differences for each comparison are estimated from a Poisson regression model. The response variable in the model is the number of patients with a new malignancy. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariate in the model includes cohort.

[b] The estimate of adjusted incidence rates, rate ratio, rate differences and corresponding 95% CIs for each comparison are calculated using a weighted Poisson regression model. The weight used in the model is the inverse propensity score (1/propensity score for benralizumab cohort, 1/ (1-propensity score) for other cohorts). The response variable in the model is the number of patients with a new malignancy. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariates in the model include cohort, age, sex, region, smoking and BMI.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

Total time at risk is defined as from the index date to the date of first new malignancy or censoring due to death, loss to follow-up, data cut-off or end of study, whichever comes first.

Patients without cohort switch is defined as patients who stay in only one cohort from the beginning of the study.

Source: Table 14.2.2.1.4

10.4.3.4 Adjusted Incidence Rates of New Malignancies by Strata

Stratified analysis was performed to determine incidence rates per strata, where each stratum included patients from all 3 cohorts with a similar probability of being assigned to the benralizumab cohort, given baseline characteristics. The analysis was limited due to the low number of malignancies reported and the calculation of an overall estimate of malignancy risk was not possible. Where it was possible to determine incidence rates and rate ratios for individual strata, strata 5 (patients with the highest probability of receiving benralizumab) was the only strata to indicate a statistically significant difference in incidence rates between the benralizumab and non-biologic cohorts. The number of patients reporting a new malignancy in strata 5 were 0.4% (1/278) in the benralizumab cohort and 3.2% (6/189) in the non-biologic cohort. The respective adjusted incidence rates per 1000 PY (95% CI) in these 2 cohorts and stratum were 1.1 (0.23 – 5.61) and 7.7 (3.75 – 15.75), respectively (p = 0.0189) (Table 14.2.2.1.5).

There were no statistically significant comparisons between the cohorts in any of the strata in the individual ISAR and CHRONICLE datasets (Table 14.2.2.1.6 and Table 14.2.2.1.7).

When comparing incidence rates excluding NMSC, a statistically significant comparison between benralizumab and non-biologic cohort in strata 1 (patients with the lowest probability of receiving benralizumab) (p = 0.0223) as well as strata 5 (p = 0.0392) was observed. The number of patients with a new malignancy in each of these cohorts in strata 1 was 1.4% (4/277) for benralizumab cohort and 0.3% (4/1484) for non-biologics, with adjusted incidence rates (95% CI) of 3.1 (1.65 – 5.82) and 1.0 (0.35 – 2.67) per 1000 PY, respectively. In strata 5, 0.4% (1/278) patient reported a new malignancy in the benralizumab cohort compared to 2.6% (5/189) patients in the non-biologic cohort. Respective adjusted incidence rates per 1000 PY (95% CI) for this stratum were 1.5 (0.34 – 7.14) and 8.4 (4.31 – 16.30) (Table 14.2.2.1.8). There was no significant difference in malignancy incidence between cohorts for the majority of the strata. However, given the limited data available, the stratified analysis should be interpreted with caution.

In the combined analysis set, rate ratios (95% CI) between benralizumab and non-benralizumab biologics cohorts was 1.0 (0.58 – 1.80) and 0.7 (0.43 – 1.21) for the comparison between benralizumab and non-biologic cohorts, respectively.

10.4.4 Crude Event Rates for New Malignancy: Overall Population

The observed crude event rates of new malignancies for overall and subpopulation (excluding NMSC) by Poisson regression from ISAR and CHRONICLE combined analysis set for each cohort are presented in Table 12.

The number of new malignancies in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts were 8, 21, and 19, respectively. The crude event rates per 1000 PY (95% CI) in these respective cohorts were 2.0 (1.00 – 3.99), 1.6 (1.02 – 2.39), and 2.0 (1.26 – 3.09).

10.4.4.1 Subpopulation-excluding Non-melanoma Skin Cancer

The number of new malignancies (excluding NMSC) in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts were 7, 18, and 16, respectively. The crude event rates per 1000 PY (95% CI) in these respective cohorts were 1.7 (0.83 – 3.67), 1.3 (0.84 – 2.12), and 1.7 (1.02 – 2.71), respectively.

10.4.4.2 Crude Event Rates for New Malignancy: ISAR and CHRONICLE

In the ISAR registry, the number of new malignancies in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts was 2, 7, and 13, respectively. The crude event rates per 1000 PY (95% CI) in these respective cohorts were 0.7 (0.19 – 2.97), 0.7 (0.33 – 1.47), and 1.7 (0.96 – 2.85).

In the CHRONICLE study, the number of new malignancies was 6, 14, and 6 in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts, respectively. The crude event rates per 1000 PY (95% CI) in these respective cohorts were 4.6 (2.05 – 10.15), 4.0 (2.38 – 6.78), and 3.4 (1.52 – 7.51).

For observed crude event rates for new malignancies, refer to Table 14.2.2.2.2 for ISAR and Table 14.2.2.2.3 for CHRONICLE.

Table 12 Observed Crude Event Rates for New Malignancy, Poisson Regression (ISAR and CHRONICLE Combined Analysis Set)

	Comparison	Number of new malignancies	Total time at risk (years)	Event rate (per 1000 PY) (95% CI)	Comparison (rate difference) between groups (95% CI)
Overall	Benralizumab cohort (N = 1554) versus Other-biologic cohort (N = 4436)	8 versus 21	4005.16 versus 13458.95	2.0 (1.00, 3.99) versus 1.6 (1.02, 2.39)	0.4 (-1.10, 1.97)
	Benralizumab cohort (N = 1554) versus Non-biologic cohort (N = 4036)	8 versus 19	4005.16 versus 9626.51	2.0 (1.00, 3.99) versus 2.0 (1.26, 3.09)	0.0 (-1.62, 1.67)
Without NMSC	Benralizumab cohort (N = 1554) versus Other-biologic cohort (N = 4436)	7 versus 18	4005.16 versus 13458.95	1.7 (0.83, 3.67) versus 1.3 (0.84, 2.12)	0.4 (-1.02, 1.84)
	Benralizumab cohort (N = 1554) versus Non-biologic cohort (N = 4036)	7 versus 16	4005.16 versus 9626.51	1.7 (0.83, 3.67) versus 1.7 (1.02, 2.71)	0.1 (-1.44, 1.62)

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; NMSC = non-melanoma skin cancer; PY = person-years.

The 95% CIs for crude rates and rate differences for each comparison are estimated from a Poisson regression model. The response variable in the model is the number of new malignancies. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariate in the model includes cohort.

If a patient has two malignancy records with same diagnosis within 3 months, the two records are considered as the same malignancy case and counted only once.

Total time at risk is defined as from the index date to the date of censoring due to death, loss to follow-up, switching the cohort, data cut-off or end of study, whichever comes first.

Source: Table 14.2.2.2.1

10.4.5 Time to First New Malignancy: Overall Population

The time to first new malignancy analysis by a Cox-proportional hazard model in the ISAR and CHRONICLE combined analysis set for each cohort is presented in Table 13 and Figure 7. Based on overall population, adjusting for age, sex, BMI, region, and smoking status, the number of patients with a new malignancy was 0.5% (7/1389), 0.4% (17/4109), and 0.5% (19/3654) in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts, respectively. In the subpopulation (excluding NMSC), the number of patients with a new malignancy in these 3 cohorts were 0.5% (7/1389), 0.4% (15/4109), and 0.4% (16/3654), respectively. As noted in Section 10.4.3, this analysis excludes one malignancy reported in the benralizumab cohort and 4 malignancies in the non-benralizumab biologic cohort because the patients had incomplete baseline covariate information. There was no significant difference in the time to first new malignancy between cohorts.

There was no statistically significant increase in risk of new malignancy in each comparison of the benralizumab cohort with non-benralizumab biologics and non-biologic cohorts was observed.

Table 13 Time to First New Malignancy, Cox-proportional Hazard Model (ISAR and CHRONICLE Combined Analysis Set)

			Comparison between groups [a]	
	Treatment group	Number (%) of patients with a new malignancy	Hazard ratio	95% CI
Overall	Benralizumab cohort (N = 1389) versus Other-biologic cohort (N = 4109)	7 (0.5) versus 17 (0.4)	1.0	(0.57, 1.77)
	Benralizumab cohort (N = 1389) versus Non-biologic cohort (N = 3654)	7 (0.5) versus 19 (0.5)	0.7	(0.42, 1.18)
Without NMSC	Benralizumab cohort (N = 1389) versus Other-biologic cohort (N = 4109)	7 (0.5) versus 15 (0.4)	1.2	(0.64, 2.07)
	Benralizumab cohort (N = 1389) versus Non-biologic cohort (N = 3654)	7 (0.5) versus 16 (0.4)	0.9	(0.50, 1.46)

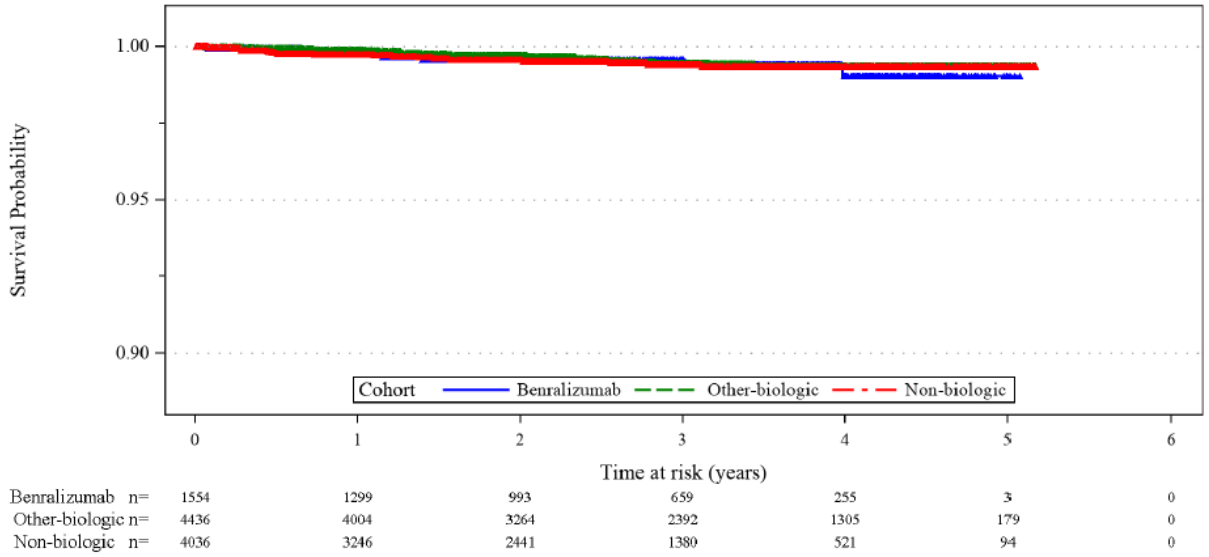
Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; NMSC = non-melanoma skin cancer.

[a] The hazard ratio and 95% CI for each comparison are estimated using a weighted Cox regression model. The weights for the model are inverse propensity scores (1/propensity score for benralizumab cohort, 1/(1-propensity score) for other cohorts). The covariates in the model include cohort, age, sex, region, smoking and BMI.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

Source: Table 14.2.3.2.1

Figure 7 Time to First Malignancy (ISAR and CHRONICLE Combined Analysis Set)



Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; n = number of patients in analysis.

The time to first new malignancy = (the diagnosis date of first new malignancy - the index date + 1)/365.25. For patients who have not developed malignancy over the follow-up, their time to first new malignancy was right-censored at the earliest date of either death, last visit before loss to follow-up, switch to another cohort, data cut-off, or end of the study.

Source: Figure 14.2.3.1.1

10.4.6 Characteristics of New Malignancy Cases: Overall Population

The characteristics of new malignancy cases from the ISAR and CHRONICLE combined analysis set for each cohort are given in Table 14. For the characteristics of new malignancy cases of the ISAR analysis set and CHRONICLE analysis set refer to Table 14.2.4.1.2. For the characteristics of new malignancy cases of the subgroup (excluding NMSC) from the ISAR and CHRONICLE combined analysis set, refer to Table 14.2.4.1.3.

Overall, the majority of the newly reported malignancies where data was available were Stage I malignancies: 37.5% (3/8) in the benralizumab cohort, 9.5% (2/21) in the non-benralizumab biologics cohort, and 21.1% (4/19) in the non-biologic cohort.

The most common locations of newly reported malignancies varied by cohorts. The most common locations were breast (25.0% [2/8]) and male genital organ (25.0% [2/8]) in the benralizumab cohorts, digestive organ (28.6% [6/21]) in the non-benralizumab biologics cohort, and respiratory/intrathoracic organs (26.3% [5/19]) in the non-biologic cohort.

At the time of data cut-off, most of the newly reported malignancies were either ongoing (50.0% [4/8] in the benralizumab cohort and 61.9% [13/21] in the non-benralizumab biologics cohort) or in remission (36.8% [7/19] in the non-biologic cohort).

Table 14 Characteristics of New Malignancy Cases (ISAR and CHRONICLE Combined Analysis Set)

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N = 8)**	**Other-biologic cohort (N = 21)**	**Non-biologic cohort (N = 19)**
Status at diagnosis	New onset	8 (100)	21 (100)	19 (100)
	Total	8 (100)	21 (100)	19 (100)
Location/site	Breast	2 (25.0)	3 (14.3)	3 (15.8)
	Digestive organ	1 (12.5)	6 (28.6)	1 (5.3)
	Female genital organs	0	0	1 (5.3)
	Lymphoid, haematopoietic, and related tissue	1 (12.5)	0	3 (15.8)
	Male genital organ	2 (25.0)	3 (14.3)	1 (5.3)
	Melanoma and other malignancy neoplasms of skin	1 (12.5)	3 (14.3)	3 (15.8)
	Respiratory and intrathoracic organs	0	3 (14.3)	5 (26.3)
	Urinary tract	1 (12.5)	2 (9.5)	1 (5.3)
	Total	8 (100)	20 (95.2)	18 (94.7)
	Missing	0	1	1

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N = 8)**	**Other-biologic cohort (N = 21)**	**Non-biologic cohort (N = 19)**
Cell type	Adenocarcinoma	0	2 (9.5)	2 (10.5)
	Blood cell	0	0	1 (5.3)
	Epithelial	1 (12.5)	0	1 (5.3)
	Hepatocytes	0	1 (4.8)	0
	White blood cell	0	0	1 (5.3)
	Basal cell	1 (12.5)	0	1 (5.3)
	Glandular cell	2 (25.0)	6 (28.6)	4 (21.1)
	Squamous cell	0	2 (9.5)	4 (21.1)
	Urothelial cell	0	2 (9.5)	0
	Total	4 (50.0)	13 (61.9)	14 (73.7)
	Missing	4	8	5
Stage (number staging system)	Stage I	3 (37.5)	2 (9.5)	4 (21.1)
	Stage II	0	1 (4.8)	1 (5.3)
	Stage III	0	1 (4.8)	0
	Stage IV	1 (12.5)	2 (9.5)	2 (10.5)
	Total	4 (50.0)	6 (28.6)	7 (36.8)
	Missing	4	15	12
Stage (TNM staging system)				
T (Primary tumour)	X	1 (12.5)	0	0
	0	0	0	1 (5.3)
	1	1 (12.5)	4 (19.0)	3 (15.8)
	2	2 (25.0)	2 (9.5)	1 (5.3)
	3	0	1 (4.8)	0
	4	0	1 (4.8)	1 (5.3)
	Total	4 (50.0)	8 (38.1)	6 (31.6)
	Missing	4	13	13
N (Lymph nodes)	X	1 (12.5)	0	1 (5.3)
	0	1 (12.5)	5 (23.8)	2 (10.5)
	1	1 (12.5)	1 (4.8)	1 (5.3)
	2	1 (12.5)	1 (4.8)	2 (10.5)
	Total	4 (50.0)	7 (33.3)	6 (31.6)
	Missing	4	14	13

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N = 8)**	**Other-biologic cohort (N = 21)**	**Non-biologic cohort (N = 19)**
M (Distant metastasis)	X	1 (12.5)	1 (4.8)	0
	0	1 (12.5)	4 (19.0)	3 (15.8)
	1	1 (12.5)	1 (4.8)	3 (15.8)
	Total	3 (37.5)	6 (28.6)	6 (31.6)
	Missing	5	15	13
Outcome	Ongoing	4 (50.0)	13 (61.9)	5 (26.3)
	Remission	2 (25.0)	6 (28.6)	7 (36.8)
	Death	1 (12.5)	1 (4.8)	0
	Unknown status (not death)	0	1 (4.8)	3 (15.8)
	Total	7 (87.5)	21 (100)	15 (78.9)
	Missing	1	0	4

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; n = number of patients in analysis.

Missing category only counts missing values for patients with new onset malignancy cases.

If not stated otherwise, percentages are based upon number of patients with new malignancies in each cohort within the combined analysis set.

Source: Table 14.2.4.1.1

10.4.6.1 Demographic and Baseline Clinical Characteristics of Patients with New Malignancy Cases

Demographic and baseline characteristics of patients with new malignancies across the cohorts, summary statistics in ISAR and CHRONICLE combined, separate analysis sets, and subpopulation (excluding NMSC) are described in Table 14.2.4.2.1 to Table 14.2.4.2.3, respectively, and for an abbreviated table, refer to Table 15.

The majority of new malignancies were reported for patients in the United States. The mean (SD) age and BMI of patients with new malignancies ranged from 62.9 (6.12) to 66.6 (10.94) years and 29.432 (5.6832) to 31.260 (7.2650) kg/m^2 across cohorts. Overall, the asthma status across cohorts was mostly partially controlled or not controlled.

Table 15 Demographic and Baseline Clinical Characteristics of Patients with New Malignancy Cases (ISAR and CHRONICLE Combined Analysis Set)

Demographic/ baseline clinical characteristics	**Statistics or category**	**Benralizumab cohort (N = 8)**	**Other-biologic cohort (N = 21)**	**Non-biologic cohort (N = 19)**
Age (years)	n	8	21	19

Demographic/ baseline clinical characteristics	Statistics or category	Benralizumab cohort (N = 8)	Other-biologic cohort (N = 21)	Non-biologic cohort (N = 19)
	Mean (SD)	63.9 (8.08)	62.9 (6.12)	66.6 (10.94)
	Median	63.6	63.0	68.0
	Q1, Q3	60.5, 69.0	58.0, 66.0	61.2, 74.0
	Min, Max	49, 76	53, 75	45, 85
Age (years) subgroups n (%)	≥ 18 to ≤ 39	0	0	0
	≥ 40 to ≤ 64	4 (50.0)	13 (61.9)	7 (36.8)
	≥ 65 to ≤ 79	4 (50.0)	8 (38.1)	10 (52.6)
	≥ 80	0	0	2 (10.5)
	Total	8 (100)	21 (100)	19 (100)
Sex n (%)	Female	6 (75.0)	8 (38.1)	12 (63.2)
	Male	2 (25.0)	13 (61.9)	7 (36.8)
	Total	8 (100)	21 (100)	19 (100)
Race n (%)	White	4 (50.0)	16 (76.2)	9 (47.4)
	Black or African American	3 (37.5)	4 (19.0)	0
	Asian	1 (12.5)	1 (4.8)	9 (47.4)
	Native Hawaiian or Other Pacific Islander	0	0	0
	American Indian or Alaska Native	0	0	0
	Other	0	0	1 (5.3)
	Total	8 (100)	21 (100)	19 (100)
Country [a]	Canada	1 (12.5)	4 (19.0)	2 (10.5)
	Colombia	0	0	1 (5.3)
	Japan	1 (12.5)	0	5 (26.3)
	Kuwait	0	1 (4.8)	0
	South Korea	0	1 (4.8)	0
	Taiwan	0	0	3 (15.8)
	United Arab Emirates	0	1 (4.8)	0
	United States of America	6 (75.0)	14 (66.7)	8 (42.1)
	Total	8 (100)	21 (100)	19 (100)
BMI (kg/m^2)	n	7	17	19
	Mean (SD)	31.260 (7.2650)	30.843 (6.5211)	29.432 (5.6832)
	Median	31.100	29.400	30.100

Demographic/ baseline clinical characteristics	Statistics or category	Benralizumab cohort (N = 8)	Other-biologic cohort (N = 21)	Non-biologic cohort (N = 19)
	Q1, Q3	23.200, 35.900	26.639, 35.800	24.889, 32.105
	Min, Max	21.12, 42.00	18.50, 41.50	21.20, 41.40
BMI (kg/m^2) subgroups	< 18.5	0	0	0
	≥ 18.5 to < 25	2 (25.0)	4 (19.0)	5 (26.3)
	≥ 25 to < 30	0	5 (23.8)	4 (21.1)
	≥ 30 to < 35	3 (37.5)	2 (9.5)	7 (36.8)
	≥ 35	2 (25.0)	6 (28.6)	3 (15.8)
	Total	7 (87.5)	17 (81.0)	19 (100)
	Missing	1	4	0
Smoking status	Non-smoker	7 (87.5)	11 (52.4)	12 (63.2)
	Previous and/or current smoker	1 (12.5)	10 (47.6)	7 (36.8)
	Total	8 (100)	21 (100)	19 (100)
Pack (years) [b]	n	0	9	7
	Mean (SD)		16.361 (12.7243)	20.964 (35.7399)
	Median		18.750	8.000
	Q1, Q3		3.000, 29.000	0.750, 21.000
	Min, Max		0.75, 30.00	-1.00, 100.00
Age at asthma onset (years)	n	8	20	17
	Mean (SD)	26.125 (18.8410)	44.300 (19.3665)	43.176 (19.2069)
	Median	25.500	48.500	50.000
	Q1, Q3	8.500, 42.500	35.000, 57.000	35.000, 57.000
	Min, Max	5.00, 51.00	2.00, 70.00	0.00, 68.00
Number of exacerbations [c]	n	8	21	19
	Mean (SD)	1.5 (1.60)	1.0 (1.75)	0.8 (2.06)
	Median	1.0	1.0	0.0
	Q1, Q3	0.0, 3.0	0.0, 1.0	0.0, 1.0
	Min, Max	0, 4	0, 8	0, 9
	0	3 (37.5)	9 (42.9)	12 (63.2)
	1	2 (25.0)	8 (38.1)	5 (26.3)
	2	0	3 (14.3)	1 (5.3)
	3	2 (25.0)	0	0
	4	1 (12.5)	0	0

Demographic/ baseline clinical characteristics	Statistics or category	Benralizumab cohort (N = 8)	Other-biologic cohort (N = 21)	Non-biologic cohort (N = 19)
	> 4	0	1 (4.8)	1 (5.3)
Number of invasive ventilations	n	8	21	19
	Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
	Median	0.0	0.0	0.0
	Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
	Min, Max	0, 0	0, 0	0, 0
Number of hospital admissions	n	8	21	19
	Mean (SD)	0.3 (0.71)	0.7 (1.59)	0.0 (0.00)
	Median	0.0	0.0	0.0
	Q1, Q3	0.0, 0.0	0.0, 1.0	0.0, 0.0
	Min, Max	0, 2	0, 7	0, 0
Number of emergency department visits	n	8	21	19
	Mean (SD)	0.4 (0.74)	0.7 (1.76)	0.1 (0.46)
	Median	0.0	0.0	0.0
	Q1, Q3	0.0, 0.5	0.0, 1.0	0.0, 0.0
	Min, Max	0, 2	0, 8	0, 2
Maintenance OCS	Yes	4 (50.0)	9 (42.9)	7 (36.8)
	No	4 (50.0)	12 (57.1)	12 (63.2)
	Total	8 (100)	21 (100)	19 (100)
Maintenance OCS dose per days (mg)	n	4	8	6
	Mean (SD)	31.25 (23.936)	24.88 (19.239)	26.67 (18.619)
	Median	30.00	20.00	20.00
	Q1, Q3	12.50, 50.00	7.50, 45.00	10.00, 50.00
	Min, Max	5.0, 60.0	4.0, 50.0	10.0, 50.0
Medication adherence status [d]	Yes	8 (100)	16 (76.2)	17 (89.5)
	No	0	1 (4.8)	0
	Total	8 (100)	17 (81.0)	17 (89.5)
	Missing	0	4	2
Asthma control status [e]	Well controlled	1 (12.5)	2 (9.5)	1 (5.3)
	Partially controlled	2 (25.0)	4 (19.0)	8 (42.1)
	Not controlled	3 (37.5)	9 (42.9)	7 (36.8)

Demographic/ baseline clinical characteristics	Statistics or category	Benralizumab cohort (N = 8)	Other-biologic cohort (N = 21)	Non-biologic cohort (N = 19)
	Total	6 (75.0)	15 (71.4)	16 (84.2)
	Missing	2	6	3

Abbreviations: BMI = body mass index; CHRONICLE = AZ sponsored United States Severe Asthma Study; GINA = Global Initiative for Asthma; ISAR = International Severe Asthma Registry; Max = maximum; Min = minimum; n = number of patients in analysis; N = number of patients with new malignancies in each cohort; OCS = oral corticosteroids; PY = person-years; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

[a] The list of countries may change in subsequent years with more countries added.

[b] Number of pack years = Number of years smoked × [number of cigarettes smoked per day/20] (1 pack/20 cigarettes).

[c] The number of exacerbations only counts severe asthma exacerbations, which are defined as events that require rescue steroids.

[d] The medication adherence status is evaluated based on either clinical impression or objective measures (eg, review of prescription records).

[e] Categorised according to the GINA Asthma Control Criteria.

If not stated otherwise, percentages are based upon number of patients with new malignancies in each cohort within the combined analysis set.

Missing category only counts missing values for patients with new onset malignancy cases. Baseline is defined as the last record on or prior to the index date. For patients who switch treatment, the baseline for the new cohort is the last record before the switch.

Number of exacerbations, hospital admissions, emergency department admissions and invasive ventilations (except ISAR) includes all events occurring within 12 months preceding each index date. For ISAR, number of invasive ventilations summarise all events ever preceding index dates within each cohort.

Source: Table 14.2.4.2.1

10.4.7 Sensitivity Analyses

10.4.7.1 Lag Time Sensitivity Analysis

A sensitivity analysis which implemented a one-year lag period for malignancy ascertainment was also conducted. After excluding patients with new malignancies diagnosed within one year of their initial index date, there were 0.3% (4/1549) new malignancies reported in the benralizumab cohort, and 0.3% (15/4429) and 0.2% (9/4026) new malignancies reported in the non-benralizumab biologics and non-biologic cohorts, respectively.

In the adjusted sensitivity analysis, the incidence rates per 1000 PY (95% CI) were 0.4 (0.19 – 0.92) and 0.6 (0.32 – 1.19) for benralizumab and non-benralizumab biologics cohorts, respectively. In the adjusted analysis for the benralizumab and non-biologic cohort, the incidence rates per 1000 PY (95% CI) were 1.0 (0.55 – 1.75) and 1.3 (0.75 – 2.29), respectively.

A stratified sensitivity analysis only indicated a statistically significant difference between benralizumab and non-biologic incidence rates in the lowest strata (p = 0.0359), with

0.7% (2/275) new malignancies reported in benralizumab cohort and 0.1% (2/1480) reported in the non-biological cohort, resulting in adjusted incidence rates per 1000 PY (95% CI) of 0.9 (0.26 – 2.82) and 0.2 (0.03 – 1.08) for the respective cohorts in strata 1 (Table 14.2.5.1.2).

There were no patients with new malignancies diagnosed within one year of a cohort switch date and extending the sensitivity analysis to assigning such patients to their previous cohort did not change the results of the above sensitivity analysis.

10.4.7.2 Index Date Sensitivity Analyses

In these sensitivity analyses, 17478 patients were included in the cohorts for the crude analyses (1950 patients contributed 5150.3 PY in the benralizumab cohort, 7808 patients contributed 39527.3 PY in the non-benralizumab biologics cohort, and 7720 patients contributed 43431.1 PY in the non-biologic cohort).

With the increase in sample size in this sensitivity analysis compared to the main analysis, there was more precision in the incidence rates calculated, with tighter confidence intervals (Table 16). The point estimates from this sensitivity analysis remained very similar to the point estimates from the main analysis for both the crude and adjusted incidence rates.

After adjusting for age, sex, BMI, region, and smoking status, incidence rates (95% CI) for the benralizumab and non-benralizumab biologics cohorts were 0.9 (0.62 – 1.39) and 1.1 (0.82 – 1.51), respectively. Adjusted incidence rates (95% CI) for the benralizumab and non-biologic comparison were 1.3 (0.87 – 1.85) and 1.3 (0.94 – 1.74), respectively.

Furthermore, comparing the benralizumab cohort with the non-benralizumab biologics cohort, the incidence rate ratio (95% CI) was 0.8 (0.57 - 1.24, p = 0.38). In the benralizumab versus non-biologic cohort comparison the incidence rate ratio was 1.0 (0.67 - 1.48, p = 0.98).

Adjusted incidence rates by strata also indicated no significant difference between the cohorts in every stratum (Table 14.2.5.3.2).

The crude event rates were also very similar across both cohort comparisons, with the difference in rates per 1000 PY close to 0 and 95% CIs including the value of 0 (Table 17). Similarly, the time to first new malignancy hazard ratios were less than one for all comparisons of the benralizumab cohort with non-benralizumab biologics and non-biologic cohorts, with all 95% CIs including the value of one (Table 18). Time to first new malignancy with the other index date definition is illustrated in Figure 8. Due to the much earlier index date applied in this sensitivity analysis, the non-benralizumab biologics and non-biologic cohorts were followed up for a much longer period than the benralizumab cohort and the increased probability of a new malignancy is observed beyond 4 years of follow-up for these cohorts.

Table 16 Observed Crude and Adjusted Incidence Rates for New Malignancy with the Other Index Date Definition, Poisson Regression (ISAR and CHRONICLE Combined Analysis Set)

					Rate difference	Rate ratio	
	Comparison	**Number (%) of patients with a new malignancy**	**Total time at risk (PY)**	**Incidence rate (per 1000 PY) (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**p-value**
Crude [a]							
Overall	Benralizumab cohort (N = 1950) versus Other-biologic cohort (N = 7808)	10 (0.5) versus 69 (0.9)	5150.26 versus 39527.29	1.9 (1.04, 3.61) versus 1.8 (1.38, 2.21)	0.2 (-1.08, 1.47)	NC	NC
	Benralizumab cohort (N = 1950) versus Non-biologic cohort (N = 7720)	10 (0.5) versus 92 (1.2)	5150.26 versus 43431.07	1.9 (1.04, 3.61) versus 2.1 (1.73, 2.60)	-0.2 (-1.46, 1.10)	NC	NC
Adjusted [b]							
	Benralizumab cohort (N = 1736) versus Other-biologic cohort (N = 7172)	9 (0.5) versus 59 (0.8)	4529.54 versus 35824.10	0.9 (0.62, 1.39) versus 1.1 (0.82, 1.51)	-0.2 (-0.57, 0.21)	0.8 (0.57, 1.24)	0.3821
	Benralizumab cohort (N = 1746) versus Non-biologic cohort (N = 6122)	9 (0.5) versus 59 (1.0)	4573.06 versus 30605.97	1.3 (0.87, 1.85) versus 1.3 (0.94, 1.74)	-0.0 (-0.51, 0.50)	1.0 (0.67, 1.48)	0.9806

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; NC = not calculated; PY = person-years.

[a] The 95% CIs for crude rates and rate differences for each comparison are estimated from a Poisson regression model. The response variable in the model is the number of patients with a new malignancy. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariate in the model includes cohort.

[b] The estimate of adjusted incidence rates, rate ratio, rate differences and corresponding 95% CIs for each comparison are calculated using a weighted Poisson regression model. The weight used in the model is the inverse propensity score (1/propensity score for benralizumab cohort, 1/(1-propensity score) for other cohorts). The response variable in the model is the number of patients with a new malignancy. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariates in the model include cohort, age at other index date, sex, region, smoking and BMI.

The index date of benralizumab/other-biologic cohort is the date of the first biologic use at any time. For non-biologic cohort, the index date is still the date of database entry at any time.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

Total time at risk is defined as from the index date to the date of first new malignancy or censoring due to death, loss to follow-up, switching the cohort, data cut-off or end of study, whichever comes first.

Source: Table 14.2.5.3.1

Table 17 Observed Crude Event Rates for New Malignancy with the Other Index Date Definition, Poisson Regression (ISAR and CHRONICLE Combined Analysis Set)

	Comparison	Number of new malignancies	Total time at risk (PY)	Event rate (95% CI)	Comparison (rate difference) between groups (95% CI)
Overall	Benralizumab cohort (N = 1950) versus Other-biologic cohort (N = 7808)	10 versus 74	5170.35 versus 39812.77	1.9 (1.04, 3.59) versus 1.9 (1.48, 2.33)	0.1 (-1.20, 1.35)
	Benralizumab cohort (N = 1950) versus Non-biologic cohort (N = 7720)	10 versus 95	5170.35 versus 43950.40	1.9 (1.04, 3.59) versus 2.2 (1.77, 2.64)	-0.2 (-1.50, 1.05)

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; PY = person-years.

The 95% CIs for crude rates and rate differences for each comparison are estimated from a Poisson regression model. The response variable in the model is the number of new malignancies. The logarithm of the patient's corresponding follow-up time is used as an offset variable in the model. The covariate in the model includes cohort.

The index date of benralizumab/other-biologic cohort is the date of the first biologic use at any time. For non-biologic cohort, the index date is still the date of database entry.

Total time at risk is defined as from the index date to the date of censoring due to death, loss to follow-up, switching the cohort, data cut-off or end of study, whichever comes first.

If a patient has two malignancy records with same diagnosis within 6 months, the two records are considered as the same malignancy case and counted only once.

Source: Table 14.2.5.3.3

Table 18 Time to First New Malignancy with the Other Index Date Definition, Cox-proportional Hazard Model (ISAR and CHRONICLE Combined Analysis Set)

			Comparison between groups	
	Treatment group	**Number (%) of patients with a new malignancy**	**Hazard ratio**	**95% CI**
Overall	Benralizumab cohort (N = 1736) versus Other-biologic cohort (N = 7172)	9 (0.5) versus 59 (0.8)	0.9	(0.62, 1.45)
	Benralizumab cohort (N = 1746) versus Non-biologic cohort (N = 6122)	9 (0.5) versus 59 (1.0)	0.8	(0.54, 1.25)

Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; BMI = body mass index; CI = confidence interval; ISAR = International Severe Asthma Registry; N = number of patients in cohort; PY = person-years.

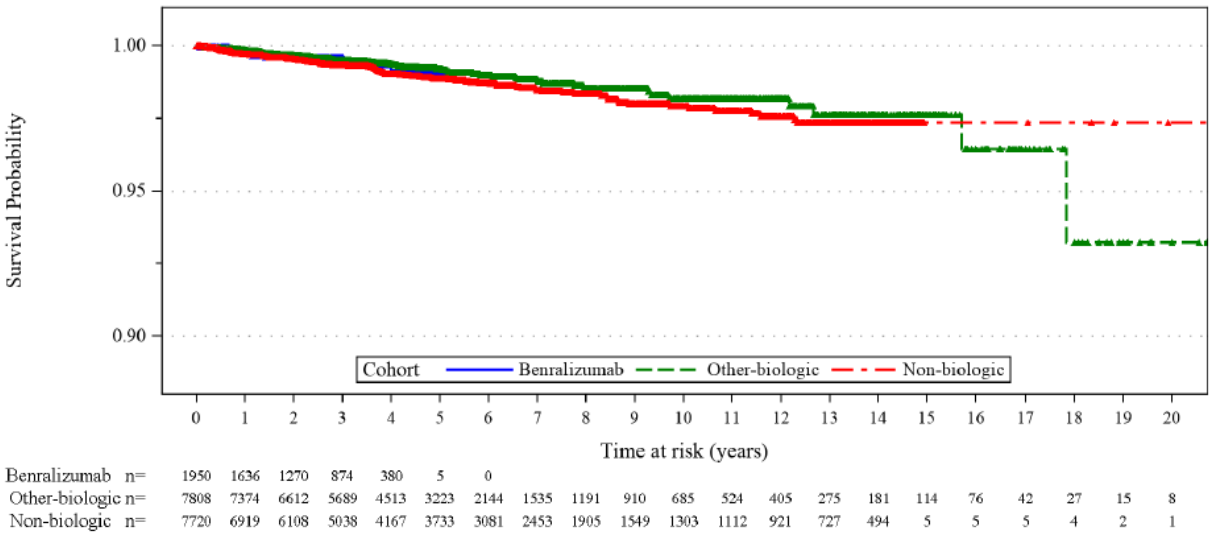
The hazard ratio and 95% CI for each comparison are estimated using a weighted Cox regression model. The weights for the model are inverse propensity scores (1/propensity scores for benralizumab cohort, 1/[1-propensity scores] for other cohorts). The covariates in the model include cohort, age, sex, smoking, region and BMI.

The index date of benralizumab/other-biologic cohort is the date of the first biologic use at any time. For non-biologic cohort, the index date is still the date of database entry at any time.

If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

Source: Table 14.2.5.3.5

Figure 8 **Time to First New Malignancy with the Other Index Date Definition, Kaplan-Meier Plot (ISAR and CHRONICLE Combined Analysis Set)**



Abbreviations: CHRONICLE = AZ sponsored United States Severe Asthma Study; ISAR = International Severe Asthma Registry; n = number of patients in analysis.

The time to first new malignancy= (the diagnosis date of first new malignancy–the index date + 1)/365.25. For patients who have not developed malignancy over the follow-up, their time to first new malignancy is right-censored at the earliest date of either death, last visit before loss to follow-up, switch to another cohort, data cut-off or end of the study.

The index date of benralizumab/other-biologic cohort is the date of the first biologic use at any time. For non-biologic cohort, the index date is still the date of database entry at any time.

Source: Figure 14.2.5.3.4

For the complete tables on sensitivity analyses refer to Table 14.2.5.1.1 to Table 14.2.5.3.5.

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

Not applicable. This is an observational study analysing secondary data that are being collected through the ISAR and CHRONICLE. Adverse Event reporting is not required for this secondary data collection study.

11. DISCUSSION

11.1 Key Results

This study is conducted in severe asthma patients enrolled in the ISAR or CHRONICLE databases. The objectives are to assess the incidence rates and clinical characteristics of new malignancy cases among patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics in severe asthma patients. The data which accrued during the period of 01 January 2018 to 31 December 2022 was analysed for this third IA report. This IA3 builds upon previous results from IA2, with more precise incidence rate estimates due to the increase in sample size.

The primary finding in this report is that with the large data that has accrued, there has been no observed increase in risk of malignancies associated with benralizumab use. In the adjusted analysis in which benralizumab patients were compared with non-benralizumab biologics patients, the incident rate ratio (95% CI) was 1.0 (0.58 - 1.80). Similarly, in the adjusted analysis in which benralizumab patients were compared with non-biologic users, the incident rate ratio (95% CI) was 0.7 (0.43 - 1.21). This finding was replicated in all the additional analysis, including a sensitivity analysis which included data for 17478 patients in the three cohorts (some patients contributed to more than one cohort) where the incidence rate ratio (95% CI) was 0.8 (0.57 – 1.24) comparing the benralizumab cohort with the non-benralizumab biologics cohort and 1.0 (0.67 - 1.48) in the benralizumab versus non-biologic cohort comparison. The findings from this study are consistent with previously published data (Gonzalez-Perez et al 2006; Long et al 2014; Salameh et al 2021).

In addition to the comparisons by cohort, this study provides estimates of the absolute risk (incidence rate) of malignancies among patients with severe asthma receiving benralizumab, non-benralizumab biologics and non-biologics. In unadjusted crude estimates, the incidence rate (95% CI) per 1000 PY of malignancies in this study was 2.0 (1.00 – 4.01), 1.6 (1.02 – 2.40) and 2.0 (1.26 – 3.11) for the benralizumab, non-benralizumab biologics and non-biologic cohorts, respectively. Sensitivity analysis with the larger cohort of patients had similar incidence rates (95% CI) for unadjusted crude estimates of 1.9 (1.04 - 3.61), 1.8 (1.38 - 2.21) and 2.1 (1.73 - 2.60) for the benralizumab, non-benralizumab biologics, and

non-biologic cohorts, respectively. These estimates may be considered to be consistent with the observed background incidence rates for patients with asthma as well as the general population where incidence rates range between 3 to 6 per 1000 PY (Gonzalez-Perez et al 2006; Long et al 2014; Salameh et al 2021). However, estimates from this study are slightly lower than the estimates observed in published literature. One plausible explanation for this difference could be the different geographic locations in which these studies have been conducted. While our study has a major strength of being global, due to the inclusion of data from the ISAR registry, geographic variations was also explored in the ISAR and CHRONICLE subgroup analysis. In the subgroup analysis, the crude incidence rate of malignancies in the three cohorts ranged between 0.7 and 4.6 per 1000 PY, with the higher incidence rates observed in the CHRONICLE (United States data). The subgroup analysis is consistent with previously reported incidence rates among patients with severe asthma.

At the time of CSP development, the planned patients' recruitment across the 2 databases was 14000 by end of 2023. By 31 December 2022, which was the cut-off date for the analysis of this third IA study report, 9572 patients met the malignancy study's eligibility criteria (refer to Section 9.3, Table 2) and were included in the main analysis, while 17478 patients were eligible to be included in the sensitivity analysis. Although some of these patients contributed follow-up time to both benralizumab and other biologic cohorts, the overall number of patients included in the sensitivity analysis surpasses the original planned sample size at the time of CSP development.

At the time of IA1 and IA2, there were concerns about the ability to meet the projected sample size, due to challenges in patient recruitment as a result of the COVID-19 pandemic. Since then, efforts have been made to increase the sample size. These efforts have included increased collaboration between the ISAR registry and more countries as well as improving data quality to reduce the number of patients excluded. These corrective measures have led to an approximately two-fold increase in the number of patients included in the main analysis for IA3 compared to IA2, as well as an attainment of a sample size in the sensitivity analysis report in this IA3 that is greater than the projected final sample size. Additionally, there are ongoing efforts to increase the number of patients included in the main analysis for the final report which is due in 2024.

Despite the ongoing efforts to increase the total number of patients included in the main analysis, it is likely that the projected number of 14000 patients will not be reached in the final report for 2024 (with a data cut-off date of 31 December 2023). The major reason for this is that the malignancy aspect of the ISAR registry is scheduled to end in October 2023. As ISAR is run and governed independent of AstraZeneca, there is no opportunity for AstraZeneca to request an extension to the end date of the malignancy arm of the ISAR registry. Given ISAR provides most (approximately 74%) of the patients included in the study, AstraZeneca is continuing to implement as many corrective measures as possible to maximise the final

sample size as much as possible. These corrective measures include enhancing patient recruitment in participating sites within the ISAR registry, continued efforts to minimise data quality issues and missing data that would lead to patient exclusion. Despite this limitation, the evidence provided in this IA3, particularly the sensitivity analysis that included 17478 patients in the three cohorts, does not indicate any increase in risk of malignancy associated with benralizumab use.

In addition to the projected number of 14000 patients, at the time of CSP development, 39500 PY was estimated to provide sufficient follow-up time to address the research question. In this IA3, the total PY was 27090.6 PY (which is approximately 127% increase over the PY reported in IA2 [11948.9]) for the main analysis and 88108 PY (which is approximately 211.7% increase over the PY reported in IA2 [28263.9]) for the sensitivity analysis. This significant increase has allowed the characterisation of risk of malignancy in each of the cohorts of interest with more precision than was possible in IA2. With the increase in follow-up time, results presented in this IA3 are still consistent with the absence of an increased risk of malignancy among benralizumab users.

As with the limitations in attaining the projected patient numbers, there is a possibility that the projected PY may not be attained at the final report due in 2024, although the deficit is likely to be less than the deficit in patient numbers. Current projections estimate the deficit to be approximately 1000 PY for the main analysis, with the shortfall occurring mainly in the non-biologic cohort. The focus of the analysis is the comparison between patients receiving benralizumab with the two other cohorts using descriptive statistics rather than hypothesis testing. Sample size calculations in the protocol estimate that with patient follow-up of 5900 PY in the benralizumab cohort and 15700 PY in the non-biologic cohort, and assuming a true incidence of 3 per 1000 PY in both cohorts, the expected 95% CI for the observed rate ratio would be between 0.58 and 1.73 (see CSP v5 Section 9.5). Similarly, for the benralizumab versus non-benralizumab biologics cohort, assuming an estimated follow-up time of 5900 PY and 17900 PY respectively, the expected 95% CI for the observed rate ratio would be between 0.59 and 1.71. The 95% CIs for the incidence rate ratios in the combined analysis set in this report are close to these estimates with a shorter follow-up period, and it is therefore expected that the study will reach the projected precision for the final report.

Taking all this information together, and considering the effect estimates that have observed in this interim report and previous interim reports, where there has been no increase in risk, additional patients and/or follow-up time in PY is likely to further increase the precision of the effect estimates. However, the additional data is unlikely to identify an increase in risk, unless the magnitude of the increase in risk is very small, which may not be clinically meaningful. Therefore, it is anticipated that the data that will accrue at the time of the final report, even if short of the projected patient numbers, will be sufficient to address the research question.

In conclusion, findings from the data accrued in this study provide the incidence rates of malignancies in severe asthma patients receiving benralizumab, non-benralizumab biologics, and no biologics. The incidence rate estimates are consistent with previously published data, with no increase in risk among benralizumab patients as compared with non-benralizumab biologics and non-biologic patients. The effect estimates and absolute risk estimates provided in this report build upon the previous interim analysis with more precise estimates.

11.2 Limitations

Missing Data: discontinuation date in ISAR: in the ISAR registry, some data elements (date of discontinuation from registry, deaths other than for serious infections, anaphylaxis, or malignancy) required to determine duration of follow-up are not available. Therefore, patients who do not die from serious infections, anaphylaxis, or malignancy are assumed to be under follow-up until administrative censoring of the data. Therefore, the total person time of follow-up in ISAR is overestimated, leading to an underestimate of incidence rate. To mitigate this limitation, the subgroup analysis by registry provides important insights on the absolute risk of malignancies. Within the CHRONICLE study, which is not subject to the same limitation, there were no statistically significant increase in risk of malignancies in both the benralizumab cohort versus non-benralizumab cohort and benralizumab versus non-biologic cohort comparisons. Furthermore, although the absolute risks in ISAR may be underestimated, the absence of discontinuation data is not differential among the cohorts. Therefore, the incidence rate ratios and hazard rates comparing the cohorts in the ISAR registry are still valid for inference.

Erroneous data: unlikely values have been observed in the data, for example, in patient characteristics (high age, higher than expected BMI) or with baseline asthma medications (unusually high doses present, which may be an issue with incorrect units). These values have been reported as per the data. To mitigate in the final analysis, the following steps will be taken: additional querying with sites, additional cleaning and checking of the raw data to look for implausible values, additional checking of correct conversion to the correct units.

Misclassification: the average follow-up in this study is 2.7 years (total follow-up of 27090.6 PY), but the development and detection of some types of malignancy may take longer than this duration. Additionally, switching across cohorts may confound the attribution of any potential malignancy risks to a specific biologic (see Section 10.4.7). The other index date sensitivity analysis does, however, allow the comparison of incidence rates over a much longer follow-up period of approximately 5 years (total follow-up of 88108.7 PY).

Unmeasured confounders (residual confounding) will always exist in observational studies. Laboratory results and spirometry related variables had a high proportion of missing data. These are possibly unmeasured confounders and their impact on the analysis in this study

cannot be evaluated at this point. There may be other factors related to treatment and malignancy but not measured and captured in this study.

11.2.1 Presence of Study Bias

Immortal time bias: for some patients in the benralizumab and the non-benralizumab biologics cohorts, there was some time between database entry and date of first exposure to the biologic therapy. This time between database entry and start of biologic treatment was excluded from the analysis. The effect of this potential bias could be an underestimate of the total PY in the non-biologic cohort, resulting in a potential overestimate of the incidence rate in this cohort. To explore the impact of this, this bias was further quantified. Of the 5900 patients in the benralizumab and non-benralizumab biologics cohorts, 1920 had index dates (start of biologic therapy) after a mean period of approximately 12 months per patient (total of 1915.83 PY) after database entry. Using methods described in Karim et al 2016, the bias was estimated to be 0.833, where values of 1 indicate no bias in the estimate. Adjusting the crude incidence estimates among the non-biologic cohort by a factor of 0.833, the crude incidence rate per 1000 PY would be 1.7, rather than 2.0.

Prevalence bias: the index date for the non-biologic cohort in the main analysis is the database entry on or after 1 November 2017. This could lead to some selection bias in the analysis which compares the benralizumab and non-biologic cohort. As the non-biologic cohort could have started their treatment for severe asthma prior to enrolling in the database, they may be considered prevalent users. Prevalent users generally tend to be individuals who survive the early period of pharmacotherapy; therefore, the non-biologic cohort would be enriched for the "healthy users" or "survivors". This type of bias is particularly problematic if the risk of the outcome of interest varies over time such that the risk would be overestimated among the cohort of benralizumab compared to the non-biologic cohort. Despite the potential of this limitation, the results obtained from this study may be considered reassuring, as the risk difference between the benralizumab cohort and the non-biologic cohort could be potentially less than observed in this study. Furthermore, in sensitivity analysis in which index date could occur prior to November 2017, results were similar to the main analysis, highlighting the robustness of the study findings to the presence of a prevalence user bias.

11.3 Interpretation

As more data has accrued, there has been an increase in precision in the estimates observed. This is consistent with the previous interim reports, ie, that no increase in risk of malignancies was observed between the cohorts of interest. In addition, the observed risk estimates are consistent with the expected background incidence of malignancy among severe asthma patients.

11.4 Generalisability

Findings from the data accrued in this study are consistent with other published literature. As this is a global study, the absolute risk measures (incidence rates) may be more reflective of global burden of disease rather than risk by geographic regions. Despite this the comparisons of incidence rate by cohorts may be considered to be generalisable as the comparisons were adjusted for confounding factors including region.

12. OTHER INFORMATION

12.1 Patient Narratives

Not applicable.

13. CONCLUSION

The pre-defined analyses, which included both crude and adjusted analyses, do not show evidence of a difference in the underlying risk of malignancies in patients receiving benralizumab compared to those receiving non-benralizumab biologics or non-biologic therapy. This result builds upon results from previous interim reports with a consistent observation of an absence of increased risk among benralizumab users, in addition to more precise risk estimates for each cohort due to increased data accrual in this report compared to previous reports. Furthermore, the observed crude and adjusted incident rates in the cohorts are consistent with the background incidence of malignancy among severe asthma patients reported in published literature.

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Appendix A List of Stand-alone Documents

Table 19 List of Stand-alone Documents

Number	Document reference number	Date	Title
1	16.1.1	19 April 2022	Protocol amendment
2	16.1.3	26 June 2018	CHRONICLE study informed consent form
3	16.1.9	10 November 2023	Statistical analysis plan

Appendix B Additional Information

Patient data listings/final tables, figures, and listings.