First Interim Study Report PASS

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Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies: The First Interim Analysis of a Post Authorisation Safety Study

Marketing Authorisation Holder(s)

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Deputy Qualified Person for Pharmacovigilance in the EU as delegated by PPD **Qualified Person for Pharmacovigilance in the EU**

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PASS INFORMATION

Title	*Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies: The First Interim Analysis of a Post Authorisation Safety Study*
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Joint PASS	*'No'*
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 other-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.* *This is the first of three annual reports of the study followed by one final report.*
Countries of study	*United States, Canada, UK, Spain, Italy, Denmark, South Korea, Japan, Bulgaria, Ireland, Greece, Argentina, Colombia, India,*

	Kuwait, Mexico, Saudi Arabia, Taiwan, and United Arab Emirates
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1. ABSTRACT

Title

Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies: The First Interim Analysis of a Post Authorisation Safety Study

Keywords

CHRONICLE	US severe asthma registry
EMA	European Medicines Agency
ISAR	International Severe Asthma Registry
MAH	Marketing Authorisation Holder
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee

Rationale and background

Benralizumab is an eosinophil-depleting monoclonal antibody (Immunoglobulin [Ig]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 (US), 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, malignancy is an important potential risk of eosinophil-lowering therapies such as benralizumab. This study intends to describe the occurrence of malignancy in severe asthma patients receiving benralizumab compared with those receiving other-biologics, and those receiving non-biologic treatment only. This is being accomplished through analysis of data from two registries 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 (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). Herein we report the first of three annual interim analyses (IA) of this study, which precede a final report at the end of the data collection. Data collection and enrolment into this post authorisation safety study (PASS) study is ongoing, and as such any conclusions are preliminary and subject to change with further 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 other-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 AstraZeneca (AZ) sponsored US severe asthma registry (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 receiving other-biologics, and patients 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.

Setting

ISAR is being conducted by Optimum Patient Care in collaboration with the Respiratory Effectiveness Group (REG) and AZ. CHRONICLE is an AZ sponsored study with study operations led in collaboration with PAREXEL, a global contract research organisation. Recruitment is expected to complete by end of 2022 for both ISAR and CHRONICLE. Longitudinal data on the occurrence of malignancy is being collected on enrolled patients from registry entry, with the exception of ISAR patients enrolled prior to initiation of malignancy data collection. Data from ISAR and CHRONICLE were pooled to create the analysis dataset. Annual IA are planned for 2021 to 2023 for data accrued by 2020 to 2022 respectively. The final analysis and report are planned for 2024 for data accrued until the end of follow-up in December 2023. In this first IA, data accrued by 31 December 2020 were used.

Subjects and study size

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.

ISAR and CHRONICLE are targeted to recruit at least 10,000 and 4,000 severe asthma patients by 2022, respectively.

For a detailed explanation of the study sample size considerations, refer to Section 9.5 of the Clinical study protocol (CSP) v4.0. It is important to note that these considerations are based

on expected precision around estimates at the time of the final report, not at the time of the annual interim analyses 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 were collected.

This study analyses data from the ISAR and CHRONICLE registries. ISAR prospectively collects routine specialist care data on severe asthma patients from the following countries, including Canada, UK, Spain, Italy, Denmark, South Korea, Japan, Bulgaria, Ireland, Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Taiwan, and United Arab Emirates (http://www.encepp.eu/encepp/viewResource.htm?id=23721). These countries committed to the collection of malignancy data. CHRONICLE is a multi-centre, observational, prospective cohort study of adults with severe asthma in the US that routinely collects data on malignancies (https://clinicaltrials.gov/ct2/show/NCT03373045).

Results and Discussion

By the end of December 2020, which is the cut-off date for the analysis of this first IA report, a total of 8,012 patients were enrolled in both ISAR and CHRONICLE registries as of 31 December 2020, of which 4,319 patients met the malignancy study's eligibility criteria and were included in the main analysis. Overall, 3,693 patients were excluded, the majority of these were due to the date of other-biologic initiation being before 01 November 2017, benralizumab initiation before 01 November 2017, a lack of malignancy data (presence or absence of malignancy), other missing information and application of study age inclusion criteria. The overall PYs of follow-up in this IA is 6896.0 as of 31 December 2020, with the follow-up for the benralizumab cohort at 895.7 PYs, the other-biologic cohort at 3487.0 PYs, and the non-biologic cohort at 2513.3 PYs. Baseline characteristics (medication use, hospitalisations, exacerbations) were consistent with a severe asthma population.

At the time of this first report, the primary analysis included a total of 10 new malignancy cases reported from index date: 2/578 (0.2%), 4/1870 (0.2%), and 4/2024 (0.2%) in the benralizumab, other-biologic and non-biologic cohorts respectively. The crude incidence rate per 1000 PYs in these three cohorts were 2.2, 1.1, and 1.6, respectively. The pre-defined analyses, which included both crude and adjusted analyses, do not show clear evidence of a difference in the underlying risk of malignancies or trends in malignancy types between cohorts.

Conclusion

In this first IA study report, the incidence of malignancies is low in all comparison groups. The current evidence does not suggest an increase in risk of new malignancy in patients receiving benralizumab compared to those receiving other-biologics or non-biologic therapy,

although the interpretation of this finding should be done with caution given limited follow-up time and the small number of new malignancies accrued.

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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AZ	AstraZeneca
BMI	Body Mass Index
CHRONICLE	AZ sponsored US severe asthma registry
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
CSP	Clinical study protocol
COVID-19	Coronavirus Disease 2019
eCRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume during 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GPRD	General Practitioner Research Database
HIV	Human immunodeficiency virus
IA	Interim Analyses
ICS	Inhaled Corticosteroid
Ig	Immunoglobulin
IL5	Interleukin 5
ISAR	International Severe Asthma Registry
LABA	Long-acting β-adrenoreceptor agonists
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MAH	Marketing Authorisation Holder
NA	Not applicable
NAEPP	National Asthma Education and Prevention Program
NMSC	Non-melanoma skin cancer
OCS	Oral Corticosteroids
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcomes

Abbreviation or special term	Explanation
PS	Propensity Scores
PY	Person-Years
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SMD	Standardised mean difference
UK	United Kingdom
US	United States

3. INVESTIGATORS

For the details of investigators, refer to Section 3 of the clinical study protocol (CSP) v4.0.

4. OTHER RESPONSIBLE PARTIES

For the details of other responsible parties, refer to Section 3 of the CSP v4.0.

5. MILESTONES

The study is planned to run for 7 years from 2018 to 2024. Three annual interim study reports are planned 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	
Registration in the EU PAS register	November 2018	14 November 2018
Interim report 1 (Data cut-off)	26 September 2021 (31 December 2020)	17 September 2021
Interim report 2 (Data cut-off)	31 July 2022 (31 December 2021)	
Interim report 3 (Data cut-off)	31 July 2023 (31 December 2022)	
Final report of study results (Data cut-off)	September 2024 (31 December 2023)	

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 inhaled corticosteroid (ICS) plus long-acting β-adrenoreceptor agonists [LABA; most commonly used] [1, 2]. However, a subset of patients does 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 [1, 2].

Benralizumab is an eosinophil-depleting monoclonal antibody (Immunoglobulin [Ig]G1 kappa), indicated as an add-on maintenance treatment in adult patients (in Europe and United States [US]) with severe eosinophilic asthma that is inadequately controlled despite ICS and LABA treatment. It is administered as a 30 mg subcutaneous (SC) injection given every 4 weeks for the first 3 doses, followed by 30 mg SC injection every 8 weeks thereafter.

Although there is no current evidence suggesting a causal relationship, based on the putative effect of eosinophils in neoplastic diseases, malignancy is considered to be an important potential risk of eosinophil-lowering therapies [3,4]. However, 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 [5,6].

Several observational studies have evaluated the association of asthma and malignancies, which resulted in two different 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 [7-10]. 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 [11-13].

Gonzales-Perez et al. conducted a cohort study with a nested case-control analysis using the General Practitioner Research Database (GPRD) in the United Kingdom (UK). In this study, patients with asthma (129,860 patients) did not exhibit an overall greater risk of malignancy compared to the general population (200,000 patients) [14]. Long et al. [15] conducted a prospective, observational cohort, phase IV (EXCELS) study of omalizumab-treated and non-omalizumab-treated patients (7857 patients total) enrolled from multiple US 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.

Data collected from the patients enrolled in the International Severe Asthma Registry (ISAR) and an AstraZeneca (AZ) sponsored US severe asthma registry (CHRONICLE) describes the occurrence of malignancy in patients with severe asthma, including those receiving benralizumab and not receiving benralizumab.

This study fulfils the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee's (PRAC) request for a Category 3 post authorisation safety study (PASS) to evaluate the risk of malignancies in benralizumab users. Herein we report on the first of three annual interim analyses (IA) for this study, which will be followed by a final analysis and report after data collection is completed.

7. RESEARCH QUESTIONS AND OBJECTIVES

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

Primary objective: To assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving other-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 v4.0.

9. RESEARCH METHODS

For additional details of the research methods, refer to the CSP v4.0 and the statistical analysis plan (SAP) v3.0.

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 registries 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 take part in the study contribute data to this PASS (refer to list of countries in Section 9.2 below). Information on the occurrence, type of malignancy, location, date of diagnosis, staging, and outcome are collected prospectively and irrespective of asthma treatment in both ISAR and CHRONICLE.

The main objective of this study is to assess the incident rates of malignancies, event rates, and time to first malignancies across the three cohorts i.e. the benralizumab, other-biologic, and non-biologic cohorts.

9.2 Setting

Data from ISAR and CHRONICLE were pooled to create the analysis dataset from US (CHRONICLE), Canada, UK, Spain, Italy, Denmark, South Korea, Japan, Bulgaria, Ireland,

Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Taiwan, and United Arab Emirates (ISAR). Annual IA are planned for 2021 to 2023 for data accrued by 2020 to 2022 respectively. This is the first IA that reports on patients who were present in the registry and met inclusion/inclusion criteria in the period from 01 January 2018 to 31 December 2020. The final analysis report is planned for September 2024, with a final data cut-off date of 31 December 2023.

The index date for the benralizumab cohort is the date of first benralizumab use on or after 01 November 2017. The index date for other-biologic cohort is the date of the first other-biologic use on or after 01 November 2017. For those patients who did not receive any biologics, the index date is the date of registry entry on or after 01 November 2017. A patient can contribute person-time to more than one study cohort but can only contribute person-time to one cohort at a time.

For this first IA, patients from both registries were followed up to the end of December 2020, or until patients withdrew from the registry, or death, whichever occurred first.

9.3 Subjects

Only subjects who met the study eligibility criteria (refer Table 2 below) and enrolled in ISAR and CHRONICLE registries are included in the analyses. A total of 3,693 patients were excluded from the analysis; the majority of these were due to the date of other-biologic initiation being before 01 November 2017, benralizumab initiation before 01 November 2017, a lack of malignancy data (presence or absence of malignancy), other missing information and application of study age inclusion criteria (refer to Table 3 for breakdown).

Patients may change treatment cohorts during the study. For patients who switched from the benralizumab cohort to the other-biologic 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 other-biologic 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 two cohorts.

Patients were summarised in their original biologic cohort if they discontinued benralizumab or other-biologic 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 v3.0.

The calculation of person-years (PYs) for patients with treatment switch is specified in Section 6.4 of SAP v3.0. Considering the possible lag period between a treatment and cancer

development, a lag time sensitivity analyses was also performed (refer to Section 6.11.5 of SAP v3.0).

Table 2: Study Population (ISAR and CHRONICLE)	
ISAR	**CHRONICLE**
Inclusion Criteria	
1. Individuals, 18 years of age or older, with a diagnosis of severe asthma which requires treatment with guidelines suggested medications for global initiative for asthma (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). 2. Uncontrolled[1] asthma	1. 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 (e.g., pulmonologists and/or allergists) at the Investigator's or sub-investigators' site. 2. Meeting at least one of the following three criteria (a, b, or c): a. Uncontrolled[1] on asthma treatment consistent with GINA Step 4 or 5, receiving high-dose ICS[2] with additional controllers. b. Current use of a Food and Drug Administration (FDA)-approved monoclonal antibody agent for treatment of severe asthma (use is not primarily for an alternative condition). c. 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	
1. 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.	1. 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. 2. Not fluent in English or Spanish.

Table 2: Study Population (ISAR and CHRONICLE)	
ISAR	**CHRONICLE**
	3. 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 patient reported outcome is permitted (i.e. receiving the email and/or assisting patient in navigating to the web page); PROs must be completed by the patient. 4. 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.

1. 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 NAEPP/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 forced expiratory volume during 1 second (FEV_1) < 80% predicted (in the face of reduced FEV_1/forced vital capacity (FVC) defined as less than the lower limit of normal).
2. High-dose ICS is defined as: 1) ICS at a cumulative dose of > 500 µg fluticasone propionate equivalents daily or 2) Highest labelled dose of a combination of ICS/LABA.

9.4 Variables

The new onset malignancy data were collected at the baseline visit (for the period of one year prior to the baseline visit) and at follow-up visits (i.e. since the last visit for ISAR and during the prior 6 months for CHRONICLE).

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 v3.0.

9.5 Data sources and measurement

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

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. In addition, CHRONICLE routinely collects data on malignancies.

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 most variables from the domains can be mapped directly. There were some challenges merging on the following fields: occupation, medication, co-morbidities, and medication dose. The challenges stemmed mainly from differences in terminology and coding across the countries. These were circumvented 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 propensity scores (PS) align between ISAR and CHRONICLE databases allowing for a smooth data pooling.

9.6 Bias

Given the nature of the non-interventional study, patients in the three cohorts may differ with regards to important demographics and baseline characteristics. To assess signs of potential imbalances, differences between cohorts with regards to potential risk factors of malignancy (described in Section 5.3 of SAP v3.0) 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 9.9.3 on sensitivity analyses.

9.7 Study size

The planned patients' recruitment across the two registries is 14,000 by 2022. By the end of December 2020, which is the cut-off date for the analysis of this first IA study report, a total of 8,012 severe asthma patients were recruited to ISAR and CHRONICLE and 4,319 of them met the malignancy study's eligibility criteria (refer to Section 9.3). The patient recruitment was lower than planned due to the Coronavirus Disease 2019 (COVID-19) pandemic, which posed multiple challenges in patient recruitment and follow-up. Overall, 3,693 patients were excluded primarily due to lack of malignancy data (e.g. presence/absence of malignancy, malignancy status) and the date of other-biologic initiation being before 01 November 2017. (Note: a sensitivity analysis including patients excluded due to the date criterion was performed).

The overall PYs of follow-up in this IA is 6896.0 as of 31 December 2020. In the benralizumab cohort, a total of 895.7 patient-years were accrued (refer to Section 10.3.2), while in the other-biologic cohort and in the non-biologic cohort, there 3487.0 PYs and 2513.3 PYs accrued, respectively. Please note that data collection and enrolment into this PASS study is ongoing, and patient enrolment will be monitored with each interim report. For a detailed explanation of the study sample size refer to Section 9.5 of CSP v4.0. It is important to note that these considerations are based on expected precision around estimates at the time of the final report, not at the time of the annual IAs where the extent of follow-up and reported cases will be less.

9.8 Data transformation

All the data transformation methods are being followed as per CSP (refer to Section 9.6 of CSP v4.0). Data from the two datasets were pooled to create the analysis dataset prior to statistical analyses. Details of the collected variables are included in the Case Report Forms (CRFs) for the study (a list of the CRFs is included in Annex 1 of the CSP v4.0). 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 registries were reviewed for quality and then coded using ICD-10 codes by an oncologist. This ensures harmonization of the outcome across registries and a seamless data merging of this key variable.

9.9 Statistical methods

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 v3.0 that was finalised prior to performing this first IA report. 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 Statistical Analysis System (SAS)® version 9.4 or higher.

9.9.1 Main statistical methods

9.9.1.1 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.

9.9.1.2 Propensity Score

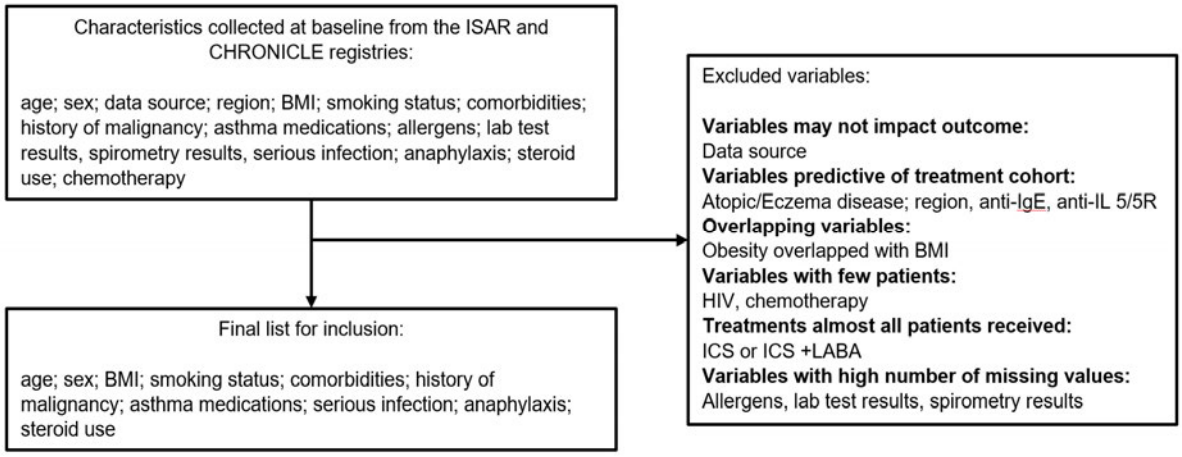
Propensity score (PS) is the probability that patients would receive a particular treatment given their baseline characteristics. In this study, it was used to balance the three cohorts in terms of baseline characteristics to account for confounding. Since there was no intent to compare between the other-biologic vs. non-biologic cohort, separate sets of PS for each comparison between benralizumab vs. other-biologic cohorts, and between benralizumab vs. non-biologic cohorts were generated. The PS model was adjusted for the following covariates: age, sex, Body Mass Index (BMI), smoking status, comorbid conditions (allergic rhinitis, cardiovascular disease, liver disease, Chronic obstructive pulmonary disease [COPD], chronic rhinosinusitis, diabetes, hypertension and nasal polyps), asthma medications (LABA, long-acting muscarinic antagonist [LAMA], theophylline, leukotriene receptor antagonist [LTRA], macrolide antibiotics and steroid-sparing agents), steroid use, previous serious infection, previous anaphylaxis 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 v3.0 section 6.11.1. Lab 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. The flow chart states detailed reasons for excluding baseline variables in Figure 1.

The PS were also calculated for each subpopulation analysis set. The balance of the covariates across three cohorts before and after adjusting PS were examined. As previously stated in the approved SAP v3.0, extreme weights (values above the 99th and below the 1st percentile point) were excluded in estimating incidence rates (refer to Section 6.11.2 of SAP v3.0) and the weighted Cox-proportional hazard model (refer to Section 6.11.3 of SAP v3.0).

Stratified analysis of PS was performed but due to the small number of malignancies, or absence of malignancies in many of the strata, the outcome model in some of the strata did not converge; therefore, the results of stratified analysis were not included in this IA report.

Figure 1: Variables excluded from propensity score model



9.9.1.3 Incidence Rates and Event Rates

The definition of incidence rates and event rates, and time at risk for incidence rates and event rates were described in Section 6.11.2 and 6.4.2 of SAP v3.0 respectively. Poisson regression models were used to estimate the incidence rate, difference in incidence rate, incidence rate ratio and corresponding 95% Confidence Intervals (CIs). For adjusted estimates, Poisson regression models controlled for cohort, age, sex, region, smoking and BMI. All incidence rates were reported as new malignancies incidence rates per 1000 PYs.

9.9.1.4 Time to Event Analysis

Time from the index date (defined in Section 6.11.3 of SAP v3.0) 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.

9.9.2 Missing values

The procedures for handling missing values were discussed in Section 6.6 of the SAP v3.0.

9.9.3 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 (i.e., one year after initiation of benralizumab or any other-biologic).

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, with exposure data and events within this time not included in the cohort they switched to. However, at the time of this interim analysis, because all new malignancies within one year of switching were also within a year of the initial index date, the analysis was found to be identical to that noted above, and was therefore not presented separately as part of this IA.

Alternative Definition of Index Date

Since there were many more other biologic users who initiated biologics before 1 November 2017, an alternative definition of the index date was used to minimize this exclusion. In this sensitivity analysis, the index date for the benralizumab and other-biologic cohort were defined as the first biologic use, for the non-biologic cohort as registry 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.

9.10 Quality control

All patients enrolled in the ISAR and CHRONICLE 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.

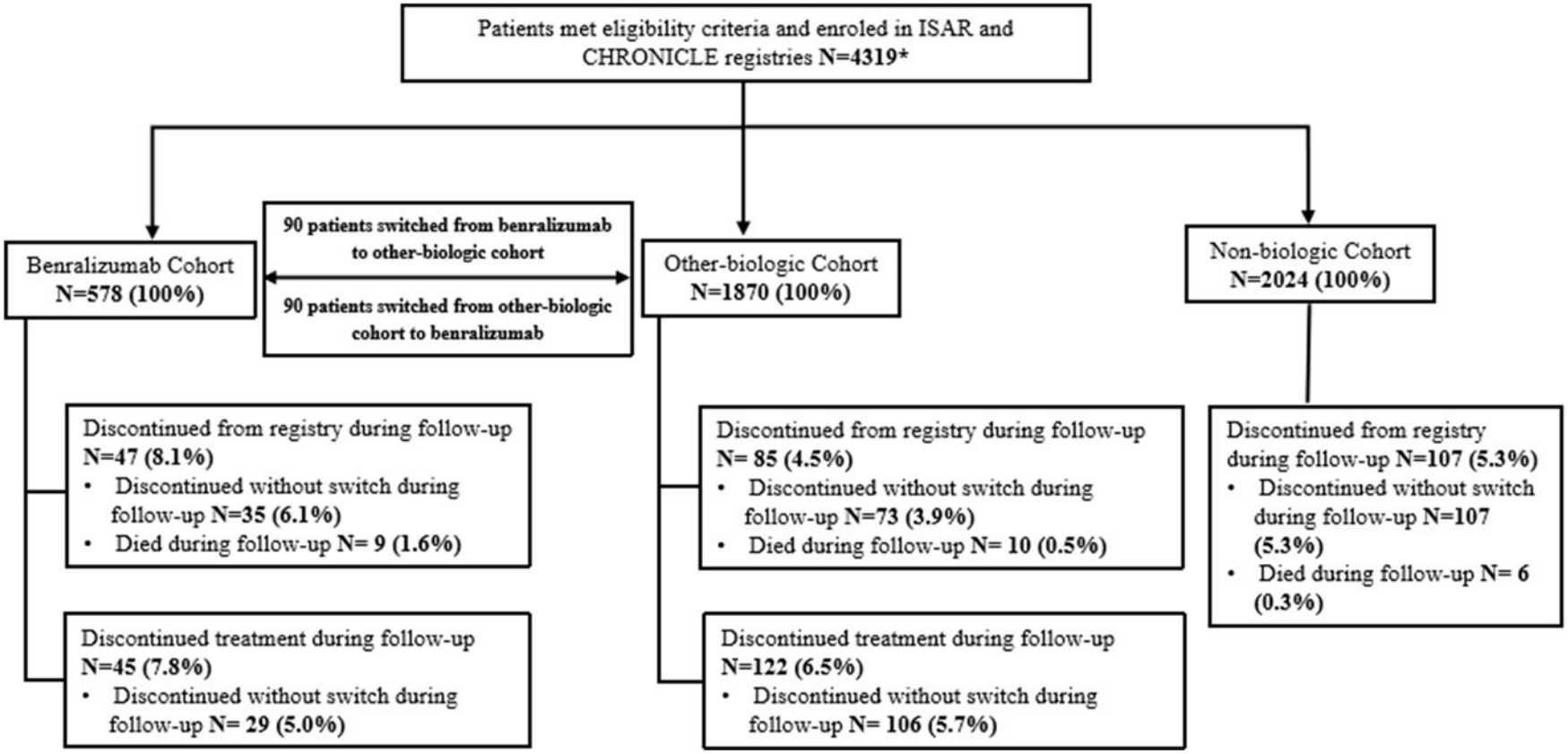
Data quality was assessed via a series of pre-programmed data quality checks that automatically detect out-of-range or anomalous data on the data collection instrument, the electronic case report form (eCRF). To minimise data entry errors, most of the fields requested on the ISAR eCRF were numeric. Data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

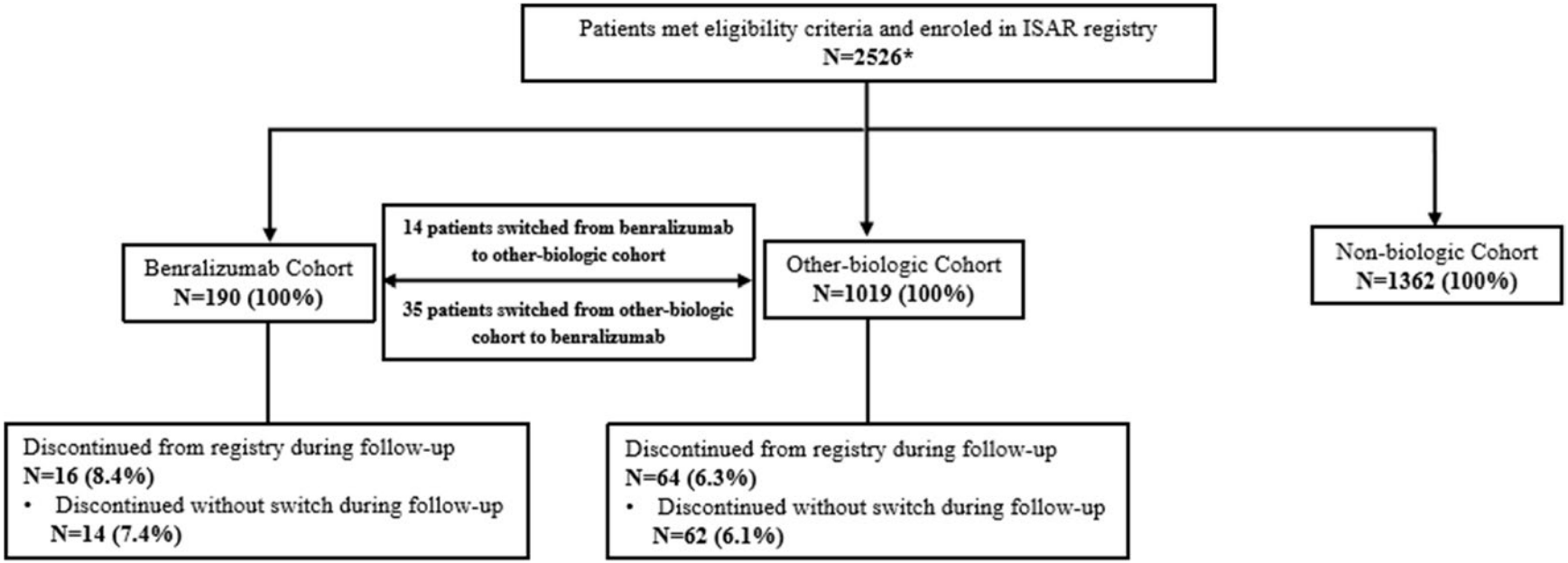
Figure 2: ISAR and CHRONICLE Combined



The average (SD) follow-up time in years was 1.5 (0.72) in the benralizumab cohort, 1.8 (0.81) in the other-biologic cohort, and 1.2 (0.74) in the non-biologic cohort.

* Number of patients in total may not be equal to the sum of numbers of patients in each cohort because patients who switched cohort were counted in each of the cohorts in turn.

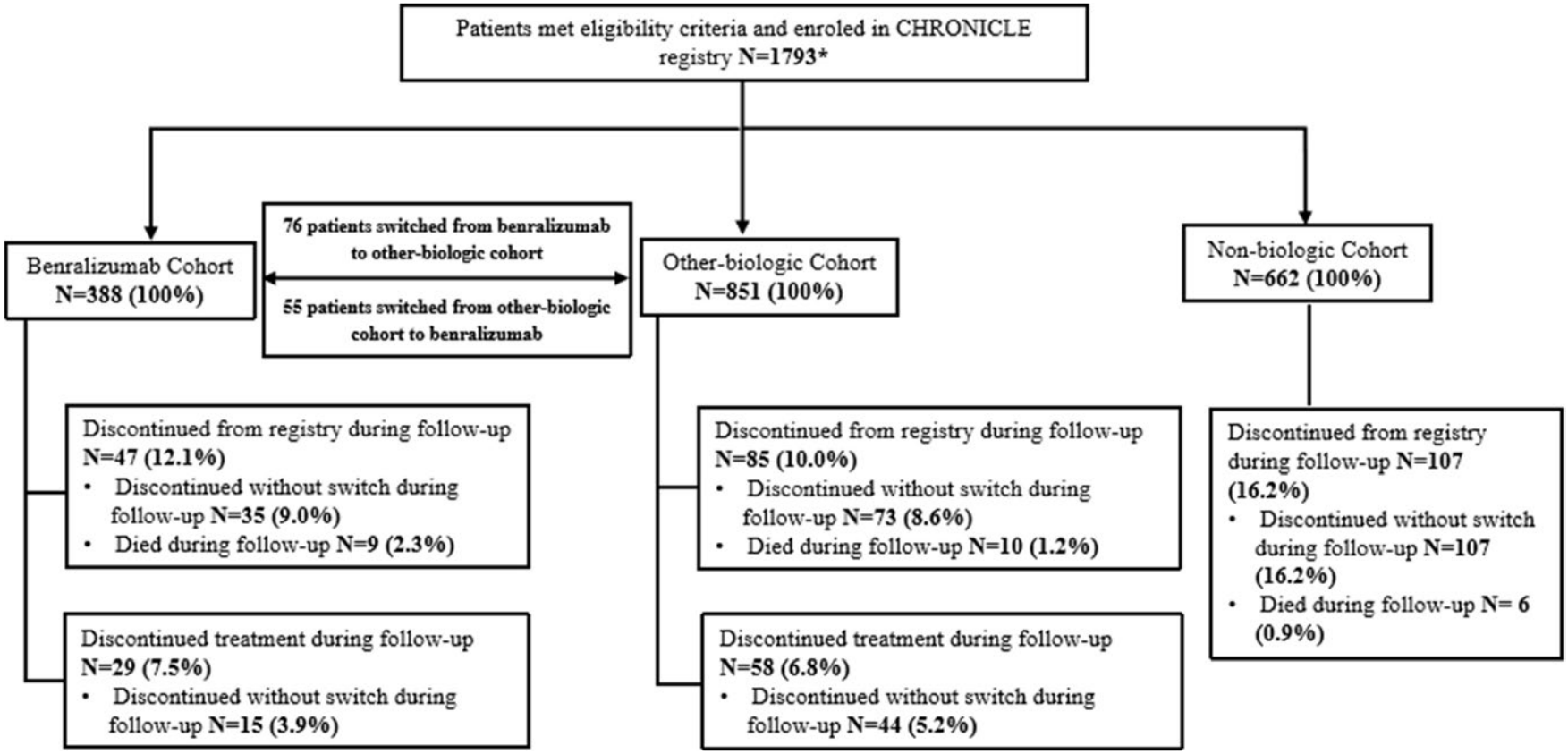
Figure 3: ISAR



The average (SD) follow-up time in years was 1.7 (0.61) in the benralizumab cohort, 2.1 (0.75) in the other-biologic cohort, and 1.2 (0.75) in the non-biologic cohort.

* Number of patients in total may not be equal to the sum of numbers of patients in each cohort because patients who switched cohort were counted in each of the cohort in turn.

Figure 4: CHRONICLE



The average (SD) follow-up time in years was 1.4 (0.76) in the benralizumab cohort, 1.5 (0.75) in the other-biologic cohort, and 1.3 (0.69) in the non-biologic cohort.

* Number of patients in total may not be equal to the sum of numbers of patients in each cohort because patients who switched cohort were counted in each of the cohort in turn.

10.1 Participants

10.1.1 Overall population

A total of 8,012 patients were enrolled in both ISAR and CHRONICLE registries as of 31 December 2020, with 4,319 included in the main analysis. Overall, 3,693 patients were excluded. The majority of these were due to the date of other-biologic initiation being before 01 November 2017, benralizumab initiation before 01 November 2017, a lack of malignancy data (presence or absence of malignancy), other missing information and application of study age inclusion criteria (Note that a sensitivity analysis including patients excluded due to the date criterion was performed).

Patient disposition from ISAR and CHRONICLE registries are summarised in Table 3 and Figure 2 (refer to Figure 3 and Figure 4 above for separate analysis sets). Amongst the 4,319 patients in main analysis, there were 578 patients in the benralizumab cohort, 1,870 patients in the other-biologic cohort, and 2,024 patients in the non-biologic cohort. The overall PYs of follow-up in this IA is 6896.0 as of 31 December 2020, with the follow-up for the benralizumab cohort at 895.7 PYs, the other-biologic cohort at 3487.0 PYs, and the non-biologic cohort at 2513.3 PYs.

A total of 47 (8.1%) patients in the benralizumab cohort, 85 (4.5%) patients in the other-biologic cohort, and 107 (5.3%) patients in the non-biologic cohort discontinued during the follow-up from the registries. All patients who discontinued were from the CHRONICLE registry as discontinuation date was not recorded for subjects in the ISAR registry. Unless there was information confirming a specific reason for discontinuation from the ISAR registry, such as death from malignancy, serious infection or anaphylaxis, it was assumed that the follow-up of patients in the ISAR registry was ongoing at data cut-off (31 December 2020).

Of the 227 (5.3%) patients who discontinued from the registry, 23 (0.5%) patients died during the follow-up: 9 (1.6%) patients in the benralizumab cohort, 10 (0.5%) patients in the other-biologic cohort, and 6 (0.3%) patients in the non-biologic cohort. Among these deaths, two patients reported follow-up time in both the benralizumab and the other-biologic cohorts, hence the total of 23 deaths.

The number of patients who switched to the benralizumab cohort from the other-biologic cohort was 90 (4.8%). The number of patients who switched from benralizumab to the other-biologic cohort was 90 (15.6%). The mean (SD) of total PYs of follow-up (years) were 1.5 (0.72) years in the benralizumab cohort, 1.8 (0.81) years in the other-biologic cohort, and 1.2 (0.74) years in the non-biologic 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 [a]	578	1870	2024	4319
Patients discontinued [b]	47 (8.1)	85 (4.5)	107 (5.3)	227 (5.3)
Patients died during follow-up	9 (1.6)	10 (0.5)	6 (0.3)	23 (0.5)
Patients discontinued without a switch [c]	35 (6.1)	73 (3.9)	107 (5.3)	215 (5.0)
Patients discontinued treatment [d]	45 (7.8)	122 (6.5)	NA	151 (3.5)
Patients discontinued treatment without a switch [c, d]	29 (5.0)	106 (5.7)	NA	135 (3.1)
Patients switched to another cohort	90 (15.6)	90 (4.8)	NA	153 (3.5)
Switch to Benralizumab cohort	NA	90 (4.8)	NA	NA
Switch to other-biologic cohort	90 (15.6)	NA	NA	NA
Total follow-up time (years)				
Mean (SD)	1.5 (0.72)	1.8 (0.81)	1.2 (0.74)	1.5 (0.82)
Median	1.5	1.9	1.2	1.5
Min, Max	0.0, 3.1	0.0, 3.2	0.0, 3.2	0.0, 3.2
Q1, Q3	1.0, 2.1	1.2, 2.6	0.6, 1.8	0.9, 2.1
Total person-years of follow-up (years)	895.7	3487.0	2513.3	6896.0

NA Not applicable. SD Standard deviation. Q1 First quartile. Q3 Third quartile.
[a] A total of 3,693 patients are excluded from analysis. Among them, 1,612 patients are excluded from analysis because they do not have malignancy status (presence or absence of malignancy). 4 patients are excluded due to lack of review for malignancy data. 3,092 patients are excluded from analysis because their first use of benralizumab is before 01 November 2017, first use of other-biologic treatment is before 01 November 2017 or index date of non-biologic cohort is before 01 November 2017. 45 patients are excluded from analysis because their cohort cannot be derived from data. 30 patients are excluded from analysis because their age is less than 18 years. Patients excluded from analysis with multiple reasons are counted once in each of those reasons. Missing data have been queried thoroughly with the sites where possible, with persistently missing data resulting in the disposition above.
[b] Discontinuation of study and death date are not collected in ISAR. Note: ISAR only records deaths resulting from malignancy, anaphylaxis event and serious infection. Deaths due to other reasons are not captured.
[c] Patients without cohort switch is defined as patients who stay in only one cohort from the beginning of the study.
[d] Discontinuation of treatment is defined as discontinuation from either benralizumab or other-biologic without receiving any further biologic treatment in the study. Patients who discontinue still contribute person time to their respective cohort after discontinuation.
Non-biologic cohort is defined as patients who never receive benralizumab or other-biologic treatment.
Patients who switched cohort are counted in each of the cohort in turn, but are 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 are based on number of patients enrolled in the registry.
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.

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 List of tables (Table 14.1.2.1) and for separate analysis sets refer to List of tables (Table 14.1.2.2).

Baseline demographic characteristics were assessed at initial index date (refer to Sections 6.3.1 and 6.3.2 of SAP v3.0). More than half of the study population were aged between 40 to 64 years which was consistent across the cohorts. The majority of patients from the study population were white and were female across the cohorts.

Table 4: Demographic characteristics prior to PS trimming (ISAR and CHRONICLE combined analysis set)

Demographic characteristic	Statistics or category	Benralizumab cohort (N=578)	Other-biologic cohort (N=1870)	Non-biologic cohort (N=2024)	Total (N=4319)
Age (years)	N	577	1868	2009	4301
	Mean	55.1	53.0	54.8	54.2
	SD	13.98	14.54	15.49	14.94
Age (years) subgroups n (%)	>= 18 to <= 39	78 (13.5)	343 (18.3)	349 (17.2)	739 (17.1)
	>= 40 to <= 64	351 (60.7)	1108 (59.3)	1108 (54.7)	2474 (57.3)
	>= 65 to <= 79	138 (23.9)	392 (21.0)	471 (23.3)	974 (22.6)
	>= 80	10 (1.7)	25 (1.3)	81 (4.0)	114 (2.6)
	Total	577 (99.8)	1868 (99.9)	2009 (99.3)	4301 (99.6)
	Missing	1	2	15	18
Sex n (%)	Female	379 (65.6)	1223 (65.4)	1385 (68.4)	2884 (66.8)
	Male	199 (34.4)	647 (34.6)	634 (31.3)	1430 (33.1)
	Total	578 (100)	1870 (100)	2019 (99.8)	4314 (99.9)
	Missing	0	0	5	5
Data source n (%)	ISAR	190 (32.9)	1019 (54.5)	1362 (67.3)	2526 (58.5)
	CHRONICLE	388 (67.1)	851 (45.5)	662 (32.7)	1793 (41.5)
Race n (%)	White	420 (72.7)	1381 (73.9)	1147 (56.7)	2847 (65.9)
	Black or African American	71 (12.3)	156 (8.3)	140 (6.9)	339 (7.8)
	Asian	32 (5.5)	95 (5.1)	398 (19.7)	518 (12.0)
	Native Hawaiian or Other Pacific Islander	1 (0.2)	3 (0.2)	0	4 (0.1)
	American Indian or Alaska Native	1 (0.2)	3 (0.2)	1 (0.0)	5 (0.1)
	Other	24 (4.2)	79 (4.2)	265 (13.1)	365 (8.5)
	Total	549 (95.0)	1717 (91.8)	1951 (96.4)	4078 (94.4)
	Missing	29	153	73	241

N Number of patients in cohort. n Number of patients in analysis. 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 are counted in each of the cohort in turn, but are 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.

10.2.2 Baseline Clinical Characteristics (Prior to PS Trimming)

For complete patient baseline clinical characteristics of the ISAR and CHRONICLE combined analysis set refer to List of tables (Table 14.1.3.1) and for separate analysis sets refer to List of tables (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 1 year prior to index date. Other variables were assessed at initial index date.

At baseline, the mean number (SD) of asthma exacerbations, hospital admissions, and baseline emergency department visits were slightly higher in the benralizumab cohort (1.1 (1.74), 0.2 (0.73), and 0.3 (1.09) respectively) when compared to the other-biologic cohort (0.6 (1.32), 0.1 (0.48), and 0.1(0.66)) and the non-biologic cohort (0.9 (1.42), 0 (0.32), and 0.1(0.40)). One third of the overall study population were smokers and the distribution of smoking status was comparable across the cohorts. The age at asthma onset ranged from approximately 31 to 34 years, across the cohorts.

When comparing across the cohorts, the percentage of patients on maintenance OCS treatment at baseline was lower in the other-biologic cohort (30.9%) compared to the benralizumab cohort (41.2%) and the non-biologic cohort (42.4%).

Medication adherence across all cohorts was high, with the benralizumab cohort reporting 90.1%, the other-biologic cohort reporting 86.8% and the non-biologic cohorts reporting 74.4% as adherent to each respective medication group. Please note that adherence is evaluated by the physician of each patient based on either clinical impression or objective measures (e.g. review of prescription records).

At baseline, asthma status across cohorts was either well controlled or partly controlled in most patients. The non-biologic cohort had the greatest percentage of uncontrolled asthma status 48.1% compared to 37.7% for the benralizumab, and 33.9% for the other-biologic.

Table 5: Patient clinical characteristics at baseline prior to PS trimming (ISAR and CHRONICLE combined analysis set)

Baseline clinical characteristic	Statistics or category	Benralizumab cohort (N=578)	Other-biologic cohort (N=1870)	Non-biologic cohort (N=2024)	Total (N=4319)
Body Mass Index (kg/m^2)	N	548	1790	1919	4106
	Mean	31.275	30.074	29.363	29.859
	SD	8.3739	7.7088	7.6321	7.7648
Smoking status n (%)	Non-smoker	391 (67.6)	1237 (66.1)	1346 (66.5)	2870 (66.5)
	Previous and/or current smoker	180 (31.1)	578 (30.9)	599 (29.6)	1312 (30.4)
	Total	571 (98.8)	1815 (97.1)	1945 (96.1)	4182 (96.8)
Pack years [a]	N	161	506	553	1181
	Mean	16.716	17.658	16.543	17.076
	SD	19.0291	19.7177	17.8318	18.6305
Age at asthma onset (years)	N	508	1624	1882	3887
	Mean	33.193	31.250	34.215	32.975
	SD	20.7080	19.5264	20.1756	20.0226
Number of exacerbations [b]	N	578	1870	2024	4319
	Mean	1.1	0.6	0.9	0.8
	SD	1.74	1.32	1.42	1.41
Number of invasive ventilations	N	578	1870	2024	4319
	Mean	0.0	0.0	0.0	0.0
	SD	0.15	0.10	0.03	0.08
Number of hospital admissions	N	578	1870	2024	4319
	Mean	0.2	0.1	0.0	0.1
	SD	0.73	0.48	0.32	0.45
Number of emergency department visits	N	578	1870	2024	4319
	Mean	0.3	0.1	0.1	0.1
	SD	1.09	0.66	0.40	0.61
Maintenance oral corticosteroids (OCS)	Yes	238 (41.2)	578 (30.9)	858 (42.4)	1588 (36.8)
	No	340 (58.8)	1292 (69.1)	1166 (57.6)	2731 (63.2)
	Total	578 (100)	1870 (100)	2024 (100)	4319 (100)
Maintenance OCS dose (mg/day)	N	218	537	811	1491
	Mean	32.90	27.92	32.32	30.87
	SD	18.446	18.774	21.867	20.607

Table 5: Patient clinical characteristics at baseline prior to PS trimming (ISAR and CHRONICLE combined analysis set)

Baseline clinical characteristic	Statistics or category	Benralizumab cohort (N=578)	Other-biologic cohort (N=1870)	Non-biologic cohort (N=2024)	Total (N=4319)
Medication adherence status n (%) [c]	Yes	521 (90.1)	1623 (86.8)	1506 (74.4)	3510 (81.3)
	No	34 (5.9)	142 (7.6)	392 (19.4)	555(12.9)
	Total	555 (96.0)	1765 (94.4)	1898 (93.8)	4065 (94.1)
Asthma control status n (%) [d]	Well controlled	133 (23.0)	459 (24.5)	298 (14.7)	867 (20.1)
	Partially controlled	124 (21.5)	428 (22.9)	586 (29.0)	1117 (25.9)
	Not controlled	218 (37.7)	633 (33.9)	974 (48.1)	1757 (40.7)
History of malignancy n (%)	Yes	32 (5.5)	60 (3.2)	88 (4.3)	173 (4.0)
	No	546 (94.5)	1810 (96.8)	1936 (95.7)	4146 (96.0)
	Total	578 (100)	1870 (100)	2024 (100)	4319 (100)

GINA Global Initiative for Asthma. N Number of patients in cohort. n Number of patients in analysis. SD Standard deviation. Q1 First quartile. Q3 Third quartile.

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

[b] Number of exacerbations only counts severe asthma exacerbations which are defined as events that require rescue steroids.

[c] The medication adherence status of asthma treatment is evaluated based on either clinical impression or objective measures (e.g. 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 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 summarise all events occurring within 12 months preceding index dates within each cohort. Patients who switched cohort are counted in each of the cohort in turn but are 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).

10.2.3 Baseline Comorbidities (Prior to PS Trimming)

The baseline comorbidities from the ISAR and CHRONICLE registries are summarised in the Table 6 below.

At baseline, asthma-related comorbidities such as allergic rhinitis, chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps), and atopic diseases/eczema were generally comparable across the cohorts. Allergic rhinitis was common in all three cohorts (benralizumab cohort had 59.7%, non-biologic cohort 65.7%, and the other-biologic cohort 68.4%). Atopic diseases/eczema were reported in all three cohorts (benralizumab cohort 35.8%, the other-biologic cohort 56.7%, and non-biologic cohort 68.2%). Nasal polyps were less common (other-biologic cohort reported 30.5%, the non-biologic cohort 19.6%, and the benralizumab cohort 26.1%).

Obesity was the most common OCS-related comorbidity at baseline with the benralizumab cohort reporting 45.8% with this comorbidity, followed by the other-biologic cohort 40.4%, and the non-biologic cohort 35.2%. The second most common OCS-related comorbidity at baseline was cardiovascular disease. Diabetes was the least reported OCS-related comorbidity at baseline and is similar across the cohorts.

COPD was uncommon across the cohorts, with 7.4% of patients reporting COPD in the benralizumab cohort compared to 2.6% of the non-biologic cohort, and 5.2% of the other-biologic cohort.

Table 6: Comorbidities at baseline prior to PS trimming (ISAR and CHRONICLE combined analysis set)

	Number (%) of patients		
Comorbidity Term	**Benralizumab cohort (N=578)**	**Other-biologic cohort (N=1870)**	**Non-biologic cohort (N=2024)**
Patients with any comorbidities at baseline	543 (93.9)	1794 (95.9)	1940 (95.8)
Asthma-related comorbidities			
Allergic rhinitis	345 (59.7)	1280 (68.4)	1329 (65.7)
Atopic diseases / Eczema [a]	207 (35.8)	1061 (56.7)	1381 (68.2)
Chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps)	196 (33.9)	674 (36.0)	633 (31.3)
Nasal polyps	151 (26.1)	571 (30.5)	396 (19.6)
Oral corticosteroids (OCS)-related comorbidities			
Cardiovascular disease [b]	194 (33.6)	491 (26.3)	351 (17.3)
Diabetes	63 (10.9)	166 (8.9)	135 (6.7)
Hypertension	159 (27.5)	403 (21.6)	293 (14.5)
Obesity	265 (45.8)	756 (40.4)	712 (35.2)
Other comorbidities			
Chronic obstructive pulmonary disease (COPD)	43 (7.4)	98 (5.2)	53 (2.6)
Human immunodeficiency virus (HIV)	0	1 (0.1)	0
Liver disease	1 (0.2)	4 (0.2)	3 (0.1)

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 is accounted for separately
[b] Cardiovascular disease includes hypertension. Examples of cardiovascular disease are hypertension, coronary artery disease, arterial hypertension, and unspecified cardiovascular disease.
Number (%) of patients are sorted alphabetically by comorbidity term. A patient can have one or more comorbidities.
Patients with multiple events in the same category are counted only once in that category.
If not stated otherwise, percentages are 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 have been ongoing at the first index date.

10.2.4 Baseline Asthma Medication (Prior to PS Trimming)

Overall population

For the complete description of baseline asthma medications at baseline of the ISAR and CHRONICLE combined analysis set refer to List of tables (Table 14.1.5.1) and for separate analysis set refer to List of tables (Table 14.1.5.2). Asthma medication at baseline from the ISAR and CHRONICLE registries are summarised in Table 7 below.

Most of the patients across the cohorts used at least one asthma medication at baseline, with 100% of benralizumab cohort, 91% of the non-biologic cohort, and 100% of the other-biologic cohort reporting use. The most commonly used asthma medication at baseline was ICS+LABA, with 72.7% reported in the benralizumab cohort, 81.5% in the non-biologic cohort and 63.9% in the other-biologic cohort, followed by LTRA with use ranging from 42.6% in the other-biologic cohort to 51.4% in the benralizumab cohort.

Table 7: Asthma medication at baseline prior to PS trimming (ISAR and CHRONICLE combined analysis set)

Asthma medication term	Statistics or category	Benralizumab cohort (N=578)	Other-biologic cohort (N=1870)	Non-biologic cohort (N=2024)
Patients with any asthma medication	Yes	578 (100)	1870 (100)	1842 (91.0)
	No	0	0	182 (9.0)
Inhaled corticosteroids (ICS) only	Yes	118 (20.4)	268 (14.3)	249 (12.3)
	No	460 (79.6)	1602 (85.7)	1775 (87.7)
ICS dose (mg/day)	N	118	262	244
	Mean	0.47	3.05	11.32
	SD	0.416	23.281	77.549
Long-acting β-adrenoreceptor agonists (LABA) only	Yes	13 (2.2)	53 (2.8)	29 (1.4)
	No	565 (97.8)	1817 (97.2)	1995 (98.6)
ICS+LABA	Yes	420 (72.7)	1194 (63.9)	1649 (81.5)
	No	158 (27.3)	676 (36.1)	375 (18.5)
Long-acting muscarinic antagonists (LAMA)	Yes	207 (35.8)	671 (35.9)	740 (36.6)
	No	371 (64.2)	1199 (64.1)	1284 (63.4)
Theophylline	Yes	27 (4.7)	64 (3.4)	94 (4.6)
	No	551 (95.3)	1806 (96.6)	1930 (95.4)
Leukotriene receptor antagonist (LTRA)	Yes	297 (51.4)	796 (42.6)	924 (45.7)
	No	281 (48.6)	1074 (57.4)	1100 (54.3)
Anti-immunoglobulin E (anti-IgE)	Yes	32 (5.5)	753 (40.3)	0
	No	546 (94.5)	1117 (59.7)	2024 (100)
Anti-interleukin 5 / 5 receptor (anti-IL5/5R)	Yes	NA	931 (49.8)	0
	No	NA	939 (50.2)	2024 (100)
Macrolide antibiotics	Yes	38 (6.6)	79 (4.2)	118 (5.8)
	No	540 (93.4)	1791 (95.8)	1906 (94.2)
Steroid-sparing agents	Yes	1 (0.2)	5 (0.3)	1 (< 0.1)
	No	577 (99.8)	1865 (99.7)	2023 (100)

N Number of patients in cohort. SD Standard deviation.
Patients with multiple medications are counted once for each asthma medication term.
Doses of ICS and LABA combination treatment are recorded differently in ISAR and CHRONICLE studies and are not summarised in this table.
Steroid-sparing agents include azathioprine, intravenous gammaglobulin, methotrexate, and mycophenolate.
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 first index date or have been ongoing at the first index date.

10.3 Main results

10.3.1 Propensity Score by cohort

The balance of the covariates across three cohorts were examined by checking the distribution of PS (graphic approach) and standardised mean difference (tabular approach).

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 other-biologic cohort (Figure 5) and the non-biologic cohort (Figure 6) suggests that the PS model has largely balanced baseline variables between the cohorts for the characteristics included in the model.

Figure 5: Overlaid distribution of propensity score for the benralizumab cohort versus the other-biologic cohort, histogram (ISAR and CHRONICLE combined analysis set)

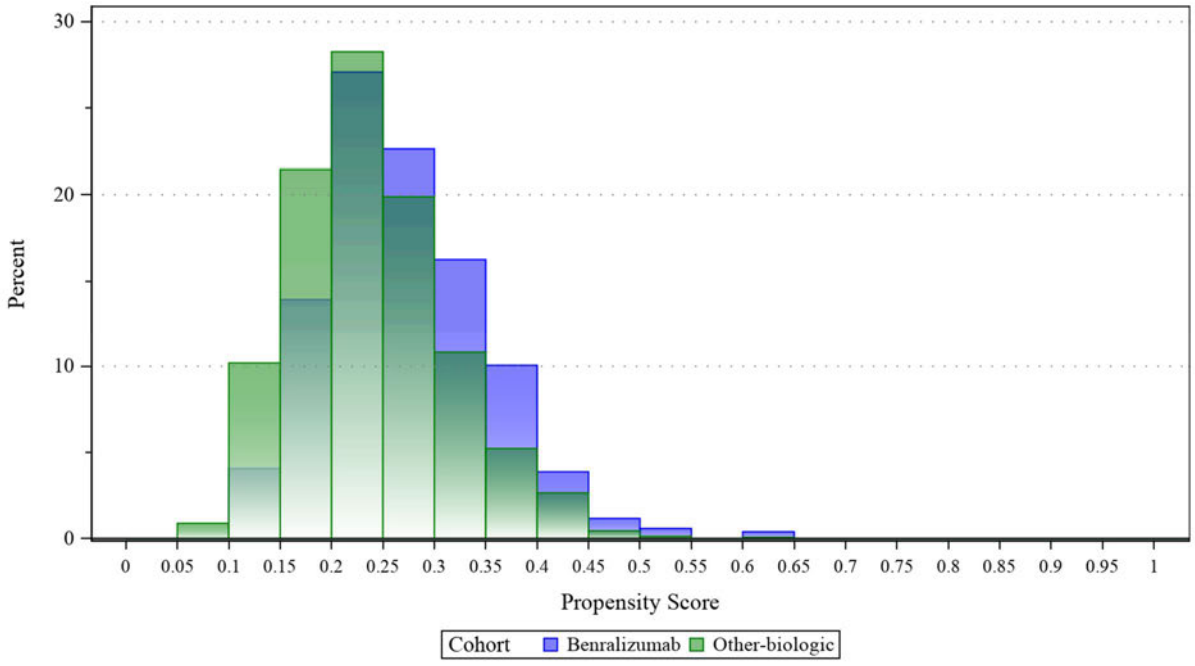
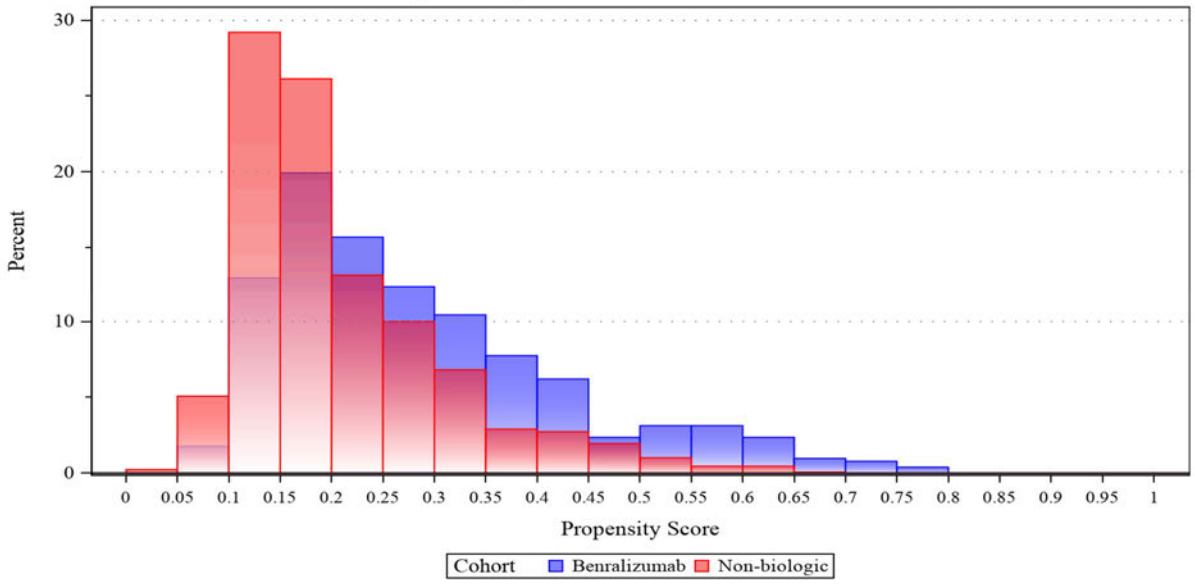


Figure 6: Overlaid distribution of propensity score for the benralizumab cohort versus non-biologic cohort, histogram (ISAR and CHRONICLE combined analysis set)



10.3.1.1 Comparison of baseline characteristics before trimming-Overall population

Baseline characteristics have already been summarised in the above sections. Subsequent sub-sections are technical sections discussing the impact of weighting and trimming on the balance of characteristics across the cohorts (refer to Table 8 below).

Benralizumab cohort versus other-biologic cohort

Pre-weighting and post-weighting SMDs are reported below in Table 8; for more details refer to List of tables, 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 (e.g. $p<0.05$) may not represent clinically meaningful differences between cohorts:

Variables such as sex, smoking status, and chronic rhinosinusitis were balanced at baseline, and no differences reaching nominal significance ($p<0.05$) between the benralizumab and the other-biologic cohort were observed for these variables.

A standardised mean difference (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 (see Table 8 for pre- and post-weighting SMDs). Of note, SMD for age decreased from 0.169 to 0.003 post-weighting and cardiovascular disease improved from -0.174 to -0.003.

Benralizumab cohort versus non-biologic cohort

Pre-weighting SMDs and post-weighting are reported below in Table 8; for further details, refer to List of tables Table 14.2.1.1.2). 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.

For the following variables (age, sex, smoking status, chronic rhinosinusitis, liver disease, history of malignancy, previous serious infection, LABA only, LAMA, macrolide antibiotics, theophylline, and steroid-sparing agents) there was balance at baseline, i.e. no differences reaching nominal significance ($p<0.05$) between the benralizumab cohort and the non-biologic cohort were observed.

Post-weighting SMD was < 0.10 for all the variables, which confirmed that weighting balanced the baseline characteristics across the cohorts (see Table 8 for pre- and post-weighting SMDs).Clear improvements in SMD were observed post-weighting in BMI, several comorbidities (allergic rhinitis, nasal polyps, cardiovascular disease, diabetes, hypertension, COPD) and the baseline use of LTRA and steroids.

Table 8: Standardised Mean Difference (SMD) 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)	0.169	0.003	0.006	-0.012
Sex	-0.028	0.003	0.080	0.005
Body Mass Index (kg/m^2)	0.149	0.003	0.253[1]	0.041
Smoking status	0.015	-0.010	-0.016	0.011
Allergic rhinitis	0.155[1]	0.014	0.146	-0.022
Chronic rhinosinusitis	0.052	-0.008	-0.004	0.004
Nasal polyps	0.074	-0.002	-0.128[1]	-0.028
Cardiovascular disease	-0.174[1]	-0.003	-0.415[1]	-0.012
Diabetes	-0.058	-0.001	-0.168[1]	-0.019
Hypertension	-0.149	0.001	-0.356[1]	-0.010
COPD	-0.089	0.017	-0.229[1]	-0.003
Liver disease	0.012	0.011	-0.021	0.004
History of malignancy	-0.099	-0.008	-0.046	-0.023
Previous anaphylaxis	-0.064	0.003	-0.088	0.003
Previous serious infection	0.062	0.017	0.115	-0.019
LABA only	0.058	0.014	-0.063	0.012
LAMA	0.061	-0.017	0.045	0.008
Theophylline	-0.055	-0.017	0.006	0.010
LTRA	-0.155[1]	0.001	-0.116	-0.007
Macrolide antibiotics	-0.119	0.001	-0.034	-0.001
Steroid-sparing agents	0.012	0.012	-0.039	0.000
Steroid use	-0.161[1]	-0.025	0.239[1]	0.001

COPD Chronic Obstructive Pulmonary Disease. LABA Long-acting β-adrenoreceptor agonists. LAMA Long-acting muscarinic antagonist. LTRA Leukotriene receptor antagonist

[1]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

10.3.1.2 Comparison of baseline characteristics after trimming – Overall population

Benralizumab cohort versus other-biologic 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 (refer to Table 9 below). The total number of patients (N) for baseline characteristics before and after trimming were 578 and 495 in the benralizumab cohort; 1,870 and 1,567 in the other-biologic cohort, respectively.

Pre-weighting and post-weighting SMDs are reported below in Table 9; for more details refer to List of tables Table 14.2.1.3.1). 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 ($p<0.05$) may not represent clinically meaningful differences between cohorts.

When PS weighting was applied to the trimmed data, the SMD for age decreased from 0.201 to 0.033 post-weighting. Similar improvements in SMD were observed post-weighting in other variables.

After weighting and trimming the datasets, the benralizumab and other-biologic cohorts' baseline characteristics were comparable, with reduced bias (see Table 8 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 578 and 494 in the benralizumab cohort; 2,024 and 1,758 in the non-biologic cohort, respectively. Pre-weighting and post-weighting SMDs are reported below in Table 9; for more details refer to List of tables Table 14.2.1.3.2).

When PS weighting was applied to the data, the SMD for BMI decreased from 0.279 to 0.074. 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 (see Table 8 for pre- and post-weighting SMDs).

Table 9: Standardised Mean Difference (SMD) 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[1]	0.033	0.006	-0.023
Sex	-0.030	0.004	0.100	0.037
Body Mass Index (kg/m^2)	0.173[1]	0.022	0.279[1]	0.074
Smoking status	0.007	-0.017	-0.023	0.007
Allergic rhinitis	0.172[1]	0.036	0.176[1]	0.006
Chronic rhinosinusitis	0.076	0.015	-0.000	0.027
Nasal polyps	0.099	0.023	-0.142	-0.037
Cardiovascular disease	-0.195[1]	-0.021	-0.442[1]	-0.047
Diabetes	-0.067	-0.008	-0.174[1]	-0.023
Hypertension	-0.171[1]	-0.016	-0.380[1]	-0.038
COPD	-0.098	0.013	-0.239[1]	-0.009
Liver disease	-0.002	0.006	-0.022	0.003
History of malignancy	-0.098	-0.009	-0.043	-0.012
Previous anaphylaxis	-0.068	0.003	-0.091	0.002
Previous serious infection	0.049	0.011	0.140	0.011
LABA only	0.084	0.052	-0.069	0.013
LAMA	0.091	0.002	0.034	-0.005
Theophylline	-0.056	-0.016	0.009	0.042
LTRA	-0.177[1]	-0.017	-0.137	-0.032
Macrolide antibiotics	-0.127	-0.004	-0.023	0.040
Steroid-sparing agents	0.011	0.013	-0.040	-0.001
Steroid use	-0.182[1]	-0.046	0.252[1]	0.007

COPD Chronic Obstructive Pulmonary Disease. LABA Long-acting β-adrenoreceptor agonists. LAMA Long-acting muscarinic antagonist. LTRA Leukotriene receptor antagonist

[1]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

10.3.2 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 10 patients reported a new malignancy during the study, 2 (0.3%), 4 (0.2%), and 4 (0.2%) in the benralizumab cohort, the other-biologic cohort, and the non-biologic cohort, respectively. The crude incidence rate per 1000 PYs in these three cohorts were 2.2, 1.1, and 1.6, respectively. The 95% CIs for rate differences between cohorts (both crude as well as adjusted), included zero for all comparisons, as did comparisons excluding NMSC.

After adjustment for age, sex, BMI, region, and smoking status, the number (%) of patients reporting a new malignancy decreased to 3 (0.2%) in the other-biologic cohort. Note that PS are only calculated for patients with non-missing data for all variables in the PS model. One subject in the other-biologic cohort had no information on occurrence of previous serious infections, resulting in a missing PS for this subject, and because missing data is not imputed in this IA (refer to Section 6.6 of SAP v3.0), the subject was excluded from the adjusted analysis. The adjusted annual incidence rate per 1000 PYs, when comparing the benralizumab and the other-biologic cohort decreased to 0.5 for both cohorts.

For the comparison between the benralizumab and the non-biologic cohorts, the adjusted annual incidence rate per 1000 PYs decreased to 0.9 and 0.8, respectively. The adjusted 95% CIs for rate ratio between cohorts, included 1 for all comparisons, as did comparisons excluding NMSC.

10.3.2.1 Subpopulation-excluding non-melanoma skin cancer (NMSC)

Due to the multicentric/multifocal nature of NMSCs, common occurrence of the same NMSCs to occur at different sites and the potential to inflate incidence rates, it was stipulated in the protocol and SAP v3.0 to perform sensitivity analyses excluding these NMSCs that may inflate incidence rates on their own.

The crude incidence rate of new malignancies after excluding one 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, excluding NMSC, was 2 (0.3%), 4 (0.2%) and 3 (0.1%) in the benralizumab cohort, the other-biologic cohort, and the non-biologic cohort, respectively.

After adjustment for age, sex, BMI, region, and smoking status, the adjusted incidence rate per 1000 PYs in the benralizumab cohort and other-biologic cohort decreased to 0.5 for both cohorts. The adjusted incidence rate per 1000 PYs for the benralizumab cohort and non-biologic cohort decreased to 1.1 and 0.7, respectively.

10.3.2.2 Crude and adjusted incidence rates of new malignancies: ISAR and CHRONICLE

In the ISAR registry there were 2 new malignancies reported in each of the other-biologic and non-biologic cohorts, but no new malignancy cases reported in the benralizumab cohort.

In the CHRONICLE registry, the number (%) of patients reporting a new malignancy was 2 (0.5%), 2 (0.2%) and 2 (0.3%) in the benralizumab cohort, the other-biologic cohort, and the non-biologic cohort, respectively. The crude incidence rate per 1000 PYs in these three cohorts were 3.5, 1.5, and 2.3, respectively. The 95% CIs for rate differences between cohorts (both crude as well as adjusted), included zero for all comparisons.

There was no observed increased risk of new malignancy as no significant differences were observed in the incidence rate across the cohorts. There was also no clear evidence for difference between cohorts when data were analysed by separate analysis set (refer to List of tables [Table 14.2.2.1.2] for ISAR, and [Table 14.2.2.1.3] for CHRONICLE).

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 (person-years)**	**Incidence rate (per 1000 PY) (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**p value**
Crude [a]							
Overall	Benralizumab cohort (N=578) versus Other-biologic cohort (N=1870)	2 (0.3) versus 4 (0.2)	893.05 versus 3483.04	2.2 (0.56, 8.95) versus 1.1 (0.43, 3.06)	1.1 (-2.21, 4.39)		
	Benralizumab cohort (N=578) versus Non-biologic cohort (N=2024)	2 (0.3) versus 4 (0.2)	893.05 versus 2509.39	2.2 (0.56, 8.95) versus 1.6 (0.60, 4.25)	0.6 (-2.83, 4.12)		
Without NMSC	Benralizumab cohort (N=578) versus Other-biologic cohort (N=1870)	2 (0.3) versus 4 (0.2)	893.05 versus 3483.04	2.2 (0.56, 8.95) versus 1.1 (0.43, 3.06)	1.1 (-2.21, 4.39)		
	Benralizumab cohort (N=578) versus Non-biologic cohort (N=2024)	2 (0.3) versus 3 (0.1)	893.05 versus 2510.27	2.2 (0.56, 8.95) versus 1.2 (0.39, 3.71)	1.0 (-2.34, 4.43)		
Adjusted [b]							
Overall	Benralizumab cohort (N=495) versus Other-biologic cohort (N=1567)	2 (0.4) versus 3 (0.2)	756.85 versus 2847.99	0.5 (0.13, 2.27) versus 0.5 (0.14, 2.04)	0.0 (-0.67, 0.70)	1.0 (0.29, 3.65)	0.9662
	Benralizumab cohort (N=494) versus Non-biologic cohort (N=1758)	2 (0.4) versus 4 (0.2)	750.90 versus 2143.66	0.9 (0.28, 3.11) versus 0.8 (0.22, 2.80)	0.2 (-0.83, 1.14)	1.2 (0.38, 3.74)	0.7575
Without NMSC	Benralizumab cohort (N=495) versus Other-biologic cohort (N=1567)	2 (0.4) versus 3 (0.2)	756.85 versus 2847.99	0.5 (0.13, 2.27) versus 0.5 (0.14, 2.04)	0.0 (-0.67, 0.70)	1.0 (0.29, 3.65)	0.9662

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 (person-years)**	**Incidence rate (per 1000 PY) (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**p value**
	Benralizumab cohort (N=494) versus Non-biologic cohort (N=1758)	2 (0.4) versus 3 (0.2)	750.90 versus 2144.55	1.1 (0.36, 3.66) versus 0.7 (0.18, 2.60)	0.5 (-0.71, 1.64)	1.7 (0.48, 5.91)	0.4101

BMI Body Mass Index. CI Confidence Interval. N Number of patients in cohort. NMSC Non-melanoma skin cancer. 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. Crude rate ratios are not calculated, as stated in the SAP. The weight used in the model is the inverse propensity score (1/propensity score for the 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.

10.3.2.3 Crude and adjusted incidence rates of new malignancies: Patients with No Cohort Switch

An analysis was performed to exclude cohort switches, as reported in Table 11. In this analysis, the number (%) of patients reporting a new malignancy was 1 (0.2%) and 3 (0.2%) in the benralizumab cohort and other-biologic cohort, respectively. The respective crude incidence rates per 1000 PYs in these two cohorts were 1.4, and 0.9, respectively. The 95% CIs for crude rate differences between cohorts included zero for all comparisons.

After adjustment for age, sex, BMI, region, and smoking status, the incidence rates for new malignancies in both the benralizumab and other-biologic cohort were zero. However, there were no patients in this subgroup with current/ex-smoker status, leading to an over-parameterised model and a reliable estimate cannot be performed (refer to rate difference for the adjusted model in Table 11).

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 (person-years)	Incidence rate (per 1000 PY) (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p value
Crude [a]	Benralizumab cohort (N=425) versus Other-biologic cohort (N=1717)	1 (0.2) versus 3 (0.2)	726.34 versus 3318.22	1.4 (0.19, 9.77) versus 0.9 (0.29, 2.80)	0.5 (-2.41, 3.36)		
Adjusted [b]	Benralizumab cohort (N=363) versus Other-biologic cohort (N=1429)	1 (0.3) versus 2 (0.1)	615.37 versus 2698.95	0.0 (0.00, 0.00) versus 0.0 (0.00, 0.00)	0.0 (NC, NC)	0.6 (0.10, 3.95)	0.6199

BMI Body Mass Index. CI Confidence Interval. 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. Crude rate ratios are not calculated, as stated in the SAP. The weight used in the model is the inverse propensity score (1/propensity score for the 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.

10.3.3 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 sets for each cohort are given in Table 12.

The number of new malignancies in the benralizumab, other-biologic and non-biologic cohorts were 2, 4, and 4, respectively. The event rate in the three respective cohorts were 0.002, 0.001, and 0.002, respectively. The 95% CIs for rate differences between cohorts, included zero for all comparisons, as did comparisons excluding NMSC.

10.3.3.1 Subpopulation-excluding non-melanoma skin cancer (NMSC)

The number of new malignancies (excluding NMSC) in the benralizumab, other-biologic and non-biologic cohorts were 2, 4, and 3, respectively. The event rate in the three respective cohorts were 0.002, 0.001, and 0.001, respectively. Note, these incidence rates are reported per person year of follow-up rather than per 1000 years of follow-up.

10.3.3.2 Crude event rates for new malignancy: ISAR and CHRONICLE

In the ISAR registry there were no new malignancy cases reported in the benralizumab cohort.

In the CHRONICLE registry, the number of a new malignancies was 2 each in the benralizumab cohort, the other-biologic cohort, and the non-biologic cohort, respectively. The crude event rates in these cohorts were 0.004, 0.002, and 0.002, respectively. The 95% CIs for rate differences between cohorts, included zero for all comparisons. There was no clear evidence of difference in event rates between cohorts when data were analysed by separate analysis set (refer to List of tables [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 (person-years)	Incidence rate (Per PY) (95% CI)	Comparison (rate difference) between groups (95% CI)
Overall	Benralizumab cohort (N=578) versus Other-biologic cohort (N=1870)	2 versus 4	895.70 versus 3487.00	0.002 (0.001, 0.009) versus 0.001 (0.000, 0.003)	0.001 (-0.002, 0.004)
	Benralizumab cohort (N=578) versus Non-biologic cohort (N=2024)	2 versus 4	895.70 versus 2513.31	0.002 (0.001, 0.009) versus 0.002 (0.001, 0.004)	0.001 (-0.003, 0.004)
Without NMSC	Benralizumab cohort (N=578) versus Other-biologic cohort (N=1870)	2 versus 4	895.70 versus 3487.00	0.002 (0.001, 0.009) versus 0.001 (0.000, 0.003)	0.001 (-0.002, 0.004)
	Benralizumab cohort (N=578) versus Non-biologic cohort (N=2024)	2 versus 3	895.70 versus 2513.31	0.002 (0.001, 0.009) versus 0.001 (0.000, 0.004)	0.001 (-0.002, 0.004)

CI Confidence Interval. N Number of patients in cohort. NMSC Non-melanoma skin cancer.
Crude incident rates are annualized rates. 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.

10.3.4 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, the number of patients with a new malignancy was 2, 3, and 4 in the benralizumab cohort, the other-biologic cohort, and the non-biologic cohort, respectively. The patients with a new malignancy (subpopulation excluding NMSC) in these three cohorts were 2, 3, and 3, respectively. As noted in Section 10.3.2, this analysis excludes one malignancy report because the patient had incomplete baseline covariate information. There was no difference in the time to first new malignancy between cohorts.

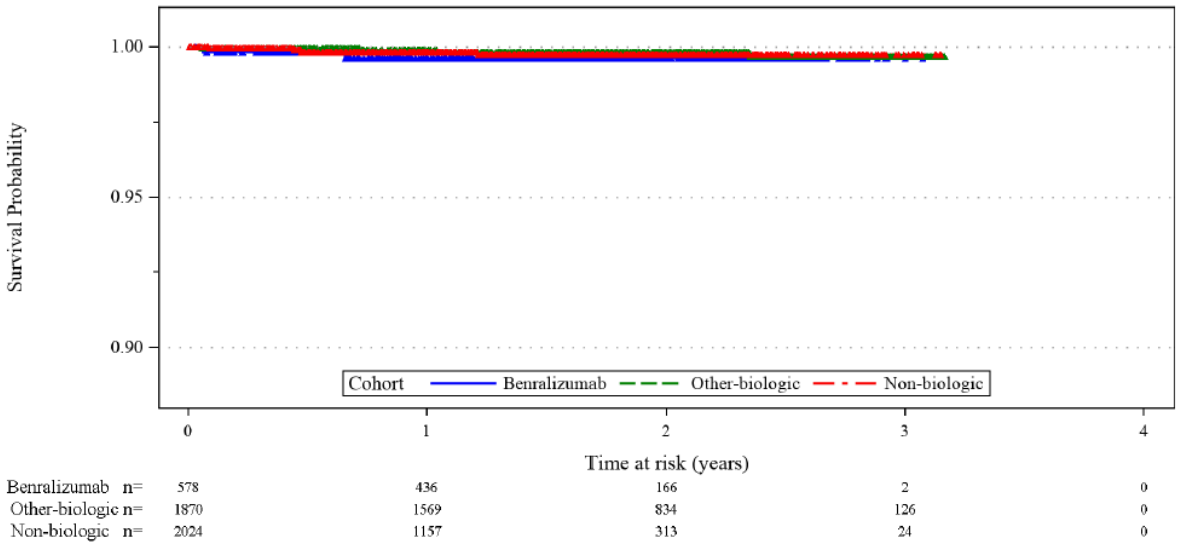
No clear risk of new malignancy in each comparison of the benralizumab cohort with other-biologic and non-biologic cohorts was observed, as the 95% CIs of the hazard ratios were wide and included the value of one (both overall as well as excluding NMSC).

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=495) versus Other-biologic cohort (N=1567)	2 (0.4) versus 3 (0.2)	1.0	(0.29, 3.64)
	Benralizumab cohort (N=494) versus Non-biologic cohort (N=1758)	2 (0.4) versus 4 (0.2)	1.3	(0.42, 4.16)
Without NMSC	Benralizumab cohort (N=495) versus Other-biologic cohort (N=1567)	2 (0.4) versus 3 (0.2)	1.0	(0.29, 3.64)
	Benralizumab cohort (N=494) versus Non-biologic cohort (N=1758)	2 (0.4) versus 3 (0.2)	1.9	(0.53, 6.63)

CI Confidence Interval. N Number of patients in cohort. NMSC Non-melanoma skin cancer. BMI Body Mass Index.
[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 the 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.

Figure 7: Time to first new malignancy (ISAR and CHRONICLE combined analysis set)



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.

10.3.5 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.

The total number of patients reporting new onset of malignancy cases was: 2 in the benralizumab cohort, 4 in the other-biologic cohort, and 4 in the non-biologic cohort. The narratives for each patient malignancy are listed below. Please note that the data which are reported as unknown in the patient narratives were reconfirmed from the respective sites and have remained unknown after this querying process. Patients are classified according to the cohort time when the new malignancy falling within the study period was coded.

Benralizumab Cohort

- Patient Z2170D86141/H9113189 was a 49-year-old black female enrolled into the CHRONICLE registry on 12 April 2019. She was a non-smoker with allergic rhinitis, chronic sinusitis/rhinosinusitis (separately coded from allergic rhinitis), and obesity (BMI 35.9 kg/m^2). She received oral corticosteroids (OCS) with a prednisone-equivalent dose of 20 mg per day for severe asthma. There was no history of malignancy and chemotherapy. She received dupilumab from 28 June 2019 to 06 January 2020. She switched to benralizumab on 10 March 2020 and benralizumab was discontinued in March 2020 (date unknown). On April 2020 (date unknown), she was diagnosed with an unknown stage bone marrow malignancy with a hematopoietic cell type. As of 31 December 2020, the status of the malignancy was ongoing.

- Patient Z2170D86141/H9266064 was a 76-year-old white female enrolled into the CHRONICLE registry on 17 January 2019. She was a non-smoker with hypertension and obesity (BMI 31.1 kg/m^2). She received an OCS with a prednisone-equivalent dose of 60 mg per day for severe asthma. There was no history of malignancy and chemotherapy. She received benralizumab on 11 June 2018 (ongoing). On 05 February 2019, she was diagnosed with Stage I gastric malignancy with a glandular cell type. As of 31 December 2020, the status of the malignancy was ongoing.

Other-biologic Cohort

- Patient ISAR_KOR_00017 was a 60-year-old Asian male enrolled into the ISAR registry on 12 December 2018. He was an ex-smoker (30 pack-years) with atopic disease. He received an OCS with a prednisone-equivalent dose of 25 mg per day for severe asthma. There was no history of malignancy and chemotherapy. He received reslizumab on 12 December 2018 (ongoing). On 30 December 2019, he was diagnosed with an unknown stage rectal malignancy with a glandular cell type. As of 31 December 2020, the status of the malignancy was ongoing.

- Patient ISAR_KUW_SITE1_19761 was a 63-year-old white male enrolled into the ISAR registry on 21 November 2019. He was a non-smoker with atopic disease, type 2 diabetes mellitus, and obesity (BMI 31.55 kg/m^2). He did not receive OCS medication for severe asthma. There was no history of malignancy and chemotherapy. He received omalizumab from

24 June 2018 to 29 April 2019. On 17 March 2019, he was diagnosed with an unknown stage urethral malignancy with a urothelial cell type. As of 31 December 2020, the status of the malignancy was remission.

- Patient Z2170D86141/H9110042 was a 65-year-old black female enrolled into the CHRONICLE registry on 16 March 2019. She was a non-smoker with hypertension and obesity (BMI 35.4 kg/m^2). She received OCS with a prednisone-equivalent dose of 40 mg per day for severe asthma. There was no history of malignancy and chemotherapy. She received mepolizumab on 07 April 2018 (ongoing). On 11 August 2020, she was diagnosed with an unknown stage colon malignancy with a glandular cell type. As of 31 December 2020, the status of the malignancy was ongoing.

- Patient Z2170D86141/H9413348 was a 72-year-old white male enrolled into the CHRONICLE registry on 22 March 2019. He was an ex-smoker (29 pack-years) with allergic rhinitis, COPD, chronic sinusitis/rhinosinusitis (separately coded from allergic rhinitis), type 2 diabetes mellitus, hypertension, and obesity (BMI 41.5 kg/m^2). He received OCS with a prednisone-equivalent dose of 20 mg per day for severe asthma. There was no history of malignancy and chemotherapy. He received mepolizumab 300 mg (02 July 2019 to an unknown day of September 2019), and the dose was reduced to 100 mg (14 January 2020 to an unknown day of April 2020). He switched to benralizumab on 25 May 2020 (ongoing). On 22 July 2019, he was diagnosed with an unknown stage right upper lobe pulmonary nodule with a glandular cell type. As of 31 December 2020, the status of the malignancy was ongoing.

Non-biologic Cohort

- Patient ISAR_Kinki-19 was a 74-year-old Asian male enrolled into the ISAR registry on 05 June 2019. He was a current-smoker (20.8 pack-years) with atopic disease, nasal polyps, and chronic rhinosinusitis. He did not receive OCS medication for severe asthma. There was no history of malignancy and chemotherapy. He did not receive any biologic treatment. On 21 August 2020, he was diagnosed with stage IV prostate malignancy with a glandular cell type. As of 31 December 2020, the status of the malignancy was ongoing.

- Patient ISAR_Kinki-7 was a 65-year-old Asian female enrolled into the ISAR registry on 10 May 2019. She was a non-smoker with allergic rhinitis, atopic disease, eczema, chronic rhinosinusitis (coded separately from allergic rhinitis), and nasal polyps. She did not receive OCS medication for severe asthma. There was no history of malignancy and chemotherapy. She did not receive any biologic treatment. On 29 October 2019, she was diagnosed with Stage I lung malignancy with a glandular cell type. As of 31 December 2020, the status of the malignancy was remission.

- Patient Z2170D86141/H9607474 was a 76-year-old white female enrolled into the CHRONICLE registry on 03 September 2019. She was a non-smoker with allergic rhinitis and coronary artery disease. She also had a history of unknown stage malignancy (left breast) in

1994 and remission was reported on an unknown day in January 1995. She did not receive OCS medication for severe asthma. She did not receive any biologic treatment. On 11 February 2020, she was diagnosed with an unknown stage melanoma on the left breast. As of 31 December 2020, the status of the malignancy was unknown, but she is still actively following up.

- Patient Z2170D86141/H9963941 was a 72-year-old white female enrolled into the CHRONICLE registry on 31 May 2019. She was an ex-smoker (100 pack-years) with obesity (BMI 31.6 kg/m2). She did not receive OCS medication for severe asthma. There was no history of malignancy and chemotherapy. She did not receive any biologic treatment. On 01 July 2019, she was diagnosed with stage IV left upper lobe lung malignancy with a squamous cell type. As of 31 December 2020, the status of the malignancy was unknown, but she is still actively following up.

Table 14: Characteristics of new malignancy cases (ISAR and CHRONICLE analysis set)

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N=2)**	**Other-biologic cohort (N=4)**	**Non-biologic cohort (N=4)**
Status at diagnosis	New onset	2 (100)	4 (100)	4 (100)
	Total	2 (100)	4 (100)	4 (100)
Location/site	Digestive organ	1 (50.0)	2 (50.0)	0
	Lymphoid, hematopoietic and related tissue	1 (50.0)	0	0
	Male genital organ	0	0	1 (25.0)
	Melanoma and other malignancy neoplasms of skin	0	0	1 (25.0)
	Respiratory and intrathoracic organs	0	1 (25.0)	2 (50.0)
	Urinary tract	0	1 (25.0)	0
	Total	2 (100)	4 (100)	4 (100)
Cell type	Hematopoietic cell	1 (50.0)	0	0
	Glandular cell	1 (50.0)	3 (75.0)	2 (50.0)
	Squamous cell	0	0	2 (50.0)
	Urothelial cell	0	1 (25.0)	0
	Total	2 (100)	4 (100)	4 (100)
Stage (Number staging system)	Stage I	1 (50.0)	0	0
	Stage IV	0	0	1 (25.0)
	Total	1 (50.0)	0	1 (25.0)
	Missing	1	4	3
T (Primary tumour)	1	0	1 (25.0)	1 (25.0)
	2	1 (50.0)	0	0
	4	0	1 (25.0)	1 (25.0)
	Total	1 (50.0)	2 (50.0)	2 (50.0)
	Missing	1	2	2
N (Lymph Nodes)	X	0	0	0
	0	0	1 (25.0)	1 (25.0)
	1	1 (50.0)	1 (25.0)	1 (25.0)
	Total	1 (50.0)	2 (50.0)	2 (50.0)
	Missing	1	2	2
M (Distant Metastasis)	X	0	1 (25.0)	0
	0	0	1 (25.0)	1 (25.0)
	1	0	0	1 (25.0)
	Total	0	2 (50.0)	2 (50.0)
	Missing	2	2	2

Table 14: Characteristics of new malignancy cases (ISAR and CHRONICLE analysis set)

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N=2)**	**Other-biologic cohort (N=4)**	**Non-biologic cohort (N=4)**
Outcome	Ongoing	2 (100)	3 (75.0)	1 (25.0)
	Remission	0	1 (25.0)	1 (25.0)
	Death	0	0	0
	Unknown status (not death)	0	0	2 (50.0)
	Total	2 (100)	4 (100)	4 (100)

N Number of patients with new malignancies in each cohort.
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 each analysis set.
For the complete characteristics of new malignancy cases of the ISAR analysis set and CHRONICLE analysis set refer to List of tables (Table 14.2.4.1.1). For the complete characteristics of new malignancy cases of the subgroup (excluding NMSC) from the ISAR and CHRONICLE combined analysis set, refer to List of tables (Table 14.2.4.1.3).

10.3.5.1 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 set, subpopulation are described in List of tables (Table 14.2.4.2.1 to Table 14.2.4.2.3, respectively) and for an abbreviated table, refer to Table 15. Due to the small numbers of malignancies reported to date, it is difficult to draw conclusions between groups

Table 15: Demographic and baseline clinical characteristics of patients with new malignancy cases (ISAR and CHRONICLE combined analysis set)

Demographic/baseline clinical characteristic	Statistics or category	Benralizumab cohort (N=2)	Other-biologic cohort (N=4)	Non-biologic cohort (N=4)
Age (years)	N	2	4	4
	Mean	62.5	65.0	71.8
	SD	19.09	5.10	4.79
	Min	49	60	65
	Q1	49.0	61.5	68.5
	Median	62.5	64.0	73.0
	Q3	76.0	68.5	75.0
	Max	76	72	76
Age (years) subgroups n (%)	>= 18 to <= 39	0	0	0
	>= 40 to <= 64	1 (50.0)	2 (50.0)	0
	>= 65 to <= 79	1 (50.0)	2 (50.0)	4 (100)
	Total	2 (100)	4 (100)	4 (100)
Sex n (%)	Female	2 (100)	1 (25.0)	3 (75.0)
	Male	0	3 (75.0)	1 (25.0)
	Total	2 (100)	4 (100)	4 (100)
Race n (%)	White	1 (50.0)	2 (50.0)	2 (50.0)
	Black or African American	1 (50.0)	1 (25.0)	0
	Asian	0	1 (25.0)	2 (50.0)
	Total	2 (100)	4 (100)	4 (100)
Country n (%) [a]	Japan	0	0	2 (50.0)
	Kuwait	0	1 (25.0)	0
	South Korea	0	1 (25.0)	0
	United States of America	2 (100)	2 (50.0)	2 (50.0)
	Total	2 (100)	4 (100)	4 (100)
Body Mass Index (kg/m^2)	N	2	4	4
	Mean	33.500	34.160	24.968
	SD	3.3941	5.7116	4.5752
	Min	31.10	28.19	21.20
	Q1	31.100	29.870	22.115
	Median	33.500	33.475	23.535
	Q3	35.900	38.450	27.820
	Max	35.90	41.50	31.60
Body Mass Index (kg/m^2) subgroups	>= 18.5 to < 25.0	0	0	3 (75.0)
	>= 25.0 to < 30.0	0	1 (25.0)	0
	>= 30.0 to < 35.0	1 (50.0)	1 (25.0)	1 (25.0)
	>= 35.0	1 (50.0)	2 (50.0)	0
	Total	2 (100)	4 (100)	4 (100)

Table 15: Demographic and baseline clinical characteristics of patients with new malignancy cases (ISAR and CHRONICLE combined analysis set)

Demographic/baseline clinical characteristic	Statistics or category	Benralizumab cohort (N=2)	Other-biologic cohort (N=4)	Non-biologic cohort (N=4)
Smoking status	Non-smoker	2 (100)	2 (50.0)	2 (50.0)
	Previous and/or current smoker	0	2 (50.0)	2 (50.0)
	Total	2 (100)	4 (100)	4 (100)
Pack years [b]	N	0	2	2
	Mean		29.500	60.400
	SD		0.7071	56.0029
	Min		29.00	20.80
	Q1		29.000	20.800
	Median		29.500	60.400
	Q3		30.000	100.000
	Max		30.00	100.00
Age at asthma onset (years)	N	2	4	4
	Mean	6.000	35.750	55.283
	SD	1.4142	13.8173	3.9905
	Min	5.00	18.00	51.10
	Q1	5.000	25.000	52.065
	Median	6.000	38.000	55.015
	Q3	7.000	46.500	58.500
	Max	7.00	49.00	60.00
Number of exacerbations [c]	N	2	4	4
	Mean	3.5	0.8	0.0
	SD	0.71	0.96	0.00
	Min	3	0	0
	Q1	3.0	0.0	0.0
	Median	3.5	0.5	0.0
	Q3	4.0	1.5	0.0
	Max	4	2	0
	0	0	2 (50.0)	4 (100)
	1	0	1 (25.0)	0
	2	0	1 (25.0)	0
	3	1 (50.0)	0	0
	4	1 (50.0)	0	0
Number of invasive ventilations	N	2	4	4
	Mean	0.0	0.0	0.0
	SD	0.00	0.00	0.00
	Min	0	0	0
	Q1	0.0	0.0	0.0
	Median	0.0	0.0	0.0

Table 15: Demographic and baseline clinical characteristics of patients with new malignancy cases (ISAR and CHRONICLE combined analysis set)

Demographic/baseline clinical characteristic	Statistics or category	Benralizumab cohort (N=2)	Other-biologic cohort (N=4)	Non-biologic cohort (N=4)
	Q3	0.0	0.0	0.0
	Max	0	0	0
Number of hospital admissions	N	2	4	4
	Mean	1.0	0.3	0.0
	SD	1.41	0.50	0.00
	Min	0	0	0
	Q1	0.0	0.0	0.0
	Median	1.0	0.0	0.0
	Q3	2.0	0.5	0.0
	Max	2	1	0
Number of emergency department visits	N	2	4	4
	Mean	1.0	0.3	0.0
	SD	1.41	0.50	0.00
	Min	0	0	0
	Q1	0.0	0.0	0.0
	Median	1.0	0.0	0.0
	Q3	2.0	0.5	0.0
	Max	2	1	0
Maintenance oral corticosteroids (OCS)	Yes	2 (100)	3 (75.0)	0
	Total	2 (100)	3 (75.0)	0
	Missing	0	1	4
Maintenance OCS doses per day (mg)	N	2	3	0
	Mean	40.000	28.333	
	SD	28.2843	10.4083	
	Min	20.0	20.0	
	Q1	20.00	20.00	
	Median	40.00	25.00	
	Q3	60.00	40.00	
	Max	60.0	40.0	
Medication adherence status [d]	Yes	2 (100)	3 (75.0)	4 (100)
	No	0	1 (25.0)	0
	Total	2 (100)	4 (100)	4 (100)
Asthma control status [e]	Well controlled	0	1 (25.0)	1 (25.0)
	Partially controlled	1 (50.0)	0	1 (25.0)
	Not controlled	1 (50.0)	3 (75.0)	2 (50.0)
	Total	2 (100)	4 (100)	4 (100)

Table 15: Demographic and baseline clinical characteristics of patients with new malignancy cases (ISAR and CHRONICLE combined analysis set)

Demographic/baseline clinical characteristic	Statistics or category	Benralizumab cohort (N=2)	Other-biologic cohort (N=4)	Non-biologic cohort (N=4)

GINA Global Initiative for Asthma. Max Maximum. Min Minimum. N Number of patients with new malignancies in each cohort. n Number of patients in analysis. 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 (e.g. 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 includes all events occurring within 12 months preceding each index date.

10.3.6 Sensitivity analyses

For the sensitivity analyses excluding patients with new malignancies within one year of initial index date, there were no malignancies reported in the benralizumab cohort, as all occurred within a year of the patient's initial index date. Assigning patients with new malignancies within one year of a switch date to the previous cohort did not change the results.

Similar results were observed after using the other index date in estimation. The crude and adjusted incidence rates of new malignancies were comparable across the cohorts before and after adjustment of variables age, sex, BMI, region, and smoking status.

These sensitivity analyses will be more interpretable in future analyses when a larger population will have been followed for a longer period. For the complete tables on sensitivity analyses refer to List of tables (Table 14.2.5.1.1 to Table 14.2.5.3.5).

The crude and adjusted incidence rates of new malignancies were comparable across the cohorts before and after adjustment for age, sex, BMI, region, and smoking status.

There were no clear differences in crude or adjusted incidence rates between the cohorts when first use of biologics was considered at any time, Similarly, the adjusted rate ratio and time to first new malignancy hazard ratio had wide 95% CIs including the value of one across all comparisons of the benralizumab cohort with other-biologic and non-biologic cohorts (refer to Table 16, Table 17, and Table 18). Time to first new malignancy when the other index date is considered is illustrated in Figure 8. Due to the much earlier index date applied in this sensitivity analysis, the other-biologic cohort was followed up for a much longer period than the other two cohorts and the increased probability of a new malignancy is observed beyond 3 years of follow up for this cohort.

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)

	Comparison	Number (%) of patients with a new malignancy	Total time at risk (person-years)	Incidence rate (Per 1000 PY) (95% CI)	Rate difference	Rate ratio	
					Estimate (95% CI)	Estimate (95% CI)	p value
Crude [a]							
Overall	Benralizumab cohort (N=793) versus Other-biologic cohort (N=3774)	3 (0.4) versus 33 (0.9)	1306.13 versus 15158.68	2.3 (0.74, 7.12) versus 2.2 (1.55, 3.06)	0.1 (-2.58, 2.82)		
	Benralizumab cohort (N=793) versus Non-biologic cohort (N=2113)	3 (0.4) versus 4 (0.2)	1306.13 versus 2849.51	2.3 (0.74, 7.12) versus 1.4 (0.53, 3.74)	0.9 (-2.05, 3.83)		
Adjusted [b]							
Overall	Benralizumab cohort (N=669) versus Other-biologic cohort (N=3088)	3 (0.4) versus 29 (0.9)	1092.65 versus 12222.40	0.6 (0.25, 1.35) versus 1.2 (0.64, 2.09)	-0.6 (-1.14, 0.00)	0.5 (0.25, 1.02)	0.0553
	Benralizumab cohort (N=682) versus Non-biologic cohort (N=1830)	3 (0.4) versus 4 (0.2)	1113.54 versus 2426.78	1.2 (0.44, 3.11) versus 0.8 (0.27, 2.36)	0.4 (-0.66, 1.43)	1.5 (0.52, 4.24)	0.4644

BMI Body Mass Index. CI Confidence Interval. N Number of patients in cohort. 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, 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 registry 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.

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 (person-years)	Event rate (95% CI)	Comparison (rate difference) between groups (95% CI)
Overall	Benralizumab cohort (N=793) versus Other-biologic cohort (N=3774)	3 versus 38	1309.98 versus 15279.57	0.002 (0.001, 0.007) versus 0.002 (0.002, 0.003)	-0.000 (-0.003, 0.003)
	Benralizumab cohort (N=793) versus Non-biologic cohort (N=2113)	3 versus 4	1309.98 versus 2853.43	0.002 (0.001, 0.007) versus 0.001 (0.001, 0.004)	0.001 (-0.002, 0.004)

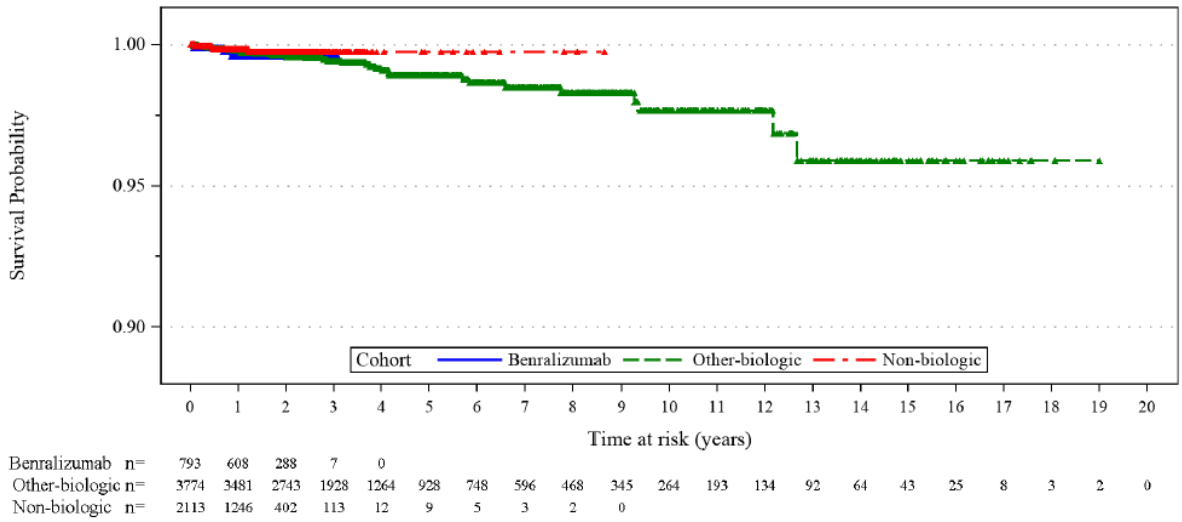
CI Confidence Interval. N Number of patients in cohort.
The 95% CIs for crude rates and rate differences for each comparison are estimated from a Poisson regression model. The response variable in the model is the number of new malignancies. The logarithm of the patient's corresponding follow-up time 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 registry 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.

Table 18: Time to first new malignancy with the other index date definition, Cox-proportional hazard model (ISAR and CHRONICLE combined analysis set)

	Treatment group	Number (%) of patients with a new malignancy	Comparison between groups [a]	
			Hazard ratio	95% CI
Overall	Benralizumab cohort (N=669) versus Other-biologic cohort (N=3088)	3 (0.4) versus 29 (0.9)	0.6	(0.28, 1.35)
	Benralizumab cohort (N=682) versus Non-biologic cohort (N=1830)	3 (0.4) versus 4 (0.2)	1.7	(0.58, 4.77)

BMI Body Mass Index. CI Confidence Interval. N Number of patients in cohort.
[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 scores). 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 registry entry at any time.
If not stated otherwise, percentages are based upon number of patients in each cohort within the combined analysis set.

Figure 8: Time to first new malignancy with the other index date definition, Kaplan-Meier plot (ISAR and CHRONICLE combined analysis set)



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 registry entry at any time.

10.4 Other analyses

Not applicable.

11. DISCUSSION

11.1 Key results

This study was conducted in severe asthma patients enrolled in the ISAR and CHRONICLE registries. The objectives were to assess the incidence rates and clinical characteristics of new malignancy cases receiving benralizumab compared with those receiving other-biologics, and those not receiving biologics in severe asthma patients. The data accrued during the period of 01 January 2018 to 31 December 2020 was analysed for this first IA report.

A total of 8,012 patients were enrolled in both ISAR and CHRONICLE registries as of 31 December 2020, and 3,693 patients were excluded from the main analysis, the majority of these were due to the date of other-biologic initiation being before 01 November 2017, benralizumab initiation before 01 November 2017, a lack of malignancy data (presence or absence of malignancy), other missing information and application of study age inclusion criteria. A total of 4,319 patients included in the main analysis and the overall PYs of follow-up in this IA is 6896.0.

The majority of patients were white, female, non-smokers, and had a high percentage of physician-reported asthma medication adherence. The most used asthma medication at baseline was ICS+LABA, although LTRA use was also common across the three cohorts. Allergic rhinitis, atopic disease/eczema, and cardiovascular disease were common comorbidities.

The overall and subpopulation (excluding NMSC) incidence rates, crude event rates and new malignancy frequencies were low across the study cohorts. There was no clear evidence of any differences (in both main and sensitivity analyses) in the risk of malignancy or trends in malignancy types in the benralizumab cohort when compared to the other-biologic or non-biologic cohorts.

In this first IA, given the small number of new malignancies and limited follow-up, caution should be used in the interpretation of results.

11.2 Limitations

a. Misclassification – The average follow-up in this study is only 1.5 years, 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. The performance of the sensitivity analysis excluding switches did not provide evidence of increased risk for malignancy in this IA.

b. Unmeasured confounders (residual confounding) will always exist in observational studies. Lab 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.

11.3 Interpretation

The current evidence does not suggest an increase in risk of malignancy in patients receiving benralizumab compared to those receiving other-biologics or non-biologic therapy although interpretation of this finding should be made with caution given limited follow-up time and the small number of new malignancies accrued.

11.4 Generalisability

Since ISAR includes national or regional registries, and CHRONICLE is the largest registry of severe asthma to date in the US, we expect findings to be generalizable to the target patient population for benralizumab and other-biologics.

12. CONCLUSIONS

At the time of this first IA study report, the primary analysis included a total of 10 new malignancy cases reported since index date; 2/578 (0.2%), 4/1870 (0.2%), and 4/2024 (0.2%) in the benralizumab, other-biologic, and non-biologic cohorts respectively. The incidence of malignancies is low in all comparison groups. The crude incidence rate per 1000 PYs in these three cohorts were 2.2, 1.1, and 1.6, respectively. The CIs for rate differences between cohorts (both crude as well as adjusted), included zero for all comparisons, as did comparisons excluding NMSC. The pre-defined analyses, which included both crude and adjusted analyses, and the sensitivity analyses do not show clear evidence of a difference in the underlying risk of malignancies between cohorts.

The current evidence does not suggest an increase in risk of new malignancy in patients receiving benralizumab compared to those receiving other-biologics or non-biologic therapy although interpretation of this finding must be made with caution given limited follow-up time and the small number of new malignancies accrued.

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Appendix A List of stand-alone documents

Table 19: List of stand-alone documents

S.No.	Document	Date	Title
1	AZ-PASS-Malignancy-IA1-Tables-v7_20210913	13 September 2021	List of tables
2	AZ-PASS-Malignancy-IA1-Figures-v7_20210913	13 September 2021	List of figures
3	AZ-PASS-Malignancy-IA1-Listings-v7_20210913	13 September 2021	Listings