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

Marketing Authorisation Holder

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PASS INFORMATION

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. ABSTRACT

Title

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

Report dated [redacted] by Eileen Dareng, MD, PhD, Associate Director, Safety Epidemiology, AstraZeneca Global Patient Safety.

Keywords

Benralizumab, Post-authorisation, Active Surveillance, Malignancy, Safety

Rationale and background

Benralizumab is an eosinophil-depleting monoclonal antibody (immunoglobulin G1 kappa). In Europe, it is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-adrenoreceptor agonists. In the United States (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 non-benralizumab biologics, and those receiving non-biologic treatment only. This is being accomplished through analysis of data from 2 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 Pharmacovigilance Risk Assessment Committee (PRAC). Herein we report the second of 3 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 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 non-benralizumab biologics and those not receiving biologics. The secondary objective is to describe the clinical characteristics of the new malignancy cases that develop in severe asthma patients and relevant subgroups.

Study design

This is an ongoing real-world, observational, prospective cohort study in patients with severe asthma recruited into the International Severe Asthma Registry (ISAR) and the 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 non-benralizumab biologics and patients not receiving biologics. New malignancy cases developed during the follow-up period are described with regard to history of prior malignancy, malignancy type, location, stage, and outcomes. Data from ISAR and CHRONICLE were pooled to increase the precision of the study.

Setting

ISAR is being conducted by Optimum Patient Care (OPC) in collaboration with the Respiratory Effectiveness Group and AZ. CHRONICLE is an AZ sponsored study with study operations led in collaboration with Parexel, a global contract research organisation. Recruitment is expected to be completed for ISAR by end of 2023 and for CHRONICLE by February 2024. Longitudinal data on the occurrence of malignancy is being collected on enrolled patients from registry entry. Countries not yet contributing malignancy data in the ISAR registries are excluded from the database transfer to AZ. Data from ISAR and CHRONICLE were pooled to create the analysis dataset. Annual IA1 was submitted in 2021, the current IA2 will be submitted in 2022, and IA3 is planned for submission in 2023. Each IA has a data lag period of one year. Therefore, IA1 for 2021 included data that was accrued up until 2020, and the current IA2 for 2022, includes data that was accrued up until 31 December 2021.

Subjects and study size, including dropouts

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

Collectively, ISAR and CHRONICLE recruited 8676 severe asthma patients by the end of 2021.

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

Variables and data sources

The primary outcome for this study is new malignancy cases, which are ascertained by the treating physicians during office visits. Potential risk factors for malignancies as well as

patient characteristics including demographics, asthma features, comorbidities, asthma treatment were collected.

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

Results and Discussion

A total of 8676 patients were enrolled in ISAR or CHRONICLE as of 31 December 2021, with 5324 patients included in the main analysis. Overall, 3352 patients were excluded. Among them, 939 patients were excluded due to lack of malignancy data (e.g., presence/absence of malignancy, malignancy status). A total of 2630 patients were excluded from analysis because their date of non-benralizumab biologics initiation was before 01 November 2017 (note that a sensitivity analysis including patients excluded due to the date criterion was performed).

Among the 5324 patients in main analysis, there were 825 patients in the benralizumab cohort, 2410 patients in the non-benralizumab biologics cohort, and 2328 patients in the non-biologic cohort. More than half of the study population (2980/5324, 56.0%) were aged between 40 to 64 years which was consistent across all the cohorts. The majority of patients from the study population were white (3305/5324, 62.1%) and were female (3553/5324, 66.7%) across the cohorts. The overall PY of follow-up in this IA is 11948.8 as of 31 December 2021, with the follow-up for the benralizumab cohort at 1766.5 PY, the non-benralizumab biologics cohort at 6004.8 PY, and the non-biologic cohort at 4177.5 PY. At baseline, asthma-related comorbidities such as allergic rhinitis (benralizumab cohort 57.9%, non-benralizumab biologics cohort 64.4%, and non-biologic cohort 64.3%) and chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps) (benralizumab cohort 35.3%, non-benralizumab biologics cohort 36.1%, and non-biologic cohort 29.9%) were generally comparable across the cohorts. The benralizumab cohort had a higher rate of comorbid obesity, diabetes, hypertension, and chronic obstructive pulmonary disease which can be a risk factor for lung cancer. Other baseline comorbidities were not generally comparable, e.g., atopic disease 42.8% in benralizumab cohort compared to 69.1% in non-biologic cohort. Atopic diseases/eczema were reported in all 3 cohorts (benralizumab cohort 42.8%, non-benralizumab biologics cohort 56.6%, and non-biologic cohort 69.1%). Nasal polyps were less common (benralizumab cohort 28.4%, non-benralizumab biologics cohort 29.0%, and non-biologic cohort 18.0%). Chronic obstructive pulmonary disease was reported in all 3 cohorts (benralizumab cohort 10.2%, non-benralizumab biologics cohort 8.7%, and non-biologic cohort 5.3%). Differences

in baseline comorbidities and characteristics were adjusted across the cohorts in the analysis by means of propensity score (PS) weighting.

At the time of this IA2 report, the primary analysis included a total of 27 new malignancy cases reported since index date (10 new malignancies were reported in first IA report). The incidence of malignancies is low (6 [0.7%], 8 [0.3%], and 13 [0.6%] in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively) in all comparison groups.

Before PS adjustment, the crude incidence rate per 1000 PY in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort were 3.4, 1.3, and 3.1, respectively. In the PS adjusted benralizumab and non-biologic cohorts, the adjusted incidence rate per 1000 PY were 2.1 for the benralizumab cohort and 2.4 for the PS matched non-biologic cohort. In the PS adjusted benralizumab and non-benralizumab biologics cohorts, the adjusted incidence rate per 1000 PY were 2.0 for the benralizumab cohort, and 1.2 for the PS matched non-benralizumab biologics cohort. Incidence rates have generally increased in analysis sets for ISAR and for CHRONICLE and in all cohorts from IA1, most noticeably in the benralizumab and non-biologic cohorts. Rate ratios between benralizumab and non-benralizumab biologics have increased from IA1, but decreased between benralizumab and non-biologic cohorts. There is no significant difference noted in risk between the cohorts, with the 95% confidence interval for rate differences between benralizumab and the other 2 cohorts including zero for all crude and adjusted comparisons.

Conclusion

The pre-defined analyses, which included both crude and adjusted analyses, do not show evidence of a difference in the underlying risk of malignancies in patients receiving benralizumab compared to those receiving non-benralizumab biologics or non-biologic therapy. However, given the small number of new malignancies and limited follow-up time, the results of this IA should be interpreted with caution.

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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
EU	European Union
FEV_1	Forced Expiratory Volume during 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
IA	Interim Analyses/Interim Analysis
ICS	Inhaled Corticosteroid
Ig	Immunoglobulin
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
NMSC	Non-melanoma skin cancer
OCS	Oral Corticosteroids
OPC	Optimum Patient Care
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcomes
PS	Propensity Score(s)
PY	Person-Years
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous

Abbreviation or special term	Explanation
SD	Standard deviation
SMD	Standardised mean difference
UK	United Kingdom
US	United States

3. INVESTIGATORS

The details of the principal investigator are as below.

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4. OTHER RESPONSIBLE PARTIES

For the details of other responsible parties, refer to Section 3 of the clinical study protocol (CSP) v5.0.

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	[redacted]	[redacted]
End of data collection	[redacted]	
Registration in the EU PAS register	[redacted]	[redacted]
Interim report 1 (Data cut-off)	[redacted]	[redacted]
Interim report 2 (Data cut-off)	Q4 2022 ([redacted])	[redacted]
Interim report 3 (Data cut-off)	Q4 2023 ([redacted])	
Final report of study results (Data cut-off)	Q4 2024 ([redacted])	

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 a second controller (most commonly long-acting β-adrenoreceptor agonists [LABA]). However, a subset of patients do not adequately respond to current standard therapy leading to increased health care costs. Approximately 30% to 50% of severe asthma patients are reported to have severe eosinophilic asthma, a phenotype associated with increased eosinophils in the blood or sputum (Zeiger et al 2018, Wenzel 2005).

Benralizumab is an eosinophil-depleting anti-interleukin-5 receptor α binding monoclonal antibody (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.

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

Several observational studies have evaluated the association of asthma and malignancies, which resulted in 2 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 (Alderson 1974, Allegra et al 1976, Cockcroft et al 1979, Fisherman 1960). The second postulates that chronic immune stimulation due to atopy may result in mutations in stem cells which could be associated with an increased risk of malignancy (Bernard et al 1984, Gallagher et al 1983, Logan and Saker 1953).

Gonzalez-Perez et al. conducted a cohort study with a nested case-control analysis using the General Practitioner Research Database in the United Kingdom (UK). In this study, patients with asthma (129860 patients) did not exhibit an overall greater risk of malignancy compared to the general population (20000 patients) (Gonzalez-Perez et al 2006). Long et al. conducted a prospective, observational cohort, phase IV (EXCELS) study of omalizumab-treated and non-omalizumab-treated patients (7857 patients total) enrolled from multiple 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 (Long et al 2014).

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

This study combines the data collected from the patients enrolled in the International Severe Asthma Registry (ISAR) and an AstraZeneca (AZ) sponsored US severe asthma registry (CHRONICLE) database to investigate the risk of malignancy in patients with severe asthma, comparing the patients receiving benralizumab with the patients not receiving benralizumab.

This study fulfils the European Medicines Agency 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 second of 3 annual IA for this study, which will be followed by a final analysis and report after data collection is completed.

7. RESEARCH QUESTION AND OBJECTIVES

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

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

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

8. AMENDMENTS AND UPDATES

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

9. RESEARCH METHODS

For additional details of the research methods, refer to the CSP v5.0 and the statistical analysis plan (SAP) v4.0.

9.1 Study design

This is an ongoing real-world, observational, prospective cohort study in patients with severe asthma recruited into the ISAR and CHRONICLE and followed up to assess the occurrence of new malignancies. Note that all CHRONICLE sites are part of this malignancy PASS and contribute data, while in ISAR, only sites that have agreed to take part in the study contribute data to this PASS (refer to list of countries in Section 9.2). Information on the occurrence, type of malignancy, location, date of diagnosis, staging, and outcome are collected prospectively and irrespective of asthma treatment in both ISAR and CHRONICLE. Data from ISAR and CHRONICLE were pooled to increase the precision of the study.

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

9.2 Setting

Data from ISAR and CHRONICLE were pooled to create the analysis dataset from US (CHRONICLE only), Canada, UK, Spain, Italy, Denmark, South Korea, Japan, Bulgaria, Ireland, Greece, Argentina, Colombia, India, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, Taiwan, and United Arab Emirates (ISAR). The ISAR data from Australia and the US were not transferred to AZ because these countries do not contribute malignancy data. Annual IA1 was submitted in 2021, the current IA2 will be submitted in 2022 and IA3 is planned for submission in 2023. Each IA has a data lag period of one year. Therefore, IA1 for 2021 included data that was accrued up until 2020, and the current IA2 for 2022, includes data that was accrued up until 31 December 2021.

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

For this second IA, patients from both registries were followed up to the end of December 2021, or until patients withdrew from the registry, or death, whichever occurred first.

9.3 Subjects

Only patients who met the study eligibility criteria (refer to Table 2) and enrolled in ISAR or CHRONICLE are included in the analyses. A total of 3352 patients were excluded from the analysis; the majority of these were due to lack of malignancy data (e.g., presence/absence of malignancy, malignancy status) and the date of non-benralizumab biologics initiation being before 01 November 2017 (refer to Table 3 for breakdown).

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

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

Patients were summarised in their original biologic cohort if they discontinued benralizumab or non-benralizumab biologics use and did not receive any biologic treatment after discontinuation. The definition of index dates and baseline for patients who switched treatment during the study is detailed in Section 6.3 of SAP v4.0.

The calculation of person-years (PY) for patients with treatment switch is specified in Section 6.4 of SAP v4.0. 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 v4.0).

Table 2: Study population (ISAR and CHRONICLE)

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

Table 2: Study population (ISAR and CHRONICLE)

ISAR	CHRONICLE
[a] Uncontrolled is defined by meeting at least one of the following (as outlined by American Thoracic Society/European Respiratory Society guidelines): 1) Poor symptom control: Asthma Control Questionnaire consistently > 1.5, Asthma Control Test < 20 (or "not well controlled" by National Asthma Education and Prevention Program/Global Initiative for Asthma [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). [b] High-dose ICS is defined as: ICS at a cumulative dose of > 500 µg fluticasone propionate equivalents daily or highest labelled dose of a combination of ICS/LABA.	

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 (for CHRONICLE follow-up visits are scheduled every 6 months, for ISAR follow-up visits occur as needed).

Both ISAR and CHRONICLE collected data on demographic characteristics, relevant medical history, laboratory tests of interest, diagnostic procedures, lung function testing, presence of confirmed allergy, asthma control, asthma medications, serious infection, and anaphylaxis. For further details refer to Section 5.3 of the SAP v4.0.

9.5 Data sources and measurement

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

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

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

9.6 Bias

Given the nature of this observational study, patients in the 3 cohorts may differ with regard to important demographics and baseline characteristics. For the details about limitations of the research method refer to Section 9.9 of CSP v5.0 and Section 11.2. To assess signs of potential imbalances, differences between cohorts with regard to potential risk factors of malignancy (described in Section 5.3 of SAP v4.0) were explored in the main and subpopulation analysis sets using descriptive summaries. Considering the impact of potential imbalances between study cohorts, estimates in this study were adjusted based on PS. The PS determine the probabilities of patients receiving benralizumab and were calculated using a logistic regression model. Other methods to tackle bias are discussed in Section 9.9.4 on sensitivity analyses.

9.7 Study size

The planned patients' recruitment across the 2 registries was 14000 by 2022. By the end of December 2021, which is the cut-off date for the analysis of this second IA study report, a total of 8676 severe asthma patients were recruited to ISAR or CHRONICLE and 5324 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, 3352 patients were excluded primarily due to lack of malignancy data (e.g., presence/absence of malignancy, malignancy status) and the date of non-benralizumab biologics initiation being before 01 November 2017. (Note: a sensitivity analysis including patients excluded due to the date criterion was performed).

The following PRAC comment was received on IA1 regarding sample size: Based on the number of patients enrolled until the cut-off for this first interim report, it seems questionable if it is possible to enrol the projected number of 14000 patients before the planned end of data collection. The MAH is hence asked to assess this risk in the next interim report, apply corrective measures if needed and, if necessary, submit a variation application in order to extend the timeline of the study.

A projection of the patients and patient follow-up time in PY was performed during the preparation of this IA report to assess whether the figures outlined in the protocol can be reached. Using the most recent enrolment figures provided by the registries for to date and to the end of the enrolment period (end of 2023), assuming the same attrition rate and loss to follow-up, it is expected that at least 39500 total PY follow-up time from approximately 14000 patients will be attained by the end of the planned data collection. ISAR recruitment, in particular, is expected to increase significantly in 2022-2023 as a result of collaboration with more countries and improved data collection. This will be further assessed during the next interim phase. If there is a risk of insufficient patient enrolment, corrective measures to increase patient numbers will be applied and a variation application will be submitted to extend the timeline of the study.

The overall PY of follow-up in this IA is 11948.8 as of 31 December 2021. In the benralizumab cohort, a total of 1766.5 PY were accrued (refer to Section 10.4.2), while in the non-benralizumab biologics cohort and in the non-biologic cohort, 6004.8 PY and 4177.5 PY were accrued, respectively. The 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 v5.0. The sample size considerations were 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 v5.0). Data from the 2 datasets were pooled to create the analysis dataset prior to statistical analyses. Details of the collected variables are included in the Case Report Forms (CRFs) for the study (a list of the CRFs is included in Annex 1 of the CSP v5.0). There was no coding system for the exposure or the covariates as information was entered directly to the clinical report form which was standard across sites and countries for ISAR and across sites for CHRONICLE.

Collected data for new malignancy cases (outcome) from both registries were reviewed for quality and then coded using international statistical classification of diseases and related health problems (ICD)-10 codes by an oncologist. This ensures harmonisation of the outcome across registries and a seamless data merging of this key variable.

9.9 Statistical methods

9.9.1 Main summary measures

All analyses are made based on the aforementioned analysis sets, including pooled data from ISAR and CHRONICLE, and separately by data source (ISAR and CHRONICLE). The main analysis was conducted on pooled data. Subpopulation analysis was performed to support the main analysis. For detailed methodology, refer to Section 6 of the SAP v4.0. 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.

9.9.2 Main statistical methods

9.9.2.1 Characteristics of patients and new malignancy cases

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

9.9.2.2 Propensity score

Propensity score is the probability that patients would receive a particular treatment given their baseline characteristics. In this study, it was used to balance the 3 cohorts in terms of baseline characteristics to account for confounding. Separate sets of PS were generated for each comparison between benralizumab vs non-benralizumab biologics cohorts and between benralizumab vs non-biologic cohorts. Since there was no intent to compare between the non-benralizumab biologics vs non-biologic cohort, no PS was generated for this comparison. 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],

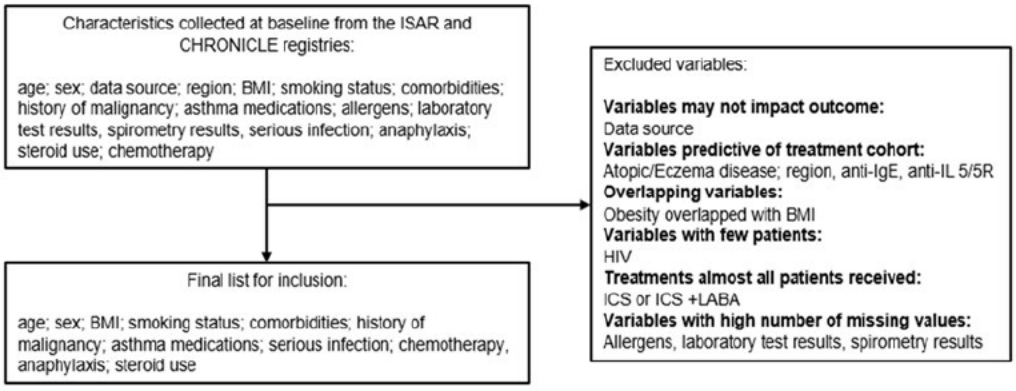
theophylline, leukotriene receptor antagonist [LTRA], macrolide antibiotics and steroid-sparing agents), steroid use, previous serious infection, previous anaphylaxis, previous chemotherapy as well as history of malignancy.

Because a patient needed to have a complete set of covariates for inclusion in weighted PS analyses, the covariates in the PS model were reduced from the original full variables list based on missingness and data quality/availability as proposed in SAP v4.0 Section 6.11.1. Laboratory results (blood eosinophil, IgE, fractional exhaled nitric oxide, allergen sensitisation) and spirometry (% forced expiratory volume during 1 second [FEV_1], % forced vital capacity [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.

A separate PS was also calculated for each subpopulation analysis set. The balance of the covariates across 3 cohorts before and after adjusting PS was examined. As previously stated in the approved SAP v4.0, 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 v4.0) and the weighted Cox-proportional hazard model (refer to Section 6.11.3 of SAP v4.0).

Stratified analysis by PS deciles 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



Abbreviations: BMI: Body mass index, ICS: Inhaled corticosteroid, IgE: Immunoglobulin E, IL: Interleukin, HIV: Human immunodeficiency virus, LABA: Long-acting β-adrenoreceptor agonists.

9.9.2.3 Incidence rates and event rates

The definition of incidence rates and event rates, and time at risk for incidence rates and event rates were described in Section 6.11.2 and 6.4.2 of SAP v4.0, respectively. Poisson regression models were used to estimate the incidence rate, difference in incidence rate, incidence rate ratio and corresponding 95% confidence intervals (CIs). The response variable in the model was the number of patients with a new malignancy. Cohort, age, sex, region, smoking, and BMI were included in the model as covariates. All incidence rates were reported as new malignancies per 1000 PY.

9.9.2.4 Time to event analysis

Time from the index date (defined in Section 6.11.3 of SAP v4.0) to first new malignancy for each cohort, subgroup and data source was displayed graphically using Kaplan-Meier plots. Cox-proportional hazard models were used to estimate the hazard ratio and 95% CIs after adjusting for cohort, age, sex, region, smoking, and BMI.

9.9.3 Missing values

The procedures for handling missing values were discussed in Section 6.6 of the SAP v4.0.

9.9.4 Sensitivity analyses

The following sensitivity analyses were performed:

Lag Time Considerations

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

Alternative Definition of Index Date

Since there were many more non-benralizumab biologics users who initiated biologics before 01 November 2017, an alternative definition of the index date was used to minimise this exclusion. In this sensitivity analysis, the index dates for the benralizumab and non-benralizumab biologics cohort were defined as the first biologic use, and for the non-biologic cohort as 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.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

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 CRF (e-CRF). 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, North Carolina) 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

10.1 Participants

10.1.1 Overall population

A total of 8676 patients were enrolled in both ISAR or CHRONICLE as of 31 December 2021, with 5324 patients included in the main analysis. Overall, 3352 patients were excluded. Among them, 939 patients were excluded due to lack of malignancy data (e.g., presence/absence of malignancy, malignancy status). A total of 2630 patients were excluded from analysis because their date of non-benralizumab biologics initiation was before 01 November 2017 (note that a sensitivity analysis including patients excluded due to the date criterion was performed).

Patient disposition from ISAR and CHRONICLE are summarised in Table 3. For registry-specific analysis refer to Table 14.1.1.2 (for ISAR) and Table 14.1.1.3 (for CHRONICLE). The non-benralizumab biologics cohort is presented as other-biologic cohort in the in-text data tables and in Appendix B.

Among the 5324 patients in the main analysis, there were 825 patients in the benralizumab cohort, 2410 patients in the non-benralizumab biologics cohort, and 2328 patients in the non-biologic cohort. The overall PY of follow-up in this IA is 11948.8 as of 31 December 2021, with the follow-up for the benralizumab cohort at 1766.5 PY, the non-benralizumab biologics cohort at 6004.8 PY, and the non-biologic cohort at 4177.5 PY.

A total of 290 (5.4%) patients discontinued from the study, but since discontinuation date was not recorded for patients in the ISAR registry unless it was death caused by malignancy, serious infection, or anaphylaxis, all discontinuation data is for patients in the CHRONICLE. Of the 290 patients who discontinued, 56 (6.8%) patients were in the benralizumab cohort, 103 (4.3%) patients were in the non-benralizumab biologics cohort, and 144 (6.2%) patients were in the non-biologic cohort.

The primary reasons for discontinuation included patients lost-to-follow-up and other general reasons e.g. site closure. There were 28 (0.5%) patients with reported reason for discontinuation as death, 5 more than reported in IA1 report, of which 9 (1.1%) patients were in the benralizumab cohort, 12 (0.5%) patients were in the non-benralizumab biologics cohort, and 9 (0.4%) patients were in the non-biologic cohort.

The number of patients who switched to the benralizumab cohort from the non-benralizumab biologics cohort was 150 (6.2%). The number of patients who switched from benralizumab to the non-benralizumab biologics cohort was 131 (15.9%). The mean (standard deviation [SD]) of total of follow-up (years) were 2.1 (1.03) years in the benralizumab cohort, 2.5 (1.05) years in the non-benralizumab biologics cohort, and 1.8 (0.90) 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 and enrolled in either registry [a]	825 (100)	2410 (100)	2328 (100)	5324 (100)
Patients discontinued [CHRONICLE] [b]	56 (11.5)	103 (9.4)	144 (19.4)	290 (13.4)
Patients died during follow-up [CHRONICLE] [b]	9 (1.8)	12 (1.1)	9 (1.2)	28 (1.3)
Patients discontinued without a switch [CHRONICLE] [b, c]	43 (8.8)	90 (8.2)	144 (19.4)	277 (12.8)

Table 3: Patient disposition (ISAR and CHRONICLE combined analysis set)

	Number (%) of patients			
	Benralizumab cohort	**Other-biologic cohort**	**Non-biologic cohort**	**Total**
Patients discontinued treatment [d]	67 (8.1)	210 (8.7)	NA	244 (4.6)
Patients discontinued treatment without a switch [c, d]	34 (4.1)	177 (7.3)	NA	211 (4.0)
Patients switched to another cohort	131 (15.9)	150 (6.2)	NA	239 (4.5)
Switch to benralizumab cohort	NA	150 (6.2)	NA	NA
Switch to other-biologic cohort	131 (15.9)	NA	NA	NA
Total follow-up time (years)				
Mean (SD)	2.1 (1.03)	2.5 (1.05)	1.8 (0.90)	2.1 (1.04)
Median	2.2	2.5	1.8	2.1
Min, Max	1.2, 2.9	1.7, 3.3	1.1, 2.5	1.3, 2.9
Q1, Q3	0.0, 4.1	0.0, 4.2	0.0, 4.1	0.0, 4.2
Total person-years of follow-up (years) [e]	1766.5	6004.8	4177.5	11948.8

Abbreviations: NA: Not applicable, SD: Standard deviation, Q1: First quartile, Q3: Third quartile.

[a] A total of 3352 patients are excluded from analysis. Among them, 939 patients are excluded from analysis because they do not have malignancy status (presence or absence of malignancy). Four patients are excluded due to lack of review for malignancy data. A total of 2630 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. One hundred four patients are excluded from analysis because their cohort cannot be derived from data. Thirty 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. Percentages are relative to the number of patients enrolled in CHRONICLE.

[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.

[e] 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

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.

Source: Table 14.1.1.1 and Table 14.1.1.3 [b]

10.2 Descriptive data

10.2.1 Baseline demographic characteristics (prior to PS trimming)

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

More than half of the study population (2980/5324, 56.0%) were aged between 40 to 64 years which was consistent across all cohorts. The majority of patients from the study population were white (3305/5324, 62.1%) and were female (3553/5324, 66.7%) 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=825)	Other-biologic cohort (N=2410)	Non-biologic cohort (N=2328)	Total (N=5324)
Age (years)	n	823	2404	2315	5304
	Mean (SD)	55.3 (14.09)	52.8 (14.64)	53.8 (15.88)	53.7 (15.15)
	Median	57.0	54.0	55.0	55.0
Age (years) subgroups n (%)	>= 18 to <= 39	112 (13.6)	466 (19.3)	468 (20.1)	998 (18.7)
	>= 40 to <= 64	488 (59.2)	1402 (58.2)	1233 (53.0)	2980 (56.0)
	>= 65 to <= 79	207 (25.1)	498 (20.7)	526 (22.6)	1186 (22.3)
	>= 80	16 (1.9)	38 (1.6)	88 (3.8)	140 (2.6)
	Total	823 (99.8)	2404 (99.8)	2315 (99.4)	5304 (99.6)
	Missing	2	6	13	20
Sex n (%)	Female	540 (65.5)	1586 (65.8)	1584 (68.0)	3553 (66.7)
	Male	285 (34.5)	824 (34.2)	739 (31.7)	1766 (33.2)
	Total	825 (100)	2410 (100)	2323 (99.8)	5319 (99.9)
	Missing	0	0	5	5
Data source n (%)	ISAR	337 (40.8)	1317 (54.6)	1587 (68.2)	3153 (59.2)
	CHRONICLE	488 (59.2)	1093 (45.4)	741 (31.8)	2171 (40.8)
Race n (%)	White	584 (70.8)	1660 (68.9)	1219 (52.4)	3305 (62.1)
	Black or African American	92 (11.2)	195 (8.1)	154 (6.6)	402 (7.6)
	Asian	60 (7.3)	174 (7.2)	470 (20.2)	693 (13.0)
	Native Hawaiian or Other Pacific Islander	2 (0.2)	3 (0.1)	0	5 (0.1)

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

Demographic characteristic	Statistics or category	Benralizumab cohort (N=825)	Other-biologic cohort (N=2410)	Non-biologic cohort (N=2328)	Total (N=5324)
	American Indian or Alaska Native	1 (0.1)	6 (0.2)	1 (0.0)	8 (0.2)
	Other	44 (5.3)	197 (8.2)	372 (16.0)	601 (11.3)
	Total	783 (94.9)	2235 (92.7)	2216 (95.2)	5014 (94.2)
	Missing	42	175	112	310

Abbreviations: 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.

Source: Table 14.1.2.1

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

At baseline, patients' asthma exacerbations, hospital admissions, emergency department visits, and invasive ventilations include events up to one year prior to index date. Baseline oral corticosteroids (OCS) use is assessed as use at any time within one year prior to index date, but baseline OCS dose is the dose at the latest record prior to index date. Serious infection, anaphylaxis and history of malignancy at any time on or prior to index date are included in the count. Other variables were assessed at initial index date.

One third of the overall study population were smokers and the distribution of smoking status was comparable across the cohorts. The mean age at asthma onset ranged from approximately 31 to 33 years across the cohorts.

When comparing across the cohorts, the percentage of patients on maintenance OCS treatment at baseline was lower in the non-benralizumab biologics cohort (32.7%) compared to the benralizumab cohort (41.3%) and the non-biologic cohort (43.8%).

Medication adherence across all cohorts was high, with the benralizumab cohort reporting 90.8%, the non-benralizumab biologics cohort reporting 87.3%, and the non-biologic cohort

reporting 74.2% 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 partly controlled in most patients. The non-biologic cohort had the greatest percentage of uncontrolled asthma status, 46.3%, compared to 38.9% for the benralizumab cohort, and 36.5% for the non-benralizumab biologics cohort.

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=825)	Other-biologic cohort (N=2410)	Non-biologic cohort (N=2328)	Total (N=5324)
Body Mass Index (kg/m^2)	n	790	2313	2234	5103
	Mean	30.957	30.111	29.326	29.850
	SD	8.2755	7.5513	7.6454	7.7075
Smoking status n (%)	Non-smoker	563 (68.2)	1608 (66.7)	1574 (67.6)	3576 (67.2)
	Previous and/or current smoker	249 (30.2)	739 (30.7)	661 (28.4)	1585 (29.8)
	Total	812 (98.4)	2347 (97.4)	2235 (96.0)	5161 (96.9)
	Missing	13	63	93	163
Pack years [a]	n	237	690	620	1481
	Mean	16.766	16.956	16.551	16.803
	SD	19.1251	19.5005	17.9868	18.7420
Age at asthma onset (years)	n	717	2107	2213	4827
	Mean	33.016	31.228	33.633	32.646
	SD	20.8070	19.8297	20.2242	20.1813
Number of exacerbations [b]	n	825	2410	2328	5324
	Mean	1.0	0.6	0.9	0.7
	SD	1.64	1.32	1.24	1.32
Number of invasive ventilations [c]	n	488	1093	741	2171
	Mean	0.0	0.0	0.0	0.0
	SD	0.16	0.13	0.06	0.11
Number of hospital admissions [c]	n	488	1093	741	2171

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=825)	Other-biologic cohort (N=2410)	Non-biologic cohort (N=2328)	Total (N=5324)
	Mean	0.3	0.2	0.1	0.2
	SD	0.86	0.73	0.56	0.68
Number of emergency department visits [c]	n	488	1093	741	2171
	Mean	0.4	0.3	0.2	0.3
	SD	1.23	0.94	0.61	0.88
Maintenance oral corticosteroids (OCS)	Yes	341 (41.3)	788 (32.7)	1019 (43.8)	2013 (37.8)
	No	484 (58.7)	1622 (67.3)	1309 (56.2)	3311 (62.2)
	Total	825 (100)	2410 (100)	2328 (100)	5324 (100)
Maintenance OCS dose (mg/day)	n	291	690	954	1824
	Mean	33.42	29.41	32.38	31.37
	SD	20.050	19.503	21.570	20.718
Medication adherence status n (%) [d]	Yes	749 (90.8)	2103 (87.3)	1727 (74.2)	4363 (81.9)
	No	53 (6.4)	236 (9.8)	514 (22.1)	781 (14.7)
	Total	802 (97.2)	2339 (97.1)	2241 (96.3)	5144 (96.6)
	Missing	23	71	87	180
Asthma control status n (%) [e]	Well controlled	224 (27.2)	681 (28.3)	381 (16.4)	1243 (23.3)
	Partially controlled	178 (21.6)	585 (24.3)	632 (27.1)	1348 (25.3)
	Not controlled	321 (38.9)	880 (36.5)	1077 (46.3)	2161 (40.6)
	Total	723 (87.6)	2146 (89.0)	2090 (89.8)	4752 (89.3)
	Missing	102	264	238	572
History of malignancy n (%)	Yes	41 (5.0)	88 (3.7)	102 (4.4)	222 (4.2)
	No	784 (95.0)	2322 (96.3)	2226 (95.6)	5102 (95.8)
	Total	825 (100)	2410 (100)	2328 (100)	5324 (100)

Abbreviations: 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] Only includes data from CHRONICLE. Data is not available in ISAR.

[d] The medication adherence status of asthma treatment 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 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).

Source: Table 14.1.3.1

10.2.3 Baseline comorbidities (prior to PS trimming)

For complete baseline comorbidities of the ISAR and CHRONICLE combined analysis set refer to Table 14.1.4.1 and for separate analysis sets refer to Table 14.1.4.2. The baseline comorbidities from the ISAR and CHRONICLE are summarised in Table 6.

At baseline, asthma-related comorbidities such as allergic rhinitis and chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps) were generally comparable across the cohorts. Other baseline comorbidities were not generally comparable and differences in baseline comorbidities and characteristics were adjusted across the cohorts in the analysis by means of PS weighting. Atopic diseases/eczema were reported in all 3 cohorts (benralizumab cohort 42.8%, non-benralizumab biologics cohort 56.6%, and non-biologic cohort 69.1%). Chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps) was reported in all 3 cohorts (benralizumab cohort 35.3%, non-benralizumab biologics cohort 36.1%, and non-biologic cohort 29.9%). Nasal polyps were less common (benralizumab cohort 28.4%, non-benralizumab biologics cohort 29.0%, and non-biologic cohort 18.0%). Chronic obstructive pulmonary disease was reported in all 3 cohorts (benralizumab cohort 10.2%, non-benralizumab biologics cohort 8.7%, and non-biologic cohort 5.3%). Allergic rhinitis was common in all 3 cohorts (benralizumab cohort 57.9%, non-benralizumab biologics cohort 64.4%, and non-biologic cohort 64.3%).

Obesity was the most common OCS-related comorbidity at baseline with the benralizumab cohort reporting 44.8% with this comorbidity, followed by the non-benralizumab biologics cohort 40.8%, and the non-biologic cohort 35.3%. Diabetes was the least reported OCS-related comorbidity at baseline and is similar across the cohorts.

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

	Number (%) of patients		
Comorbidity Term	**Benralizumab cohort (N=825)**	**Other-biologic cohort (N=2410)**	**Non-biologic cohort (N=2328)**
Patients with any comorbidities at baseline	778 (94.3)	2293 (95.1)	2232 (95.9)
Asthma-related comorbidities			
Allergic rhinitis	478 (57.9)	1552 (64.4)	1498 (64.3)
Atopic diseases/Eczema [a]	353 (42.8)	1365 (56.6)	1609 (69.1)
Chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps)	291 (35.3)	869 (36.1)	696 (29.9)
Nasal polyps	234 (28.4)	700 (29.0)	419 (18.0)
Oral corticosteroids-related comorbidities			
Cardiovascular disease [b]	259 (31.4)	647 (26.8)	524 (22.5)
Diabetes	114 (13.8)	275 (11.4)	222 (9.5)
Hypertension	224 (27.2)	582 (24.1)	462 (19.8)
Obesity	370 (44.8)	983 (40.8)	822 (35.3)
Other comorbidities			
Chronic obstructive pulmonary disease	84 (10.2)	210 (8.7)	124 (5.3)
Human immunodeficiency virus	0	1 (0.0)	0
Liver disease	2 (0.2)	6 (0.2)	2 (0.1)

Abbreviations: 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 were ongoing at the first index date.

Source: Table 14.1.4.1

10.2.4 Baseline asthma medication (prior to PS trimming)

Overall Population

For the complete description of baseline asthma medications of the ISAR and CHRONICLE combined analysis set refer to Table 14.1.5.1 and for separate analysis sets refer to

Table 14.1.5.2. Asthma medications at baseline for the ISAR and CHRONICLE are summarised in Table 7.

Nearly all the patients across the cohorts used at least one asthma medication at baseline. The most commonly used asthma medication at baseline was ICS+LABA, with 69.9% in the benralizumab cohort, 65.4% in non-benralizumab biologics cohort, and 80.9% in the non-biologic cohort, followed by LTRA (benralizumab cohort 49.9%, non-benralizumab biologics cohort 44.6%, and non-biologic cohort 44.6%).

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=825)	Other-biologic cohort (N=2410)	Non-biologic cohort (N=2328)
Patients with any asthma medication	Yes	825 (100)	2410 (100)	2122 (91.2)
	No	0	0	206 (8.8)
Inhaled corticosteroids (ICS) only	Yes	141 (17.1)	333 (13.8)	273 (11.7)
	No	684 (82.9)	2077 (86.2)	2055 (88.3)
Long-acting β-adrenoreceptor agonists (LABA) only	Yes	16 (1.9)	61 (2.5)	30 (1.3)
	No	809 (98.1)	2349 (97.5)	2298 (98.7)
ICS+LABA	Yes	577 (69.9)	1576 (65.4)	1884 (80.9)
	No	248 (30.1)	834 (34.6)	444 (19.1)
Long-acting muscarinic antagonists (LAMA)	Yes	300 (36.4)	853 (35.4)	819 (35.2)
	No	525 (63.6)	1557 (64.6)	1509 (64.8)
Theophylline	Yes	46 (5.6)	108 (4.5)	105 (4.5)
	No	779 (94.4)	2302 (95.5)	2223 (95.5)
Leukotriene receptor antagonist (LTRA)	Yes	412 (49.9)	1075 (44.6)	1038 (44.6)
	No	413 (50.1)	1335 (55.4)	1290 (55.4)
Anti-immunoglobulin E (anti-IgE)	Yes	46 (5.6)	950 (39.4)	0
	No	779 (94.4)	1460 (60.6)	2328 (100)
Anti-interleukin 5/5 receptor (anti-IL5/5R)	Yes	NA	1156 (48.0)	0
	No	NA	1254 (52.0)	2328 (100)
Macrolide antibiotics	Yes	51 (6.2)	99 (4.1)	116 (5.0)
	No	774 (93.8)	2311 (95.9)	2212 (95.0)
Steroid-sparing agents	Yes	1 (0.1)	5 (0.2)	0

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=825)	Other-biologic cohort (N=2410)	Non-biologic cohort (N=2328)
	No	824 (99.9)	2405 (99.8)	2328 (100)

Abbreviations: N: Number of patients in cohort, n: Number of patients in analysis, NA: Not applicable, 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 were ongoing at the first index date.

Source: Table 14.1.5.1

10.3 Outcome data

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

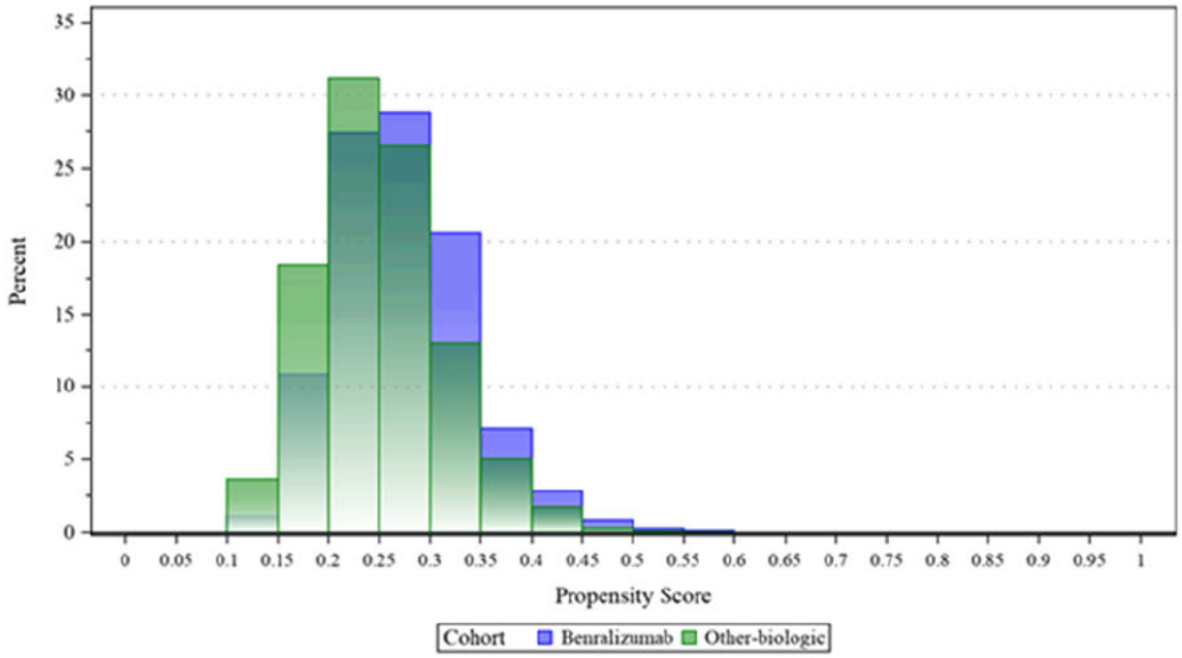
10.4 Main results

10.4.1 Propensity score by cohort

Propensity scores are calculated based on baseline characteristics and indicate the probability that patients would receive benralizumab. The overlaid distribution of PS for the benralizumab cohort versus the non-benralizumab biologics cohort is provided in Figure 2 and for the non-biologic cohort is provided in in Figure 3.

The balance of the covariates across 3 cohorts were examined by checking the distribution of PS (graphic approach) and standardised mean difference (SMD) (tabular approach). The overlapping histograms indicate that the PS model has balanced the baseline characteristics included in the model across the cohorts.

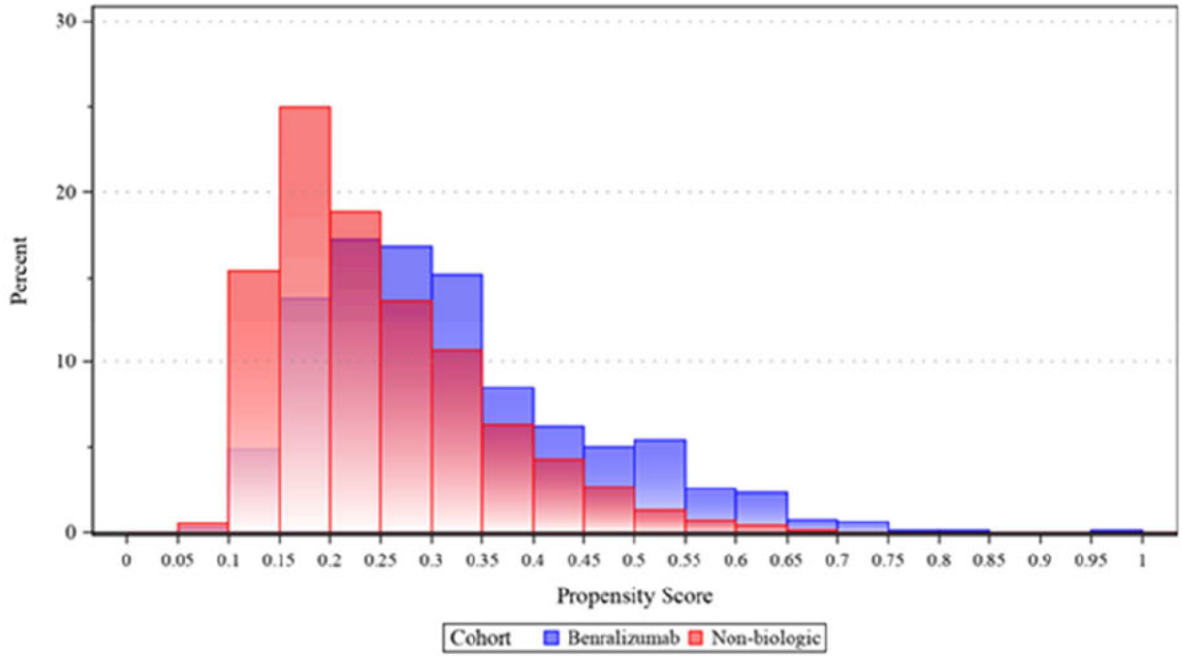
Figure 2 **Overlaid distribution of propensity score for the benralizumab cohort versus the non-benralizumab biologics cohort, histogram (ISAR and CHRONICLE combined analysis set)**



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

Source: Figure 14.2.1.2.1

Figure 3 **Overlaid distribution of propensity score for the benralizumab cohort versus non-biologic cohort, histogram (ISAR and CHRONICLE combined analysis set)**



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

Source: Figure 14.2.1.2.2

10.4.1.1 Comparison of baseline characteristics before trimming: Overall population

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

Benralizumab cohort versus non-benralizumab biologics cohort

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

Variables such as sex, smoking status, chronic rhinosinusitis, and nasal polyps were balanced at baseline, and no differences reaching nominal significance ($p < 0.05$) between the benralizumab and the non-benralizumab biologics cohort were observed for these variables. Other significant variables are reported in Table 8.

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

Benralizumab cohort versus non-biologic cohort

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

The variables sex, smoking status, liver disease, history of malignancy, previous chemotherapy, previous anaphylaxis, previous serious infection, ICS dose, LABA only, LAMA, theophylline, anti-IgE, macrolide antibiotics, and steroid-sparing agents were balanced 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 < 0.1 for all the variables, which confirmed that weighting balanced the baseline characteristics across the cohorts (Table 8 for pre- and post-weighting SMDs). Clear improvements in SMD were observed post-weighting in BMI, allergic rhinitis, nasal polyps, cardiovascular disease, and the baseline use of steroids.

Table 8: Standardised mean difference before trimming

Variable [a]	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)	0.177 [a]	0.006	0.083	0.011
Sex	0.002	0.002	0.070	0.003
Body Mass Index (kg/m^2)	0.106	-0.000	0.198 [a]	0.022
Smoking status	0.011	-0.010	-0.027	0.016
Comorbidities				
Allergic rhinitis	0.138 [a]	0.014	0.143	-0.007
Chronic rhinosinusitis	0.032	0.002	-0.103	0.010
Nasal polyps	0.013	-0.004	-0.262 [a]	-0.014
Cardiovascular disease	-0.108	0.001	-0.215 [a]	-0.012
Diabetes	-0.064	0.001	-0.128 [a]	-0.018
Hypertension	-0.074	0.002	-0.185 [a]	-0.008
COPD	-0.048	0.010	-0.179 [a]	-0.003
Liver disease	0.002	0.003	-0.054	-0.002
History of malignancy	-0.063	-0.006	-0.024	0.001
Previous chemotherapy	0.001	-0.001	-0.028	0.000
Previous anaphylaxis	-0.038	-0.003	-0.053	-0.001
Previous serious infection	0.008	0.007	0.030	-0.027
Asthma medication				
LABA only	0.049	0.019	-0.050	0.012
LAMA	-0.009	-0.004	-0.007	-0.005
Theophylline	-0.051	-0.009	-0.045	-0.004
LTRA	-0.111	-0.007	-0.093	-0.014
Macrolide antibiotics	-0.105	-0.002	-0.059	-0.018
Steroid-sparing agents	0.022	0.012	NC	NC
Steroid use	-0.112	-0.003	0.275 [a]	0.001

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease, LABA: Long-acting β-adrenoreceptor agonists, LAMA: Long-acting muscarinic antagonist, LTRA: Leukotriene receptor antagonist, NC: Not calculated.

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

Source: Table 14.2.1.1.1 and Table 14.2.1.1.2

10.4.1.2 Comparison of baseline characteristics after trimming - Overall population

Benralizumab cohort versus non-benralizumab biologics cohort

Patients with extreme PS (< 1% and > 99%) were trimmed from the analysis set to further balance the cohorts and differences between baseline characteristics were assessed again. Pre-weighting and post-weighting SMDs are reported in Table 9; for more details refer to Table 14.2.1.3.1. The total number of patients (N) for baseline characteristics before and after trimming were 825 and 747 in the benralizumab cohort; 2410 and 2221 in the non-benralizumab biologics cohort, respectively. Here also, P-values testing the difference between cohorts prior to PS weighting are included, but these do not account for multiplicity, and differences reaching nominal significance ($p < 0.05$) may not represent clinically meaningful differences between cohorts.

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

Benralizumab cohort versus non-biologic cohort

The total number of patients (N) for baseline characteristics before and after trimming were 825 and 747 in the benralizumab cohort; 2328 and 2121 in the non-biologic cohort, respectively. Pre-weighting and post-weighting SMDs are reported in Table 9; for more details refer to Table 14.2.1.3.2.

When PS weighting was applied to the data, the SMD for BMI decreased from 0.219 to 0.054 for the benralizumab vs non-biologic cohort. Similar improvements in SMD were observed post-weighting in other variables. PS weighting and trimming improved balance in baseline characteristics between the benralizumab and non-biologic cohorts (Table 9 for pre- and post-weighting SMDs).

Table 9: Standardised mean difference after trimming

Variable [a]	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)	0.216 [a]	0.031	0.078	0.019
Sex	0.006	0.005	0.072	0.011
Body Mass Index (kg/m^2)	0.121	0.008	0.219 [a]	0.054
Smoking status	0.016	-0.013	-0.032	0.011
Comorbidities				
Allergic rhinitis	0.151 [a]	0.027	0.162 [a]	0.013
Chronic rhinosinusitis	0.046	0.012	-0.115	-0.000
Nasal polyps	0.015	-0.007	-0.279 [a]	-0.033
Cardiovascular disease	-0.120	-0.004	-0.232 [a]	-0.034
Diabetes	-0.072	-0.003	-0.136 [a]	-0.029
Hypertension	-0.084	-0.003	-0.200 [a]	-0.027
COPD	-0.054	0.008	-0.189 [a]	-0.011
Liver disease	0.000	0.004	-0.056	-0.003
History of malignancy	-0.069	-0.012	-0.032	-0.012
Previous chemotherapy	0.000	0.000	-0.029	-0.000
Previous anaphylaxis	-0.040	-0.006	-0.056	-0.004
Previous serious infection	0.004	0.005	0.038	-0.027
Asthma medication				
LABA only	0.051	0.024	-0.054	0.011
LAMA	-0.005	-0.005	-0.017	-0.018
Theophylline	-0.052	-0.009	-0.034	0.005
LTRA	-0.122	-0.015	-0.111	-0.042
Macrolide antibiotics	-0.113	-0.006	-0.061	-0.021
Steroid-sparing agents	0.000	0.005	NC	NC
Steroid use	-0.148 [a]	-0.023	0.289 [a]	0.010

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease, LABA: Long-acting β-adrenoreceptor agonists, LAMA Long-acting muscarinic antagonist, LTRA: Leukotriene receptor antagonist, NC: Not calculated.

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

Source: Table 14.2.1.3.1 and Table 14.2.1.3.2

10.4.2 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 27 patients reported a new malignancy during the study, 6 (0.7%), 8 (0.3%), and 13 (0.6%) in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively. Before PS adjustment, the crude incidence rate per 1000 PY in these 3 cohorts were 3.4, 1.3, and 3.1, respectively.

After adjustment for age, sex, BMI, region, and smoking status, the number (%) of patients reporting a new malignancy decreased to 12 (0.6%) in the non-biologic cohort. One patient in the non-biologic cohort had missing data on baseline smoking status and was excluded from the adjusted analysis. In the PS adjusted benralizumab and non-biologic cohort, the adjusted incidence rates per 1000 PY were 2.1 for the benralizumab cohort, and 2.4 for the PS matched non-biologic cohort. In the PS adjusted benralizumab and non-benralizumab biologics cohorts, the adjusted incidence rates per 1000 PY were 2.0 for the benralizumab cohort, and 1.2 for the PS matched non-benralizumab biologics cohort.

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

Due to the multicentric/multifocal nature of NMSCs, the same NMSCs may occur at different sites with a potential to inflate incidence rates. Therefore, it was stated in the protocol and SAP v4.0 to perform sensitivity analyses excluding NMSCs.

The crude incidence rate of new malignancies after excluding patient with NMSC, is given in Table 10. Overall, the crude incidence rates were low across all populations. The number (%) of patients reporting a new malignancy, excluding NMSC, was 6 (0.7%), 8 (0.3%) and 11 (0.5%) in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively.

After adjustment for age, sex, BMI, region, and smoking status, the adjusted incidence rate per 1000 PY in the benralizumab cohort and non-benralizumab biologics cohort decreased to 2.0 and 1.2, respectively. The adjusted incidence rate per 1000 PY for the benralizumab cohort and non-biologic cohort decreased to 2.2 for both cohorts.

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

In the ISAR registry, the number (%) of patients reporting a new malignancy was 1 (0.3%), 3 (0.2%), and 8 (0.5%) in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively. The crude incidence rates per 1000 PY in these 3 cohorts were 1.2, 0.8, and 2.9, respectively.

In CHRONICLE, there were 5 new malignancies reported in each of the 3 cohorts. Crude incidence rates per 1000 PYs for CHRONICLE benralizumab, non-benralizumab biologics and non-biologic cohorts were 5.3, 2.1 and 3.7, respectively. Adjusted rates for benralizumab vs non-benralizumab biologics were 4.1 vs 2.0, respectively, and for benralizumab vs non-biologic 1.8 and 1.2, respectively.

There was also no clear evidence for difference between cohorts when data were analysed by separate analysis set (refer to [Table 14.2.2.1.2] for ISAR, and [Table 14.2.2.1.3] for CHRONICLE).

In the combined analysis set, rate ratios between benralizumab and non-benralizumab biologics cohorts was 1.60 (95% CI: 0.77 – 3.22) and 0.90 (95% CI:0.47 - 1.74) for the comparison between benralizumab and non-biologic cohorts.

Table 10: Observed crude and adjusted incidence rates for new malignancy, Poisson regression (ISAR and CHRONICLE combined analysis set)

					Rate difference	Rate ratio	
	Comparison	**Number (%) of patients with a new malignancy**	**Total time at risk (years)**	**Incidence rate (per 1000 PY) (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**p value**
Crude [a]							
Overall	Benralizumab cohort (N=825) versus Other-biologic cohort (N=2410)	6 (0.7) versus 8 (0.3)	1757.51 versus 5993.94	3.4 (1.53, 7.60) versus 1.3 (0.67, 2.67)	2.1 (-0.80, 4.96)	NC	NC
	Benralizumab cohort (N=825) versus Non-biologic cohort (N=2328)	6 (0.7) versus 13 (0.6)	1757.51 versus 4158.42	3.4 (1.53, 7.60) versus 3.1 (1.82, 5.38)	0.3 (-2.93, 3.50)	NC	NC
Without NMSC	Benralizumab cohort (N=825) versus Other-biologic cohort (N=2410)	6 (0.7) versus 8 (0.3)	1757.51 versus 5993.94	3.4 (1.53, 7.60) versus 1.3 (0.67, 2.67)	2.1 (-0.80, 4.96)	NC	NC
	Benralizumab cohort (N=825) versus Non-biologic cohort (N=2328)	6 (0.7) versus 11 (0.5)	1757.51 versus 4162.35	3.4 (1.53, 7.60) versus 2.6 (1.46, 4.77)	0.8 (-2.38, 3.92)	NC	NC
Adjusted [b]							
Overall	Benralizumab cohort (N=747) versus Other-biologic cohort (N=2221)	6 (0.8) versus 8 (0.4)	1588.31 versus 5527.77	2.0 (1.07, 3.59) versus 1.2 (0.64, 2.40)	0.7 (-0.46, 1.88)	1.6 (0.77, 3.22)	0.2135
	Benralizumab cohort (N=747) versus Non-biologic cohort (N=2121)	6 (0.8) versus 12 (0.6)	1584.23 versus 3812.53	2.1 (1.22, 3.78) versus 2.4 (1.31, 4.31)	-0.2 (-1.72, 1.27)	0.9 (0.47, 1.74)	0.7634

Table 10: Observed crude and adjusted incidence rates for new malignancy, Poisson regression (ISAR and CHRONICLE combined analysis set)

					Rate difference	Rate ratio	
	Comparison	Number (%) of patients with a new malignancy	Total time at risk (years)	Incidence rate (per 1000 PY) (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p value
Without NMSC	Benralizumab cohort (N=747) versus Other-biologic cohort (N=2221)	6 (0.8) versus 8 (0.4)	1588.31 versus 5527.77	2.0 (1.07, 3.59) versus 1.2 (0.64, 2.40)	0.7 (-0.46, 1.88)	1.6 (0.77, 3.22)	0.2135
	Benralizumab cohort (N=747) versus Non-biologic cohort (N=2121)	6 (0.8) versus 10 (0.5)	1584.23 versus 3816.47	2.2 (1.27, 3.92) versus 2.2 (1.15, 4.01)	0.1 (-1.41, 1.57)	1.0 (0.52, 2.05)	0.9191

Abbreviations: BMI: Body Mass Index, CI: Confidence Interval, N: Number of patients in cohort, NC: Not calculated, 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.

Source: Table 14.2.2.1.1

10.4.2.3 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 5 (0.9%) and 7 (0.3%) in the benralizumab cohort and the non-benralizumab biologics cohort, respectively. The respective crude incidence rates per 1000 PY in these 2 cohorts were 3.6, and 1.2, respectively.

After adjustment for age, sex, BMI, region, and smoking status, the incidence rates for new malignancies in both the benralizumab and the non-benralizumab biologics cohort were 1.9 and 1.2, respectively.

Table 11: Observed crude and adjusted incidence rates for new malignancy, patients taken benralizumab/other-biologics and without cohort switches, Poisson regression (ISAR and CHRONICLE combined analysis set)

					Rate difference	Rate ratio	
	Comparison	**Number (%) of patients with a new malignancy**	**Total time at risk (years)**	**Incidence rate (per 1000 PY) (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**p value**
Crude [a]	Benralizumab cohort (N=586) versus Other-biologic cohort (N=2171)	5 (0.9) versus 7 (0.3)	1408.41 versus 5635.45	3.6 (1.48, 8.53) versus 1.2 (0.59, 2.61)	2.3 (-0.94, 5.55)	NC	NC
Adjusted [b]	Benralizumab cohort (N=535) versus Other-biologic cohort (N=1996)	5 (0.9) versus 7 (0.4)	1281.47 versus 5189.45	1.9 (1.00, 3.77) versus 1.2 (0.58, 2.37)	0.8 (-0.49, 2.03)	1.7 (0.76, 3.60)	0.2044

Abbreviations: 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.

Source: Table 14.2.2.1.4

10.4.3 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 set for each cohort are presented in Table 12.

The number of new malignancies in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts were 6, 8, and 13, respectively. The crude event rates per 1000 PY in these respective cohorts were 3.4, 1.3, and 3.1.

10.4.3.1 Subpopulation-excluding non-melanoma skin cancer

The number of new malignancies (excluding NMSC) in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts were 6, 8, and 11, respectively. The crude event rates per 1000 PY in these respective cohorts were 3.4, 1.3, and 2.6.

10.4.3.2 Crude event rates for new malignancy: ISAR and CHRONICLE

In the ISAR registry, the number of new malignancies in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts was 1, 3, and 8, respectively. The crude event rates per 1000 PY in these respective cohorts were 1.2, 0.8, and 2.9.

In the CHRONICLE, the number of new malignancies was 5 each in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts. The crude event rates per 1000 PY in these respective cohorts were 5.2, 2.1, and 3.6.

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

Table 12: Observed crude event rates for new malignancy, Poisson regression (ISAR and CHRONICLE combined analysis set)

	Comparison	Number of new malignancies	Total time at risk (years)	Event rate (per 1000 PY) (95% CI)	Comparison (rate difference) between groups (95% CI)
Overall	Benralizumab cohort (N=825) versus Other-biologic cohort (N=2410)	6 versus 8	1766.53 versus 6004.79	3.4 (1.53, 7.56) versus 1.3 (0.67, 2.66)	2.1 (-0.81, 4.93)
	Benralizumab cohort (N=825) versus Non-biologic cohort (N=2328)	6 versus 13	1766.53 versus 4177.52	3.4 (1.53, 7.56) versus 3.1 (1.81, 5.36)	0.3 (-2.92, 3.49)
Without NMSC	Benralizumab cohort (N=825) versus Other-biologic cohort (N=2410)	6 versus 8	1766.53 versus 6004.79	3.4 (1.53, 7.56) versus 1.3 (0.67, 2.66)	2.1 (-0.81, 4.93)
	Benralizumab cohort (N=825) versus Non-biologic cohort (N=2328)	6 versus 11	1766.53 versus 4177.52	3.4 (1.53, 7.56) versus 2.6 (1.46, 4.75)	0.8 (-2.37, 3.90)

Abbreviations: CI: Confidence Interval, N: Number of patients in cohort, NMSC: Non-melanoma skin cancer, PY: Person-years.

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

If a patient has 2 malignancy records with same diagnosis within 3 months, the 2 records are considered as the same malignancy case and counted only once.

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

Source: Table 14.2.2.2.1

10.4.4 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 4. Based on overall population, the number of patients with a new malignancy was 6, 8, and 12 in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts, respectively. In the subpopulation (excluding NMSC), the number of patients with a new malignancy in these 3 cohorts were 6, 8, and 10, respectively. As noted in Section 10.4.2, this analysis excludes one malignancy report in the non-biologic cohort because the patient had incomplete baseline covariate information. There was no significant difference in the time to first new malignancy between cohorts.

No clear risk of new malignancy in each comparison of the benralizumab cohort with non-benralizumab biologics and non-biologic cohorts was observed.

Table 13: Time to first new malignancy, Cox-proportional hazard model (ISAR and CHRONICLE combined analysis set)

			Comparison between groups [a]	
	Treatment Group	Number (%) of patients with a new malignancy	Hazard Ratio	95% CI
Overall	Benralizumab cohort (N=747) versus Other-biologic cohort (N=2221)	6 (0.8) versus 8 (0.4)	1.5	(0.75, 3.12)
	Benralizumab cohort (N=747) versus Non-biologic cohort (N=2121)	6 (0.8) versus 12 (0.6)	0.9	(0.47, 1.79)
Without NMSC	Benralizumab cohort (N=747) versus Other-biologic cohort (N=2221)	6 (0.8) versus 8 (0.4)	1.5	(0.75, 3.12)
	Benralizumab cohort (N=747) versus Non-biologic cohort (N=2121)	6 (0.8) versus 10 (0.5)	1.0	(0.53, 2.09)

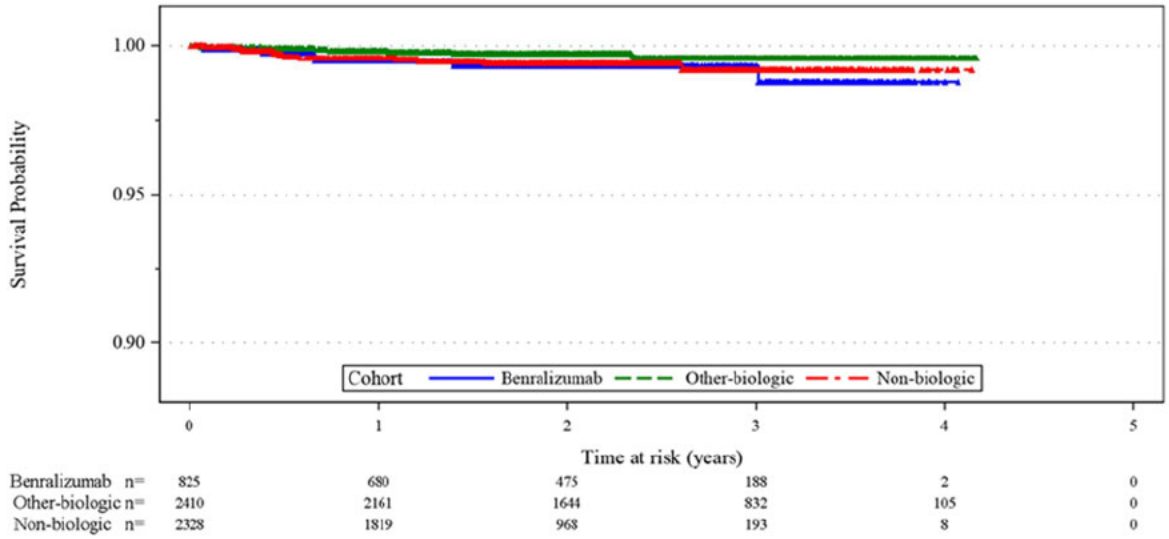
Abbreviations: CI: Confidence Interval, N: Number of patients in cohort, NMSC: Non-melanoma skin cancer, BMI: Body Mass Index.

[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.

Source: Table 14.2.3.2.1

Figure 4 **Time to first new malignancy (ISAR and CHRONICLE combined analysis set)**



Abbreviations: 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.

Source: Table 14.2.3.1.1

10.4.5 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. For the complete characteristics of new malignancy cases of the ISAR analysis set and CHRONICLE analysis set refer to Table 14.2.4.1.2. For the complete characteristics of new malignancy cases of the subgroup (excluding NMSC) from the ISAR and CHRONICLE combined analysis set, refer to Table 14.2.4.1.3.

The total number of patients reporting new onset of malignancy cases was 6, 8, and 13 in the benralizumab, the non-benralizumab biologics, and non-biologic cohorts, respectively.

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

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N=6)**	**Other-biologic cohort (N=8)**	**Non-biologic cohort (N=13)**
Status at diagnosis	New onset	6 (100)	8 (100)	13 (100)
	Total	6 (100)	8 (100)	13 (100)
Location/site	Breast	1 (16.7)	1 (12.5)	3 (23.1)
	Digestive organ	1 (16.7)	2 (25.0)	1 (7.7)
	Lymphoid, hematopoietic and related tissue	1 (16.7)	0	0
	Male genital organ	2 (33.3)	2 (25.0)	1 (7.7)
	Melanoma and other malignancy neoplasms of skin	0	0	3 (23.1)
	Respiratory and intrathoracic organs	0	2 (25.0)	4 (30.8)
	Urinary tract	1 (16.7)	1 (12.5)	1 (7.7)
	Total	6 (100)	8 (100)	13 (100)
Cell type	Epithelial cell	0	0	1 (7.7)
	Basal cell	0	0	1 (7.7)
	Glandular cell	2 (33.3)	5 (62.5)	3 (23.1)
	Squamous cell	0	0	4 (30.8)
	Urothelial cell	0	1 (12.5)	0
	Total	2 (33.3)	6 (75.0)	9 (69.2)
	Missing	4	2	4
Stage (Number staging system)	Stage I	2 (33.3)	2 (25.0)	3 (23.1)
	Stage II	0	0	1 (7.7)
	Stage IV	1 (16.7)	0	1 (7.7)
	Total	3 (50.0)	2 (25.0)	5 (38.5)
	Missing	3	6	8
Stage (TNM staging system)				
T (Primary tumour)	X	1 (16.7)	0	0
	1	0	3 (37.5)	2 (15.4)
	2	2 (33.3)	1 (12.5)	1 (7.7)
	4	0	1 (12.5)	1 (7.7)
	Total	3 (50.0)	5 (62.5)	4 (30.8)
	Missing	3	3	9
N (Lymph Nodes)	X	1 (16.7)	0	0
	0	0	2 (25.0)	3 (23.1)
	1	1 (16.7)	1 (12.5)	1 (7.7)
	2	1 (16.7)	1 (12.5)	0

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

		Number (%) of patients		
Characteristics	**Category**	**Benralizumab cohort (N=6)**	**Other-biologic cohort (N=8)**	**Non-biologic cohort (N=13)**
	Total	3 (50.0)	4 (50.0)	4 (30.8)
	Missing	3	4	9
M (Distant Metastasis)	X	1 (16.7)	1 (12.5)	0
	0	0	3 (37.5)	3 (23.1)
	1	1 (16.7)	0	1 (7.7)
	Total	2 (33.3)	4 (50.0)	4 (30.8)
	Missing	4	4	9
Outcome	Ongoing	5 (83.3)	5 (62.5)	2 (15.4)
	Remission	0	2 (25.0)	7 (53.8)
	Unknown status (not death)	0	1 (12.5)	3 (23.1)
	Total	5 (83.3)	8 (100)	12 (92.3)
	Missing	1	0	1

Abbreviation: 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.

Source: Table 14.2.4.1.1

10.4.5.1 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 sets and subpopulation are described in Table 14.2.4.2.1 to Table 14.2.4.2.3, respectively, and for an abbreviated table, refer to Table 15.

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=6)**	**Other-biologic cohort (N=8)**	**Non-biologic cohort (N=13)**
Age (years)	n	6	8	13
	Mean (SD)	64.8 (9.45)	62.4 (5.37)	69.8 (9.60)
	Median	66.5	62.5	71.0
	Q1, Q3	60.0, 71.0	59.0, 65.0	65.0, 76.0

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=6)	Other-biologic cohort (N=8)	Non-biologic cohort (N=13)
	Min, Max	49, 76	54, 72	46, 85
Age (years) subgroups n (%)	>= 18 to <= 39	0	0	0
	>= 40 to <= 64	2 (33.3)	5 (62.5)	3 (23.1)
	>= 65 to <= 79	4 (66.7)	3 (37.5)	9 (69.2)
	>= 80	0	0	1 (7.7)
	Total	6 (100)	8 (100)	13 (100)
Sex n (%)	Female	4 (66.7)	2 (25.0)	10 (76.9)
	Male	2 (33.3)	6 (75.0)	3 (23.1)
	Total	6 (100)	8 (100)	13 (100)
Race n (%)	White	3 (50.0)	4 (50.0)	7 (53.8)
	Black or African American	2 (33.3)	3 (37.5)	0
	Asian	1 (16.7)	1 (12.5)	5 (38.5)
	Native Hawaiian or Other Pacific Islander	0	0	0
	American Indian or Alaska Native	0	0	0
	Other	0	0	1 (7.7)
	Total	6 (100)	8 (100)	13 (100)
Country n (%) [a]	Canada	0	1 (12.5)	3 (23.1)
	Colombia	0	0	1 (7.7)
	Japan	1 (16.7)	0	3 (23.1)
	Kuwait	0	1 (12.5)	0
	South Korea	0	1 (12.5)	0
	Taiwan	0	0	1 (7.7)
	United States of America	5 (83.3)	5 (62.5)	5 (38.5)
	Total	6 (100)	8 (100)	13 (100)
Body Mass Index (kg/m^2)	n	6	8	13
	Mean (SD)	29.470 (6.0352)	32.836 (5.7500)	28.379 (6.1672)
	Median	30.950	32.299	26.100
	Q1, Q3	23.200, 34.700	28.645, 37.400	24.038, 31.600
	Min, Max	21.12, 35.90	24.50, 41.50	21.20, 41.40

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=6)	Other-biologic cohort (N=8)	Non-biologic cohort (N=13)
Body Mass Index (kg/m^2) subgroups	>= 18.5 to < 25.0	2 (33.3)	1 (12.5)	5 (38.5)
	>= 25.0 to < 30.0	0	2 (25.0)	3 (23.1)
	>= 30.0 to < 35.0	3 (50.0)	2 (25.0)	3 (23.1)
	>= 35.0	1 (16.7)	3 (37.5)	2 (15.4)
	Total	6 (100)	8 (100)	13 (100)
Smoking status	Non-smoker	5 (83.3)	3 (37.5)	7 (53.8)
	Previous and/or current smoker	1 (16.7)	5 (62.5)	5 (38.5)
	Total	6 (100)	8 (100)	12 (92.3)
	Missing	0	0	1
Pack years [b]	n	0	5	4
	Mean (SD)	NA	19.950 (13.4935)	42.250 (39.2107)
	Median	NA	29.000	26.900
	Q1, Q3	NA	8.500, 30.000	18.000, 66.500
	Min, Max	NA	2.25, 30.00	15.20, 100.00
Age at asthma onset (years)	n	6	8	13
	Mean (SD)	20.673 (18.0351)	36.500 (17.6068)	47.696 (18.9026)
	Median	14.000	39.500	53.030
	Q1, Q3	7.000, 33.040	25.000, 49.000	49.720, 57.000
	Min, Max	5.00, 51.00	6.00, 59.00	0.10, 68.16
Number of exacerbations [c]	n	6	8	13
	Mean (SD)	1.5 (1.64)	0.8 (0.71)	0.3 (0.63)
	Median	1.0	1.0	0.0
	Q1, Q3	0.0, 3.0	0.0, 1.0	0.0, 0.0
	Min, Max	0, 4	0, 2	0, 2
	0	2 (33.3)	3 (37.5)	10 (76.9)
	1	2 (33.3)	4 (50.0)	2 (15.4)
	2	0	1 (12.5)	1 (7.7)
	3	1 (16.7)	0	0
	4	1 (16.7)	0	0
Number of invasive ventilations [d]	n	5	5	5

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=6)	Other-biologic cohort (N=8)	Non-biologic cohort (N=13)
	Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
	Median	0.0	0.0	0.0
	Q1, Q3	0.0, 0.0	0.0, 0.0	0.0, 0.0
	Min, Max	0, 0	0, 0	0, 0
Number of hospital admissions [d]	n	5	5	5
	Mean (SD)	0.4 (0.89)	1.0 (0.71)	0.0 (0.00)
	Median	0.0	1.0	0.0
	Q1, Q3	0.0, 0.0	1.0, 1.0	0.0, 0.0
	Min, Max	0, 2	0, 2	0, 0
Number of emergency department visits [d]	n	5	5	5
	Mean (SD)	0.4 (0.89)	1.0 (0.71)	0.4 (0.89)
	Median	0.0	1.0	0.0
	Q1, Q3	0.0, 0.0	1.0, 1.0	0.0, 0.0
	Min, Max	0, 2	0, 2	0, 2
Maintenance oral corticosteroids (OCS)	Yes	3 (50.0)	5 (62.5)	4 (30.8)
	No	3 (50.0)	3 (37.5)	9 (69.2)
	Total	6 (100)	8 (100)	13 (100)
Maintenance OCS doses per day (mg)	n	3	4	4
	Mean (SD)	35.00 (21.794)	23.75 (12.500)	32.50 (20.616)
	Median	25.00	22.50	35.00
	Q1, Q3	20.00, 60.00	15.00, 32.50	15.00, 50.00
	Min, Max	20.0, 60.0	10.0, 40.0	10.0, 50.0
Medication adherence status [e]	Yes	6 (100)	6 (75.0)	12 (92.3)
	No	0	2 (25.0)	1 (7.7)
	Total	6 (100)	8 (100)	13 (100)
Asthma control status [f]	Well controlled	0	1 (12.5)	4 (30.8)
	Partially controlled	3 (50.0)	1 (12.5)	2 (15.4)
	Not controlled	3 (50.0)	4 (50.0)	6 (46.2)
	Total	6 (100)	6 (75.0)	12 (92.3)
	Missing	0	2	1

Abbreviations: 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, NA: Not applicable, 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] Only includes data from CHRONICLE. Data is not available in ISAR.

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

[f] 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.

Source: Table 14.2.4.2.1

10.4.6 Sensitivity analyses

A one-year lag sensitivity analysis was also conducted. After excluding patients with new malignancies diagnosed within one year of their initial index date, there were 2 (0.2%) new malignancies reported in the benralizumab cohort, and 4 (0.2%) new malignancies reported each in the non-benralizumab biologics and non-biologic cohorts. An adjusted sensitivity analysis of the benralizumab and non-benralizumab biologics cohorts resulted in incidence rates per 1000 PY of 0.7 and 0.6, respectively. Similarly, a comparison of benralizumab and non-biologic cohorts resulted in adjusted incidence rates per 1000 PY of 0.5 and 0.3, respectively.

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

There were no clear differences in crude or adjusted incidence and event rates between the cohorts when the other index date of first use of biologics at any time (or registry entry at any time for the non-biologic cohort) was considered (Table 16, Table 17). After adjusting for age, sex, BMI, region, and smoking status, incidence rates for the benralizumab and non-benralizumab biologics cohorts were 1.4 and 1.8, respectively. Adjusted incidence rates for the benralizumab and non-biologic comparison were 2.2 and 2.5, respectively.

Similarly, the adjusted rate ratios and time to first new malignancy hazard ratios were less than one for all comparisons of the benralizumab cohort with non-benralizumab biologics and non-biologic cohorts (Table 16, Table 17), with all 95% CIs including the value of one (Table 16, Table 18). Time to first new malignancy with the other index date definition is illustrated in Figure 5. Due to the much earlier index date applied in this sensitivity analysis, the non-benralizumab biologics cohort was followed up for a much longer period than the other 2 cohorts and the increased probability of a new malignancy is observed beyond 4 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=1133) versus Other-biologic cohort (N=4631)	7 (0.6) versus 46 (1.0)	2499.43 versus 21288.07	2.8 (1.34, 5.87) versus 2.2 (1.62, 2.88)	0.6 (-1.53, 2.81)		
	Benralizumab cohort (N=1133) versus Non-biologic cohort (N=2383)	7 (0.6) versus 14 (0.6)	2499.43 versus 4476.37	2.8 (1.34, 5.87) versus 3.1 (1.85, 5.28)	-0.3 (-2.97, 2.32)		
Adjusted [b]							
	Benralizumab cohort (N=1018) versus Other-biologic cohort (N=4263)	7 (0.7) versus 45 (1.1)	2242.34 versus 19456.58	1.4 (0.86, 2.18) versus 1.8 (1.28, 2.50)	-0.4 (-1.10, 0.26)	0.8 (0.49, 1.20)	0.2461
	Benralizumab cohort (N=1035) versus Non-biologic cohort (N=2167)	7 (0.7) versus 13 (0.6)	2275.93 versus 4086.60	2.2 (1.33, 3.68) versus 2.5 (1.49, 4.35)	-0.3 (-1.77, 1.11)	0.9 (0.48, 1.58)	0.6453

Abbreviations: 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 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.

Source Table 14.2.5.3.1

Table 17: Observed crude event rates for new malignancy with the other index date definition, Poisson regression (ISAR and CHRONICLE combined analysis set)

	Comparison	Number of new malignancies	Total time at risk (person-years)	Event rate (95% CI)	Comparison (rate difference) between groups (95% CI)
Overall	Benralizumab cohort (N=1133) versus Other-biologic cohort (N=4631)	7 versus 48	2510.64 versus 21465.79	2.8 (1.33, 5.85) versus 2.2 (1.69, 2.97)	0.6 (-1.61, 2.71)
	Benralizumab cohort (N=1133) versus Non-biologic cohort (N=2383)	7 versus 14	2510.64 versus 4498.57	2.8 (1.33, 5.85) versus 3.1 (1.84, 5.25)	-0.3 (-2.96, 2.31)

Abbreviations: 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 the date of registry entry at any time.

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 2 malignancy records with same diagnosis within 3 months, the 2 records are considered as the same malignancy case and counted only once.

Source: Table 14.2.5.3.3

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

	Treatment group	Number (%) of patients with a new malignancy	Comparison between groups [a]	
			Hazard ratio	95% CI
Overall	Benralizumab cohort (N=1018) versus Other-biologic cohort (N=4263)	7 (0.7) versus 45 (1.1)	0.8	(0.51, 1.38)
	Benralizumab cohort (N=1035) versus Non-biologic cohort (N=2167)	7 (0.7) versus 13 (0.6)	0.9	(0.50, 1.69)

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

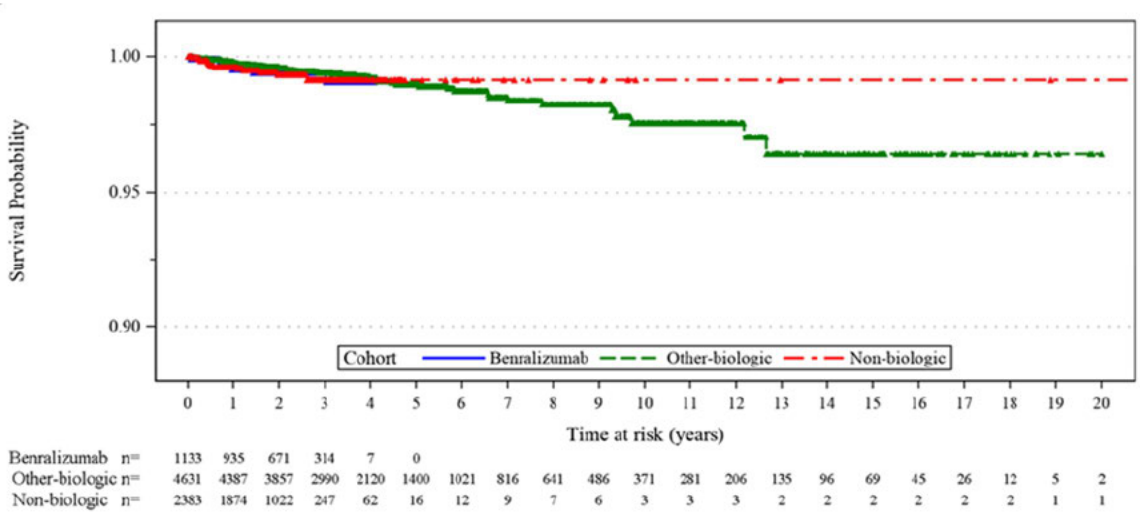
[a] The hazard ratio and 95% CI for each comparison are estimated using a weighted Cox regression model. The weights for the model are inverse propensity scores (1/propensity scores). The covariates in the model include cohort, age, sex, smoking, region and BMI.

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 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.

Source: Table 14.2.5.3.5

Figure 5 **Time to first new malignancy with the other index date definition, Kaplan-Meier plot (ISAR and CHRONICLE combined analysis set)**



Abbreviation: 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 the date of registry entry at any time.

Source: Figure 14.2.5.3.4

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 Table 14.2.5.1.1 to Table 14.2.5.3.5.

10.5 Other analyses

Not applicable.

10.6 Adverse events/adverse reactions

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

11. DISCUSSION

11.1 Key results

This study is conducted in severe asthma patients enrolled in the ISAR or CHRONICLE. The objectives are 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 2021 was analysed for this second IA report.

A total of 8676 patients were enrolled in ISAR or CHRONICLE as of 31 December 2021, with 5324 patients included in the main analysis. Overall, 3352 patients were excluded. The majority of these were due to lack of malignancy data (e.g., presence/absence of malignancy, malignancy status) and the date of non-benralizumab biologics initiation being before 01 November 2017.

Among the 5324 patients in main analysis, there were 825 patients in the benralizumab cohort, 2410 patients in the non-benralizumab biologics cohort, and 2328 patients in the non-biologic cohort. More than half of the study population were aged between 40 to 64 years which was consistent across all cohorts. The majority of patients from the study population were white and were female across the cohorts. The overall PY of follow-up in this IA is 11948.8 as of 31 December 2021, with the follow-up for the benralizumab cohort at 1766.5 PY, the non-benralizumab biologics cohort at 6004.8 PY, and the non-biologic cohort at 4177.5 PY. At baseline, asthma-related comorbidities such as allergic rhinitis and chronic rhinosinusitis (excluding allergic rhinitis and nasal polyps) were generally comparable across the cohorts. The benralizumab cohort had a higher rate of comorbid obesity, diabetes, hypertension, and COPD which can be risk factors for cancer. Other baseline comorbidities were not generally comparable, e.g., atopic disease 42.8% in benralizumab cohort compared to 69.1% in non-biologic cohort. Differences in baseline comorbidities and characteristics were adjusted across the cohorts in the analysis by means of PS weighting. The most commonly used asthma medication at baseline was ICS+LABA, although LTRA use was also common across the 3 cohorts.

At the time of this IA2 report, the primary analysis included a total of 27 new malignancy cases reported since index date (10 new malignancies were reported in first IA report). The incidence of malignancies is low (6 [0.7%], 8 [0.3%], and 13 [0.6%] in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort, respectively) in all comparison groups.

Before PS adjustment, the crude incidence rate per 1000 PY in the benralizumab cohort, the non-benralizumab biologics cohort, and the non-biologic cohort were 3.4, 1.3, and 3.1, respectively. Incidence rates have generally increased in analysis sets for ISAR and for CHRONICLE and in all cohorts from IA1, most noticeably in the benralizumab and non-biologic cohorts. Rate ratios between benralizumab and non-benralizumab biologics have increased from IA1, but decreased between benralizumab and non-biologic cohorts. There is no significant difference noted in risk between the cohorts, with the 95% CI for rate

differences between benralizumab and the other 2 cohorts including zero for all crude and adjusted comparisons.

11.2 Limitations

Missing data: a large number of patients are excluded as they have missing data on whether they had a record of malignancy (binary variable). This may impact the overall rates: if a higher proportion of patients without a malignancy are being excluded due to missing data, this would show a higher rate of malignancy overall in each respective group. To mitigate the impact of this limitation, contributing sites are being followed up to complete the missing data to allow for inclusion of these patients in the study.

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

Data collection: certain data is not provided in the ISAR database, namely discontinuation or withdrawal from the registry and deaths for reasons other than serious infection, anaphylaxis, or malignancy. This may result in a longer average follow-up time for patients in the ISAR database, as follow-up time is calculated from index date to the earliest date of death, withdrawal, lost-to-follow-up or data cut-off (31 December 2021). Information on the number of baseline hospitalisations, emergency department visits, and non-invasive ventilations is also not available for ISAR in the current analysis, and the total counts for these events are under-reported. Improved data collection is being addressed by OPC and it is expected that this information may be available for future analyses.

Misclassification: the average follow-up in this study is only 2.1 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.

Unmeasured confounders (residual confounding) will always exist in observational studies. Laboratory results and spirometry related variables had a high proportion of missing data. These are possibly unmeasured confounders and their impact on the analysis in this study cannot be evaluated at this point. There may be other factors related to treatment and malignancy but not measured and captured in this study.

11.3 Interpretation

The current evidence does not suggest an increase in risk of malignancy in patients receiving benralizumab compared with those receiving non-benralizumab 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, these findings could be generalisable to the target patient population for benralizumab and non-benralizumab biologics. However, inferences need to be made with caution.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

The pre-defined analyses, which included both crude and adjusted analyses, do not show evidence of a difference in the underlying risk of malignancies in patients receiving benralizumab compared to those receiving non-benralizumab biologics or non-biologic therapy. However, given the small number of new malignancies and limited follow-up time, the results of this IA should be interpreted with caution.

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Appendix A List of stand-alone documents

Table 19 List of stand-alone documents.

Number	Document reference number	Date	Title
1	16.1.1	[redacted]	Protocol amendment
2	16.1.3	[redacted]	CHRONICLE study informed consent form
3	16.1.9	[redacted]	Statistical analysis plan

Appendix B Additional information

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