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

Study dates: Initiation of Data Extraction: 26 Feb 2021
Final Analytic Dataset: 05 Apr 2024

Phase of development: Post Authorisation Safety Study

Study Sponsor: AstraZeneca

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study site(s)

Data from the International Severe Asthma Registry (ISAR) and an AZ sponsored United States Severe Asthma Study (CHRONICLE) was pooled for this study. This data sources included patients recruited from Argentina, Belgium, Bulgaria, Canada, Colombia, Denmark, Estonia, France, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, the United Arab Emirates, United Kingdom, and United States.

Publications

None at the time of writing this report.

Objectives

Study Objectives are provided in Table S1.

Table S1 Objectives

Objectives*
Primary
• 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
• To describe the clinical characteristics of new malignancy cases that develop in severe asthma patients and relevant subgroups
*Additional sensitivity analyses for the primary objectives are not included in this synopsis but can be found in the clinical study report.

Study design

This was a real world, observational, cohort study in patients with severe asthma recruited into ISAR and CHRONICLE and followed up to assess the occurrence of new malignancies. Study population included three cohorts: severe asthma patients receiving benralizumab; severe asthma patients receiving non-benralizumab biologics; and severe asthma patients not receiving biologics. The main analysis in the final report includes data that was accrued between 01 November 2017 and 31 December 2023.

Target subject population and sample size

Severe asthma patients were defined as those receiving treatment consistent with Global Initiative for Asthma (GINA) Step 5 or who were uncontrolled on GINA Step 4 treatment regimens.

Collectively, ISAR and CHRONICLE recruited 21852 patients with severe asthma from countries contributing malignancy data by the end of 2023. Of these, 12493 patients met all of the eligibility criteria, with a combined follow-up time of 43434.8 PY (7749.1 PY for the benralizumab biologics cohort, 21054.1 PY for the non-benralizumab biologics cohort, and 14631.6 PY for the non-biologic cohort).

The follow-up data provided in this final report has met the sample size calculations as stated in the CSP for the overall cohort (43434.8 PY achieved compared with the 39500 PY estimated in the CSP). The follow-up data also meets the estimated sample size calculations for the benralizumab cohort (7749.1 PY achieved compared with 5900 PY estimate in the CSP) and the non-benralizumab biologics cohort (21054.1 PY achieved compared with the 17900 PY estimate in the CSP).

Statistical methods

The main analysis was conducted on pooled ISAR and CHRONICLE data.

An inverse probability of treatment weighting approach with propensity score (PS) was used to balance the three cohorts in terms of baseline characteristics to account for confounding. The PS model was adjusted for the following baseline covariates: age, sex, BMI, smoking status, comorbid conditions (allergic rhinitis, cardiovascular disease, liver disease, COPD, chronic rhinosinusitis, diabetes, and nasal polyps), asthma medications (LABA, LAMA, theophylline, LTRA, macrolide antibiotics and steroid sparing agents), steroid use (including maintenance OCS, ICS and ICS + LABA use), previous serious infection, previous anaphylaxis, previous chemotherapy as well as history of malignancy.

Incidence rates per 1000 person-years (PY) were calculated for severe asthma patients receiving benralizumab and compared with patients with severe asthma receiving non-benralizumab biologics and patients with severe asthma not receiving biologics. Poisson regression models were used to estimate the incidence rate, difference in incidence rate, incidence rate ratio and corresponding 95% CIs. For adjusted estimates, Poisson regression models controlled for cohort, age, sex, region, smoking and BMI. All incidence rates were reported as new malignancies incidence rates per 1000 PY

Study population

Among the 12493 patients in the main analysis, there were 2531 patients in the benralizumab cohort, 5834 patients in the non-benralizumab biologics cohort, and 4927 patients in the non biologic cohort. The overall PY of follow-up in this report is 43434.8, with the follow-up for the benralizumab cohort at 7749.1 PY, the non benralizumab biologics cohort at 21054.1 PY, and the non-biologic cohort at 14631.6 PY.

Of the 12493 patients included in the main analysis, a total of 5.1% (639/12493) 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, most of the discontinuation data are for patients in the CHRONICLE study

Within the cohorts, the proportion of patients who discontinued were 5.5% (140/2531) in the benralizumab cohort, 4.9% (285/5834) in the non-benralizumab biologics cohort, and 5.2% (254/4927) in the non-biologic cohort.

More than half of the study population (55.5% [6939/12493]) were aged ≥ 40 to < 65 years, which was consistent across all cohorts. The majority of patients from the overall study population were White (62.2% [7766/12493]) and were female (64.1% [8004/12493]). Most patients in the biologic cohorts (1781 [70.4%] and 4024 [69.0%] in the benralizumab and non-benralizumab biologics cohorts, respectively), and half of the patients (2504 [50.8%]) in the non-biologic cohort were White.

Summary of safety results

The crude and adjusted incidence rates for new malignancies are given in Table S2. Overall, the crude incidence rates were low across all populations.

Table S2: 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 = 2531) versus Other-biologic cohort (N = 5834)	17 (0.7) versus 34 (0.6)	7707.81 versus 20979.96	2.2 (1.37, 3.55) versus 1.6 (1.16, 2.27)	0.6 (-0.60, 1.77)	NC	NC
	Benralizumab cohort (N = 2531) versus Non-biologic cohort (N = 4927)	17 (0.7) versus 24 (0.5)	7707.81 versus 14566.51	2.2 (1.37, 3.55) versus 1.6 (1.10, 2.46)	0.6 (-0.68, 1.80)	NC	NC
Without NMSC	Benralizumab cohort (N = 2531) versus Other-biologic cohort (N = 5834)	16 (0.6) versus 27 (0.5)	7710.78 versus 20995.12	2.1 (1.27, 3.39) versus 1.3 (0.88, 1.88)	0.8 (-0.34, 1.92)	NC	NC
	Benralizumab cohort (N = 2531) versus Non-biologic cohort (N = 4927)	16 (0.6) versus 21 (0.4)	7710.78 versus 14575.29	2.1 (1.27, 3.39) versus 1.4 (0.94, 2.21)	0.6 (-0.55, 1.82)	NC	NC
Adjusted [b]							
Overall	Benralizumab cohort (N = 2215) versus Other-biologic cohort (N = 5287)	15 (0.7) versus 30 (0.6)	6737.71 versus 18999.17	1.3 (0.88, 1.87) versus 1.1 (0.74, 1.56)	0.2 (-0.28, 0.70)	1.2 (0.79, 1.81)	0.3972
	Benralizumab cohort (N = 2216) versus Non-biologic cohort (N = 4253)	15 (0.7) versus 24 (0.6)	6754.37 versus 12412.32	1.8 (1.28, 2.57) versus 1.7 (1.18, 2.51)	0.1 (-0.63, 0.82)	1.1 (0.70, 1.59)	0.7921

					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 = 2215) versus Other-biologic cohort (N = 5287)	15 (0.7) versus 24 (0.5)	6737.71 versus 19011.25	1.3 (0.88, 1.90) versus 0.9 (0.57, 1.30)	0.4 (-0.05, 0.92)	1.5 (0.97, 2.33)	0.0673
	Benralizumab cohort (N = 2216) versus Non-biologic cohort (N = 4253)	15 (0.7) versus 21 (0.5)	6754.37 versus 12421.10	1.9 (1.32, 2.63) versus 1.6 (1.11, 2.40)	0.2 (-0.49, 0.96)	1.1 (0.75, 1.74)	0.5290

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

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

[b] The estimate of adjusted incidence rates, rate ratio, rate differences and corresponding 95% CIs for each comparison are calculated using a weighted Poisson regression model. The weight used in the model is the inverse PS (1/PS for benralizumab cohort, 1/(1-PS) 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.

The subgroup was decided based on ICD 10 code if skin cancer was not defined as non-melanoma.

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 S3.

There was no statistically significant increase in risk of new malignancy in each comparison of the benralizumab cohort with non-benralizumab biologics and non-biologic cohorts was observed. Hazard ratios (95% CI) for the overall comparisons of benralizumab with non-benralizumab biologics and non-biologic cohorts were 1.1 (0.76 – 1.74) and 1.0 (0.68 – 1.56) respectively, indicating no statistically significant difference in risk of new malignancy in each comparison.

Table S3 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 = 2215) versus Other-biologic cohort (N = 5287)	15 (0.7) versus 30 (0.6)	1.1	(0.76, 1.74)
	Benralizumab cohort (N = 2216) versus Non-biologic cohort (N = 4253)	15 (0.7) versus 24 (0.6)	1.0	(0.68, 1.56)
Without NMSC	Benralizumab cohort (N = 2215) versus Other-biologic cohort (N = 5287)	15 (0.7) versus 24 (0.5)	1.4	(0.92, 2.22)
	Benralizumab cohort (N = 2216) versus Non-biologic cohort (N = 4253)	15 (0.7) versus 21 (0.5)	1.1	(0.73, 1.70)

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

[c] The hazard ratio and 95% CI for each comparison are estimated using a weighted Cox regression model. The weights for the model are inverse PS (1/PS for benralizumab cohort, 1/(1-PS) 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.

The subgroup was decided based on ICD 10 code if skin cancer was not defined as non-melanoma.

Conclusion(s)

The primary finding in this report with the large data that has accrued, is that there has been no observed increase in risk of malignancies associated with benralizumab use. In the adjusted analysis (after adjustments for PS weighting, age, sex, BMI, region, and smoking status) in which benralizumab patients were compared with non-benralizumab biologics patients, the incident rate ratio (95% CI) was 1.2 (0.79 – 1.81). Similarly, in the adjusted analysis in which benralizumab patients were compared with non-biologic cohorts, the incident rate ratio (95% CI) was 1.1 (0.7 – 1.59). This finding was replicated in all the additional analysis, including a sensitivity analysis which included data for 21742 patients in the 3 cohorts (some patients contributed to more than one cohort) where the incidence rate ratio (95% CI) was 0.9 (0.65 – 1.18) comparing the benralizumab cohort with the non-benralizumab biologics cohort and 1.1 (0.78 – 1.48) in the benralizumab cohort versus non-biologic cohort comparison. The findings from this study are consistent with previously published data.

This study also provides estimates of the absolute risk (incidence rate) of malignancies among patients with severe asthma receiving benralizumab, non-benralizumab biologics and non-biologics. In unadjusted crude estimates, the incidence rate (95% CI) per 1000 PY of malignancies in this study was 2.2 (1.37 – 3.55), 1.6 (1.16 – 2.27), and 1.6 (1.10 – 2.46) for the benralizumab, non-benralizumab biologics and non-biologic cohorts, respectively.