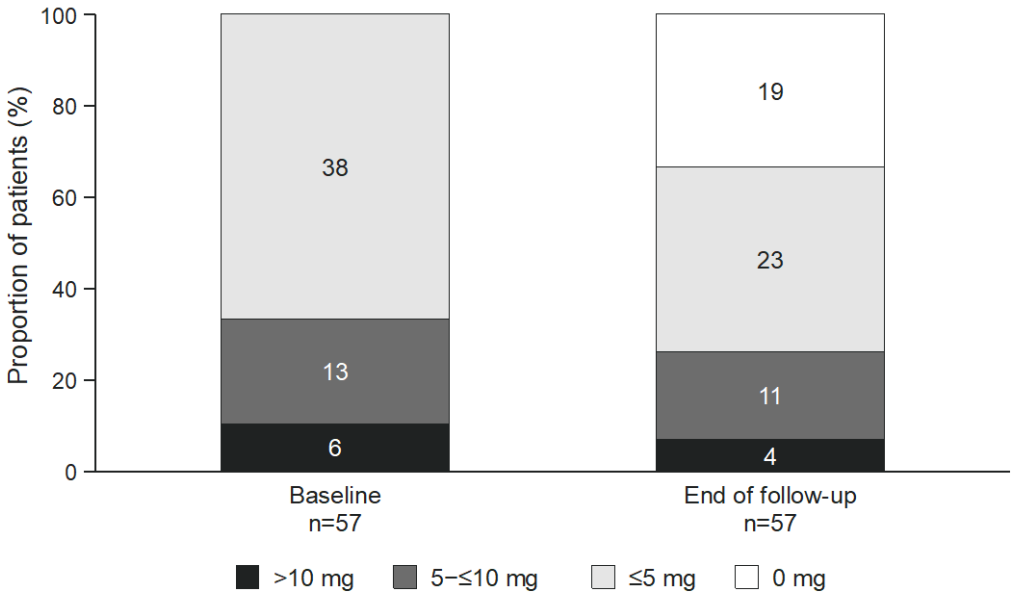
Supplementary Materials

Supplementary Figure 1 Changes in maintenance oral corticosteroid dose

Abbreviation: SD, standard deviation



	Baseline (n=57)	End of follow-up (n=57)
Mean (SD)	6.7 (4.2)	4.4 (4.6)
Min, Max	1.0, 20.0	0.0, 20.0
Median	5.0	4.2

Supplementary Table 1. Status of onset of adverse drug reactions/infections

	Safety population (n=632)
Patients with adverse drug reactions[a], n (%)	80 (12.7)
SOC/PT	**n (%)**
Infectious and parasitic diseases	9 (1.4)
Pneumonia	5 (0.8)
Gastroenteritis	1 (0.2)
Otitis media	1 (0.2)
Pharyngitis	1 (0.2)
Oral herpes	1 (0.2)
Allergic bronchopulmonary mycosis	1 (0.2)
Immune system disorder	2 (0.3)
Anaphylactic reaction	1 (0.2)
Atopy	1 (0.2)
Metabolism and nutrition disorders	1 (0.2)
Decreased appetite	1 (0.2)
Nervous system disorder	21 (3.3)
Headache	17 (2.7)
Guillain-Barre syndrome	1 (0.2)
Hypoesthesia	1 (0.2)
6th nerve paralysis	1 (0.2)
Taste disorder	1 (0.2)
Ear and labyrinth disorders	3 (0.5)
Eosinophilic otitis media	2 (0.3)
Ear discomfort	1 (0.2)
Cardiac disorders	1 (0.2)
Arrhythmia	1 (0.2)
Vascular disorders	1 (0.2)
Hot flash	1 (0.2)
Respiratory, thoracic and mediastinal disorders	19 (3.0)
Asthma	10 (1.6)
Epistaxis	2 (0.3)
Upper respiratory tract inflammation	2 (0.3)
Alveolar proteinosis	1 (0.2)
Cough	1 (0.2)
Dyspnea	1 (0.2)
Hemoptysis	1 (0.2)
Lung infiltration	1 (0.2)
Rhinorrhea	1 (0.2)
Oropharyngeal pain	1 (0.2)
Chronic eosinophilic rhinosinusitis	1 (0.2)
Respiratory symptom	1 (0.2)

Gastrointestinal disorders	6 (0.9)
Vomiting	2 (0.3)
Abdominal pain	1 (0.2)
Abdominal pain upper	1 (0.2)
Diarrhea	1 (0.2)
Oral discomfort	1 (0.2)
Stomatitis	1 (0.2)
Skin and subcutaneous tissue disorders	10 (1.6)
Rash	4 (0.6)
Angioedema	1 (0.2)
Dermatitis atopic	1 (0.2)
Drug eruption	1 (0.2)
Erythema annulare	1 (0.2)
Pruritus	1 (0.2)
Rash pruritic	1 (0.2)
Urticaria	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (0.5)
Musculoskeletal stiffness	2 (0.3)
Muscular weakness	1 (0.2)
General disorders and administration site conditions	24 (3.8)
Pyrexia	15 (2.4)
Malaise	5 (0.8)
Edema	2 (0.3)
Chest pain	1 (0.2)
Death	1 (0.2)
Edema peripheral	1 (0.2)
Injection site discomfort	1 (0.2)
Investigations	5 (0.8)
Eosinophil count increased	3 (0.5)
C-reactive protein increased	1 (0.2)
Weight increased	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)
Infusion related reaction	1 (0.2)

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[a] Defined as any adverse event causally related to benralizumab or for which a causal relationship with benralizumab was unknown due to insufficient or contradictory information.

Abbreviations: PT, preferred term; SOC, system organ class.

Supplementary Table 2. Summary of serious adverse events by system organ class and preferred term

	Safety population (n=632)
Patients with serious adverse events[a], n (%)	82 (13.0)
SOC/PT	**n (%)**
Infectious and parasitic diseases	24 (3.8)
Pneumonia	9 (1.4)
Bronchitis	4 (0.6)
Pneumonia aspiration	4 (0.6)
Gastroenteritis	2 (0.3)
Pneumonia bacterial	2 (0.3)
Influenza	1 (0.2)
Nasopharyngitis	1 (0.2)
Pneumonia pneumococcal	1 (0.2)
Sepsis	1 (0.2)
Psoas abscess	1 (0.2)
Respiratory tract infection	1 (0.2)
Post procedural infection	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)
Metastases to liver[b]	1 (0.2)
Rectosigmoid cancer stage IV[b]	1 (0.2)
Blood and lymphatic system disorders	1 (0.2)
Anemia	1 (0.2)
Immune system disorder	3 (0.5)
Anaphylactic reaction	2 (0.3)
Eosinophilic granulomatosis with polyangiitis	1 (0.2)
Metabolism and nutrition disorders	3 (0.5)
Decreased appetite	2 (0.3)
Marasmus	1 (0.2)
Nervous system disorder	6 (0.9)
Cerebral infarction	2 (0.3)
Dementia	1 (0.2)
Guillain-Barre syndrome	1 (0.2)
Subarachnoid hemorrhage	1 (0.2)
6th nerve paralysis	1 (0.2)
Cardiac disorders	3 (0.5)
Acute myocardial infarction	1 (0.2)
Myocardial infarction	1 (0.2)
Coronary artery dissection	1 (0.2)
Vascular disorders	1 (0.2)
Aortic aneurysm rupture	1 (0.2)
Respiratory, thoracic and mediastinal disorders	47 (7.4)
Asthma	44 (7.0)

Alveolar proteinosis	1 (0.2)
Atelectasis	1 (0.2)
Interstitial lung disease	1 (0.2)
Upper respiratory tract inflammation	1 (0.2)
Bronchial secretion retention	1 (0.2)
Gastrointestinal disorders	3 (0.5)
Gastrointestinal perforation	1 (0.2)
Intestinal obstruction	1 (0.2)
Large intestine perforation	1 (0.2)
Hepatobiliary disorders	1 (0.2)
Hepatic function abnormal	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)
Angioedema	1 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.3)
Muscular weakness	1 (0.2)
Immobilization syndrome	1 (0.2)
Renal and urinary disorders	1 (0.2)
Chronic kidney disease	1 (0.2)
General disorders and administration site conditions	2 (0.3)
Death	1 (0.2)
Malaise	1 (0.2)
Injury, poisoning and procedural complications	3 (0.5)
Fall	1 (0.2)
Multiple fractures	1 (0.2)
Road traffic accident	1 (0.2)
Face injury	1 (0.2)
Infusion-related reaction	1 (0.2)

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[a] An adverse event was defined as any undesirable or unintended signs, symptoms, and disease regardless of the causality with the administration of benralizumab.

[b] Rectosigmoid cancer and liver metastasis occurred in the same patient.

Abbreviations: PT, preferred term; SOC, system organ class.

Supplementary Table 3. Status of onset of adverse drug reactions by patient background factors

		Safety population (n=632)	Patients with adverse drug reactions[a] (n = 80)	Number of onsets of adverse drug reactions	Fisher's exact test p value
Sex	Male	243 (38.4)	32 (13.2)	53	0.8060
	Female	389 (61.6)	48 (12.3)	78	
Age (years)	<20	2 (0.3)	1 (50.0)	3	0.1973
	20 to <30	11 (1.7)	1 (9.1)	1	
	30 to <40	42 (6.6)	5 (11.9)	7	
	40 to <50	74 (11.7)	11 (14.9)	22	
	50 to <60	96 (15.2)	17 (17.7)	28	
	60 to <70	117 (18.5)	14 (12.0)	20	
	70 to <80	200 (31.6)	17 (8.5)	25	
	≥80	90 (14.2)	14 (15.6)	25	
Age (years)	<70	342 (54.1)	49 (14.3)	81	0.1876
	≥70	290 (45.9)	31 (10.7)	50	
Pre-treatment severity	Mild intermittent	7 (1.1)	1 (14.3)	2	0.9977
	Mild persistent	9 (1.4)	1 (11.1)	3	
	Moderate persistent	83 (13.1)	10 (12.0)	15	
	Severe persistent	344 (54.4)	45 (13.1)	74	
	Most severe persistent	185 (29.3)	23 (12.4)	37	
	Unknown	4 (0.6)	0	0	-
Disease duration (years)	<10	123 (19.5)	7 (5.7)	9	0.0257
	10 to <20	109 (17.2)	14 (12.8)	22	
	20 to <30	57 (9.0)	7 (12.3)	10	
	≥30	77 (12.2)	15 (19.5)	37	
	Unknown	266 (42.1)	37 (13.9)	53	-
BMI (kg/m^2)	<25.0	365 (57.8)	52 (14.2)	88	0.3663
	≥25.0	204 (32.3)	23 (11.3)	36	
	Not calculated	63 (10.0)	5 (7.9)	7	

Smoking habit	Current	29 (4.6)	4 (13.8)	5	0.8465
	Past	197 (31.2)	27 (13.7)	42	
	Never	372 (58.9)	46 (12.4)	79	
	Unknown	34 (5.4)	3 (8.8)	5	-
Atopic predisposition	Yes	275 (43.5)	41 (14.9)	64	0.2094
	No	290 (45.9)	32 (11.0)	57	
	Unknown	67 (10.6)	7 (10.4)	10	-
History of AERD	Yes	49 (7.8)	14 (28.6)	26	0.0011
	No	525 (83.1)	57 (10.9)	91	
	Unknown	58 (9.2)	9 (15.5)	14	-
Outpatient/inpatient	Outpatient	590 (93.4)	69 (11.7)	115	0.0109
	Inpatient	40 (6.3)	11 (27.5)	16	
	Unknown	2 (0.3)	0	0	-
Previous treatment for asthma[b]	Anti-IL5 antibody	114 (18.2)	16 (14.0)	28	-
	Anti-IgE antibody	48 (7.7)	7 (14.6)	15	
	Anti-IL4 receptor α antibody	5 (0.8)	2 (40.0)	2	
Comorbidities[b]	Yes	502 (79.4)	68 (13.5)	118	0.1763
	Rhinitis allergic	220 (43.8)	34 (15.5)	56	
	Chronic sinusitis	172 (34.3)	31 (18.0)	61	
	COPD	115 (22.9)	16 (13.9)	21	
	Eosinophilic otitis media	62 (12.4)	14 (22.6)	22	
	Nasal polyps	61 (12.2)	9 (14.8)	13	
	Reflux esophagitis	52 (10.4)	7 (13.5)	10	
	Eosinophilic rhinosinusitis	16 (3.2)	3 (18.8)	4	
	Renal disease	12 (2.4)	3 (25.0)	5	
	ABPA	10 (2.0)	1 (10.0)	1	
	Malignant tumor	9 (1.8)	0	0	
	EGPA	7 (1.4)	0	0	
	Atopic dermatitis	2 (0.4)	0	0	
	Hepatic disease	4 (0.8)	0	0	
	Hepatitis viral	4 (0.8)	2 (50.0)	6	

	Others	298 (59.4)	45 (15.1)	86	
	No	125 (19.8)	11 (8.8)	12	
	Unknown	5 (0.8)	1 (20.0)	1	-
Exacerbations that required systemic corticosteroid in the past 12 months[c]	Yes	442 (69.9)	59 (13.3)	96	0.3192
	No	151 (23.9)	15 (9.9)	22	
	Unknown	39 (6.2)	6 (15.4)	13	-
Number of treatments with systemic steroid or dose increases of oral steroid[c, d]	<3 times	300 (47.5)	34 (11.3)	54	0.2195
	≥3 times	197 (31.2)	30 (15.2)	50	
	Unknown	95 (15.0)	10 (10.5)	14	-
	Not reported	1 (0.2)	0	0	
Exacerbations resulting in emergency department visit in the past 12 months[e]	Yes	326 (51.6)	39 (12.0)	53	0.8025
	No	267 (42.2)	34 (12.7)	63	
	Unknown	39 (6.2)	7 (17.9)	15	-
Exacerbations resulting in hospital admission in the past 12 months	Yes	173 (27.4)	24 (13.9)	31	0.4928
	No	430 (68.0)	50 (11.6)	85	
	Unknown	29 (4.6)	6 (20.7)	15	-
Eosinophil count (/μL)	<150	159 (25.2)	16 (10.1)	24	0.5576
	150 to <300	60 (9.5)	8 (13.3)	16	
	≥300	266 (42.1)	36 (13.5)	64	
	Unknown	147 (23.3)	20 (13.6)	27	-
FeNO (ppb)	<37	135 (21.4)	16 (11.9)	23	0.5999
	≥37	148 (23.4)	21 (14.2)	41	
	Unknown	349 (55.2)	43 (12.3)	67	-
Serum total IgE level (IU/mL)	<150	121 (19.1)	10 (8.3)	19	0.0227
	≥150	215 (34.0)	37 (17.2)	63	

	Unknown	296 (46.8)	33 (11.1)	49	-
Biomarker subtype: Eosinophils ×FeNO	Eosinophil count <300/μL and FeNO <37 ppb	80 (12.7)	9 (11.3)	13	0.5901
	Eosinophil count <300/μL and FeNO ≥37 ppb	37 (5.9)	3 (8.1)	11	
	Eosinophil count ≥300/μL and FeNO <37 ppb	50 (7.9)	6 (12.0)	9	
	Eosinophil count ≥300/μL and FeNO ≥37 ppb	103 (16.3)	17 (16.5)	27	
	Unknown	362 (57.3)	45 (12.4)	71	-
Biomarker subtype: Eosinophils ×serum total IgE level	Eosinophil count <300/μL and serum total IgE level <150 IU/mL	66 (10.4)	5 (7.6)	8	0.1506
	Eosinophil count <300/μL and serum total IgE level ≥150 IU/mL	73 (11.6)	14 (19.2)	27	
	Eosinophil count ≥300/μL and serum total IgE level <150 IU/mL	54 (8.5)	5 (9.3)	11	
	Eosinophil count ≥300/μL and serum total IgE level ≥150 IU/mL	139 (22.0)	22 (15.8)	33	
	Unknown	300 (47.5)	34 (11.3)	52	-
FEV_1 (L)	<1.7	220 (34.8)	24 (10.9)	41	0.4253
	≥1.7	157 (24.8)	22 (14.0)	37	
	Unknown	255 (40.3)	34 (13.3)	53	-

Data are n (%).

[a] Defined as any adverse event causally related to benralizumab or for which a causal relationship with benralizumab was unknown due to insufficient or contradictory information.

[b] Details may overlap.

[c] Administration of systemic steroid (other than control drugs) for ≥3 days or increase of the maintenance dose of oral steroid for ≥3 days (a single administration of a systemic steroid depot preparation is considered equivalent to a 3-day administration) due to worsening of asthma within 1 year before the start of benralizumab.

[d] Patients reported as having no events were counted as having zero events.

[e] Emergency room or emergency outpatient visit requiring administration of systemic corticosteroids due to exacerbation of asthma up to 1 year before the start of treatment with benralizumab.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin.

Supplementary Table 4. Change from baseline in biomarkers

		Baseline	At 4 weeks	At 8 weeks	At 16 weeks	At 1 year	Last observation
Eosinophil count (/μL)	n	217	147	152	142	95	217
	Mean (SD)	642 (721)	5 (18)	6 (23)	13 (75)	23 (82)	13 (61)
	Min, Max	0, 5305	0, 149	0, 185	0, 851	0, 590	0, 590
	Median	422	0	0	0	0	0
Change from baseline	Mean (SD)	–	−682 (695)	−649 (774)	−633 (740)	−634 (687)	−629 (715)
	Min, Max	–	−3948, 73	−5301, 155	−5305, 201	−3226, 151	−5305, 151
	Median	–	−493	−431	−447	−402	−410
	95% CI	–	−796, −569	−773, −525	−755, −510	−774, −494	−725, −533
FeNO (ppb)	n	130	76	75	83	37	130
	Mean (SD)	65.6 (61.8)	71.4 (67.7)	62.5 (53.8)	59.6 (55.3)	35.3 (32.8)	52.5 (52.7)
	Min, Max	0, 278	5, 285	5, 227	6, 288	7, 164	5, 288
	Median	40.0	45.5	44.0	44.0	24.0	37.0
Change from baseline	Mean (SD)	–	9.4 (47.5)	−2.8 (46.8)	−4.2 (42.7)	−26.7 (49.4)	−13.1 (50.8)
	Min, Max	–	−142, 163	−161, 126	−136, 98	−153, 129	−200, 129
	Median	–	4.0	1.0	0.0	−13.0	−5.5
	95% CI	–	−1.5, 20.3	−13.6, 8.0	−13.5, 5.1	−43.1, −10.2	−22.0, −4.3
Serum total IgE level (IU/mL)	n	122	63	71	75	49	122
	Mean (SD)	821.6 (1685.1)	889.7 (1989.9)	941.8 (2147.3)	830.6 (1638.6)	783.2 (1069.2)	836.0 (1822.2)
	Min, Max	3.0, 11092.0	12.0, 14600.0	2.0, 14000.0	2.0, 12300.0	4.0, 4780.0	4.0, 14000.0
	Median	344.9	418.0	391.3	382.0	422.1	306.0
Change from baseline	Mean (SD)	–	−0.3 (993.2)	−2.9 (869.9)	−33.3 (981.4)	−115.5 (1382.2)	14.4 (1071.3)
	Min, Max	–	−5658.0, 5140.0	−5634.0, 4000.0	−6725.0, 3596.0	−9178.0, 1634.0	−9178.0, 4000.0
	Median	–	−8.0	−6.0	−11.0	4.7	−2.5
	95% CI	–	−250.5, 249.8	−208.8, 203.0	−259.1, 192.5	−512.5, 281.6	−177.6, 206.4

Patients in the effectiveness population who had data at baseline and at one or more time points from the start of treatment administration to the last observation.

Abbreviations: CI, confidence interval; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; SD, standard deviation.

Supplementary Table 5. Response rates of asthma control by Asthma Control Questionnaire-5 (ACQ-5) score

ACQ-5 at baseline		**n**	**Well-controlled ACQ score ≤0.75**	**Partly controlled ACQ score 0.75–1.5**	**Not well-controlled ACQ score ≥1.5**
ACQ <1.5	Baseline	49	21 (42.9)	28 (57.1)	0
	Week 4	37	23 (62.2)	10 (27.0)	4 (10.8)
	Week 8	37	26 (70.3)	10 (27.0)	1 (2.7)
	Week 16	31	19 (61.3)	9 (29.0)	3 (9.7)
	Year 1	19	13 (68.4)	5 (26.3)	1 (5.3)
	Last observation	49	33 (67.3)	12 (24.5)	4 (8.2)
ACQ ≥1.5	Baseline	139	0	0	139 (100.0)
	Week 4	111	17 (15.3)	35 (31.5)	59 (53.2)
	Week 8	106	31 (29.2)	28 (26.4)	47 (44.3)
	Week 16	98	34 (34.7)	20 (20.4)	44 (44.9)
	Year 1	53	19 (35.8)	11 (20.8)	23 (43.4)
	Last observation	139	42 (30.2)	25 (18.0)	72 (51.8)
ACQ-5 at baseline[a]		**n**	**Improved: reduced by ≥0.5 (Week 4/ Week 8/ Week 16/ Year 1/ last observation – baseline score)**		
ACQ <1.5	Week 4	26	15 (57.7)		
	Week 8	23	12 (52.2)		
	Week 16	20	11 (55.0)		
	Year 1	13	6 (46.2)		
	Last observation	33	16 (48.5)		
ACQ ≥1.5	Week 4	111	74 (66.7)		
	Week 8	106	84 (79.2)		
	Week 16	98	73 (74.5)		
	Year 1	53	44 (83.0)		
	Last observation	139	104 (74.8)		

Data are n (%).

[a] Patients in the effectiveness population who had data at baseline and at one or more time points from the start of treatment administration to the last observation. Patients with an initial ACQ score <0.5 were excluded.