

Characteristics of severe asthma patients on biologics; a real-life European registry study

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Supplementary Material

Table S1: missing variables in SHARP Central registry

	Number of missing	Percentage of missing
Trial participation (n)	152	12.3
Age (yrs)	3	0.2
Smoking History	1	0.08
Pack years	28	5.5
BMI	155	12.6
History of Frequent respiratory infections n(%)	146	11.9
Bronchiectasis	148	12.0
EGPA	145	11.8
Eosinophilic pneumonia	147	11.9
ABPA	146	11.9
OCS dosage	1	0.08
FEV1 preBD (%)	98	8.0
FVC preBD(%)	102	8.3

FEV1/FVC preBD (%)	186	15.1
Eosinophils (cell/μL)	24	1.9
FeNO (ppb)	285	23.1
ACQ 5	852	69.2

Figure S1: flow chart of the literature selection of RCTs for the evaluation of the main inclusion/exclusion criteria[1–10].

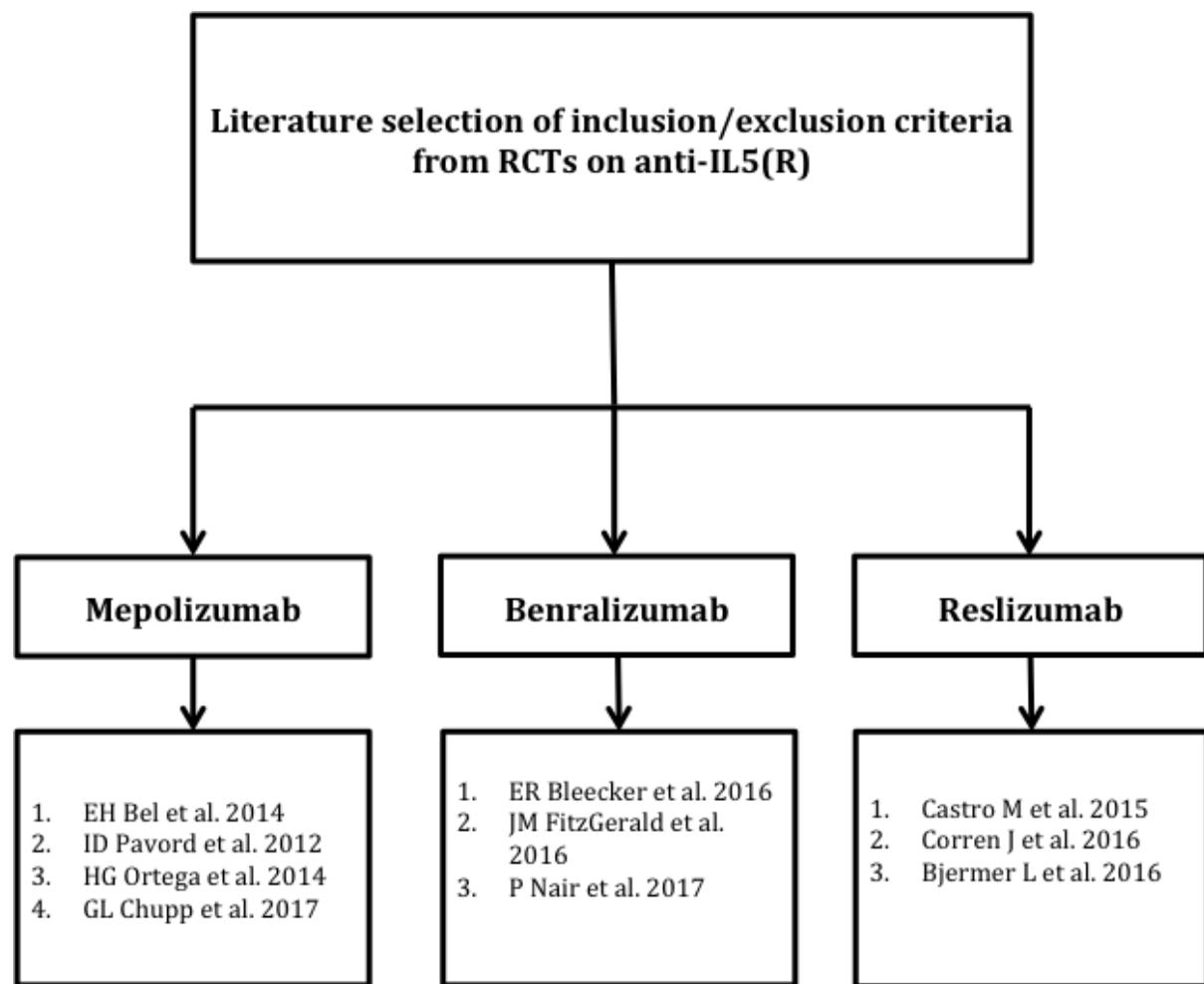


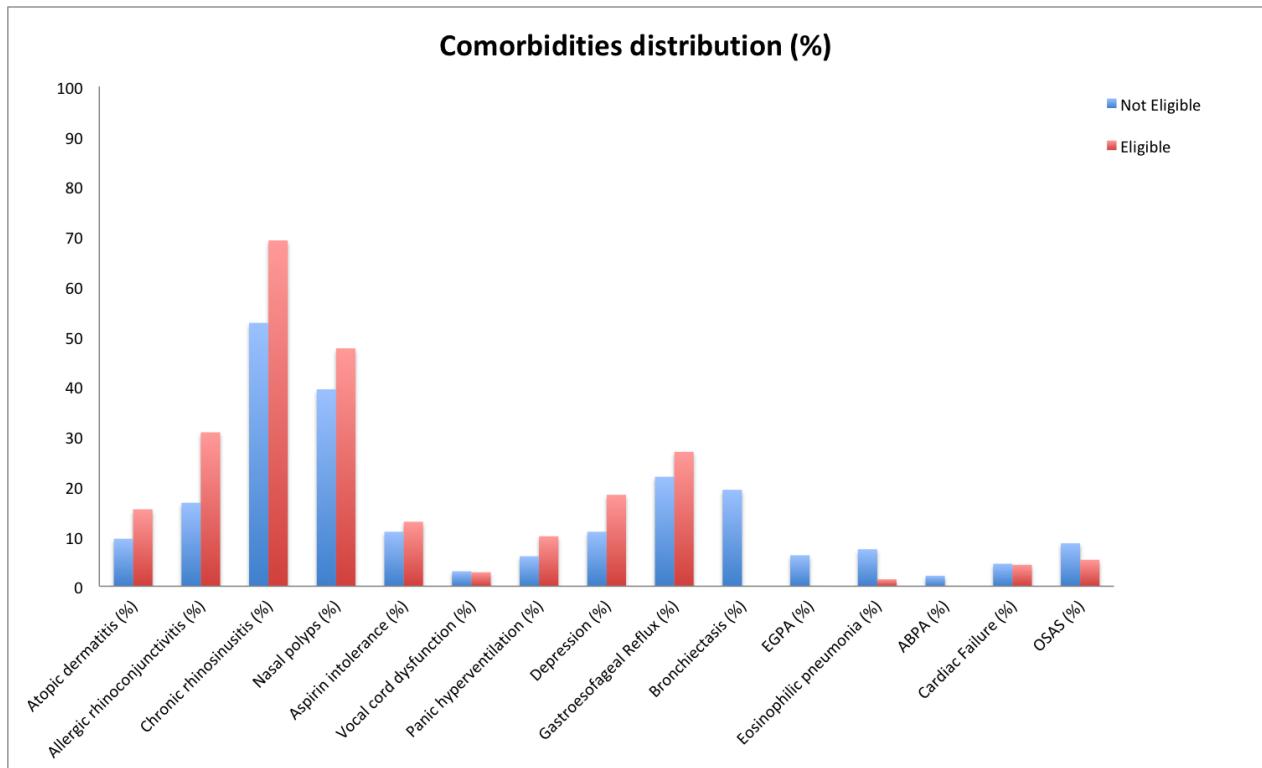
Table S2: List of trials' inclusion/exclusion criteria for the assessment of ineligibility[1–10].

	Mepolizumab				Benralizumab			Reslizumab		
Inclusion criteria	DREAM	SIRIUS	MENSA	MUSCA	SIROCCO	CALIMA	ZONDA	Castro M (2015)	Corren J (2016)	Bjermer L (2016)
Age ≥ 18 years to 65 years								□		□
Age ≥ 12 years to 75 years	□	□	□	□	□	□		□		□
Systemic Corticosteroids: Requirement for regular treatment with maintenance systemic corticosteroids (prednisone or equivalent)		□					□			
Inhaled Corticosteroids: High dose ICS usage	□	□	□	□	□	□	□	□	□	□
FEV1: Persistent airflow obstruction as indicated by a pre-bronchodilator FEV1 <80% predicted.	□	□			□		□			
Eosinophilic Asthma: Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma.	□	□	□	□	□	□	□	□		□
Compliance: related to inhaler therapy, OCS assumption, asthma daily diary							□			
Controller Medication: Usage of controller-medication (current usage of LABA, LTRA or theophylline for at least 3 months)	□	□	□	□	□	□				
At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained	□						□	□		
ACQ score of at least 1.5.					□			□	□	□
Weight: > 45 kg	□	□	□	□	□					
Asthma: Evidence of asthma indicated by airway reversibility, hyperresponsiveness or airway variability.	□	□	□	□			□	□	□	□
Exclusion criteria										
Smoking history: Current smokers or former smokers (> 6 months)	□	□	□	□	□	□	□	□	□	
Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma.	□	□	□	□	□	□	□	□	□	□
Malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior screening		□	□	□						

Liver Disease: Unstable liver disease		□	□	□	□	□	□			
Cardiovascular: Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment.		□	□	□	□	□	□			
Other Concurrent Medical Conditions: Subjects who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.	□	□	□	□	□	□	□	□	□	□
Eosinophilic Diseases: Subjects with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophagitis. Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also to be excluded.	□	□	□	□	□	□	□	□	□	□
Immunodeficiency: A known immunodeficiency (e.g. human immunodeficiency virus - HIV), other than that explained by the use of corticosteroids taken as therapy for asthma.	□	□	□	□				□	□	□
Other Monoclonal Antibodies: Subjects who have received any monoclonal antibody (other than Xolair)	□	□	□	□				□	□	□
Investigational Medications: Subjects who have received treatment with an investigational drug within the past 30 days or with other investigational biologics	□	□	□	□				□	□	
Pregnancy: Subjects who are pregnant or breastfeeding.	□	□	□	□				□	□	□
Hypersensitivity: Subjects with a known allergy or intolerance to a monoclonal antibody or biologic.	□	□	□	□						
Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse within 2 years		□	□	□						
Adherence: Subjects who have known evidence of lack of adherence to controller	□	□	□	□						□

medications and/or ability to follow physician's recommendations.								
Acute upper or lower respiratory infections	☒				☒	☒	☒	☒
Patient is currently using systemic corticosteroids (includes use of oral corticosteroids).	☒						☒	☒
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 times the upper limit of normal (ULN) confirmed during screening period						☒		
The patient has presence of or suspected parasitic infestation/infection.	☒						☒	
Patients may not have received any live attenuated vaccine within the 12-week period before study entry.							☒	

Figure S2: Comorbidities distribution in the eligible and not eligible severe asthma anti-IL5(R) starters in SHARP Central. EGPA: Eosinophilic granulomatosis with polyangiitis; ABPA: Allergic bronchopulmonary aspergillosis; OSAS: Obstructive sleep apnea syndrome.



Comparison of baseline severe eosinophilic asthma patients' characteristics commenced on anti-IL5(R) and baseline characteristics of severe eosinophilic asthma patients recruited in RCTs

Table S3: Comparison between patients' characteristics from mepolizumab trials and SHARP. BMI: Body Mass Index; OCS: oral corticosteroids; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Mepolizumab				SHARP
	SIRIUS	DREAM	MENSA	MUSCA	
N	135	616	576	551	1231
Age mean (SD)	49.9 (12.34)	48.6 (11.28)§	50.1 (14.28)§	51(13.52)§	56.5(13.20)
Gender (F n)	74	387	329§	325§	602
BMI mean(SD)	28.66 (6.01)§	28.5(5.95)§	27.77(5.83)	28.2 (6.4)§	27.8 (5.49)
OCS (mg) mean(SD)	12.8 (6.73)§	17.4 (16.77)§	13.2 (11.89)§	13.0 (10.84)§	4.78 (8.87)
FEV1 preBD(L) mean(SD)	1.89 (0.75)	1.88 (0.66)§	1.82 (0.67)§	1.74 (0.62)§	2.21 (0.87)
FEV1 preBD (%) mean(SD)	57 (18.1)§	57.7(15.8)§	56.7(15.48)§	55.4(14.46)§	72.95 (22.11)
FEV1/FVC preBD(L) mean(SD)	0.61(0.12)	0.63(0.14)	0.63(0.12)	0.58 (0.11)	0.60 (0.13)
ACQ 5 mean (SD)	2.07(1.22)	2.35(1.05)	2.22(1.20)	2.19(1.13)	1.96 (1.22)
LABA (n (%))	21 (15.6) §	590 (95.8)	85 (14.8) §	547 (99.3)§	1187 (94.4)
LAMA (n (%))	26 (19.3)	45 (7.3) §	85 (14.8)§	114 (20.7)	468 (38)
LTRA (n (%))	57 (42.2)§	160 (26)	280 (48.6)§	222 (40.3)	325 (26.4)

Table S3.1: Comparison between patients' characteristics from mepolizumab trials and eligible mepolizumab starters in SHARP Central. BMI: Body Mass Index; OCS: oral corticosteroids; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Mepolizumab				SHARP Mepolizumab eligible
	SIRIUS	DREAM	MENSA	MUSCA	
N	135	616	576	551	24
Age mean (SD)	49.9 (12.34)	48.6 (11.28)	50.1 (14.28)§	51(13.52)§	49.9 (13.4)
Gender (F n)	74	387§	329	325§	13
BMI mean(SD)	28.66 (6.01)	28.5(5.95)	27.77(5.83)	28.2 (6.4)	28.3 (4.14)
OCS (mg) mean(SD)	12.8 (6.73)§	17.4 (16.77)§	13.2 (11.89)§	13.0 (10.84)§	7.54 (6.02)
FEV1 preBD(L) mean(SD)	1.89 (0.75)§	1.88 (0.66)§	1.82 (0.67)§	1.74 (0.62)§	2.10 (0.85)
FEV1 preBD (%) mean(SD)	57 (18.1)§	57.7(15.8)§	56.7(15.48)§	55.4(14.46)§	68.2(25.31)
FEV1/FVC preBD(L) mean(SD)	0.61(0.12)	0.63(0.14)	0.63(0.12)	0.58 (0.11)§	0.60 (0.14)
ACQ 5 mean (SD)	2.07(1.22)	2.35(1.05)§	2.22(1.20)	2.19(1.13)	2.26 (1.16)
LABA (n (%))	21 (15.6)§	590 (95.8)	85 (14.8) §	547 (99.3)	24 (100.0)
LAMA (n (%))	26 (19.3)	45 (7.3) §	85 (14.8)§	114 (20.7)	8 (33.4)
LTRA (n (%))	57 (42.2)	160 (26)	280 (48.6)§	222 (40.3)	5 (20.8)

Table S4: Comparison between patients' characteristics from benralizumab trials and SHARP. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Benralizumab			SHARP
	SIROCCO	CALIMA	ZONDA	
N	1204	1306	220	1231
Age mean (SD)	48.8 (14.03)§	49.3(14.4)§	51(11.3)	56.5(13.20)
Gender (M/F)	408/796§	499/807	85/135§	602/629
BMI mean(SD)	28.8(6.8)§	28.8(6.6)§	29.6(6.2)§	27.8 (5.49)
FEV1 preBD(L) mean(SD)	1.66 (0.57)§	1.76(0.63)§	1.85 (0.68)	2.21 (0.87)
FEV1 preBD (%) mean(SD)	56.7(14.6)§	58.3(14.9)§	59.5(17.5)§	72.95 (22.11)
FEV1/FVC preBD (%) mean(SD)	61(13)§	61(13)§	60(13)§	71.98(24.77)
ACQ 5 mean (SD)	2.81(0.93)§	2.71(0.92)§	2.6(1.1)	1.96 (1.22)
LABA (n (%))	1204 (100)	1300 (99.5)	NA	1187 (94.4)
LAMA (n (%))	101 (8.4)§	106 (8.1)§	NA	468 (38)
LTRA (n (%))	431 (35.8)	363 (27.8)	82 (37.3)§	325 (26.4)

Table S4.1: Comparison between patients' characteristics from benralizumab trials and eligible Benralizumab starters in SHARP Central. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; LABA: Long-acting beta-agonists; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonists. § p or q value < 0.05.

	Benralizumab			SHARP Benralizumab eligible
	SIROCCO	CALIMA	ZONDA	
N	1204	1306	220	100
Age mean (SD)	48.8 (14.03)	49.3(14.4)	51(11.3)	50.7(16.32)
Gender (M/F)	408/796	499/807	85/135	20/80
BMI mean(SD)	28.8(6.8)	28.8(6.6)	29.6(6.2)	28.0(5.37)
FEV1 preBD(L) mean(SD)	1.66 (0.57)	1.76(0.63)	1.85 (0.68)	1.80 (0.59)
FEV1 preBD (%) mean(SD)	56.7(14.6)	58.3(14.9)	59.5(17.5)	56.9 (14.70)
FEV1/FVC preBD (%) mean(SD)	61(13)§	61(13)§	60(13)§	54.64(11.87)
ACQ 5 mean (SD)	2.81(0.93)	2.71(0.92)	2.6(1.1)	2.37 (1.42)
LABA (n (%))	1204 (100)	1300 (99.5)	NA	97 (97)
LAMA (n (%))	101 (8.4)§	106 (8.1)§	NA	61 (61)
LTRA (n (%))	431 (35.8)	363 (27.8)	82 (37.3)§	43 (43)

Table S5: Comparison between patients' characteristics from benralizumab trials and SHARP. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists. § p or q value < 0.05.

	Reslizumab			SHARP
	Castro M	Corren J	Bjermer	
N	953	496	315	1231
Age mean (SD)	46.8 (14)§	44.9 (12.27)§	43.9 (14.42)§	56.5(13.20)
Gender (M/F)	356/597	181/315	132/183§	602/629
BMI mean(SD)	27.5 (5.7)	32.2 (8.33)§	27.6 (6.51)	27.8 (5.49)
FEV1 preBD(L) mean(SD)	1.99(0.75)§	2.12 (0.68)	NA	2.21 (0.87)
FEV1 preBD (%) mean(SD)	66.7(19.7)	66.7(16.1)	NA	72.95 (22.11)
ACQ 5 mean (SD)	2.65(0.85)§	2.56(0.69)§	NA	1.96 (1.22)
Blood eosinophils (cell/mCL) mean(SD)	654(629)	280(240.1)	NA	320.1 (259.58)
ICS dose (mcg/day) mean(SD)	821.5(436.7)	NA	NA	774.8 (621.3)
LABA (n (%))	803 (84.3)§	387 (78) §	245 (77.8) §	1187 (94.4)

Table S5.1: Comparison between patients' characteristics from reslizumab trials and eligible reslizumab starters in SHARP Central. BMI: Body Mass Index; FEV1: Forced Expiratory Volume in the 1st second; preBD: pre-bronchodilator; ACQ: Asthma Control Questionnaire; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists. § p or q value < 0.05.

	Reslizumab			SHARP Reslizumab eligible
	Castro M	Corren J	Bjermer	
N	953	496	315	52
Age mean (SD)	46.8 (14)§	44.9 (12.27)§	43.9 (14.42)§	53.2(12.56)
Gender (M/F)	356/597	181/315	132/183§	29/23
BMI mean(SD)	27.5 (5.7)	32.2 (8.33)§	27.6 (6.51)	28.2 (5.33)
FEV1 preBD(L) mean(SD)	1.99(0.75)§	2.12 (0.68)	NA	2.24 (0.87)
FEV1 preBD (%) mean(SD)	66.7(19.7)§	66.7(16.1)§	NA	72.84 (23.05)
ACQ 5 mean (SD)	2.65(0.85)§	2.56(0.69)	NA	2.16 (1.36)
Blood eosinophils (cell/mCL) mean(SD)	654(629)	280(240.1)§	NA	731.6 (434.71)

ICS dose (mcg/day) mean(SD)	821.5(436.7)§	NA	NA	1473.2 (622.9)
LABA (n (%))	803 (84.3)§	387 (78) §	245 (77.8) §	52 (100)

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