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Early View

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Randomised Controlled Trials in Severe Asthma: Selection by Phenotype or Stereotype

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TB, TJ, AC and PH contributed to the literatures search, study design, data collection, data analysis, data interpretation and writing of this manuscript. KG, CB and SE contributed to the data collection, data analysis and the writing of this manuscript. All other members of the Wessex Severe Asthma Cohort Team contributed to the data collection.

Take home message
RCTs of biological therapies in severe asthma are poorly generalisable with most patients excluded by outmoded disease concepts despite possessing the trait addressed by the treatment, leading to a paucity of evidence upon which to base guidelines.

Randomised Controlled Trials in Severe Asthma: Selection by Phenotype or Stereotype

Abstract:

Background: Previous publications have highlighted the disparity between research trial populations and clinical practice but it is not established how this relates to randomised controlled trials (RCTs) of phenotype targeted biological therapies in severe asthma.

Methods: Detailed characterisation data for 342 severe asthma patients within the Wessex Severe Asthma Cohort (WSAC) was compared against comprehensive trial eligibility criteria for published phase IIB and III RCTs evaluating biological therapies in severe asthma since 2000.

Results: 37 RCTs evaluating 20 biological therapies were identified. Only 9.8% (median; range 3.5%-17.5%) of severe asthma patients would have been eligible for enrolment in the phase III trials. Stipulations for airflow obstruction, bronchodilator reversibility and smoking history exclude significant numbers of patients. 78.9% (median; range 73.2%-86.6%) of patients with severe eosinophilic asthma would have been excluded from participation in the phase III licensing trials of IL-5/5R targeted therapies.

Conclusion: Despite including only well characterised and optimally treated severe asthmatics under specialist care within the Wessex Severe Asthma Cohort study, the vast majority were excluded from trial participation by criteria designed to re-confirm diagnostic labels rather than by biomarker criteria that predict the characteristic addressed by the treatment.

Introduction:

Asthma affects over 300 million people worldwide with an estimated total annual cost in the UK approaching £5 billion.[1, 2] Whilst the majority of people with asthma can be treated effectively with inhaled corticosteroids and bronchodilators, 5-10% with severe asthma suffer persistent symptoms, frequent exacerbations and an accelerated decline in lung function despite treatment.[3] Severe asthma is significantly more expensive with increased healthcare resource usage and high-cost medications accounting for much of this additional cost.[4]

Cohort studies and cluster analyses have advanced our understanding of severe asthma, establishing it to be a heterogeneous condition encompassing multiple phenotypes with underlying endotypes,[5–9] defined by specific pathobiological pathways, that underpin the manifestations of the disease. To address the significant unmet clinical need in severe asthma, there has been a focus since the turn of the millennium on developing biological therapies to target specific components of these inflammatory pathways (predominantly in those with type 2 inflammation).[10] These targeted interventions are recognised as an important step towards personalised medicine for patients with severe asthma. However, such treatments are expensive mandating their use is rationalised by high-quality clinical evidence of efficacy and effectiveness and the use of biomarkers to stratify patients and determine those most likely to benefit from treatment.

Recent expert commentary has proposed less emphasis be placed on historical definitions of asthma with a focus on 'treatable traits' to identify clinical trial populations who are most likely to benefit from an intervention, highlighting that most randomised controlled trials (RCTs) study populations that are poorly generalisable to clinical practice.[11, 12] Previous studies have shown that only 3.3-6% of patients with asthma fulfilled the eligibility criteria for the clinical trials upon which asthma guidelines are based.[13, 14] However, these studies did not focus on patients with severe asthma

under specialist care or biological therapies targeting specific asthma phenotypes and thus it is unclear whether a similar impact on the generalisability of trial data exists.

We have therefore aligned the data from a large well characterised cohort of severe asthma patients, the Wessex Severe Asthma Cohort (WSAC), with the clinical trial eligibility criteria of published RCTs assessing biological therapies in severe asthma to investigate this. Additionally we have compared the profile of the WSAC with published data from other severe asthma cohorts to evaluate how representative this cohort is of the broader severe asthma population, so that the implications of these findings can be fully appreciated.

Methods:

Study Design
The Wessex Severe Asthma Cohort (WSAC) is an observational, cross-sectional study providing detailed characterisation of severe asthma patients recruited from specialist severe asthma clinics at Portsmouth and Southampton Hospitals between April 2009 and January 2014. Study participants had asthma confirmed by a Specialist in accordance with the BTS/SIGN guidelines 2009 which remained poorly controlled with persisting symptoms and exacerbations despite treatment with high-dose inhaled corticosteroids (or maintenance systemic corticosteroids) and a long acting beta-2 agonist and/or alternative controller medications (equivalent to step 4 or step 5 of GINA management guidelines for asthma 2017) and focused management of any co-morbid conditions (full inclusion criteria are included in on-line supplement).[15]

Characterisation Protocol
All participants underwent a detailed characterisation protocol including clinical, physiological, and biological assessments (full details are included in on-line supplement). The study was funded by the UK MRC/NIHR Patient Research Cohorts Initiative and was conducted in accordance with the International Conference on Harmonisation and Good Clinical Practice standards and the ethical principles outlined in the Declaration of Helsinki. Independent ethics committee approval was obtained (MREC No. 09/H0502/37) and all participants provided written informed consent prior to study participation.

Identification of Trials and Eligibility Analysis
A systematic search was used to identify all Phase IIB and III RCTs studying novel treatments in severe asthma between January 2000 and January 2018. Abstracts were reviewed and primary publications sought for relevant RCT's (reference lists of these publications were also reviewed). Key eligibility criteria were extracted from primary publications, published trial protocols, and clinical trial databases where available. Each patient from WSAC was assessed against the eligibility criteria for each trial to determine the numbers that would have been deemed suitable for enrolment and key criteria excluding patients from trial participation were reviewed. Criteria were divided into diagnostic criteria (e.g. airflow obstruction and reversibility) and biomarker criteria (e.g. peripheral blood eosinophil count) with the latter used to identify a specific disease phenotype. Where relevant data was not available it was assumed patients remained eligible with the exception of studies mandating sputum eosinophilia where failure of sputum production precluded enrolment. In addition each patient was assessed against the National Institute for Health and Care Excellence (NICE) treatment recommendations for biological therapies currently licensed for use in asthma in the UK. The primary outcome was the proportion of patients eligible for each of the RCTs identified.

Role of the Funding Source
The UK MRC and NIHR provided joint funding for the study but did not contribute to the design, data collection, analysis or interpretation.

Results:

WSAC enrolled 342 severe asthmatics, all of whom fulfilled the ATS/ERS 2014 definition of severe asthma. A summary of the characteristics of this group is shown in Table 1 (further details included within on-line supplement). The severe asthma patients within WSAC are demographically comparable to previous cohorts/registries (see on-line supplement).

37 RCTs, 23 phase II and 14 phase III, assessing 20 novel therapies in over 15,000 patients with severe asthma were identified. 29 (78%) of these RCTs assessed treatments targeting the type-2 high inflammatory pathway. The most frequent primary endpoint was a reduction in exacerbation frequency (71% of phase III trials).

Only 9.8% (median; range 3.5%-17.5%) of severe asthma patients within WSAC would have been eligible for enrolment in the phase III trials of biological therapies in severe asthma. Table 2 shows the proportion of patients within WSAC who would have been suitable for enrolment in each RCT. Whilst there is an increment in eligibility between phase II and III RCTs, overall suitability remains low.

Table 3 highlights commonly used eligibility criteria and their impact on trial enrolment. The requirements for persistent airflow obstruction and/or significant bronchodilator reversibility were key reasons for trial exclusion and when both criteria were required only 33.6% of severe asthma patients in WSAC remained eligible. The cumulative effect of multiple eligibility criteria dramatically restricts eligibility for trial participation. The use of composite inclusion criteria allowing bronchodilator reversibility, bronchial hyperresponsiveness and/or measures of variable airflow obstruction modestly increased median eligibility from 7.6% (range 2.1%-30.7%) to 15.8% (range 4.1%-39.5%).

In Table 2 eligibility is subdivided into asthma and biomarker criteria demonstrating the majority of patients are excluded by non-phenotypic criteria. Figure 1 illustrates the percentage of patients with blood eosinophils ≥300 cells/μL who would have been eligible for enrolment in published phase III IL-5 and IL-5R targeted therapies and demonstrates again that most are excluded by non-phenotypic criteria. A similar effect is seen with an eosinophilic population defined by ≥2% or ≥3% sputum eosinophils or blood eosinophils ≥150 cells/μL (data shown in online supplement). The median eligibility for RCTs assessing biological agents targeting type 2 asthma (8.8%; range 2.1%-26.9%) was lower than for non-type 2 asthma (14%; range 5.3%-39.5%) and comparative RCTs of novel non-biological therapies for severe asthma (33.9%; range 20.8-76.9%).

26% of severe asthmatics within WSAC were current smokers or ex-smokers with ≥10 pack-year smoking history and, of those who successfully produced sputum (59 of 90 patients; 62%) or had a peripheral blood count (81 of 90 patients; 90%), 56%% had a sputum eosinophil count ≥2% and/or a peripheral blood eosin count ≥300 cells/μL but were not eligible for enrolment in most trials targeting type-2 high disease due to their smoking status. Table 4 shows the impact of smoking on type 2 biomarker status in WSAC.

Figure 2 demonstrates that less than 50% of the severe asthmatics in WSAC fulfilling the NICE recommendations for treatment with Mepolizumab and Reslizumab would have been eligible for inclusion in the phase III trials of these therapies (Mepolizumab 45.3%; Reslizumab 33.9%).

Discussion:

WSAC was established with the aim of evaluating real-world severe asthma patients and is comparable to the severe asthma populations described in previously published cohorts and registries,[7, 16–19] from which cluster analyses have identified the currently recognised asthma phenotypes. Despite including only well characterised and optimally treated severe asthmatics under specialist care, the vast majority of patients (90.2%; range 82.5-96.5) in WSAC would have been excluded from the landmark phase III trials of biological therapies published to date.

Severe asthma is a heterogeneous condition and biological therapies are only likely to benefit subsets of the population. It would seem reasonable to assume that the majority of patients with poorly-controlled severe eosinophilic asthma despite high-dose inhaled steroids should have been eligible for inclusion in RCTs of therapies targeting inflammatory mediators of the type 2 asthma pathway. However, only 21.1% (median; range 13.4%-26.8%) of patients with severe eosinophilic asthma (defined by blood eosinophils ≥300 cells/μL) in WSAC would have been eligible for the phase III trials of these therapies.

There is significant heterogeneity in the eligibility criteria used between trials despite aiming to reconfirm a diagnosis of asthma in a similar target population. For example, whilst 30 of the 37 RCTs required demonstrable airflow obstruction, 12 unique criteria were used to define this. Whilst some studies have adopted pragmatic composite eligibility criteria to broaden inclusion, many still required specific evidence of bronchodilator FEV_1 reversibility and/or persistent airflow limitation which dramatically reduced patient eligibility. In WSAC, of patients with sputum eosinophil count ≥3%, ACQ score >1.5, and at least one severe exacerbation in the past year, 23% had no evidence of persistent airflow limitation, 56% did not have 12% bronchodilator reversibility and 61% were excluded when both features were required.

26% of severe asthmatics in WSAC were current (5.8%) or ex-smokers with ≥10 pack-year smoking history (20.5%), similar to other cohorts. Whilst it is reported that asthma in smokers is generally associated with non-eosinophilic inflammation,[20] a significant proportion in WSAC did have a demonstrable airway eosinophilia. It is recognised that asthmatics who smoke have impaired responsiveness to corticosteroids and suffer more frequent exacerbations and an accelerated rate of lung function decline.[21, 22] Arbitrary exclusion of these patients from trials has led to a paucity of evidence upon which to base treatment decisions for these patients. It is also important to reflect that other factors impacting upon airway biology including obesity, persisting allergen exposure, and bacterial dysbiosis are not commonly included within trial eligibility criteria, raising a question of equity.

RCTs of type-2 targeted therapies excluded significantly more participants on the basis of diagnostic criteria than those evaluating non-type 2 and non-biological therapies. This suggests hyper-selection within this population, further limiting generalisability of the results. Licensing body and healthcare funder recommendations extrapolate from RCTs which we have demonstrated to be poorly representative of real-life severe asthma populations. Figure 2 highlights the disparity between NICE treatment recommendations and the trial populations. The residual uncertainty this has created as to the benefit of treatment for many patients has led to a reliance on treatment trials. Avoiding eligibility criteria that are not relevant to the biological trait targeted would allow a more inclusive trial population better generalizable to the subsequent treatment population.

Regulatory authorities have a major influence over the design of RCTs required for product licencing. The European Medicines Agency guidelines for asthma trials specify ‘the aim should be to study a homogeneous population of patients with asthma’ and recommend evidence of reversible airflow

obstruction for a secure diagnosis of asthma substantially limiting trial eligibility.[23] Phase IV pragmatic and non-randomised trials have proved crucial in demonstrating treatment efficacy in those patients excluded from licencing trials,[24–26] however this creates a significant delay in the generation of evidence for many severe asthma patients and carries the risk of inflating the impact, as 'real world' evidence is not placebo-controlled. Pragmatic phase III RCTs which better reflect real-world populations and clinical practice may improve external validity and equity of access.[27] This will require engagement between clinicians, licencing authorities, funding bodies and the pharmaceutical industry.

Our findings show that RCTs in severe asthma lack external validity with the majority of patients excluded by criteria designed to re-confirm 'arbitrary diagnostic labels' rather than by biomarker criteria that predict the characteristic or 'trait' addressed by the treatment.[11, 12] Failure to adopt an exclusively phenotypic approach to trial inclusion will perpetuate the limited generalisability of effectiveness and health economic evidence used by regulatory bodies. This risks missing opportunities for application of novel therapies and propagating the vast unmet need in severe asthma.

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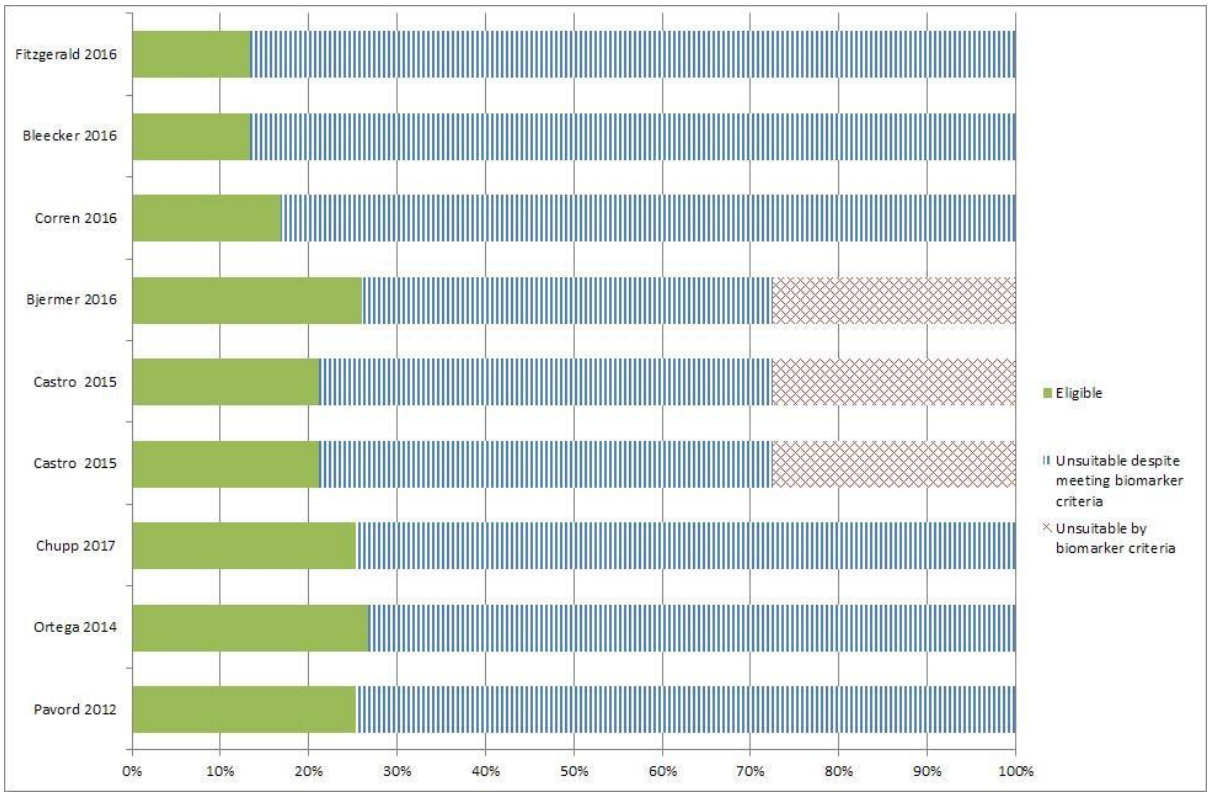
Fitzgerald 2016
Bleecker 2016
Corren 2016
Bjermer 2016
Castro 2015
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Chupp 2017
Ortega 2014
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0%
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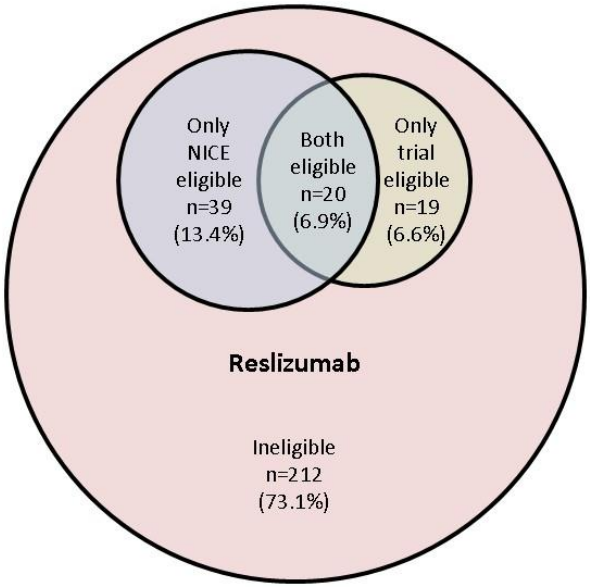
70%
80%
90%
100%
Eligible
Unsuitable despite meeting biomarker criteria
Unsuitable by biomarker criteria


Only NICE eligible n=39 (13.4%)
Both eligible n=20 (6.9%)
Only trial eligible n=19 (6.6%)
Reslizumab
Ineligible n=212 (73.1%)

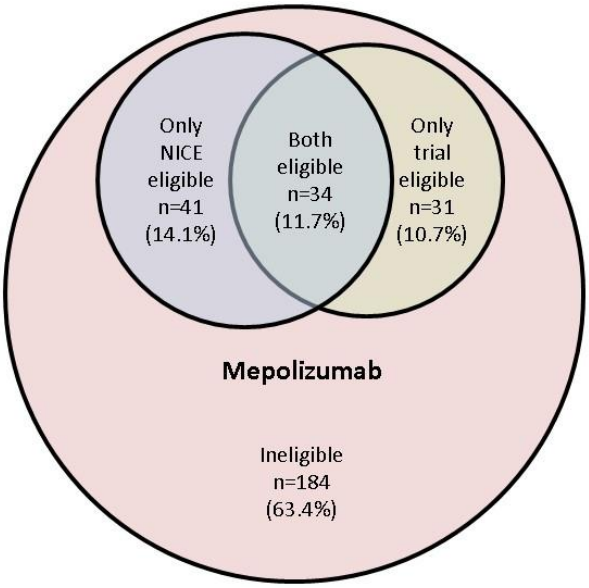

Only NICE eligible n=41 (14.1%)
Both eligible n=34 (11.7%)
Only trial eligible n=31 (10.7%)
Mepolizumab
Ineligible n=184 (63.4%)

Table 1: WSAC Cohort Characteristics Summary:

		Severe Asthma
Number (n)		342
Patient Demographics:		
Age (y)		49.4±13.6
Female (%)		67.5%
BMI (Kg/m^2); BMI>30 (%)		29.7 (25.6-35.6); 48.2%
Smoking status:		
Never smoker (%)		55%
Ex-smoker (%); Pack-years (y)		39.2%; 10 (4.4-22.5)
Current smoker (%); Pack-years (y)		5.8%; 20 (8.4 -35)
***Asthma History*:**		
Asthma duration (y)		26±17
ICS dose (BDP equivalent µg/day)		2369±1149
LABA/LTRA/LAMA/Theophylline (%)		95.8%/67.6%/31.3%/26.2%
Maintenance OCS (%); Prednisolone equivalent dose (mg)		34.2%; 15.9±12
Asthma Control:		
Rescue OCS courses in previous year		2 (1-4)
≥1 hospital admissions in previous year (%)		50.3%
ACQ 6; ACQ6 >1.5 (%)		2.74±1.24; 82.5%
Previous intensive care admission for asthma (%)		18.1%
AQLQ		4.09 ± 1.26
Co-morbidities:		
Gastro-oesophageal reflux disease (%); PPI use (%)		48.5%; 45.5%
Rhinosinusitis (%); Rhinosinusitis treatment (%)		72.5%; 72.8%
Nasal polyps (%)		14%
Physiological Measures:		
FEV_1 pre-BD (% predicted)		69.6±24.9
FEV_1 reversibility (% from baseline); ≥12% reversibility[§] (%)		13.3 (5.2-26.4); 43.3%
Atopic status:		
Atopic* (%)		72.4%
Measures of inflammation:		
$FeNO_{50}$ (ppb); $FeNO_{50}$ ≥50ppb (%)		20.7(12.7-41); 20.7%
Sputum Inflammatory Phenotype (%):	Eosinophilic (≥3%)	41.1%
	Neutrophilic (≥60%)	37.3%
	Mixed granulocytic	10.5%
	Paucigranulocytic	32.1%
Blood Eosinophil Count (x10^9/L); ≥0.3 (%)		0.2 (0.1-0.5); 49%
ATS/ERS Severe Asthma Criteria 2014[3]		
GINA Step 4/5 treatment		100%
ACQ(6)>1.5, ≥2 OCS bursts in previous year, ≥1 hospital admission in previous year, persistent airflow limitation or deterioration in asthma control on tapering steroid dose		100%

Data presented as mean±SD or median (IQR)

[§] Reversibility testing performed 15-minutes after 2.5mg nebulised Salbutamol

* Atopic defined as ≥1 positive skin prick test

BMI (Body Mass Index), BDP (Beclometasone Diproprionate), ICS (Inhaled Corticosteroids), LABA (Long Acting Beta-2 Agonist), LTRA (Leukotriene Receptor Antagonist), LAMA (Long Acting Muscarinic Antagonist), OCS (Oral Corticosteroids), ACQ (Asthma Control Questionnaire), AQLQ (Asthma Quality of Life Questionnaire), PPI (Proton Pump Inhibitor), Pre-BD (Pre-Bronchodilator), $FeNO_{50}$ (Exhaled Nitric Oxide level at 50ml/sec flow rate).

Table 2: Summary of WSAC Trial Exclusions (full details and references available in on-line supplement)

Target	Drug	First Author* (Year)	Phase	WSAC % Eligible		
				Biomarker criteria	Asthma criteria	Overall
IgE	Omalizumab	Holgate (2004)	III	36.84%	12.57%	3.51%
		Humbert (2005)	II	36.84%	11.70%	4.09%
		Hanania (2011)	III	36.84%	18.42%	6.14%
IL-5	Mepolizumab	Haldar (2009)	II	25.15%	23.10%	7.89%
		Nair (2009)	II	25.15%	23.10%	5.56%
		Pavord (2012)	III	57.31%	23.10%	17.54%
		Bel (2014)	III	69.59%	8.77%	4.09%
		Ortega (2014)	III	69.59%	23.98%	15.79%
		Chupp (2017)	III	69.59%	23.39%	14.91%
	Reslizumab	Castro (2011)	II	25.15%	22.81%	4.68%
		Castro (2015)	III	45.32%	23.68%	8.77%
		Castro (2015)	III	45.32%	23.68%	8.77%
		Bjermer (2016)	III	45.32%	29.24%	10.82%
		Corren (2016)	III	100.00%	15.50%	15.50%
	Benralizumab	Bleeker (2016)	III	100.00%	11.11%	11.11%
		FitzGerald (2016)	III	100.00%	11.11%	11.11%
IL-13	Tralokinumab	Piper (2013)	II	100.00%	26.90%	26.90%
		Brightling (2015)	II	100.00%	11.40%	11.40%
	Lebrikizumab	Corren (2011)	II	100.00%	6.14%	6.14%
		Hanania (2016)	III	100.00%	7.60%	7.60%
		Hanania (2016)	III	100.00%	7.60%	7.60%
	GSK679586	De Boever (2014)	II	100.00%	18.42%	18.42%
IL-4Rα	AMG317	Corren (2010)	II	73.68%	3.80%	3.51%
	Dupilumab	Wenzel (2013)	II	36.55%	2.92%	2.05%
		Wenzel (2016)	II	100.00%	10.53%	10.53%
	Pitrakinra	Slager (2012)	II	100.00%	23.39%	23.39%
IL-4/5	Suplatast	Tamaoki (2000)	II	100.00%	6.43%	6.43%
DP2 receptor	Fevipiprant	Gonem (2016)	II	27.19%	59.65%	16.67%
IL-2Rα	Daclizumab	Busse (2008)	II	73.68%	6.73%	5.26%
TSLP	Tezepelumab	Corren (2017)	II	100.00%	6.43%	6.43%
c-kit/PDGF	Masitinib	Humbert (2009)	II	99.12%	5.56%	5.26%
CXCR2	Navarixin	Nair (2012)	II	36.84%	55.56%	19.88%
	AZD5069	O'Byrne (2016)	II	71.93%	37.72%	25.15%
IL17RA	Brodalumab	Busse (2013)	II	100.00%	6.73%	6.73%
TNFα	Etanercept	Morjaria (2008)	II	100.00%	39.47%	39.47%
		Holgate (2011)	II	100.00%	8.19%	8.19%
	Golimumab	Wenzel (2009)	II	100.00%	30.70%	30.70%
Non-biological	BT	Castro (2010)	III	100.00%	26.32%	26.32%
	Azithromycin	Brusselle (2013)	III	73.98%	31.58%	20.76%
		Gibson (2017)	III	100.00%	76.90%	76.90%
	TLA	Storrar (2017)	III	73.68%	53.80%	41.52%

BT (Bronchial Thermoplasty), TLA (Temperature Controlled Laminar Airflow)

* Full References available within the on-line supplement

Table 3: The Impact of Commonly Used Eligibility Criteria

Eligibility Criteria	Trials (n)	Criteria Variants (n)	Specific Criteria Examples	Trials (n)	WSAC % Eligible
Airflow Obstruction	29	12	FEV_1 (pre-bronchodilator) ≤80%	23	66.7%
			FEV1 (pre-bronchodilator) ≥40%	11	87.72%
			FEV_1 (pre-bronchodilator) 40-80%	9	54.4%
Bronchodilator Reversibility	35*	6	≥12%	32	43.3%
			≥12% and 200ml	16	38.9%
Exacerbation Frequency	18	5	≥2 in last 12-months	11	74%
			≥2 (OCS) or ≥1 (hospital)	3	79.5%
Asthma Control Questionnaire (ACQ)	21[§]	6	ACQ(7) ≥1.5	5	86%
			ACQ(6) ≥1.5	8	86.6%
Smoking Status	35	7	Current Smokers Excluded	34	83.3%
			<10 pack years	24	79.5%
ICS dose (BDP equivalent)	35	9	≥1000 µg/day	16	93.9%
			≥2000 µg/day	3	69.6%
OCS use	37	5	No	11	65.8%
			≤10 mg /day	6	84.2%

*14 Trials used a composite criterion allowing bronchodilator reversibility or bronchial hyperresponsiveness and in some cases other measures of variable airflow obstruction e.g. diurnal peak expiratory flow rate variability

[§]1 Trial used the Asthma Control Test

FEV_1 (Forced Expiratory Volume in 1 Second), ICS (Inhaled Corticosteroids), BDP (Beclometasone Diproprionate); OCS (Oral Corticosteroids).

Table 4: The Impact of Smoking on the Type 2 Biomarker Status in the Wessex Severe Asthma Cohort

Smoking Status	n	Sputum n (%)	Blood n (%)	Biomarker Status				
				Sputum Eosinophils		Blood Eosinophils		
				≥2%	≥3%	≥150/µl	≥300/µl	≥400/µl
Never smoker	188	107 (56.9%)	156 (83%)	55 (51.4%)	51 (47.7%)	98 (62.8%)	79 (50.7%)	60 (38.5%)
Ex-smoker <10 pack years	64	43 (67.2%)	53 (82.8%)	13 (30.2%)	12 (27.9%)	36 (67.9%)	29 (54.7%)	19 (35.8%)
Ex-smoker ≥10 pack-years	70	43 (61.4%)	64 (91.4%	20 (46.5%)	18 (41.9%)	45 (70.3%)	30 (46.9%)	21 (32.8%)
Current smokers	20	16 (80%)	17 (85%)	5 (31.3%)	5 (31.3%)	7 (41.2%)	4 (23.5%)	3 (17.6%)

The Wessex Severe Asthma Cohort Study

The Wessex Severe Asthma Cohort (WSAC) is an observational cross-sectional study providing detailed characterisation of severe asthma patients recruited from specialist severe asthma clinics at Portsmouth and Southampton Hospitals between April 2009 and January 2014. In addition to the severe asthma group two comparator groups including a healthy control group and a group with stable mild/moderate asthma were recruited and underwent the same detailed characterisation.

1.1 Study Participants

The eligibility criteria were designed to create an inclusive cohort representative of the patients seen in the specialist severe asthma clinics at the two sites. Participants were aged between 18 and 80 years with no restrictions according to gender, race or smoking status.

Eligibility for the severe asthma group required:

- A diagnosis of asthma confirmed by an asthma specialist in accordance with the BTS/SIGN guidelines 2009 with alternative causes for symptoms excluded and treatment for co-morbidities optimised and had been under follow up with a specialist for at least 6 months at the time of enrolment as recommended in the ERS severe asthma guidelines 1999.
- Features of poor disease control with persistent symptoms requiring regular short acting beta-agonist rescue medication and at least one severe exacerbation in the preceding year despite high-intensity maintenance asthma treatment.

Severe exacerbations defined as a worsening of asthma requiring systemic corticosteroids, or an increase in maintenance dose of systemic corticosteroids, for at least three days[1].
High-intensity maintenance asthma treatment included patients taking ≥1000µg/day BDP equivalent inhaled corticosteroid (or maintenance systemic corticosteroids) and a long acting beta-2 agonist or alternative controller medications (steps 4 and 5 of the BTS/SIGN Asthma Guideline treatment algorithm 2009[2]).

Participants eligible for the mild-moderate asthma group were taking ≤800 µg/day BDP equivalent inhaled corticosteroid (steps 1-3 of the BTS/SIGN Asthma Guideline treatment algorithm 2009) and had well controlled disease with no disease exacerbations requiring systemic corticosteroids over the preceding year. Participants eligible for the healthy control group had no current or historical symptoms suggestive of asthma and normal lung function. Patients with significant co-morbid disease other than asthma and those unable to comply with investigational procedures were excluded.

Potential participants with severe asthma who fulfilled the trial eligibility criteria were identified in the specialist severe asthma clinics and provided with a Patient Information Sheet. Those wishing to take part returned for a specific study appointment. Adverts and existing databases were used to identify participants for the healthy and milder asthma groups.

1.2 Data Collection

All participants underwent a detailed characterisation protocol (see Table 5) including a detailed asthma and medical history; disease control, quality of life, and comorbidity questionnaires; pulmonary physiology; allergy testing; exhaled nitric oxide testing; HRCT imaging of the chest; sputum induction, nasal lavage, blood, and urine samples for biological measures of inflammation and genomic testing. The characterisation procedures used are all standard, and established guidelines were followed. Study-specific Standard Operating Procedures (SOPs) were created for sputum induction, nasal lavage and sample processing to ensure consistency between the two recruiting sites.

All data was entered onto a paper Case Report Form (CRF) at the time of review and uploaded onto the secure WSAC database after completion of all study procedures.

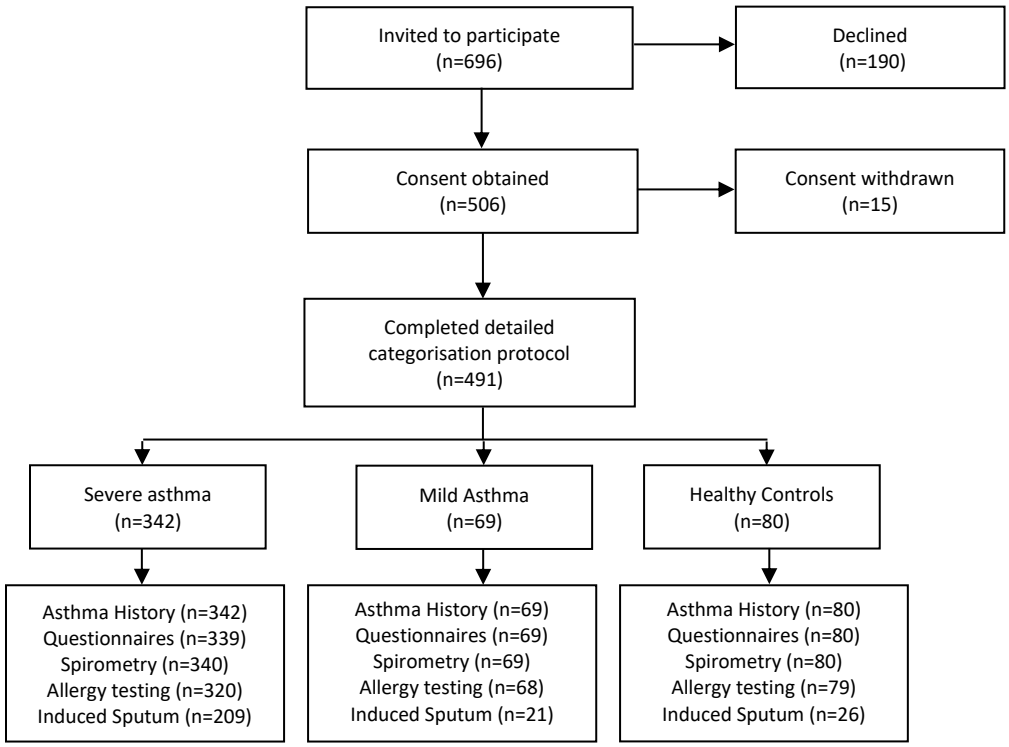
1.3 Confidentiality and Ethics

The study was conducted in accordance with the International Conference on Harmonisation Guidance for Good Clinical Practice and the clinical principles outline in the Declaration of Helsinki. Independent ethics committee approval was obtained (MREC No. 09/H0502/37), and all participants provided written informed consent. Unique identification codes were used to identify participants within the trial database as well as their biological samples. All participant data has been stored securely and is only accessible to study staff and authorised personnel. The study is funded by the UK Medical Research Council Patient Research Cohorts Initiative. The study was sponsored by University Hospital Southampton NHS Foundation Trust and was adopted onto the UKCRN Portfolio (http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=7547).

2. Recruitment

491 participants were recruited and underwent the detailed characterisation protocol between April 2009 and January 2014. Details of recruitment are shown in Figure 1.

Figure 1: Wessex Severe Asthma Cohort Study Recruitment



Within the severe asthma group induced sputum was obtained from 61.1% of participants but in the milder and control cohorts this was lower at 30.4% and 32.5% respectively. This reflected participants being either unable to produce sputum (particularly in the healthy control population) or not being willing to have this procedure performed. However, sputum samples were obtained in a similar number of participants when compared to other published severe asthma cohorts (see Table 1).

Table 1: Sputum Induction in Severe Asthma Cohorts/Registries

	WSAC	**SARP**[3]	**UBIOPRED**[4]	**BSAR**[5]	**BIOAIR**[6]
Cohort size (n)	342	204	421	350	93
Successful sputum induction (%)	61.1	60.7	43.0	32.2	24.6

3. Study Procedures

3.1 Spirometry

Spirometry was performed using a portable spirometer (Vitalograph Alpha Touch®, Vitalograph Ltd, Buckingham, UK) in accordance with ATS/ERS guidelines[7] . The best forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) values, from three acceptable manoeuvres, were recorded and analysed according to the European Coal and Steel Community (ECSC) 1993 predicted values. Bronchodilator reversibility testing was performed 15 minutes after the administration of 2.5mg nebulised salbutamol with significant reversibility defined as a 200ml and 12% increase in FEV_1.

3.2 Single Breath Gas Transfer

Single Breath Gas Transfer measures were performed in accordance with ATS/ERS guidelines. Mean results of the transfer factor for carbon monoxide (TL_{CO}) and the transfer coefficient of the lung for carbon monoxide K_{CO} (not corrected for haemoglobin) were reported as a percent predicted using equations recommended by the ATS/ERS taskforce[8].

3.3 Impulse Oscillometry (IOS)

Impulse oscillometry (CareFusion MasterScreen™ IOS) was measured on a sub population of the cohort. A minimum of three tests of 30 seconds tidal breathing at Functional Residual capacity (FRC) were performed as per ERS taskforce recommendations[9]. Impulse oscillometry was performed before and after 2.5mg nebulised salbutamol. Mean oscillometric parameters were recorded and included but not limited to Z5, R5, R20, X5, R5-R20.

3.4 Exhaled Nitric Oxide (FeNO)

The fraction of exhaled nitric oxide (FeNO) was measured at the standard flow rate of 50ml/sec (NIOX MINO®, Aerocrine AB®, Solna, Sweden) in accordance with ATS/ERS guidelines[10]. FeNO was measured prior to other lung function tests and at least 2-hours after eating or drinking with the mean of at least two reproducible values recorded as parts per billion (ppb). In a sub population, FeNO was measured at higher flow rates of 100 and 200ml/sec (NIOX Flex®, Aerocrine AB®, Solna, Sweden) to calculate alveolar NO (CANO) and bronchial NO flux (JawNO) using the linear NO model.

3.5 Nasal Nitric Oxide (nNO)

Nasal nitric oxide measures (NIOX Flex®, Aerocrine AB®, Solna, Sweden) were performed in a sub population. A minimum of two reproducible values (ppb) were obtained from each nostril using the breath hold manoeuvre and the mean value from each nostril was reported.

4. Sample collection

All biological samples were obtained under consistent conditions with standardised processing procedures followed by the cohort characterisation team.

4.1 Sputum Induction

Sputum was induced using a DeVilbiss® Ultraneb (DeVilbiss, NY, USA) following a standardised protocol based on the methods described by ten Brinke et al[11]. Patients were bronchodilated with short acting beta-agonist (SABA) medication prior to sputum induction and lung function (FEV_1) was measured after each 5 minute nebulisation (4.5% saline) to check if a 20% drop from post bronchodilator FEV_1 had been reached at which point the induction would be stopped. For severe asthmatics at risk of bronchoconstriction, clinical judgement determined if nebulisation protocol should begin with 0.9% saline followed by 3% and finally 4.5% if tolerated. Lung function (FEV_1) was measured after each 5 minute nebulisation and after 2 minutes of nebulisation if the subject's FEV_1<1.5L. After a maximum of 20 minutes total nebulisation time for stable subjects, 15 minutes for at risk subjects or when an adequate sample was obtained, the procedure was stopped. Samples were stored on ice

during collection and transport to the laboratory for processing. Sputum samples were processed as soon as possible and within 2 hours of expectoration.

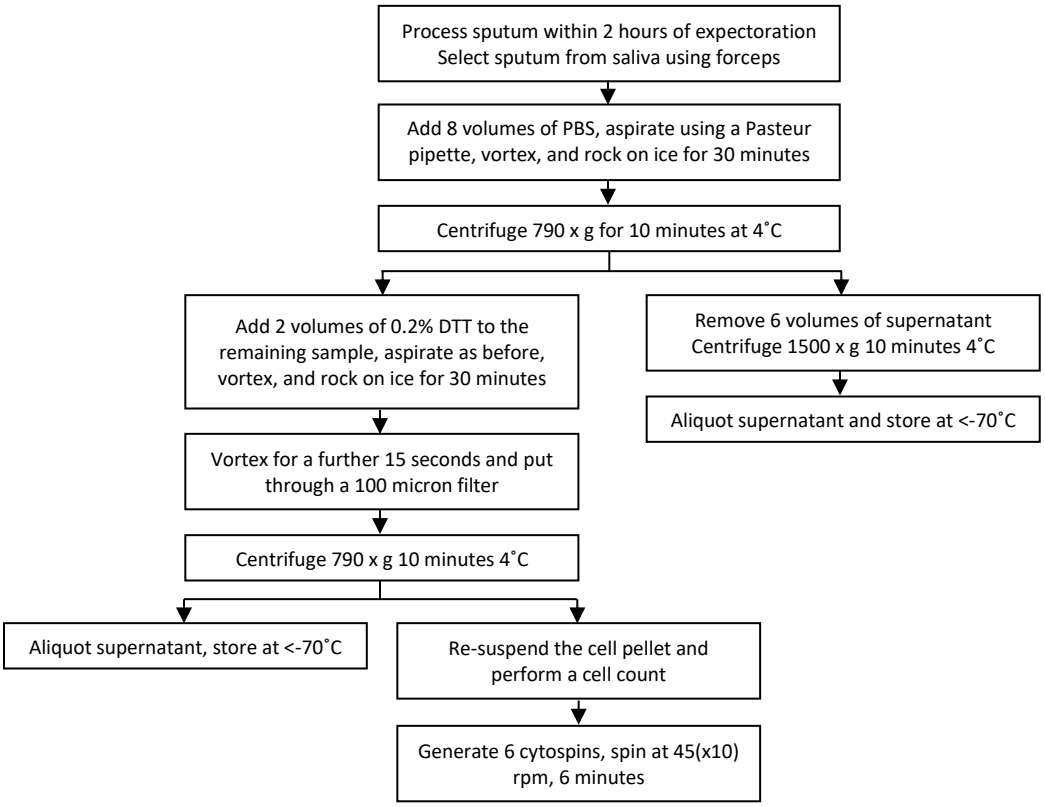
4.2 Nasal Lavage

Subjects were seated in a forward-flexed position and for each nostril, 2.5ml of 0.9% saline (warmed to 37%) was passed slowly into the nasal cavity using a 10ml syringe and then left to dwell for 10 seconds. The saline was withdrawn into the syringe and collected in a sterile tube kept cool on ice. This process was repeated twice. The sample was then passed through a 100µm nylon mesh filter before centrifuging at 4◦C for 10 minutes at 790g. The supernatant was stored at <-70°C.

5. Sample Processing

- Serum samples were coagulated for 30-60 minutes, centrifuged for 15 minutes at 1500g at 4°C, the serum layer removed and stored at <-70°C until analysis.
- Whole blood was stored at <-70°C and a simple salting procedure was performed for extracting DNA[12].
- The concurrent method of sputum processing was performed providing PBS and DTE supernatant for analysis[13]. Sputum samples were processed as soon as possible and within 2 hours of expectoration with 8x volume of phosphate buffered saline (PBS) and a proportion of supernatant was then removed and the sample was further incubated with 0.2% dithioerythritol (DTE) giving a final concentration of 0.1% DTE using the process described in Figure 2. Cytospins were stained using by rapid Romanowski staining (Fisher Scientific, Loughborough, UK). The proportion of inflammatory cells were assessed by counting 400 respiratory cells + squamous to give a mean percentage of respiratory cells and an independent mean percentage of squamous cells counted to indicate the level of salivary contamination.

Figure 2: Sputum Processing



- Nasal lavage was stored on ice and processed as soon as possible and within 30 minutes of collection. A small portion was removed for bacteriology analysis and the remaining sample was filtered through a 100µm cell strainer. Samples were then centrifuged at 790 x G and stored at <-70°C until further analysis.
- Urine was aliquotted and stored as soon as possible at <-70°C until further analysis. A small portion was analysed immediately for urinary cotinine.
- Inflammatory mediators were measured by:
    - Enzyme-linked immunosorbent assays (ELISA) – myeloperoxidase, elastase (Hycult® Biotech, Uden, The Netherlands), eosinophil cationic protein (MBL® International, MA, USA), interleukin (IL)-5 (Abnova®, Taiwan), IL-6, high-sensitivity-CRP (Biomerica®, CA, USA), ENA-78, eotaxin, FGF, osteopontin, ST2/IL-1 R4, VEGF,YKL-40 (Quidel Corporation, CA, USA), periostin (K Izuhara), tryptase, and α2-macroglobulin (A Walls)
    - Fluoroenzyme immunoassay – total IgE (ImmunoCAP, Phadia®, Uppsala, Sweden)
    - Cytokine bead array (Luminex®, R&D Systems, Oxford, UK): matrix metalloproteases (MMPs), metallopeptidase inhibitor 1 (TIMP-1), G-CSF, GM-CSF, Gro-α, CCL1, ICAM-1, IFN-γ, IL-1 α, IL-1 β, IL-1RA, IL-2, IL-4, IL-8, IL-10, IL-12, IL-13, IL-17, MCP-1, MIP-1 α, MIP-1 β, TNF-α (R&D Systems, Abingdon, Oxford, UK)
- Urinary cotinine was measured by lateral flow chromatographic immunoassay NicoScreen® One Step Cotinine Test Device (Modern Health Systems Ltd, Shipley, UK).

Table 2: Characteristics of the Wessex Severe Asthma Cohort

		Severe Asthma	Mild-Mod Asthma	Healthy Controls
Number (n)		342	69	80
Patient Demographics:				
Age (y)		48.2±13.8	38.9±12.6	37.2±12.8
Female (%)		67.5%	58%	63.8%
BMI (Kg/m^2); BMI>30 (%)		29.7 (25.6-35.6); 48.2%	27.8 (25.2-33.3); 43.5%	23.7 (21.9-26.9); 13.8%
Smoking status:				
Never smoker (%)		55%	68%	66.3%
Ex-smoker (%); Pack-years (y)		39.2%; 10 (4.4-22.5)	29%; 2.5 (1.5 -8)	25%; 2 (1-6)
Current smoker (%); Pack-years (y)		5.8%; 20 (8.4 -35)	3%; 1 (1-1)	8.8%; 5 (2.5 -7.2)
Asthma Characteristics:				
Age at asthma onset (y); onset ≤12 years (%)		22±19; 40.4%	18±14; 50.7%	-
Asthma duration (y)		26±17	21±14	-
Family history of asthma or allergy (%)		43.9%	73.9%	50%
Asthma Treatment:				
ICS dose (BDP equivalent µg/day)		2369±1149	278±302	-
LABA/LTRA/LAMA/Theophylline (%)		95.8%/67.6%/31.3%/26.2%	29%/1.4%/0%/0%	-
Maintenance OCS (%); Prednisolone equivalent dose (mg)		34.2%; 15.9±12	0%; 0	0%; 0
BTS Step 1/2/3[2] (%)		0%/0%/0%	46.4%/26.1%/27.5%	-
BTS Step 4/5 (%)		65.1%/34.9%	0%/0%	-
Omalizumab/Long-term macrolide/Antifungal		2.9%/11%/3%	0%/1.4%/0%	0%/1.3%/0%
Asthma Control:				
Rescue OCS courses in previous year		2 (1-4)	0 (0-0)	-
≥1 Hospital admission in previous year		50.3%	0%	-
ACQ 6; ACQ6 >1.5 (%)		2.74±1.24; 82.5%	0.85±0.73; 14.5%	0.01± 0.04; 0%
Previous intensive care admission for asthma (%)		18.1%	0%	-
Co-morbidities:				
Gastro-oesophageal reflux disease (%); PPI use (%)		48.5%; 45.5%	8.7%; 5.8%	10%; 6.3%
Rhinosinusitis (%); Rhinosinusitis treatment[∞] (%)		72.5%; 72.8%	31.9%; 4.3%	5%; 3.8%
Nasal polyps (%)		14%	1.4%	2.5%
Aspirin sensitivity (%)		27.7%	5.9%	1.3%
SNOT-20 score		35.5±19.4	15.5±11.3	7.2±8.2
HADS anxiety/depression		7.3±5.2/8.6±4.3	3.4±3.8/3.1±3.5	2.7±2.6/2.7±2.5
Antidepressant use (%)		20.2%	7.2%	2.5%
Diabetes/OSA/Osteoporosis (%)		7.6%/2.9%/9.6%	2.9%/1.4%/0%	2.5%/0%/0%
Asthma and Generic Quality of Life Questionnaires:				
AQLQ		4.09 ± 1.26	6.15 ± 0.76	6.96 ± 0.1
Short Form-36 Health Survey		47.9 ± 20.4	81.0 ± 13.5	86.2 ± 9.7
Physiological Measures:				
FEV_1 pre-BD (% predicted)		69.6±24.9	94.3±18.4	104.6±11.7
FEV_1/FVC ratio pre-BD (%)		66.9 (55-76)	76.1 (71.1 – 81.4)	82.1 (77.1-86.5)
FEV_1 pre-BD <80% predicted and FEV_1/FVC <0.7 (%)		66.5%	20.3%	1.3%
FEV_1 reversibility (% from baseline); ≥12% reversibility[§]		13.3 (5.2-26.4); 43.3%	12.9 (9.4-32.9); 26.5%	8.6 (7.1-10.2); 0%
K_{CO} (% predicted)		99.2±17.5	98.6±14.1	92.3±14.2
Atopic status:				
Atopic* (%)		72.4%	82.4%	45.6%
Serum total IgE (IU/ml)		91.7 (23-331)	104 (30-200)	33 (15.7-106)
Measures of inflammation:				
$FeNO_{50}$ measured (%)		94.7%	100%	100%
$FeNO_{50}$ (ppb); $FeNO_{50}$ ≥50ppb		20.7(12.7-41); 20.7%	22 (15-41); 18.8%	15.1 (11-24); 8.8%
Sputum induction successful (%)		61.1%	30.4%	32.5%
Sputum Inflammatory Phenotype (%):	Eosinophilic (≥3%)	41.1%	28.6%	11.5%
	Neutrophilic (≥61%)	35.9%	0%	15.4%
	Mixed granulocytic	10.5%	0%	3.8%
	Paucigranulocytic	32.1%	71.4%	76.9%
Blood Eosinophil Count (x10^9/L); ≥0.3 (%)		0.2 (0.1-0.5); 49%	0.2 (0.1-0.4); 38.2%	0.1 (0.1-0.2); 18.4%
Serum Periostin (ng/ml); ≥50 (%)		67 (56-83); 85.9%	66.5 (54-75.5); 85.3%	73.5 (58-92); 92.3%
Blood Neutrophil Count (x10^9/L)		5.6 (4.2-7.8)	3.7 (3.3-4.4)	3.6 (2.9-4.5)

Type2-high phenotype[†]	56.2%	37.7%	25%
ATS/ERS Severe Asthma Criteria 2014[14]			
GINA Step 4/5 treatment	100%	0%	-
ACQ(6)>1.5, ≥2 OCS bursts in previous year, ≥1 hospital admission in previous year, persistent airflow limitation or deterioration in asthma control on tapering steroid dose	100%	29%	-

Data presented as mean±SD, median (IQR), n or %

[∝]Rhinosinusits treatment includes the use of nasal corticosteroids, oral corticosteroids and oral antihistamines

[§] Reversibility testing performed 15-mintues after 2.5mg nebulised Salbutamol

* Atopic defined as ≥1 positive skin prick test

[†] TH2-high phenotype identified by either FeNO≥50ppb, ≥3% Sputum Eosinophils, Blood Eosinophil count >$0.3x10^9$/L

BMI (Body Mass Index), ICS (Inhaled Corticosteroids), BDP (Beclometasone Diproprionate), LABA (Long Acting Beta-2 Agonist), LTRA (Leukotriene Receptor Antagonist), LAMA (Long Acting Muscarinic Antagonist), OCS (Oral Corticosteroids), BTS (British Thoracic Society), ACQ (Asthma Control Questionnaire), PPI (Proton Pump Inhibitor), SNOT-20 (20 Question Sino-Nasal Outcome Test Score), HADS (Hospital Anxiety and Depression Score), OSA (Obstructive Sleep Apnoea), AQLQ (Asthma Quality of Life Questionnaire), Pre-BD (Pre-Bronchodilator), $FeNO_{50}$ (Exhaled Nitric Oxide level at 50ml/sec flow rate).

Table 3: Comparison of WSAC with Existing Severe Asthma Cohorts/Registries

	WSAC	**ENFUMOSA**[15]	**SARP**[3]	**BTS**[16]	**BSAR**[5]	**BIOAIR**[6]
Cohort size (n)	342	163	204	382	350	93
Patient Demographics:						
Age (y)	49.4±13.6	42.4±12.1	41±13	NA	55±14	50.0±12.5
Female (%)	67.5%	81.6%	64.0%	63.1%	55%	58.0%
BMI (Kg/m^2)	29.7 (25.6-35.6)	27±5	NA	28 (24-32)	26 (16-43)	28.5±5.8
Smoking status:						
Never smoker (%)	55%	NA	NA	61%	57%	NA
Ex-smoker (%); Pack-years (y)	39.2%; 10 (4.4-22.5)	NA	NA	29.8%	31%; 15 (11-24)	NA
Current smoker (%); Pack-years (y)	5.8%; 20 (8.4 -35)	NA	NA	5.8%	12%; 11 (10-15)	NA
Clinical Characteristics:						
Age at asthma onset (y)	22 ± 19	NA	16±16	17 (3-35)	NA	NA
Asthma onset ≤12 years (%)	40.4%	NA	NA	NA	32%	NA
Asthma duration (y)	26±17	20.8±2.5	25±14	NA	NA	NA
Asthma medications:						
ICS dose (BDP equivalent µg/day)	2000 (1600-3000)	1676±667	NA	2000 (1000-2000)	2000 (190-6000)	2064±939
Maintenance OCS (%)	34.2%	32.5%	32%	41.7%	24%	NA
Co-morbidities:						
Aspirin sensitivity (%)	27.7%	NA	NA	9.5%	8%	NA
Rhinosinusitis (%)	72.5%	NA	54%	36.6%	49%	NA
GORD (%)	48.5%	NA	41%	41.4%	36%	NA
Quality of Life:						
AQLQ	4.09 ± 1.26	NA	NA	NA	4.14 (1.2-7)	NA
Disease Control:						
Rescue OCS courses in previous year	2 (1 - 4)	NA	NA	4 (2-6)	2.03 (0-7)	NA
Hospital admissions in previous year	0 (0 – 1)	NA	NA	0 (0-2)	0.95 (0-7)	NA
ACQ6	2.74±1.24	NA	NA	NA	2.57±1.31	2.03±0.96
ACQ6 >1.5 (%)	82.5%	NA	NA	NA	77%	NA
Physiological Measures:						
FEV1 Pre-BD (% predicted)	69.6±24.9	71.8±23.1	62±22	65.9±23.6	68±21	70.4±20.3
FEV1 <80% predicted (%)	66.5%	NA	78%	NA	60%	NA
FEV1/FVC ratio Pre-BD (%)	66.9 (55-76)	79.9±16.6	65±13	63.1±15.2	63±12	67±9.6
FEV1 reversibility (% from baseline)	13.3 (5.2-26.4)	NA	20±24	NA	11±13	9.4±7.7
≥12% reversibility (%)	43.3%	NA	61%	NA	36%	NA
K_{CO} (% predicted)	99.2±17.5	90.6±19	NA	101.5±17	97±20	NA
Atopic status:						
Atopic (%)	72.4%	58%	71%	NA	70%	43%
SPT Positive HDM (%)	55.3%	NA	NA	71.0%	NA	NA
SPT Positive Cat (%)	34.6%	NA	NA	65.4%	NA	NA
Serum total IgE (IU/ml)	91.7 (23-331)	109 (85-139)	NA	130 (53.5-292)	207 (2-10000)	NA
Measures of inflammation:						
FeNO measured (% of cohort)	94.7%	NA	66.2%	34.8%	77.4%	NA
$FeNO_{50}$ (ppb)	20.7(12.7-41)	NA	40±38	34.5(16-65)	26 (4-250)	46.3±59.7
Sputum induction successful (%)	61.1%	NA	60.7%	NA	32.2%	24.6%
Sputum Eosinophil Count (%)	1.5 (0.3 - 8.5)	11±2	NA	3 (0.3-11.3)	7 (0-92)	16.7±33.7
Sputum Neutrophil Count (%)	49.6 (26.3 – 67.3)	37±3	NA	NA	51 (0-99)	42.2±35.7
Sputum Inflammatory Phenotype (%):						
Eosinophilic (≥3%)	41.1%	NA	NA	NA	60.5%	NA
Neutrophilic (≥61%)	35.9%	NA	NA	NA	27.9%	NA
Mixed granulocytic	10.5%	NA	NA	NA	5.8%	NA
Paucigranulocytic	32.1%	NA	NA	NA	17.4%	NA
Blood Eosinophil Count ($x10^9/L$)	0.2 (0.1-0.5)	NA	NA	0.3 (0.2-11)	0.24 (0-3.1)	NA

Data presented as mean±SD, median (IQR), n or %; NA= data not available

BMI (Body Mass Index), ICS (Inhaled Corticosteroids), BDP (Beclometasone Diproprionate), OCS (Oral Corticosteroids), GORD (Gastro-oesophageal Reflux Disease), AQLQ (Asthma Quality of Life Questionnaire), ACQ (Asthma Control Questionnaire), Pre-BD (Pre-Bronchodilator), SPT (Skin Prick Test), $FeNO_{50}$ (Exhaled Nitric Oxide level at 50ml/sec flow rate).

Table 4: Comparison of WSAC with UBIOPRED (Severe Asthmatics)

	Non-smokers*		Smokers and Ex-smokers*	
	WSAC	**UBIOPRED**	**WSAC**	**UBIOPRED**
Cohort size (n)	215	311	115	110
Patient Demographics:				
Age (y)	47.4±14.1	51.01±0.8	51.0±12.1	54.51±1.08
Female (%)	68.9%	66%	31.1%	51%
BMI (Kg/m^2); BMI>30 (%)	31.0±8.1; 47.7%	29.11±6.34; 38.6%	31.5±7.0; 51.8%	29.59±6.29; 40%
Smoking status:				
Never smoker (%)	83.3%	84.9%	0%	0%
Ex-smoker (%); Pack-years (y)	16.7%; 1.5 (0.9-3.0)	2 (1-4)	83.5%;15.2(8.8-30)	17.38(10-26)
Current smoker (%); Pack-years (y)	0%		16.5%; 20(8.4-35)	
Clinical Characteristics:				
Age at diagnosis (y)	17 (4-32)	20 (7-38)	32 (9-43)	38 (20-48)
Asthma onset ≤12 years (%)	43.3%	NA	30.4%	NA
Asthma duration (y)	27±16	NA	23±18	NA
Asthma medications:				
ICS dose (BDP equivalent µg/day)	2000 (1600-3000)	NA	2000 (1600-2800)	NA
Maintenance OCS (%)	36.3%	45.8%	29.6	44.7%
Co-morbidities:				
Rhinosinusitis (%)	75.3%	74.0%	66.1%	60.4%
GORD (%)	47.9%	46.7%	48.7%	63.6%
Quality of Life:				
AQLQ	4.1±1.3	4.48±1.16	4.0±1.3	4.44±1.25
Disease Control:				
Rescue OCS courses in previous year	3.2±2.7	2.48±2.29	2.8±2.2	2.55±2.73
ACQ7	2.75±1.10	2.67±1.33	2.90±1.23	2.62±1.18
Physiological Measures:				
FEV1 Pre-BD (% predicted)	71.5±25.7	67.5±22.1	65.7±22.1	67.2±19.3
FEV1/FVC ratio Pre-BD (%)	0.67±0.14	0.64±0.18	0.63±0.13	0.61±0.10
Atopic status:				
Atopic (%)	74.4%	78.3%	67.3%	71.3%
Serum total IgE (IU/ml)	78 (20-304)	119.5(45-342)	110 (36.7-353)	126(63-328)
Measures of inflammation:				
FeNO measured (% of cohort)	95.3%	93.2%	94.8%	94.5%
$FeNO_{50}$ (ppb)	22.4 (13.9-47.0)	26.5 (16-47)	18.0 (11.0-36.0)	23.5 (12-42)
Sputum induction successful (%)	59.1%	41.1%	67.0%	48.2%
Sputum Eosinophil Count (%)	2.0 (0.3-11.3)	2.75 (0-19)	1.0 (0.3-6.5)	4.13 (1-14)
Sputum Neutrophil Count (%)	52.0 (26.5-67.5)	53.69 (34-75)	46.5 (25.0-64.0)	55.15 (35-65)
Sputum Eosinophils >1.9%	50.4%	57.81%	37.7%	60.38%
Blood Eosinophil Count ($x10^9/L$)	0.3 (0.1-0.5)	0.2±0.3	0.2 (0.1-0.4)	0.22±0.29

Data presented as mean±SD or median (IQR), n or %; NA= data not available

*Non-smokers defined as having not smoked for 12-months with <5-pack year smoking history

BMI (Body Mass Index), ICS (Inhaled Corticosteroids), BDP (Beclometasone Diproprionate), OCS (Oral Corticosteroids), GORD (Gastro-oesophageal Reflux Disease), AQLQ (Asthma Quality of Life Questionnaire), ACQ (Asthma Control Questionnaire), Pre-BD (Pre-Bronchodilator), $FeNO_{50}$ (Exhaled Nitric Oxide level at 50ml/sec flow rate).

Table 5 – Wessex Severe Asthma Cohort Detailed Characterisation Protocol

Demographics	• Age (yrs) • Gender • Predominant Race (Caucasian/Asian/Black/Other) • Smoking history (pack year history if ever smoked) • Height • Weight • BMI
Clinical Characteristics	**Asthma History:** • Age at diagnosis (yrs) • Predominant symptoms (Wheeze/Chest tightness/Breathlessness/Cough/Other) • Triggers (Cold air/Exercise/Climate/ Air pollution/Fumes/Allergens/Medications including aspirin sensitivity/Emotion/Hormonal/Foods/Workplace/Alcohol/Viral RTI/Other • Family history of asthma • Asthma treatments (BTS Stage/ICS Dose/Controller Medications/Anti-IgE) • Exacerbation history **Medical History:** • Medical& surgical co-morbidity including rhino-sinusitis / gastro-oesophageal reflux / depression • Current treatments
Questionnaires	**Disease Control:** • Asthma Control Questionnaire 7 • Asthma Control Diary **General Quality of Life:** • Short Form 36 Health Survey **Asthma Specific Quality of Life:** • Asthma Quality of Life Questionnaire (Symptoms / Activity / Emotional / Environmental / Total) **Rhino-sinusitis Assessment:** • Sino-nasal Outcome Test (20) **Anxiety and Depression Assessment:** • Hospital Anxiety and Depression Score (Anxiety / Depression / Total)
Physiological Measures	• Random oscillometry pre and post-bronchodilator (R4-16 / R0 / I / FN) • Impulse oscillometry pre and post-bronchodilator (Z at 5Hz / R at 20 Hz / R at 5 Hz / X at 5Hz / AX / Resonant Frequency) • Spirometry pre and post-bronchodilator (FEV_1 / FVC / FEV_1/FVC Ratio / MEF 75 / MEF 50 / MEF25 / PEF) with % reversibility derived from this. • Carbon monoxide transfer factor (Vinsp / V Asb / TLco / Kco) • 2-week PEF diary
Measures of Atopic Status	• Allergy history (Perennial or seasonal allergy / Food allergy / Drug allergy / Antihistamine use) • Skin prick testing(Aspergillus fumigatus / Alternaria tenuis / Grass pollen / Birch / Rape / Dermatophagoides pteronyssinus / Dermatophagoides farinae / Dog / Cat • Serum total IgE
Biological Measures	• Exhaled Nitric Oxide (FeNO) at 50ml/sec low rate (ppb) • Nasal Nitric Oxide Measurements **Nasal Lavage:** • Tryptase (ng/ml) • Eosinophilic Cationic Protein (ng/ml) • Myeloperoxidase (ng/ml) • α-2 macroglobulin (ng/ml) **Serum:** • Periostin level • Staphylococcus aureus enterotoxin IgE • Peripheral blood eosinophil & neutrophil count ($x10^9$/L) • High-sensitivity C-Reactive Protein (mg/L) • Eosinophilic Cationic Protein (ng/ml) • IL-6 (pg/ml) • ST2/IL-1R4(pg/ml) • YKL-40(ng/ml)

	Induced Sputum: • Inflammatory Cell Counts (Macrophages / Neutrophils / Eosinophils / Lymphocytes / Epithelial Cells / Squamous Cells) • IL-10(pg/ml) • IL-5(pg/ml) • IL-4 (pg/ml) • IL-1receptor antagonist(pg/ml) • IL-1α (pg/ml) • IL-1 β (pg/ml) • Granulocyte Macrophage Colony-Stimulating Factor (pg/ml) • Vascular Endothelial Growth Factor (pg/ml) • IL-17 (pg/ml) • Monocyte Chemotactic Protein 1/CCL2 (pg/ml) • Tumour Necrosis Factor-α (pg/ml) • Macrophage Inflammatory Protein 1β/CCL4 (pg/ml) • Fibroblast Growth Factor (pg/ml) • Granulocyte Colony-Stimulating Factor (pg/ml) • Interferon-γ (pg/ml) • IL-2 (pg/ml) • Macrophage Inflammatory Protein 1α/CCL3(pg/ml) • Eotaxin (pg/ml) • TIMP MetallopeptidaseInhibitor 1(ng/ml) • Matrix metalloproteinase-1 (pg/ml) • Matrix metalloproteinase-2 (pg/ml) • Matrix metalloproteinase-3 (pg/ml) • Matrix metalloproteinase-7 (pg/ml) • Matrix metalloproteinase-8 (pg/ml) • Matrix metalloproteinase-9 (pg/ml) • Matrix metalloproteinase-12 (pg/ml) • Matrix metalloproteinase-13 (pg/ml) • IL-6 (pg/ml) (PBS & DTE) • IL-6 Soluble Receptor (pg/ml) • Tryptase(ng/ml) (DTE) • Eosinophilic Cationic Protein (ng/ml) (DTE) • Myeloperoxidase (ng/ml) (DTE) • YKL-40 (ng/ml) (DTE) • Osteopontin(pg/ml) • CXCL5/ENA-78 (pg/ml) • IL-8 (pg/ml) (DTE) • CXCL1/Gro-α (pg/ml) (DTE) • α-2 macroglobulin (ng/ml) (DTE) • Elastase (ng/ml) • IL-13 (pg/ml) **Urine:** • Urinary eosinophil-derived neurotoxin/protein X (mg/ml) • Urinary Cotinine
Additional Measures:	• University of Pennsylvania Smell Identification Test • HRCT Chest

Table 6: Summary of Trial Eligibility Criteria (Phase IIb/III RCTs of Novel Therapies in Severe Asthma since 2000)

Target	Drug	Authors	Year	Phase	Trial Number	N	Eligibility Criteria								
							Steroid Dose		Airflow Obstruction	Reversibility	Exacerbation Frequency	Asthma Control	BMI or Weight	Smoking	Biomarker criterion
							ICS	OCS							
IgE	Omalizumab	Holgate et al[17]	2004	III	x	246	•		•	•				•	•
		Humbert et al[18]	2005	II	x	419	•	•	•	•	•			•	•
		Hanania et al[19]	2011	III	NCT00314575	850	•		•	§	•		•	•	•
IL-5	Mepolizumab	Haldar et al[20]	2009	II	ISRCTN75169762	61	•		•	§	•			•	•
		Nair et al[21]	2009	II	NCT00292877	20	•	•	•					§	•
		Pavord et al[22]	2012	III	NCT01000506	621	•		•	§	•		•	•	§
		Bel et al[23]	2014	III	NCT01691508	135	•	•	•	§			•	•	•
		Ortega et al[24]	2014	III	NCT01691521	576	•		•	§	•		•	•	•
		Chupp et al[25]	2017	III	NCT02281318	556	•		•	§	•			•	•
	Reslizumab	Castro et al[26]	2011	II	x	106	•	•	•	§		•		•	•
		Castro et al[27]	2015	III	NCT01287039	489	•	•		•	•	•		•	•
		Castro et al[27]	2015	III	NCT01285323	464	•	•		•	•	•		•	•
		Bjermer et al[28]	2016	III	NCT01270464	315	•			•		•		•	•
		Corren et al[29]	2016	III	NCT01508936		•	•		•		•		•	
	Benralizumab	Bleecker et al[30]	2016	III	NCT01928771	1205	•		•	•	•	•	•	•	
		FitzGerald et al[31]	2016	III	NCT01914757	1306	•		•	•	•	•	•	•	
IL-13	Tralokinumab	Piper et al[32]	2013	II	NCT00873860	194		•	•	§	•	•	•	•	
		Brightling et al[33]	2015	II	NCT01402986	452	•		§	§	•	§	•	•	
	Lebrikizumab	Corren et al[34]	2011	II	NCT00930163	219	•	•	•	•		•	•	•	
		Hanania et al[35]	2016	III	NCT01867125	1081	•	•	•	•		•		•	
		Hanania et al[35]	2016	III	NCT01868061	1068	•	•	•	•		•		•	
	GSK679586	De Boever et al[36]	2014	II	NCT00843193	198	•		•	•		•		•	
IL-4Rα	AMG317	Corren et al[37]	2010	II	NCT00436670	294	•	•	•	•		•		•	•
	Dupilumab	Wenzel et al[38]	2013	II	NCT01312961	104	•	•	•	•	•	•		•	§
		Wenzel et al[39]	2016	II	NCT01854047	769	•	•	•	•	•	•		•	
	Pitrakinra	Slager et al[40]	2012	II	NCT00801853	534	•	•	•	§	•	•		•	
IL-4/5	Suplatast	Tamaoki et al[41]	2000	II	x	85	•	•	•	•				•	
DP2 receptor	Fevipiprant	Gonem et al[42]	2016	II	NCT01545726	61		•		§	•	•		•	•
IL-2Rα	Daclizumab	Busse et al[43]	2008	II	NCT00028288	115	•	•	•	•				•	•
TSLP	Tezepelumab	Corren et al[44]	2017	II	NCT02054130	584	•	•	•	•	•	•	•	•	
c-kit/PDGF	Masitinib	Humbert et al[45]	2009	II	NCT00842270	44	•	•		•				•	•
CXCR2	Navarixin	Nair et al[46]	2012	II	NCT00632502	34	•		•	§				•	•
	AZD5069	O'Byrne et al[47]	2016	II	NCT01704495	640	•		•		•			•	•
IL17RA	Brodalumab	Busse et al[48]	2013	II	NCT01199289	302	•	•	•	•		•			
TNFα	Entanercept	Morjaria et al[49]	2008	II	x	39	•			§				•	
		Holgate et al[50]	2011	II	NCT00141791	132	•	•	•	•		•		•	
	Golimumab	Wenzel et al[51]	2009	II	NCT00207740	309	•			§	•	•		•	
Multiple	BT	Castro et al[52]	2010	III	NCT00231114	288	•	•	•		•			•	
	Azithromycin	Brusselle et al[53]	2013	III	NCT00760838	109	•			§	•			•	•
		Gibson et al[54]	2017	III	AZNCTR12609000197235	420	•			§				•	
	TLA	Storrar et al[55]	2017	III	ISRCTN46346208	222	•			§	•	•		•	•

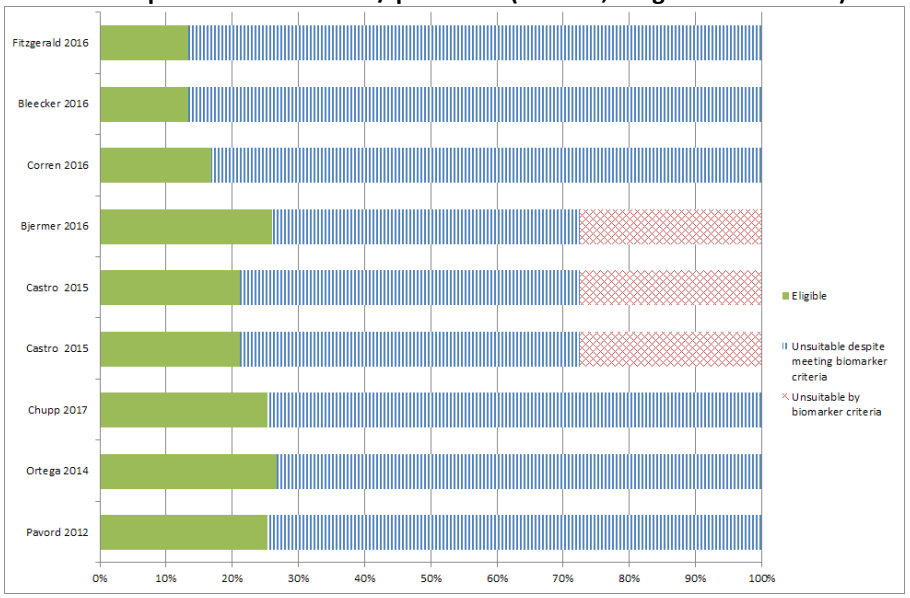
• Criteria used; § Composite criteria used

Table 7: Summary of Trial Eligibility (Phase IIb/III RCTs of Novel Therapies in Severe Asthma since 2000)

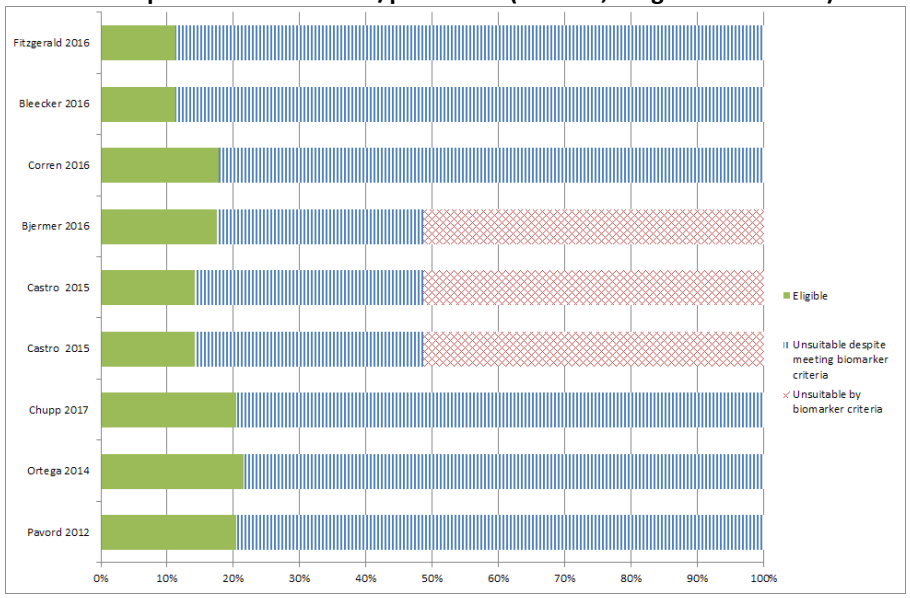
Drug	Authors	Year	Phase	Meet Eligibility Criteria (%)									Eligible (%)	
				Steroid Dose		Airflow Obstruction	Reversibility	Exacerbation Frequency	Asthma Control	BMI	Smoking	Biomarker criteria	Asthma Criteria	Overall
				ICS	OCS									
Omalizumab	Holgate et al[17]	2004	III	69.6%	100.0%	54.4%	38.9%	100.0%	100.0%	100.0%	67.3%	36.8%	12.6%	3.5%
	Humbert et al[18]	2005	II	93.9%	92.7%	54.4%	43.3%	79.5%	100.0%	100.0%	67.3%	36.8%	11.7%	4.1%
	Hanania et al[19]	2011	III	69.6%	100.0%	54.4%	81.9%	100.0%	100.0%	98.8%	67.3%	36.8%	18.4%	6.1%
Mepolizumab	Haldar et al[20]	2009	II	85.1%	100.0%	66.7%	81.6%	74.0%	100.0%	100.0%	72.8%	25.2%	23.1%	7.9%
	Nair et al[21]	2009	II	85.7%	34.2%	87.7%	100.0%	100.0%	100.0%	100.0%	82.7%	25.2%	23.1%	5.6%
	Pavord et al[22]	2012	III	72.2%	100.0%	66.7%	100.0%	74.0%	100.0%	99.7%	67.3%	57.3%	23.1%	17.5%
	Bel et al[23]	2014	III	72.2%	28.9%	66.7%	100.0%	100.0%	100.0%	99.7%	68.7%	69.6%	8.8%	4.1%
	Ortega et al[24]	2014	III	72.2%	100.0%	66.7%	100.0%	74.0%	100.0%	99.7%	68.7%	69.6%	24.0%	15.8%
	Chupp et al[25]	2017	III	72.2%	100.0%	66.7%	100.0%	74.0%	100.0%	100.0%	67.3%	69.6%	23.4%	14.9%
Reslizumab	Castro et al[26]	2011	II	72.2%	65.8%	76.3%	86.3%	100.0%	86.5%	100.0%	83.3%	25.2%	22.8%	4.7%
	Castro et al[27]	2015	III	93.9%	84.2%	100.0%	43.3%	100.0%	86.0%	100.0%	83.3%	45.3%	23.7%	8.8%
	Castro et al[27]	2015	III	93.9%	84.2%	100.0%	43.3%	100.0%	86.0%	100.0%	83.3%	45.3%	23.7%	8.8%
	Bjermer et al[28]	2016	III	93.9%	100.0%	100.0%	43.3%	100.0%	86.0%	100.0%	83.3%	45.3%	29.2%	10.8%
	Corren et al[29]	2016	III	93.9%	65.8%	100.0%	43.3%	100.0%	86.5%	100.0%	83.3%	100%	15.5%	15.5%
Benralizumab	Bleecker et al[30]	2016	III	93.9%	100.0%	66.7%	38.9%	74.0%	86.5%	99.7%	67.3%	100%	11.1%	11.1%
	FitzGerald et al[31]	2016	III	93.9%	100.0%	66.7%	38.9%	74.0%	86.5%	99.7%	67.3%	100%	11.1%	11.1%
Tralokinumab	Piper et al[32]	2013	II	100.0%	84.2%	87.7%	81.9%	100.0%	86.5%	86.3%	67.3%	100%	26.9%	26.9%
	Brightling et al[33]	2015	II	93.9%	100.0%	54.4%	81.9%	63.2%	86.5%	86.8%	68.7%	100%	11.4%	11.4%
Lebrikizumab	Corren et al[34]	2011	II	59.6%	65.8%	54.4%	43.3%	100.0%	86.5%	98.5%	68.7%	100%	6.1%	6.1%
	Hanania et al[35]	2016	III	89.5%	65.8%	54.4%	43.3%	100.0%	86.5%	100.0%	68.7%	100%	7.6%	7.6%
	Hanania et al[35]	2016	III	89.5%	65.8%	54.4%	43.3%	100.0%	86.5%	100.0%	68.7%	100%	7.6%	7.6%
GSK679586	De Boever et al[36]	2014	II	93.9%	100.0%	58.2%	43.3%	100.0%	86.0%	100.0%	70.5%	100%	18.4%	18.4%
AMG317	Corren et al[37]	2010	II	59.6%	65.8%	43.0%	43.3%	100.0%	86.5%	100.0%	67.3%	73.7%	3.8%	3.5%
Dupilumab	Wenzel et al[38]	2013	II	93.9%	65.8%	43.0%	38.9%	100.0%	47.7%	100.0%	68.7%	36.6%	2.9%	2.1%
	Wenzel et al[39]	2016	II	93.9%	84.2%	54.4%	38.9%	100.0%	86.5%	100.0%	68.7%	100%	10.5%	10.5%
Pitrakinra	Slager et al[40]	2012	II	93.9%	65.8%	61.4%	81.9%	100.0%	100.0%	100.0%	67.3%	100%	23.4%	23.4%
Suplatast	Tamaoki et al[41]	2000	II	83.6%	65.8%	62.6%	34.5%	100.0%	100.0%	100.0%	83.3%	100%	6.4%	6.4%
Fevipiprant	Gonem et al[42]	2016	II	100.0%	84.2%	100.0%	100.0%	100.0%	86.0%	100.0%	83.3%	27.2%	59.7%	16.7%
Daclizumab	Busse et al[43]	2008	II	93.9%	65.8%	43.0%	43.3%	100.0%	100.0%	100.0%	67.3%	73.7%	6.7%	5.3%
Tezepelumab	Corren et al[44]	2017	II	99.4%	84.2%	54.4%	38.9%	79.5%	86.5%	86.3%	67.3%	100%	6.4%	6.4%
Masitinib	Humbert et al[45]	2009	II	93.9%	22.5%	100.0%	43.3%	100.0%	100.0%	100.0%	67.3%	99.1%	5.6%	5.3%
Navarixin	Nair et al[46]	2012	II	93.9%	100.0%	93.6%	81.9%	100.0%	100.0%	100.0%	74.0%	36.8%	55.6%	19.9%
AZD5069	O'Byrne et al[47]	2016	II	93.9%	100.0%	67.8%	100.0%	79.5%	100.0%	100.0%	74.0%	71.9%	37.7%	25.2%
Brodalumab	Busse et al[48]	2013	II	59.6%	65.8%	43.0%	43.3%	100.0%	86.5%	100.0%	100.0%	100%	6.7%	6.7%
Entanercept	Morjaria et al[49]	2008	II	69.6%	100.0%	100.0%	86.3%	100.0%	100.0%	100.0%	67.3%	100%	39.5%	39.5%
	Holgate et al[50]	2011	II	93.9%	84.5%	43.0%	51.8%	100.0%	74.6%	100.0%	67.3%	100%	8.2%	8.2%
Golimumab	Wenzel et al[51]	2009	II	93.9%	100.0%	100.0%	86.3%	74.0%	74.6%	100.0%	67.3%	100%	30.7%	30.7%
BT	Castro et al[52]	2010	III	93.9%	84.2%	62.6%	100.0%	68.4%	100.0%	100.0%	67.3%	100%	26.3%	26.3%
Azithromycin	Brusselle et al[53]	2013	III	69.6%	100.0%	100.0%	86.3%	74.0%	100.0%	100.0%	67.3%	74.0%	31.6%	20.8%
	Gibson et al[54]	2017	III	99.4%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	81.0%	100%	76.9%	76.9%
TLA	Storrar et al[55]	2017	III	93.9%	100.0%	100.0%	100.0%	74.0%	94.7%	100.0%	72.8%	73.7%	53.8%	41.5%

Figure 3: Trial Eligibility for Phase III IL-5 Targeted Treatments in Severe Eosinophilic Asthmatics Defined by Varying Levels of Sputum or Blood Eosinophilia

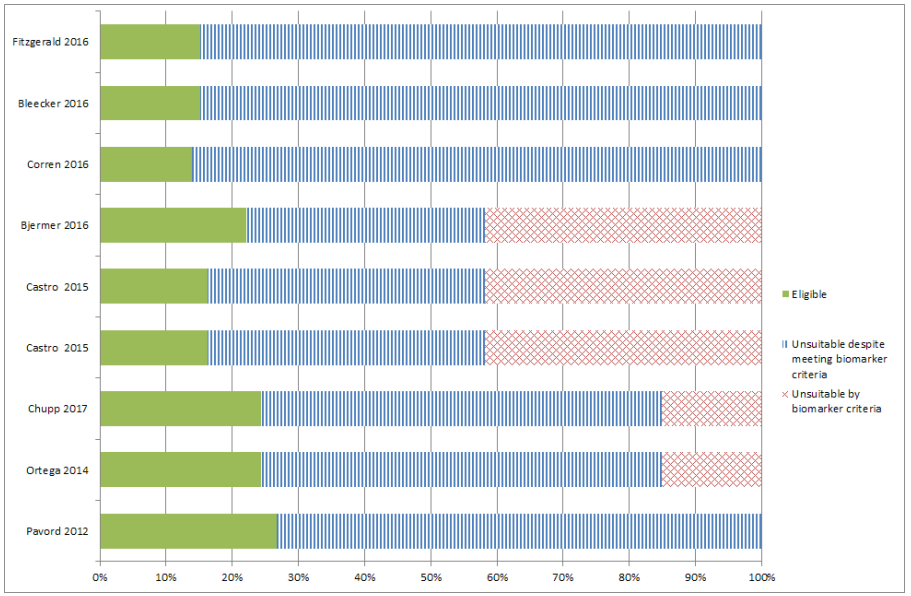
Blood Eosinophil Count ≥300 Cells/ µL - 21.1%(median; range 13.4% - 26.8%)



Blood Eosinophil Count ≥150 Cells/µL - 17.7% (median; range 11.3%-20.4%)



Sputum Eosinophil ≥3% - 16.3% (median; range 14.0% - 26.7%)



Sputum Eosinophil ≥2% - 16.1% (median; range 12.9% - 25.8%)

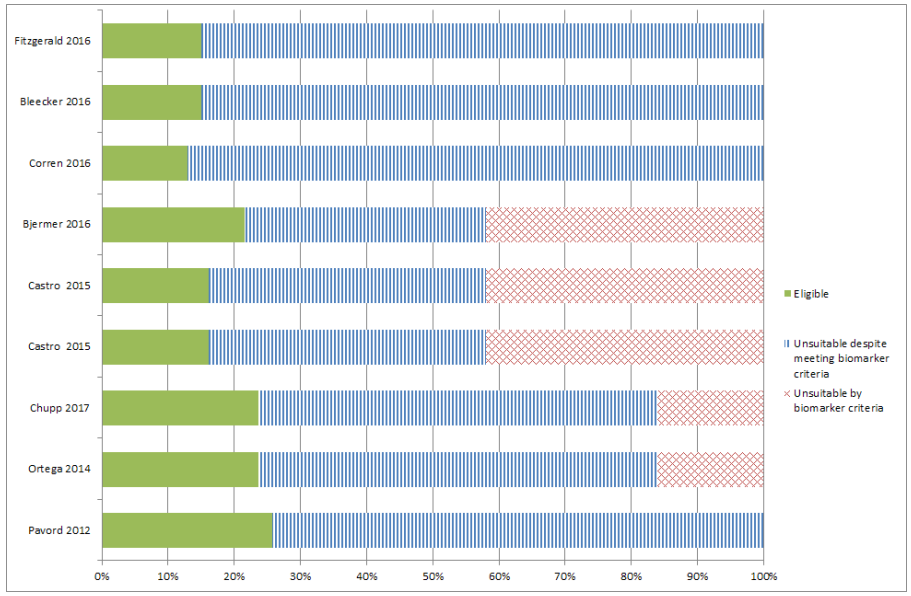


Table 8: NICE Eligibility Criteria for Biological Therapies Licensed for use in Severe Asthma

Mepolizumab (*NICE TA431; Jan 2017)*	**Reslizumab (***NICE TA479; Oct 2017)*
Severe refractory eosinophilic asthma	
Blood eosinophil count ≥300 cells/μL in last 12 months	Blood eosinophil count ≥400 cells/μL in last 12 months
≥4 severe exacerbations in last 12-months or maintenance oral corticosteroids	≥3 severe exacerbations in last 12-months
Adherence confirmed, treatment optimised, co-morbidities and asthma triggers addressed	

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