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Take home message: Analysis of a real-world registry shows clinical remission rates of 18%; pre-biologics characteristics associated with clinical remission include male sex, never smoking, BMI <30kg/m2, shorter disease duration, high-T2 biomarkers & lower symptom burden.

Abstract:

Novel biologic therapies have revolutionised the management of severe asthma with more ambitious treatment aims. Here we analyse the definition of clinical remission as a suggested treatment goal and consider the characteristics associated with clinical remission in a large, real-world severe asthma cohort.

Methods: Retrospective analysis of severe asthma patients registered in the UK Severe Asthma Registry (UKSAR) who met strict national access criteria for biologics. Patients had a pre-biologics baseline assessment and annual review. Primary definition of clinical remission applied included Asthma Control Questionnaire <1.5 and no oral corticosteroids for disease control and FEV_1 ≥lower limit of normal (LLN) or ≤-100mls change from baseline.

Results: 18.3% of patients achieved the primary definition of remission. The adjusted odds of remission on biologic therapy were 7.44-fold higher in patients with high T2-biomarkers (95%CI 1.73,31.95). The adjusted odds of remission were lower in patients who were female (OR 0.61, 95%CI 0.45,0.93), obese (OR 0.49, 95%CI 0.24,0.65) or have an ACQ≥1.5 (OR 0.19, 95%CI 0.12,0.31) pre-biologic therapy. The likelihood of remission reduced by 14% for every 10-year increase in disease duration (95%CI 0.76,0.97).

12 to 21% of the cohort attained clinical remission depending on the definition applied; most of those who did not achieve remission failed to meet multiple criteria.

Conclusion: 18.3% of patients achieved the primary definition of clinical remission. Remission was more likely in T2 biomarker high patients with shorter duration of disease and less comorbidity. Further research on the optimum time to commence biologics in severe asthma is required.

Introduction:

Asthma is a heterogenous disease of the airways characterised by variable airways hyper-responsiveness and chronic inflammation. It is estimated that 5-10% of asthmatic patients have 'severe asthma', defined by the European Respiratory Society/American Thoracic Society as 'asthma which requires treatment with GINA step 4-5 treatment or oral corticosteroids (OCS) for 50% of the last year to prevent it becoming uncontrolled' (see online supplement).[1,2]

Biologics targeting the Type-2 (T2) cytokine pathway have reduced reliance on oral corticosteroids (OCS) and revolutionised the management of severe asthma to the extent that there is a need for a defined treatment goal that reflects disease quiescence or stability on treatment.[3] In other chronic inflammatory diseases, such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), this is termed 'clinical remission'.[4–6]

In severe asthma, a modified Delphi exercise identified core components of disease remission based on the definitions in other chronic inflammatory diseases.[8] They identified different targets noting that complete remission (no evidence of T2 biomarkers, absence of symptoms and no corticosteroid exposure) was unlikely to be an achievable goal in severe asthma, but that clinical remission on treatment was a 'pragmatic, valuable goal'.[8] The Delphi exercise defined clinical remission as a multi-component outcome including (a) no use of systemic corticosteroids for exacerbation or disease control (b) absence of significant symptoms using a validated instrument, (c) lung function optimisation/stabilization, and (d) patient/provider agreement that clinical remission has been achieved. Although a useful first step in defining clinical remission, it was recognised that a precise definition of ' absence of significant symptoms' and 'lung function optimization and stabilisation' needed further work, and perhaps more importantly, by its own admission, did not attempt to apply this definition to a patient cohort. Another view has suggested that short acting beta-agonist (SABA) use should be an important part of the definition of remission.[9]

Clinical remission in severe asthma is not the same as spontaneous remission which can occur in mild asthma, or a 'cure', which usually refers to complete remission from all manifestations of the disease, whilst off all treatment for a prolonged period of time. Clinical remission has been explored in clinical trial populations and real-world cohorts of patients with severe asthma,[10–13] although direct comparison of these analyses is difficult given different treatments, variable definitions of clinical remission and heterogeneity of asthma severity within these studies.[10–13] In other inflammatory diseases, the definition of clinical remission has been refined over many years,[14–17] and a similar evolution of the definition is anticipated in the future.

The UK Severe Asthma Registry (UKSAR) is a national database of patients with uncontrolled asthma referred to specialist UK severe asthma centres.[18] Biologic access for severe asthma in the UK is restricted on the basis of cost-effectiveness by the National Institute of Clinical Healthcare Excellence (NICE), so only patients on maintenance OCS for disease control or requiring ≥3 courses of prednisolone/year meet access criteria. The objective of this analysis was to utilise this large, real-world cohort of well-characterised severe asthma patients to examine various definitions of clinical remission and assess the pre-biologic clinical characteristics associated with achieving remission.

Methods:

This retrospective, observational analysis includes severe asthma patients registered in UKSAR from specialist, severe asthma services in the UK since January 2016. All patients were ≥18 years old, met ERS/ATS criteria for severe asthma, met NICE access criteria for biologics (see online supplement), had baseline assessment at registration and at least one annual review assessment within 9-24

months. The registry has been described elsewhere (17) and has ethical approval for collecting and storing such data with each patient's written consent (Office of Research Ethics Northern Ireland reference 15/ NI/0196). A flow diagram for construction of the cohort is given in Figure S1.

The primary definition of remission was as follows: at annual-review, asthma control questionnaire (ACQ) <1.5 and no OCS for disease control (no OCS bursts for exacerbations in the last 12 months, no maintenance OCS (mOCS) for disease control (OCS ≤5mg/day for Hypothalamic-pituitary-adrenal (HPA) axis suppression permitted), and an FEV_1 above the lower limit of normal (LLN) or no more than 100mls less than baseline, pre-biologics FEV_1. Sensitivity analysis with different definitions of clinical remission were applied as below.

Statistical methods:

No formal sample size calculation was performed and all available data from UKSAR was used. Descriptive statistics were used to summarise the cohort. Demographic and clinical characteristics at baseline were compared by remission status at 12-months using the Mann-Whitney U, Chi-squared and Fishers' Exact tests. Within-patient differences between initial assessment and annual review were compared using the one sample Mann-Whitney U and McNemar's tests.

Multivariable associations between baseline demographic-clinical characteristics and remission were estimated using logistic regression, adjusting for time to first review and hospital. We chose this limited set of adjustment variables to prevent overadjustment bias, in which adjustment is made for variables that lie on the causal path between the exposure and outcome.(19,20) Model coefficients were converted to adjusted probabilities of remission for each category with confounders fixed at their mean values; both marginal probabilities and Odds Ratios (OR) are reported. Supplementary analyses additionally adjusted for baseline ACQ5 and baseline exacerbations. Discrimination for the full model (including all explanatory variables) was assessed using a receiver operating characteristic curve, and the discriminatory performance was quantified using the area under the curve (AUC).

Where analysis includes T2-biomarker values, a blood eosinophil count (BEC) of ≥0.15x10^9 and fractional exhaled nitric oxide (FeNO) ≥20ppb are used to describe evidence of T2 inflammation in keeping with GINA guidelines.(21) Obesity was defined as a BMI ≥30Kg/m^2.

Sensitivity analyses were undertaken to examine the impact of different definitions of clinical remission:

a) ACQ <1.5, AND no OCS for disease control, AND an FEV_1 above the LLN or no more than 100mls less than baseline, pre-biologics FEV_1
b) ACQ5 <1.5, AND no OCS for disease control AND FEV_1 above LLN or no more than 5% lower than at pre-biologics assessment
c) ACQ5 <1.5, AND no OCS for disease control AND FEV_1 above LLN or no lower than at pre-biologics assessment
d) ACQ5 <1.5, AND no OCS for disease control
e) ACQ5 <1.5, AND no OCS for disease control, AND no SABA
f) ACQ5 <1.5, AND no OCS for disease control AND ≤2 puffs of SABA per day
g) ACQ <=0.75, AND no OCS for disease control, AND an FEV_1 above the LLN or no more than 100mls less than baseline, pre-biologics FEV_1

STATA 16.0SE (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC) was used to perform the analyses using a complete-case framework.

Results:

A total of 1111 patients met study inclusion criteria across 14 specialist centres (Fig S1). The baseline demographic and clinical details for the entire cohort are outlined in Table 1 (data completeness and scalar variables Tables S1,S2,S3). Of this cohort, 830 had all explanatory variables for the primary definition of remission, their baseline demographics are displayed in Table S4 (data completeness and scalar variables Tables S5,S6). This cohort had substantial OCS exposure, a high exacerbation count, high T2 biomarkers and symptom burden. Table S7 outlines changes in outcomes from commencing biologics to 1-year review with significant clinical improvements in exacerbations, acute care utilization, FEV_1 and reported symptom burden.

Baseline characteristics of remission; remission definition ACQ <1.5, and no OCS for disease control or exacerbation, and FEV_1 above LLN or ≤-100mls from baseline.

In total, 18.3% (152/830, (95% CI15.7%,21.1%) of patients met the primary definition for clinical remission after one year of biologic therapy. Remission was more common in males (males 22% (75/341) versus females 15.7% (77/489), p=0.022), who were slightly older commencing biologics (55 (48,65) *versus* 51 (41,59) years, p<0.001) and had a shorter duration of asthma (20 (8,32) *versus* 25 (12,37) years, p=0.008) (Table 2). Remission was associated with never smoking, nasal polyps, white ethnicity, and a lower BMI. The remission cohort were more likely to be T2 composite high (BEC/FeNO) prior to commencing biologics, with both higher FeNO and highest-recorded BEC (Table 2, Tables S4-S6).

The non-remission cohort had a greater incidence of depression-anxiety (13% *versus* 2%, p<0.001), higher number of exacerbations (5 (3,8) *versus* 4 (3,6), p<0.001), ED attendances (39% *versus* 23%, p<0.001) and hospital admissions (41% *versus* 30%, p=0.004). FEV_1(%) was slightly lower in the non-remission cohort, although FEV_1/FVC was no different. Baseline symptom burden was greater (ACQ5 3.2 (2.2,4.2) *versus* 2.0 (1.2,3.4), p<0.001), quality of life more impaired and a trend towards increased mOCS use in than those who did not achieve remission (Table 2, S8).

There were distinct differences between the group of patients that achieved remission and those that did not; age commencing biologics, obesity, smoking status, composite T2-status, comorbid anxiety-depression and ACQ5, continue to be significantly different between the cohorts when adjusting for potential confounders including hospital site and time to review (Figure 1, Table S9).

Clinical remission was more likely with a shorter duration of symptoms; every increasing 10 years duration of asthma symptoms before commencing biologics was associated with a 14% decreased odds of achieving remission (adjOR 0.86 (0.76,0.97), p=0.013), such that, an individual commencing biologics with over 30 years of asthma symptoms is 49% less likely to achieve remission than someone with a duration of symptoms of less than 10 years (adjOR 0.51 (0.31,0.84),p=0.008). Being older when commencing biologics was associated with increased remission, with every increasing 10 years of age at pre-biologics assessment, the odds of remission increased by 31% (adjOR1.31, (1.15,1.50),p<0.001). The odds of remission for those who were composite T2-high (BEC/FeNO high) was 7.44 times as high as the composite T2-low group (adjOR 7.44 (1.73,31.95), p=0.007), Figure 1, Table S9.

Women were 36% less likely to achieve remission (adjOR 0.64 (0.45,0.93), p=0.018). The odds of remission were 47% lower in obese compared to non-obese patients (adjOR 0.53 (0.34,0.82), p=0.004), and with every increased unit of BMI ≥30 kg/m^2 a patient was 5% less likely to achieve remission (adjOR 0.95 (0.92,0.98), p<0.001). Comorbid depression-anxiety (adjOR 0.13 (0.04,0.43), p=0.001), and a higher pre-biologics symptom burden (ACQ ≥1.5 adjOR remission 0.19 (0.12,0.31), p<0.001) were associated with a significantly lower odds of remission. Anti-IgE therapy was

associated with 81% lower odds of remission than anti-IL5 biologics [n.b. access criteria and thereby patient population receiving these therapies are different] (Figure 1, Table S9). Ethnic disparities lose significance when adjusted for hospital site and baseline morbidity (adjOR 0.53 (0.26,1.07), p=0.077), Figure 1, Table S9. The adjusted probabilities of achieving clinical remission for each covariate are plotted in Figure S2.

A receiver operating curve (ROC) suggests good discrimination of the full model predicting remission (AUC 0.81, (95%CI 0.76,0.86) Figure 2), with ACQ5 being the best prognostic marker (Table S10). Most of those who did not meet the criteria for remission failed to meet a number of individual remission criteria (Figure 3).

Remission: definition ACQ <1.5, and no OCS for disease control, and FEV_1 above LLN or ≥ -5% FEV_1 reduction from baseline

Using a proportional reduction in FEV_1 (5%), rather than an actual volume reduction (100mls), in the definition of remission did not affect the rates of remission (18.3%, 152/830, (95% CI15.7%,21.1%). This definition did not change the baseline characteristics associated with remission and non-remission (Table S11 and Figure S3).

Remission: definition ACQ <1.5, and no OCS for disease control, and FEV_1 above LLN or ≥ baseline FEV_1

Applying a stricter FEV_1 criteria for remission (FEV_1 no lower than baseline) had minimal impact on the remission analysis (17.7% (147/830, (95% CI 15.2%, 20.4%) achieved remission), and did not substantially change the characteristic differences between the remission and non-remission cohorts (See Table S12 and Figure S4).

Remission: definition ACQ <1.5, and no OCS for disease control

A definition of remission which included only two criteria for remission and did not have any lung function criteria resulted in a slightly higher rate of remission (21.2% (196/925) remission, (95% CI 18.6%, 24.0%). Compared to analyses including FEV_1 in the remission definition, this definition had no difference in outcomes in ethnicity (p=0.060). (Table S13 and Figure S5).

Remission: definition ACQ5 <1.5, AND no OCS for disease control, AND no SABA

Only 13.8% (123/891, (95% CI 11.6%, 16.2%) of the cohort reached remission using this criterion, of which 75% (667/891) did not meet SABA criteria, 67% (594/891) did not meet OCS criteria and 60% (533/891) did not meet the ACQ criteria. In this analysis, compared to the primary definition of remission, the difference in gender, ethnicity, atopic disease and T2-biomarker composite groups was lost between those who met the difference in remission and those who did not. (Table S14, Figure S6).

Remission definition using ACQ5 <=0.75 and no OCS for disease control, and FEV_1 above LLN or ≤-100mls from baseline.

When applying a definition of remission which includes more stringent asthma control (ACQ5<=0.75, no mOCS or bursts for exacerbations and FEV_1≥100mls from baseline or ≥LLN), only 11.9% (99/830, (95% CI 9.8%, 14.3%) met the definition of remission (Table S16, Figure S8)

Discussion:

In this analysis of patients with severe asthma from a large national registry, 18% met the primary definition of remission, with distinct clinical and demographic characteristics seen in the remission versus non-remission cohorts.

At baseline, this cohort were typical of a severe asthma patient population and had considerable corticosteroid use with elevated T2-biomarkers, high exacerbation rate, impaired lung function and a high symptom burden. With use of biologic therapy, after 1-year, acute exacerbations and emergency healthcare utilisation were substantially reduced with improved patient reported outcome measures (PROMS), however only a minority of patients achieved clinical remission.

Clinical remission was more commonly achieved in males, never smokers and non-obese individuals with higher T2-biomarkers. These patients were older at disease onset, with shorter disease duration, lower symptom score and fewer exacerbations at initiation of biologic therapy.

Non-remission was more common with earlier asthma onset and longer disease duration prior to commencing biologics, with greater exacerbation burden and resultant OCS exposure. Asthma exacerbations are associated with accelerated lung function decline compared to aged-matched peers (healthy controls and non-exacerbating asthmatics), with the effect of multiple exacerbations being cumulative, and we see lung function was lower in the non-remission cohort with a higher exacerbation burden.(22) Further, there is evidence for OCS toxicities at relatively low exposure, increasing with cumulative dose, and a greater risk of comorbidities in young adults compared to age-matched non-OCS exposed controls.(23-25) Non-remission was associated with female sex, obesity, comorbid depression-anxiety and frequent exacerbations and these factors have previously been associated with poor asthma outcomes in non-biologic severe asthma cohorts.(26-28) It is recognised that comorbid conditions such as obesity, anxiety-depression and breathing-pattern disorder can cause persistent symptoms in this population which are captured on asthma control PROMs.(29-31) Whilst biologics can effectively address T2-inflammation, they are unlikely to address symptoms driven by these non-T2 related comorbidities, which require a different, multi-disciplinary team approach.(29) Patients who achieved clinical remission had higher T2-biomarkers, which is in keeping with previous findings that these predict a better response to biologics.(3,32-36) Taken together, this data suggests that introduction of biologics earlier in the disease course, before comorbid disease associated with OCS exposure accumulates, may make asthma-remission a more realistic target for future generations of severe asthma patients.

The described clinical and demographic features associated with remission are present at initial assessment and the ROC analysis confirms that together the variables included in the regression model are highly discriminatory for predicting remission; however, no single feature was able to predict remission. Recognition of these clinical and demographic characteristics at baseline will help clinicians identify patients who are more likely to achieve clinical remission, and importantly to inform patient discussion about what can realistically be achieved with biologic treatment.

The criteria for clinical remission on treatment have been the subject of a series of consensus statements (8,9,37) but none of these have been prospectively validated to show that achieving clinical remission improves long-term clinical outcome. An essential criterion of all these statements is the removal of 'OCS for exacerbations and disease control'. In this cohort, there was an overall substantial reduction in exacerbations (5 (3,8) versus 1 (0,3) after one year of biologics, however despite this substantial impact, many patients failed to reach remission criteria because of ongoing OCS use.

Another criterion is the 'absence of significant symptoms', which is challenging as severe asthma patients are often highly symptomatic (18,38) and as discussed above, symptoms may be due to non-asthma comorbidity. Applying a 'controlled asthma' cut point of ACQ5 ≤0.75 (39) sets an ambitious target for most severe asthma patients and was only achieved in 21% (178/830) of this cohort. However, even when using a threshold of ACQ<1.5, (the threshold for uncontrolled asthma(39) only 40% (330/830) achieved this target. The cut point for symptom control in the definition of remission will be part of the evolving discussion on this topic, and a recent consensus statement suggested remission should be reserved for an ACQ<0.75 and reliever use ≤1/month.(40) Accepting that a good clinical response is not the same as clinical remission, it therefore may not be appropriate to use an ACQ5 cut point of <1.5 for this definition. Patient input and evaluation of symptom burden in patients where biologics have been introduced earlier with a shorter duration of disease and less OCS exposure will be useful in considering this matter in the future.

Lung function criterion is not straightforward to consider longitudinally in severe asthma; FEV_1 measurement is influenced by natural daily variation, bronchodilator medication and natural lung function decline which varies with gender (~30ml/year in healthy women, and ~43ml/year in healthy men).(41-42) Additionally, there is no good evidence of what constitutes 'stable lung function' over time in severe asthma. This analysis demonstrates that using absolute value reduction of -100 ml, proportional reduction of -5% or baseline FEV_1 as a cut point for the definition of remission does not substantially affect the proportion of patients achieving remission, or significantly change the clinical characteristics of the remission/non-remission groups. Lung function assessment in biologic-treated severe asthma cohorts will require longitudinal assessment over years to draw evidence-based conclusions on what constitutes 'lung function stability', and whether the use of age-adjusted lung function equations is sufficient.(43)

In terms of the final criterion, specifically 'patient/clinician agreement on the achievement of remission', information on this issue was not available in this retrospective analysis. It will be important to explore this prospectively in future studies as shared decision making and agreement is an important aspect of clinical remission in other inflammatory diseases.(44-46)

Advantages of this analysis are its size and the 'real world' nature of the cohort. Limitations include the possibility of Type 1 error due to testing across multiple variables within the cohort, however, this is a hypothesis-generating study and logistic regression modelling was limited to a smaller number of variables. As with all 'real world' observational studies, there is an inherent possibility that the proportion of patients achieving remission may be overestimated due to regression to the mean, but it would be unethical to have a control arm for comparison.(47) Lastly, longitudinal data is needed to assess if clinical remission is maintained over time in severe asthma patients on biologics, and whether this improves clinical outcomes.

In summary, this severe asthma cohort benefited substantially from biologic therapy, although only 18% of patients achieved clinical remission using the proposed definition. The characteristics of those who attain remission and those who do not are described, with the suggestion that remission is achieved in patients with shorter duration of disease, fewer comorbidities and greater T2-imflammation. Further studies are needed to demonstrate that achievement and maintenance of disease remission improve long-term clinical outcomes in severe asthma and specifically whether earlier intervention with effective biologic treatment can improve long-term disease trajectory.

Table 1. Baseline demographics of the whole cohort at initial assessment prior to commencing biologics (n=1,111)

Variable	n	Category	Result
Time to first Annual Review (Years)	1,111		1.1 (1.0,1.3)
Sex	1,111	Female	667 (60.0%)
Age At First Assessment (Years)	1,111		52.0 (41.0,61.0)
Ethnicity	1,109	White	966 (87.1%)
Smoking Status	1,083	Never	723 (66.8%)
BMI (kg-m2)	1,099		29.8 (26.1,34.8)
Atopic Disease	1,111		567 (51.0%)
Depression or Anxiety	1,111		129 (11.6%)
Gastro-oesophageal Reflux	1,111		224 (20.2%)
Nasal polyps	1,111		237 (21.3%)
OCS bursts for exacerbation (Last Year)	1,086		5 (3,8)
Any OCS bursts (Last Year)	1,086		1,020 (93.9%)
Invasive Ventilations (Ever)	1,058		101 (9.5%)
Any ED Attendance for asthma (Last Year)	1,073		435 (40.5%)
Hospital Admissions for asthma (Last Year)	1,081		431 (39.9%)
Highest Blood Eosinophil Count recorded (N/10^9L) †	1,093		0.70 (0.44,1.10)
FeNO (ppb)	831		43.0 (24.0,75.0)
Composite T2-biomarker Group	811	Eos Low (<0.15) / FeNO Low (<20)	48 (5.9%)
		Eos High (≥0.15) / FeNO Low (<20)	111 (13.7%)
		Eos Low (<0.15) / FeNO High (≥20)	126 (15.5%)
		Eos High (≥0.15) / FeNO High (≥20)	526 (64.9%)
FEV_1 (L)	1,089		2.0 (1.5,2.6)
FEV_1 (% Predicted)	1,077		66.9 (52.1,81.5)
FVC (L)	1,062		3.1 (2.5,3.9)
FVC (% Predicted)	1,026		85.9 (73.4,97.8)
FEV_1/FVC	1,062		63.6 (53.7,72.1)
ACQ5 Score	954		3.2 (2.0,4.0)
Uncontrolled Asthma	954	ACQ5≥1.5	807 (84.6%)
Maintenance OCS	1,106		638 (57.7%)
Maintenance OCS (mg)	1,102634		10 (8,15)
Inhaled corticosteroids (ICS)	1,111		1,103 (99.3%)
ICS Dose (BDP equivalent-µg)	1,025		2000 (1600,2000)
Theophylline	1,099		299 (27.2%)
Long-acting β2-agonist (LABA)	1,094		1,013 (92.6%)
Long acting anti-muscarinic agent (LAMA)	1,095		709 (64.7%)
Leukotriene Receptor Antagonists	1,059		548 (51.7%)
Maintenance Macrolides	1,087		100 (9.2%)
Nebuliser use	1,092		241 (22.1%)
Biologic type commenced	981	Anti-IL5	828 (84.4%)
		Anti-IgE	150 (15.3%)
		Anti-IL4 Rα	3 (0.3%)
ERS-ATS Severe Asthma	1,111	Yes	1,111 (100.0%)

‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated.*among patients on oral corticosteroids**among patients on inhaled corticosteroids

BMI: Body Mass Index; OCS: Oral Corticosteroid Steroids; ED: Emergency Department; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: ICS: Inhaled Corticosteroid Steroids: BDP: Beclometasone Dipropionate; SABA: Short-Acting Beta-2 Agonists; LABA: Long-Acting Beta-2 Agonists; LAMA: Long-Acting Muscarinic Antagonist; ERS-ATS: European Respiratory Society-American Thoracic Society definition severe asthma 'asthma which requires treatment with GINA step 4-5 treatment or oral corticosteroids (OCS) for 50% of the last year to prevent it becoming uncontrolled'

Table 2: Baseline pre-biologics characteristics of those who meet remission versus those who do not meet remission at annual review (remission criteria ACQ5 <1.5, no mOCS or OCS bursts, FEV$_1$ above LLN or <100mls less than pre-biologic FEV$_1$).

Baseline variable	n	Category	Non-remission	Remission	p-value
	830		81.7% (678)	18.3% (152)	
Time to first Annual Review (Years)	830		1.1 (1.0,1.4)	1.1 (1.0,1.2)	0.097
Sex	830	Female	412 (60.8%)	77 (50.7%)	0.022
Age At First Assessment (Years)	830		51.0 (41.0,59.0)	55.0 (48.0,65.0)	<0.001
Age at Onset of Symptoms (Years)	737		20.0 (6.0,39.0)	32.0 (14.0,52.0)	<0.001
Duration Of Symptoms From Baseline (Years)	737		24.5 (12.0,37.0)	20.0 (8.0,32.0)	0.008
Ethnicity	828	White	583 (86.2%)	141 (92.8%)	0.028
Smoking status	809	Never	430 (64.9%)	109 (74.7%)	0.023
BMI (kg-m2)	823		30.5 (26.6,35.1)	27.9 (25.4,31.8)	0.001
Atopic Disease	830		355 (52.4%)	72 (47.4%)	0.226
Depression or Anxiety	830		85 (12.5%)	3 (2.0%)	<0.001
Gastro-oesophageal Reflux	830		119 (17.6%)	25 (16.4%)	0.745
Nasal polyps	830		123 (18.1%)	48 (31.6%)	<0.001
OCS bursts for exacerbation (Last Year)	817		5 (3,8)	4 (3,6)	<0.001
Any OCS bursts (Last Year)	817		624 (93.6%)	138 (92.0%)	0.493
Frequent Exacerbator at baseline	817	Yes (≥3 in Last Year)	554 (83.1%)	114 (76.0%)	0.043
Invasive Ventilations (Ever)	798		68 (10.5%)	8 (5.4%)	0.058
Any ED Attendance for asthma (Last Year)	807		259 (39.2%)	34 (23.3%)	<0.001
Any Hospital Admissions for asthma (Last Year)	814		270 (40.5%)	45 (30.4%)	0.022
Highest Blood Eosinophil Count (N/10^{9}L) †	821		0.68 (0.40,1.00)	0.79 (0.58,1.33)	<0.001
FeNO (ppb)	638		41.0 (22.0,72.0)	51.0 (35.0,81.0)	0.002
Composite Type 2 status	627	Eos Low (<0.15) / FeNO Low (<20)	38 (7.7%)	2 (1.5%)	0.004
		Eos High (≥0.15) / FeNO Low (<20)	69 (13.9%)	10 (7.6%)	
		Eos Low (<0.15) / FeNO High (≥20)	86 (17.3%)	21 (16.0%)	
		Eos High ≥0.15) / FeNO High (≥20)	303 (61.1%)	98 (74.8%)	
FEV$_1$ (L)	818		2.0 (1.5,2.6)	2.1 (1.6,2.7)	0.073
FEV$_1$ (% Predicted)	811		67.0 (52.4,81.2)	68.6 (55.0,88.2)	0.027
FVC (L)	802		3.1 (2.5,3.9)	3.3 (2.7,4.2)	0.048
FVC (% Predicted)	772		85.2 (73.8,97.0)	86.7 (75.8,99.4)	0.065
FEV$_1$/FVC	802		63.7 (54.3,72.2)	64.5 (54.4,73.6)	0.498
ACQ5 Score	736		3.2 (2.2,4.2)	2.0 (1.2,3.4)	<0.001
Uncontrolled Asthma	711	ACQ5 ≥1.5	531 (88.8%)	91 (65.9%)	<0.001
EuroQoL Health Scale	350		60.0 (40.0,70.0)	75.0 (50.0,85.0)	<0.001
EuroQoL Utility	362		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	826		398 (59.1%)	77 (50.7%)	0.059
Maintenance OCS (mg)*	474		10 (8,15)	10 (7,10)	0.001
Inhaled corticosteroids (ICS)	830		676 (99.7%)	151 (99.3%)	0.500
ICS Dose (BDP equivalent-μg)**	775		2000 (1600,2000)	2000 (1600,2000)	0.556
Theophylline	821		184 (27.3%)	32 (21.6%)	0.153
Short-acting β2-agonist (SABA)	823		643 (95.5%)	142 (94.7%)	0.644
Long-acting β2-agonist (LABA)	818		619 (92.8%)	144 (95.4%)	0.258
Long acting anti-muscarinic agent (LAMA)	821		420 (62.7%)	105 (69.5%)	0.113
Leukotriene Receptor Antagonists	799		327 (50.1%)	80 (54.8%)	0.303
Maintenance Macrolides	816		60 (9.0%)	9 (6.0%)	0.202
Nebuliser	819		164 (24.5%)	16 (10.7%)	<0.001

*among patients on oral corticosteroids**among patients on inhaled corticosteroids

‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV$_1$: Forced Expiratory Volume (1 second); FVC:

Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta-2 Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta-2 Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure 1: Forest plot of variables associated with remission included in the regression analysis*, adjusted for time to follow up and hospital site.

*ACQ5 <1.5, and no mOCS or OCS bursts and, FEV_1 above LLN or <100mls less than pre-biologic FEV1CI: Confidence Interval; BMI: Body Mass Index; Eos: Blood eosinophil count $(N/10^9L)$; FeNO: Fractional exhaled Nitric Oxide; OCS: Oral Corticosteroids; mOCS; maintenance OCS; ACQ: Asthma Control Questionnaire; FEV_1; Forced Expiratory Volume (1 second)

Figure 2: Receiver operating curve for explanatory variables included in clinical remission model*

Area under the curve (95% CI) 0.81 (0.76,0.86)

 * variables in the remission model include gender, age at commencing biologics, symptom duration, ethnicity, BMI, smoking history, depression/anxiety, composite T2 status, OCS bursts in the year prior to biologics, maintenance OCS, biologic mechanism, ACQ5.

Figure 3: Reasons for not meeting remission criteria after 1-year on biologic therapy

30% (202) failed to meet lung function criteria, 74% (500) failed to meet AQ5 criteria and 83% (562) failed to meet steroid criteria; 67% of those who did not achieve remission, failed to meet ≥2 of the remission criterion.

ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids: FEV_1; Forced Expiratory Volume (1 second); LLN: Lower Limit of Normal

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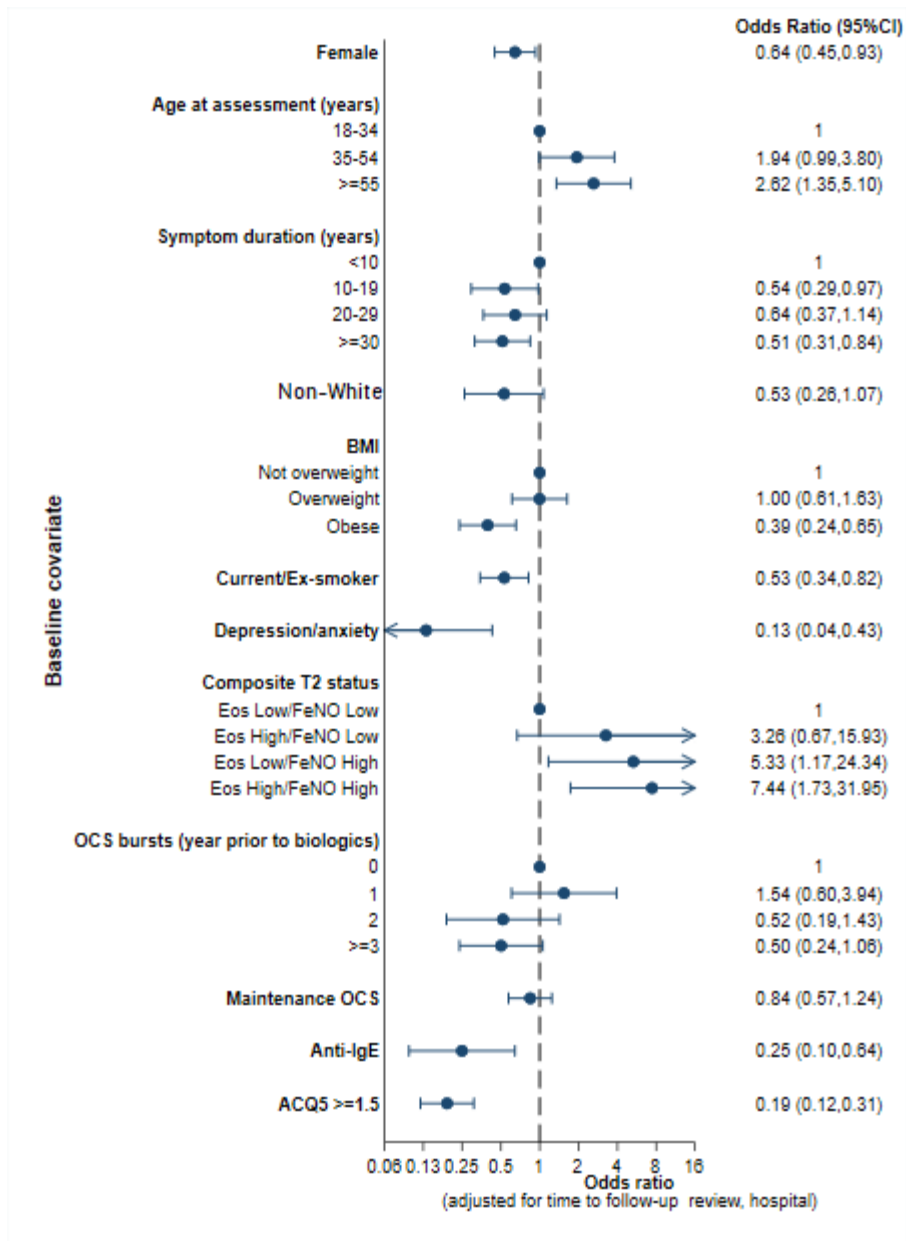
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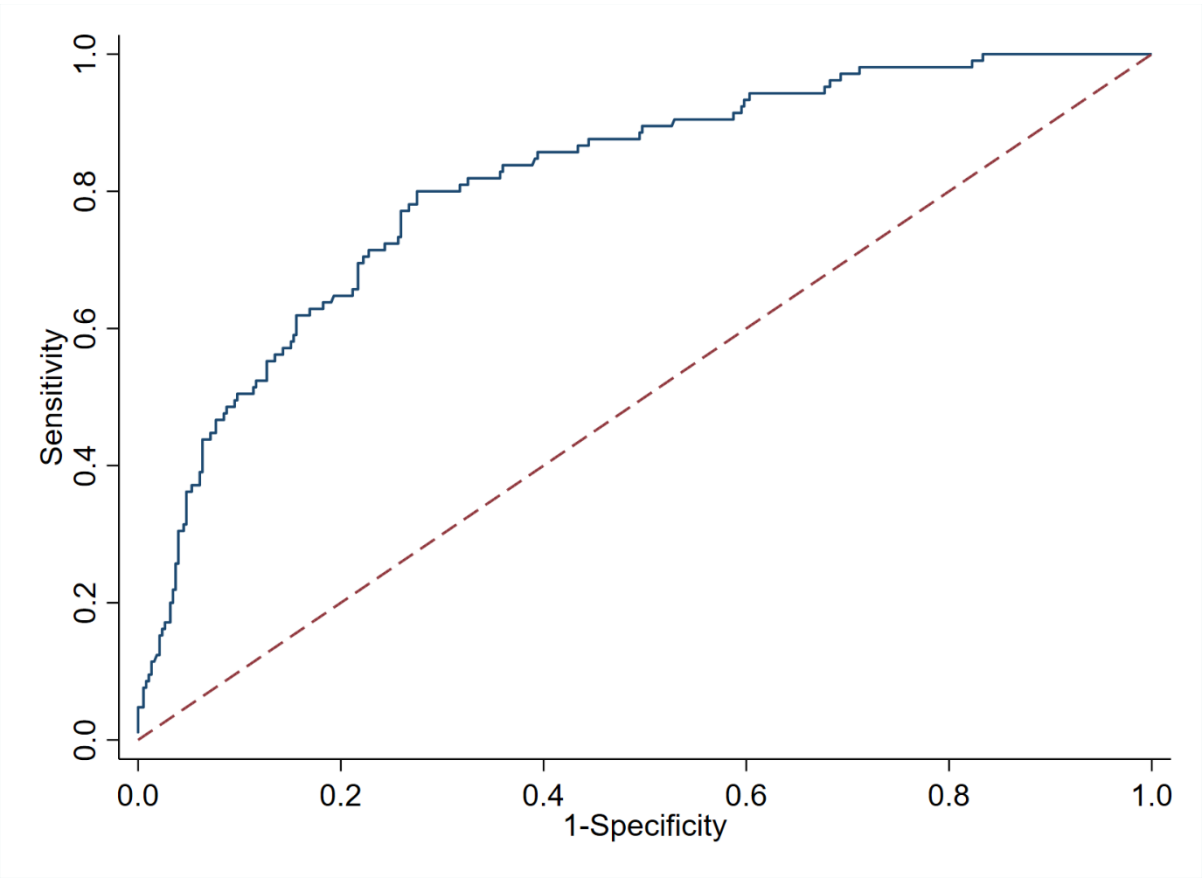
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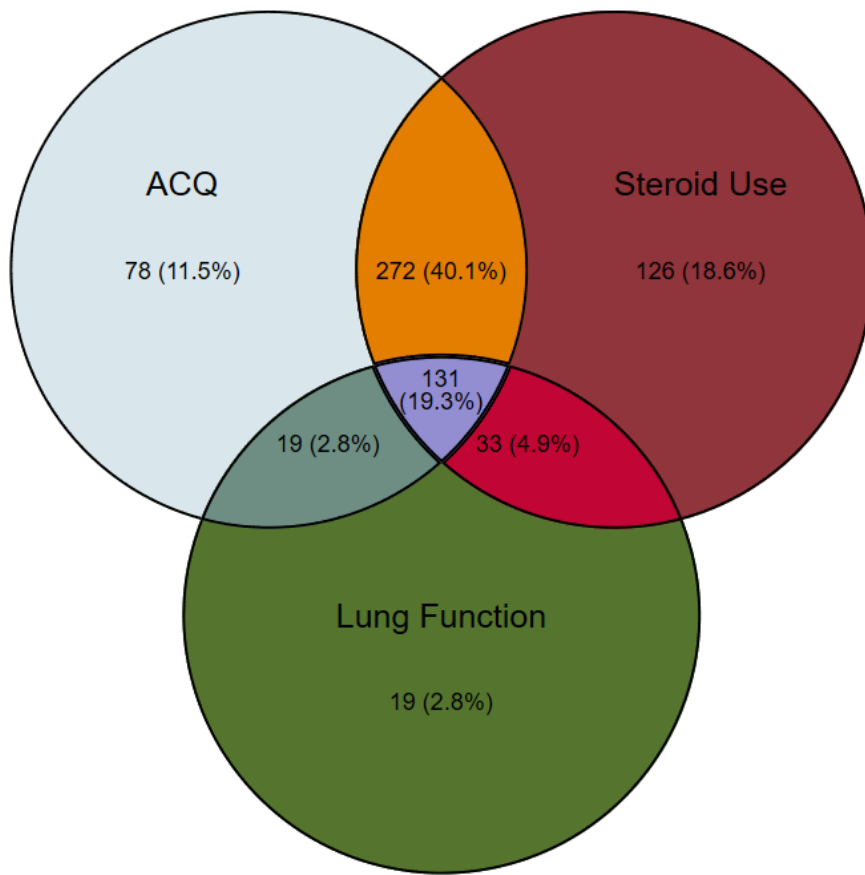
ACQ: ACQ5 >=1.5
Steroid Use: At least 1 exacerbation and/or mOCS dose >5mg
Lung Function: FEV1 below LLN and FEV1 >100mls less than baseline

Figure 3

Clinical remission in severe asthma with Biologic Therapy: an analysis from the UK Severe Asthma Registry: Online Supplement.

Definitions of severe asthma (ATS/ERS and GINA) [E1]

Definition of severe asthma: American Thoracic society/ European Respiratory Society

Severe asthma is defined as asthma which requires GINA step 4–5 asthma treatment (high dose inhaled corticosteroid (ICS) and long acting Beta-agonist (LABA) or leukotriene modifier/theophylline) and/or systemic corticosteroids (OCS) for 50% of the previous year to prevent it from becoming ''uncontrolled'' or which remains ''uncontrolled'' despite this therapy.
> Uncontrolled asthma is defined as at least one of the following:
1. Poor symptom control: Asthma Control Questionnaire (ACQ) consistently ≥1.5, Asthma Control Test (ACT) <20 (or ''not well controlled'' by NAEPP/GINA guidelines)
2. Frequent severe exacerbations: two or more bursts of systemic OCS (3 days each) in the previous year
3. Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4. Airflow limitation: after appropriate bronchodilator withhold FEV1 ,80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

> Controlled asthma that worsens on tapering of these high doses of ICS or systemic OCS (or additional biologics)

Definition of severe asthma: Global initiative for asthma (GINA) [E2]

Severe asthma is uncontrolled (poor symptom control, ≥ 2 exacerbations per year, requiring OCS, ≥1 severe exacerbation requiring hospitalisation) despite adherence factors with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased.

Definitions of remission set forth by the 'expert consensus framework for asthma remission as a treatment goal'.[(E3)]

Clinical remission: on treatment

≥12 months:
1) Sustained absence of significant asthma symptoms using validated instrument AND
2) Optimisation and stabilization of lung function AND
3) Patient & HCP agreement regarding remission AND
4) No OCS for exacerbation or disease control

Clinical remission: off treatment

Same criteria but without asthma treatment in ≥12 months

Complete remission: on treatment

1. Meets definition for clinical remission AND
2. Current, objective evidence of the resolution of previous asthma-related inflammation* AND
3. In appropriate research settings: current negative bronchial hyperresponsiveness

Complete remission: off treatment

Same criteria but without asthma treatment in ≥12 months

NICE criteria for commencing biologics in the UK for uncontrolled asthma despite optimisation and assessment of adherence:

Benralizumab:[E4]

Benralizumab, as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists, only if:

➢ the person has agreed to and followed the optimised standard treatment plan and
➢ the blood eosinophil count has been recorded as 300 cells per microlitre or more and the person has had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the person is eligible for mepolizumab) or
➢ he blood eosinophil count has been recorded as 400 cells per microlitre or more with 3 or more exacerbations needing systemic corticosteroids in the past 12 months (that is, the person is eligible for reslizumab).

Dupilumab:[E5]

Dupilumab as add-on maintenance therapy is recommended as an option for treating severe asthma with type 2 inflammation that is inadequately controlled in people 12 years and over, despite maintenance therapy with high-dose inhaled corticosteroids and another maintenance treatment, only if:

➢ the dosage used is 400 mg initially and then 200 mg subcutaneously every other week
➢ the person has agreed to and follows an optimised standard treatment plan
➢ the person has a blood eosinophil count of 150 cells per microlitre or more and fractional exhaled nitric oxide of 25 parts per billion or more, and has had at least 4 or more exacerbations in the previous 12 months
➢ the person is not eligible for mepolizumab, reslizumab or benralizumab, or has asthma that has not responded adequately to these biological therapies

Mepolizumab:[E6]

Mepolizumab, as an add-on therapy, is recommended as an option for treating severe refractory eosinophilic asthma, only if:

➢ for adults who have agreed to and followed the optimised standard treatment plan and
➢ the blood eosinophil count has been recorded as 300 cells per microlitre or more and the person has had at least 4 exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months or

> ➢ the blood eosinophil count has been recorded as 400 cells per microlitre or more and the person has had at least 3 exacerbations needing systemic corticosteroids in the previous 12 months (so they are also eligible for either benralizumab or reslizumab).

Omalizumab:[E7]

> Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

> ➢ who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)

Reslizumab:[E8]

Reslizumab, as an add-on therapy, is recommended as an option for the treatment of severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if:

> ➢ the blood eosinophil count has been recorded as 400 cells per microlitre or more
> ➢ the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months and

Assessments:

Baseline pre-biologics assessment:

Demographic details
Asthma history (acute care use)
Medical history
Medication history
Lung function
Blood Eosinophils
FeNO
Patient reported outcomes

→

Annual review assessment:

Asthma history (acute care use)
Medication history
Lung function
Blood Eosinophils
FeNO
Patient reported outcomes
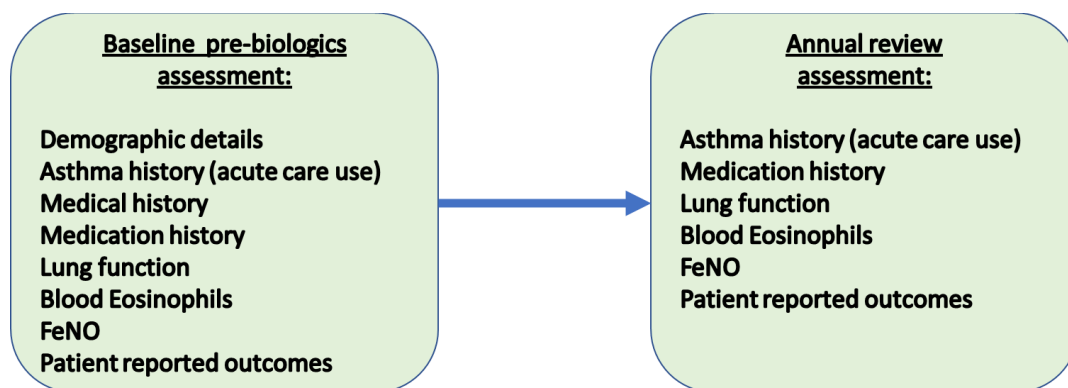
Data recorded at baseline assessment, includes demographic details, asthma/atopy history, comorbidities, exacerbation/acute care attendance in the last 12 months, medication history, biomarkers (blood eosinophil count (BEC) and fractional exhaled nitric oxide (FeNO) and lung function (GLI 2012 predictive values, [E9]). Patient reported outcome measures (PROMs) completed at each assessment included asthma control assessment (ACQ5, asthma control questionnaire and quality of life measures (EuroQOL 5L5D). At annual review, acute care use, medication history,

biomarkers, lung function and PROMS are recorded. To reduce bias towards biologic classes, all biologics approved for use for severe asthma treatment in the UK were included in the analysis, including anti-IL5, anti-IL5R, anti-IL4αr and anti-IgE.

Patient-reported outcome measures (PROMs) in this study addressed change in quality-of-life and asthma severity.

Asthma Control Questionnaire (ACQ5):

Asthma control. Asthma control was assessed by the five item asthma control questionnaire.[E10] An ACQ5 score of 0.75 reflects adequate asthma control, whereas a score of 1.5 or over signals inadequate asthma control. The MCID is a reduction in ACQ5 score of 0.5 or greater.[E11]

EuroQol:

Quality of life. The EuroQoL-5L5D Health scale is a visual analogue scale with which patients report their overall health,[E12] 100 is the best health possible and 0 reflects the worst overall health. The EuroQoL-5L5D Index value reflects impairment of activities of daily living, the closer the score is to 1, the less the impairment of daily living. The change in Index Value following an intervention allows evaluation of the health economics of the intervention through calculation of quality-adjusted life years.

Figure S1: Flow diagram for construction of UKSAR cohort

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┌─────────────────────────────────────────────────────────────────────┐
│   ERS-ATS severe asthmatic adults receiving first biologic at severe  │
│                          asthma centre                                │
│                            (n=3,734)                                  │
└─────────────────────────────────────────────────────────────────────┘
                                   │
                                   ▼
┌─────────────────────────────────────────────────────────────────────┐
│             Patients have at least one annual review                  │
│                            (n=1,775)                                  │
└─────────────────────────────────────────────────────────────────────┘
                                   │
                                   ▼
┌─────────────────────────────────────────────────────────────────────┐
│  First annual review takes places within 9-24 months of initial       │
│  assessment  (n=1,432)                                                │
└─────────────────────────────────────────────────────────────────────┘
                                   │
                                   ▼
┌─────────────────────────────────────────────────────────────────────┐
│  Remission at first annual review can be estimated for at least 50%   │
│                    of patients within each centre                     │
│                            (n=1,111)                                  │
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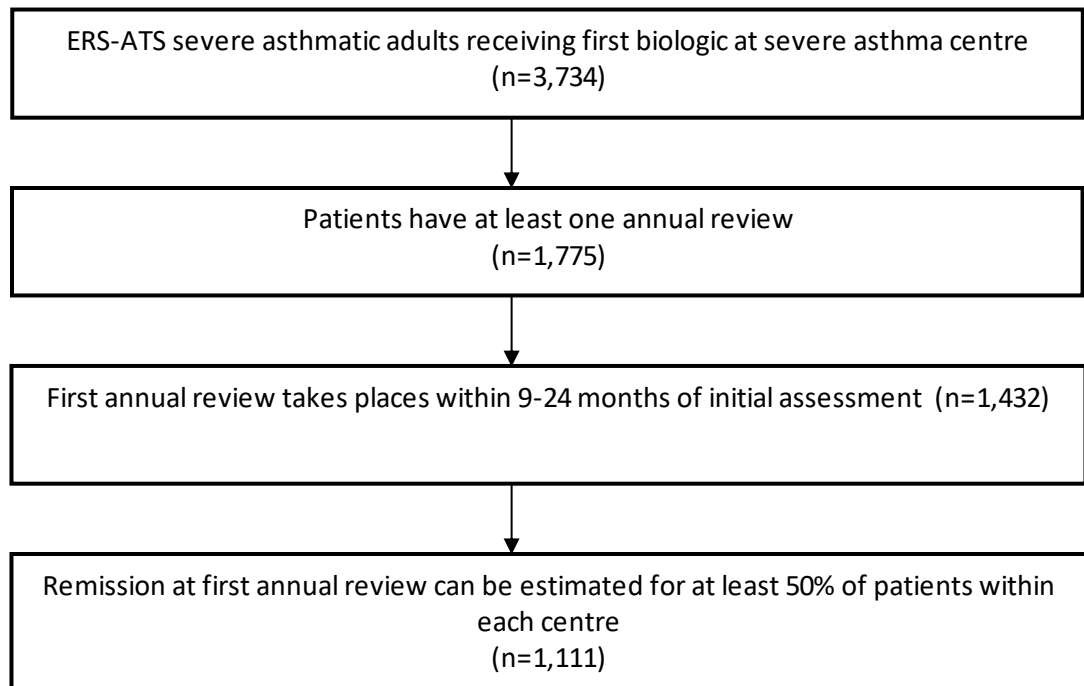
Table S1: Data completeness (whole cohort (n=1,111)

Variable	n (%) non-missing	n (%) missing
Time until Annual review (Years)	1,111 (100.0%)	0 (0.0%)
Sex	1,111 (100.0%)	0 (0.0%)
Age At First Assessment (Years)	1,111 (100.0%)	0 (0.0%)
Age at Onset of Symptoms (Years)	976 (87.8%)	135 (12.2%)
Duration Of Symptoms From Baseline (Years)	976 (87.8%)	135 (12.2%)
Ethnicity	1,109 (99.8%)	2 (0.2%)
Smoking Status	1,083 (97.5%)	28 (2.5%)
BMI (kg-m2)	1,099 (98.9%)	12 (1.1%)
Atopic Disease	1,111 (96.8%)	37 (3.2%)
Depression or Anxiety	1,111 (100.0%)	0 (0.0%)
Gastro-oesophageal Reflux	1,111 (100.0%)	0 (0.0%)
Nasal polyps	1,111 (100.0%)	0 (0.0%)
OCS bursts (Last Year)	1,086 (97.7%)	25 (2.3%)
Frequent exacerbator at baseline	1,086 (97.7%)	25 (2.3%)
Invasive Ventilations (Ever)	1,058 (95.2%)	53 (4.8%)
ED Attendances For Asthma (Last Year)	1,073 (96.6%)	38 (3.4%)
Hospital Admissions For Asthma (Last Year)	1,081 (97.3%)	30 (2.7%)
Highest Blood Eosinophil Count (N/10^{9}L) †	1,093 (98.4%)	18 (1.6%)
Blood Eosinophil Count (N/10^{9}L)	1,085 (97.7%)	26 (2.3%)
FeNO (ppb)	831 (74.8%)	280 (25.2%)
Composite Type 2 status	811 (73.0%)	300 (27.0%)
FEV$_1$ (L)	1,089 (98.0%)	22 (2.0%)
FEV$_1$ (% Predicted)	1,077 (96.9%)	34 (3.1%)
FVC (L)	1,062 (95.6%)	49 (4.4%)
FVC (% Predicted)	1,026 (92.3%)	85 (7.7%)
FEV$_1$/FVC	1,062 (95.6%)	49 (4.4%)
ACQ5 Score	954 (85.9%)	157 (14.1%)
Uncontrolled asthma	954 (85.9%)	157 (14.1%)
Puffs of SABA most days (ACQ Q6)	924 (83.2%)	187 (16.8%)
EuroQoL Health Scale	454 (40.9%)	657 (59.1%)
EuroQoL Utility	470 (42.3%)	641 (57.7%)
Maintenance OCS	1,106 (99.5%)	5 (0.5%)
Maintenance OCS (mg) *	634 (99.4%)	4 (0.6%)
Inhaled corticosteroids (ICS)	1,111 (100.0%)	0 (0.0%)
ICS Dose (BDP equivalent-μg) **	1,025 (92.9%)	78 (7.1%)
Theophylline	1,099 (98.9%)	12 (1.1%)
Short-acting β2-agonist (SABA)	1,099 (98.9%)	12 (1.1%)
Long-acting β2-agonist (LABA)	1,094 (98.5%)	17 (1.5%)
Leukotriene Receptor Antagonists	1,059 (95.3%)	52 (4.7%)
Maintenance Macrolides	1,087 (97.8%)	24 (2.2%)
Nebuliser	1,092 (98.3%)	19 (1.7%)
Biologic commenced	981 (88.3%)	130 (11.7%)
Biologic type commenced	981 (88.3%)	130 (11.7%)
ERS-ATS Severe Asthma	1,111 (100.0%)	0 (0.0%)
Hospital	1,111 (100.0%)	0 (0.0%)

† highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated.*among patients on oral corticosteroids**among patients on inhaled corticosteroids

BMI: Body Mass Index; OCS: Oral Corticosteroid Steroids; ED: Emergency Department; FeNO: Fractional Exhaled Nitric Oxide; ppb : Parts per Billion; FEV$_1$: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: ICS: Inhaled Corticosteroid Steroids: BDP: Beclometasone Dipropionate; SABA: Short-Acting Beta Agonists; LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist; ERS-ATS: European Respiratory Society-American Thoracic Society definition severe asthma 'asthma which requires treatment with GINA step 4-5 treatment or oral corticosteroids (OCS) for 50% of the last year to prevent it becoming uncontrolled'

Table S2: Summary statistics for scalar variables (whole cohort (n=1,111)

Variable	Mean (SD)	Median (IQR)
Time until Annual review (Years)	1.2 (0.3)	1.1 (1.0,1.3)
Age At First Assessment (Years)	50.8 (14.5)	52.0 (41.0,61.0)
Age at Onset of Symptoms (Years)	25.7 (19.9)	21.0 (7.0,41.0)
Duration Of Symptoms From Baseline (Years)	25.1 (17.3)	23.0 (10.0,37.0)
BMI (kg-m2)	30.8 (7.4)	29.8 (26.1,34.8)
OCS bursts (Last Year)	5.9 (4.0)	5 (3,8)
ED Attendances For Asthma (Last Year)	1.7 (3.9)	0 (0,2)
Hospital Admissions For Asthma (Last Year)	1.1 (2.1)	0 (0,1)
Highest Blood Eosinophil Count (N/10^{9}L) †	0.94 (1.11)	0.70 (0.44,1.10)
Blood Eosinophil Count (N/10^{9}L)	0.50 (0.57)	0.40 (0.20,0.65)
FeNO (ppb)	57.8 (49.0)	43.0 (24.0,75.0)
FEV_1 (L)	2.1 (0.8)	2.0 (1.5,2.6)
FEV_1 (% Predicted)	67.3 (21.3)	66.9 (52.1,81.5)
FVC (L)	3.3 (1.0)	3.1 (2.5,3.9)
FVC (% Predicted)	85.9 (19.1)	85.9 (73.4,97.8)
FEV_1/FVC	63.1 (18.7)	63.6 (53.7,72.1)
ACQ5 Score	3.0 (1.4)	3.2 (2.0,4.0)
EuroQoL Health Scale	56.5 (21.3)	60.0 (40.0,70.0)
EuroQoL Utility	0.7 (0.3)	0.8 (0.6,0.9)
Maintenance OCS (mg) *	12.9 (8.7)	10 (8,15)
ICS Dose (BDP equivalent-µg) **	1950.5 (640.1)	2000 (1600,2000)

† highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

* among patients on OCS

** among patients on inhaled corticosteroids

SD: Standard Deviation; IQR: InterQuartile Range; BMI: Body Mass Index; ED: Emergency Department; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FeNO: Fractional exhaled Nitric Oxide; ACQ: Asthma Control Questionnaire; OCS: Oral Corticosteroids; ICS: Inhaled Corticosteroids: BDP: Beclometasone Diproprionate

Table S3. Baseline demographics of the whole cohort at initial assessment prior to commencing biologics (n=1,111)

Variable	n	Category	Result
Time to first Annual Review (Years)	1,111		1.1 (1.0,1.3)
Time to first Annual Review (Months)	1,111	>=9 & <12 months	352 (31.7%)
		>=12 & <18 months	587 (52.8%)
		>=18 & <=24 months	172 (15.5%)
Sex	1,111	Female	667 (60.0%)
Age At First Assessment (Years)	1,111		52.0 (41.0,61.0)
Ethnicity	1,109	White	966 (87.1%)
		Non-White	143 (12.9%)
Smoking Status	1,083	Never	723 (66.8%)
BMI (kg-m2)	1,099		29.8 (26.1,34.8)
BMI ≥30kg-m2		≥30	540 (49.1%)
Atopic Disease	1,111		567 (51.0%)
Depression or Anxiety	1,111		129 (11.6%)
Gastro-oesophageal Reflux	1,111		224 (20.2%)
Nasal polyps	1,111		237 (21.3%)
OCS bursts (Last Year)	1,086		5 (3,8)
Any OCS bursts (Last Year)	1,086		1,020 (93.9%)
Frequent exacerbator at baseline	1,086	≥3 exacerbations in last year	906 (83.4%)
Invasive Ventilations (Ever)	1,058		101 (9.5%)
ED Attendances For asthma (Last Year)	1,073		0 (0,2)
Any ED Attendance for asthma (Last Year)	1,073		435 (40.5%)
Any Hospital Admissions for asthma (Last Year)	1,081		431 (39.9%)
Hospital Admissions for asthma (Last Year)	1,081	≥2	253 (23.4%)
Highest Blood Eosinophil Count recorded (N/10^{9}L) †	1,093		0.70 (0.44,1.10)
Blood Eosinophil Count (N/10^{9}L)	1,085		0.40 (0.20,0.65)
Blood Eosinophil Count (N/10^{9}L)	1,085	<0.15	219 (20.2%)
		≥0.15 & <0.30	131 (12.1%)
		≥0.30 & ≤0.45	264 (24.3%)
		>0.45	471 (43.4%)
FeNO (ppb)	831		43.0 (24.0,75.0)
FeNO	831	<20ppb	167 (20.1%)
		≥20 & <50ppb	299 (36.0%)
		≥50ppb	365 (43.9%)
Composite T2-Group	811	Eos Low (<0.15) / FeNO Low (<20)	48 (5.9%)
		Eos High (≥0.15) / FeNO Low (<20)	111 (13.7%)
		Eos Low (<0.15) / FeNO High (≥20)	126 (15.5%)
		Eos High (≥0.15) / FeNO High (≥20)	526 (64.9%)
Clinic FEV$_1$ (L)	1,089		2.0 (1.5,2.6)
Clinic FEV$_1$ (% Predicted)	1,077		66.9 (52.1,81.5)
Clinic FVC (L)	1,062		3.1 (2.5,3.9)
Clinic FVC (% Predicted)	1,026		85.9 (73.4,97.8)
Clinic FEV$_1$/FVC	1,062		63.6 (53.7,72.1)
ACQ5 Score	954		3.2 (2.0,4.0)
Uncontrolled Asthma	954	ACQ5≥1.5	807 (84.6%)
Maintenance OCS	1,106		638 (57.7%)
Maintenance OCS (mg)	1,102634		10 (8,15)
Inhaled corticosteroids (ICS)	1,111		1,103 (99.3%)
ICS Dose (BDP equivalent-µg)	1,025		2000 (1600,2000)
Theophylline	1,099		299 (27.2%)
Long-acting β2-agonist (LABA)	1,094		1,013 (92.6%)
Long acting anti-muscarinic agent (LAMA)	1,095		709 (64.7%)
Leukotriene Receptor Antagonists	1,059		548 (51.7%)

Maintenance Macrolides	1,087		100 (9.2%)
Biologic type commenced	981	Anti-IL5	828 (84.4%)
		Anti-IgE	150 (15.3%)
		Anti-IL4 Rα	3 (0.3%)
ERS-ATS Severe Asthma	1,111	Yes	1,111 (100.0%)

‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated. *among patients on oral corticosteroids**among patients on inhaled corticosteroids

BMI: Body Mass Index; OCS: Oral Corticosteroid Steroids; ED: Emergency Department; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: ICS: Inhaled Corticosteroid Steroids: BDP: Beclometasone Dipropionate; SABA: Short-Acting Beta-2 Agonists; LABA: Long-Acting Beta-2 Agonists; LAMA: Long-Acting Muscarinic Antagonist; ERS-ATS: European Respiratory Society-American Thoracic Society

Table S4: Baseline demographics of the primary remission/non-remission‡ cohort (n=830)

Variable	n	Category	Result
Time to first Annual Review (Years)	**830**		1.1 (1.0,1.3)
Time to first Annual Review (Months)	**830**	>=9 & <12 months	279 (33.6%)
		>=12 & <18 months	430 (51.8%)
		>=18 & <=24 months	121 (14.6%)
Sex	830	Female	489 (58.9%)
Age At First Assessment (Years)	830		52.0 (42.0,61.0)
Age at Onset of Symptoms (Years)	737		22.0 (7.0,41.0)
Age Of Onset of Symptoms (Years)	737	≥40	209 (28.4%)
Duration Of Symptoms From Baseline (Years)	737		23.0 (11.0,37.0)
Duration Of Symptoms From Baseline (Years)		<20	308 (41.8%)
		≥12 & <18	147 (19.9%)
		≥18	282 (38.3%)
Ethnicit	828	White	724 (87.4%)
Smoking Status	809	Never	539 (66.6%)
BMI (kg-m2)	823		30.0 (26.3,34.8)
BMI (kg-m2)	823	<25	144 (17.5%)
		≥25 & <30	271 (32.9%)
		≥30	408 (49.6%)
Atopic Disease	830		427 (51.4%)
Depression or Anxiety	830		88 (10.6%)
Gastro-oesophageal Reflux	830		144 (17.3%)
Nasal polyps	830		171 (20.6%)
OCS bursts (Last Year)	817		5 (3,8)
Any OCS bursts (Last Year)	817		762 (93.3%)
Frequent exacerbator at baseline	817	≥3 exacerbations in last year	668 (81.8%)
Invasive Ventilations (Ever)	798		76 (9.5%)
ED Attendances For asthma (Last Year)	807		0 (0,2)
Any ED Attendance for asthma (Last Year)	807		293 (36.3%)
Hospital Admissions for asthma (Last Year)	814		0 (0,1)
Any Hospital Admissions for asthma (Last Year)	814		315 (38.7%)
Hospital Admissions for asthma (Last Year)	814	≥2	183 (22.4%)
Highest Blood Eosinophil Count recorded (N/10⁹L) †	821		0.70 (0.45,1.08)
Blood Eosinophil Count (N/10⁹L)	819		0.40 (0.20,0.62)
Blood Eosinophil Count (N/10⁹L)	819	<0.15	175 (21.4%)
		≥0.15 & <0.30	96 (11.7%)
		≥0.30 & ≤0.45	196 (23.9%)
		>0.45	352 (43.0%)
FeNO (ppb)	638		43.0 (24.0,74.0)
FeNO (ppb)	638	<20ppb	123 (19.3%)
		≥20 & <50ppb	234 (36.7%)
		≥50ppb	281 (44.0%)
Composite Type 2 status	627	Eos Low (<0.15) / FeNO Low (<20)	40 (6.4%)
		Eos High (≥0.15) / FeNO Low (<20)	79 (12.6%)
		Eos Low (<0.15) / FeNO High (≥20)	107 (17.1%)
		Eos High (≥0.15) / FeNO High (≥20)	401 (64.0%)
FEV₁ (L)	818		2.0 (1.5,2.6)
FEV₁ (% Predicted)	811		67.2 (52.5,81.9)
FVC (L)	802		3.2 (2.5,3.9)
FVC (% Predicted)	772		85.5 (74.1,97.7)
FEV₁/FVC	802		64.0 (54.3,72.3)
ACQ5 Score	736		3.0 (2.0,4.0)
Uncontrolled Asthma	736	ACQ5≥1.5	622 (84.5%)
EuroQoL Health Scale	350		60.0 (44.0,73.0)
EuroQoL Utility	362		0.7 (0.5,0.9)
Maintenance OCS	826		475 (57.5%)

Maintenance OCS (mg) *	474		10 (8,15)
Inhaled corticosteroids (ICS)	830		827 (99.6%)
ICS Dose (BDP equivalent-μg) **	775		2000 (1600,2000)
Theophylline	821		216 (26.3%)
Short- acting β2-agonist (SABA)	823		785 (95.4%)
Long-acting β2-agonist (LABA)	818		763 (93.3%)
Long acting anti-muscarinic agent (LAMA)	821		525 (63.9%)
Leukotriene Receptor Antagonists	799		407 (50.9%)
Maintenance Macrolides	816		69 (8.5%)
Nebuliser	819		180 (22.0%)
ERS-ATS Severe Asthma	830	Yes	830 (100.0%)

‡ ACQ5 <1.5, no mOCS or OCS bursts, FEV_1 above LLN or <100mls less than pre-biologic FEV

‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

* among patients on oral corticosteroids

** among patients on inhaled corticosteroids

BMI: Body Mass Index; OCS: Oral Corticosteroid Steroids; ED: Emergency Department; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: ICS: Inhaled Corticosteroid Steroids: BDP: Beclometasone Dipropionate; SABA: Short-Acting Beta Agonists; LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist; ERS-ATS: European Respiratory Society-American Thoracic Society

Table S5: Data completeness of the primary remission cohort by remission status‡ (n=830)

Variable	Non remission (81.7% (678))		Remission (18.3% (152))	
	n (%) non-missing	n (%) missing	n (%) non-missing	n (%) missing
Time until Annual review (Years)	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Sex	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Age At First Assessment (Years)	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Age at Onset of Symptoms (Years)	600 (88.5%)	78 (11.5%)	137 (90.1%)	15 (9.9%)
Duration Of Symptoms From Baseline (Years)	600 (88.5%)	78 (11.5%)	137 (90.1%)	15 (9.9%)
Ethnicity	676 (99.7%)	2 (0.3%)	152 (100.0%)	0 (0.0%)
Smoking Status	663 (97.8%)	15 (2.2%)	146 (96.1%)	6 (3.9%)
BMI (kg-m2)	671 (99.0%)	7 (1.0%)	152 (100.0%)	0 (0.0%)
Atopic Disease	678 (98.0%)	14 (2.0%)	152 (100.0%)	0 (0.0%)
Depression or Anxiety	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Gastro-oesophageal Reflux	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Nasal polyps	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Rescue Steroids In Last Year	667 (98.4%)	11 (1.6%)	150 (98.7%)	2 (1.3%)
Frequent exacerbator at baseline	667 (98.4%)	11 (1.6%)	150 (98.7%)	2 (1.3%)
Invasive Ventilations (Ever)	650 (95.9%)	28 (4.1%)	148 (97.4%)	4 (2.6%)
A&E Attendances For Asthma In Last Year	661 (97.5%)	17 (2.5%)	146 (96.1%)	6 (3.9%)
Hospital Admissions For Asthma In Last Year	666 (98.2%)	12 (1.8%)	148 (97.4%)	4 (2.6%)
Highest Blood Eosinophil Count (N/10⁹L) †	671 (99.0%)	7 (1.0%)	150 (98.7%)	2 (1.3%)
Blood Eosinophil Count (N/10⁹L)	670 (98.8%)	8 (1.2%)	149 (98.0%)	3 (2.0%)
FeNO (ppb)	504 (74.3%)	174 (25.7%)	134 (88.2%)	18 (11.8%)
Composite T2 status	496 (73.2%)	182 (26.8%)	131 (86.2%)	21 (13.8%)
FEV1 (L)	667 (98.4%)	11 (1.6%)	151 (99.3%)	1 (0.7%)
FEV1 (% Predicted)	660 (97.3%)	18 (2.7%)	151 (99.3%)	1 (0.7%)
FVC (L)	653 (96.3%)	25 (3.7%)	149 (98.0%)	3 (2.0%)
FVC (% Predicted)	629 (92.8%)	49 (7.2%)	143 (94.1%)	9 (5.9%)
FEV1/FVC	653 (96.3%)	25 (3.7%)	149 (98.0%)	3 (2.0%)
ACQ5 Score	598 (88.2%)	80 (11.8%)	138 (90.8%)	14 (9.2%)
Puffs of SABA most days (ACQ Q6)	582 (85.8%)	96 (14.2%)	129 (84.9%)	23 (15.1%)
EuroQoL Health Scale	273 (40.3%)	405 (59.7%)	77 (50.7%)	75 (49.3%)
EuroQoL Utility	285 (42.0%)	393 (58.0%)	77 (50.7%)	75 (49.3%)
Maintenance OCS	674 (99.4%)	4 (0.6%)	152 (100.0%)	0 (0.0%)
Maintenance OCS (mg) *	397 (99.7%)	1 (0.3%)	77 (100.0%)	0 (0.0%)
Inhaled corticosteroids (ICS)	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
ICS Dose (BDP equivalent-µg) **	632 (93.2%)	46 (6.8%)	143 (94.7%)	8 (5.3%)
Theophylline	673 (99.3%)	5 (0.7%)	148 (97.4%)	4 (2.6%)
Short-acting β2-agonist (SABA)	673 (99.3%)	5 (0.7%)	150 (98.7%)	2 (1.3%)
Long-acting β2-agonist (LABA)	667 (98.4%)	11 (1.6%)	151 (99.3%)	1 (0.7%)
Long acting anti-muscarinic agent (LAMA)	670 (98.8%)	8 (1.2%)	151 (99.3%)	1 (0.7%)
Leukotriene Receptor Antagonists	653 (96.3%)	25 (3.7%)	146 (96.1%)	6 (3.9%)
Maintenance Macrolides	665 (98.1%)	13 (1.9%)	151 (99.3%)	1 (0.7%)
Nebuliser	670 (98.8%)	8 (1.2%)	149 (98.0%)	3 (2.0%)
Biologic commenced	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Biologic type commenced	609 (89.8%)	69 (10.2%)	138 (90.8%)	14 (9.2%)
ERS-ATS Asthma	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)
Hospital	678 (100.0%)	0 (0.0%)	152 (100.0%)	0 (0.0%)

‡ ACQ5 <1.5, no mOCS or OCS bursts, FEV₁ above LLN or <100mls less than pre-biologic FEV₁

† highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated
*among patients on OCS
** among patients on inhaled corticosteroids

BMI: Body Mass Index; OCS: Oral Corticosteroid Steroids; ED: Emergency Department; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV₁: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: ICS: Inhaled Corticosteroid Steroids: BDP: Beclometasone Dipropionate; SABA: Short-Acting Beta Agonists; LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist; ERS-ATS: European Respiratory Society-American Thoracic Society

Table S6: Summary statistics for scalar variables in the primary remission cohort by remission status‡ (n=830)

Variable	Non remission (81.7% (678))		Remission (18.3% (152))	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Time until Annual review (Years)	1.2 (0.3)	1.1 (1.0,1.4)	1.1 (0.3)	1.1 (1.0,1.2)
Age At First Assessment (Years)	49.7 (14.4)	51.0 (41.0,59.0)	55.2 (13.2)	55.0 (48.0,65.0)
Age at Onset of Symptoms (Years)	23.9 (18.8)	20.0 (6.0,39.0)	33.6 (21.4)	32.0 (14.0,52.0)
Duration Of Symptoms From Baseline (Years)	25.7 (17.1)	24.5 (12.0,37.0)	21.6 (16.6)	20.0 (8.0,32.0)
BMI (kg-m2)	31.4 (7.3)	30.5 (26.6,35.1)	29.2 (7.2)	27.9 (25.4,31.8)
Rescue Steroids In Last Year	6.1 (4.1)	5 (3,8)	4.7 (3.1)	4 (3,6)
A&E Attendances For Asthma (Last Year)	1.6 (3.9)	0 (0,2)	0.6 (1.8)	0 (0,0)
Hospital Admissions For Asthma (Last Year)	1.2 (2.1)	0 (0,1)	0.6 (1.2)	0 (0,1)
Highest Blood Eosinophil Count (N/10^9L) †	0.88 (1.11)	0.68 (0.40,1.00)	1.13 (1.25)	0.79 (0.58,1.33)
Blood Eosinophil Count (N/10^9L)	0.49 (0.64)	0.39 (0.18,0.60)	0.52 (0.50)	0.46 (0.22,0.70)
FeNO (ppb)	55.1 (46.9)	41.0 (22.0,72.0)	64.0 (45.8)	51.0 (35.0,81.0)
FEV1 (L)	2.0 (0.8)	2.0 (1.5,2.6)	2.2 (0.9)	2.1 (1.6,2.7)
FEV1 (% Predicted)	66.8 (20.7)	67.0 (52.4,81.2)	72.2 (23.5)	68.6 (55.0,88.2)
FVC (L)	3.2 (1.0)	3.1 (2.5,3.9)	3.4 (1.1)	3.3 (2.7,4.2)
FVC (% Predicted)	85.1 (18.8)	85.2 (73.8,97.0)	89.3 (19.8)	86.7 (75.8,99.4)
FEV1/FVC	63.5 (21.3)	63.7 (54.3,72.2)	63.6 (12.9)	64.5 (54.4,73.6)
EuroQoL Health Scale	54.6 (20.1)	60.0 (40.0,70.0)	67.4 (19.8)	75.0 (50.0,85.0)
EuroQoL Utility	0.6 (0.3)	0.7 (0.5,0.8)	0.8 (0.2)	0.9 (0.8,1.0)
ACQ5 Score	3.2 (1.3)	3.2 (2.2,4.2)	2.2 (1.4)	2.0 (1.2,3.4)
Maintenance OCS (mg) *	13.5 (9.1)	10 (8,15)	10.0 (5.2)	10 (7,10)
ICS Dose (BDP equivalent-μg) **	1961.0 (624.6)	2000 (1600,2000)	2005.8 (767.9)	2000 (1600,2000)

‡ ACQ5 <1.5, no mOCS or OCS bursts, FEV$_1$ above LLN or <100mls less than pre-biologic FEV$_1$

† highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

* among patients on OCS

* among patients on inhaled corticosteroids

SD: Standard Deviation; IQR: InterQuartile Range; BMI: Body Mass Index; ED: Emergency Department; FEV$_1$: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FeNO: Fractional exhaled Nitric Oxide; ACQ: Asthma Control Questionnaire; OCS: Oral Corticosteroids; ICS: Inhaled Corticosteroids: BDP: Beclometasone Diproprionate

Table S7: Clinical characteristics and outcomes at baseline and after 1 year on biologics

	N	Baseline	Annual Review 1	p-value
Time to first annual review (years)	1,111	-	1.1 (1.0,1.3)	-
BMI (kg/m²)	955	30.0 (26.1,35.0)	29.9 (26.1,35.1)	0.011
Rescue Steroids In Last Year	1040	5 (3,8)	1 (0,3)	<0.001
Any Rescue Steroids in Last Year	1040	975 (93.8%)	656 (63.1%)	<0.001
Frequent exacerbator (≥3 exacerbations in last year)	1040	864 (83.1%)	302 (29.0%)	0.002
ED attendances for asthma (last year)	1015	0 (0,2)	0 (0,0)	<0.001
Any ED attendance for asthma (last year)	1015	397 (39.1%)	139 (13.7%)	<0.001
Hospital admissions for asthma (last year)	984	0 (0,1)	0 (0,0)	<0.001
Any hospital admission for asthma (last year)	984	395 (40.1%)	140 (14.2%)	<0.001
Blood eosinophil count (10/⁹L)	738	0.37 (0.16,0.61)	0.06 (0.00,0.14)	<0.001
FEV1 (L)	941	2.0 (1.5,2.6)	2.2 (1.6,2.7)	<0.001
FEV1 (% predicted)	929	67.4 (52.4,81.9)	73.3 (58.7,87.5)	<0.001
FVC (L)	870	3.2 (2.5,3.9)	3.2 (2.5,4.0)	0.507
FVC (% predicted)	831	86.2 (74.0,98.3)	87.8 (74.5,100.0)	0.065
FEV1/FVC	868	63.6 (53.6,72.3)	68.0 (58.7,75.7)	<0.001
FeNO (ppb)	567	43.0 (23.0,73.0)	36.0 (16.0,69.0)	<0.001
ACQ5 Score	851	3.0 (2.0,4.0)	2.0 (0.8,3.2)	<0.001
ACQ5≥1.5	851	721 (84.7%)	514 (60.0%)	<0.001
ACQ6 Score	806	3.0 (2.0,4.0)	1.8 (0.8,3.2)	<0.001
ACQ6 ≥1.5	806	690 (85.6%)	491 (60.9%)	<0.001
ACQ7 Score	806	3.1 (2.2,4.0)	2.1 (1.3,3.3)	<0.001
ACQ7 ≥1.5	806	712 (88.3%)	549 (68.1%)	<0.001
Reported number of SABA puffs most days (ACQ Q6)	806			
None		96 (11.9%)	203 (25.2%)	<0.001
1-2 puffs		120 (14.5%)	168 (20.8%)	
3-4 puffs		155 (19.2%)	135 (16.8%)	
5-8 puffs		165 (20.5%)	135 (16.8%)	
9-12 puffs		123 (15.3%)	85 (10.6%)	
13-16 puffs		73 (9.1%)	36 (4.5%)	
>16 puffs		74 (9.2%)	44 (5.5%)	
Maintenance OCS	1085	625 (57.6%)	517 (47.7%)	<0.001

Median (IQR) or count (%) as appropriate 'Last Year' refers to measures assessed using clinical records in the 12 months prior to either baseline visit to the severe asthma clinic or at annual review, otherwise measures were as observed or recorded at the relevant time-point.

BMI: Body Mass Index; OCS: Oral Corticosteroid Steroids; ED: Emergency Department; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV[1]: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists

Table S8: Baseline pre-biologics characteristics of those who meet remission versus those who do not meet remission at annual review (remission criteria ACQ5 <1.5, no mOCS or OCS bursts, FEV$_1$ above LLN or <100mls less than pre-biologic FEV$_1$).

Baseline variable	n	Category	Non-remission	Remission	p-value
	830		**81.7% (678)**	**18.3% (152)**	
Time to first Annual Review (Years)	**830**		1.1 (1.0,1.4)	1.1 (1.0,1.2)	0.097
Sex	830	Female	412 (60.8%)	77 (50.7%)	0.022
		Male	266 (39.2%)	75 (49.3%)	
Age At First Assessment (Years)	830		51.0 (41.0,59.0)	55.0 (48.0,65.0)	<0.001
Age At First Assessment (Years)	830	18-34	111 (16.4%)	12 (7.9%)	0.005
		35-54	296 (43.7%)	61 (40.1%)	
		>=55	271 (40.0%)	79 (52.0%)	
Age at Onset of Symptoms (Years)	737		20.0 (6.0,39.0)	32.0 (14.0,52.0)	<0.001
Age of Onset of Symptoms (Years)	737	<12	202 (33.7%)	29 (21.2%)	0.012
		≥12 & <18	57 (9.5%)	12 (8.8%)	
		≥18	341 (56.8%)	96 (70.1%)	
Age Of Onset of Symptoms (Years)	737	(≥40)	146 (24.3%)	63 (46.0%)	<0.001
Duration Of Symptoms From Baseline (Years)	737		24.5 (12.0,37.0)	20.0 (8.0,32.0)	0.008
Ethnicity	828	White	583 (86.2%)	141 (92.8%)	0.028
		Non-White	93 (13.8%)	11 (7.2%)	
Smoking status	809	Never	430 (64.9%)	109 (74.7%)	0.023
		Current/Ex-smoker	233 (35.1%)	37 (25.4%)	
BMI (kg-m2)	823		30.5 (26.6,35.1)	27.9 (25.4,31.8)	0.001
BMI (kg-m2)	823	<25	110 (16.4%)	34 (22.4%)	<0.001
		≥25 & <30	204 (30.4%)	67 (44.1%)	
		≥30	357 (53.2%)	51 (33.6%)	
Atopic Disease	830		355 (52.4%)	72 (47.4%)	0.226
Depression or Anxiety	830		85 (12.5%)	3 (2.0%)	<0.001
Gastro-oesophageal Reflux	830		119 (17.6%)	25 (16.4%)	0.745
Nasal polyps	830		123 (18.1%)	48 (31.6%)	<0.001
OCS bursts (Last Year)	817		5 (3,8)	4 (3,6)	<0.001
Any OCS bursts (Last Year)	817		624 (93.6%)	138 (92.0%)	0.493
Frequent Exacerbator at baseline	817	Yes (≥3 in Last Year)	554 (83.1%)	114 (76.0%)	0.043
Invasive Ventilations (Ever)	798		68 (10.5%)	8 (5.4%)	0.058
Any ED Attendance for asthma (Last Year)	807		259 (39.2%)	34 (23.3%)	<0.001
Any Hospital Admissions for asthma (Last Year)	814		270 (40.5%)	45 (30.4%)	0.022
Highest Blood Eosinophil Count (N/10^{9}L) †	821		0.68 (0.40,1.00)	0.79 (0.58,1.33)	<0.001
Highest Blood Eosinophil Count (N/10^{9}L) †	821	<0.15	13 (1.9%)	4 (2.7%)	0.006
		≥0.15 & <0.3	27 (4.0%)	4 (2.7%)	
		≥0.3 & <0.5	157 (23.4%)	20 (13.3%)	
		≥0.5 & <1.0	292 (43.5%)	61 (40.7%)	
		≥1.0	182 (27.1%)	61 (40.7%)	
Blood Eosinophil Count (N/10^{9}L)	819		0.39 (0.18,0.60)	0.46 (0.22,0.70)	0.011
FeNO (ppb)	638		41.0 (22.0,72.0)	51.0 (35.0,81.0)	0.002
FeNO (ppb)	638	<20	111 (22.0%)	12 (9.0%)	0.001
		≥20 & <50	184 (36.5%)	50 (37.3%)	
		≥50	209 (41.5%)	72 (53.7%)	
Composite Type 2 status	627	Eos Low (<0.15) / FeNO Low (<20)	38 (7.7%)	2 (1.5%)	0.004
		Eos High (≥0.15) / FeNO Low (<20)	69 (13.9%)	10 (7.6%)	
		Eos Low (<0.15) / FeNO High (≥20)	86 (17.3%)	21 (16.0%)	
		Eos High ≥0.15) / FeNO High (≥20)	303 (61.1%)	98 (74.8%)	
FEV$_1$ (L)	818		2.0 (1.5,2.6)	2.1 (1.6,2.7)	0.073
FEV$_1$ (% Predicted)	811		67.0 (52.4,81.2)	68.6 (55.0,88.2)	0.027
FVC (L)	802		3.1 (2.5,3.9)	3.3 (2.7,4.2)	0.048
FVC (% Predicted)	772		85.2 (73.8,97.0)	86.7 (75.8,99.4)	0.065
FEV$_1$/FVC	802		63.7 (54.3,72.2)	64.5 (54.4,73.6)	0.498

ACQ5 Score	736		3.2 (2.2,4.2)	2.0 (1.2,3.4)	<0.001
Uncontrolled Asthma	711	ACQ5 ≥1.5	531 (88.8%)	91 (65.9%)	<0.001
EuroQoL Health Scale	350		60.0 (40.0,70.0)	75.0 (50.0,85.0)	<0.001
EuroQoL Utility	362		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	826		398 (59.1%)	77 (50.7%)	0.059
Maintenance OCS (mg)*	474		10 (8,15)	10 (7,10)	0.001
Inhaled corticosteroids (ICS)	830		676 (99.7%)	151 (99.3%)	0.500
ICS Dose (BDP equivalent-ug)**	775		2000 (1600,2000)	2000 (1600,2000)	0.556
Theophylline	821		184 (27.3%)	32 (21.6%)	0.153
SABA	823		643 (95.5%)	142 (94.7%)	0.644
Long-acting β2-agonist (LABA)	818		619 (92.8%)	144 (95.4%)	0.258
Long acting anti-muscarinic agent (LAMA)	821		420 (62.7%)	105 (69.5%)	0.113
Leukotriene Receptor Antagonists	799		327 (50.1%)	80 (54.8%)	0.303
Maintenance Macrolides	816		60 (9.0%)	9 (6.0%)	0.202
Nebuliser	819		164 (24.5%)	16 (10.7%)	<0.001

*among patients on oral corticosteroids

**among patients on inhaled corticosteroids

‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta-2 Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta-2 Agonists; LAMA: Long-Acting Muscarinic Antagonist

Table S9: Odds ratios associated with remission‡ for selected covariates (plus 10 unit increase for age and symptom duration, 1 unit increase in BMI)

‡ ACQ5 <1.5, no mOCS or OCS bursts, FEV_1 above LLN or <100mls less than pre-biologic FEV_1

		Unadjusted model		Adjusted for time to first Annual Review, hospital		Adjusted for time to Annual Review, hospital, baseline ACQ5, baseline exacerbations (ie baseline morbidity)	
OR: Odds Ratio; CI: Confidence							
Variable	**Category**	**N**	**OR (95%CI, p-value)**	**N**	**OR (95%CI, p-value)**	**N**	**OR (95%CI, p-value)**
Sex	Male	830	1	830	1	726	1
	Female		0.66 (0.46,0.94), p=0.021		0.64 (0.45,0.93), p=0.018		0.76 (0.51,1.15), p=0.199
Age at first assessment (years)	Increase of 10 years	830	1.31 (1.15,1.50), p<0.001	830	1.31 (1.15,1.50), p<0.001	726	1.25 (1.07,1.45), p=0.004
	18-34	830	1	830	1	726	1
	35-54		1.90 (0.99,3.67), p=0.055		1.94 (0.99,3.80), p=0.053		1.94 (0.93,4.03), p=0.077
	>=55		2.69 (1.41,5.15), p=0.003		2.62 (1.35,5.10), p=0.005		2.18 (1.05,4.56), p=0.037
Duration of symptoms at baseline (years)	Increase of 10 years	737	0.86 (0.76,0.97), p=0.011	737	0.86 (0.76,0.97), p=0.013	667	0.92 (0.81,1.05), p=0.226
	<10	737	1	737	1	667	1
	10-19		0.49 (0.27,0.87), p=0.015		0.54 (0.29,0.97), p=0.040		0.66 (0.34,1.28), p=0.224
	20-29		0.61 (0.35,1.05), p=0.073		0.64 (0.37,1.14), p=0.128		0.77 (0.41,1.44), p=0.410
	>=30		0.51 (0.32,0.82), p=0.006		0.51 (0.31,0.84), p=0.008		0.70 (0.40,1.22), p=0.210
Ethnicity	White	828	1	828	1	724	1
	Non-White		0.51 (0.26,0.98), p=0.043		0.53 (0.26,1.07), p=0.077		0.59 (0.26,1.34), p=0.207
BMI (kg-m2)	Increase of 1 kg-m2	823	0.96 (0.93,0.98), p=0.001	823	0.95 (0.92,0.98), p<0.001	7220	0.96 (0.94,0.99), p=0.016
	Not overweight (<25)	823	1	823	1	722	1
	Overweight (>=25 & <30)		1.03 (0.64,1.66), p=0.899		1.00 (0.61,1.63), p=0.992		0.98 (0.56,1.71), p=0.945
	Obese (>=30)		0.46 (0.28,0.74), p=0.002		0.39 (0.24,0.65), p<0.001	722	0.53 (0.30,0.93), p=0.026
Smoking status	Never smoker	809	1	809	1	710	1
	Current/ex-smoker		0.61 (0.40,0.91), p=0.017		0.53 (0.34,0.82), p=0.004		0.64 (0.39,1.03), p=0.066
Depression/anxiety	No	830	1	830	1	726	1
	Yes		0.13 (0.04,0.42), p=0.001		0.13 (0.04,0.43), p=0.001		0.11 (0.02,0.50), p=0.004
Composite Type 2 status	Eos Low (<0.15) / FeNO Low (<20)	627	1	627	1	556	1
	Eos High (>=0.15) / FeNO Low (<20)		2.83 (0.59,13.61), p=0.194		3.26 (0.67,15.93), p=0.144		3.79 (0.73,19.75), p=0.113
	Eos Low (<0.15) / FeNO High (>=20)		4.61 (1.03,20.66), p=0.046		5.33 (1.17,24.34), p=0.031		6.23 (1.28,30.34), p=0.023
	Eos High (>=0.15) / FeNO High (>=20)		6.34 (1.50,26.78), p=0.012		7.44 (1.73,31.95), p=0.007		7.48 (1.64,34.16), p=0.009
OCS bursts (year prior to biologics)	0	817	1	817	1	726	1
	1		2.03 (0.81,5.04), p=0.129		1.54 (0.60,3.94), p=0.363		1.44 (0.54,3.87), p=0.465
	2		0.66 (0.25,1.73), p=0.394		0.52 (0.19,1.43), p=0.203		0.57 (0.20,1.65), p=0.302
	>=3		0.70 (0.35,1.37), p=0.292		0.50 (0.24,1.06), p=0.070		0.62 (0.28,1.38), p=0.244
Maintenance OCS	No	826	1	826	1	722	1
	Yes		0.74 (0.52,1.05), p=0.092		0.84 (0.57,1.24), p=0.390		0.83 (0.52,1.30), p=0.408
Biologic Therapy Type	Anti-IL5	745	1	745	1	674	1
	Anti-IgE		0.22 (0.09,0.55), p=0.001		0.25 (0.10,0.64), p=0.004		0.22 (0.08,0.65), p=0.006
ACQ5	<1.5	736	1	736	1	726	1
	>=1.5		0.23 (0.15,0.36), p<0.001		0.19 (0.12,0.31), p<0.001		0.20 0.20 (0.12,0.32), p<0.001

Figure S2: Estimated adjusted probability of achieving clinical remission* at the means for selected covariates

‡ ACQ5 <1.5, and no mOCS or OCS bursts and, FEV$_1$ above LLN or <100mls less than pre-biologic FEV$_1$ CI: Confidence Interval; BMI: Body Mass Index; Eos: Blood eosinophil count (N/10^{9}L); FeNO: Fractional exhaled Nitric Oxide; OCS: Oral Corticosteroids; mOCS; maintenance OCS; ACQ: Asthma Control Questionnaire; FEV$_1$; Forced Expiratory Volume (1 second)

Baseline covariate	prob(remission) (95%CI)*
Sex	
Male	0.21 (0.16,0.25)
Female	0.14 (0.11,0.18)
Age at assessment (years)	
18-34	0.09 (0.04,0.14)
35-54	0.16 (0.12,0.20)
>=55	0.21 (0.16,0.25)
Symptom duration (years)	
<10	0.24 (0.18,0.31)
10-19	0.15 (0.09,0.21)
20-29	0.17 (0.11,0.23)
>=30	0.14 (0.10,0.18)
Ethnicity	
White	0.18 (0.15,0.21)
Non-White	0.10 (0.04,0.17)
BMI	
Not overweight	0.23 (0.16,0.31)
Overweight	0.23 (0.18,0.29)
Obese	0.11 (0.08,0.14)
Smoking status	
Non-smoker	0.19 (0.16,0.23)
Current/Ex-smoker	0.11 (0.07,0.15)
Depression/anxiety	
No	0.19 (0.16,0.22)
Yes	0.03 (0.00,0.06)
Composite T2 status	
Eos Low/FeNO Low	0.04 (0.00,0.10)
Eos High/FeNO Low	0.12 (0.05,0.19)
Eos Low/FeNO High	0.18 (0.11,0.26)
Eos High/FeNO High	0.24 (0.19,0.28)
OCS bursts (year prior to biologics)	
0	0.26 (0.13,0.40)
1	0.35 (0.20,0.51)
2	0.16 (0.06,0.25)
>=3	0.15 (0.12,0.18)
Maintenance OCS	
No	0.18 (0.14,0.23)
Yes	0.16 (0.13,0.19)
Biologic type	
Anti-IL5	0.19 (0.16,0.22)
Anti-IgE	0.06 (0.01,0.10)
ACQ5	
<1.5	0.43 (0.33,0.53)
>=1.5	0.13 (0.10,0.15)

Predicted probability at the means
(model adjusts for time to follow-up review, hospital)
*estimated for largest hospital (n=220)

Table S10: Individual area under the curve for each variable included in the regression model.

Variable	Individual AUC (95% CI)
Hospital	0.618 (0.567,0.669)
Time to Follow-up	0.618 (0.567,0.669)
Age At Initial Assessment (Years)	0.655 (0.605,0.706)
Gender	0.644 (0.591,0.696)
Duration Of Symptoms At Baseline (Years)	0.661 (0.614,0.709)
Ethnicity	0.627 (0.576,0.677)
BMI (kg-m2)	0.683 (0.636,0.730)
Smoking Status	0.666 (0.617,0.715)
Depression or Anxiety	0.652 (0.604,0.700)
T2-Group	0.652 (0.600,0.704)
Exacerbations (Last Year)	0.657 (0.615,0.700)
Maintenance OCS	0.630 (0.581,0.678)
Biologic Therapy Type	0.651 (0.603,0.700)
Baseline ACQ5	0.709 (0.661,0.756)

Table S11: Remission criteria ACQ <1.5 AND no OCS bursts or mOCS >5mg/day AND FEV$_1$ above LLN or <5% from pre-biologics FEV$_1$: baseline characteristics of those who meet remission at annuak review and those who do not.

Baseline variable	n		Non-remission	Remission	p-value
	830		81.7% (678)	18.3% (152)	
Time until Annual Review (Years)	830		1.1 (1.0,1.4)	1.1 (1.0,1.2)	0.067
Time until Annual Review (Years)	830	>=9 & <12 months	223 (32.9%)	56 (36.8%)	0.175
		>=12 & <18 months	349 (51.5%)	81 (53.3%)	
		>=18 & <=24 months	106 (15.6%	15 (9.9%)	
Sex	830	Female	413 (60.9%)	76 (50.0%)	0.013
Age At First Assessment (Years)	830		51.0 (41.0,59.0)	55.0 (48.0,65.0)	<0.001
Age at Onset of Symptoms (Years)	737		20.0 (6.0,39.0)	33.5 (14.0,52.0)	<0.001
Age Of Onset of Symptoms (Years)	737	(≥40 years)	146 (24.3%)	63 (46.3%)	<0.001
Duration Of Symptoms From Baseline (Years)	737		25.0 (12.0,37.0)	20.0 (8.0,31.5)	0.007
Duration of Symptoms From Baseline (Years)	737	<20	243 (40.4%)	65 (47.8%)	0.227
		20-29	120 (20.0%)	27 (19.9%)	
		>=30	238 (39.6%)	44 (32.4%)	
Ethnicity	828	White	583 (86.2%)	141 (92.8%)	0.028
Smoking status	809	Never smoked	430 (64.9%)	109 (74.7%)	0.023
BMI (kg-m2)	823		30.5 (26.6,35.2)	27.8 (25.3,31.6)	<0.001
BMI (kg-m2)	823	<25	109 (16.2%)	35 (23.0%)	<0.001
		≥25 & <30	204 (30.4%)	67 (44.1%)	
		≥30	358 (53.4%)	50 (32.9%)	
Atopic Disease	830		355 (52.4%)	72 (47.4%)	0.226
Depression or Anxiety	830		85 (12.5%)	3 (2.0%)	<<0.001
Gastro-oesophageal Reflux	830		119 (17.6%)	25 (16.4%)	0.745
Nasal polyps	830		124 (18.3%)	47 (30.9%)	0.001
OCS bursts (Last Year)	817		5 (3,8)	4 (3,6)	<0.001
Any OCS bursts (Last Year)	817		624 (93.6%)	138 (92.0%)	0.493
Frequent Exacerbator at baseline	817	Yes (≥3 in Last Year)	554 (83.1%)	114 (76.0%)	0.043
Invasive Ventilations (Ever)	798		68 (10.5%)	8 (5.4%)	0.058
Any ED Attendance for asthma (Last Year)	807		259 (39.2%)	34 (23.3%)	<0.001
Any Hospital Admissions for asthma (Last Year)	814		270 (40.5%)	45 (30.4%)	0.022
Highest Blood Eosinophil Count (N/10^{9}L) †	821		0.68 (0.41,1.00)	0.79 (0.58,1.33)	0.001
Blood Eosinophil Count (N-109L)	819		0.40 (0.18,0.60)	0.46 (0.22,0.70)	0.127
Blood Eosinophil Count (N-109L)	819	<0.15	148 (22.1%)	27 (18.1%)	0.102
		≥0.15 & <0.30	76 (11.3%)	20 (13.4%)	
		≥0.30 & ≤0.45	169 (25.2%)	27 (18.1%)	
		>0.45	277 (41.3%)	75 (50.3%)	
FeNO (ppb)	638		41.0 (22.0,72.0)	51.0 (35.0,81.0)	0.002
FeNO (ppb)	638	<20ppb	111 (22.0%)	12 (9.0%)	0.001
		≥20 & <50ppb	185 (36.6%)	49 (36.8%)	
		≥50ppb	209 (41.4%)	72 (54.1%)	
Composite Type 2 status	627	Eos Low (<0.15) / FeNO Low (<20)	38 (7.6%)	2 (1.5%)	0.004
		Eos High (≥0.15) / FeNO Low (<20)	69 (13.9%)	10 (7.7%)	
		Eos Low (<0.15) / FeNO High (≥20)	86 (17.3%)	21 (16.2%)	
		Eos High (≥0.15) / FeNO High (≥20)	304 (61.2%)	97 (74.6%)	
FEV$_1$ (L)	818		2.0 (1.5,2.6)	2.1 (1.6,2.7)	0.048
FEV$_1$ (% Predicted)	811		66.9 (52.4,81.2)	68.6 (55.0,88.2)	0.024
FVC (L)	802		3.1 (2.5,3.9)	3.3 (2.7,4.2)	0.0129
FVC (% Predicted)	772		85.2 (73.6,97.0)	86.7 (76.2,99.4)	0.055
FEV$_1$/FVC	802		63.7 (54.3,72.2)	64.5 (54.4,72.6)	0.530
ACQ5 Score	736		3.2 (2.2,4.2)	2.0 (1.2,3.4)	<0.001
Uncontrolled Asthma	736	ACQ5 ≥1.5	532 (89.0%)	90 (65.2%)	<0.001
EuroQoL Health Scale	350		60.0 (40.0,70.0)	75.0 (50.0,85.0)	<0.001
EuroQoL Utility	362		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	826		397 (58.9%)	78 (51.3%)	0.087

Maintenance OCS (mg) *	474		10 (8,15)	10 (6,10)	0.001
Inhaled corticosteroids (ICS)	830		676 (99.7%)	151 (99.3%)	0.500
ICS Dose (BDP equivalent-μg) **	775		2000 (1600,2000)	2000 (1600,2000)	0.619
Theophylline	821		184 (27.3%)	32 (21.6%)	0.153
Short-acting β2-agonist (SABA)	823		643 (95.5%)	142 (94.7%)	0.644
Long-acting β2-agonist (LABA)	818		620 (93.0%)	143 (94.7%)	0.439
Long acting anti-muscarinic agent (LAMA)	821		421 (62.8%)	104 (68.9%)	0.163
Leukotriene Receptor Antagonists	799		328 (50.2%)	79 (54.1%)	0.397
Maintenance Macrolides	816		60 (9.0%)	9 (6.0%)	0.222
Nebuliser	819		164 (24.5%)	16 (10.7%)	<0.001

*among patients on oral corticosteroids

**among patients on inhaled corticosteroids

‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure S3: Reasons for not meeting remission criteria after 1 year on biologic therapy. Remission definition: ACQ5 <1.5, no mOCS or OCS bursts, FEV$_1$ above LLN or ≤5% less than pre-biologic FEV$_1$
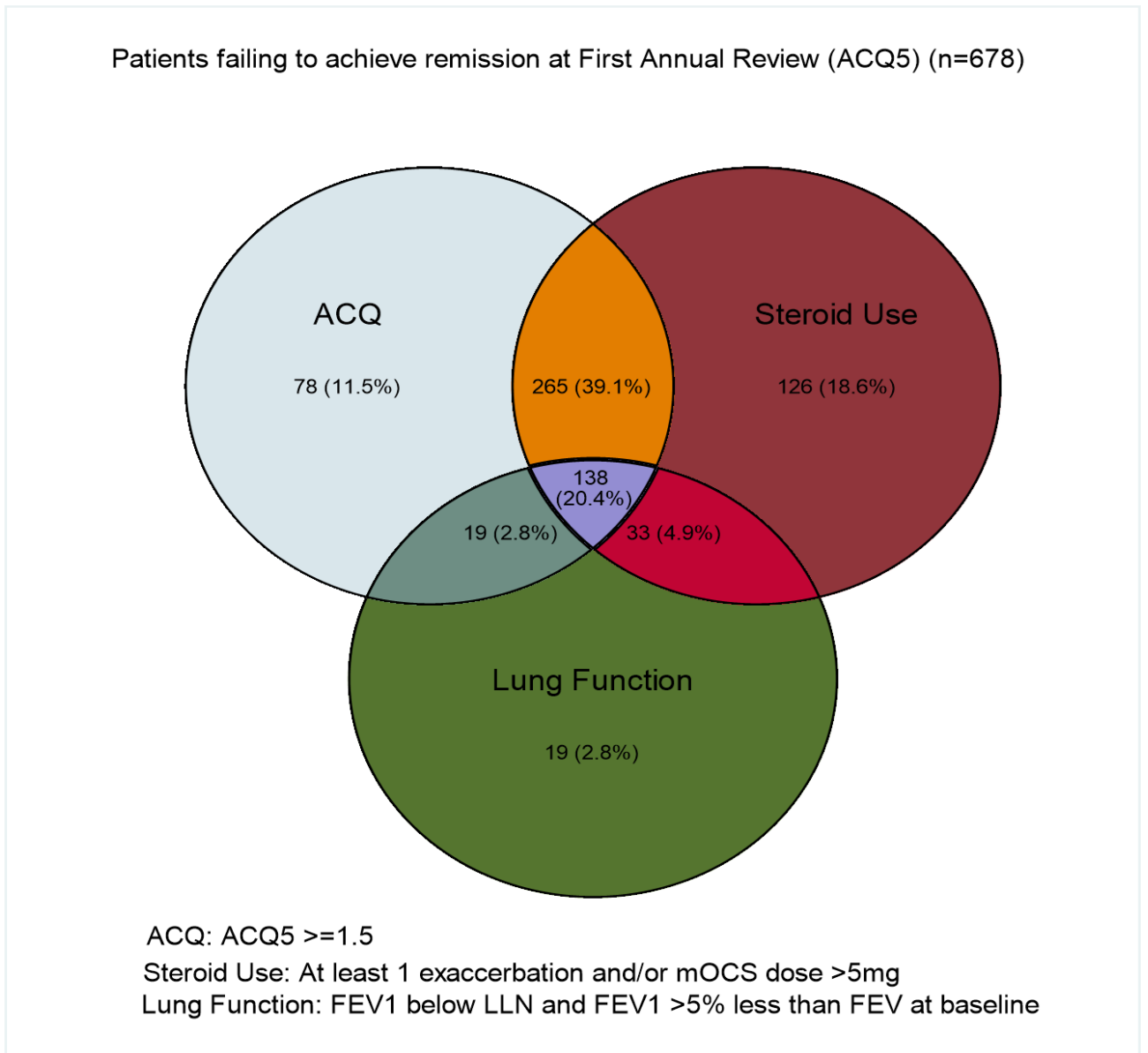
Patients failing to achieve remission at First Annual Review (ACQ5) (n=678)

ACQ
78 (11.5%)

265 (39.1%)

Steroid Use
126 (18.6%)

138 (20.4%)

19 (2.8%)

33 (4.9%)

Lung Function
19 (2.8%)

ACQ: ACQ5 >=1.5
Steroid Use: At least 1 exaccerbation and/or mOCS dose >5mg
Lung Function: FEV1 below LLN and FEV1 >5% less than FEV at baseline

ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids: FEV$_1$; Forced Expiratory Volume (1 second); LLN: Lower Limit of Normal

Table S12: Remission criteria ACQ <1.5 AND no OCS bursts or mOCS >5mg/day AND FEV$_1$ above LLN or no lower than pre-biologics: baseline characteristics of those who meet remission at annual review and those who do not.

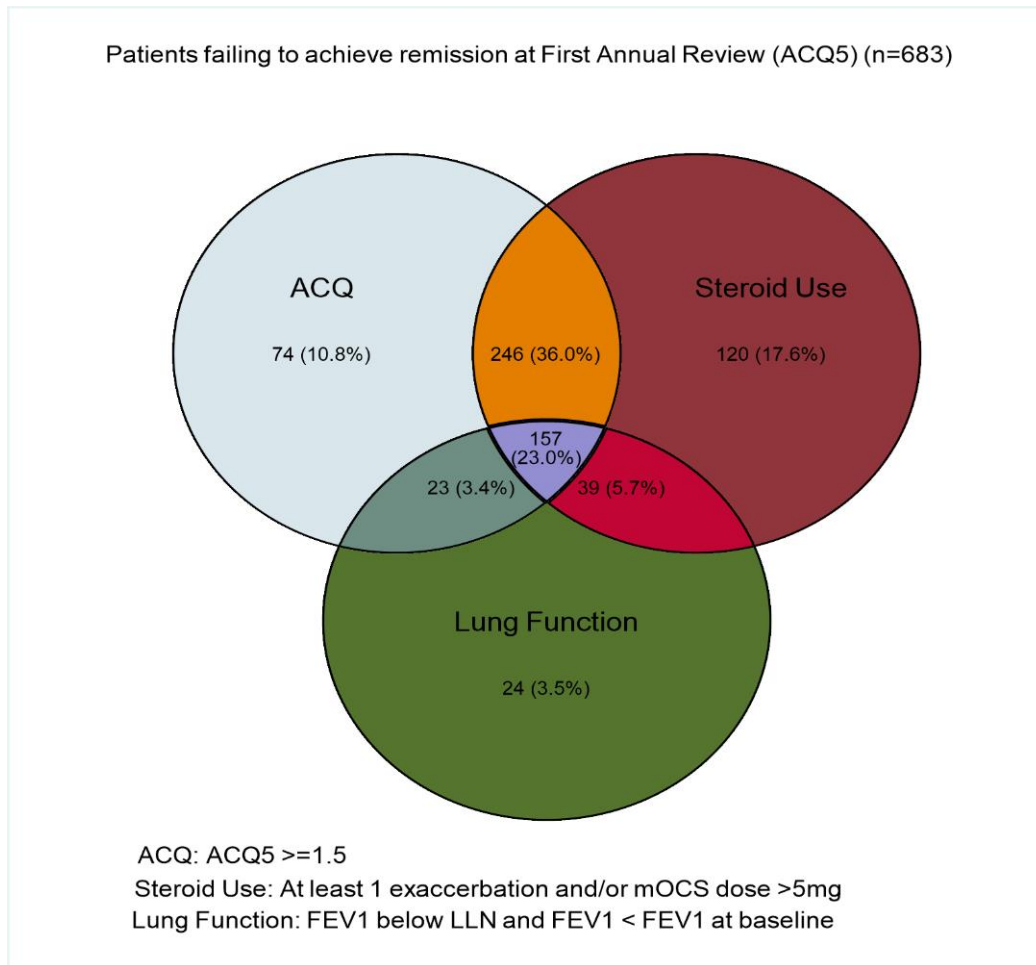|	n	Category	Non-remission	Remission	p-value
	830		**82.3% (683)**	**17.7% (147)**	
Time until Annual Review (Years)	**830**		1.1 (1.0,1.4)	1.1 (1.0,1.2)	0.054
Time until Annual Review (Years)	**830**	>=9 & <12 months	225 (32.9%)	54 (36.7%)	0.151
		>=12 & <18 months	351 (51.4%)	79 (53.7%)	
		>=18 & <=24 months	107 (15.7%)	14 (9.5%)	
Sex	830	Female	414 (60.6%)	75 (51.0%)	0.032
Age At First Assessment (Years)	830		51.0 (41.0,59.0)	55.0 (48.0,65.0)	<0.001
Age at Onset of Symptoms (Years)	737		20.0 (6.0,39.0)	33.5 (15.0,52.0)	<0.001
Age Of Onset of Symptoms (≥40 years)	737		148 (24.5%)	61 (46.2%)	<0.001
Duration Of Symptoms From Baseline (Years)	737		25.0 (12.0,37.0)	20.0 (8.0,31.0)	0.004
Duration Of Symptoms From Baseline (Years)	737	0-19	245 (40.5%)	63 (47.7%)	0.210
		20-29	120 (19.8%)	27 (20.5%)	
		>=30	240 (39.7%)	42 (31.8%)	
Ethnicity	828	White	587 (86.2%)	137 (93.2%)	0.020
Smoking status	809	Never smoked	433 (64.8%)	106 (75.2%)	0.018
BMI (kg-m2)	823		30.5 (26.6,35.2)	27.8 (25.3,31.4)	<0.001
BMI (kg-m2)	823	<25	111 (16.4%)	33 (22.4%)	<0.001
		≥25 & <30	204 (30.2%)	67 (45.6%)	
		≥30	361 (53.4%)	47 (32.0%)	
Atopic Disease	830		358 (52.4%)	69 (46.9%)	0.195
Depression or Anxiety	830		86 (12.6%)	2 (1.4%)	<0.001
Gastro-oesophageal Reflux	830		120 (17.6%)	24 (16.3%)	0.718
Nasal polyps	830		124 (18.2%)	47 (32.0%)	<0.001
OCS bursts (Last Year)	817		5 (3,8)	4 (3,6)	<0.001
Any OCS bursts (Last Year)	817		629 (93.6%)	133 (91.7%)	0.413
Frequent Exacerbator at baseline	817	Yes (≥3 in Last Year)	559 (83.2%)	109 (75.2%)	0.023
Invasive Ventilations (Ever)	798		70 (10.7%)	6 (4.2%)	0.017
Any ED Attendance for asthma (Last Year)	807		261 (39.2%)	32 (22.7%)	<0.001
Any Hospital Admissions for asthma (Last Year)	814		272 (40.5%)	43 (30.1%)	0.020
Highest Blood Eosinophil Count (N/10^{9}L) †	821		0.69 (0.41,1.00)	0.79 (0.58,1.33)	<0.001
Blood Eosinophil Count (N/10^{9}L)	819		0.39 (0.18,0.60)	0.47 (0.20,0.70)	0.086
Blood Eosinophil Count (N/10^{9}L)	819	<0.15	148 (21.9%)	27 (18.8%)	0.049
		≥0.15 & <0.30	78 (11.6%)	18 (12.5%)	
		≥0.30 & ≤0.45	172 (25.5%)	24 (16.7%)	
		>0.45	277 (41.0%)	75 (52.1%)	
FeNO (ppb)	638		41.0 (22.0,72.0)	53.0 (36.0,81.0)	<0.001
FeNO (ppb)	638	<20ppb	113 (22.2%)	10 (7.8%)	<0.001
		≥20 & <50ppb	186 (36.5%)	48 (37.2%)	
		≥50ppb	210 (41.3%)	71 (55.0%)	
Composite Type 2 status	627	Eos Low (<0.15) / FeNO Low (<20)	38 (7.6%)	2 (1.6%)	0.002
		Eos High (≥0.15) / FeNO Low (<20)	71 (14.2%)	8 (6.3%)	
		Eos Low (<0.15) / FeNO High (≥20)	86 (17.2%)	21 (16.7%)	
		Eos High (≥0.15) / FeNO High (≥20)	306 (61.1%)	95 (75.4%)	
FEV$_1$ (L)	818		2.0 (1.5,2.6)	2.1 (1.6,2.7)	0.047
FEV$_1$ (% Predicted)	811		66.9 (52.4,81.1)	68.7 (55.0,88.9)	0.018
FVC (L)	802		3.1 (2.5,3.9)	3.3 (2.7,4.2)	0.038
FVC (% Predicted)	772		85.1 (73.8,97.0)	87.1 (76.2,99.4)	0.018
FEV$_1$/FVC	802		63.7 (54.3,72.2)	64.6 (55.0,73.7)	0.43
ACQ5 Score	736		3.2 (2.2,4.2)	2.0 (1.2,3.2)	<0.001
Uncontrolled Asthma	736	ACQ5 ≥1.5	536 (88.9%)	86 (64.7%)	<0.001
EuroQoL Health Scale	350		55.0 (40.0,70.0)	75.0 (50.0,85.0)	<0.001
EuroQoL Utility	362		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	826		401 (59.1%)	74 (50.3%)	0.053
Maintenance OCS (mg) *	474		10 (8,15)	10 (7,10)	0.004

ICS	830		681 (99.7%)	146 (99.3%)	0.478
ICS Dose (BDP equivalent-µg) **	775		2000 (1600,2000)	2000 (1600,2000)	0.426
Theophylline	821		185 (27.3%)	31 (21.7%)	0.166
Short-acting β2-agonist (SABA)	823		648 (95.6%)	137 (94.5%)	0.569
Long-acting β2-agonist (LABA)	818		624 (92.9%)	139 (95.2%)	0.304
Long acting anti-muscarinic agent (LAMA)	821		423 (62.7%)	102 (69.9%)	0.101
Leukotriene Receptor Antagonists	799		330 (50.2%)	77 (54.6%)	0.337
Maintenance Macrolides	816		61 (9.1%)	8 (5.5%)	0.154
Nebuliser	819		166 (24.6%)	14 (9.7%)	<0.001

*among patients on oral corticosteroids**among patients on inhaled corticosteroids‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated.

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure S4: Reasons for not meeting remission criteria after 1 year on biologic therapy. Remission definition: ACQ5 <1.5, no mOCS or OCS bursts, FEV$_1$ above LLN or ≤less than pre-biologic FEV1

Patients failing to achieve remission at First Annual Review (ACQ5) (n=683)

ACQ
74 (10.8%)

246 (36.0%)

Steroid Use
120 (17.6%)

157
(23.0%)

23 (3.4%)

39 (5.7%)

Lung Function
24 (3.5%)

ACQ: ACQ5 >=1.5
Steroid Use: At least 1 exaccerbation and/or mOCS dose >5mg
Lung Function: FEV1 below LLN and FEV1 < FEV1 at baseline

ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids: FEV$_1$; Forced Expiratory Volume (1 second); LLN: Lower Limit of Normal

Table S13: Remission criteria ACQ <1.5 AND no OCS bursts or mOCS >5mg/day: baseline characteristics of those who meet remission at 1 year and those who do not

	n	Category	Non-remission	Remission	p-value
	925		**78.8% (729)**	**21.2% (196)**	
Time until Annual Review (Years)	925		1.1 (1.0,1.4)	1.1 (1.0,1.3)	0.035
Sex	925	Female	445 (61.0%)	100 (51.0%)	0.011
Age At First Assessment (Years)	925		51.0 (40.0,59.0)	55.0 (48.0,65.0)	<0.001
Age at Onset of Symptoms (Years)	818		20.0 (6.0,38.5)	35.0 (14.0,50.0)	<0.001
Age Of Onset of Symptoms (≥40 years)	818		155 (24.1%)	81 (46.6%)	<0.001
Duration Of Symptoms From Baseline (Years)	818		25.0 (12.0,38.0)	20.0 (8.0,32.0)	0.003
Duration of symptoms From Baseline (Years)	818	0-19	260 (40.4%)	80 (46.0%)	0.175
		20-29	123 (19.1%)	37 (21.3%)	
		>=30	261 (40.5%)	57 (32.8%)	
Ethnicity	923	White	623 (85.7%)	178 (90.8%)	0.060
Smoking status	903	Never smoked	460 (64.4%)	140 (74.1%)	0.012
BMI (kg-m2)	917		30.7 (26.6,35.2)	27.8 (24.9,31.8)	<0.001
BMI (kg-m2)	917	<25	119 (16.5%)	50 (25.6%)	<0.001
		≥25 & <30	215 (29.8%)	78 (40.0%)	
		≥30	388 (53.7%)	67 (34.4%)	
Atopic Disease	925		382 (52.4%)	92 (46.9%)	0.166
Depression or Anxiety	925		100 (13.7%)	5 (2.6%)	<0.001
Gastro-oesophageal Reflux	925		138 (18.9%)	34 (17.3%)	0.613
Nasal polyps	925		134 (18.4%)	62 (31.6%)	<0.001
OCS bursts (Last Year)	908		6 (4,8)	4 (3,6)	<0.001
Any OCS bursts (Last Year)	908		672 (94.1%)	178 (91.8%)	0.232
Frequent Exacerbator at baseline	908	Yes (≥3 in Last Year)	602 (84.3%)	151 (77.8%)	0.033
Invasive Ventilations (Ever)	888		76 (10.9%)	10 (5.2%)	0.019
Any ED Attendance for asthma (Last Year)	898		296 (41.7%)	50 (26.6%)	<0.001
Any Hospital Admission for asthma (Last Year)	908		299 (41.7%)	58 (30.4%)	0.004
Highest Blood Eosinophil Count (N/10⁹L) †	912		0.68 (0.40,1.00)	0.79 (0.55,1.33)	<0.001
Blood Eosinophil Count (N/10⁹L)	908		0.40 (0.20,0.60)	0.46 (0.21,0.72)	0.082
Blood Eosinophil Count (N/10⁹L)	819	<0.15	148 (20.7%)	37 (19.2%)	0.179
		≥0.15 & <0.30	85 (11.9%)	22 (11.4%)	
		≥0.30 & ≤0.45	181 (25.3%)	37 (19.2%)	
		>0.45	301 (42.1%)	97 (50.3%)	
FeNO (ppb)	704		39.0 (22.0,72.0)	51.0 (33.0,80.0)	0.001
FeNO (ppb)	704	<20ppb	121 (22.5%)	19 (11.4%)	0.002
		≥20 & <50ppb	198 (36.9%)	59 (35.3%)	
		≥50ppb	218 (40.6%)	89 (53.3%)	
Composite Type 2 status	691	Eos Low (<0.15) / FeNO Low (<20)	38 (7.2%)	3 (1.8%)	0.007
		Eos High (≥0.15) / FeNO Low (<20)	79 (15.0%)	15 (9.2%)	
		Eos Low (<0.15) / FeNO High (≥20)	84 (15.9%)	27 (16.6%)	
		Eos High (≥0.15) / FeNO High (≥20)	327 (61.9%)	118 (72.4%)	
FEV₁ (L)	907		1.9 (1.5,2.6)	2.1 (1.5,2.7)	0.023
FEV₁ (% Predicted)	899		66.4 (51.6,80.6)	70.7 (55.6,87.9)	0.004
FVC (L)	887		3.1 (2.5,3.9)	3.2 (2.7,4.2)	0.016
FVC (% Predicted)	853		84.6 (72.6,96.7)	86.9 (76.2,99.4)	0.012
FEV₁/FVC	887		63.7 (54.3,71.9)	64.5 (56.4,73.4)	0.427
ACQ5 Score	822		3.4 (2.2,4.2)	2.2 (1.2,3.2)	<0.001
Uncontrolled asthma	822	ACQ5 ≥1.5	579 (89.9%)	117 (65.7%)	<0.001
EuroQoL Health Scale	389		55.0 (40.0,70.0)	70.0 (50.0,80.0)	<0.001
EuroQoL Utility	404		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	920		422 (58.2%)	101 (51.8%)	0.109
Maintenance OCS (mg) *	521		10 (8,15)	10 (6,10)	<0.001
ICS	920		422 (58.2%)	101 (51.8%)	0.109
ICS Dose (BDP equivalent-µg) **	521		2000 (1600,2000)	2000 (1600,2000)	0.896
Theophylline	914		202 (27.9%)	38 (20.1%)	0.031
Short-acting β2-agonist (SABA)	918		693 (95.7%)	185 (95.4%)	0.829
Long-acting β2-agonist (LABA)	912		668 (93.2%)	183 (93.8%)	0.736

Long acting anti-muscarinic agent (LAMA)	916		455 (63.0%)	125 (64.4%)	0.717
Leukotriene Receptor Antagonists	888		359 (51.4%)	98 (51.9%)	0.904
Maintenance Macrolides	908		70 (9.8%)	12 (6.2%)	0.119
Nebuliser	913		179 (24.8%)	23 (12.0%)	<0.001

*among patients on oral corticosteroids**among patients on inhaled corticosteroids‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated.

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure S5: Reasons for not meeting remission criteria after 1 year on biologic therapy. Remission definition: ACQ5 <1.5, no mOCS or OCS bursts

Patients failing to achieve remission at First Annual Review (ACQ5) (n=729)

ACQ

112 (15.4%)

444
(60.9%)

Steroid Use

173 (23.7%)
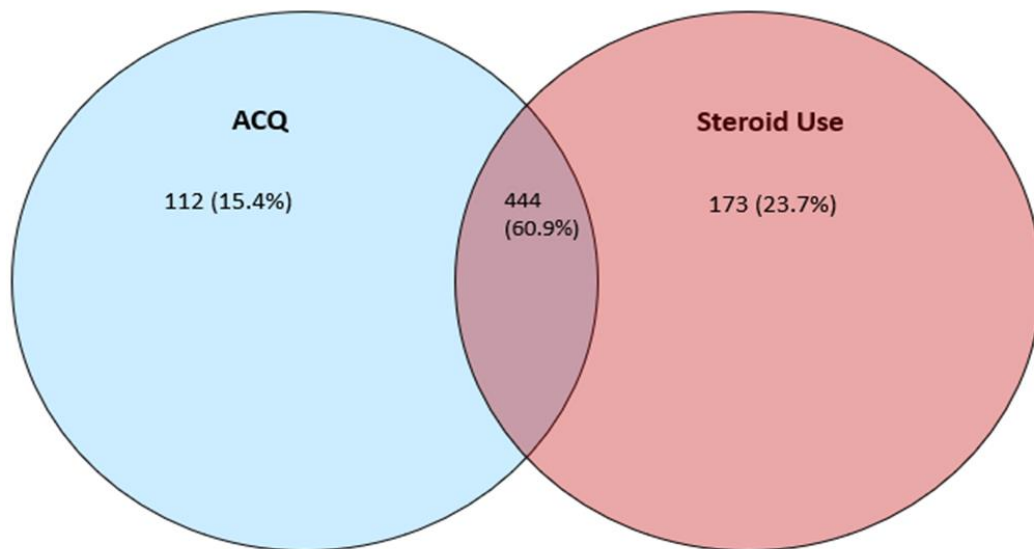
ACQ: ACQ5 >=1.5
Steroid Use: At least 1 exacerbation and/or mOCS dose >5mg

ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids

Table S14: Remission criteria ACQ <1.5 AND no OCS bursts or mOCS >5mg/day AND no SABA use: baseline characteristics of those who meet remission at annual review and those who do not
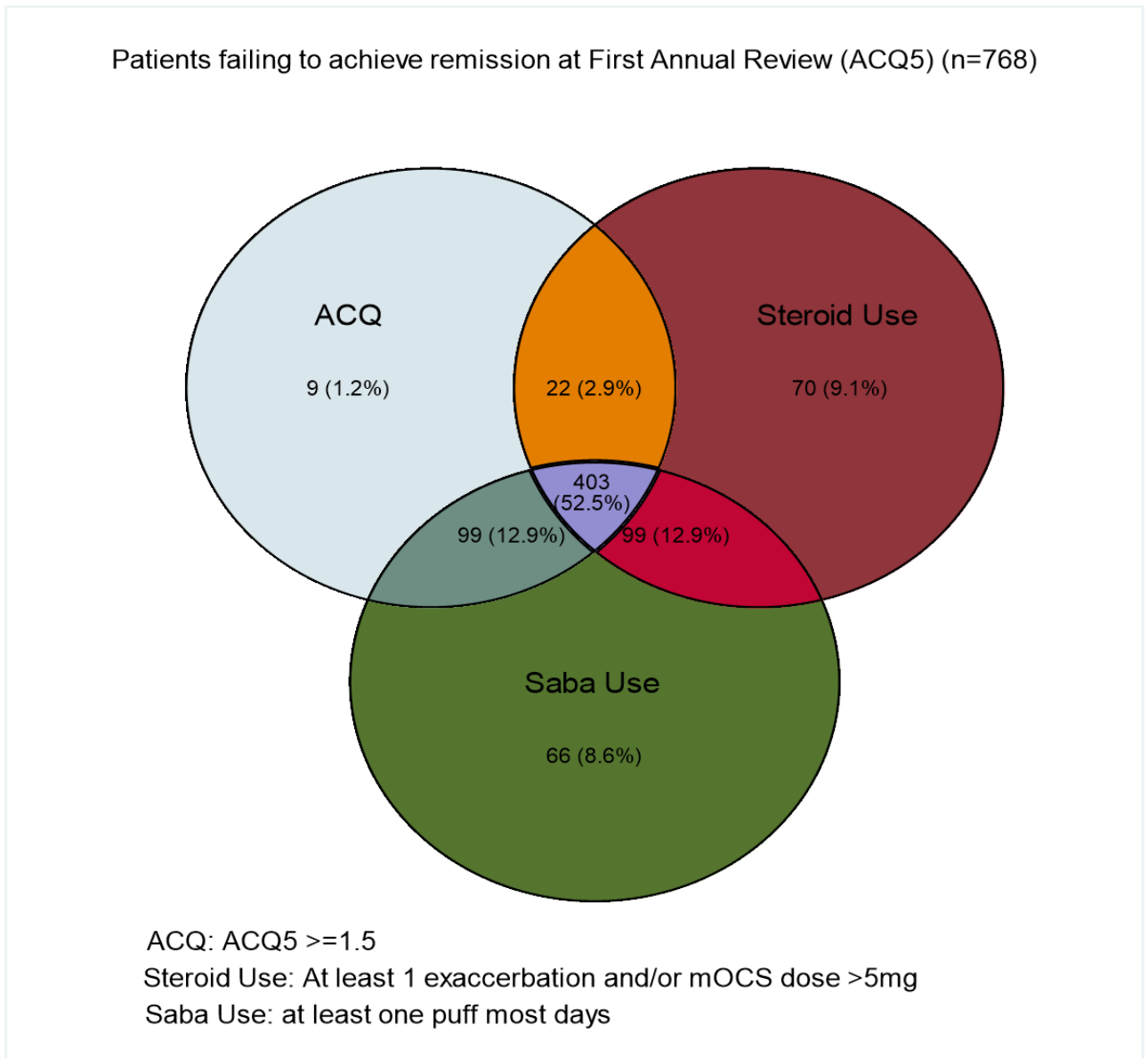
	n 891	Category	Non-remission 86.2% (768)	Remission 13.8% (123)	p-value
Time until Annual Review (Years)	891		1.1 (1.0,1.4)	1.1 (1.0,1.3)	0.023
Time until Annual Review (Years)	891	>=9 & <12 months	226 (29.4%)	49 (39.4%)	0.031
		>=12 & <18 months	409 (53.3%)	61 (49.6%)	
		>=18 & <=24 months	133 (17.3%)	13 (10.6%)	
Sex	891	Female	463 (60.3%)	63 (51.2%)	0.058
Age At First Assessment (Years)	891		51.0 (41.0,60.0)	55.0 (48.0,65.0)	<0.001
Age at Onset of Symptoms (Years)	785		20.0 (6.0,40.0)	40.0 (17.0,53.0)	<0.001
Age Of Onset of Symptoms (≥40 years)	785		171 (25.3%)	56 (51.9%)	<0.001
Duration Of Symptoms From Baseline (Years)	785		24.0 (12.0,38.0)	19.5 (7.5,31.0)	0.002
Duration of symptoms From Baseline (Years)	785	0-19	276 (40.8%)	54 (50.0%)	0.196
		20-29	134 (19.8%)	18 (16.7%)	
		>=30	267 (39.4%)	36 (33.3%)	
Ethnicity	889	White	657 (85.8%)	112 (91.1%)	0.111
Smoking status	869	Never smoked	485 (64.5%)	87 (74.4%)	0.036
BMI (kg-m2)	885		30.5 (26.6,35.2)	26.7 (24.7,30.5)	<0.001
BMI (kg-m2)	885	<25	133 (17.4%)	33 (27.0%)	<0.001
		≥25 & <30	227 (29.8%)	54 (44.3%)	
		≥30	403 (52.8%)	35 (28.7%)	
Atopic Disease	891		397 (51.7%)	58 (47.2%)	0.436
Depression or Anxiety	891		97 (12.6%)	1 (0.8%)	<0.001
Gastro-oesophageal Reflux	891		147 (19.1%)	23 (18.7%)	0.908
Nasal polyps	891		147 (19.1%)	46 (37.4%)	<0.001
OCS bursts (Last Year)	874		6 (3,8)	5 (3,6)	<0.001
Any OCS bursts (Last Year)	874		707 (93.9%)	109 (90.1%)	0.118
Frequent Exacerbator at baseline	874	Yes (≥3 in Last Year)	631 (83.8%)	95 (78.5%)	0.150
Invasive Ventilations (Ever)	855		81 (11.0%)	3 (2.5%)	0.002
Any ED Attendance for asthma (Last Year)	864		311 (41.6%)	31 (26.5%)	0.001
Any Hospital Admission for asthma (Last Year)	874		312 (41.3%)	35 (29.4%)	0.003
Highest Blood Eosinophil Count (N/10^9L) †	878		0.67 (0.40,1.00)	0.90 (0.55,1.41)	<0.001
Blood Eosinophil Count (N/10^9L)	874		0.40 (0.20,0.62)	0.44 (0.20,0.78)	0.410
Blood Eosinophil Count (N/10^9L)	819	<0.15	149 (19.8%)	26 (21.5%)	0.173
		≥0.15 & <0.30	81 (10.8%)	15 (12.4%)	
		≥0.30 & ≤0.45	195 (25.9%)	20 (16.5%)	
		>0.45	328 (43.6%)	60 (49.6%)	
FeNO (ppb)	671		42.0 (23.0,74.0)	50.0 (35.5,75.5)	0.026
FeNO	671	<20ppb	120 (21.2%)	11 (10.6%)	0.038
		≥20 & <50ppb	205 (36.2%)	40 (38.5%)	
		≥50ppb	242 (42.7%)	53 (51.0%)	
Composite Type 2 status	658	Eos Low (<0.15) / FeNO Low (<20)	33 (5.9%)	2 (2.0%)	0.067
		Eos High (≥0.15) / FeNO Low (<20)	83 (14.9%)	8 (7.9%)	
		Eos Low (<0.15) / FeNO High (≥20)	87 (15.6%)	20 (19.8%)	
		Eos High (≥0.15) / FeNO High (≥20)	354 (63.6%)	71 (70.3%)	
FEV$_1$ (L)	873		1.9 (1.4,2.6)	2.2 (1.7,2.8)	0.002
FEV$_1$ (% Predicted)	865		65.8 (51.4,79.8)	74.1 (59.1,89.7)	<0.001
FVC (L)	853		3.1 (2.5,3.9)	3.3 (2.8,4.3)	0.007
FVC (% Predicted)	819		84.3 (72.4,96.7)	87.8 (79.6,100.6)	0.004
FEV$_1$/FVC	853		63.5 (53.6,71.7)	65.9 (58.6,74.4)	0.030
ACQ5 Score	788		3.2 (2.2,4.0)	1.8 (0.9,2.8)	<0.001
Uncontrolled Asthma	788	ACQ5 ≥1.5	604 (89.3%)	65 (58.0%)	<0.001
EuroQoL Health Scale	358		55.0 (40.0,70.0)	75.0 (50.0,80.0)	<0.001
EuroQoL Utility	375		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	886		444 (58.1%)	59 (48.4%)	0.043
Maintenance OCS (mg) *	501		10 (8,15)	10 (6,10)	<0.001
ICS	891		764 (99.5%)	122 (99.2%)	0.687
ICS Dose (BDP equivalent-µg) **	830		2000 (1600,2000)	2000 (1600,2000)	0.083

Theophylline	880		204 (26.7%)	21 (17.9%)	0.042
Short-acting β2-agonist (SABA)	884		729 (95.7%)	116 (95.1%)	0.769
Long-acting β2-agonist (LABA)	878		705 (93.3%)	112 (91.8%)	0.559
Long acting anti-muscarinic agent (LAMA)	882		472 (62.1%)	77 (63.1%)	0.831
Leukotriene Receptor Antagonists	854		369 (50.2%)	65 (54.6%)	0.371
Maintenance Macrolides	875		69 (9.2%)	6 (5.0%)	0.126
Nebuliser	879		173 (22.8%)	9 (7.5%)	<0.001

*among patients on oral corticosteroids**among patients on inhaled corticosteroids‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure S6: Reasons for not meeting remission criteria after 1 year on biologic therapy. Remission definition: ACQ5 <1.5, no mOCS or OCS bursts, no daily SABA use

Patients failing to achieve remission at First Annual Review (ACQ5) (n=768)

ACQ

9 (1.2%)

22 (2.9%)

Steroid Use

70 (9.1%)

403
(52.5%)

99 (12.9%)

99 (12.9%)

Saba Use

66 (8.6%)

ACQ: ACQ5 >=1.5
Steroid Use: At least 1 exaccerbation and/or mOCS dose >5mg
Saba Use: at least one puff most days

ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids; SABA: Short-Acting Beta Agonists

Table S15: Remission criteria ACQ <1.5 AND no OCS bursts or mOCS >5mg/day AND <=2 SABA/day: baseline characteristics of those who meet remission at annual review and those who do not.

	n		Non-remission	Remission	p-value
	891		**80.6% (718)**	**19.4% (173)**	
Time until Annual Review (Years)	891		1.1 (1.0,1.4)	1.1 (1.0,1.3)	0.020
Sex	891	Female	437 (60.9%)	89 (51.4%)	0.024
Age At First Assessment (Years)	891		51.0 (40.0,59.0)	56.0 (48.0,65.0)	<0.001
Age at Onset of Symptoms (Years)	785		20.0 (5.5,39.0)	36.0 (16.0,52.0)	<0.001
Age of Onset of Symptoms (Years)	785	<12	221 (35.0%)	32 (20.9%)	0.002
		≥12 & <18	62 (9.8%)	13 (8.5%)	
		≥18	349 (55.2%)	108 (70.6%)	
Age Of Onset of Symptoms (≥40 years)	785		153 (24.2%)	74 (48.4%)	<0.001
Duration Of Symptoms From Baseline (Years)	785		24.0 (12.0,38.0)	20.0 (8.0,32.0)	0.005
Ethnicity	889	White	613 (85.6%)	156 (90.2%)	0.115
Smoking status	869	Never	450 (64.0%)	122 (73.5%)	0.021
BMI (kg-m2)	885		30.6 (26.6,35.3)	27.5 (24.9,30.9)	<0.001
BMI (kg-m2)	885	<25	122 (17.1%)	44 (25.6%)	<0.001
		≥25 & <30	208 (29.2%)	73 (42.4%)	
		≥30	383 (53.7%)	55 (32.0%)	
Atopic Disease	891		377 (52.5%)	78 (45.1%)	0.080
Depression or Anxiety	891		95 (13.2%)	3 (1.7%)	<0.001
Gastro-oesophageal Reflux	891		138 (19.2%)	32 (18.5%)	0.828
Nasal polyps	891		134 (18.7%)	59 (34.1%)	<0.001
OCS bursts (Last Year)	874		6 (4,8)	4 (3,6)	<0.001
Any OCS bursts (Last Year)	874		661 (94.0%)	155 (90.6%)	0.111
Frequent Exacerbator at baseline	874	Yes (≥3 in Last Year)	595 (84.6%)	131 (76.6%)	0.012
Invasive Ventilations (Ever)	855		77 (11.2%)	7 (4.2%)	0.006
Any ED Attendance for asthma (Last Year)	864		298 (42.6%)	44 (26.7%)	<0.001
Any Hospital Admission for asthma (Last Year)	874		300 (42.5%)	47 (28.0%)	<0.001
Highest Blood Eosinophil Count (N/10^9L) †	878		0.67 (0.40,1.00)	0.79 (0.55,1.33)	<0.001
Blood Eosinophil Count (N/10^9L)	874		0.40 (0.20,0.62)	0.46 (0.20,0.76)	0.128
Blood Eosinophil Count (N/10^9L)	819	<0.15	140 (19.9%)	35 (20.5%)	0.155
		≥0.15 & <0.30	79 (11.2%)	17 (9.9%)	
		≥0.30 & ≤0.45	183 (26.0%)	32 (18.7%)	
		>0.45	301 (42.8%)	87 (50.9%)	
FeNO (ppb)	671		41.0 (22.0,72.0)	51.0 (35.0,81.0)	0.002
FeNO (ppb)	671	<20ppb	116 (22.1%)	15 (10.3%)	0.003
		≥20 & <50ppb	192 (36.6%)	53 (36.3%)	
		≥50ppb	217 (41.3%)	78 (53.4%)	
Composite Type 2 status	658	Eos Low (<0.15) / FeNO Low (<20)	32 (6.2%)	3 (2.1%)	0.011
		Eos High (≥0.15) / FeNO Low (<20)	80 (15.5%)	11 (7.7%)	
		Eos Low (<0.15) / FeNO High (≥20)	81 (15.7%)	26 (18.2%)	
		Eos High (≥0.15) / FeNO High (≥20)	322 (62.5%)	103 (72.0%)	
FEV_1 (L)	873		1.9 (1.4,2.6)	2.0 (1.6,2.7)	0.031
FEV_1 (% Predicted)	865		66.5 (51.5,80.1)	69.0 (55.6,88.0)	0.005
FVC (L)	853		3.1 (2.5,3.9)	3.2 (2.7,4.2)	0.035
FVC (% Predicted)	819		84.6 (72.9,96.7)	86.8 (75.7,100.0)	0.029
FEV_1/FVC	853		63.7 (54.0,71.8)	64.4 (56.5,73.4)	0.49
ACQ5 Score	788		3.2 (2.2,4.0)	2.2 (1.0,3.2)	<0.001
Uncontrolled Asthma	788	ACQ5 ≥1.5	567 (89.9%)	102 (65.0%)	<0.001
EuroQoL Health Scale	358		55.0 (40.0,70.0)	70.0 (50.0,80.0)	<0.001
EuroQoL Utility	375		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	886		410 (57.4%)	93 (54.1%)	0.426
Maintenance OCS (mg) *	501		10 (8,15)	10 (6,10)	<0.001
ICS	830		715 (99.6%)	171 (98.8%)	0.243
ICS Dose (BDP equivalent-µg) **	830		2000 (1600,2000)	2000 (1600,2000)	0.671
Theophylline	880		191 (26.8%)	34 (20.5%)	0.095
Short-acting β2-agonist (SABA)	884		682 (95.7%)	163 (95.3%)	0.850
Long-acting β2-agonist (LABA)	878		657 (93.1%)	160 (93.0%)	0.987

Long acting anti-muscarinic agent (LAMA)	882		439 (61.7%)	110 (64.3%)	0.532
Leukotriene Receptor Antagonists	854		348 (50.7%)	86 (51.5%)	0.845
Maintenance Macrolides	875		67 (9.5%)	8 (4.7%)	0.043
Nebuliser	879		167 (23.5%)	15 (8.9%)	<0.001

*among patients on oral corticosteroids**among patients on inhaled corticosteroids‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure S7: Reasons for not meeting remission criteria after 1 year on biologic therapy. Remission definition: ACQ5 <1.5, no mOCS or OCS bursts, ≤2 puffs SABA/day
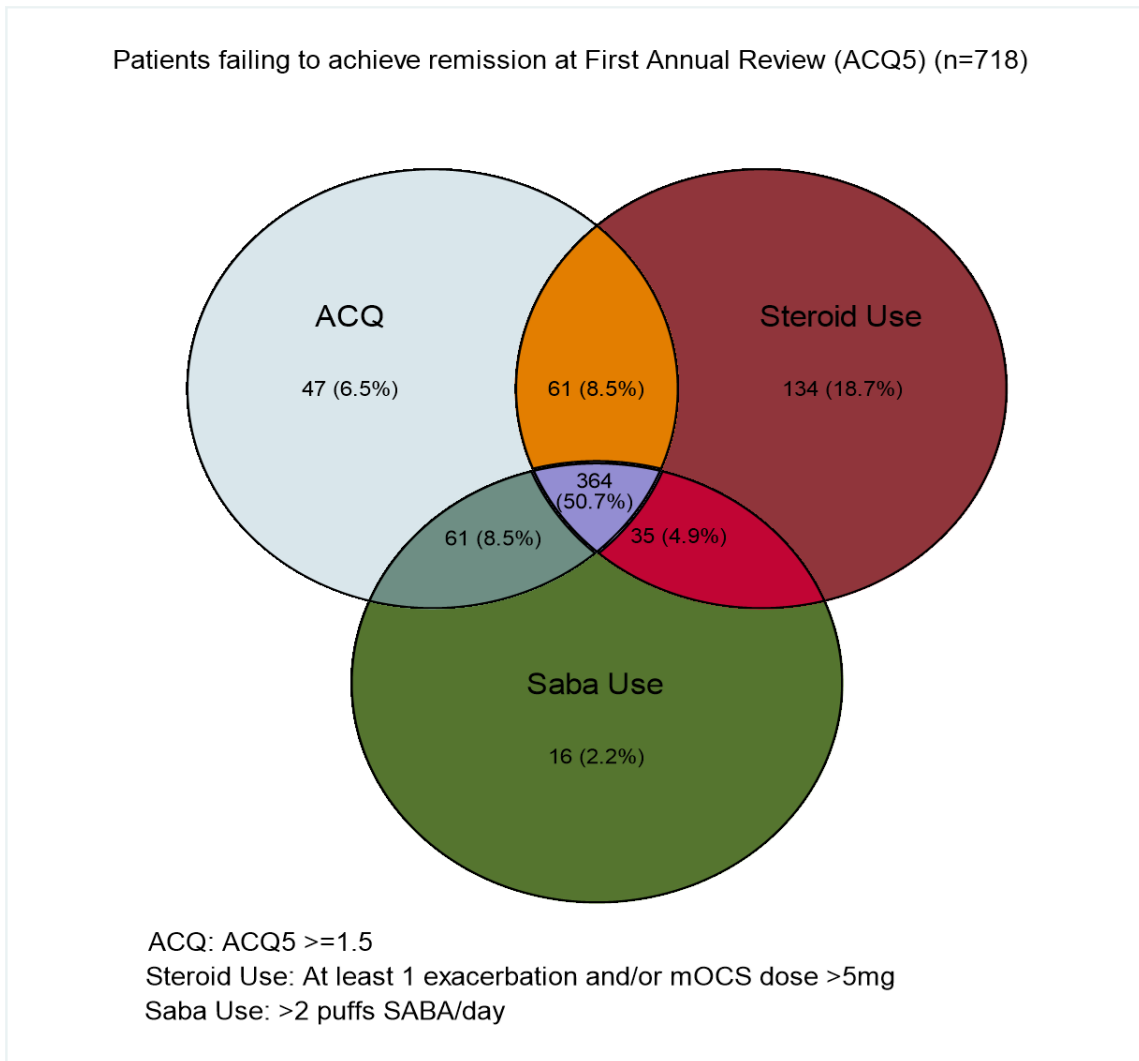
Patients failing to achieve remission at First Annual Review (ACQ5) (n=718)

ACQ

47 (6.5%)

61 (8.5%)

Steroid Use

134 (18.7%)

364 (50.7%)

61 (8.5%)

35 (4.9%)

Saba Use

16 (2.2%)

ACQ: ACQ5 >=1.5
Steroid Use: At least 1 exacerbation and/or mOCS dose >5mg
Saba Use: >2 puffs SABA/day

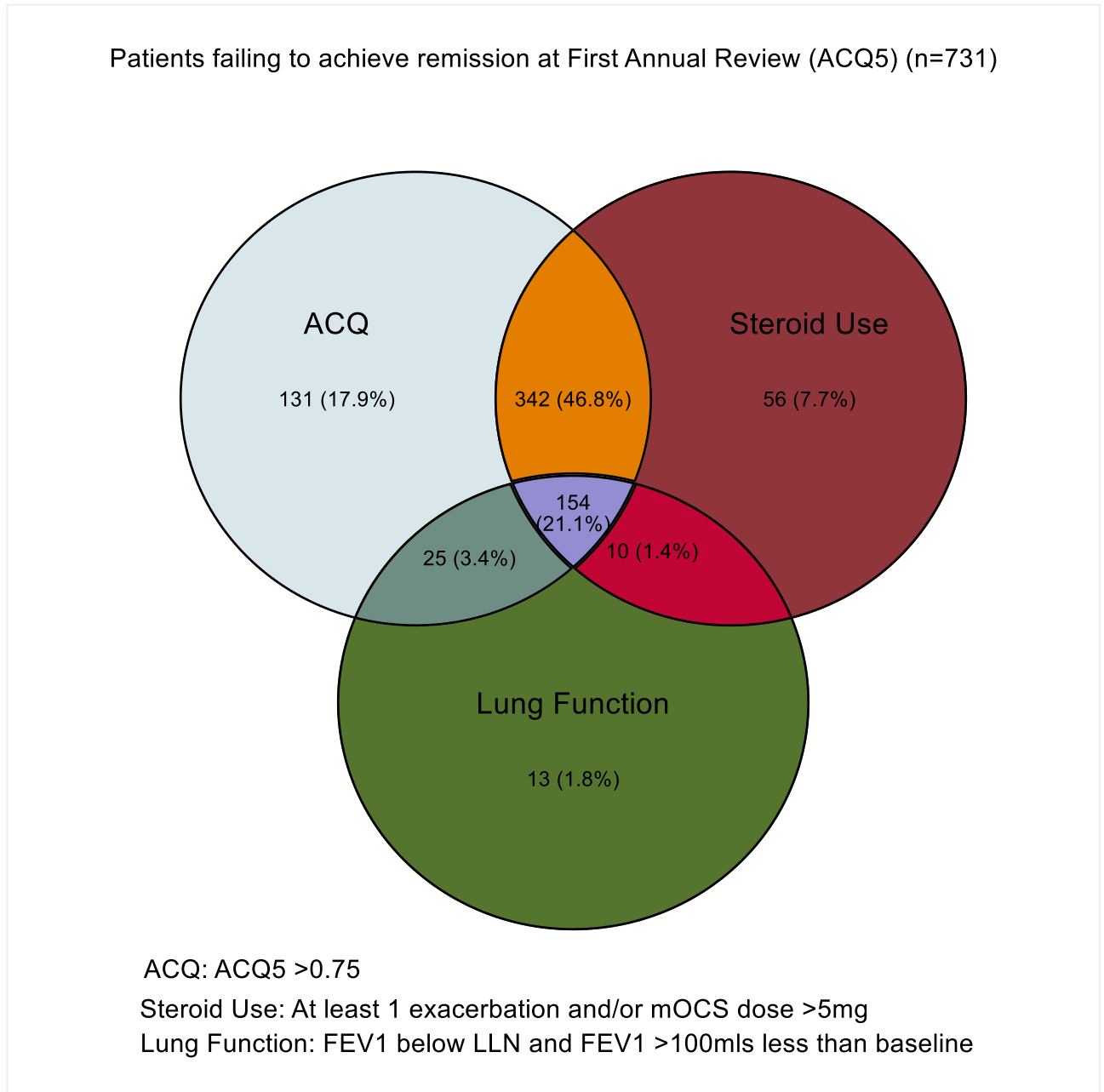ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids; SABA: Short-Acting Beta Agonists

Table S16: Remission criteria ACQ5 <=0.75 AND no OCS bursts or mOCS >5mg/day AND FEV$_1$ above LLN or <100mls less than pre-biologic FEV$_1$: baseline characteristics of those who meet remission at 1 year and those who do not

	n		Non-remission	Remission	p-value
	830		**88.1% (731)**	**11.9 % (99)**	
Time until Annual Review (Years)	830		1.1 (1.0,1.4)	1.1 (1.0,1.2)	0.168
Sex		Female	437 (59.8%)	52 (52.5%)	0.168
Age At First Assessment (Years)	830		51.0 (41.0.60)	55.0 (47.0,66.0)	0.001
Age at Onset of Symptoms (Years)	737		21.0 (6.0,40.0)	31.0 (16.0,52.0)	<0.001
Duration Of Symptoms From Baseline (Years)	737		24.0 (11.0,37.0)	20.0 (8.0,33.0)	0.057
Ethnicity	828	White	629 (86.3%)	95 (96.0%)	0.006
Smoking status	809	Never smoked	468 (65.5%)	71 (74.7%)	0.179
BMI (kg-m2)	823		30.3 (26.6,35.1)	27.3 (25.0,31.0)	<0.001
Atopic Disease	830		382 (52.3%)	45 (45.5%)	0.202
Depression or Anxiety	830		88 (12.0%)	0(0.0%)	<0.001
Gastro-oesophageal Reflux	830		128 (17.5%)	16 (16.2%)	0.739
Nasal polyps	830		136 (18.6%)	35 (35.4%)	<0.001
OCS bursts (Last Year)	817		5 (3,8)	4 (2,6)	0.001
Any OCS bursts (Last Year)	817		676 (94.0%)	86 (87.8%)	0.020
Frequent Exacerbator at baseline	817	Yes (≥3 in Last Year)	595 (82.8%)	73 (74.5%)	0.047
Invasive Ventilations (Ever)	798		0 (0,0)	0 (0,0)	0.059
Any ED Attendance for asthma (Last Year)	807		276 (38.8%)	17 (17.9%)	<0.001
Any Hospital Admissions for asthma (Last Year)	814		289 (40.3%)	26 (26.8%)	0.010
Highest Blood Eosinophil Count (N/10^{9}L) †	821		0.69 (0.43,1.00)	0.90 (0.60,1.41)	<0.001
Blood Eosinophil Count (N/10^{9}L)	819		0.39 (0.18,0.60)	0.53 (0.21,0.78)	0.028
Blood Eosinophil Count (N/10^{9}L)	819	<0.15	158 (21.9%)	17 (17.5%)	0.018
		≥0.15 & <0.30	82 (11.4%)	14 (14.4%)	
		≥0.30 & ≤0.45	183 (25.3%)	13 (13.4%)	
		>0.45	299 (41.4%)	53 (54.6%)	
FeNO (ppb)	638		42.0 (23.0,71.0)	54.0 (38.0,88.0)	0.001
FeNO (ppb)	638	<20ppb	118 (21.4%)	5 (5.7%)	0.001
		≥20 & <50ppb	203 (36.8%)	31 (35.6%)	
		≥50ppb	230 (41.7%)	51 (58.6%)	
Composite Type 2 status	627	Eos Low (<0.15) / FeNO Low (<20)	40 (7.4%)	0(0.0%)	0.002
		Eos High (≥0.15) / FeNO Low (<20)	74 (13.7%)	5 (5.9%)	
		Eos Low (<0.15) / FeNO High (≥20)	93 (17.2%)	14 (16.5%)	
		Eos High (≥0.15) / FeNO High (≥20)	335 (61.8%)	66 (77.6%)	
FEV$_1$ (L)	818		2.0 (1.4,2.6)	2.2 (1.7,2.8)	0.001
FEV$_1$ (% Predicted)	811		66.5 (52.0,81.1)	74.1 (61.1,89.9)	<0.001
FVC (L)	802		3.1 (2.5,3.9)	3.3 (2.8,4.3)	0.014
FVC (% Predicted)	772		85.1 (73.4,97.1)	87.2 (79.8,102.9)	0.011
FEV$_1$/FVC	802		63.6 (53.6,72.1)	66.4 (58.1,74.1)	0.072
ACQ5 Score	736		3.2 (2.2,4.0)	1.7 (0.7,3.0)	<0.001
Uncontrolled asthma	736	ACQ5 ≥1.5	569 (88.4%)	53 (57.6%)	<0.001
EuroQoL Health Scale	350		60.0 (40.0,70.0)	80.0 (60.0,85.0)	<0.001
EuroQoL Utility	362		0.7 (0.5,0.8)	0.9 (0.8,1.0)	<0.001
Maintenance OCS	826		424 (58.3%)	51 (51.5%)	0.199
Maintenance OCS (mg) *	474		10 (8,15)	10 (5,10)	0.001
ICS	830		729 (99.7%)	98 (99.0%)	0.252
ICS Dose (BDP equivalent-μg) **	775		2000 (1600,2000)	2000 (1600,2000)	0.469
Theophylline	821		194 (26.8%)	22 (22.9%)	0.422
Short-acting β2-agonist (SABA)	823		694 (95.6%)	91 (93.8%)	0.433
Long-acting β2-agonist (LABA)	818		670 (93.1%)	93 (94.9%)	0.494
Long acting anti-muscarinic agent (LAMA)	821		462 (63.9%)	63 (64.3%)	0.941
Leukotriene Receptor Antagonists	799		354 (50.2%)	53 (56.4%)	0.261
Maintenance Macrolides	816		62 (8.6%)	7 (7.1%)	0.618
Nebuliser	819		170 (23.5%)	10 (10.4%)	0.004

*among patients on oral corticosteroids**among patients on inhaled corticosteroids‡ Median (IQR) or count (%) as appropriate; † highest recorded according to prior medical records. 'Last Year' refers to measures assessed using clinical records in the 12 months prior to initial presentation at the severe asthma centre, other measures were as observed or recorded at initial presentation unless otherwise indicated

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; ED: Emergency Department; OCS: Oral Corticosteroid Steroids; FeNO: Fractional Exhaled Nitric Oxide; ppb: Parts per Billion; FEV_1: Forced Expiratory Volume (1 second); FVC: Forced Vital Capacity; ACQ: Asthma Control Questionnaire: SABA: Short-Acting Beta Agonists; ICS: Inhaled Corticosteroid Steroids: LABA: Long-Acting Beta Agonists; LAMA: Long-Acting Muscarinic Antagonist

Figure S8: Reasons for not meeting remission criteria after 1 year on biologic therapy. Remission definition: ACQ5 <=0.75, no mOCS or OCS bursts, FEV$_1$ above LLN or <100mls less than pre-biologic FEV$_1$

Patients failing to achieve remission at First Annual Review (ACQ5) (n=731)

ACQ
131 (17.9%)

342 (46.8%)

Steroid Use
56 (7.7%)

154 (21.1%)

25 (3.4%)

10 (1.4%)

Lung Function
13 (1.8%)

ACQ: ACQ5 >0.75
Steroid Use: At least 1 exacerbation and/or mOCS dose >5mg
Lung Function: FEV1 below LLN and FEV1 >100mls less than baseline

ACQ: Asthma Control Questionnaire; mOCS: maintenance Oral Corticosteroid Steroids: FEV$_1$; Forced Expiratory Volume (1 second); LLN: Lower Limit of Normal

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