Exacerbation Profile and Risk Factors in a T2-Low Severe Asthma Population

Sub-title: Exacerbation profile in T2-low severe asthma

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At a Glance

What is the current scientific knowledge on this subject?

Understanding the clinical presentation, physiological changes and underlying inflammatory processes in non-T2 exacerbations in severe asthma is a critically important, and currently an unmet research need as supported by the absence of any published prospective observational data describing T2 low exacerbations in severe asthma, [PubMed search, 04 March 2022].

What does this study add to the field?

This data shows that asthma exacerbations without evidence of T2 biology were physiologically and symptomatically similar to T2 high exacerbations. The T2 phenotype was not stable, suggesting that exacerbation phenotyping should occur at the time of exacerbation. The clinically significant exacerbations in participants without evidence of T2 biology at the time of exacerbation highlights the unmet and pressing need to further understand the mechanisms at play in non-T2 asthma.

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ABSTRACT

BACKGROUND: The last 25 years have seen huge progress in understanding of the pathobiology of T2 asthma, identification of measurable biomarkers and the emergence of novel monoclonal antibody treatments. Although present in a minority of severe asthmatics, very little is known about the mechanisms underlying T2-low asthma, making it a significant unmet need in asthma research.

METHODS: Exacerbation assessment was a pre-specified secondary analysis of data from a 48-week, multicentre, randomised controlled clinical study comparing the use of biomarkers and symptoms to adjust steroid treatment in a T2-low severe asthma-enriched cohort.

Participants were phenotyped as $T2^{LOW}$(fractional exhaled nitric oxide [FeNO] ≤20 ppb and blood eosinophil count [PBE] ≤150 cells/μL) or $T2^{HIGH}$ (FeNO>20 or PBE>150) at study enrolment and at each exacerbation. Here, we report the findings of the exacerbation analyses, including comparison of exacerbators and non-exacerbators, the physiological changes at exacerbation in those who had evidence of T2 biology at exacerbation versus those that did not, and the stability of inflammatory phenotypes when stable and at exacerbation.

RESULTS: Of the 301 participants, 60.8% (183/301) had one or more self-reported exacerbations (total of 390). Exacerbators were more likely to be female, have a higher BMI and more exacerbations requiring oral corticosteroid (OCS) and unscheduled primary care attendances for exacerbations.

At enrolment, 23.6% (71/301) were $T2^{LOW}$, and 76.4% (230/301) $T2^{HIGH}$. The $T2^{LOW}$ group had more asthma primary care attendances, were more likely to have a previous admission to HDU/ICU and to be receiving maintenance OCS.

At exacerbation the $T2^{LOW}$ events were indistinguishable from $T2^{HIGH}$ exacerbations in terms of lung function (mean fall in $T2^{LOW}$ FEV_1 - 200 [400] mL v $T2^{HIGH}$ 200 [300] mL, p=0.93) and symptom

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increase (ACQ5: $T2^{LOW}$ 1.4 [0.8] v $T2^{HIGH}$1.3 [0.8], p=0.72), with no increase in T2 biomarkers from stable to exacerbation state in the $T2^{LOW}$ exacerbations.

The inflammatory phenotype within individual patients was dynamic; inflammatory phenotype at study entry did not have a significant association with exacerbation phenotype.

CONCLUSION:

Asthma exacerbations demonstrating a $T2^{LOW}$ phenotype were physiologically and symptomatically similar to $T2^{HIGH}$exacerbations. $T2^{LOW}$ asthma was an unstable phenotype, suggesting that exacerbation phenotyping should occur at the time of exacerbation. The clinically significant exacerbations in participants without evidence of T2 biology at the time of exacerbation highlights the unmet and pressing need to further understand the mechanisms at play in non-T2 asthma.

Key words: severe asthma; T2-Low; Exacerbation

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INTRODUCTION

Patients with inadequately controlled severe asthma despite optimised controller therapies shoulder much of the disability, economic burden and health care consumption attributed to asthma [1–5]. Exacerbation events that result from type-2 (T2) cytokine-driven eosinophilic inflammation are an important aspect of poor asthma control and T2 biomarkers (peripheral blood eosinophils [PBE], and fractional exhaled nitric oxide [FeNO]) serve well as predictors of exacerbation risk [6–9]. Despite the involvement of cytokine-driven eosinophilic inflammation in exacerbations, patients with well-suppressed T2 biology, including those receiving T2-suppressing biological agents, continue to experience exacerbations [9–14].

A proportion of patients in severe asthma clinics are characterised as having non-eosinophilic, 'type-2 low' asthma; a phenotype often associated with smoking, obesity and recurrent or persistent bacterial infection. Recent studies suggest that in many cases, patients with apparent 'type-2 low' severe asthma, expressing with low disease biomarkers (FeNO and PBE), also have underlying type-2 biology suppressed by corticosteroids administered in response to their poor symptom control [15–17]. Ongoing corticosteroid suppression serves to confound our understanding of disease in this patient group [18–20].

A recent trial comparing biomarker versus symptom-based treatment titration in severe asthmatics enrolled a population of patients with a FeNO of less than 45ppb to enrich for a cohort that included a substantial T2 low population [21]. A prespecified secondary endpoint was analysis of asthma exacerbations. Here we report the findings of the exacerbation analysis in this T2-low enriched severe asthma cohort, including comparison of study exacerbators and non-exacerbators, the physiological changes at exacerbation in those who had evidence of T2 biology at exacerbation versus those that did not, and the stability of inflammatory phenotypes when stable and at exacerbation.

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METHODS

Study design

This was a 48-week, multicentre, randomised controlled clinical study in severe asthma, where the primary objective was to compare a treatment algorithm led by composite type-2 biomarkers (FeNO, blood eosinophils and serum periostin) with a symptom/risk-based algorithm to optimise the maintenance dose of corticosteroids (see **Supplementary Appendix** for details on the patient inclusion and exclusion criteria) [15]. Comparison of exacerbation rates between the treatment algorithms was an important pre-specified secondary outcome.

Participants were recruited from 12 specialist Severe Asthma Centres in the United Kingdom between 8th January 2016 and 12th July 2018 (see **Supplementary Appendix**), with the last study visit on 18th June 2019. Full inclusion and exclusion criteria are presented in the supplementary appendix, but of note, all enrolled participants had severe asthma (Global Initiative for Asthma (GINA) steps 4 and 5) [2], were aged 18–80 years old and were enrolled in a non-selective manner. Inclusion criteria included a documented history of ≥12% change in forced expiratory volume in 1 second (FEV_1) within the last 24 months, or a positive methacholine or mannitol challenge, and no 'rescue' oral corticosteroids (OCS) for an exacerbation in the 4 weeks prior to enrolment. The study aimed to enrich for a T2 biomarker low population within the cohort, so patients only proceeded to study enrolment if they had a fractional exhaled nitric oxide (FeNO) of <45 ppb at the screening visit.

All participants had one scheduled study visit at study entry, and all other study visits were unscheduled exacerbation study visits. All participants were asked to contact their study centre for clinical assessment (unscheduled exacerbation study visit) when their asthma control deteriorated to a level where they would usually seek medical advice or activate their personalised asthma action plan (PAAP). During these unscheduled visits, detailed clinical evaluation, medication review and spirometry were performed, asthma control questionnaire-7 (ACQ-7) completed, and FeNO, peripheral blood eosinophils (PBE), and serum C-reactive protein (CRP) measured. A urine sample

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and a spontaneous sputum sample for differential cell counting and biobanking of the supernatant were collected where feasible. An exacerbation was defined as 'severe asthma symptoms worsening outside of a patient's normal daily variation' and following assessment, a clinical decision was provided by the clinical team on the need to prescribe oral corticosteroids (OCS) and/or antibiotic therapy. Where participants were unable to attend the clinical centre for this unscheduled study visit, exacerbation information was collected at the subsequent scheduled study visit, which occurred every 8 weeks from the time of enrolment until study completion at 48 weeks.

The inflammatory phenotype was attributed contemporaneously at each study visit, (at baseline and at each exacerbation), using peripheral biomarkers of T2 inflammation, namely FeNO and PBE. Biomarker cut-points similar to those described by the GINA guidelines were used to describe phenotypes; a FeNO ≤20 ppb *and* PBE ≤0.15 x 10^9/L was termed '$T2^{LOW'}$, and FeNO >20 ppb *or* PBE >0.15 x 10^9/L, termed '$T2^{HIGH'}$ to indicate the presence of detectable T2 biology [2].

As this was an observational analysis, all outcome measures were treated as exploratory.

The study protocol and primary study outcome have been previously published [15, 21]. Prior to participant recruitment, the protocol was approved by the Office for Research Ethics Northern Ireland (NI0158), local National Health Service Research and Development approval obtained for each site (NHS R&D) and the study registered on Clinicaltrials.gov (NCT02717689). All participants provided informed, written consent.

Procedures

Spirometry was conducted according to the American Thoracic Society/European Respiratory Society guidelines, with Global Lung Function 2012 (GLI 2012) equations used to calculate FEV_1 and forced vital capacity (FVC) predictive values [22]. NIOX Vero devices (Circassia, USA) were used for FeNO measurement. Spontaneous sputum samples were collected and processed in line with a standard operating procedure applied across all centres; RNA was extracted and underwent analysis following

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polymerase chain reaction (PCR) using LightCycler® 480 II instrumentation (Roche Molecular Diagnostics) to test for respiratory viruses including influenza A/B, respiratory syncytial virus A/B, rhinovirus, metapneumovirus, adenovirus, parainfluenza 1-4, and coronavirus.

Bacterial load within the DNA extracted from sputum plugs was measured by quantitative PCR (qPCR), using ThermoFisher Quantstudio 5, based on abundance of 16S ribosomal subunit encoding genes and pathogen specific genes including *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumonia* [23]. We used a specific bacteria threshold of $\geq 10^6$ genome copies/mL on sputum qPCR as significant as this threshold of detection had a 98% concordance with bacteria detection on routine culture and was associated with an increased percentage sputum neutrophils in COPD exacerbations [24].

Statistical analysis

As this was a pre-specified secondary analysis of existing data, no sample size calculation was conducted. Depending on distribution, descriptive statistics are presented as means (SD), medians [IQR] or counts (%). Univariate analyses were conducted using t-tests, chi-square tests and Mann-Whitney U as appropriate. To ensure that bias wasn't introduced as a consequence of repeated exacerbations in an individual participant, each participant's first exacerbation was used when comparing inflammatory phenotypes in the cohort.

The stability of the exacerbation phenotype across multiple exacerbations in an individual patient was assessed using McNemar's test and the Kappa statistic. Data for assessed exacerbations were collected prospectively during exacerbations and there were few missing data. Therefore, all analyses under a complete-case framework. Analyses were conducted using STATA 16 (StataCorp, Texas, USA).

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RESULTS

Demographics and baseline clinical descriptors for the study cohort are presented in the **Supplementary Appendix Table E1**. This cohort were generally middle aged (mean (SD) 55.7 (13.1) years), with a female preponderance (64.5%) and high BMIs (31.6 (7.2) Kg/m^2). During the 12 month period prior to enrolment patients reported a median [IQR] of 2 [1,4] exacerbations; one fifth had a history of ICU admission and their symptom-burden and quality of life impairment were high, respectively judged by ACQ-7 and AQLQ patient reported outcomes.

Clinical and biomarker characteristics of exacerbating patients

301 study participants reported a total of 390 exacerbation events, with 60.8% (183/301) experiencing ≥1 exacerbation (**Figure 1 and Table E1 supplement**). Baseline characteristics of those who exacerbated and those who did not are shown in the **Table 1**. When compared to non-exacerbators, patients who exacerbated during the study were more likely to be female [70.5% vs. 55.1%], have a higher BMI [33.1 kgm^{-2} vs. 29.4 kgm^{-2} on enrolment] and had more frequent exacerbations requiring OCS and unscheduled primary care attendances for exacerbations in year prior to the study (**Table 1**). Those who exacerbated were more likely to be receiving maintenance OCS and had a lower sputum eosinophil count at study entry, though other T2 biomarkers (PBE, FeNO or serum periostin) were not different. There was no difference between the exacerbators and non-exacerbators in the proportion of patients who reduced (24.4% vs. 29.3%), maintained (39.6% vs. 38.4%) or increased (36.0% vs. 32.3%) their steroid dose (OCS / ICS) during the study (p=0.66).

When phenotyping at study enrolment, 23.6% (71/301) of participants met the criteria for T2^{LOW} and 76.4% (230/301) had evidence of T2 biology (T2^{HIGH}) (**Supplementary Appendix, Table E2**). The T2^{HIGH} group had more obstructive lung function, higher sputum eosinophil count, higher periostin levels and a higher incidence of nasal polyposis. The T2^{LOW} group had more primary care attendances for asthma and were more likely to have had an ICU or HDU admission for asthma. There was no

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difference in symptom burden (ACQ7: 2.1 vs. 1.9) or impact on quality-of-life (AQL: 4.7 vs. 5.0) between the $T2^{LOW}$ and $T2^{HIGH}$ cohorts. A higher proportion of the $T2^{LOW}$ cohort were receiving maintenance OCS (34 (47.9%) v 77 (33.5%), p=0.03), at a higher dose (10 mg [10, 12] v 8 mg [5, 10], p=0.04) than the $T2^{HIGH}$ cohort, and were significantly more likely to be advised to down-titrate their CS usage as per the biomarker treatment strategy within the study.

A total of 118 exacerbation events (118/390, 30%) in 80 patients were assessed by study clinicians during unscheduled study visits (**Figure 1**). There was no evidence that the unassessed exacerbations differed in severity to those that were assessed, with a similar proportion of patients admitted to hospital during the event (8 of 118 [6.8%] vs. 23 of 272 [8.5%], p>0.5). As has been described in previous exacerbation studies [20], patients with unassessed exacerbations who followed their PAAP or had non-specialist assessment, were more likely to receive rescue OCS than those treated by asthma specialists during an unscheduled study visit (265 of 272 [97.4%] vs. 84 of 118 [71.2%], respectively; p<0.0001) or antibiotics (145 of 272 [53.3%] vs. 45 of 118 [38.1%], respectively; p=0.0059). In patients assessed by asthma specialists, those who did not receive OCS had a lower FeNO compared to those who received OCS ((15 ppb [IQR: 10, 23)] vs. 28 ppb [IQR: 14, 45], respectively p=0.001). Thirty-four patients did not receive OCS during an unscheduled study visit, and of these, only four (11.8%) went on to have systemic CS from another source (General Practitioners) within the following 7 days to address persistent or worsening symptoms (treatment failure).

Clinical and biomarker characteristics during exacerbations

At first assessed exacerbation for each patient, 27% (19/71) exacerbations were phenotyped as $T2^{LOW}$ and 73% (52/71) of exacerbations as $T2^{HIGH}$ (**Table 2**). The exacerbations in both groups looked clinically similar with comparable increase in symptoms, fall in FEV_1 (mean ~200 mL), decline in FVC, FEV_1/FVC and peak flow from study entry. $T2^{HIGH}$ had a greater increase in FeNO and PBE from study

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entry to time of exacerbation compared to the $T2^{LOW}$ cohort who had no associated increase in any T2 biomarkers from baseline, despite the similar physiological changes and symptom increase.

Of the first assessed exacerbation episodes for each patient, 26 of 71 (33%) produced spontaneous sputum and had a cell differential: 7/26 (27%) had a sputum eosinophil count <2% and neutrophil count ≥65%; 6/26 (23%) had a sputum eosinophil count <2% and neutrophil count <65%; 4/26 (15%) a sputum eosinophil count ≥2% and neutrophil count ≥65% and 9/26 (35%) had a sputum eosinophil count ≥2% and neutrophil count <65%. Sputum eosinophils were higher in the $T2^{HIGH}$group, with the $T2^{HIGH}$ group showing a median 2.9% (IQR: -3.8, 10.3) increase in sputum eosinophils from the stable to exacerbation state. The $T2^{LOW}$ group had a greater number of sputum samples positive for virus at exacerbation, and all of the $T2^{LOW}$ cohort had a virus or bacteria detected on qPCR above threshold, however, there was no concomitant elevation of the sputum neutrophil count or serum CRP (described in **Table 2**). The was no significant difference between the $T2^{LOW}$ and $T2^{HIGH}$ cohorts with regards to systemic corticosteroids (CS) or antibiotics prescribed by the asthma team.

Within the cohort who were $T2^{LOW}$ at study entry, those who went on to exacerbate had a higher number of primary care attendances for asthma prior to study entry, more OCS rescue courses in the previous year and higher baseline ACQ-7 score compared to those who did not exacerbate (**Table 3**). Comparing T2 status at baseline (when stable) and exacerbation, 45/75 (60%) of patients had T2 biology detectable at baseline and exacerbation. T2 biology was also evident during exacerbation in 11/17 (65%) who were $T2^{LOW}$ at study entry. The observed change in exacerbation phenotype may be related to changes in corticosteroid exposure, as 5/7 who were $T2^{LOW}$ at baseline and subsequently reduced the dose of CS demonstrated a $T2^{HIGH}$ phenotype at exacerbation (see **Supplementary Appendix Table E3**). However, further analysis showed the inflammatory phenotype at study entry was not associated significantly with the phenotype at exacerbation (p=0.84, kappa=0.12), **Table 4a**). Inflammatory phenotype at first exacerbation was not associated significantly with the phenotype at secondary exacerbation (p=1.00, kappa=0.19), **Table 4b**).

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DISCUSSION

The advent of biologic therapies targeting the T2-cytokine axis has reduced the frequency of asthma exacerbations in patients with severe asthma with an underlying T2-driven eosinophilic phenotype [9–12]. Under these conditions, T2 biomarkers (FeNO and PBE) have been shown to perform well both as prognostic biomarkers for exacerbation events (as shown in placebo arms of clinical trials) and as predictors of good therapeutic responses to T2 biologic therapies. The RASP-UK study population for the present analysis was purposefully enriched for patients with severe asthma expressing a T2 biomarker low phenotype, within a clinical setting where residual exacerbation events represent an unmet medical need as the mechanisms are poorly understood. In this cohort, T2-biomarkers (FeNO, PBE and serum periostin) at randomisation were not prognostic for the frequency of exacerbation events, an observation consistent with mechanisms other than type-2 inflammation being responsible. Baseline sputum eosinophil counts were significantly lower in patients who went on to have an exacerbation, but as this biomarker was only obtained in approximately one third of patients at baseline (which is a common limitation when using sputum as source of a biomarkers), we cannot exclude some selection bias for sputum eosinophil counts in this subgroup. However, the biomarker measurement data appear to confirm recruitment of an exacerbation prone T2-biomarker low non-eosinophilic population as planned for the study.

In the present study, poor asthma symptom control, female sex, obesity, restrictive lung function and multiple unscheduled prior healthcare visits for exacerbation events in the prior year to study emerged as clinical factors associated with patients experiencing exacerbations. Poor asthma control and prior exacerbation history has consistently been associated with exacerbation risk and specifically in heavily treated severe asthma populations [25, 26].

The association between higher symptom burden and higher exacerbation rate was also seen in the MEX study, which examined exacerbation phenotype in patients with severe eosinophilic asthma established on mepolizumab [20], this association between higher symptom burden and higher pre-

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biologic exacerbation rates was also seen in those patients who went on to exacerbate while being treated with mepolizumab, suggesting that these factors are important for future risk despite significant background treatment. There may be a smaller 'window' for symptom deterioration in these highly symptomatic patients with severe asthma, prior to them self-identifying asthma deterioration, as they more easily cross a threshold, whereby they revert to their personal action plan and seek medical intervention.

The interaction between female sex, obesity and severe asthma needs further analysis but importantly the obese female phenotype has been described previously in severe asthma cohorts, and this group is often T2 biomarker low with a high symptom burden despite high dose ICS and systemic CS [15, 26–28]. These data extend our knowledge for this high symptom burden clinical group, identifying them (both retrospectively and prospectively) as being particularly exacerbation prone. Defining the relationship between these clinical parameters and risk of exacerbation is key to understanding the underlying mechanism.

Those patients who self-treated according to their asthma plan or were seen in primary care almost always received systemic CS (97.4%), whereas those assessed by treating clinicians with broader access to clinical assessments, specifically FeNO measurement (as blood eosinophil data would not be available at the time of consultation) were less likely to receive these (70%). The similarity in rates of hospitalisation for assessed and unassessed exacerbations suggests that the exacerbation severity in both groups was similar. However, interpretation of the present data is limited by the absence of markers of exacerbation severity in patients not attending clinical assessments, such as symptom diary and peak flow measurements. Although the study did not mandate that FeNO be used to decide on prescription of systemic CS, mean FeNO was significantly lower in those not receiving OCS, and it is possible that this easily measured biomarker was being used to determine the perceived requirement for OCS during exacerbations. Importantly, there was a low observed incidence of treatment failure (defined as requirement for OCS or hospital admission in the 7 days

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after clinical assessment) when OCS were not prescribed after study clinical assessment. This fits with the findings of a recent study with mepolizumab (and assumed PBE suppression), FeNO measurement emerged as a useful means of discriminating between eosinophilic and non-eosinophilic events, with the latter more likely to be infection driven [20]. An important clinical consideration is the nature of all exacerbation events and specifically whether treatment with OCS is an appropriate treatment in T2 biomarker low events. Describing the clinical and demographic features associated with the T2 biomarker low frequent exacerbator phenotype will allow these patients to be better identified, and given the potential harm caused by regular systemic CS exposure, we believe that the routine use of systemic CS for all exacerbation events in severe asthma requires further study and that clinical assessment and biomarker measurement may be helpful in making more targeted treatment choices. This hypothesis, and specifically the use of FeNO to guide therapeutic use of OCS during exacerbation needs to be formally tested via controlled clinical trials.

We were particularly interested in the $T2^{LOW}$ phenotype in this cohort and wished to identify clinical and demographic features associated with exacerbation events. Importantly, the $T2^{LOW}$ events had a similar increase in symptoms and fall in lung function compared to those in the $T2^{HIGH}$population, suggesting that the $T2^{LOW}$ events are clinically significant, albeit indistinguishable on the basis of symptoms or lung function. In contrast, measurement of T2 biomarkers showed greater increases in FeNO and PBE from baseline values at the time of exacerbation. In contrast, the T2 $T2^{LOW}$ cohort showed no increase in any T2 biomarker expression, despite similar physiological changes and symptom increase.

A limitation of the current study was the use of spontaneous rather than induced sputum measures, meaning that only a third of patients produced a spontaneous sputum sample at exacerbation. Peripheral biomarkers (PBE and FeNO) were used primarily to determine T2 status, however, as anticipated, the $T2^{LOW}$ cohort as defined by FeNO and PBE, were non-eosinophilic on sputum

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cytology, whereas the T2-Biology cohort had sputum eosinophilia, consistent with the use of composite T2 biomarker profiling with FeNO and PBE as a surrogate of eosinophilic airways inflammation [29,30]. Exacerbations with sputum data demonstrated a mixed inflammatory profile, with evidence of eosinophilic, neutrophilic and mixed eosinophilic-neutrophilic inflammation on sputum differential cell count, in keeping with previous reports of exacerbation analysis in mild-moderate asthmatic patients [13, 14]. However, this contrasts with observations from the MEX study, which explored exacerbation events on mepolizumab and where it was noted that eosinophilic and non-eosinophilic events were predominantly mutually exclusive [20]. This difference may reflect the greater PBE suppression with mepolizumab, allowing for clearer differentiation of the inflammatory phenotype. It is not yet clear whether the neutrophilic, infection-driven exacerbations seen in patients treated with mepolizumab reflect natural infections, immunosuppression due to biologics-induced reduction in airway eosinophils, or a broader suppression of the T2-cytokine axis and anti-infective pathways from high dose inhaled corticosteroids.

The $T2^{LOW}$ group had a greater number of sputum samples positive for virus at exacerbation, and all of the $T2^{LOW}$ cohort had a virus or bacteria detected on qPCR above threshold, although did not have a concomitant elevated sputum neutrophil count or CRP. The proportion of exacerbations with bacteria identified was similar between both groups at exacerbation, however, the number of sputum samples available at exacerbation are a limiting factor for drawing conclusions on the role of infectious agents being drivers of $T2^{LOW}$ exacerbations. The dynamic nature of inflammatory phenotype seen between the different study visits, (from stable to exacerbation, and from one exacerbation to the next in the same individual), is in keeping with descriptions in the literature [20,31].

The need to elicit the pathways underlying these $T2^{LOW}$ exacerbations is a prerequisite to establishing effective treatments, and minimising the unwanted side effects of treatments that are

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known to have limited effectiveness, i.e. the use of OCS in $T2^{LOW}$ exacerbations and asthma management more generally. Within the $T2^{LOW}$ cohort, exacerbation risk during the study, was related to higher primary care asthma attendances and rescue systemic CS courses in the previous year, and a higher ACQ-7 score suggesting that these parameters are consistently associated with exacerbation risk in all patients with severe asthma.

The present study demonstrated how asthma exacerbations in patients expressing the $T2^{LOW}$ phenotype are similar physiologically and symptomatically, and occur as frequently as those with underlying T2 biology. $T2^{LOW}$ asthma emerged as an unstable phenotype that needs to be assessed at the time of exacerbation. These data highlight our limited understanding of the underlying pathology and lack of effective, evidence-based management strategies for asthma in the absence of T2 biology, as well as the need for further mechanistic and clinical studies.

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Table 1. Table of baseline characteristics of study exacerbators versus non-exacerbators (N=301).

		No Exacerbations (n=118)	≥1 Exacerbation (n=183)	P-value
Number of Exacerbations 0 1 2 3 4 5 6		118 (100%)	0 (0.0%) 77 (42.1%) 47 (25.7%) 33 (18.0%) 15 (8.2%) 6 (3.3%) 5 (2.7%)	
Age At Study Enrolment (Y)	**N=301**	56.5 (13.1)	55.2 (13.2)	0.41
Gender Female Male	**N=301**	 65 (55.1%) 53 (44.9%)	 129 (70.5%) 54 (29.5%)	0.0064
BMI (kg/m2)	**N=300**	29.4 (5.4)	33.1 (7.8)	<0.0001
Smoking Status Never Smoked Ex-Smoker	**N=301**	83 (70.3%) 35 (29.7%)	141 (77.0%) 42 (23.0%)	0.19
Atopic Disease	**N=300**	81 (68.6%)	126 (69.2%)	0.91
Hospital Admissions for Asthma In Last Year	**N=301**	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.087
ED Visits in Last Year	**N=301**	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.23
GP Visits for Asthma in The Last Year	**N=301**	0.0 (0.0,2.0)	1.0 (0.0,4.0)	<0.0001
Rescue Courses of Oral Steroids In The Last Year	**N=301**	1.0 (0.0,3.0)	3.0 (1.0,4.0)	<0.0001
Prior Admission for Asthma to HDU/ICU	**N=301**	19 (16.1%)	45 (24.6%)	0.079
Number Of Prior Admission for Asthma to HDU/ ICU	**N=63**	1.0 (1.0,1.0)	1.0 (1.0,3.0)	0.027
Ever Been Ventilated	**N=63**	6 (31.6%)	25 (56.8%)	0.066
ACQ7 Score	**N=301**	1.7 (1.1)	2.1 (1.1)	0.0043
AQLQ Total Score	**N=291**	5.1 (1.3)	4.8 (1.4)	0.039
FEV_1 (L)	**N=301**	2.4 (0.7)	2.0 (0.7)	0.0002
% Predicted FEV_1	**N=301**	80.1 (18.8)	72.5 (19.0)	0.0008
FVC (L)	**N=301**	3.6 (0.9)	3.1 (0.8)	<0.0001
% Predicted FVC	**N=301**	96.1 (16.9)	87.9 (16.1)	<0.0001
FEV_1/FVC	**N=301**	0.66 (0.11)	0.65 (0.12)	0.83
PEFR (L/min)	**N=298**	403.8 (135.7)	358.4 (119.6)	0.0026
Sputum Eosinophils (%)	**N=123**	2.3 (1.0,8.0)	1.0 (0.3,8.0)	0.043
Sputum Neutrophils (%)	**N=123**	64.8 (35.5,79.3)	58.3 (31.0,78.0)	0.67
FeNO (ppb)	**N=301**	22 (13,30)	19 (13,28)	0.17
Blood Eosinophils (10^9/L)	**N=301**	0.20 (0.12,0.35)	0.21 (0.10,0.33)	0.39
Periostin (ng/mL)	**N=298**	55.2 (16.7)	51.4 (15.8)	0.052
OCS User	**N=301**	35 (29.7%)	76 (41.5%)	0.037
OCS Dose	**N=111**	10 (6,10)	10 (5,10)	0.71
~ICS Dose (BDP*)	**N=301**	2207 (681)	2256 (739)	0.56
T2 Status at study enrolment T2-LOW T2-BIOLOGY	**N=301**	 24 (20.3%) 94 (79.7%)	 47 (25.7%) 136 (74.3%)	0.29

'maintenance oral corticosteroid ~Inhaled corticosteroid *Beclometasone Dipropionate equivalent ^Corticosteroid

OCS = Oral corticosteroid; CS = corticosteroid; ACQ7 = asthma control questionnaire-7; FEV_1 = forced expiratory volume in 1 second; forced vital capacity; peak expiratory flow rate = PEFR; High dependency unit = HDU; Intensive care unit = ICU

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Table 2. Characteristics of features of $T2^{LOW}$ versus $T2^{HIGH}$ exacerbations at first assessed exacerbation (n=71).

		T2-LOW (n=19)	T2-BIOLOGY (n=52)	P-value
Characteristics at study entry				
Age At Study Enrolment	**N=71**	56.3 (12.8)	52.9 (14.0)	0.35
Gender Female Male	**N=71**	 15 (78.9%) 4 (21.1%)	 33 (63.5%) 19 (36.5%)	 0.22
BMI (kg/m^2)	**N=70**	35.8 (10.2)	33.5 (6.7)	0.27
Atopic Disease	**N=71**	15 (78.9%)	36 (69.2%)	0.42
Rescue Courses of Oral Steroids in the Last Year	**N=71**	3.0 (2.0,3.0)	2.5 (2.0,4.0)	0.46
Prior Admission for Asthma To A HDU/ICU	**N=71**	4 (21.1%)	14 (26.9%)	0.61
Number Of Prior Admission for Asthma to HDU/ICU	**N=18**	1.0 (1.0,1.0)	1.0 (1.0,2.0)	0.24
At exacerbation				
FEV_1 (L)	**N=70**	1.7 (0.7)	1.8 (0.8)	0.64
Difference from Baseline in FEV_1 (L)	***N=70***	*-0.2 (0.4)*	*-0.2 (0.3)*	*0.93*
% Predicted FEV_1	**N=70**	64.0 (24.1)	61.4 (17.6)	0.63
Difference from Baseline in % Predicted FEV_1	***N=70***	*-8.5 (12.8)*	*-8.3 (11.4)*	*0.96*
FVC (L)	**N=70**	1.7 (0.7)	1.8 (0.8)	0.64
Difference from Baseline in FVC (L)	***N=70***	*-0.4 (0.7)*	*-0.3 (0.4)*	*0.55*
% Predicted FVC	**N=70**	81.9 (20.1)	78.0 (14.4)	0.37
Difference from Baseline in % Predicted FVC	***N=70***	*-11.6 (22.7)*	*-8.1 (11.4)*	*0.40*
FEV_1/FVC	**N=69**	0.61 (0.15)	0.63 (0.11)	0.60
Difference from Baseline in FEV_1/FVC	***N=69***	*-0.01 (0.07)*	*-0.02 (0.06)*	*0.45*
PEFR (L/min)	**N=64**	301.9 (109.5)	305.7 (109.6)	0.90
Difference From Baseline in PEFR (L/min)	***N=63***	*-47.9 (52.7)*	*-46.6 (56.1)*	*0.93*
Sputum Eosinophils (%)*	**N=26**	0.0 (0.0,1.5)	3.3 (1.3,15.8)	0.018
Difference from baseline sputum eosinophils (%)	***N=21***	*-0.3 (-2.0,0.0)*	*2.9 (-3.8,10.3)*	*0.14*
Sputum Neutrophils (%)*	**N=26**	56.2 (25.7,73.2)	53.3 (30.7,78.8)	0.85
Difference from Baseline in Sputum Neutrophils (%)	***N=21***	*-5.6 (-37.3,4.2)*	*-5.1 (-13.8,11.0)*	*0.65*
FeNO (ppb)	**N=71**	11 (9,14)	32 (22,44)	<0.0001
Difference from Baseline in FeNO (ppb)	**N=71**	-3 (-11,0)	9 (-2,20)	0.0005
Blood Eosinophils (109/L)	**N=71**	0.04 (0.02,0.10)	0.21 (0.12,0.41)	<0.0001
Difference From Baseline in Blood Eosinophils (10^9/L)	***N=71***	*-0.15 (-0.19,-0.01)*	*-0.00 (-0.11,0.16)*	*0.0028*
Periostin (ng/mL)	**N=70**	47.2 (14.1)	53.7 (19.5)	0.19
Difference from Baseline in Periostin (ng/mL)	***N=69***	*-1.0 (6.8)*	*1.2 (18.6)*	*0.62*
ACQ7 Score	**N=69**	3.4 (1.1)	3.7 (0.9)	0.24
Difference From Baseline in ACQ7 Score	***N=69***	*1.4 (0.8)*	*1.3 (0.8)*	*0.72*
Temperature (C)	**N=69**	37.0 (36.6,37.4)	36.7 (36.3,36.9)	0.028
Difference From Baseline in Temperature (C)	***N=68***	*0.3 (-0.1,0.7)*	*0.1 (-0.1,0.4)*	*0.072*
CRP (mg/L)	**N=55**	4.8 (2.0,9.3)	7.7 (5.0,11.0)	0.31
Any Virus (PCR)	**N=24**	8 (88.9%)	6 (40.0%)	0.019
Any Bacteria (Spec qPCR)	**N=23**	4 (50.0%)	6 (40.0%)	0.65
Any Bacteria or Virus (Spec qPCR)	**N=23**	8 (100.0%)	10 (66.7%)	0.065
Oral/IV CS	**N=71**	12 (63.2%)	40 (76.9%)	0.25
ABX	**N=71**	12 (63.2%)	21 (40.4%)	0.089
Oral/IV CS & ABX	**N=71**	10 (52.6%)	19 (36.5%)	0.22

CS = corticosteroid; ACQ7 = asthma control questionnaire-7; FEV_1 = forced expiratory volume in 1 second; forced vital capacity; peak expiratory flow rate = PEFR; High dependency unit = HDU; Intensive care unit = ICU; IV = Intravenous; ABX = antibiotics, PCR= Polymerase chain reaction. qPCR=quantitative polymerase chain reaction. Spec= specific bacteria threshold of $\geq 10^6$ genome copies/ml on quantitative PCR. *Sputum differential cell count at first exacerbation (n=26), 9/26 were $T2^{LOW}$, 17/26 were $T2^{HIGH}$.

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Table 3. $T2^{LOW}$ **cohort at study entry: factors associated with those who proceeded to exacerbation, and those who did not.**

		No Exacerbation (N=24)	≥1 exacerbation during study (N=47)	P-value
Age At Inclusion	**N=71**	56.5 (12.5)	50.7 (12.5)	0.06
Gender Female Male	**N=71**	16 (66.7%) 8 (33.3%)	32 (68.1%) 15 (31.9%)	0.90
BMI (kg/m²)	**N=71**	30.7 (6.4)	32.4 (6.3)	0.29
Atopic Disease	**N=71**	17 (70.8%)	34 (72.3%)	0.89
Hospital Admissions for Asthma in Last Year	**N=71**	0.0 (0.0,0.0)	0.0 (0.0,1.0)	0.06
A&E Visits in Last Year	**N=71**	0.0 (0.0,0.0)	0.0 (0.0,1.0)	0.16
GP Visits for Asthma in the Last Year	**N=71**	0.5 (0.0,4.0)	3.0 (1.0,4.0)	0.050
Rescue Courses of Oral Steroids in the Last Year	**N=71**	2.0 (0.0,3.5)	3.0 (2.0,5.0)	0.012
Prior Admission for Asthma to HDU or ICU	**N=71**	4 (16.7%)	19 (40.4%)	0.043
Number of Prior Admission for Asthma to HDU or ICU	**N=22**	1.0 (1.0,2.0)	1.0 (1.0,4.0)	0.71
Ever Been Ventilated	**N=22**	1 (25.0%)	9 (50.0%)	0.36
ACQ7 Score	**N=71**	1.7 (0.8)	2.4 (1.1)	0.010
AQL Total Score	**N=69**	5.0 (1.1)	4.5 (1.3)	0.14
FEV_1 (L)	**N=71**	2.3 (0.7)	2.2 (0.8)	0.47
% Predicted FEV_1	**N=71**	82.7 (19.6)	74.8 (20.5)	0.12
FVC (L)	**N=71**	3.4 (0.9)	3.2 (0.8)	0.25
% Predicted FVC	**N=71**	94.3 (17.4)	86.7 (15.1)	0.06
FEV1/FVC	**N=71**	0.69 (0.11)	0.69 (0.14)	0.81
PEFR (L/min)	**N=70**	387.8 (136.7)	380.2 (132.3)	0.82
Sputum Eosinophils (%)	**N=24**	1.0 (0.0,2.8)	0.3 (0.0,0.8)	0.35
Sputum Neutrophils (%)	**N=24**	60.8 (43.0,83.0)	72.0 (53.4,87.8)	0.55
FeNO (ppb)	**N=71**	13 (10,17)	12 (9,16)	0.71
Blood Eosinophils (10^9/L)	**N=71**	0.08 (0.05,0.11)	0.08 (0.03,0.12)	0.73
Periostin (ng/mL)	**N=70**	49.1 (14.6)	44.1 (11.7)	0.12
OCS User	**N=71**	8 (33.3%)	26 (55.3%)	0.08
OCS Dose	**N=34**	10 (8,13)	10 (10,12)	0.63
ICS Dose (BDP)	**N=71**	2208 (655)	2221 (726)	0.94
CS Study Change Reduce Maintain Increase	**N=56**	13 (65.0%) 6 (30.0%) 1 (5.0%)	20 (55.6%) 8 (22.2%) 8 (22.2%)	0.24

A&E = Accident and Emergency; OCS = oral corticosteroid; ACQ7 = asthma control questionnaire-7; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; peak expiratory flow rate = PEFR; FeNO = Fractional excretion of nitrous oxide; BMI = Body mass index; High dependency unit = HDU; Intensive care unit = ICU

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Table 4A. Stability of inflammatory phenotype from baseline study entry to first assessed exacerbation.

	First Exacerbation		
Baseline	**$T2^{LOW}$**	**$T2^{HIGH}$**	**Total**
$T2^{LOW}$	6	11	17
$T2^{HIGH}$	13	45	58
Total	19	56	75
McNemars (P-value) = 0.84, Kappa = 0.12			

Table 4B. Stability of inflammatory phenotype from first to second assessed exacerbation.

	Second Exacerbation		
First Exacerbation	**$T2^{LOW}$**	**$T2^{HIGH}$**	**Total**
$T2^{LOW}$	2	3	5
$T2^{HIGH}$	4	16	20
Total	6	19	25
McNemars (P-value) = 1.00, Kappa = 0.19			

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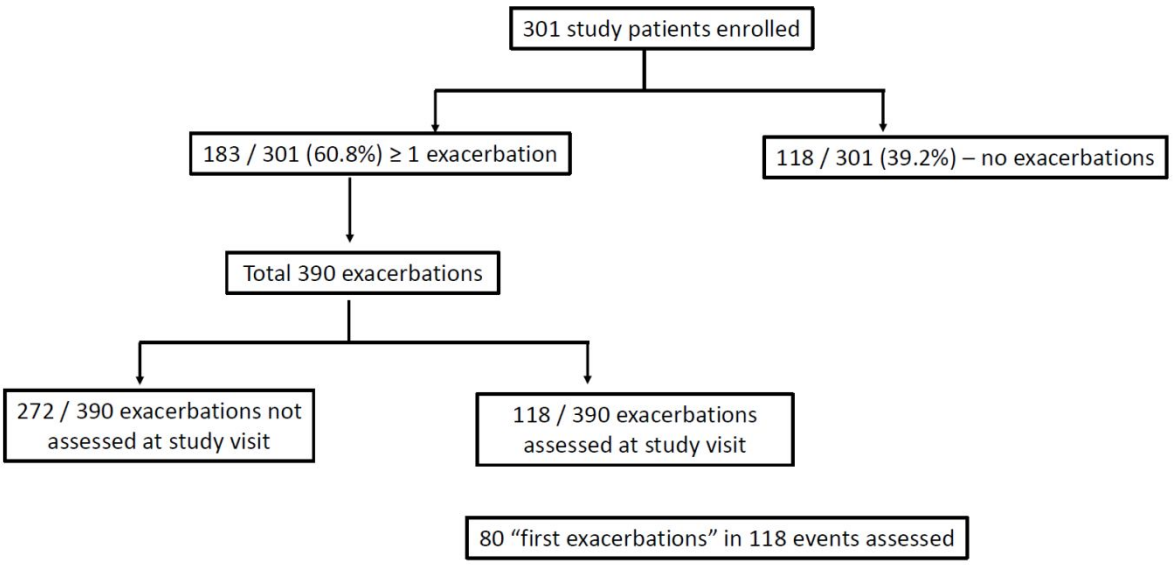
Figure 1: Cohort flow diagram of all exacerbations during the study. A 'first exacerbation' was the initial exacerbation assessed as a clinical study visit for any individual patient.



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Exacerbation Profile and Risk Factors in a T2-Low Severe Asthma Population

LIST OF PARTICIPATING CLINICAL CENTRES

NHS Clinical Centres with a dedicated tertiary care in difficult asthma service that recruited to the study

- Belfast Health & Social Care Trust
- Oxford University Hospitals NHS Trust
- Glenfield Hospital, University Hospitals of Leicester NHS Trust
- Wythenshawe Hospital, University Hospitals of South Manchester NHS Trust
- University Hospital Southampton NHS Foundation Trust
- Royal Brompton & Harefield NHS Foundation Hospital
- King's College Hospital NHS Foundation Trust
- Nottingham University Hospitals NHS Foundation Trust
- Sheffield Teaching Hospitals NHS Foundation Trust
- Gartnavel and Stobhill/Glasgow Royal Infirmary Hospitals, Greater Glasgow Health Board
- Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust
- Freemans Hospital, Newcastle upon Tyne NHS Foundation Trust

List of industrial partners in RASP-UK consortium"

- GlaxoSmithKline
- Hoffman la Roche / Genentech Inc
- Amgen

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- Astra Zeneca / Medimmune
- Boehringer Ingelheim
- Jannsen
- Circassia
- Vitalograph

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Study inclusion and exclusion criteria

Inclusion criteria

Patients must meet the following criteria at screening for study entry (patients can be rescreened for study entry up to 3 times):

1. Age ≥ 18 and ≤ 80 years at screening visit

2. Able and willing to provide written informed consent and to comply with the study protocol

3. Baseline FeNO< 45 ppb at screening

4. Severe asthma confirmed after assessment by an asthma specialist. Diagnosed with asthma at least 12 months prior to screening

5. Current asthma treatment with LABA plus high doses of inhaled corticosteroids (≥1000 µg FP daily or equivalent)

6. Patients on an ICS/LABA single inhaler strategy must be switched to fixed dosing ICS/LABA for 4 weeks prior to screening

7. Documented history of reversibility of ≥12% change in FEV1 within the past 24 months or during screening period, as demonstrated by:

- Documented airway obstruction (forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <0.7), where FEV1 has varied by ≥12% either spontaneously or in response to oral corticosteroid (OCS) therapy or bronchodilators either between or during clinic visits

Or

- A 20% drop in FEV1 (PC20) to methacholine <8 mg/mL or a 15% fall in FEV1 (PD15) after inhaling a cumulative dose of mannitol of ≤635 mg indicating the presence of airway hyperresponsiveness. If sites customarily use histamine to perform tests of airway responsiveness, this may be used in place of methacholine.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry

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1. Acute exacerbation requiring oral corticosteroids in previous 4 weeks before screening.

2. Known severe or clinically significant immunodeficiency, including, but not limited to, human immunodeficiency virus (HIV) infection.

3. Currently receiving or have historically received intravenous immunoglobulin for treatment for immunodeficiency.

4. If recently commenced on a leukotriene receptor antagonist or theophylline, stable on treatment for 4 weeks prior to screening

5. Known current malignancy or current evaluation for a potential malignancy or history of malignancy within 5 years prior to baseline. With the exception of basal-cell and squamous-cell carcinomas of the skin and carcinoma in situ of the cervix uteri that have been excised and cured.

6. Other clinically significant medical disease or uncontrolled concomitant disease despite treatment that is likely, in the opinion of the investigator, to require a change in therapy or impact the ability to participate in the study

7. History of current alcohol, drug, or chemical abuse or past abuse that would impair or risk the subject's full participation in the study, in the opinion of the investigator

8. Current self-reported history of smoking (including electronic inhaled nicotine products) or former smoker with a smoking history of >15 pack-years

a. A current smoker is defined as someone who has smoked one or more cigarettes per day (or marijuana or pipe or cigar) for ≥ 30 days within the 24 months prior to the screening visit (Day –14) and / or cotinine positive at screening

b. Any individual who smokes (cigarettes, marijuana, pipe, or cigar) occasionally, even if for < 30 days within the 24 months prior to the screening visit (Day –14), must agree to abstain from all smoking from the time of consent through completion of study

c. A former smoker is defined as someone who has smoked one or more cigarettes per day (or marijuana or pipe or cigar) for ≥ 30 days in his or her lifetime (as long as the 30-

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day total did not include the 24 months prior to the screening visit [Day –14]).

d. A pack-year is defined as the average number of packs per day times the number of years of smoking.

9. Current use of an immunomodulatory/immunosuppressive therapy or past use within 3 months or five drug half-lives (whichever is longer) prior to the screening visit

10. Use of a biologic therapy including Omalizumab at any time during the 6 months prior to the screening visit.

11. Bronchial thermoplasty within prior 6 months of the screening visit

12. Initiation of or change in allergen immunotherapy within 3 months prior to the screening visit.

13. Treatment with an investigational agent within 30 days of the screening visit (or five half-lives of the investigational agent, whichever is longer).

14. Female patients who are pregnant or lactating.

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Table E1 - Patient demographics, biomarkers, treatment and lung function of all subjects randomised in the study

Demographics	n=301
Study follow up time (Weeks)	48.0 (47.7,48.6)
Age At Study Enrolment (Y)	55.7 (13.1)
Female Gender	194 (64.5%)
Ethnicity: Caucasian	279 (92.7%)
BMI (kg/m_2)	31.6 (7.2)
Never smoked	224 (74.4%)
Ex-smoker	77 (25.6%)
Hospital admissions for asthma in last year	0.0 (0.0,0.0)
ED visits in last year	0.0 (0.0,0.0)
GP visits for asthma in last year	1.0 (0.0,3.0)
Rescue courses of oral steroids in last year	2.0 (1.0,4.0)
Prior admission for asthma to ICU	64 (21.3%)
Number of prior admissions for asthma to ICU (n=64)	1.0 (1.0,2.0)
Ever been ventilated	31 (10.3%)
Atopic disease	207 (68.8%)
Rhinitis	208 (69.1%)
Eczema	100 (33.2%)
Nasal polyps	73 (24.3%)
Oesophageal reflux	179 (59.5%)
Aspirin sensitivity	47 (15.6%)
Depression / anxiety	92 (30.6%)
Hypertension	94 (31.2%)
Osteoporosis / osteopenia	66 (21.9%)
Hypercholesterolaemia	53 (17.6%)
Diabetes	34 (11.3%)
Cataracts	33 (11.0%)
Obstructive sleep apnoea	17 (5.6%)
Ischaemic heart disease	12 (4.0%)
Peptic ulcer	8 (2.7%)
Stroke	6 (2.0%)
Glaucoma	4 (1.3%)
FEV1	2.2 (0.7)
% predicted FEV1	75.5 (19.3)
FVC	3.3 (0.9)
% predicted FVC	91.1 (16.9)
FEV1/FVC	0.66 (0.12)
PEF	376.2 (127.9)
Sputum eosinophils (%)*	1.5 (0.4,8.0)
Sputum neutrophils (%)	60.6 (31.0,79.3)
Sputum lymphocytes (%)	0.4 (0.0,1.5)
Sputum macrophage (%)	23.5 (10.6,41.0)
FeNO (ppb)	20 (13,29)
Blood eosinophil count (10_9 cells/L)	0.21 (0.11,0.33)
Maintenance OCS user	24 (39.3%)
OCS dose (mg)	9 (5,10)
ICS dose (BDP µg equivalent)	2000 (2000,2000)
LAMA user	35 (57.4%)
LABA user	301 (100%)
ACQ-7 Score	2.0 (1.3)
AQLQ Total Score	4.7 (1.6)

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Table E2. Characteristics of participants with no evidence of T2 biology ($T2^{LOW}$) versus those with evidence of T2 biology ($T2^{HIGH}$) when in a clinically stable state at study enrolment.

		$T2^{LOW}$ (n=71)	$T2^{HIGH}$ (n=230)	P-value
Age At Inclusion	**N=301**	52.6 (12.7)	56.6 (13.1)	0.025
Gender				0.53
Female		48 (67.6%)	146 (63.5%)	
Male	**N=301**	23 (32.4%)	84 (36.5%)	
BMI (kg/m2)	**N=300**	31.8 (6.4)	31.6 (7.4)	0.79
Atopic Disease	**N=300**	51 (71.8%)	156 (68.1%)	0.56
Hospital Admissions For Asthma In Last Year	**N=301**	0.0 (0.0,1.0)	0.0 (0.0,0.0)	0.11
ED Visits In Last Year	**N=301**	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.85
GP Visits For Asthma In The Last Year	**N=301**	2.0 (0.0,4.0)	0.0 (0.0,3.0)	0.0003
Rescue Courses Of Oral Steroids In The Last Year	**N=301**	3.0 (1.0,4.0)	2.0 (1.0,4.0)	0.053
Prior Admission For Asthma To HDU/ICU	**N=301**	23 (32.4%)	41 (17.8%)	0.0087
Number Of Prior Admission For Asthma To HDU/ICU	**N=63**	1.0 (1.0,3.0)	1.0 (1.0,2.0)	0.18
Ever Been Ventilated	**N=63**	10 (45.5%)	21 (51.2%)	0.66
ACQ7 Score	**N=301**	2.1 (1.1)	1.9 (1.2)	'0.2387
AQLQ Total Score	**N=291**	4.7 (1.2)	5.0 (1.4)	'0.1730
History Of Nasal Polyps	**N=301**	6 (8.5%)	67 (29.1%)	0.0004
Prior Nasal Surgery	**N=301**	4 (5.6%)	66 (28.7%)	<0.0001
FEV1 (L)	**N=301**	2.2 (0.7)	2.1 (0.7)	0.27
% Predicted FEV1	**N=301**	77.5 (20.4)	74.9 (18.9)	0.33
FVC (L)	**N=301**	3.3 (0.9)	3.3 (0.9)	0.84
% Predicted FVC	**N=301**	89.3 (16.2)	91.7 (17.1)	0.30
FEV1/FVC	**N=301**	0.69 (0.13)	0.64 (0.11)	0.0051
PEFR (L/min)	**N=298**	382.7 (132.8)	374.2 (126.5)	0.63
Sputum Eosinophils (%)	**N=123**	0.4 (0.0,1.6)	2.0 (0.5,12.5)	0.0003
Sputum Neutrophils (%)	**N=123**	70.0 (47.2,87.8)	58.8 (27.3,77.8)	0.12
FeNO (ppb)	**N=301**	13 (9,16)	24 (16,31)	<0.0001
Blood Eosinophils (109/L)	**N=301**	0.08 (0.04,0.12)	0.26 (0.18,0.40)	<0.0001
Periostin (ng/ml)	**N=298**	45.8 (12.9)	55.1 (16.5)	<0.0001
OCS User	**N=301**	34 (47.9%)	77 (33.5%)	0.028
OCS Dose	**N=111**	10 (10,12)	8 (5,10)	0.043
ICS Dose (BDP)	**N=301**	2217 (698)	2243 (723)	0.79
CS Study Change				<0.0001
Reduce		33 (58.9%)	36 (17.4%)	
Maintain		14 (25.0%)	89 (43.0%)	
Increase	**N=263**	9 (16.1%)	82 (39.6%)	
$T2^{LOW}$ (FeNO ≤20ppb and PBE ≤0.15x10^9/L). $T2^{HIGH}$ (FeNO >20ppb or PBE >0.15x10^9/L).				

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Table E3. Baseline and exacerbation phenotypes with change in CS exposure from baseline to exacerbation.

Baseline Phenotype	Exacerbation Phenotype	CS Change from Baseline	Count
T2LOW	T2LOW	Reduce	2
T2LOW	T2LOW	Maintain	4
T2LOW	T2HIGH	Reduce	5
T2LOW	T2HIGH	Maintain	4
T2LOW	T2HIGH	Increase	2
T2HIGH	T2LOW	Reduce	1
T2HIGH	T2LOW	Maintain	12
T2HIGH	T2HIGH	Reduce	9
T2HIGH	T2HIGH	Maintain	25
T2HIGH	T2HIGH	Increase	11

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