Randomised controlled trial for the titration of oral corticosteroids using markers of inflammation in severe asthma

J Michael Ramsahai ·1,2 Jodie L Simpson ·1, Alistair Cook,1 Peter G Gibson,1 Vanessa McDonald,1 Christopher Grainge,1 Liam G Heaney,3 Peter AB Wark1

ABSTRACT
Introduction Biomarkers are used to select biologic therapies for patients with severe asthma, but not to regularly adjust therapy, especially oral corticosteroids (OCS).

Objective Our goal was to test the efficacy of an algorithm to guide the titration of OCS using blood eosinophil count and fraction of exhaled nitric oxide (FeNO) levels.

Design, participants, interventions and setting This proof-of-concept prospective randomised controlled trial assigned adult participants with severe uncontrolled asthma (n=32) to biomarker-based management (BBM) where OCS dose was adjusted based on a composite biomarker score comprised of blood eosinophil count and FeNO, or a standard best practice (SBP) arm. The study was conducted at the Hunter Medical Research Institute, Newcastle, Australia. Participants were recruited from the local Severe Asthma Clinic and were blinded to their study allocation.

Main outcome The coprimary outcomes were number of severe exacerbations and time to first severe exacerbation assessed over 12 months.

Results There was a longer median time to first severe exacerbation with BBM, although not significant (295 vs 123 days, Adj. HR: 0.714; 95% CI: 0.25 to 2.06; p=0.533). The relative risk of a severe exacerbation in the cumulative OCS dose used between the two groups.

Conclusion A treatment algorithm to adjust OCS using blood eosinophil count and FeNO is feasible in a clinical setting and resulted in a reduced odds of an ED visit. This warrants further study to optimise the use of OCS in the future.

WHAT IS ALREADY KNOWN ON THIS TOPIC ⇒ There have been multiple studies employing novel therapies and biomarker-based management (BBM) to improve outcomes in patients with severe asthma, with studies employing biologic medications demonstrating a significant reduction in the use of chronic systemic corticosteroid. Despite this, there remains a significant proportion of the population who continue to require treatment with oral corticosteroids (OCS) for various reasons and very little randomised controlled data to help guide management for these patients in an objective fashion using readily available biomarkers.

WHAT THIS STUDY ADDS ⇒ We sought to determine whether controlling airway inflammation by titrating OCS using a biomarker composite score made up of PBE and fraction of exhaled nitric oxide as a surrogate for sputum induction determined airway eosinophilia will reduce exacerbations in patients with severe asthma, compared with usual care alone, in a severe asthma clinic. This BBM approach proved feasible, although the primary endpoint of a reduction in severe exacerbation rate was not met, but a reduction in the proportion of patients who required an emergency department visit was observed, without a significant difference in the cumulative amount of OCS used.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY ⇒ This furthers the concepts of precision medicine for the chronic management of severe asthma using objective biomarkers to improve outcomes for patients, reduce healthcare resource utilisation, and serve as a catalyst for future work in this field.

INTRODUCTION
Asthma affects approximately 340 million people worldwide, with an ever increasing prevalence, particularly in developed nations. Recent estimates suggest approximately 4% of this population have severe refractory disease. This population, although small, disproportionately accounts for up to half the healthcare resource use and direct and indirect costs to society due to asthma. Thus, optimisation of the management of asthma in this population represents an important opportunity for the improvement of asthma care. While there has been
significant progress in the last 75 years in the availability of treat-
ments for the asthma population, in general, it would appear
that improvements in morbidity and mortality have plateaued
over the last decade, with only small incremental gains. Biologic
agents have been a significant advancement for the manage-
ment of severe asthma for those patients with refractory type 2 airway
inflammation demonstrating benefit in reducing the use of oral
corticosteroids (OCS) for episodic exacerbations and, in the
case of mepolizumab, benralizumab, and dupiluminab, reducing
their use for regular maintenance treatment as well. Optimisa-
tion of the use of OCS in this population is important to
ensure that risk is reduced and benefit maximised. Previous
work has demonstrated the utility of titrating therapy based on
sputum eosinophil counts and fraction of exhaled nitric oxide
(FeNO). Unfortunately, sputum cell count measures remain
difficult to obtain at many centres. Peripheral blood eosino-
phil (PBE) counts, however, are widely available and have been
used as a surrogate for sputum cell counts. As a result, we
sought to determine whether controlling airway inflammation
by titrating OCS using biomarker-based management (BBM) via
a composite score made up of PBE and FeNO, as a surrogate for
sputum induction determined airway eosinophilia, will reduce
exacerbations in patients with severe asthma, compared with
standard best practice (SBP) alone, in a severe asthma clinic. Our
hypothesis was that this would be feasible and effective for these
outcomes, while resulting in a lower cumulative dose of OCS
used.

METHODS
To explore this, we conducted a prospective randomised, single-
blind, controlled proof-of-concept study comparing BBM with
standard best practice clinical management (SBP) in participants
with severe asthma. Potential participants were recruited from
the Severe Asthma Clinic at the John Hunter Hospital, New
Lambton, New South Wales, Australia. This is a tertiary referral
specialist/multidisciplinary severe asthma clinic. All patients
of the clinic had been assessed by the clinical team within a struc-
tured programme that confirms the diagnosis of asthma, assesses
and controls factors that precipitate and trigger asthma, and
assesses and treats the presence of comorbid conditions such as
upper airway dysfunction, gastroesophageal reflux, rhinitis and
obstructive sleep apnoea.

Participants were recruited into the study if they were over
18 years of age, never or ex-smokers, and diagnosed with severe
asthma. To be classified as severe, participants had to have been
on Global Initiative for Asthma (GINA) Step 4/5 therapy and
have had uncontrolled asthma despite this treatment, with either:
a 6-point Asthma Control Questionnaire (ACQ) ≥ 1.5, or
a hospital admission for asthma in the last 12 months or at least
two severe asthma exacerbations in the past 12 months requiring
a burst of OCS (of at least 3 days). Mepolizumab was introduced
into the severe asthma clinic after the initiation of the study
protocol and participants taking any biological therapy available
were included in the study, but randomisation was not adjusted
for type of biological therapy. Participants did not have to be on
OCS at baseline to be enrolled. Participants were excluded based
on criteria in the online supplemental appendix.

Following a 4-week run-in period where participants remained
on their usual asthma treatment, those who remained stable
were randomised to either BBM or SBP in a 1:1 ratio. Block
randomisation was performed by an independent research asso-
ciate using computer-generated randomisation tables with strat-
fication based on the presence or absence of OCS maintenance
dosing and blood eosinophil count at screening above or below
0.4×10⁹ cells/L.

At baseline, inflammation was assessed with the following
markers: exhaled nitric oxide, induced sputum analysis and
peripheral full blood count. Participants were followed for a
total 12-month period and assessed for outcomes on a monthly
basis as per the study visit schedule (online supplemental table 1),
with every second visit in the latter half of the study period
being conducted by phone. At the end of each in-person visit,
medication changes were made according to study arm allo-
cation. Participants and clinicians were blinded to each partic-
iant’s treatment group allocation as well as inflammatory
marker results.

Study groups
In BBM, participants were assessed by a clinician at each visit and
adjustment of OCS dose was performed using the algorithm in
figure 1 as per the OCS adjustment table in online supplemental
table 2 based on the results of their PBE count and FeNO. PBE
count and FeNO were used to assign a participant an average
biomarker score, which dictated the titration of their OCS dose.

<table>
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<tr>
<th>Biomarker Score (BS)</th>
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<td>15 - &lt;30</td>
<td>≥30</td>
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<td>0.2 - 0.4</td>
<td>&gt;0.4</td>
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</table>

In BBM, titration of oral corticosteroids was performed using a composite biomarker
score (BS) comprised of FeNO and PBE. BS was assigned based on the measured biomarker
values at each visit. Composite BS was calculated by taking the average of the FeNO and PBE
scores and rounding up to the nearest whole number. Titration was then performed as
follows:
- BS =2: ↑ or (if treatment naïve) commence OCS at 7.5mg/day (or equivalent)
- BS =1: no change to OCS
- BS =0: reduce OCS. If off OCS, decrease ICS treatment.

The goal of this algorithm is to maintain a BS of 1 or lower using the lowest effective OCS
dose.

**Figure 1** Algorithm for biomarker-based management of oral corticosteroid dose. BBM, biomarker-based management; FeNO, fraction of exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroids.
Cut points for FeNO had been decided based on prior identification of the upper limit of FeNO at which people with asthma can undergo corticosteroid withdrawal, as well as that which is associated with control of eosinophilic inflammation. 17 Cut points for PBE have been determined as those previously associated with increased airway eosinophilia in asthma and chronic obstructive pulmonary disease (COPD). 11,18

The participants in SBP had their asthma control assessed according to standard clinical parameters based on GINA treatment guidelines and treatment step or dose escalation or de-escalation. 19 This was assessed every 4 months through the study, based on the recommendations of a consultation with a clinician (see online supplemental table 1). Standard care treatment decisions were made at these particular visits based on the result of clinician consultation without knowledge of biomarker results for that visit. This was based on the standard clinical care practice in the Severe Asthma Clinic at the John Hunter Hospital.

An additional analysis was performed on the subgroup of patients receiving mepolizumab, as it was expected their biomarkers may be affected by this treatment. PBE and FENO over the course of the study were measured in this cohort.

Outcomes
The coprimary outcomes were time to first and the number of severe exacerbations over 12 months. An asthma exacerbation was defined as a worsening of asthma control characterised by a progressive increase in symptoms requiring a change in treatment. Severe exacerbations were defined as those requiring systemic glucocorticoids or an increase in the dose of regular systemic glucocorticoids for at least 3 days. 20 Secondary outcomes that were assessed were change in asthma symptom scores using the Asthma Control Questionnaire (ACQ), 16 and Asthma Quality of Life Questionnaire (AQLQ). 20 total and maintenance dose of OCS, analysis of markers of inflammation at the final visit compared with entry (PBE, sputum eosinophil counts and FeNO), total dose of OCS used during the period of the study, and hospital admission or emergency room visit due to asthma.

Spirometry, FeNO and sputum and blood eosinophil measurements
FeNO measurements were performed using a NIOX VERO (Aerocrine, Sweden) device, as per the manufacturer’s suggestions and prior to spirometry. Spirometry was performed as per American Thoracic Society (ATS) criteria 21 using a MedGraphics CPFS/D USB-Ascensia spirometer and BreezeSuite software (Minneapolis, USA). Blood eosinophil counts were measured from samples obtained at each in-person visit through the study and processed at either Pathology North (New South Wales, Australia) laboratories or the Hunter Medical Research Institute. Sputum induction and processing were performed as previously described by Gibson et al. 22

Statistical considerations
All analyses were conducted using SAS V9.4. An intention-to-treat analysis was performed for all randomised participants. Frequencies and percentages are provided for the categorical variables, while means, SD, median, first and third quartiles are provided for the continuous variables.

Time to first severe exacerbations was compared between treatment arms using a Kaplan-Meier plot, along with a log-rank test for the crude models and Cox regressions for both the crude and adjusted models. Negative binomial models were used to analyse the total number of severe exacerbations between treatment arms.

For the secondary outcomes that were recorded more than once, treatment arms were compared using linear mixed modeling with random intercepts for within-subject correlation over time. Where the outcome was measured only once, treatments were compared using linear regression. Due to the low counts of hospital/emergency department (ED) visits and a small subgroup sample size for the participants on mepolizumab, the variables for the former were dichotomised to having had a hospital/ED visit versus not, logistic regression was used to compare the two treatment arms, and only crude models were used. Adjusted models are presented for each other outcome, which have been adjusted for age, sex, body mass index, education, smoking history, age at asthma diagnosis, baseline blood eosinophil count and baseline prednisolone dose.

Sample size was calculated based on uncontrolled prior data 23 demonstrating a reduction in exacerbations from a median of 5 (IQR 5–8) to 0 (IQR 0–1) with the use of a similar algorithm based on PBE for asthma management. Assuming α=0.05, and allowing power to range from 0.8 to 0.95, yields a desired range of sample sizes for each of the two groups of 9–16. Thus, a conservative estimate of the necessary total sample size was 30.

RESULTS
Of the 41 patients screened, 32 were eligible for randomisation; 17 were randomised to BBM and 15 to SBP from 9 January 2017 to 23 May 2018, with 29 completing the study (online supplemental figure 1). The study was ended once the required sample size was reached and the last participant completed all required visits. A total of 32 patients were analysed in the intention-to-treat analysis. In BBM, one participant was lost to follow-up due to poor health and inability to attend study visits, and one was removed due to an adverse reaction to OCS. In SBP, one participant discontinued the study to undergo investigation for a newly discovered potential malignancy. Baseline measurements for participants are presented in table 1.

There were less ex-smokers in BBM versus SBP (29% vs 47%); however, the mean pack-year history was higher in BBM (17.9 vs 7.2 pack-years), both variations likely due to a small sample size. Mean baseline lung function was similar between the groups, as was mean sputum eosinophil count percentage (5.2% in BBM vs 6.0% in SBP) and exacerbation frequency in the last year (3.9 exacerbations/year vs 4.8) (table 1). With respect to the markers of inflammation that would form the basis for the composite biomarker score and adjustment of corticosteroid dose during the study, blood eosinophils were similar while FeNO was lower in BBM (24) vs SBP (43). The median baseline dose of oral prednisolone was the same between the groups at 5 mg/day.

Outcomes
Median time to first severe exacerbation was more than two times as long at 295 days with BBM vs 123 days with SBP, though this was not statistically different (Adj. HR: 0.714; 95% CI: 0.25 to 2.06; p=0.533) (table 2, figure 2). There was no significant difference in the number of severe exacerbations with BBM versus SBP (table 2, figure 2).

There was a significant difference in the proportion of participants who had at least one ED visit with a reduced OR with BBM versus SBP (OR: 0.09 95% CI: 0.01 to 0.91, p=0.041) (table 2). Similarly, the proportion of patients with at least one hospitalisation for asthma appeared to be reduced with BBM but this was not statistically significant (OR 0.37 95% CI 0.06
to 2.37, *p=0.292*). As there were only two participants in the BBM group and six in SBP who required either a hospitalisation or ED visit for the exacerbation, numbers were considered too small to perform adjusted analyses. No reductions to inhaled corticosteroid (ICS) were undertaken during the study.

There was no difference between the two arms with respect to ACQ or AQLQ scores (figure 3). There was also no difference observed in blood or sputum eosinophil count, or FeNO levels when adjusted for outliers (online supplemental figure 2).

The mean cumulative OCS dose between groups over the duration of the study was not significantly different (1655 mg (95% CI: 935 to 2374) of prednisolone with BBM vs 1544 mg (95% CI: 318 to 2770) with SBP, *p=0.866*).

Adherence to oral prednisolone was measured over the duration of the study via pill counts for those participants on OCS. There was no difference between the two groups in terms of mean adherence detected during the study for those on OCS (96.52% (95% CI: 94.5% to 98.5%) in BBM vs 96.4% (95% CI: 93.5% to 99.2%) in SBP, *p=0.920*). Dose adjustments were followed as per protocol at a similar frequency in either group.

This was done correctly (47/51 times in BBM (92.2%, 95% CI: 84.8% to 99.5%) vs 11/12 times in SBP (91.7%, 95% CI: 76.0% to 107.3%), *p=0.955*).

A subgroup analysis of PBE and FeNO levels for those participants on mepolizumab also did not demonstrate any significant difference over time, regardless of treatment arm (online supplemental figure 3). This may be related to the suppressive effect of this medication on eosinophils. In spite of this, in 18.2% (95% CI: 8.9% to 27.5%) of all visits among participants on a biologic in BBM vs 40.0% (95% CI: 29.9% to 50.1%, *p=0.004*) in SBP biomarker measures were detectable and still elevated (FeNO>30 ppb or PBE>0.3×10⁹ cells/L).

Unfortunately, this study was underpowered to detect its primary outcomes due to an insufficient sample size. Post-hoc analysis revealed that 286 subjects would have been needed to provide a power of 80% to detect a difference at *α=0.05* for the HR and time to events observed in the study.

**DISCUSSION**

Our results demonstrate that a biomarker-based approach to the management of OCS in patients with severe asthma is feasible within a tertiary care severe asthma clinic. However, we were unable to demonstrate a significant difference in the coprimary outcomes of number of severe exacerbations and time to first exacerbation. While not significant, median time to first severe exacerbation in BBM was 295 days compared with only 123 days in SBP. The biomarker strategy may have had a greater impact on reducing more severe exacerbations as fewer participants in this arm experienced an exacerbation requiring an ED visit compared with the standard care arm and there was a trend towards a reduced proportion of participants requiring hospitalisation. Cumulatively, there was no statistical difference in the total dose of OCS used in the two treatment arms to achieve these outcomes. Unadjusted OCS trends over time were similar in both groups (online supplemental figure 4).

A reduction in ED visits is important since a large proportion of the costs attributable to the care of patients with severe asthma is associated with healthcare utilisation. In addition, recurrent emergency visits and hospitalisations are key components of severe asthma that affect quality of life for these patients. The ability to influence the need for healthcare utilisation without increasing the cumulative dose of OCS administered would be beneficial to this patient group. However, this reduction in ED costs would need to be offset against the increased number of visits required to achieve the adjustment of inflammation. The cumulative dose of OCS used in the two treatment arms to achieve reduction of corticosteroid, and conversely may have been too stringent with respect to reducing dose changes. In addition,
while a lack of participants choosing to follow the treatment directives given at visits in the Heaney et al work was thought to affect the ability to demonstrate an effect, this is not thought to be the case in this study cohort, as adherence was high, as monitored through the study based on pill counts, and treatment decisions were followed the vast majority of the time in both groups.

The authors postulate that, while titration of asthma therapy according to sputum eosinophilia has been successful in prior studies, peripheral blood eosinophilia and FeNO may not be direct enough measures of type 2 high inflammation or not sufficiently correlated with exacerbation risk, to be as useful for the adjustment of therapy longitudinally. Novel biomarkers may need to be considered in the future. Similarly, this strategy may not apply to patients without eosinophilic airway inflammation, and these participants comprised 53% of our population. Interestingly, in the studied population, among those participants on a biologic treatment, either FeNO or PBE remained detectable in upwards of 40% of participant visits, suggesting the composite biomarker score could still be considered a useful measure on which to base adjustments of medications in the biologic era (online supplemental figure 3). Direct conclusions on whether this weakened the effect of our intervention cannot be determined, however, due to the small numbers analysed. This likely affected the results with respect to time to first severe exacerbation (figure 2).

Further advances in artificial intelligence and machine learning may better allow for widespread utilisation of biomarkers as a guide, in this setting. Machine learning could allow for the exploration of which biomarkers, and at which levels, ideally predict good asthma control and improved outcomes, similar to what is being considered in other fields such as cardiology and oncology for their outcomes.

Benefits of the study and limitations
This study benefitted from its randomised and blinded design. Although participants were assessed equally as many times in both arms of the study, decisions were only made in SBP every 4 months, thus there were fewer opportunities to change the course of asthma control. Conversely, the small sample size may have limited the ability to identify a true effect. Unfortunately, although this was a pilot study with a sample size based on prior observed effects, it appears to have been underpowered to detect the primary outcome based on post-hoc calculations. A larger multicentre trial would allow for larger numbers as well as greater generalisability of the results. In addition, being a single-centre study based at a clinic specialised in the treatment of patients with severe asthma, the participants treated as per the clinical judgement of the study physicians would likely already reflect optimisation of the role of steroids in ongoing treatment.
Figure 3  Asthma Control Questionnaire-6 Score (ACQ6) (A) and Asthma Quality of Life Questionnaire (AQLQ) (B) mean scores over time in the biomarker-based management (BBM) and standard best practice (SBP) groups.
CONCLUSION
A treatment algorithm to adjust OCS using blood eosinophil count and FeNO is feasible in a clinical setting. There was a trend towards a longer time to severe exacerbation and reduced odds of a hospital admission, although these results were not significant. The treatment algorithm did result in a reduced proportion of patients requiring an emergency visit for their asthma, without a significant difference in the cumulative amount of OCS used. This warrants further study in a larger sample to optimise the use of OCS with biomarkers in the future.

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Contributors
JMR contributed to the conception and design of the work, data acquisition, analysis, interpretation, and revision, and approval of the manuscript. JMR is the guarantor of the work. JLS contributed to the conception and design of the work, data analysis and interpretation, and revision, and approval of the manuscript. AC contributed to the design of the work, data acquisition, analysis, and interpretation, and revision and approval of the manuscript. PGG contributed to the conception and design of the work, data interpretation, and revision and approval of the manuscript. PABW contributed to the conception and design of the work, data analysis, interpretation, and revision and approval of the manuscript. CG contributed to the conception and design of the work, data acquisition, analysis, and interpretation, and revision and approval of the manuscript. LGH contributed to the conception and design of the work, data acquisition, analysis, interpretation, and revision, drafting, revision, and approval of the manuscript. All authors agree to be accountable for the work.

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Competing interests
None declared.

Patient consent for publication
Not applicable.

Ethics approval
This study involves human participants and was approved by Hunter New England Human Research Ethics (16/05/183.03) and University of Newcastle Human Research Ethics Committee (H-2016-0261; Safety approval number: 62/2016). Participants gave informed consent to participate in the study, before taking part.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available upon reasonable request. Please contact the corresponding author for details.

Supplemental material
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REFERENCES
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SUPPLEMENTAL APPENDIX

Exclusion criteria

• Current smoker or smoking cessation within the last 6 months
• Severe exacerbation or alteration to asthma therapy within 4 weeks prior to Visit 1
• Eligible for commencing Omalizumab (according to current PBS criteria), or currently within the first 6 months of commencing Omalizumab.
• Eligible for commencing Mepolizumab or currently within the first 6 weeks of commencing Mepolizumab
• Other medical comorbidity or research study requiring chronic systemic corticosteroid (for example rheumatologic conditions, adrenal insufficiency, etc.)
• Inability to take oral corticosteroid

Co-morbid conditions such as upper airway dysfunction, reflux, rhinitis and OSA are not exclusion criteria, provided they have been assessed and their management optimised according to current clinical guidelines prior to randomisation.

Exacerbation Definition

Protocol definition of asthma exacerbation:

An asthma exacerbation will be defined as a worsening of asthma control (characterized by a progressive increase in symptoms and progressive decrease in lung function requiring a change in treatment). Severe exacerbations will require systemic glucocorticoids or an increase in the dose of regular systemic glucocorticoids for at least 3 days. ¹⁸

For episodes where two periods of exacerbation (i.e. worsening symptoms, hospitalization or use of corticosteroids for the purposes of treating an asthma exacerbation) occur consecutively, they will be counted as two separate events if separated by at least a week.
Supplemental Table 1: Study Visit Schedule
Participants were assessed at a total of 14 study clinic visits over a 52 week period for the following:

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<td>Serum and Peripheral blood eosinophils (FBC)</td>
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*Denotes telephone visit.
Supplemental Table 2: Instructions for OCS titration based on biomarker score and current OCS dose for participants in BBM.

<table>
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<tr>
<th>BS Score</th>
<th>OCS Titration by current OCS dose</th>
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<tr>
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</tr>
<tr>
<td>5</td>
<td>7.5</td>
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<td>30</td>
<td>37.5</td>
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<tr>
<td>37.5</td>
<td>50</td>
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For BS Score 2:
- +7.5mg/day OCS (or equivalent) if Prednisone is 0 and Dexamethasone is 0.
- Increase to 7.5mg/day OCS (or equivalent) if Prednisone is 5 and Dexamethasone is 0.75.
- Increase to 10mg/day OCS (or equivalent) if Prednisone is 7.5 and Dexamethasone is 1.25.
- Increase to 15mg/day OCS (or equivalent) if Prednisone is 10 and Dexamethasone is 1.5.
- Increase to 20mg/day OCS (or equivalent) if Prednisone is 15 and Dexamethasone is 2.25.
- Increase to 25mg/day OCS (or equivalent) if Prednisone is 20 and Dexamethasone is 3.0.
- Increase to 30mg/day OCS (or equivalent) if Prednisone is 25 and Dexamethasone is 3.75.
- Increase to 37.5mg/day OCS (or equivalent) if Prednisone is 30 and Dexamethasone is 4.5.
- Increase to 50mg/day OCS (or equivalent) if Prednisone is 37.5 and Dexamethasone is 5.75.

For BS Score 1:
- No change, consider ICS reduction if Prednisone is 0 and Dexamethasone is 0.

For BS Score 0:
- No change, consider ICS reduction if Prednisone is 0 and Dexamethasone is 0.
Supplemental Figure 1: CONSORT Flow Diagram of enrolment for Markers of Inflammation in the Management Of Severe Asthma: A randomised controlled trial of biomarker based titration of oral corticosteroids study.

Supplemental Figure 2: Markers of inflammation (PBE (Supplemental Figure 2A) and FeNO (Supplemental Figure 2B)) over the course of the study for the biomarker based management (BBM) and standard best practice (SBP) groups. Sputum eosinophil counts are presented at enrolment and the final visit of the study. (Figure 2C)

Supplemental Figure 3: PBE (Supplemental Figure 3A) and FeNO (Supplemental Figure 3B) in participants on mepolizumab over the course of the study in BBM and SBP.

Supplemental Figure 4: OCS dose (mg/day) administered over the study period in BBM and SBP groups.