Adv Ther (2024) 41:3196–3216
https://doi.org/10.1007/s12325-024-02914-w

ORIGINAL RESEARCH

A Simulation Study of the Effect of Clinical Characteristics and Treatment Choice on Reliever Medication Use, Symptom Control and Exacerbation Risk in Moderate–Severe Asthma

Gabriel Garcia · Sven C. van Dijkman · Ian Pavord · Dave Singh · Sean Oosterholt · Sourabh Fulmali · Anurita Majumdar · Oscar Della Pasqua

Received: April 29, 2024 / Accepted: May 29, 2024 / Published online: June 25, 2024

ABSTRACT

***Introduction*:** The relationship between immediate symptom control, reliever medication use and exacerbation risk on treatment response and factors that modify it have not been assessed in an integrated manner. Here we apply simulation scenarios to evaluate the effect of individual baseline characteristics on treatment response in patients with moderate–severe asthma on regular maintenance dosing monotherapy with fluticasone propionate (FP) or combination therapy with fluticasone propionate/salmeterol (FP/SAL) or budesonide/formoterol (BUD/FOR).

***Methods*:** Reduction in reliever medication use (puffs/24 h), change in symptom control scores (ACQ-5), and annualised exacerbation rate over 12 months were simulated in a cohort of patients with different baseline characteristics (e.g. time since diagnosis, asthma control questionnaire (ACQ-5) symptom score, smoking status, body mass index (BMI) and sex) using drug–disease models derived from large phase III/IV clinical studies.

***Results*:** Simulation scenarios show that being a smoker, having higher baseline ACQ-5 and BMI, and long asthma history is associated with increased reliever medication use ($p<0.01$). This increase correlates with a higher exacerbation risk and higher ACQ-5 scores over the course of treatment, irrespective of the underlying maintenance therapy. Switching non-responders to ICS monotherapy to combination therapy after 3 months resulted in immediate reduction in reliever medication use (i.e. 1.3 vs. 1.0 puffs/24 h for FP/SAL and BUD/FOR, respectively). In addition, switching patients with ACQ-5 > 1.5 at baseline to FP/SAL resulted in 34% less exacerbations than those receiving regular dosing BUD/FOR ($p<0.01$).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-02914-w.

G. Garcia
Respiratory Research Center, CEPIR, La Plata, Argentina

S. C. van Dijkman · S. Oosterholt · O. Della Pasqua (✉)
Clinical Pharmacology Modelling and Simulation, GSK, GSK House, 980 Great West Rd, London TW8 9GS, UK
e-mail: odp72514@gsk.com

I. Pavord
Nuffield Department of Medicine, University of Oxford, Oxford, UK

D. Singh
University of Manchester, Manchester University NHS Foundations Trust, Manchester, UK

S. Fulmali · A. Majumdar
GSK, Global Classic and Established Medicines, Singapore, Singapore

O. Della Pasqua
Clinical Pharmacology & Therapeutics Group, University College London, London, UK

Conclusions: We have identified baseline characteristics of patients with moderate to severe asthma that are associated with greater reliever medication use, poor symptom control and higher exacerbation risk. Moreover, the effects of different inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combinations vary significantly when considering long-term treatment performance. These factors should be considered in clinical practice as a basis for personalised management of patients with moderate–severe asthma symptoms.

PLAIN LANGUAGE SUMMARY

In this study we looked at how different factors affect the response to asthma treatment in people with moderate to severe asthma who are taking regular medication. Specifically, we wanted to quantify how much asthma duration, differences in the degree of symptom control and lung function, as well as smoking habit, body weight, and sex influence how well someone responds to regular maintenance therapy. Using computer simulations based on models obtained from data in a large patient population with moderate–severe asthma, we explored scenarios that reflect real-life management of patients undergoing treatment with inhaled corticosteroids alone or in combination with long-acting beta agonists over a 12-month period. We looked at how much reliever inhaler they use, how well they rate their asthma control, and how often they have asthma attacks. By considering these results together, we evaluated how well the treatments work on ongoing symptoms and/or reduce the risk of future asthma attacks. Our simulations showed that smokers, people with higher asthma symptom scores, who are obese, and have a longer history of asthma tend to use their reliever inhalers more often. This was linked to a higher risk of having asthma attacks and worse symptom control. Switching those patients who do not respond well to their initial treatment with corticosteroid to combination therapy reduced how much reliever inhaler they need. Also, the effects of fluticasone propionate/salmeterol combination therapy were greater than budesonide/formoterol. In conclusion, our study found that certain patient characteristics can predict how well someone responds to asthma treatment.

Keywords: Reliever use; Short-acting beta agonist; Exacerbation; Symptom control; Treatable traits; ICS/LABA combination therapy; Fluticasone propionate; Salmeterol; Clinical trial simulations

Key Summary Points

Why carry out this study?

Patients with asthma, especially those with moderate–severe disease, tend to use reliever medication for rapid symptom improvement. However, it remains unclear which factors determine reliance on reliever therapy.

To date, physicians have looked primarily at reliever use data arising from cross-sectional, generally retrospective studies, thereby ignoring the effect of the complex interplay between maintenance therapy and reliever medication use.

Moreover, the effect of interindividual differences in baseline characteristics and asthma treatment choices on reliever medication use and its implications for symptom control and future risk have not been evaluated in an integrated manner.

Simulation scenarios allow us to disentangle the effect of concurrent factors on immediate and long-term treatment response in patients with moderate–severe asthma.

What was learned from this study?
Despite evidence of increased reliever use in patients who exacerbate, this association appears to be a consequence of insufficient bronchoprotection in patients who do not achieve adequate levels of control on inhaled corticosteroid (ICS) or ICS/long-acting beta agonist maintenance therapy, and consequently remain exposed to a high exacerbation risk.
These results support the views that in addition to tolerance and desensitisation of the beta-adrenergic system to beta-agonists in patients with a significantly longer history of asthma, treatable traits also contribute to higher reliever medication use.
Reliever medication use depends on the underlying degree of bronchoprotection. Yet, it is significantly higher in patients with asthma who are current smokers, obese, have a longer history of asthma or have inadequate symptom control, as assessed by the asthma control questionnaire (ACQ-5 > 1.5) at baseline.
Irrespective of symptom control level at baseline or extent of reliever medication use, combination therapy with fluticasone propionate/salmeterol yields significantly greater reduction in exacerbation risk than budesonide/formoterol. Further studies including longitudinal data on markers of type 2 inflammation may help explain these differences and elucidate the interplay between baseline patient characteristics (i.e. treatable traits), anti-inflammatory and bronchodilatory drug effects.

INTRODUCTION

Asthma is a chronic condition with substantial symptom fluctuation due to multiple concomitant factors affecting individual response to therapy, such as progressive airway hyperresponsiveness, inadequate treatment-associated bronchoprotection, and exposure to triggers [1–4]. Given its heterogeneity, patients with moderate–severe asthma are inevitably exposed to multiple intercurrent events related to treatment, such as supplementary reliever medication, step-up from inhaled corticosteroid (ICS) monotherapy to ICS/long-acting beta agonist (LABA) combination therapy, as well as dose adjustments [5, 6]. However, clinical studies focused on clinical management and treatment outcomes in moderate–severe asthma tend to overlook the implications of intercurrent events and interplay between disease status, triggers and symptoms on treatment response. Consequently, it can be difficult to establish the net effectiveness of the underlying maintenance therapy, defined as achieving symptom control, maintaining normal levels of activity, and minimizing future exacerbations to avoid long-term morbidity and mortality [7, 8].

Despite the ongoing efforts to further account for disease heterogeneity in the clinical management of patients with moderate–severe symptoms, interindividual differences in treatment response are assumed to result from variable drug effects, which aim at bronchoprotection and bronchodilation by reducing airway inflammation and hyperreactivity, as well as by stabilising smooth muscle and airway geometry [9]. In consequence, patients with moderate–severe asthma who do not achieve adequate symptom control are managed according to a step-up approach with incremental steps, namely from dose increase to dual and triple combination therapy. Even though both symptom control and future risk reduction constitute important pillars for the clinical management of asthma, the use of a step-up approach does not fully consider the effect of individual baseline characteristics on symptom control, reliever medication use, and future risk reduction [10, 11]. Thus, it becomes complicated to disentangle the effects of maintenance therapy (which is aimed at sustained symptom control and future risk reduction) from those associated with reliever medication (which targets acute symptom worsening) [12–15]. In fact, it may be challenging to know and evaluate which patient groups are likely to require more reliever medication to achieve adequate bronchodilation, or how

deterioration of symptoms correlates with reliever medication use [16].

An additional confounding factor is the individual patterns of adherence to treatment [17]. Unfortunately, real-life observations suggest that a significant proportion of patients fail to accept the chronic nature of asthma and the importance of regular maintenance therapy as the basis for ensuring lasting bronchoprotection, exacerbation risk reduction and improved quality of life. Needless to say, this hampers the evaluation of clinically important questions through conventional randomised controlled trials, or prospective/retrospective observational studies, since it is not possible to control for all relevant baseline factors. Evidence generation by modelling and simulation is warranted [18], as recently illustrated by the development of parametric drug–disease models describing the effect of clinical and demographic baseline characteristics on the time course of symptom scores [19], individual patterns of reliever medication use [16], and exacerbation risk reduction [11].

Hence, there remains an opportunity to establish how patient characteristics (i.e. potential treatable traits) and treatment choices determine immediate and long-term clinical response, and how interindividual differences in bronchoprotection correlate with the observed heterogeneity of symptoms and exacerbation risk [19, 20]. Here, we aimed to assess the effect of baseline differences on the pattern of reliever medication use, symptom scores and exacerbation risk in patients on maintenance therapy, taking into account intrinsic and extrinsic factors that act concurrently on immediate symptoms and long-term risk. We expand the drug–disease modelling approach developed previously to describe the overall treatment performance in an integrated manner, by simulating all three endpoints in each virtual patient, namely reliever use (puffs/24 h) along with the time course of asthma symptom scores (ACQ-5) and incidence of exacerbations (annualised exacerbation rate) following maintenance therapy with ICS or ICS/LABA.

METHODS

For clarity, an outline of the data source supporting the development of the drug–disease models and clinical and demographic patient baseline characteristics used in the different simulation scenarios is provided below.

Study Subjects

The current study describes the results from computer simulations and as such does not involve human participants. Patient baseline characteristics used for the prediction of reliever medication use, exacerbations and time course of symptom control scores during the simulations were obtained from the pooled population enrolled in the randomised clinical trials listed in the Supplementary Materials (Table S1), all of which have been performed according to relevant ethical and clinical guidelines. All participants enrolled into the original clinical trials have given informed consent. The terms of consent include the scope of the research presented here.

Our approach relies on the availability of (1) individual-level baseline patient data, which provides an accurate description of the heterogeneity of demographic and clinical characteristics of the adult population with moderate-severe asthma, and (2) parametric models describing the reliever medication use (puffs/24 h) during maintenance therapy, the time course of symptoms (ACQ-5) and the time to first moderate or severe exacerbation. The models were based on data from the maintenance phase of 10 out of 17 randomised controlled phase III/IV studies with a duration of at least 24 weeks in patients receiving ICS monotherapy or ICS/LABA combination therapy. Initially, a total of 24,402 patients with moderate–severe asthma, for which accurate individual clinical and demographic baseline details, treatment, dose and dosing regimens were identified. Additional selection criteria included the measurement of asthma symptom scores during the course of treatment. Studies which had ACQ-5 or ACT were prioritised. Finally, patients should have accurate maintenance therapy records and self-reported reliever

medication use (frequency, timing of administration). These data were integrated with details on the occurrence of the first exacerbation event. Further details on model development, internal and external validation procedures, along with evidence of their predictive performance can be found elsewhere [11, 16, 19].

Data Source

The data used for the development and evaluation of the drug–disease models selected for the current analysis were obtained from 10 different clinical trials (ADA109055, ADA109057, SAM40027, SAM40040, SAM40056, HZA113091, HZA115150, SAM40065, SAM40086, SAS115359) in adults with moderate–severe asthma, treated with regular fixed ICS dosing (i.e. not maintenance and reliever therapy) with fluticasone propionate (FP) monotherapy, combination therapy with salmeterol (FP/SAL), or budesonide/formoterol (BUD/FOR) over a period of at least 24 weeks up to 1 year. Reliever consisted of the short-acting beta agonist (SABA) albuterol/salbutamol 100 µg PRN (as needed).

Clinical Trial Simulations

Modelling and simulation has been widely applied as a tool for evidence synthesis and optimisation of the therapeutic use of medicines across different therapeutic areas [21–23]. In contrast to randomised clinical studies or prospective observational protocols, where control of the multiple factors may not be feasible or ethical during the course of treatment, simulation scenarios using in silico protocols allow an insight into the specific features of an intervention in a controlled or uncontrolled setting. In this simulation study, we use the models previously developed by Oosterholt et al. [11], van Dijkman et al. [16], and Singh et al. [19] (see Table S2, Supplementary Material) for the implementation of the simulation scenarios, which assess the implications of treatable traits and treatment choices on the time course of symptoms (ACQ-5), reliever medication use, and risk of exacerbation. The longitudinal model characterises the individual ACQ-5 trajectories over a 12-month period. Similarly, individual patterns of reliever medication use are described as puffs over the last 24 h by a Poisson function, whereas the time to first exacerbation is based on a fully parametric hazard (survival) model, taking into account the effect of baseline covariates. These models allow for an integrated evaluation of the effect of clinical and demographic baseline characteristics, along with the effect of treatment with ICS monotherapy and ICS/LABA combination therapy.

Treatment arms were defined in a way that the selected interventions reflect typical randomised protocols with fixed regimens and the stepwise approach to the management of patients with moderate–severe asthma symptoms, i.e. starting with regular dosing ICS monotherapy and progressing to regular ICS/LABA combination therapy. In the scenario describing treatment step-up in a real-life setting, only non-responders to ICS monotherapy were assigned to ICS/LABA. For scenarios in which treatment changes were envisaged, response was defined as an improvement in symptom control scores, as predicted by a longitudinal model describing the individual ACQ-5 trajectories over time. An outline of the clinical trial simulation workflow is shown in Fig. 1. Full details of the protocol design characteristics, including statistical considerations and key assumptions used for the assessment of the effect of baseline characteristics and treatment choices on reliever medication use, symptom control level and exacerbation risk are summarised in Table S3.

For the sake of clarity, in the simulations, an asthma exacerbation was defined as either (a) deterioration of symptoms requiring treatment with oral corticosteroids (>2 consecutive days), or a clinical deterioration assessed by the investigating physician as requiring oral steroid treatment; or (b) deterioration in asthma which required hospital admission. These criteria reflect the definitions mostly used to determine moderate or severe exacerbations in the selected clinical studies and correspond to the data used for the development of the model describing the time to first exacerbation.

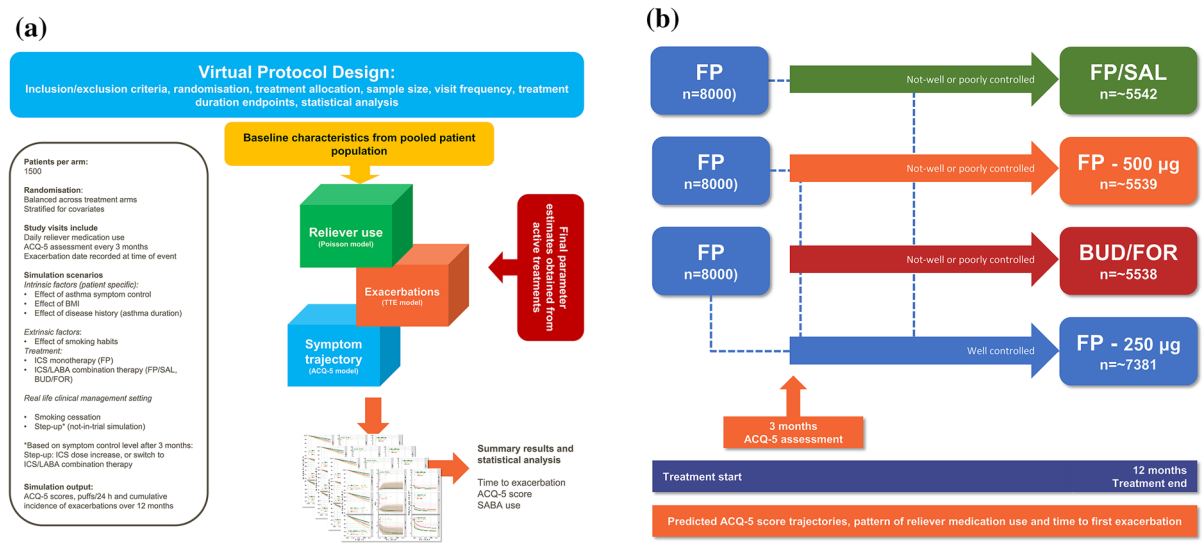


Fig. 1 **a** Schematic diagram of the clinical trial simulations describing reliever medication use, ACQ-5 and time to first exacerbation in patients with moderate–severe asthma symptoms. The scenarios implemented to disentangle the effect of baseline characteristics from that of treatment included intrinsic factors (*Scenario 1* different symptom control levels ACQ-5, *Scenario 2* varying body mass index (BMI), *Scenario 3* disease history (i.e. time since diagnosis), extrinsic factors (*Scenario 4* smoking habit) and real-life settings (*Scenario 5* smoking cessation, *Scenario 6* treatment step-up). Treatment doses and regimens were limited to those used during the maintenance phases of the clinical trials (FP: 100, 250 and 500 µg twice daily; FP/SAL: 100/50, 250/50 and 500/50 µg twice daily; BUD/FOR: 100/6, 200/6, 400/12, 160/4.5 and 320/9 µg twice daily). **b** Outline of the scenario describing the clinical management of patients with moderate–severe asthma symptoms in a real-life setting (not-in-trial simulations). *R* responder, i.e. a patient achieving symptom control (ACQ-5 ≤ 0.75) at 3 months after treatment initiation with ICS monotherapy (FP). *NR* non-responder, i.e. a patient who does not achieve symptom control (ACQ-5 > 0.75) at 3 months after treatment initiation with ICS monotherapy (FP). *ACQ-5* asthma control questionnaire, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist, *SAL* salmeterol

Simulation Scenarios

For each simulation scenario baseline characteristics were sampled from 1500 patients from a pooled population of adults (N=16,282) using random resampling. The use of baseline data from real patients with moderate–severe asthma ensured accurate representation of the range of values and correlations between demographic and clinical characteristics. Moreover, treatment was assumed to be independent of baseline characteristics and was assigned randomly to each patient. All scenarios included treatment for the period of 1 year. To ensure sufficient precision of simulated endpoints, each scenario was replicated 500 times, and for each replicate patient baseline characteristics were resampled from the pooled population. The number of puffs over the last 24 h, along with ACQ-5 symptom cores and Kaplan–Meier estimates of the simulated exacerbation events were summarised per simulation scenario. Reduction in reliever use and symptom improvement at the end of the treatment period were reported along with the change in annualised exacerbation rate.

To ensure alignment with clinical criteria, results were stratified by baseline covariates according to the following groups or categories. ACQ-5: well controlled (≤0.75), not well controlled (>0.75 to ≤1.5) and poorly controlled (>1.5); BMI: normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obese (30 to <35 kg/m^2) and extremely obese (≥35 kg/m^2);

asthma duration was split into three categories: <5 years, ≥5 to <10 years, and ≥10 years.

Not-in-Trial Simulations (NITS)

This scenario aimed to describe the clinical management of adults with moderate–severe asthma in a real-life setting. In total, 8000 patients were randomly assigned to an intervention, and each scenario was repeated 500 times. Patient baseline characteristics were resampled from the pooled population during each iteration. Treatment was assumed to be independent of baseline characteristics and was randomly assigned at the start of the intervention (Fig. 1). All patients started on the same treatment (i.e. FP). In this real-life setting, patients who did not achieve control after 3 months on monotherapy had their ICS dose increased or were switched to regular maintenance dose with SAL/FP or BUD/FOR for a period of up to 12 months. A responder was defined as a patient achieving symptom control (ACQ-5 < 0.75) at 3 months after treatment initiation, whilst a non-responder was any patient whose ACQ-5 score was > 0.75 at 3 months after treatment initiation. Estimates of the simulated patterns of reliever use, symptom scores, and exacerbation events were summarised both numerically and graphically per simulation scenario. The principles applied to the endpoints of interest are similar to those required for a sensitivity analysis [24, 25]. Given the robustness of the approach, we anticipate that these results may allow the identification of further opportunities for personalised management of patients with moderate–severe asthma. Of note is the possibility of identifying at-risk patients who rely on reliever medication for immediate symptom improvement, and whose clinical management could be adjusted to ensure both sustained symptom control and reduced long-term morbidity, and in some cases, progressive loss of lung function.

All simulation scenarios were implemented in NONMEM version 7.3 (Icon Development Solutions, MD, USA). Graphical summaries and statistical analysis were performed in R version 3.1.1. The statistical significance of the effect of baseline characteristics and treatment choices on changes in symptom scores, reliever medication use, and annualised exacerbation rates over the period of12 months was evaluated in each scenario (see Supplementary Material for further details on the statistical methods) [26–28].

RESULTS

The result from the interaction of the different factors can be visualised in a heat map (Fig. 2), which highlights how baseline characteristics, and in particular ACQ-5, affect reliever medication, symptom scores and exacerbation risk in an independent manner. An overview of the baseline characteristics of the virtual patient cohorts included in each simulation scenario is presented in Tables S4 to S9 (Supplementary Material).

A summary of the effect of baseline symptom scores (ACQ-5) on treatment response is presented in Fig. 3. Patients who are well-controlled (i.e. ACQ-5 ≤ 0.75) showed a significant reduction in reliever use whilst maintaining stable symptom control scores over the course of treatment. This pattern contrasts with patients whose ACQ-5 is greater than 0.75 at baseline. Most noticeable are the differences in exacerbations across the three groups. Significantly fewer exacerbations were observed in patients with well-controlled/not well-controlled symptoms relative to those poorly controlled at baseline ($p < 0.01$). Moreover, our results show that differences between treatment arms are independent from the effect of baseline covariates on symptom control level. The proportion of patients treated with FP/SAL who experience an exacerbation over the period of 12 months is significantly lower (8–13%, $p < 0.01$) than in those on regular dosing BUD/FOR, irrespective of baseline ACQ-5.

A similar pattern was observed for the effect of BMI on symptom score, reliever medication use and exacerbation risk (Fig. 4). A statistically significant increase in reliever medication use is observed along with an increase in the incidence of exacerbations (i.e. in patients who

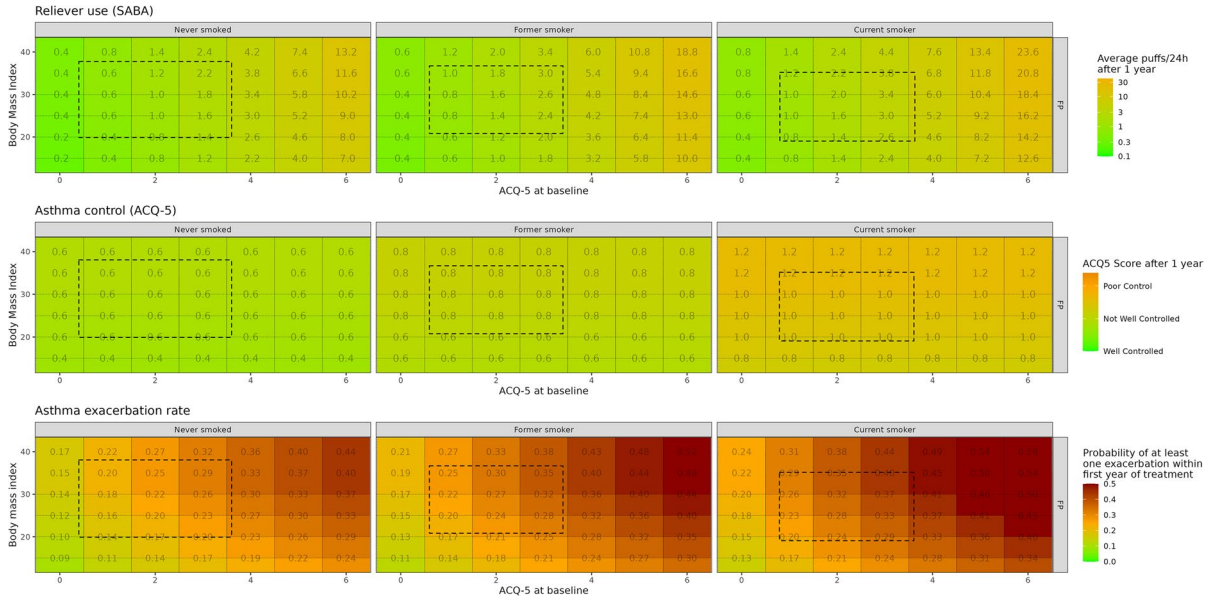
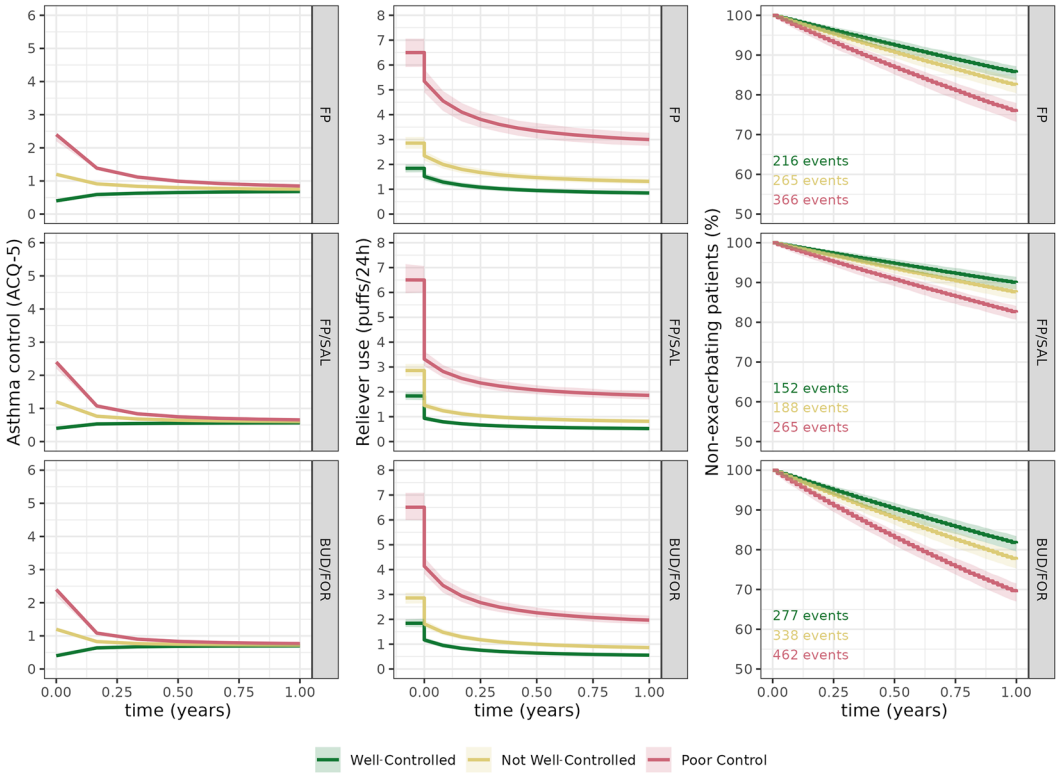


Fig. 2 Heatmap of predicted reliever use (puffs/24 h), symptom scores and exacerbation risk at 12 months after start of treatment for varying baseline ACQ-5 and smoking status following ICS monotherapy (FP). Note that subjects with comparable BMI but different ACQ-5 scores will show different risk of exacerbation, patterns of reliever use and symptom control over time, depending on smoking habit at the start of treatment. This overview highlights the relevance of assessing both immediate and long-term effects of a treatment when considering further increases in the dose or step-up to combination therapy with ICS/LABA. Dotted areas encompass the baseline characteristics of the patient population enrolled into the available clinical studies, to which inclusion and exclusion criteria apply. The overall scale (x and y axis) includes a range of values likely to occur in a real-life setting. *ACQ-5* asthma control questionnaire, *BMI* body mass index, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist

are obese (30 to <35 kg/m^2) and extremely obese (≥ 35 kg/m^2) relative to those with normal BMI (18.5 to <25 kg/m^2) irrespective of treatment (i.e. mean puffs/24 h up by 43% and 78%, respectively; median annualised exacerbation rate up by 35% and 64%, respectively ($p<0.01$)). In contrast, no significant differences in symptom control scores were observed between patients with normal BMI, who are overweight and those with obesity following combination therapy with FP/SAL or BUD/FOR. This finding suggests that for patients with obesity or morbid obesity (i.e. BMI >30 kg/m^2), a significantly high use of reliever is needed to achieve sustained asthma control.

The effect of asthma history and treatment on symptom scores, reliever medication use and exacerbation risk is shown in Fig. 5. Whilst there are marked differences in reliever medication use in patients who have been diagnosed with asthma for longer than 20 years (i.e. mean puffs/24 h up by up to 107%, $p<0.01$), mean symptom control levels seem to be comparable.

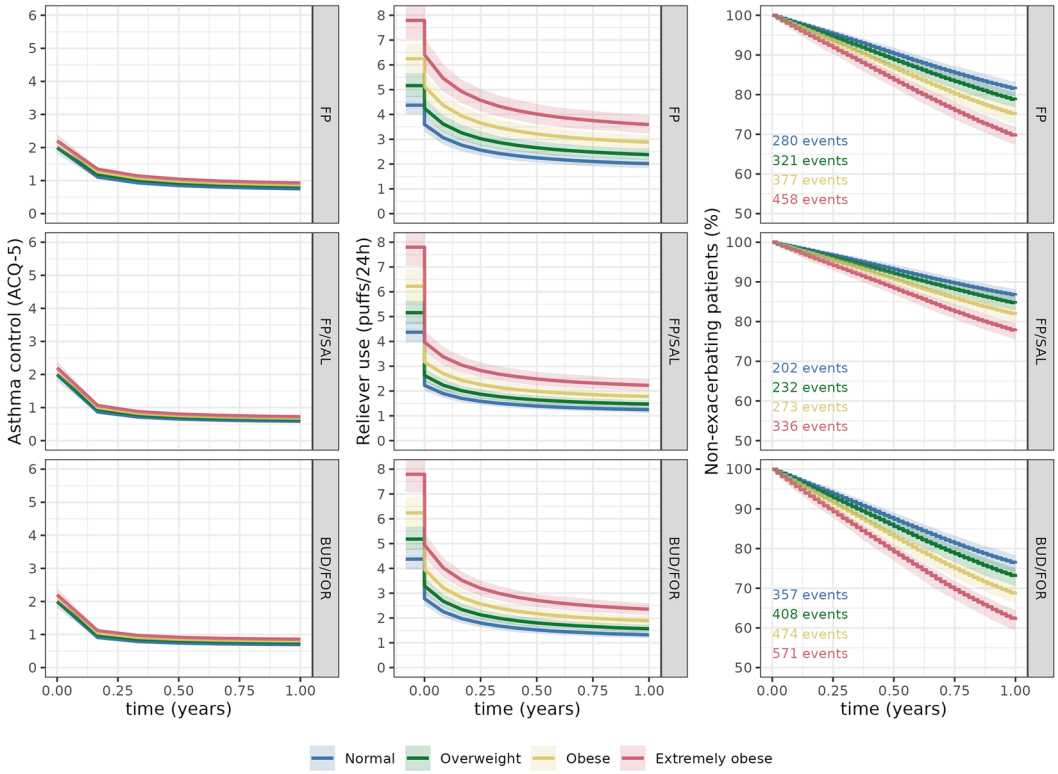
Strikingly, smoking habit altered all three endpoints, i.e. it affected both immediate symptoms, reliever medication use and long-term risk. As shown in Fig. 6, smoking results in higher symptoms scores, significantly more frequent use of reliever and a higher risk of exacerbations. On the other hand, our analysis also show that whilst smoking cessation can lead to rather fast changes in immediate symptoms, and reduce risk, important, statistically significant differences in treatment response remain between current smokers, former smokers and non-smokers (Fig. S1). Despite comparable reduction in reliever medication



		Asthma control (ACQ-5)			Reliever use (puffs/24h)			Annualised exacerbating rate (%)		
Treatment	**Asthma Control**	Median	95% Confidence interval		Mean	95% Confidence interval		Median	95% Confidence interval	
FP	Well-Controlled	0.68	0.64	0.72	0.85	0.77	0.93	85.6	83.7	87.2
	Not Well-Controlled	0.75	0.72	0.79	1.32	1.20	1.43	82.4	80.4	84.3
	Poor Control	0.85	0.81	0.89	3.00	2.75	3.27	75.7	73.2	78.0
FP/SAL	Well-Controlled	0.56	0.53	0.60	0.52	0.47	0.58	89.9	88.3	91.4
	Not Well-Controlled	0.60	0.57	0.63	0.82	0.75	0.90	87.5	85.7	89.2
	Poor Control	0.65	0.62	0.69	1.86	1.69	2.04	82.5	80.7	84.1
BUD/FOR	Well-Controlled	0.70	0.66	0.74	0.56	0.50	0.62	81.6	79.6	83.4
	Not Well-Controlled	0.72	0.68	0.75	0.86	0.78	0.94	77.5	75.3	79.6
	Poor Control	0.77	0.73	0.81	1.97	1.81	2.15	69.3	67.0	71.6

ACQ-5 categories: well-controlled (≤0.75), not well-controlled (>0.75 to ≤1.5) and poorly controlled (>1.5)

Fig. 3 *Scenario 1* – The upper panel shows the effect of baseline ACQ-5 on symptom control score, reliever medication use (puffs/24 h) and exacerbation risk. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. The lower panel summarises the response to treatment after 12 months. Treatment arms ($n = 1500$ each, 500 iterations) include FP (250 µg b.i.d.), FP/SAL (250/50 µg b.i.d.), BUD/FOR (200/6 µg b.i.d.). Parameter estimates describing treatment effect correspond to that of the mean dose during the maintenance phase. It should be highlighted that changes in symptom scores and reliever medication use do not occur at the same timescale, with reliever medication use changing initially much faster than symptom scores in patients who are poorly controlled or not well controlled at baseline. Moreover, despite comparable reduction in reliever medication use after combination therapy with ICS/LABA, FP/SAL results in a significantly lower exacerbation rate than BUD/FOR ($p < 0.01$). Further details on the clinical and demographic baseline characteristics of the simulated population and an overview of the statistical significance level of the comparisons between different groups and treatment arms at 12 months are summarised in Table S4. *ACQ-5* asthma control questionnaire, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist, *SAL* salmeterol



		Asthma control (ACQ-5)			Reliever use (puffs/24h)			Annualised exacerbating rate (%)		
Treatment	Arm	Median	95% Confidence interval		Mean	95% Confidence interval		Median	95% Confidence interval	
FP	Normal	0.75	0.71	0.79	2.02	1.84	2.19	81.4	79.6	83.2
	Overweight	0.82	0.78	0.85	2.38	2.17	2.63	78.7	76.8	80.7
	Obese	0.87	0.83	0.91	2.88	2.59	3.17	74.9	72.6	77.2
	Extremely obese	0.93	0.88	0.97	3.59	3.23	3.97	69.5	67.3	71.8
FP/SAL	Normal	0.59	0.56	0.61	1.25	1.11	1.38	86.6	84.7	88.1
	Overweight	0.64	0.60	0.67	1.47	1.33	1.61	84.6	82.8	86.4
	Obese	0.68	0.65	0.71	1.78	1.59	2.00	81.8	80.0	83.8
	Extremely obese	0.72	0.69	0.76	2.23	2.00	2.48	77.6	75.5	79.6
BUD/FOR	Normal	0.70	0.66	0.73	1.32	1.19	1.47	76.2	74.0	78.4
	Overweight	0.75	0.72	0.79	1.57	1.43	1.73	72.9	70.6	75.2
	Obese	0.80	0.76	0.84	1.89	1.70	2.10	68.5	66.3	70.7
	Extremely obese	0.86	0.82	0.90	2.36	2.11	2.59	62.0	59.5	64.5

BMI categories: normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), obese (30 to <35 kg/m^2) and extremely obese (≥35 kg/m^2)

Fig. 4 *Scenario 2* – The upper panel shows the effect of baseline BMI on symptom control score, reliever medication use (puffs/24 h) and exacerbation risk. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. The lower panel summarises the response to treatment after 12 months. Treatment arms ($n = 1500$ each, 500 iterations) include FP (250 µg b.i.d.), FP/SAL (250/50 µg b.i.d.), BUD/FOR (200/6 µg b.i.d.). Parameter estimates describing treatment effect correspond to that of the mean dose during the maintenance phase. It should be highlighted that changes in symptom scores and reliever medication use do not occur at the same timescale, with symptom score changing faster than reliever medication use in patients who are overweight (25 to < 30 kg/m^2), obese (30 to < 35 kg/m^2) and extremely obese (≥ 35 kg/m^2) relative to those with normal BMI at baseline. Moreover, despite comparable reduction in reliever medication use after 12 months on combination therapy with ICS/LABA, FP/SAL results in a significantly lower exacerbation rate than BUD/FOR irrespective of BMI ($p < 0.01$). Further details on the clinical and demographic baseline characteristics of the simulated population and an overview of the statistical significance level of the comparisons between different groups and treatment arms at 12 months are summarised in Table S5. *ACQ-5* asthma control questionnaire, *BMI* body mass index, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist, *SAL* salmeterol

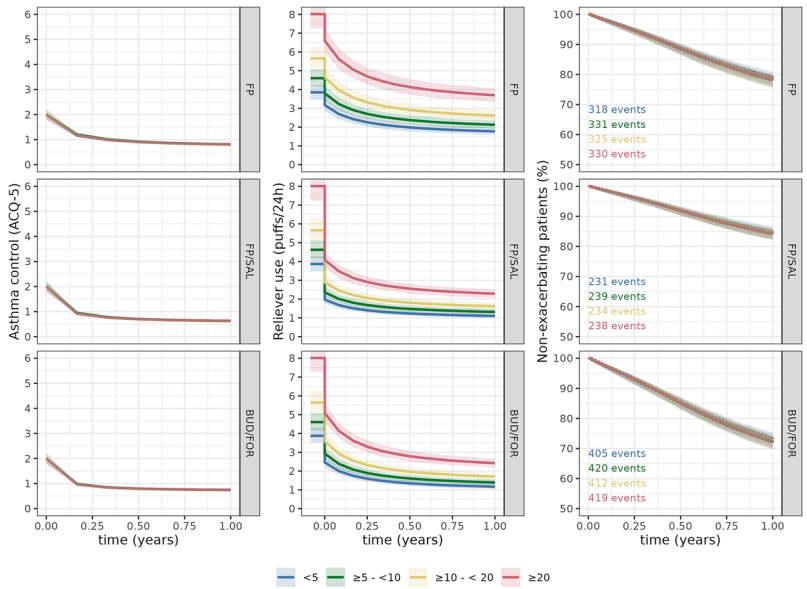
use in patients receiving ICS/LABA combination therapy, treatment with FP/SAL resulted in statistically significant lower ACQ-5 scores and significantly lower exacerbation events than BUD/FOR ($p<0.01$).

The evaluation of the effect of baseline characteristics and treatment choice on symptom control levels, reliever medication use and exacerbation risk in a real-world setting reveals that comparable, immediate symptom improvement does not imply the same degree of bronchoprotection or exacerbation risk reduction (Fig. 7). First, it is worth mentioning that patients who respond to ICS monotherapy appear to have less pronounced symptoms, and possibly suboptimal bronchoprotection, as the sustained, relatively low ACQ-5 scores are accompanied by a more frequent use of reliever medication. In fact, ICS dose increase in patients who do not achieve adequate control on ICS monotherapy does not result in further decrease in reliever medication use or reduction in exacerbation risk. By contrast, non-responders to ICS monotherapy appear to have a more marked airway inflammation and hyperresponsiveness. In this group of patients, one observes the differences in the pharmacological properties of ICS, LABA and SABA molecules, and the interplay between airway hyperresponsiveness (bronchoconstriction), airway inflammation (bronchoprotection), and vulnerability to triggers (exacerbation). Despite comparable reduction in reliever medication use, the step-up of patients who do not respond to FP monotherapy to FP/SAL combination therapy resulted in significantly lower ACQ-5 scores as well as lower exacerbation risk, as compared to BUD/FOR ($p<0.01$).

DISCUSSION

Our analysis reveals that both immediate symptoms and long-term response to ICS/LABA are greatly affected by individual patient characteristics and treatment choices. The current investigation expands on the initial findings from our initiative to personalise interventions in moderate–severe asthma, i.e. Modelling ASthma TrEatment Responses (MASTER) [11, 16, 19]. We do so by integrating and evaluating the effect of interindividual differences on the burden of disease, i.e. symptom control, airway hyperresponsiveness to triggers, and exacerbation risk. Of note is the evidence that ACQ-5 scores and BMI (intrinsic factors), as well as smoking habit (extrinsic factor) alter all three measures included in this study. Symptom scores are further affected by lung capacity and function, as assessed by age and airway calibre (FEV1p%), whilst disease history appears to influence reliever medication use independently from other factors. Lastly, sex (female), seasonal variation and limited lung function (FEV1p%) also contribute to increased exacerbation risk. Moreover, the different simulation scenarios showed that despite the use of drugs with well-defined pharmacological mechanisms (i.e. short- and long-acting β_2-agonists and corticosteroids), drug molecules with different pharmacokinetic-pharmacodynamic properties show significant differences in treatment performance [29, 30]. Depending on treatment choice, patients showing comparable symptom improvement do not necessarily experience the same exacerbation risk reduction.

Moreover, the proposed scenarios make clear that the assessment of symptom control requires careful evaluation of both the individual patterns of reliever use and response to the underlying maintenance therapy. In brief, achievement of treatment goals should be based on evidence of sustained bronchoprotection and exacerbation risk reduction, rather than merely symptom control. This is likely to be realised by the frequency of reliever medication use, relative to the maintenance therapy. This situation can be compared to that faced in the clinical management of patients in other therapeutic areas, such as the requirement for supplementary (rescue) doses of short- and rapid-acting insulin versus basal long-acting insulin in type I diabetes [31], or benzodiazepine use when (breakthrough) seizures occur more often or show a more severe pattern than what is aimed for with maintenance therapy and a seizure action plan in epilepsy [32]. Ultimately, emphasis is given to the importance of adjustments to a patient's lifestyle and underlying therapy that are necessary to



Treatment	Arm (years)	Asthma control (ACQ-5) Median	95% Confidence interval		Reliever use (puffs/24h) Mean	95% Confidence interval		Annualised exacerbating rate (%) Median	95% Confidence interval	
FP	<5	0.81	0.77	0.85	1.78	1.59	1.97	78.8	76.8	80.8
	≥5 - <10	0.81	0.77	0.85	2.13	1.90	2.37	78.1	75.6	80.0
	≥10 - < 20	0.80	0.76	0.84	2.61	2.36	2.91	78.4	76.3	80.3
	≥20	0.81	0.77	0.84	3.70	3.34	4.05	78.1	76.0	80.1
FP/SAL	<5	0.63	0.60	0.66	1.10	0.99	1.23	84.7	82.6	86.6
	≥5 - <10	0.63	0.59	0.66	1.32	1.19	1.47	84.2	82.1	85.9
	≥10 - < 20	0.62	0.59	0.65	1.62	1.44	1.79	84.5	82.5	86.1
	≥20	0.63	0.60	0.66	2.29	2.06	2.51	84.1	82.5	85.9
BUD/FOR	<5	0.75	0.71	0.79	1.17	1.05	1.30	73.0	70.9	75.4
	≥5 - <10	0.74	0.70	0.78	1.39	1.25	1.55	72.0	69.8	74.4
	≥10 - < 20	0.73	0.70	0.77	1.71	1.50	1.92	72.6	70.4	74.9
	≥20	0.75	0.71	0.78	2.42	2.17	2.66	72.2	70.0	74.4

Fig. 5 *Scenario 3* – The upper panel shows the effect of asthma history on symptom control score, reliever medication use (puffs/24 h) and exacerbation risk. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. The lower panel summarises the response to treatment after 12 months. Treatment arms ($n = 1500$ each, 500 iterations) include FP (250 µg b.i.d.), FP/SAL (250/50 µg b.i.d.), BUD/FOR (200/6 µg b.i.d.). Parameter estimates describing treatment effect correspond to that of the mean dose during the maintenance phase. Note that changes in symptom scores and reliever medication use do not occur at the same timescale, with symptom score changing faster than reliever medication use. Patients who have been diagnosed for less or more than 5 years show significant differences in reliever medication use. Such a pattern may be associated with the potentially higher dose levels of ICS to which patients with a longer history of disease are exposed. Similarly, the disease history does not seem to have further implications on exacerbation risk. This contrasts with the effect of treatment, which shows significant differences. It is worth mentioning that higher reliever medication use in patients with longer disease history may reflect known changes to the sensitivity to adrenergic effects following prolonged exposure to adrenergic drugs (i.e. tolerance). Moreover, despite comparable reduction in reliever medication use after 12 months on combination therapy with ICS/LABA, FP/SAL results in a significantly lower exacerbation rate than BUD/FOR irrespective of asthma history ($p < 0.01$). Further details on the clinical and demographic baseline characteristics of the simulated population and an overview of the statistical significance level of the comparisons between different groups and treatment arms at 12 months are summarised in Table S6. *ACQ-5* asthma control questionnaire, *BMI* body mass index, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist, *SAL* salmeterol

ensure therapeutic goals are met. Strikingly, similar emphasis does not seem to apply to asthma. Supplemental reliever medication use appears to be endorsed by some investigators, as a means to overcome inadequate bronchoprotection [33].

Our investigation also provides insight into further recommendations for personalised management of patients with moderate–severe asthma, away from symptom severity being assessed and managed primarily by varying the amount and type of medication a patient needs to maintain control [34–36]. It advocates for a potential shift towards a patient-centric approach, taking into account interindividual differences (i.e. treatable traits, risk factors), and for the assessment of treatment performance in an integrated manner [37–39]. Once considered a major challenge, ongoing efforts have now enabled the identification of treatable traits that affect or contribute to respiratory symptoms in individual patients with asthma, allowing for a more pragmatic way to personalise therapeutic goals [11, 16, 19, 40]. Essentially, the concept relies on robust evidence showing that treatment for obstructive lung diseases can achieve better outcomes if guided by specific clinical characteristics. In addition, in patients with moderate–severe asthma, poor respiratory health may also be associated with concurrent conditions or comorbidities whose symptoms may be identical to asthma. Addressing lifestyle or environmental factors could result in better control rather than simply increasing airway-directed treatment. To this purpose, further insights may arise from the evaluation of longitudinal patterns of markers of type 2 inflammation.

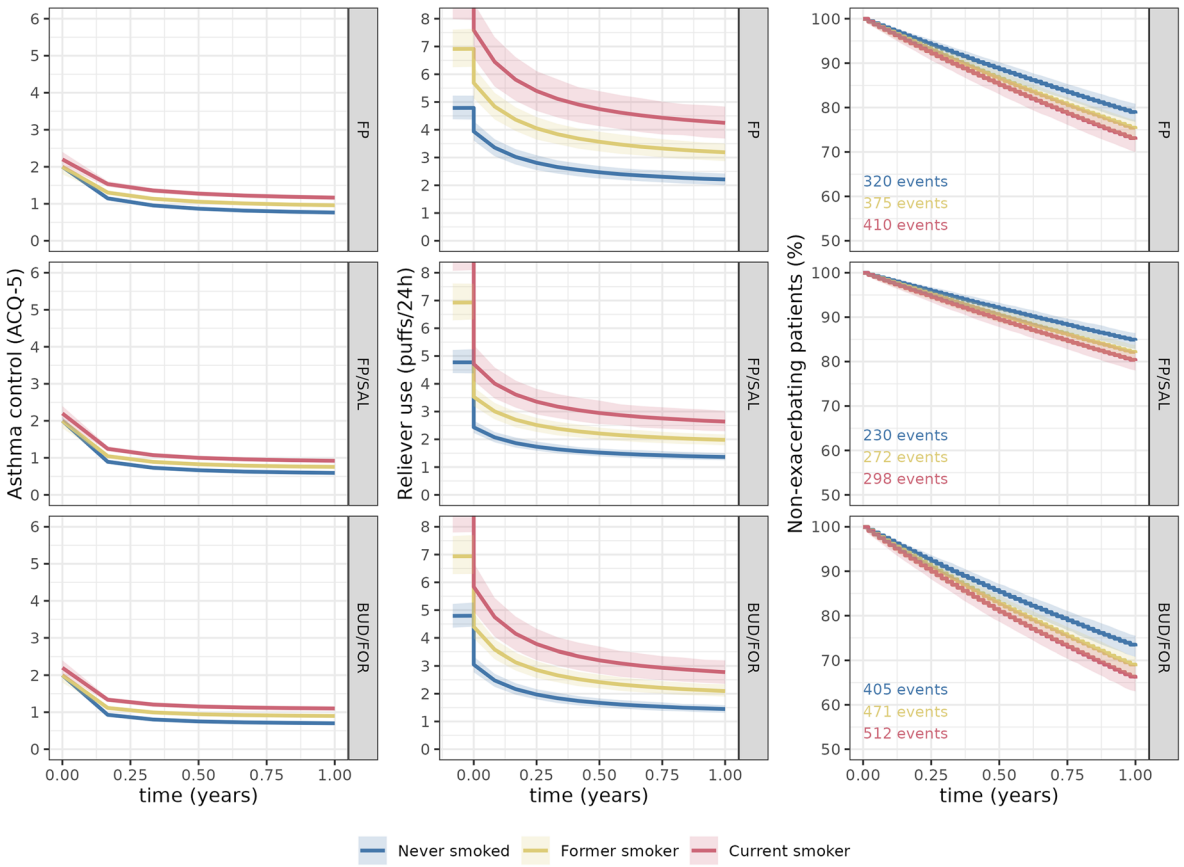
Undoubtedly, there are many factors associated with the risk and severity of asthma [41]. However, on the basis of the current results, it becomes obvious that in addition to the symptom control levels, obesity and smoking habit (cigarettes, e-cigarettes, vaping devices) are critical treatable traits, which deserve further attention in the clinical management of patients with moderate–severe asthma [42–45]. Moreover, the concurrent evaluation of symptoms, reliever medication use and exacerbation risk in simulated scenarios also sheds light on the role of the underlying disease processes, namely bronchoconstriction, airway inflammation and hyperresponsiveness.

In this regard, it is worth highlighting that the lack of distinction between the mechanisms underpinning immediate and sustained symptom improvement (i.e. bronchodilation vs. bronchoprotection) in moderate–severe asthma leads to potential misinterpretation of clinical evidence, especially if one considers that a significant proportion of patients with asthma are diagnosed and treated without any spirometry data. Here we have shown that reliever medication use is strongly correlated with worsening of symptoms, as assessed by ACQ-5 scores, and that reliever use is higher in exacerbating patients. However, dyspnoea and breathlessness are assessed as a symptom, rather than one of the mechanisms associated with airway remodelling. This conception of bronchoconstriction disregards changes in airway calibre due to abnormal smooth muscle excitation–contraction in asthma. Consequently, reliance on reliever medication represents a reaction to abnormal smooth muscle contractility and airway hyperresponsiveness, instead of proactively minimising the vulnerability to bronchoconstrictive stimuli [46, 47]. In fact, previous data suggest that there is a potential vicious positive cycle of bronchoconstriction that drives the worsening of asthma independently of inflammation. Thus, bronchoconstriction is not simply a consequence or symptom of asthma and should be considered an important contributor to airway remodelling. As such, findings focusing on the association between exacerbation events and short-acting beta agonist use are unlikely to be causal. The different simulation scenarios indicate that exacerbation risk is higher in patients who are female, show inadequate symptom control, are obese, smokers and have limited airway function. As reliever medication use is also significantly higher in patients with obesity and in those who smoke, it is easy to presume a causal link [48]. Moreover, the interplay between changes to the sensitivity of airway smooth muscle to the bronchodilatory effect of beta-adrenergic drugs and decline in airway function over time in patients with a long disease history further contributes to the poor assessment and interpretation of data on reliever medication use

and incidence of exacerbations [49, 50]. This is compounded by the differences in long-term effect on different ICS/LABA combinations on exacerbation risk reduction.

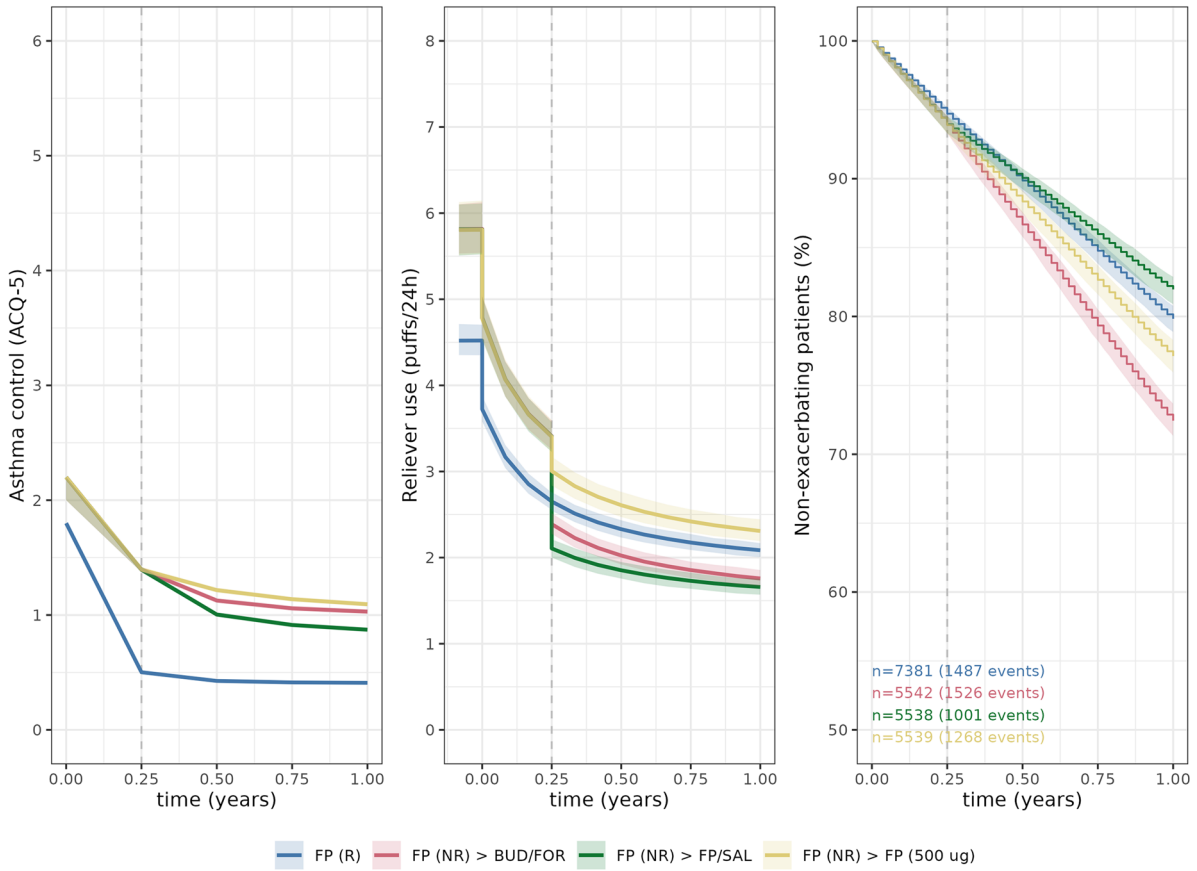
Besides the effect of individual baseline characteristics, the simulation scenarios reveal that treatment choices also play an important role in achieving and maximising treatment benefits. First, it is evident that increasing doses of ICS in patients on monotherapy has limited effect on long-term risk, even though immediate symptoms and reliever medication use are significantly reduced. Such effects are, however, limited when compared to the overall response to ICS/LABA combination therapy. Second, step-up to ICS/LABA combination therapy may provide comparable reduction in reliever medication use, but a stable pattern is achieved only after approximately 12 months on maintenance doses, irrespective of individual differences in baseline characteristics. It is worth mentioning that while a difference of 1–2 puffs/24 h observed in some of the scenarios may seem clinically small on a daily basis, the cumulative effect over time can be substantial. Over a year, a reduction of 1–2 puffs/24 h in SABA use is equivalent to using 1.8–3.6 fewer canisters, respectively. Third, statistically significant and clinically important differences in treatment response are observed with combination therapy with BUD/FOR vs FP/SAL. This is of particular interest for some patients, who are exposed to a higher risk of exacerbation. For instance, current smokers receiving FP/SAL have significantly lower ACQ-5 scores ($p<0.01$) and lower exacerbation rates ($p<0.01$) after 12 months on treatment than those on regular dosing BUD/FOR. Similarly, FP/SAL was found to produce greater reduction in exacerbation risk in obese subjects. In fact, the differences in exacerbation risk expand across the overall obese population, irrespective of the level of symptom control at the start of treatment, with FP/SAL resulting in up to 15% greater reduction in exacerbations relative to BUD/FOR in female patients who are obese or extremely obese. In addition, results from a real-world setting indicate that non-responders to ICS monotherapy who are switched to FP/SAL achieve significantly lower ACQ-5 scores and show fewer exacerbations ($p<0.01$) than those on regular dosing BUD/FOR ($p<0.01$). In addition, treatment with FP/SAL resulted in a larger proportion of patients (42%) achieving symptom improvement (i.e. ACQ-5 > 0.5) compared to BUD/FOR (30%). Such a distinction between treatment arms may not be evident in small clinical trials where the sample size affects the precision of the estimated treatment effect and patient are not stratified on the basis of symptom control level.

Our endeavour to identify treatable traits and optimise interventions in asthma is not unique. From a methodological perspective, there have been multiple efforts to explain heterogeneity and characterise risk factors in asthma, but most initiatives rely on mean (meta-analytical) or cross-sectional data, which disregard time-varying, patient-specific characteristics which can be critical for the implementation of personalised interventions [12, 51, 52]. By contrast, drug–disease modelling and simulation has evolved along with computational technologies to support evidence generation and evidence synthesis using aggregated, individual patient-level data [22, 53–56]. Differently from prospective clinical protocols or retrospective cohort studies, the use of simulation scenarios enables the assessment of the magnitude of the effect of multiple, concurrent factors on treatment outcome, whilst maintaining constant all other relevant variables of interest, including adherence to maintenance therapy. This attribute of simulations allows for the evaluation of the effect of interindividual differences in baseline characteristics on the overall response to treatment, both in controlled and real-world settings. Its applications continue to increase across drug development, regulatory approval and clinical practice [57–62]. Yet, we acknowledge that our work has some limitations. Consequently, assumptions had to be made regarding the generalisability of the findings from the different simulation scenarios, as similar protocols may not be easily implemented or controlled in a real-life setting. Among other things, we understand that in a real-life setting, other factors may play a role in symptom fluctuation and/or act as risk modifiers. For instance, many patients may have other comorbidities which often affect symptoms and potentially trigger exacerbations, such as



Treatment	Arm	Asthma control (ACQ-5)			Reliever use (puffs/24h)			Annualised exacerbating rate (%)		
		Median	95% Confidence interval		Mean	95% Confidence interval		Median	95% Confidence interval	
FP	Never smoked	0.76	0.73	0.80	2.21	2.00	2.42	78.7	76.8	80.8
	Former smoker	0.96	0.91	1.00	3.19	2.87	3.50	75.2	72.6	77.2
	Current smoker	1.17	1.11	1.22	4.25	3.68	4.83	72.8	70.0	75.3
FP/SAL	Never smoked	0.59	0.56	0.62	1.36	1.25	1.50	84.7	82.9	86.4
	Former smoker	0.76	0.72	0.79	1.98	1.79	2.18	81.9	79.9	83.7
	Current smoker	0.92	0.87	0.97	2.64	2.29	3.02	80.1	78.0	82.2
BUD/FOR	Never smoked	0.70	0.67	0.74	1.45	1.31	1.58	73.1	70.8	75.5
	Former smoker	0.90	0.86	0.94	2.10	1.90	2.34	68.7	66.2	70.8
	Current smoker	1.10	1.04	1.15	2.78	2.35	3.20	65.9	63.0	68.9

Fig. 6 *Scenario 4* – The upper panel shows the effect of smoking habit on symptom control score, reliever medication use (puffs/24 h) and exacerbation risk. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. The lower panel summarises the response to treatment after 12 months. Treatment arms ($n = 1500$ each, 500 iterations) include FP (250 µg b.i.d.), FP/SAL (250/50 µg b.i.d.), BUD/FOR (200/6 µg b.i.d.). Parameter estimates describing the treatment effect correspond to that of the mean dose during the maintenance phase. It should be highlighted that despite comparable reduction in reliever medication use after 12 months on combination therapy with ICS/LABA, FP/SAL results in significantly lower ACQ-5 scores ($p < 0.01$) and lower exacerbation rates ($p < 0.01$) than BUD/FOR. Further details on the clinical and demographic baseline characteristics of the simulated population and an overview of the statistical significance level of the comparisons between different groups and treatment arms at 12 months are summarised in Table S7. *ACQ-5* asthma control questionnaire, *BMI* body mass index, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist, *SAL* salmeterol



	Asthma control (ACQ-5)			Reliever use (puffs/24h)			Annualised exacerbating rate (%)		
Arm	Median	95% Confidence interval		Mean	95% Confidence interval		Median	95% Confidence interval	
FP (R)	0.41	0.41	0.40	2.09	2.17	2.01	79.8	78.9	80.8
FP (NR) > BUD/FOR	1.03	1.05	1.01	1.76	1.86	1.67	72.4	71.3	73.7
FP (NR) > FP/SAL	0.87	0.89	0.85	1.66	1.75	1.57	82.0	80.9	82.9
FP (NR) > FP (500 ug)	1.09	1.11	1.07	2.31	2.44	2.19	77.1	75.9	78.3

Fig. 7 *Scenario 6* – The upper panel shows ICS dose increase and treatment step-up in a real-world setting. The effect of increased ICS dose and transition to ICS/LABA combination therapy is assessed in patients who do not achieve adequate symptom control on ICS monotherapy. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. The lower panel summarises the response to treatment after 12 months. Treatment arms ($n = 8000$ each, 500 iterations) include FP (250 µg b.i.d.), FP (500 µg b.i.d.), FP/SAL (250/50 µg b.i.d.), BUD/FOR (200/6 µg b.i.d.). Parameter estimates describing the treatment effect correspond to that of the mean dose during the maintenance phase. Despite comparable reduction in reliever medication use after 12 months on combination therapy with ICS/LABA, FP/SAL results in significantly lower ACQ-5 scores and exacerbation rate than BUD/FOR ($p < 0.01$). Further details on the clinical and demographic baseline characteristics of the simulated population and an overview of the statistical significance level of the comparisons between different groups and treatment arms at 12 months are summarised in Table S9. Differences between treatments in patients with ACQ-5 > 1.5 at baseline are summarised in Fig. S2. *ACQ-5* asthma control questionnaire, *BMI* body mass index, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *FP(NR)* non-responder to FP monotherapy, *FP(R)* responder to FP monotherapy, *ICS* inhaled corticosteroid, *LABA* long-acting beta agonist, *SAL* salmeterol

allergies, small airway disease, and chronic rhinitis with nasal polyps. As this group of patients were excluded from the available clinical trials, the impact of such comorbidities has not been assessed. We do not anticipate, however, that these factors alter our conclusions regarding the effect of clinical and demographic baseline characteristics on treatment performance. It is also important to emphasise that for ethical reasons, data on the reliever medication use and incidence of exacerbation over a 12-month period cannot be obtained using placebo as a reference. Therefore, the models used for the purpose of the current simulations were based on ICS monotherapy, namely, fluticasone propionate. This means that estimates of treatment effect may differ from previously published studies, where treatment was evaluated over a shorter period of time or where placebo or other treatment options have been used. Further details on the main assumptions and limitations are summarised in Table S3.

CONCLUSIONS

Our investigation shows that interindividual differences in baseline ACQ-5, BMI, and smoking habit (treatable traits) alter treatment outcome and modify treatment performance, affecting symptom control levels, reliever medication use and exacerbation risk following maintenance therapy with ICS or ICS/LABA combination. This is compounded by the effect of additional clinical and demographic characteristics, which can independently alter immediate symptoms and/or long-term exacerbation risk, including age, sex, disease history and baseline FEV1p%, irrespective of treatment choice. The simulations also indicate that regular dosing with FP/SAL yields significantly lower symptom scores and exacerbation risk relative to BUD/FOR in patients who do not respond to ICS monotherapy. Of note is the benefit of FP/SAL in patients who are current smokers and/or obese. Such a difference may be explained by corticosteroid-specific properties, which vary between inhaled corticosteroids [41]. Consequently, these factors should be considered in clinical practice as a basis for personalised management of patients with moderate–severe asthma symptoms.

Author Contributions. Sven C. van Dijkman and Sean C. Oosterholt were involved in the analysis and interpretation of study data, drafting and critical revision of the manuscript; Ian Pavord, Dave Singh, Gabriel Garcia, Sourabh Fulmali and Anurita Majumdar were involved in the interpretation of study data, drafting and critical revision of the manuscript; Oscar Della Pasqua was involved in the conception/design and interpretation of study data, drafting and critical revision of the manuscript.

Funding. This investigation is part of the MASTER (Modelling Asthma TrEatment Responses) study, which has been funded by GSK (study no. 215310). GSK has also funded the Rapid Service and Open Access Fees.

Data Availability. Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Declarations

Conflict of Interest. Ian Pavord has received honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini and GSK, and payments for organising educational events from AstraZeneca, GSK, Sanofi/Regeneron and Teva; he has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK; he has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca, Teva and Chiesi; he has received a grant from Chiesi to support a phase 2 clinical trial in Oxford; he is co-patent holder of the rights to the Leicester Cough Questionnaire and has received payments for its use in clinical trials from Merck, Bayer and Insmed; and in 2014–2015 he was an expert witness

for a patent dispute involving AstraZeneca and Teva; Dave Singh has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GSK, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Synairgen, Teva, Theravance and Verona; Gabriel Garcia has participated in advisory boards for GSK, AstraZeneca, Sanofi, Novartis and Boehringer Ingelheim; he has received honoraria for speaking at sponsored meetings from GSK, Boehringer Ingelheim, AstraZeneca, Sanofi, Phoenix, and Novartis; and is a principal investigator in trials sponsored by GSK, Boehringer Ingelheim, AstraZeneca, Novartis, Sanofi, PPD, Zambon, Parexel, Covance, IQVIA, and Chiesi; Sean Oosterholt, Sven van Dijkman, Sourabh Fulmali, Anurita Majumdar and Oscar Della Pasqua are GSK employees and hold stocks/shares in GSK.

Ethical Approval. This article is based on in silico modelling and simulation and does not contain any new studies with human participants or animals performed by any of the authors. All clinical data used for the development and validation of the models describing individual symptom score trajectories, reliever medication use and time to first exacerbation, as well as those required for generating baseline characteristics for the virtual cohorts were derived from clinical trials, which have been performed according to the Declaration of Helsinki and were approved by the required ethics committee(s) and/or ethics review board(s). Reuse of the data for the purpose of the current investigation is in alignment with the terms of informed consent.

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