Adv Ther (2023) 40:4606–4625
https://doi.org/10.1007/s12325-023-02590-2

ORIGINAL RESEARCH

Understanding the Clinical Implications of Individual Patient Characteristics and Treatment Choice on the Risk of Exacerbation in Asthma Patients with Moderate–Severe Symptoms

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Received: April 7, 2023 / Accepted: June 21, 2023 / Published online: August 17, 2023

ABSTRACT

Introduction: The assessment of future risk has become an important feature in the management of patients with asthma. However, the contribution of patient-specific characteristics and treatment choices to the risk of exacerbation is poorly understood. Here we evaluated the effect of interindividual baseline differences on the risk of exacerbation and treatment performance in patients receiving regular maintenance doses of inhaled corticosteroids (ICS) or ICS/long-acting beta-agonists (LABA) combination therapy.

Methods: Exacerbations and changes to asthma symptoms 5-item Asthma Control Questionnaire (ACQ-5) were simulated over a 12-month period using a time-to-event and a longitudinal model developed from phase III/IV studies in patients with moderate–severe asthma (N = 16,282). Simulations were implemented to explore treatment performance across different scenarios, including randomised designs and real-world settings. Treatment options included regular dosing with ICS monotherapy [fluticasone propionate (FP)] and combination therapy [fluticasone propionate/salmeterol (FP/SAL) or budesonide/formoterol (BUD/FOR)]. Exacerbation rate was analysed using the log-rank test. The cumulative incidence of events was summarised stratified by treatment.

Results: Being a woman, smoker, having higher baseline ACQ-5 and body mass index

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-023-02590-2.

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(BMI) and lower forced expiratory volume in the first second (FEV_1) are associated with increased exacerbation risk ($p < 0.01$). This risk is bigger in winter because of the seasonal variation effect. Across the different scenarios, the use of FP/SAL resulted in a 10% lower annual incidence of exacerbations relative to FP or regular dosing BUD/FOR, independently of baseline characteristics. Similar differences in the annual incidence of exacerbations were also observed between treatments in obese patients (BMI $\geq$ 25–35 kg/m^2) ($p < 0.01$) and in patients who do not achieve symptom control on FP monotherapy.

Conclusions: Individual baseline characteristics and treatment choices affect future risk. Achieving comparable levels of symptom control whilst on treatment does not imply comparable risk reduction, as shown by the lower exacerbation rates in FP/SAL vs. BUD/FOR-treated patients. These factors should be considered as a basis for personalised clinical management of patients with moderate–severe asthma.

PLAIN LANGUAGE SUMMARY

The goal of this project was to demonstrate that individual baseline characteristics can affect the risk of exacerbation as well as the overall treatment response in patients receiving regular maintenance doses of inhaled corticosteroids, given as monotherapy or in combination with long-acting beta-agonists. Using computer simulations based on a drug–disease model previously developed from a large pool of patients with moderate–severe asthma symptoms (N = 16,282), we describe how demographic and clinical baseline patient characteristics at the time of treatment start correlate with the risk of exacerbation. Our results indicate that poor symptom control, limited lung function, obesity, smoking and sex are associated with significant increase in the incidence of asthma attacks. Such an effect is augmented in winter because of the contribution of seasonal variation. This analysis also allowed us to assess how different treatments modify or reduce the annual incidence of moderate to severe attacks. In addition, simulated scenarios showed that combination therapy with fluticasone propionate/salmeterol results in 10% fewer asthma attacks relative to budesonide/formoterol combination therapy. Such a difference may be associated with corticosteroid-specific properties, which vary between inhaled corticosteroids. Consequently, even though comparable level of immediate relief and symptom control may be achieved whilst on treatment, these effects do not imply the same long-term reduction in the risk of exacerbation. These factors should be considered as a basis for personalised clinical management of patients with moderate–severe asthma.

Keywords: Asthma exacerbation; Future risk; Symptom control; ACQ-5; Treatable traits; ICS/LABA combination therapy; Fluticasone propionate; Salmeterol; Clinical trial simulations

Key Summary Points

Why carry out this study?

The assessment of future risk is an important feature of the clinical management of patients with moderate–severe asthma symptoms and is dependent on multiple interacting factors, including the incidence of previous exacerbations, the presence of type 2 inflammation, and poor asthma control.

The effect of interindividual differences in baseline characteristics and asthma treatment choices on future risk is poorly understood.

Current clinical guidelines are based on a stepwise approach that relies primarily on symptom control, disregarding the influence that individual patient characteristics and treatment choices may have on long-term outcomes.

What was learned from the study?

Being a woman, smoking habit, and interindividual differences in baseline 5-item Asthma Control Questionnaire (ACQ-5), body mass index (BMI), and forced expiratory volume (FEV_1) alter the exacerbation risk, irrespective of treatment choice. This effect is further enhanced in winter because of seasonal variation.

After taking into account the contribution of interindividual baseline differences to exacerbation risk, it appears that regular dosing with fluticasone propionate/salmeterol (FP/SAL) results in a significantly lower exacerbation risk relative to fluticasone propionate (FP) or budesonide/formoterol (BUD/FOR), independently from baseline characteristics. This corresponds to 10% lower annual incidence of exacerbations.

Simulation scenarios in a real-world setting indicate that achieving comparable levels of symptom control whilst on treatment does not imply a comparable risk reduction. Such a difference may be associated with corticosteroid-specific properties, which vary between molecules.

INTRODUCTION

The assessment of future risk defined as exacerbation events and subsequent deterioration in lung function has become an important feature of the clinical management of patients with moderate–severe asthma symptoms [1–4]. Future risk is dependent on multiple interacting factors, including the incidence of previous exacerbations, the presence of type 2 inflammation, and poor asthma control [5, 6]. However, the interaction between individual patient characteristics and asthma treatment choices with regard to modification of future risk is poorly understood. This is an important gap, as clinical practice guidelines focus on strategies that emphasise symptom control, rather than the influence that individual patient characteristics and treatment choices have on long-term outcomes [7, 8]. Consequently, potential differences in treatment performance in terms of future risk reduction, which influences long-term outcomes, are also overlooked. An approach can be envisaged where predictors of risk could be used to personalise treatment.

Here, we expand on the concept of clinical phenotypes, which has been widely discussed with regard to patients with severe (refractory) eosinophilic asthma [9–11]. In contrast to this subgroup of patients, different arguments have been used to explain heterogeneity in response to treatment in patients with moderate–severe asthma, for which no phenotypical evidence exists to support the use of a different approach to treatment. Yet, there have been limited efforts to characterise in an integrated manner the effect of patient baseline characteristics (i.e. treatable traits) and treatment choices on both immediate response (i.e. symptom control) and future risk [12, 13]. Moreover, it is difficult to accurately estimate such a correlation in a real-world setting [14, 15].

An alternative approach is the use of in silico modelling and simulation, and in particular clinical trial simulations. This methodology has been widely applied for the evaluation of novel drugs in early and late stages of development, as well as a tool for evidence synthesis and optimisation of the therapeutic use of medicines

across different therapeutic areas [16–18]. However, its application in asthma and respiratory medicine is relatively new [19, 20]. Recently, Oosterholt and colleagues used a model-based meta-analysis to explore the influence of treatable traits on the overall risk of exacerbation in patients with moderate–severe asthma symptoms [21]. A significant effect of interindividual differences in BMI, smoking status, sex, and ACQ-5 at baseline on the overall exacerbation risk was reported. This effect was independent of treatment or other extrinsic factors (e.g. season). These results underscore that consideration should be given to individual characteristics beyond symptom control levels in order to properly personalise asthma treatment to achieve optimal long-term outcomes. Moreover, their findings show differences in the response to treatment, which appear to reflect the pharmacological properties (e.g., lung residence time, systemic absorption, glucocorticoid receptor affinity) and therapeutic index of different corticosteroids [22]. The choice of ICS can therefore influence long-term outcomes, including exacerbation risk, which may be crucial for individuals at higher risk despite achieving a comparable level of symptom control [23].

As the control of multiple concurrent factors is not feasible in a prospective randomised controlled study or in a retrospective observational cohort, the use of computer simulations including virtual patient cohorts in a controlled [also known as clinical trial simulations (CTS)] or in a real-world setting [also known as not-in-trial simulations (NITS)] represents a unique opportunity to characterise the influence of each factor, and disentangle it from treatment effect [16]. Here we apply CTS and NITS to evaluate the effect of treatable traits and treatment choice on exacerbation risk in patients with moderate–severe asthma symptoms taking into account the immediate response to treatment as assessed by ACQ-5. Using a cohort of virtual patients with baseline characteristics comparable to those enrolled in actual clinical trials, the incidence and time-to-first event, i.e. moderate or severe exacerbation, was assessed for a range of scenarios including a parallel, controlled study design and a real-world setting. The analysis is based on a time-to-event (TTE) model that describes the time to first exacerbation, and a longitudinal model that describes the individual symptom trajectories over time, considering the concurrent effect of different baseline covariate factors [17, 21].

METHODS

Study Subjects

The current investigation describes the results from computer modelling and simulations and as such does not involve human participants. Patient baseline characteristics used for the prediction of exacerbations and time course of symptom control scores were obtained from the pooled population enrolled in the clinical trials listed in the Supplementary Material, 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. Re-use of the data for the purpose of the current investigation is in alignment with the terms of the informed consent.

All clinical data used for the development and validation of the time-to-event and longitudinal models, 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).

Data Source

The data available for the development and evaluation of the statistical models used in the current analysis were obtained from nine clinical trials in adults with moderate–severe asthma (ADA109055, ADA109057, HZA113091, HZA115150, SAM40027, SAM40056, SAM40065, SAM40086, SAS115359), treated with regular fixed ICS dosing (not maintenance and reliever therapy) with fluticasone propionate (FP) monotherapy, combination therapy

with salmeterol (FP/SAL), or budesonide/formoterol (BUD/FOR). These studies were selected on the basis of the availability of accurate individual patient exacerbation event records, clinical and demographic baseline details (Table S1). The dataset includes 1816 observed exacerbation events (first only) from 16,282 adult subjects who were randomised to receive FP (n = 7490), FP/SAL (n = 8049) or BUD/FOR (n = 743) over a period of up to 1 year. An overview of the clinical study protocols along with treatment details and eventual deviations is shown in Table S2. Likewise, the data used for the development of the longitudinal model describing individual ACQ-5 trajectories consisted of a subset of the studies available for the implementation of the time-to-event model. Only those studies that had longitudinal ACQ-5 data (i.e., at baseline and throughout the course of treatment) were pooled for the purpose of the current analysis. An overview of the selected population is summarised in the Appendix, Supplementary Material.

Clinical Trial Simulations

Final parameters of the TTE model previously developed by Oosterholt and colleagues (Table 1) were used for the implementation of the simulation scenarios, which assess the potential implications of treatable traits and treatment choices on the risk of exacerbation [21]. In parallel, the time course of symptoms (ACQ-5) was evaluated using a longitudinal model based on a similar patient population. The TTE model is a fully parametric hazard (survival) model that describes the time to the first moderate or severe exacerbation, defined as the use of systemic corticosteroids for at least 3 days OR in-patient hospitalisation OR emergency department visit due to asthma requiring systemic corticosteroids. The predicted log hazard is a linear sum of functions of smoking status, ACQ-5 BMI, percentage predicted FEV_1 (FEV1p) at baseline and sex in relation to treatment choice, and a seasonal factor that includes the effect of winter. Similarly, the longitudinal model characterises the individual ACQ-5 trajectories, taking into account the effect of covariates. These models allow for an integrated estimation 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 interventions reflect the stepwise approach to the management of patients with moderate–severe asthma symptoms, i.e. starting with ICS monotherapy and progressing to regular ICS/LABA combination therapy. Only non-responders to ICS monotherapy were assigned to ICS/LABA. For scenarios in which treatment changes were necessary, response was defined as an improvement in symptom control scores, as predicted by the longitudinal model describing the individual ACQ-5 trajectories over the course of treatment (see Appendix, Supplementary Material for further details on model development and validation).

From a pharmacological perspective, these scenarios represent the effect of a drug with disease-modifying, bronchoprotective, anti-inflammatory properties (i.e. ICS) prior to the addition of a drug with primarily symptomatic, bronchodilatory properties (i.e. LABA). An outline of the clinical trial simulation workflow is shown in Fig. 1. Full details of the protocol design characteristics along with the key assumptions used for the evaluation of the effect of baseline characteristics and treatment choices on exacerbation risk are summarised in Table S4.

Simulation Scenarios

For each simulation scenario baseline characteristics were randomly sampled from 1500 patients from the pooled population of adults (N = 16,282) with moderate–severe asthma. Treatment was assumed to be independent of baseline characteristics and was assigned prior to the simulations. All scenarios included treatment for the period of 1 year, except for the scenario on the seasonal effect which had a duration of 6 months. Each scenario was repeated 500 times, and for each replicate, patient baseline characteristics were re-sampled from

Table 1 Parameter estimates of the final model describing the time to first exacerbation in patients with moderate–severe asthma

Covariate	Parameter[a]	Estimate	SE	RSE (%)	Bootstrap median (5^{th}–95^{th} percentiles)
	Base hazard (θ_{BASE})	0.188	0.0045	2.4	0.188 (0.170–0.206)
ACQ-5	$fHAZ_{ACQ\text{-}5}$	0.207	0.0629	30.4	0.199 (0.112–0.319)
	(fractional increase in hazard per unit ACQ-5)				
Sex	$fHAZ_{female}$	0.327	0.0831	25.4	0.325 (0.218–0.440)
	(fractional increase in hazard relative to male %)				
BMI	$fHAZ_{BMI}$	0.0279	0.007	25.2	0.029 (0.020–0.036)
	(fractional increase in hazard per kg/m^2)				
FEV_1	$fHAZ_{FEV1}$	− 0.00834	0.002	24.0	− 0.0083 (− 0.0118 to − 0.0045)
	(fractional change in hazard per % change in FEV_1)				
Smoking	$fHAZ_{current\ smoker}$	0.51	0.121	23.7	0.510 (0.297–0.732)
	(fractional increase in hazard relative to never smoked)				
	$fHAZ_{former\ smoker}$	0.268	0.0715	26.7	0.264 (0.146–0.419)
	(fractional increase in hazard relative to never smoked)				
Season	$fHAZ_{amplitude}$	0.304	0.0006	0.2	0.302 (0.252–0.358)
	(fractional change between season)				
	Phase shift (years)	0.27	0.0006	0.2	0.262 (0.234–0.306)
Treatment	$fHAZ_{BUD/FOR}$	0.321	0.106	33.0	0.334 (0.112–0.536)
	(fractional increase in hazard relative to FP)				
	$fHAZ_{FP/SAL}$	− 0.308	0.0348	11.3	− 0.311 (− 0.362 to − 0.251)
	(fractional increase in hazard relative to FP)				

The base hazard is described using FP monotherapy as the reference treatment. With permission from Oosterholt et al. [21]
ACQ-5 5-item Asthma Control Questionnaire, *BMI* body mass index, *BUD/FOR* budesonide/formoterol, FEV_1 forced expiratory volume, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol, *RSE* relative standard error, *SE* standard error

[a]Time-to-event model—the effects of baseline covariates, treatment and seasonal variation are described by an additive function to the base hazard. Point estimates are depicted by thetas (Θ): $Hazard = \theta_{BASE} * \left(1 + \theta_{previous\ smoker}\right) * (1 + \theta_{current\ smoker}) * (1 + (BMI - 27.6) * \theta_{BMI}) * (1 + (FEV1_P - 73) * \theta_{FEV1_P}) * \left(1 + (\text{ACQ-5}_{baseline} - 2) \cdot \theta_{ACQ-5}\right) * (1 + \theta_{FEMALE}) * \left(1 + \theta_{\frac{BUD}{FOR}}\right) * \left(1 + \theta_{\frac{FP}{SAL}}\right) * e^{\theta_{amp} \cdot \sin\left(calendar\ time + \theta_{phase}\right)}$

the pooled population. Kaplan–Meier estimates of the simulated exacerbation events were summarised both numerically and graphically per simulation scenario. Where appropriate, heat maps were used to explore the effects of individual covariates on the overall risk of exacerbation.

Figure 1 summarises the scenarios that were evaluated to disentangle the effect of relevant demographic and clinical baseline characteristics from that of treatment. 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); FEV1p—normal ($> 80\%$), mild/moderate (50–80%) and severe ($< 50\%$) airway obstruction.

Not-in-Trial Simulations (NITS)

The scenario describing the clinical management of adult patients with moderate–severe asthma in a real-life setting was randomly sampled from the pooled population, including a total of 8000 patients per intervention. Similarly to the procedures used for the CTS, each scenario was repeated 500 times, and patient baseline characteristics were re-sampled for each replicate [16]. 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. As reported by Oosterholt and colleagues [21], treatment was assumed to be independent of baseline characteristics and was assigned prior to the simulations (Fig. 1). All patients started on the same treatment (FP), and symptom control scores over time were generated for individual patients using the longitudinal model. An overview of the model parameter estimates is summarised in Table S3. In this real-life setting scenario, patients who did not achieve control after 3 months on ICS monotherapy 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. Kaplan–Meier estimates of the simulated exacerbation events were summarised both numerically and graphically per treatment arm.

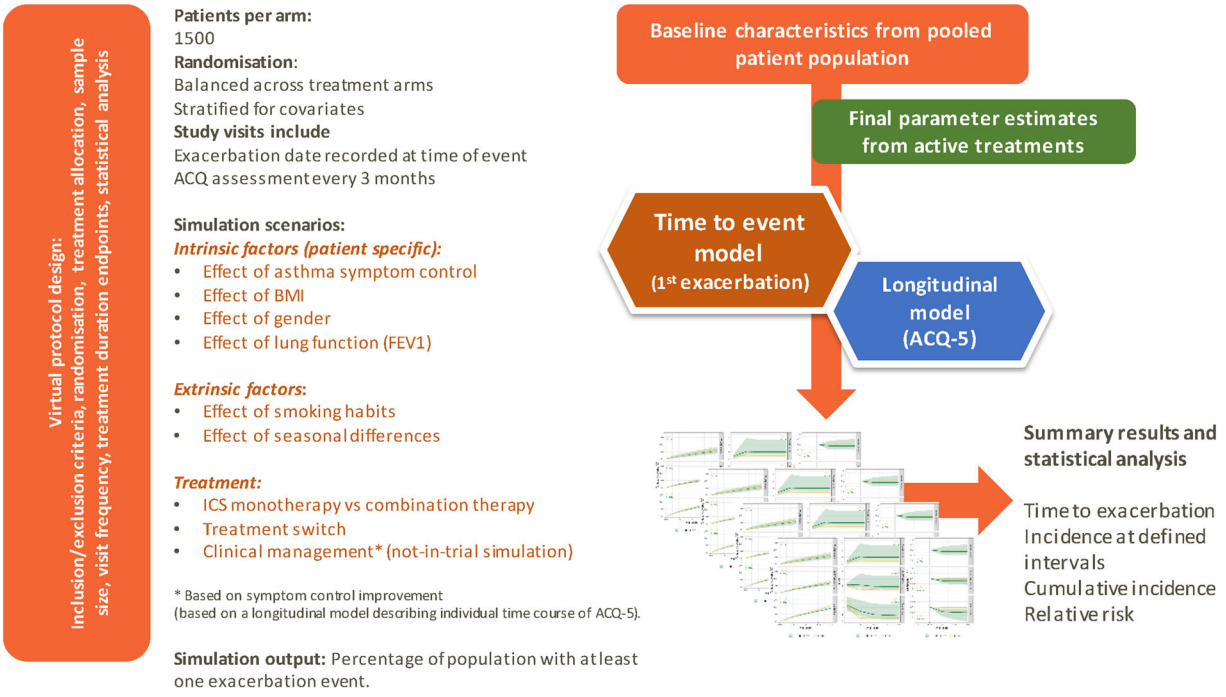
The statistical significance of the effect of baseline characteristics and treatment choices in each scenario was evaluated using cumulative exacerbation data based on a log-rank test (see Supplementary Material, Table S4 for further details) [24].

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 [25].

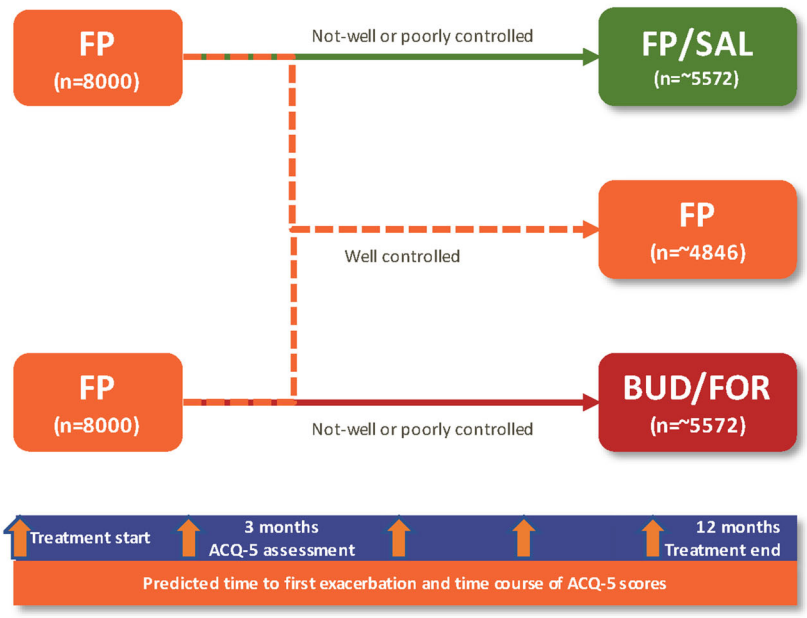
RESULTS

An assessment of the baseline risk of exacerbation for individual patients, which considers all factors concurrently (i.e. BMI, sex, smoking status, baseline ACQ-5, season and treatment), requires the use of the time-to-event model. Therefore, a heat map (Fig. 2) describing the contribution of demographic and clinical baseline characteristics to the risk of exacerbation was created to visualise the interaction between different baseline characteristics. The colour gradient clearly shows how risk varies with deteriorating symptom control (ACQ-5), lung function (%FEV1p) and increasing BMI. An overview of the baseline characteristics of the virtual patient cohorts included in each simulation scenario is presented in Tables S5 to S12 (Supplementary Material). Patient randomisation across the different treatment arms reflected the data distribution observed in previous clinical trials.

The influence of interindividual differences in baseline characteristics with the strongest effect on the risk of exacerbation (i.e. symptom control, body mass index, sex, and FEV_1) has been assessed for ICS monotherapy and combination therapy with FP/SAL and BUD/FOR after regular maintenance dosing.


Virtual protocol design:
Inclusion/exclusion criteria, randomisation, treatment allocation, sample size, visit frequency, treatment duration endpoints, statistical analysis
Patients per arm:
1500
Randomisation:
Balanced across treatment arms
Stratified for covariates
Study visits include
Exacerbation date recorded at time of event
ACQ assessment every 3 months
Simulation scenarios:
Intrinsic factors (patient specific):
Effect of asthma symptom control
Effect of BMI
Effect of gender
Effect of lung function (FEV1)
Extrinsic factors:
Effect of smoking habits
Effect of seasonal differences
Treatment:
ICS monotherapy vs combination therapy
Treatment switch
Clinical management* (not-in-trial simulation)
* Based on symptom control improvement
(based on a longitudinal model describing individual time course of ACQ-5).
Simulation output: Percentage of population with at least one exacerbation event.
Baseline characteristics from pooled patient population
Final parameter estimates from active treatments
Time to event model
(1st exacerbation)
Longitudinal model
(ACQ-5)
Summary results and statistical analysis
Time to exacerbation
Incidence at defined intervals
Cumulative incidence
Relative risk

(A)


FP
(n=8000)
Not-well or poorly controlled
FP/SAL
(n=~5572)
FP
(n=~4846)
Well controlled
FP
(n=8000)
Not-well or poorly controlled
BUD/FOR
(n=~5572)
Treatment start
3 months
ACQ-5 assessment
12 months
Treatment end
Predicted time to first exacerbation and time course of ACQ-5 scores

(B)

◀ **Fig. 1** **A** schematic diagram of the simulation scenarios based on a hazard model describing the time to first exacerbation and a longitudinal model describing the individual time course of ACQ-5 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 and obesity, BMI; scenario 3, sex—male vs. female; scenario 4, varying lung function as defined by FEV_1) and extrinsic factors (scenario 5, smoking habit; scenario 6, seasonal variation; scenario 7, treatment switch). **B** Outline of the scenario describing the clinical management of patients with asthma 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). 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). *ACQ-5* 5-item Asthma Control Questionnaire, *BMI* body mass index, *BUD/FOR* budesonide/formoterol, *FEV_1* forced expiratory volume, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol, *ICS* inhaled corticosteroids

The effect of ACQ-5 at baseline is summarised for ICS monotherapy and combination therapy with FP/SAL and BUD/FOR in Fig. 3. Cumulative exacerbation events (%) were fewer in patients with well-controlled and not well-controlled symptoms at baseline, vs. poor control ($p < 0.01$). In addition, these profiles show that differences between treatment arms are drug-specific and independent from symptom control level. FP/SAL results in significantly lower cumulative incidence of exacerbations at 1 year than regular dosing BUD/FOR (8–13%, $p < 0.01$), irrespective of baseline symptom control level.

A similar effect was observed for BMI (Fig. 4). A statistically significant increase in the cumulative incidence of exacerbations was found in obese (30 to < 35 kg/m^2) and extremely obese (35+ kg/m^2) relative those with normal weight (18.5 to < 25 kg/m^2) following treatment with BUD/FOR ($p < 0.01$). In contrast, no significant differences in exacerbation risk were observed between normal, overweight, and obese patients following treatment with FP or FP/SAL. A significant increase in the cumulative incidence of exacerbations was detected only for extremely obese patients ($p < 0.01$).

The effect of sex and treatment on exacerbation risk is shown in Fig. 5. The cumulative incidence of exacerbations differs significantly between male and female patients ($p < 0.01$). A comparable pattern was found when assessing the effect of airway obstruction, as measured by predicted FEV1 (%) (Fig. 6), which shows that exacerbation risk is higher in patients with mild/moderate (50–80%) and severe ($< 50\%$) obstruction, irrespective of treatment choice ($p < 0.01$). On the other hand, the exacerbation risk remains significantly lower following treatment with FP/SAL relative to FP monotherapy or BUD/FOR ($p < 0.01$). A summary of the results on the effect of smoking status, season and treatment switch is shown in Figs. S1, S2 and S3 (Supplementary Material).

The evaluation of the effect of baseline characteristics and treatment choice on exacerbation risk in a real-world setting reveals that achievement of comparable symptom control across treatment arms does not imply the same effect on exacerbation risk (Fig. 7). As shown by the time course of predicted ACQ-5 scores over the period of 12 months, clinical management of the patients who do not respond to FP monotherapy with FP/SAL resulted in a significantly lower exacerbation risk, as compared to BUD/FOR ($p < 0.01$). Patients remaining on FP monotherapy generally have lower ACQ-5 baseline values, i.e. patients who have adequate symptom control at baseline are more likely to remain on ICS monotherapy. Further details on the response to treatment of the total cohort population stratified by baseline asthma control level and treatment are presented in Figs. S4 and S5 (Supplementary Material).

DISCUSSION

Currently, clinical management of patients with asthma is based on a stepwise approach that relies primarily on symptom control; that is, it involves iterations in which symptoms, risk factors, treatment and response are

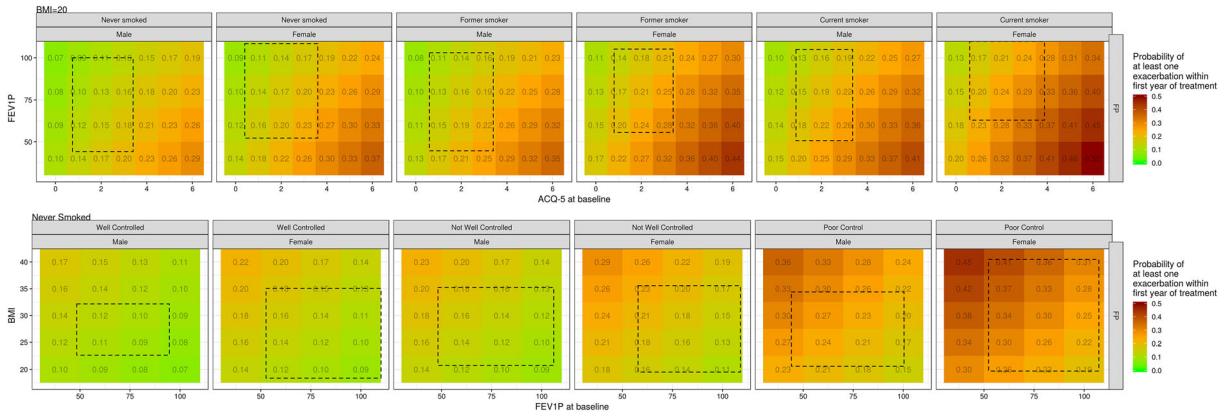
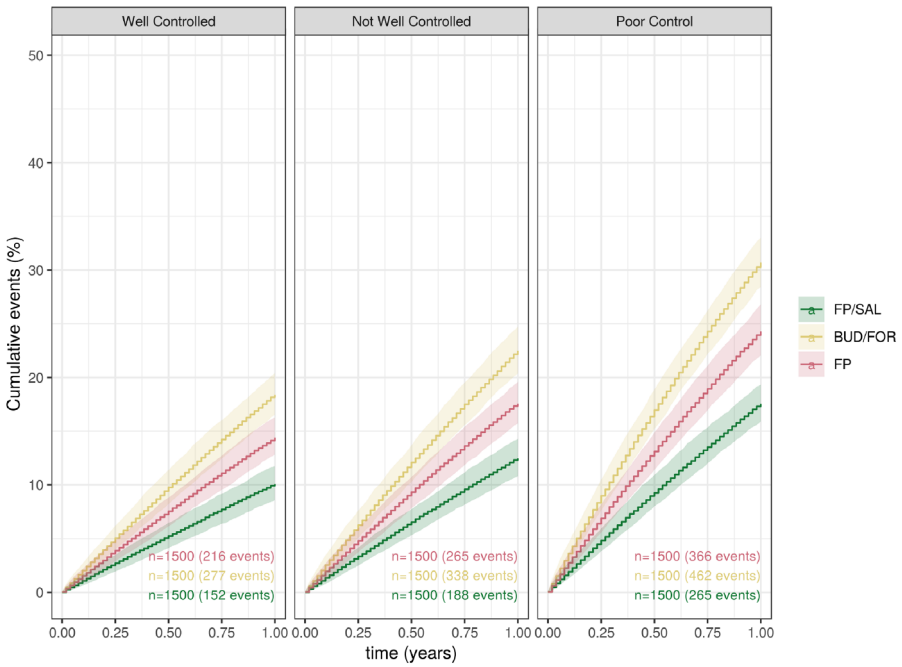


Fig. 2 Heat map describing the contribution of demographic and clinical baseline characteristics to the risk of exacerbation*. All simulation scenarios included in the current analysis have accounted for these factors and aimed at disentangling their effect from that of treatment with ICS/LABA combination therapy. As placebo-controlled studies for the period of 1 year are not feasible because of clinical and ethical reasons, all risk estimates are relative to ICS monotherapy. *Note: whilst heat maps allow visualisation of the effect of the interaction between some baseline characteristics, an assessment of the actual risk of exacerbation for individual patients which considers all these factors concurrently (i.e. ACQ-5, BMI, $FEV1_p$, sex, smoking status, season and treatment) requires the use of the time-to-event model (Table 1). Colour gradient from green to red reflects the change in the probability of an exacerbation in male and female patients across a range of symptom control (ACQ-5) and airway function ($FEV1_p$) values at baseline. Changes in probability are shown for patients who have different smoking habits, and a BMI of 20 kg/m^2 at baseline (upper panel), or those who have different symptom control level at baseline and never smoked (lower panel). The midpoint for the colour gradient was set to 0.25, which corresponds to the point estimate of the base hazard rate after FP treatment. Exacerbation incidence estimates were calculated not only taking into account the observed covariate distributions in the pooled patient population (dotted black lines) but also included covariate values across a clinically relevant range. Adapted with permission from [21]. *ACQ-5* 5-item Asthma Control Questionnaire, *BMI* body mass index, FEV_1 forced expiratory volume, *FEV1p* percentage predicted FEV_1, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol, *ICS/LABA* inhaled corticosteroids/long-acting beta-agonists

evaluated. Our analysis shows that long-term response to ICS/LABA, which was assessed in terms of future exacerbation risk, is greatly influenced by patients' characteristics as well as by the treatment choices. It provides insight into the magnitude of the effect of baseline ACQ-5, BMI, FEV_1, smoking status as well as sex and seasonal variation on exacerbation risk. It also allows separation of the treatment effect from these factors. For instance, the cumulative incidence of exacerbations at 1 year was lower for FP/SAL than regular dosing BUD/FOR (8–13%, $p < 0.01$), where patients with poor control at baseline (ACQ-5 > 1.5) appear to experience the largest effect (Fig. 3). 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 baseline symptom control varies across a wide range of ACQ-5 values. Moreover, the use of simulation scenarios indicates that transition to combination therapy with FP/SAL offers a significantly greater reduction in exacerbation risk than higher doses of FP monotherapy. This may be explained by the fact that at therapeutic doses, nearly maximal anti-inflammatory effect is achieved, with further increases in the exposure to ICS having a minor contribution to risk reduction. This is particularly important in those who are overweight or obese, as shown by the difference in the cumulative incidence.

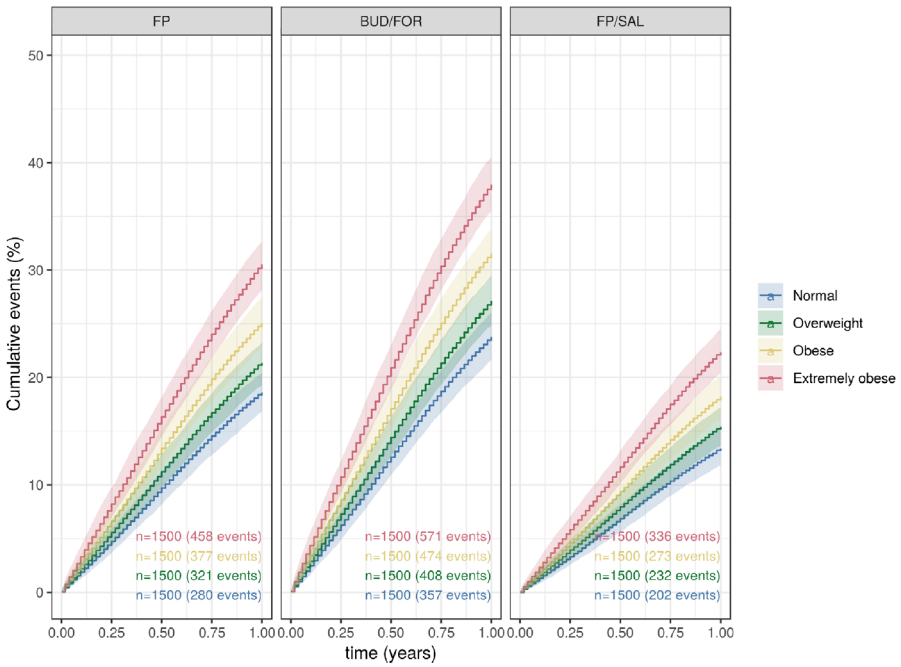
Given that loss of lung function over time in patients with asthma is partially driven by exacerbations, the evidence that differences in BMI, sex and smoking status affect future risk sheds



Cumulative incidence at 1 year	Well Controlled	Not Well Controlled	Poor Control
FP	14.4% (12.8% - 16.3%)	17.6% (15.7% - 19.6%)	24.3% (22% - 26.8%)
BUD/FOR	18.4% (16.6% - 20.4%)	22.5% (20.4% - 24.7%)	30.7% (28.4% - 33%)
FP/SAL	10.1% (8.6% - 11.7%)	12.5% (10.8% - 14.3%)	17.5% (15.9% - 19.3%)
Difference in cumulative incidence with FP/SAL	**Well Controlled**	**Not Well Controlled**	**Poor Control**
FP	4.3% (2% - 6.7%) **	5.1% (2.3% - 7.7%) **	6.7% (4.2% - 9.5%) **
BUD/FOR	8.3% (5.7% - 10.7%) **	10% (7.3% - 12.7%) **	13% (10.3% - 16.1%) **
Annualised exacerbation rate (AER)	**Well Controlled**	**Not Well Controlled**	**Poor Control**
FP	0.14 (0.13 - 0.16)	0.18 (0.16 - 0.2)	0.24 (0.22 - 0.27)
BUD/FOR	0.18 (0.17 - 0.21)	0.23 (0.2 - 0.25)	0.31 (0.29 - 0.33)
FP/SAL	0.1 (0.09 - 0.12)	0.12 (0.11 - 0.14)	0.18 (0.16 - 0.19)

Fig. 3 Scenario 1: Effect of baseline symptom control (ACQ-5) and treatment on exacerbation risk. Patients were stratified by baseline symptom control level according to the following categories: well controlled (ACQ-5 < 0.75), not well controlled (ACQ-5 ≥ 0.75 to ≤ 1.5), poorly controlled (ACQ-5 > 1.5). Upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with 95% of all simulated curves within the shaded area. Lower panels show the median and 95% prediction intervals for the cumulative incidence after 1 year, the treatment differences in cumulative incidence relative to FP/SAL combination therapy, and the annualised exacerbation rates for each treatment. Asterisks indicate the statistical significance level ($*p < 0.05$, $**p < 0.01$) based on the median log-rank test result over 500 iterations. Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S5. *ACQ-5* 5-item Asthma Control Questionnaire, *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol

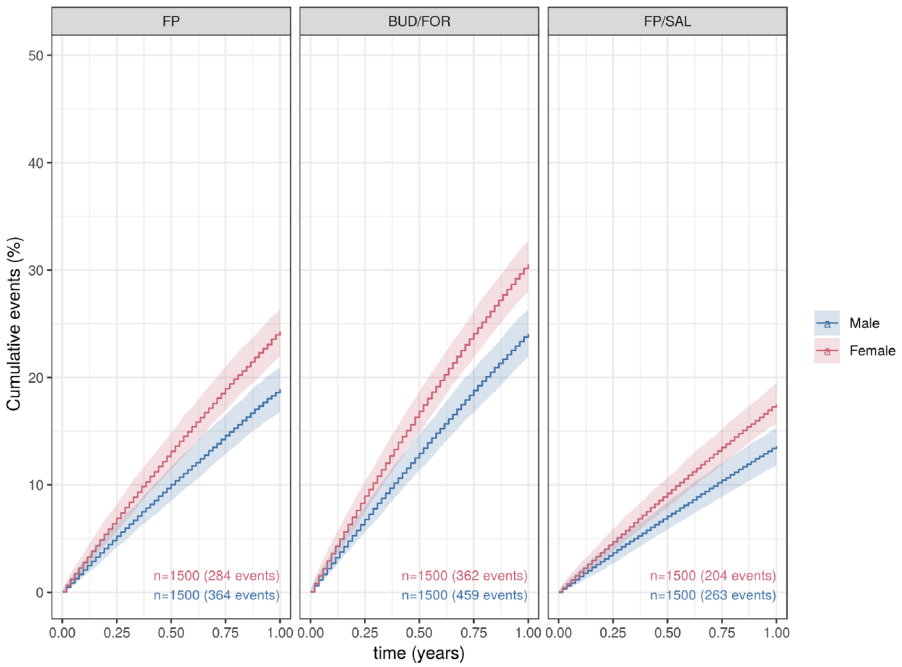
some light onto the ongoing debate about the heterogeneity in individual response to treatment and underlying clinical phenotypes [i.e. type 2 (T2) and non-T2 asthma] [26, 27]. Whilst clinical and demographic factors may not be directly associated with the complex interplay between



Cumulative incidence at 1 year	Normal	Overweight	Obese	Extremely obese
FP	18.6% (16.8% - 20.4%)	21.3% (19.3% - 23.2%)	25.1% (22.8% - 27.4%)	30.5% (28.2% - 32.7%)
BUD/FOR	23.8% (21.6% - 26%)	27.1% (24.8% - 29.4%)	31.5% (29.3% - 33.7%)	38% (35.5% - 40.5%)
FP/SAL	13.4% (11.9% - 15.3%)	15.4% (13.6% - 17.2%)	18.2% (16.2% - 20%)	22.4% (20.4% - 24.5%)
Difference in cumulative incidence with FP/SAL	**Normal**	**Overweight**	**Obese**	**Extremely obese**
FP	5.3% (2.6% - 7.6%) **	6% (3.4% - 8.5%) **	6.9% (3.9% - 10%) **	8% (4.7% - 11.2%) **
BUD/FOR	10.3% (7.5% - 13.2%) **	11.8% (9% - 14.6%) **	13.4% (10.3% - 16.6%) **	15.6% (12.1% - 18.9%) **
Annualised exacerbation rate (AER)	**Normal**	**Overweight**	**Obese**	**Extremely obese**
FP	0.19 (0.17 - 0.2)	0.21 (0.19 - 0.23)	0.25 (0.23 - 0.27)	0.31 (0.28 - 0.33)
BUD/FOR	0.24 (0.22 - 0.26)	0.27 (0.25 - 0.29)	0.32 (0.29 - 0.34)	0.38 (0.36 - 0.41)
FP/SAL	0.13 (0.12 - 0.15)	0.15 (0.14 - 0.17)	0.18 (0.16 - 0.2)	0.22 (0.2 - 0.25)

Fig. 4 Scenario 2: Effect of body mass index (BMI) and treatment on exacerbation risk. Patients were stratified by BMI according to the following 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). Upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with 95% of all simulated curves within the shaded area. Lower panels show the median and 95% prediction intervals for the cumulative incidence after 1 year, the treatment differences in cumulative incidence relative to FP/SAL combination therapy, and the annualised exacerbation rates for each treatment. Asterisks indicate the statistical significance level ($^*p < 0.05$, $^{**}p < 0.01$) based on the median log-rank test result over 500 iterations. Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S6. *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol

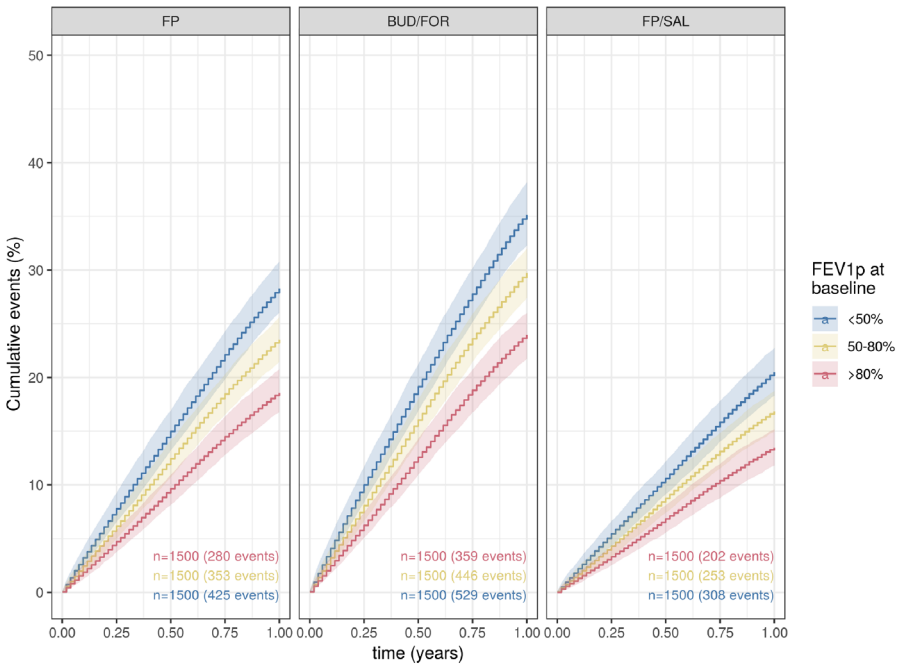
airway inflammation and airway remodelling, our results suggest that the baseline characteristics identified as covariates on the base hazard parameter describing the risk of exacerbations in moderate to severe asthma could serve as a proxy for airway hyperresponsiveness status.



Cumulative incidence after 1 year	Male	Female
FP	18.9% (16.8% - 20.9%)	24.3% (22% - 26.3%)
BUD/FOR	24.1% (22% - 26.2%)	30.6% (28% - 32.7%)
FP/SAL	13.6% (11.8% - 15.3%)	17.5% (15.6% - 19.4%)
Difference in cumulative incidence with FP/SAL	Male	Female
FP	5.3% (2.8% - 7.9%) **	6.8% (3.9% - 9.4%) **
BUD/FOR	10.5% (7.7% - 13.3%) **	13% (10.1% - 16%) **
Annualised exacerbation rate (AER)	Male	Female
FP	0.19 (0.17 - 0.21)	0.24 (0.22 - 0.26)
BUD/FOR	0.24 (0.22 - 0.26)	0.31 (0.28 - 0.33)
FP/SAL	0.14 (0.12 - 0.15)	0.18 (0.16 - 0.2)

Fig. 5 Scenario 3: Effect of sex and treatment on exacerbation risk. Patients were stratified by sex (male and female). Upper panel shows percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with 95% of all simulated curves within the shaded area. Lower panels show the median and 95% prediction intervals for the cumulative incidence after 1 year, the treatment differences in cumulative incidence relative to FP/SAL combination therapy, and the annualised exacerbation rates for each treatment. Asterisks indicate the statistical significance level ($^{*}p < 0.05$, $^{**}p < 0.01$) based on the median log-rank test result over 500 iterations. Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S7. *BUD/FOR* budesonide/formoterol, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol

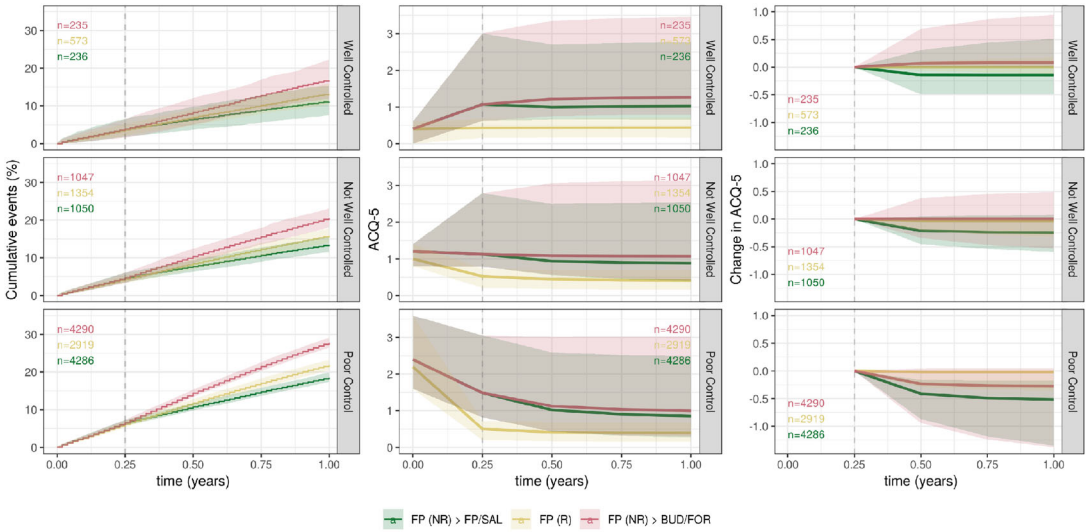
Even though the benefits of ICS/LABA in this group of patients have been evaluated extensively in different investigations [28–30], using simulation scenarios it was possible to show that FP/SAL does not only offer acute symptomatic relief but may also have disease-modifying properties, reducing the incidence of exacerbations. Whilst the definition of disease modification may vary, a disease-modifying treatment can be described as a sustained



Cumulative incidence after 1 year	FEV1p <50%	FEV1p 50-80%	FEV1p >80%
FP	28.3% (26% - 30.8%)	23.5% (21.4% - 25.6%)	18.5% (16.7% - 20.8%)
BUD/FOR	35.1% (32.2% - 38.1%)	29.7% (27.4% - 32%)	24% (21.7% - 26%)
FP/SAL	20.5% (18.3% - 22.7%)	16.9% (14.9% - 18.7%)	13.5% (11.8% - 15.1%)
Difference in cumulative incidence with FP/SAL	FEV1p <50%	FEV1p 50-80%	FEV1p >80%
FP	7.8% (4.4% - 10.9%) **	6.6% (3.9% - 9.4%) **	5.1% (2.7% - 8%) **
BUD/FOR	14.7% (11.1% - 18.2%) **	12.8% (9.6% - 15.9%) **	10.5% (7.6% - 13.4%) **
Annualised exacerbation rate (AER)	FEV1p <50%	FEV1p 50-80%	FEV1p >80%
FP	0.28 (0.26 - 0.31)	0.24 (0.22 - 0.26)	0.19 (0.17 - 0.21)
BUD/FOR	0.35 (0.32 - 0.38)	0.30 (0.27 - 0.32)	0.24 (0.22 - 0.26)
FP/SAL	0.21 (0.18 - 0.23)	0.17 (0.15 - 0.19)	0.13 (0.12 - 0.15)

Fig. 6 Scenario 4: Effect of airway obstruction, as assessed by predicted FEV1 (%) and treatment on exacerbation risk. Patients were stratified by predicted FEV1 (%) according to the following categories: normal (> 80%), mild/moderate (50–80%), and severe (< 50%) obstruction. Upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with 95% of all simulated curves within the shaded area. Lower panels show the median and 95% prediction intervals for the cumulative incidence after 1 year, the treatment differences in cumulative incidence relative to FP/SAL combination therapy, and the annualised exacerbation rates for each treatment. Asterisks indicate the statistical significance level ($^{*}p < 0.05$, $^{**}p < 0.01$) based on the median log-rank test result over 500 iterations. Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S8. *BUD/FOR* budesonide/formoterol, *FEV*$_1$ forced expiratory volume, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol

reduction in symptoms and disease activity beyond the immediate or temporary effects of an intervention [31]. Our results showed that initiation of treatment with FP/SAL in patients with poor symptom control not responding to FP monotherapy resulted in approximately



Cumulative incidence after 1 year	Well Controlled	Not Well Controlled	Poor Control
FP (R)	13% (10.2% - 15.7%)	15.4% (13.9% - 17.1%)	21.5% (19.9% - 23.2%)
FP (NR) > BUD/FOR	16.7% (12% - 21.5%)	20.1% (17.9% - 22.2%)	27.5% (26.1% - 29.1%)
FP (NR) > FP/SAL	11.2% (7.7% - 15.7%)	13% (11.3% - 14.8%)	18.3% (16.9% - 19.6%)
Difference in cumulative incidence with FP(R) →FPSAL	**Well Controlled**	**Not Well Controlled**	**Poor Control**
FP (R)	1.8% (2.5% - 0%)	2.4% (2.6% - 2.3%)	3.2% (3% - 3.6%)
FP (NR) > BUD/FOR	5.5% (4.3% - 5.8%)	7.1% (6.6% - 7.4%) **	9.2% (9.2% - 9.5%) **
Annualised exacerbation rate (AER)	**Well Controlled**	**Not Well Controlled**	**Poor Control**
FP (R)	0.13 (0.10 - 0.16)	0.15 (0.14 - 0.17)	0.22 (0.20 - 0.23)
FP (NR) > BUD/FOR	0.17 (0.12 - 0.22)	0.20 (0.18 - 0.22)	0.28 (0.26 - 0.29)
FP (NR) > FP/SAL	0.11 (0.08 - 0.16)	0.13 (0.11 - 0.15)	0.18 (0.17 - 0.20)

Fig. 7 Not-in-trial simulation describing the effect of symptom control level and treatment on exacerbation risk. Upper panel shows the predicted median cumulative incidence of exacerbations (left), time course of asthma symptom control scores (centre) and change in ACQ-5 (right) over the period of 12 months for a virtual cohort of 8000 patients allocated per treatment arm at the start of the study. The numbers of patients in each category are given as *n* values. R (responder) and NR (non-responder) indicate patients reaching or not reaching adequate symptom control (i.e. a minimum ACQ-5 score of 0.75) at 3 months, respectively. Exacerbation risk refers to moderate and severe events, defined as the use of systemic corticosteroids for ≥ 3 days OR in-patient hospitalisation OR emergency department visit due to asthma requiring systemic corticosteroids. Vertical dotted lines show the time when patients who had not achieved symptom control on FP switched to FP/SAL or BUD/FOR. Shaded areas indicate 95% confidence intervals. Lower panels show the median and 95% prediction intervals for the cumulative incidence after 1 year, the treatment differences in cumulative incidence relative to those who switched to FP/SAL combination therapy, and the annualised exacerbation rates for each treatment. Asterisks indicate the statistical significance level ($^{*}p < 0.05$, $^{**}p < 0.01$) based on the median log-rank test result over 500 iterations. Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S12. *ACQ-5* 5-item Asthma Control Questionnaire, *BUD/FOR* budesonide/formoterol, FEV_1 forced expiratory volume, *FP* fluticasone propionate, *FP/SAL* fluticasone propionate/salmeterol, *ICS* inhaled corticosteroids

3.2% reduction in the incidence of exacerbations per year relative to those responding to ICS monotherapy. Such an effect appeared to be drug-specific, as the transition to BUD/FOR did not translate into a reduction in exacerbation risk relative to FP monotherapy. This was corroborated by the effect of FP/SAL on symptom control level. Treatment with FP/SAL led to a larger proportion of patients (42%) achieving symptom improvement (i.e. ACQ-5 > 0.5) compared to BUD/FOR (30%).

Finally, our analysis illustrates that baseline characteristics affect base hazard rate and as such contribute to the instantaneous risk but are not predictive of the overall long-term response to an intervention, which is greatly determined by treatment. Indeed, demographic and clinical baseline characteristics in non-responders to FP do not differ significantly from patients on combination therapy. This implies that individual future risk at the time of diagnosis will be miscalculated if only baseline characteristics are used to predict treatment response.

From a methodological perspective, we recognise that to address the main research question from this investigation one should distinguish the contribution of multiple interacting factors to the instantaneous risk of exacerbation, including baseline covariates, trial design and treatment type. Whilst control or stratification of all these factors may not be feasible in a prospective study, CTS offer an opportunity to stratify and eventually offset the effect of confounding or uncontrolled factors [31–34]. Similarly, any attempt to use retrospective data will be fraught with difficulties, as one needs to consider the effect of censoring and other deviations, which cannot be easily accounted for during data analysis.

Our work has some limitations. Consequently, assumptions had to be made regarding the generalisability of the findings from the different simulation scenarios, as similar protocol conditions may not be easily implemented or controlled in a real-life setting. An overview of the main assumptions and limitations is summarised in Table S4. As a result of ethical reasons, data on the incidence of exacerbation following withdrawal of treatment or use of placebo administration over 12 months is not available. Therefore, a reference intervention had to be defined in order to model the effect of the baseline covariates and treatment choices on exacerbation risk. Moreover, as ICS dose was not a covariate in the TTE model; treatment comparisons were performed using the mean and/or mode dose level used during the maintenance phase of treatment. This was based on the underlying dose–response relationships of FP and BUD [21, 35–37]. As currently used ICS doses yield nearly maximum pharmacological effect, the impact of varying dose level on basal hazard was assumed to be minor. In fact, here we applied the principles endorsed by Beasley and colleagues [38]. From a statistical perspective, we have also assumed no carryover effect when treatment was switched. In addition, as transition from FP to FP/SAL or BUD/FOR was implemented by design, i.e. switching at a prespecified time, adjustment or correction in estimates was not deemed necessary [34].

The predicted differences in exacerbation risk reduction following treatment with ICS/LABA combination therapies, which seemed to differ from mean estimates of treatment effect in previously published reports [39–41], were also carefully scrutinised. A few points need to be considered to understand such a discrepancy. First, it should be noted that randomisation of patients to different treatment arms does not necessarily provide a balanced distribution of all relevant factors that may affect treatment response (i.e. exacerbation events). In fact, baseline risk is not a criterion for inclusion into a trial. Consequently, it is plausible to have cohorts whose baseline characteristics look comparable but have a different exacerbation risk level at baseline. This is illustrated by the heat maps in Fig. 2, which show that the effect of treatment on risk reduction (i.e. reduction in hazard) is comparable across patients with different baseline characteristics. Second, the short duration and relatively small number of events (i.e. exacerbations) observed in each single study may result in imprecise estimates of the treatment effect. These results are often extrapolated to describe annualised exacerbation rates, which may lead to poor generalisability of the estimates to a larger population. By

contrast, the model used for the simulations is based on combined trials that have longer duration, allowing prediction of exacerbation rates at shorter or longer intervals, which are likely to be more precise than the results observed in single, shorter clinical trials. Third, the eventual confounding or selection bias associated with the large, but yet potentially limited pool of studies available for the investigation. This has been substantially dismissed following the evaluation of the predictive performance of the model including additional data from 697 patients receiving BUD/FOR (4.5/160 μg two inhalations bid) and 693 patients receiving FP/SAL (50/250 μg one inhalation bid) who were enrolled into study SAM40040 [42]. This study was not available at the time of model development. This additional data increased the sample size of both treatment groups and corroborated the findings in the original analysis, i.e. that the effect of FP/SAL on exacerbation risk is significantly different from BUD/FOR ($p < 0.01$). The visual predictive check, including the observed exacerbations over 12 months along with the model-predicted 95% confidence intervals, is shown in Fig. S6. This was complemented by a propensity score matching (PSM) [43, 44]. Propensity scores are often used in observational research to construct an artificial control group, which matches subjects with similar propensity scores in both treatment and control, so that potential confounding is reduced. As it can be seen in Fig. S7, comparison of the survival (observed exacerbation events) in a subset of perfectly matched patients reveals similar or slightly larger differences between treatment arms (FP/SAL vs. BUD/FOR). These results show that the findings obtained with the full dataset are unlikely to be caused by confounding. Moreover, this was corroborated by the calculated E-value, i.e. an alternative approach to sensitivity analyses for unmeasured confounding in observational studies [45], which indicates how strong the unmeasured confounding should be to refute the observed results.

CONCLUSIONS

Interindividual differences in sex, baseline ACQ-5, BMI, FEV_1, and smoking habit (treatable traits), as well as season alter the exacerbation risk, irrespective of treatment choice. Our investigation also shows that regular dosing with FP/SAL yields a significantly lower exacerbation risk relative to FP or BUD/FOR, independently from baseline characteristics. Of note is the exacerbation risk reduction observed in overweight and obese patients receiving FP/SAL. Most importantly, simulation scenarios in a real-world setting indicate that achieving comparable levels of symptom control whilst on treatment does not imply a comparable risk reduction. Such a difference may be associated with corticosteroid-specific properties, which vary between inhaled corticosteroids [22]. Consequently, patients showing clinically comparable levels of immediate relief and symptom control may not achieve the same long-term reduction in exacerbation risk. These factors should be considered in clinical practice as a basis for personalised management of patients with moderate–severe asthma symptoms.

ACKNOWLEDGEMENTS

We would like to thank the clinical experts for their input into this work. We also would like to acknowledge the support from Dr Shuying Yang (Clinical Pharmacology Modelling and Simulation, GSK, UK) and Prof Li Wei (Department of Policy and Practice, School of Pharmacy, University College London, UK) for their invaluable statistical insights. Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

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

Author Contributions. Sean Oosterholt was involved in the analysis and interpretation of study data, drafting and critical revision of the manuscript; Abhijith PG was involved the design of the study and interpretation of study data, drafting and critical revision of the manuscript; Ian Pavord, Dave Singh, and Gabriel Garcia 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.

Disclosures. 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, and is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC); 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, Abhijith PG and Oscar Della Pasqua are GSK employees and hold stocks/shares in GSK.

Compliance with Ethics Guideline. 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 time-to-event and longitudinal models, as well as those required for generating baseline characteristics for the virtual cohorts 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). Re-use of the data for the purpose of the current investigation is in alignment with the terms of informed consent.

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

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