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ORIGINAL ARTICLE

Modelling ASthma TrEatment Responses (MASTER): Effect of individual patient characteristics on the risk of exacerbation in moderate or severe asthma: A time-to-event analysis of randomized clinical trials

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Aims: There is limited understanding of how clinical and demographic characteristics are associated with exacerbation risk in patients with moderate-to-severe asthma, and how these factors correlate with symptom control and treatment response. Here we assess the relationship between baseline characteristics and exacerbation risk during regular dosing with inhaled corticosteroids (ICS) monotherapy or in combination with long-acting beta2-agonists (ICS/LABA) in clinical trial patients with varying levels of symptom control, as assessed by the asthma control questionnaire (ACQ-5).

Methods: A time-to-event model was developed using pooled patient data ($N = 16\,282$) from nine clinical studies [Correction added on 26 July 2023, after first online publication: The N value in the preceding sentence has been corrected in this version.]. A parametric hazard function was used to describe the time-to-first exacerbation. Covariate analysis included the assessment of the effect of seasonal variation, clinical and demographic baseline characteristics on baseline hazard. Predictive performance was evaluated by standard graphical and statistical methods.

Results: An exponential hazard model best described the time-to-first exacerbation in moderate-to-severe asthma patients. Body mass index, smoking status, sex, ACQ-5, % predicted forced expiratory volume over 1 s (FEV_1p) and season were identified as statistically significant covariates affecting baseline hazard irrespective of ICS or ICS/LABA use. Fluticasone propionate/salmeterol (FP/SAL) combination therapy resulted in a significant reduction in the baseline hazard (30.8%) relative to FP monotherapy.

Conclusions: Interindividual differences at baseline and seasonal variation affect the exacerbation risk independently from drug treatment. Moreover, it appears that even when a comparable level of symptom control is achieved in a group of patients, each individual may have a different exacerbation risk, depending on their baseline characteristics and time of the year. These findings highlight the importance of personalized interventions in moderate-to-severe asthma patients.

Prof. Oscar Della Pasqua is the principal investigator of this study.

KEYWORDS
asthma exacerbation, asthma symptom control, fluticasone propionate/salmeterol combination therapy, inhaled corticosteroids, patient characteristics, time-to-event modelling

1 | INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways that affects over 350 million people worldwide.[1,2] Even though evolving understanding of the pathophysiology of asthma and airway inflammation has provided insight into the role of contributing factors to the clinical presentation of the disease, most asthma patients experience ongoing symptoms, which in turn can lead to interruption of daily activities and poor quality of life.[3–6] Of note is the risk of exacerbation, which may lead to hospitalization.

From a clinical perspective, the goal of asthma treatment is, therefore, to achieve and maintain asthma control and to reduce the future risk of exacerbations. Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of persistent asthma. Treatment with ICS controls asthma symptoms, improves quality of life (QoL) and lung function, decreases airway hyperresponsiveness, controls airway inflammation, and reduces the frequency and severity of asthma exacerbations, thereby reducing asthma morbidity and the need for reliever medication (e.g., short-acting beta agonists [SABA]). In patients who are symptomatic on ICS alone, add-on therapy with another controller, in particular a long-acting beta2-agonist (LABA) is preferred to increasing the dose of ICS to achieve asthma control.[7–9]

Control of asthma is monitored by the level of current control (or impairment) and long-term effects on exacerbations, progressive impairment of lung function, and medication side effects. Consequently, achieving adequate asthma control should be a proxy for future risk of exacerbations, improvement or deterioration in QoL as well as SABA use. However, despite the availability of treatments and published guidelines, patients may have asthma that is not well controlled. This may be partly explained by interindividual differences (i.e., patient characteristics) in response to triggers and varying airway hyperresponsiveness, as evidence exists of different clinical phenotypes.[10–13] On the other hand, different approaches have been proposed for the treatment of asthma, which do not fully take into account the nature of the underlying inflammatory response or the differences in the pharmacokinetic-pharmacodynamic properties of the currently available inhaled corticosteroids.[14–16]

Whilst there have been efforts to identify opportunities for personalization of treatment across the adult population with moderate and severe asthma symptoms,[17–19] very few investigations have assessed the effect of interindividual differences in baseline characteristics on the maintenance of asthma control and future risk of exacerbation. Moreover, these studies are based on small sample sizes, which may not be easily generalized. In fact, to date there are no reports describing in a strictly quantitative manner how baseline characteristics associate with future risk.

Large cohorts and individual patient-level data are required to ensure accurate assessment of the putative correlations and their predictive performance. In addition, there is limited understanding of how interindividual differences in baseline characteristics affect the overall response to treatment.

The current investigation is part of MASTER (Modelling AStthma TrEatment Responses), a broader initiative aimed at the identification of opportunities for personalizing interventions in adults with moderate or severe asthma. The approach relies on the availability of high-quality data from numerous randomized controlled trials, in which patients were assigned to different interventions. The ultimate goal is to optimize the clinical management of patients, improving asthma control, reducing exacerbation risk and the use of reliever

What is already known about this subject

- Symptom control is a critical step in the management of patients with moderate-to-severe asthma receiving inhaled corticosteroids as monotherapy or in combination with long-acting beta agonists.
- Whilst clinical guidelines focus on the role of different treatment choices for achieving symptom control, limited attention has been given to individual differences in patient characteristics at the start of treatment.
- Parametric time-to-event models have been used in different therapeutic areas to evaluate drug-specific properties, discriminating treatment effect from that of disease- or patient-related characteristics.

What this study adds

- Model-based analysis of pooled clinical trial data allowed the characterization of the relationship between baseline characteristics and the risk of exacerbation in patients with moderate or severe asthma.
- In addition to the effect of interindividual differences in baseline BMI, smoking status, sex, ACQ-5 and FEV_1p, to instantaneous risk, our analysis showed that seasonal variation also affects the risk of asthma exacerbation, independently from treatment.
- These results suggest that the clinical management of asthma based on symptom control only is not optimal. Individual baseline characteristics should be considered to ensure adequate, personalized interventions.

medication.[20] Here we focus on the methodology for the development of a hazard model and its application as a tool for predicting the effect of individual patient characteristics and treatment choice on the risk of exacerbation. More specifically, we aim to develop and evaluate the performance of a time-to-event (TTE) model describing the risk of exacerbation following administration of fluticasone propionate as monotherapy (FP) and in combination with salmeterol (FP/SAL), and budesonide-formoterol combination therapy (BUD/FOR) to patients with moderate or severe asthma. This approach provides a parametric representation of the event rate (incidence) along with the underlying hazard.[21,22] In addition, the availability of such a TTE model will allow systematic evaluation of the effect of multiple contributing factors to the risk of exacerbation, disentangling drug-specific from patient-related effects.[23]

2 | METHODS

2.1 | Data source

The data used for this analysis were obtained from nine clinical trials (ADA109055, ADA109057, HZA113091, HZA115150, SAM40027, SAM40056, SAM40065, SAM40086, SAS115359). The selection of these data was based on the requirement to have accurate individual patient exacerbation event records, clinical and demographic baseline details (Table A1). It should be noted that given the importance of generalizing the results from this analysis to clinical practice, both double–blind and open label protocols were considered in scope. Moreover, in order to account for seasonal variation in asthma symptoms and exacerbations, studies were included in which treatment lasted for at least 24 weeks. Additional study selection criteria for the time-to-exacerbation analysis included: studies in which asthma symptom scores as assessed by ACQ-5 were prioritized and integrated with individual patient data where ACQ-5 was assessed only at baseline. Finally, the analysis population was only to include patients aged 18 years or older with accurate treatment records. It includes 1816 observed exacerbation events (first only) from 16 282 subjects who were randomized 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 A1. A list of the full inclusion and exclusion criteria along with the protocol definition of an exacerbation are presented in Tables S1 and S2. In a subsequent step, data from patients assigned to the usual care arm in study HZA115150, which were treated with either beclomethasone monotherapy or beclomethasone and formoterol combination therapy were used to assess model consistency and generalizability. This was complemented by inclusion of additional data on combination therapy with FP/SAL ($n = 693$) and BUD/FOR ($n = 697$) from the Excel study (SAM40040).[24] All patients enrolled into the selected clinical trials have given informed consent for participation. The terms of consent include the scope of the investigation presented here.

2.2 | Analysis population

From a total pool of 16 282 subjects, all had accurate treatment records, baseline asthma symptom control score (ACQ-5, when available) and demographic data. The majority were of White/Caucasian heritage ($n = 8991$, 54.9%), while the next highest represented group was African American/African heritage ($n = 1581$, 9.7%). The mean age was 45.4 years old with a range of 18–91 years old. A total of 1712 patients were ≥65 years of age (10.5%). An overview of the baseline demographic and clinical characteristics of the pooled patient population included in the analysis is summarized in Table S3. Histograms describing the distribution of relevant baseline clinical and demographic characteristics were used to assess the homogeneity of the patient population across the different studies. A summary of the distributions stratified by study and treatment arm is shown in Figures S1 and S2, respectively.

Given that the individual studies did not record the same baseline variables, for the purposes of this analysis individual covariate values were imputed where missing (88.8% baseline ACQ-5, 6.8% baseline BMI, 4.6% smoking status, 63.6% FEV_1p, 67.0% PEF, 13.9% asthma duration and 84.6% previous use of inhaled corticosteroids), where appropriate. For continuous covariates, missing values for an individual patient were imputed as the median value for the study population while for categorical covariates the most frequent value was used. In view of the large sample size in this aggregated population, the use of this imputation approach should provide unbiased estimates of the covariate effect, even in cases where missing data may correspond to a significant proportion of the total population (e.g., baseline ACQ–5, FEV_1p). For completeness, the potential influence of missing baseline covariate data was further evaluated using a range of scenarios, including resampling, bootstrapping and sensitivity analysis.

In contrast, missing information on the treatment initiation and ending were imputed based on protocol treatment initiation and ending (i.e., relative to reported study visit dates and times). Patients were excluded if details on the treatment received were not available or the date and time of treatment initiation and ending could not be imputed. Similarly, individual records were excluded if missing visit dates and times could not be imputed based on protocol visit dates and times. Values were also to be excluded from the analysis based on inconsistency or a documented error. The absence of the clinical event of interest (i.e., exacerbation) was not treated as missing data. If exacerbations did not occur within the observation window defined in the original study protocol, the information from these patients was right censored to the maximum time or duration of the study.

2.3 | Time-to-event model development

Given the scope of the analysis, initially data was pooled together, irrespective of pharmacological treatment or dose level. Prior to model development, an exploratory evaluation was performed using a Kaplan–Meier estimator, in combination with a range of parametric and semiparametric models.[20] This exploratory step also served as

basis for further assessment of the assumptions underpinning this individual-level model-based meta-analysis (e.g., proportional hazard, constant relative hazard, comparable adherence to treatment). It also provided insight into potential limitations (e.g., fewer studies in the southern hemisphere) and the need for additional assumptions (e.g., non-informative dropout). Further details on the assumptions supporting this investigation and implications for model development are presented in Table S4.

Subsequently, a parametric hazard model including only data from FP-treated patients (i.e., reference treatment) was found to best describe the time-to-first exacerbation. As per standard practice in nonlinear mixed effects modelling, the available data were randomly split into two subsets to ensure evaluation of the predictive performance of the model. An overview of the data sets is shown Figure 1. Data sets for internal validation were based on a random selection of 30% of subjects from the total population pool.

The probability density function that best described the observed time-to-first event was selected based on statistical and graphical criteria (i.e., difference in log-likelihood and goodness-of-fit plots). The probability density function (Equation 1) is calculated as follows:

$$f(t) = h(t) \cdot S(t) \quad (1)$$

where $h(t)$ represents the hazard function and $S(t)$ the survivor function. The following probability density functions were considered:

- Exponential, $\lambda \cdot e^{-\lambda \cdot t}$;
- Proportional Weibull, $\lambda \cdot \alpha \cdot (\lambda \cdot t)^{\alpha-1} \cdot e^{-\lambda \cdot t^{\alpha}}$;
- Gompertz, $\lambda \cdot e^{\theta \cdot t + \frac{\lambda}{\theta}\left(1-e^{\theta \cdot t}\right)}$.

As a TTE model is used to calculate the probability distribution of events, no variance component (interindividual, inter-occasion or residual variability) is obtained for model parameters. Following the structural model selection, clinical and demographic baseline covariates were tested using a stepwise forward addition-backward elimination procedure:

- Subject baseline demographics: age, race, body mass index, smoking status, sex.
- Baseline clinical characteristics: baseline spirometry (FEV_1, FEV_1p, PEF), asthma duration, previous ICS use, ACQ question 6 (SABA use).

Seasonal effects were investigated by noting the location (i.e., northern or southern hemisphere) and calendar date corresponding to start of treatment for each patient. Concomitant medication and co-morbidities or concurrent medical conditions were not accounted for as covariates. The rationale for the exclusion of these variables from the covariate analysis is based on the fact that concomitant drugs and concurrent conditions allowed in the protocols were not expected to have a direct effect on the risk of exacerbation.

For standardization purposes, baseline measurements were defined as those collected prior to the initiation of treatment irrespective of the time span between the screening date and the first dose. Treatment was then evaluated as a discrete (covariate) effect on the underlying hazard parameters.

To ensure appropriate interpretation of the results, the final model estimates were presented as hazard ratios. For continuous

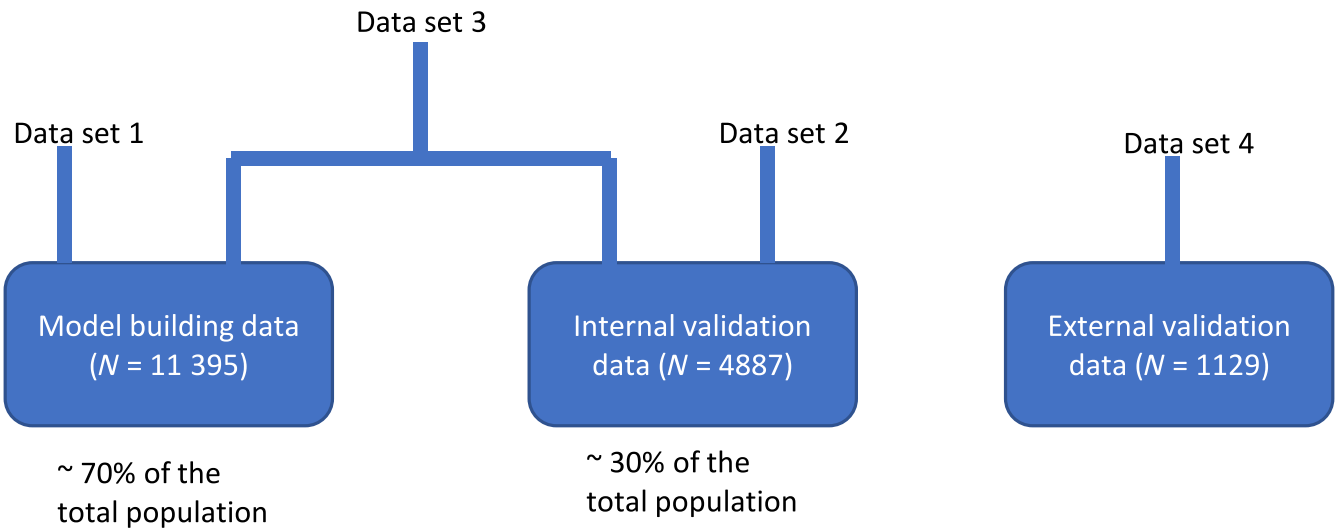


FIGURE 1 Diagram describing the different data sets used for model building (data set 1), internal validation (data set 2) and final data analysis (data set 3, N = 16 282). Data set 3 comprises the total patient population from studies ADA109055, ADA109057, HZA113091, HZA115150, SAM40027, SAM40056, SAM40065, SAM40086, SAS115359 used for this analysis. Initially, external validation aimed at the assessment of model consistency and estimation of drug-specific differences. Therefore, data set 4 included data from asthma patients enrolled into study HZA115150, who were treated with either beclomethasone monotherapy or beclomethasone and formoterol combination therapy. Data from these patients were not used for model development or internal validation. This step was complemented by further evaluation of the predictive performance of the final model following inclusion of additional data on combination therapy with FP/SAL ($n = 693$) and BUD/FOR ($n = 697$) from the Excel study (SAM40040).[24] Further details on the validation procedures are summarized in the Supporting Information.

covariates, the hazard ratio (Equation 2) was calculated as the exponent of the coefficient of each parameter in the model. The hazard ratio for exacerbation was defined as follows:

$$\frac{e^{\beta(x+1)}}{e^{\beta x}} = e^{\beta} \quad (2)$$

where β in the fitted proportional hazard model is the estimated change in the logarithm of the hazard ratio when the value of x is increased by one unit.

For categorical variables the hazard ratio (Equation 3) for an individual in any group or category is relative to an individual in the first group or category. It is defined by the exponential of α_j, where the parameter α is the logarithm of the relative hazard. The hazard function was calculated as follows:

$$h_j(t) = e^{\alpha_j} \cdot h_0(t) \quad (3)$$

As the use of a placebo-controlled arm is unethical in this type of trial, data from patients randomized to FP monotherapy were used as reference group for the purposes of estimating the effect of treatment on the hazard ratio. Furthermore, as interindividual differences in the therapeutic dose levels achieved during titration and maintenance phases of the trials are expected to have minor effect on exacerbation risk, dose levels were not considered as a separate covariate factor.

Further details on the assumptions for the parameterization of the hazard function along with the control stream file describing the final model are included in the Supporting Information.

2.4 | Model evaluation and predictive performance

Comparison of hierarchical models was based on the likelihood ratio test and standard error of the parameter estimates. Covariate model building was conducted in a stepwise manner and the likelihood ratio was used to test the effect of each covariate on model parameters with a significance level of 0.01. In the stepwise forward addition procedure, each covariate was individually included in the base model and if the reduction in the objective function value (OFV) between the base and more complex model was ≥3.84 (χ^2 < 0.05 for 1 degree of freedom, df) then the covariate was considered statistically significant. All significant covariates were then added simultaneously into a full model. Subsequently, each covariate was independently removed from the full model. If the increase in the OFV was ≥6.64 (χ^2 < 0.01 for 1 df), the covariate was considered to be significantly correlated with the model parameter and retained in the final model. It is worth mentioning that this analysis was implemented under the assumption that there is no statistically significant interaction between baseline covariates and treatment effect. In fact, there is no reason to believe that pharmacological effects would depend on or correlate with any of the baseline covariates included in the model.

Internal validation procedures were implemented by splitting the full data set into an index data set (comprising ~70% of the data) and a reference data set (comprising the remaining portion of the data). Individual empirical Bayes estimates obtained from the index data set were then used to predict the reference data. The average relative error and average relative variance (mean square error) were used to assess the precision of parameter estimates and robustness of the model obtained with the model building data set. The internal validation steps were considered as failed if an average relative error and average relative variance (mean square error) of ≥30% was observed for at least one of the model parameters (Figure S3).

Visual predictive checks (VPC) were used to assess the adequacy of the parameter estimates of the final model, including the effects of statistically significant covariates. In the VPC, 1000 replicates of the original data set were simulated, based on the final model obtained with each data set along with the 95% prediction intervals. The observed events (i.e., first exacerbation) were plotted over time along with the prediction intervals to visually assess the concordance between simulated and observed data (i.e., Kaplan–Meier survival curves). The final TTE model was assessed for its predictive performance to describe the incidence and timetofirst exacerbation based on stratification by baseline symptom control level and treatment.

Model development and evaluation were implemented in NONMEM v.7.3 using the Laplacian estimation method. The analysis was run on the Model-based Analyses Platform (MAP), a validated analysis platform entirely hosted on Amazon Web Services (AWS). The platform runs NONMEM 7.3 through gFortran compiler and Perl-speaks-NONMEM (PsN) 4.6.0. All required data manipulation, including graphical and statistical summaries were performed in R (version 3.2.5).[25]

3 | RESULTS

3.1 | Demographics and baseline characteristics

The age of the subjects across all studies included in the current analysis ranged from 18 to 91 years. In the subset of patients who have had symptom control level and airway function measured at baseline, the median ACQ-5 score and FEV_1p were 1.8 and 75.9%, respectively. Immediately prior to treatment initiation, 35.9% of the patients had been diagnosed with asthma between >1 and ≤20 years, whilst 21.6% had a history of asthma for more than 25 years. A small proportion (7.0%) of patients who met the inclusion criteria at the screening visit showed well-controlled symptom scores (i.e., ACQ-5 <0.75) at baseline. A summary of demographic and clinical baseline characteristics stratified by treatment is presented in Table 1.

3.2 | Exploratory data analysis

Prior to model parameterization, data integrity checks were performed with the objective of establishing the accuracy of the pooled

TABLE 1 Demographic and clinical baseline characteristics of the patients included during model development stratified by treatment. Summary statistics include medians (5^{th}–95^{th} percentiles) along with the number of patients available in each category. Percentage values reported for smoking status and sex refer to the proportion of patients in each treatment arm.

Baseline characteristic	FP	FP/SAL	BUD/FOR
BMI			
Not available	*NA* [$n = 561$]	*NA* [$n = 543$]	*NA* [$n = 8$]
Underweight (<18.5)	17.7 (16.2–18.4) [$n = 121$]	17.6 (15.2–18.4) [$n = 133$]	18 (16.6–18.4) [$n = 11$]
Normal weight (18.5–<25)	22.7 (19.4–24.8) [$n = 2122$]	22.7 (19.3–24.8) [$n = 2327$]	22.8 (19.6–24.9) [$n = 226$]
Overweight (25–<30)	27.4 (25.3–29.7) [$n = 2231$]	27.4 (25.2–29.6) [$n = 2404$]	27.5 (25.3–29.7) [$n = 256$]
Obese (30–<35)	32 (30.1–34.7) [$n = 1363$]	32 (30.1–34.7) [$n = 1428$]	32.1 (30.1–34.6) [$n = 142$]
Severely obese (≥35)	39 (35.3–52.1) [$n = 1092$]	38.9 (35.4–51) [$n = 1214$]	39.5 (35.2–52.7) [$n = 100$]
Smoking status			
Not available	6.6% [$n = 491$]	3.1% [$n = 250$]	0.3% [$n = 2$]
Never smoked	71.4% [$n = 5349$]	74.2% [$n = 5970$]	58% [$n = 431$]
Former smoker	16.8% [$n = 1259$]	17.4% [$n = 1397$]	28.9% [$n = 215$]
Current smoker	5.2% [$n = 391$]	5.4% [$n = 432$]	12.8% [$n = 95$]
Sex			
Male	33% [$n = 2471$]	34.4% [$n = 2765$]	38.8% [$n = 288$]
Female	67% [$n = 5019$]	65.6% [$n = 5284$]	61.2% [$n = 455$]
ACQ-5			
Not available	*NA* [$n = 6828$]	*NA* [$n = 7137$]	*NA* [$n = 492$]
Well controlled (≤0.75)	0.4 (0–0.6) [$n = 45$]	0.4 (0–0.6) [$n = 61$]	0.6 (0–0.6) [$n = 22$]
Not well controlled (>0.75–≤1.5)	1.2 (0.8–1.4) [$n = 169$]	1.2 (0.8–1.4) [$n = 246$]	1.2 (0.8–1.4) [$n = 90$]
Poorly controlled (>1.5)	2.4 (1.6–3.8) [$n = 448$]	2.4 (1.6–3.8) [$n = 605$]	2.2 (1.6–3.2) [$n = 139$]
FEV1p			
Not available	*NA* [$n = 4921$]	*NA* [$n = 5033$]	*NA* [$n = 400$]
<50%	44.5 (32.7–49.7) [$n = 147$]	45.3 (34.4–49.6) [$n = 199$]	44.8 (41.4–48.2) [$n = 2$]
50%–<80%	68.6 (53.4–78.8) [$n = 1428$]	68.2 (53–78.9) [$n = 1665$]	72.3 (55.1–79.3) [$n = 159$]
≥80%	89.3 (80.8–111.2) [$n = 994$]	88.3 (80.7–109.8) [$n = 1152$]	87 (80.6–105.7) [$n = 182$]

Abbreviations: BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

data sets. The initial exploratory analysis showed no unexpected values or deviations regarding the demographic characteristics, medical history, ACQ-5, spirometric parameters, treatment duration, dose or dosing regimen.

No correlations or interactions were found between demographic and baseline clinical characteristics, other than those due to the known collinearity between variables, for instance height and FEV_1 (see Figure S4).

3.3 | Time-to-event model building and validation

An exponential hazard model was found to best describe the time-to-first exacerbation in the overall patient population and across subgroups following stratification by treatment and baseline covariates. The final model consisted of a baseline hazard term and the associated covariate coefficients. All parameters were well estimated with good precision (RSE ≤33%) and without statistically significant correlations between parameters.

To ensure biological plausibility and prevent over-parameterization, the evaluation of demographic characteristics (e.g., BMI, body-surface area or weight) was performed taking into account collinearity. If a given covariate was identified as statistically significant, other descriptors displaying high collinearity were excluded in the subsequent steps.

At completion of the stepwise forward inclusion and backward exclusion procedures, the following baseline covariates showed statistical significance ($\chi^2 < 0.01$) and were included into the final model, namely: baseline BMI, baseline FEV_1p, baseline ACQ-5, sex and smoking status. These covariates reflect known factors associated with risk of disease progression and symptom severity and were all found to contribute significantly to the underlying base hazard, independently of pharmacological treatment. In addition, seasonal variation was also identified as a significant factor altering the base hazard.

Baseline covariates were parameterized as proportional terms to the base hazard parameter, that is, that estimated for patients receiving FP monotherapy. This approach was necessary due to the ethical limitations associated with the use of a placebo arm for at least 6 months. Therefore, it was assumed that model structure and

TABLE 2 Parameter estimates of the final model describing the time to first exacerbation in moderate or severe asthma patients.

Parameter	Value	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)
Current smoker effect relative to Never Smoked (fractional increase in hazard)	0.51	0.121	23.7%	0.510 (0.297–0.732)
Former smoker effect relative to Never Smoked (fractional increase in hazard)	0.268	0.0715	26.7%	0.264 (0.146–0.419)
BMI effect (fractional increase in hazard per kg/m^2)	0.0279	0.007	25.2%	0.029 (0.020–0.036)
Season effect amplitude (fractional change in hazard relative to between seasons)	0.304	0.0006	0.2%	0.302 (0.252–0.358)
Season effect Phase shift (years)	0.27	0.0006	0.2%	0.262 (0.234–0.306)
ACQ-5 at baseline effect (fractional increase in hazard per point)	0.207	0.0629	30.4%	0.199 (0.112–0.319)
FEV1p at baseline effect (fractional increase in hazard per % change in FEV1p)	−0.00834	0.002	24.0%	−0.0083 (−0.0118 to −0.0045)
Female effect relative to male (fractional increase in hazard)	0.327	0.0831	25.4%	0.325 (0.218–0.440)
BUD/FOR effect relative to FP (fractional increase in hazard)	0.321	0.106	33.0%	0.334 (0.112–0.536)
FP/SAL effect relative to FP (fractional increase in hazard)	−0.308	0.0348	11.3%	−0.311 (−0.362 to −0.251)

Note: Base hazard is described using FP monotherapy as reference treatment. Hazard $= \theta_{BASE} * (1+\theta_{previous\ smoker}) * (1+\theta_{current\ smoker}) * (1+(BMI-27.6)* \theta_{BMI}) * (1+(FEV1P-73) * \theta_{FEV1P}) * (1+(ACQ5_{baseline}-2)\cdot\theta_{ACQ5}) * (1+\theta_{FEMALE}) * (1+\theta_{BUD/FOR}) * (1+\theta_{FP/SAL}) * e^{\theta_{amp}\cdot\sin(calendar\ time+\theta_{phase})}$.
Abbreviations: BMI, body mass index; BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

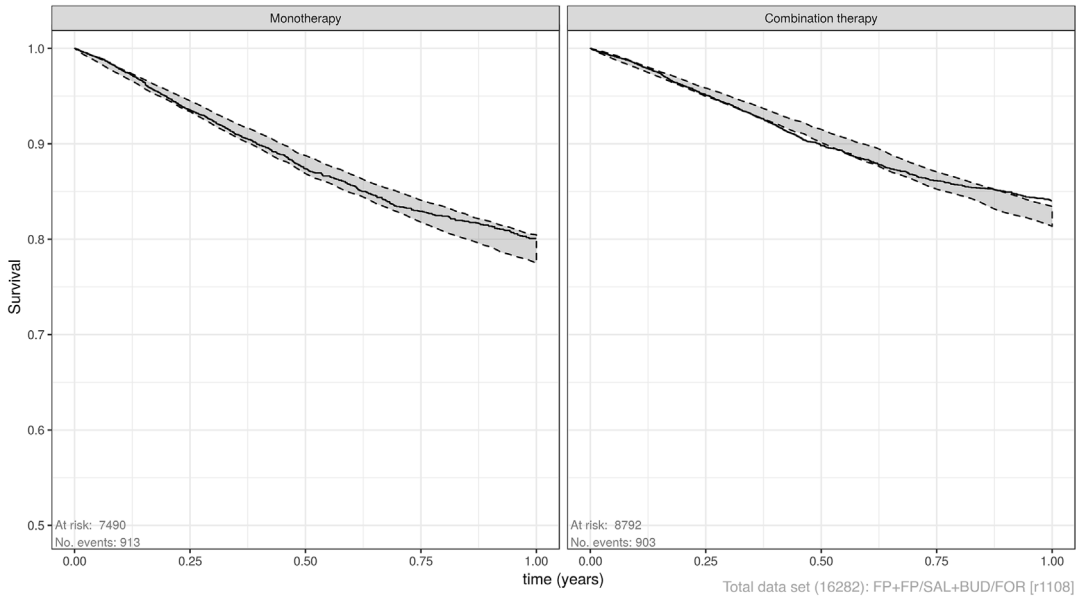


FIGURE 2 Visual predictive check showing Kaplan–Meier survival estimate over time stratified by treatment. Survival (*y*-axis) indicates the proportion of patients who have not had an event; at time zero the survival rate is 100% (i.e., no patient has experienced an exacerbation). The solid line describes the observed time to first exacerbation over the period of 12 months. Shaded areas show the model-predicted 95% confidence intervals of the survival. The slope of survival curve for patients treated with FP is used as reference for comparing the effect of combination therapy. The slightly wobbling lines describing the observed exacerbations is partly due to the varying numbers of patients over 12 months. Also, 34.7% and 39.5% of the patients on monotherapy and combination therapy, respectively, come from studies that are longer than 24 weeks. "At risk" refers to the number of patients in each stratum, "No. of events" is the number of observed exacerbations.

identified covariate effects associated with the base hazard are sufficiently precise to disentangle the contribution of patient- and disease-related factors from the effect of the intervention across the different treatment arms. Treatment-specific terms were added to the model to characterize the changes associated with combination therapy. They were all parameterized as proportional to the base hazard rate. Final parameter estimates are summarized in Table 2.

The final estimates for base hazard rates correspond to an incidence of 18.8% events per year. The effect of parameter estimates for baseline covariate factors and treatments shown in Table 2 can be interpreted as follows: starting from the median value of the covariate factor, an increase or decrease of 1 unit in the covariate results, respectively, in a percentage increase or reduction in the baseline hazard of the magnitude of the parameter point estimate. For instance, for every unit increase (i.e., kg/m^2) in baseline BMI relative to the median BMI of 27.6 kg/m^2, the instantaneous risk of an exacerbation increases by 2.79%. Hence, a patient with baseline BMI value of 32.6 (i.e., 5 units higher than the median value) will have an instantaneous risk of exacerbation that is 14% higher than a patient with median BMI of 27.6 kg/m^2. Similarly, for every unit increase in ACQ-5, the instantaneous risk of an exacerbation increases by 20.7% whereas a unit reduction in FEV_1p increases the instantaneous risk by approximately 0.83% relative to a median FEV_1p of 76% [Corrections made on 18 September 2023, after first online publication: In the previous sentence, '73%' has been changed to '76%' in this version.]. Interestingly, smoking is associated with an increase of 51% in the instantaneous risk, as compared to a patient who never smoked, and females were found to have a 32.7% higher risk of exacerbation relative to male patients. It is also worth mentioning that age and geographical ancestry were not associated with statistically significant differences in the risk of exacerbation. Given the wide age range and geographical ancestry of the patients included in this analysis, this may be explained by the correlation between age and FEV_1p and other baseline covariates, such as BMI.

In a comparable manner, the use of combination therapy FP/SAL was found to significantly reduce the base hazard rate. These results mean that at any point in time, the risk of exacerbation is 30.8% lower for patients receiving FP/SAL, as compared to patients receiving FP alone. This effect was independent of the actual base hazard rate, that is, irrespective of the contribution of baseline patient characteristics to the instantaneous risk of exacerbation.

The VPCs (Figure 2) showed that the observed event rate fell within the 95% confidence intervals of the simulated values, as depicted by the shaded area. Based on the VPCs, the final model was deemed to have acceptable predictive performance to describe the

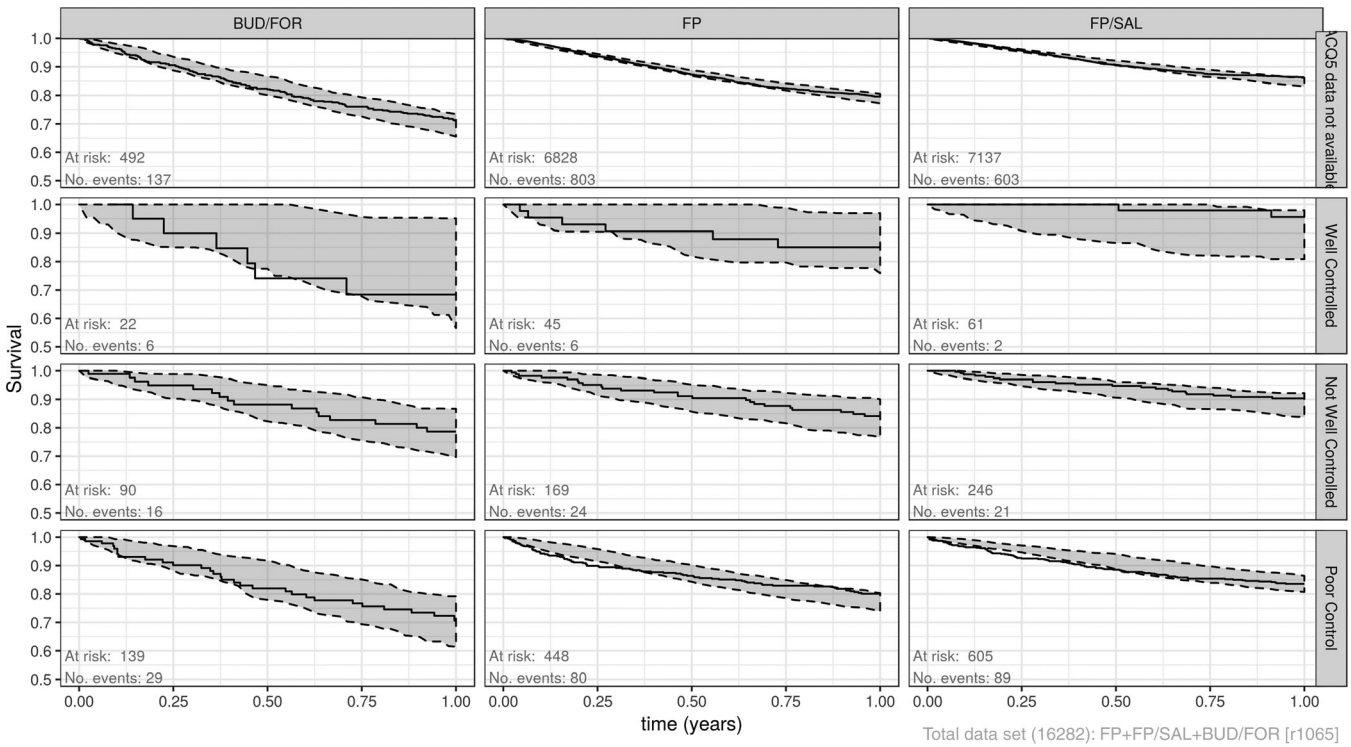


FIGURE 3 Visual predictive check showing Kaplan–Meier survival estimate over time stratified by treatment and symptom control at baseline. Survival (*y*-axis) indicates the proportion of patients who have not had an event; at time zero the survival rate is 100% (i.e., no patient has experienced an exacerbation). The solid line describes the observed time to first exacerbation over the period of 12 months across the overall population. Shaded areas show the model-predicted 95% confidence intervals of the survival. "At risk" refers to the number of patients in each stratum. The observed exacerbations in each group are well predicted by the model, irrespective of symptom control level. It should be noted that the larger the sample size, the narrower the model–predicted 95% confidence intervals. This highlights the effect of sample size on the precision of parameter estimates. It also shows that the differences in sample sizes across each strata does not result in bias. "No. of events" is the number of observed exacerbations. BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

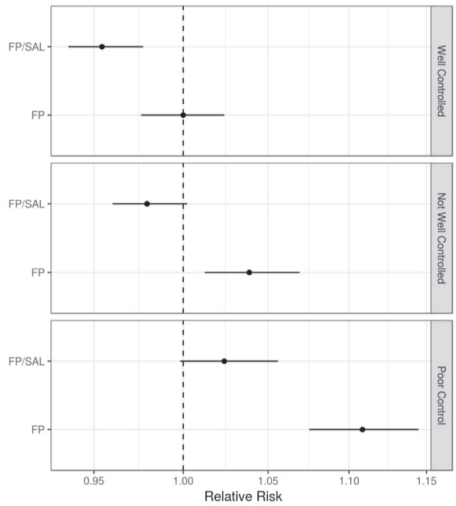
incidence and time to first exacerbation in this pool of patients with moderate or severe asthma symptoms. Overall model performance was also evaluated by comparing predicted and observed events after stratification by the selected baseline covariates. Of interest is how symptom control level at baseline is associated with the risk of exacerbation (Figure 3). Here, an attempt was made to assess the potential effect of imputation and missing baseline ACQ–5 on model performance, including resampling and conversion of the available data on asthma control test (ACT) into ACQ–5 (Figures S5, S6 and S7). An assessment of the generalizability of the model and accuracy of the estimates of the effect of clinical and demographic baseline characteristics was performed initially using an external validation data set, in which moderate and severe asthma patients were treated with beclomethasone monotherapy (BEC) or beclomethasone-formoterol combination therapy (BEC/FOR). As the external validation data set consisted of patients on a different treatment, treatment effects were re-estimated while all other parameters were fixed to the final parameter estimates. The data was adequately described by the model, yielding estimates of the treatment effect, which are in line with the known differences in pharmacological properties of beclomethasone (Figure S8). Estimates of the final model parameters and VPCs describing model performance following the inclusion of additional study data on FP/SAL and BUD/FOR are summarized in the Supporting Information file (Figure S9, Table S7).

3.4 | Relationship between symptom control level and other clinical and demographic baseline covariates and the risk and incidence of exacerbations

The effect of variable symptom control on overall risk of exacerbation was further characterized in terms of relative risk (RR). Using well-controlled patients on FP monotherapy as reference, the relative risk was calculated using the available data and model-predicted exacerbations (Figure 4). The shift in relative risk highlights the impact of variable symptom control on the risk of exacerbation. These results also show that risk reduction is also drug/treatment-specific: adding SAL to FP as combination therapy counteracts the increase in relative risk that is observed with symptom control deterioration (i.e., RR ranges between 1 and 1.06 for FP monotherapy *vs.* 0.89 and 1.02 for FP/SAL combination therapy). These findings were corroborated during the external validation step with additional data from a separate study including combination therapy with FP/SAL ($n_{total} = 8742$) and BUD/FOR ($n_{total} = 1440$) (see Table S7 in Supporting Information).

In addition to baseline ACQ-5, it is important to assess the overall impact of other contributing factors on the changes in base hazard. Even though no interaction has been identified between baseline covariates and treatment effect during model development, the magnitude of the effect of baseline characteristics (i.e., treatable traits) will differ per patient across the population. Such an overview can be obtained using simulations and subsequently stratifying the results by treatment arm and symptom control level at baseline, as assessed by ICQ-5. These simulations are summarized as heat maps in Figures 5 and 6, where the yearly incidence of events for patients with varying baseline ICQ-5, BMI, FEV_1p, smoking status and sex. To understand the impact and magnitude of the effect of concurrent factors on the risk of exacerbation, Figure 7 summarizes the relative change in the probability of an exacerbation within the first year of treatment with combination therapy for both male and female patients who have never smoked, previously smoked or are current smokers and have a BMI of 25 kg/m^2.

It is essential to highlight that even though LABA have primarily been associated with symptomatic relief, our results suggest



Asthma Control Level	FP	FP/SAL
ACQ-5 data not available	1.07 (1.05-1.09) [n=6828]	0.99 (0.97-1.00) [n=7137]
Well Controlled	1.00 (0.88-1.14) [n=45]	0.89 (0.85-0.95) [n=61]
Not Well Controlled	1.01 (0.94-1.08) [n=169]	0.94 (0.90-0.98) [n=246]
Poor Control	1.06 (1.01-1.12) [n=448]	1.02 (0.98-1.06) [n=605]

FIGURE 4 Model predicted relative risk (RR) (upper panel). The dashed line depicts the reference value (i.e., RR = 1) associated with patients receiving FP monotherapy who show well-controlled symptoms at baseline. Bars are the 95% prediction intervals ($N = 1000$ per arm and level of control, 500 iterations). RR and corresponding 95% confidence intervals calculated from the Kaplan–Meier estimates from the observed data are also summarized in tabular format, along with the number of patients in each symptom control level (lower panel). The changes in RR show that baseline symptom control level has a significant effect on the risk of exacerbation, and that this effect is independent of treatment choice. Most importantly it also shows that risk reduction is drug-specific: adding SAL to FP as combination therapy counteracts the effect of symptom control deterioration. FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

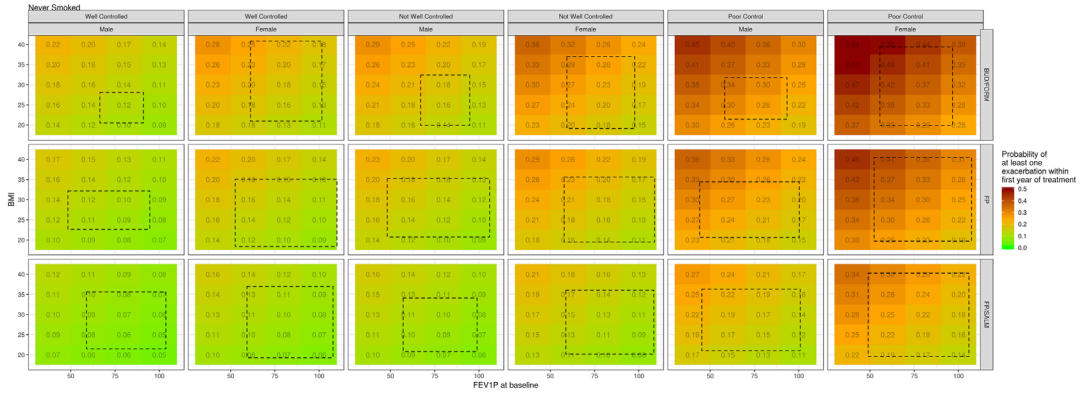


FIGURE 5 Heat map showing the probability of at least one exacerbation within the first year of treatment for patients receiving monotherapy or combination therapy. Colour gradient from green to red reflects the change in the incidence of exacerbations in patients with varying BMI or FEV_1p at baseline. Predicted risk is stratified by symptom control level for male and female patients who have never smoked. 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 (dotted black lines) in Figure S2 but also included covariate values across a clinically relevant range. BMI, body mass index; BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

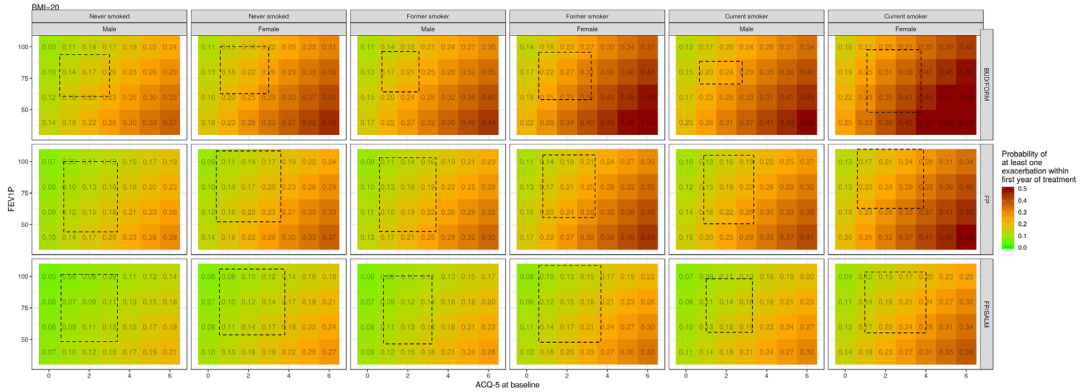


FIGURE 6 Heat map showing the probability of at least one exacerbation within the first year of treatment for patients receiving monotherapy or combination therapy. Colour gradient from green to red reflects the change in the incidence of exacerbations in patients with varying level of symptom control or FEV_1p at baseline. Predicted risk is stratified for male and female patients who have never smoked, previously smoked or are current smokers and have a BMI of 20 kg/m^2. 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 (dotted black lines) in Figure S2 but also included covariate values across a clinically relevant range. BMI, body mass index; BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

that the use of FP/SAL combination therapy appears to modify the base hazard relative to FP alone, irrespective of the magnitude of the effect of other demographic and clinical baseline covariates. In fact, based on the heat maps, it becomes evident that FP/SAL combination therapy effectively reduced the risks associated with known risk factors such as higher BMI or lower FEV_1p.

4 | DISCUSSION

There is still no consensus on which traits should form the basis of a multidimensional assessment of the disease status and which traits should be targeted for treatment. Consequently, guidelines for the clinical management of asthma patients with moderate or severe symptoms continue to overlook the effect of individual patient characteristics as potential contributors or determinants of future risk. In fact, previous investigations have shown that inflammatory mediators, including eosinophilia and increased airflow limitation, are associated with a higher risk of exacerbation in severe and refractory asthma.[26–28] However, none of these studies attempted to assess, in a parametric manner, how inflammatory markers and phenotypical characteristics correlate with symptom control (ACQ-5) and other clinical and demographic characteristics.

Our investigation assumes that personalized interventions and improved clinical management of patients require an integrated approach, by which individual differences (i.e., clinical phenotype

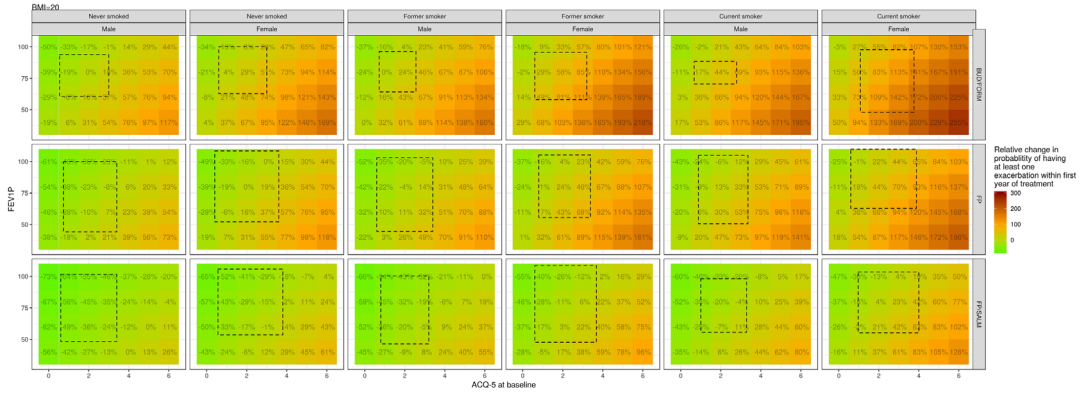


FIGURE 7 Heat map showing the relative change in the probability of an exacerbation within the first year of treatment for patients receiving monotherapy or combination therapy. Colour gradient from green to red reflects the change in the relative probability of an exacerbation in patients with varying levels of symptom control or FEV_1p at baseline. Relative changes in probability are shown for male and female patients who have never smoked, previously smoked or are current smokers and have a BMI of 20 kg/m^2. The midpoint for the colour gradient was set to 100%, 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 (dotted black lines) in Figure S2 but also included covariate values across a clinically relevant range. BMI, body mass index; BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.

[s] or treatable traits) are used not only to unravel features of the underlying pathophysiology of asthma in specific subgroups of patients, but also to inform treatment choices and predict treatment performance. Hence, the importance of data mining a large cohort of patients with moderate or severe asthma symptoms using a model-based approach.

Whilst the identification of different inflammatory profiles has been possible in patients with severe, persistent or refractory asthma (e.g., eosinophilic and neutrophilic asthma),[29–31] a large proportion of asthma patients with moderate to severe symptoms may not present such unique features. Rather, it is conceivable that a range of concurrent factors ultimately determine or contribute to individual variation in response, symptom control and future risk. Similar to the concepts underpinning epigenetic patterns in epigenetic research,[32,33] the MASTER study aimed to explore clinical characteristics and lifestyle factors that might modify future risk and treatment performance, such as baseline symptom control level, obesity and tobacco smoking.

Even though clinical guidelines highlight the benefits of a stepwise approach for the treatment of patients with moderate or severe asthma, these recommendations seem to underestimate the magnitude of the effect of both intrinsic and extrinsic factors, including environmental and lifestyle differences on the burden of disease.[34] These co-exist in clinical practice and may alter treatment response to ICS or ICS/LABA. Our results clearly show that baseline symptom control, BMI and FEV_1p are significantly associated with the risk of exacerbation. Such an effect is further modified by sex, smoking status and seasonal variation. Of note is the sex effect, which may reflect known differences in gene expression for type 2 and 3 (M2, M3) muscarinic acetylcholine receptors, which appear to be involved in small airway dysfunction and poor asthma control.[35] However, as shown in Figures 5, 6 and 7 the concurrent effect of different baseline covariates leads to differences in the risk of exacerbation, even for individuals with comparable symptom control level. In fact, our findings show that symptom control and reduction or elimination of the risk of an exacerbation are independent from each other. These findings do not contradict prior evidence of a relationship or correlation between asthma control and risk of exacerbations.[36–38] It simply shows that these are complex, nonlinear functions or matrices. Symptom control alone is not the only explanatory variable. Most importantly, our analysis shows that the effect of an ICS/LABA on symptom control scores does not imply an effect of similar magnitude on exacerbation risk (Figure S6).

It should be noted that our analysis excluded some factors that were identified as predictors or risk factors for exacerbation in previous reports, such as race (ethnicity), longer duration of symptoms, or geographic region, as these factors may be confounded by correlations (e.g., collinearity) or described by a different hierarchical relationship (e.g., seasonal variation and geographic region).[39,40] In addition, we had very limited information on type-2 biomarkers, now known to be associated with the risk of exacerbations and the likelihood of a positive response to corticosteroids or biologics in severe asthma.[41] Interestingly, previous investigations have also indicated maintenance corticosteroid use as a predictor of asthma exacerbation, but have not disentangled it from the effect of individual baseline characteristics. The use of a TTE model has allowed us to quantify the magnitude of treatment effect, providing estimates of the differences in risk reduction due to treatment choices.[39]

From a methodological point of view, it is important to emphasize that some baseline variables, such as age, are strongly correlated with airway function (e.g., spirometry) and symptom severity and have

therefore not been selected as an independent factor during covariate model building. On the other hand, as information on inflammatory markers in blood, lung and sputum were not available for the majority of patients, these measurements could not be included into the analysis. The absence of type-2 inflammatory biomarkers in our analysis does not necessarily imply that critical covariates may have been missed. Our working hypothesis assumes that interindividual differences in response to treatment are not associated with a single agent, but result from the interaction of various concurrent factors.[42] Analogously to the use of body weight as a surrogate for metabolic rate and/or hormonal homeostasis when describing interindividual differences in systemic exposure to a drug,[43–45] variation in the underlying inflammatory tonus or airway hyperresponsiveness could be associated with clinical and phenotypical traits. In fact, the multifactorial nature of so-called asthma phenotypes is reflected by the findings in numerous reports where principal component analysis has been used.[46,47]

4.1 | Clinical implications of a drug–disease model

Notwithstanding the relevance of data generation in clinical trials, the use of drug–disease models has been considered one of the most efficient approaches for knowledge integration. The implementation of a proportional hazard model to describe the time to first exacerbation can be compared to previous attempts in other therapeutic areas, such as acute urinary retention or the time to acute kidney injury in patients undergoing allogeneic stem cell transplantation.[23,48,49] Of note is the approach developed by D'Agate and colleagues, which shows how an integrated analysis has enabled the discrimination of the effect of symptomatic interventions from those with disease-modifying properties. Another important feature of our analysis was the possibility to quantify the magnitude of the effect of patient characteristics on baseline hazard, independently of treatment type. Availability of estimates of the effect of treatment and baseline characteristics on baseline hazard enable risk stratification along with prediction of long-term consequences of exacerbation risk reduction.

We anticipate, therefore, that the availability of a parametric model describing the incidence and time to first exacerbation will provide the basis for the evaluation of a range of clinical questions regarding the effect of interindividual differences on symptom control and exacerbation risk. Moreover, the proposed model offers the opportunity to identify groups of patients whose clinical characteristics at baseline could benefit from personalized interventions, ultimately reducing their future risk.

We also need to emphasize that our analysis was aimed at characterizing the mid- to long-term risk of exacerbations. The contribution of covariate factors and different ICS/LABA combination therapy to instantaneous risk may not be clinically detectable when considering shorter intervals. This is particularly relevant when considering patients showing baseline characteristics which correlate with a lower risk of exacerbation than those included in the available clinical trials. Therefore, claims regarding risk reduction based on studies that are shorter than 6 months may be inaccurate.

We acknowledge that, as with any pharmacometrics approach, model predictive performance and generalizability depend highly upon the data available and the clinical questions one aims to address. Therefore, an overview of the limitations of the clinical trial data and model parameterization used for the characterization of exacerbation risk is provided in Table S9, including the potential confounding of exacerbation history, reliever medication use, adjustable maintenance dose, and ICS dose level.

5 | CONCLUSIONS

In short, our investigation shows the relevance of a parametric approach for the assessment of the time to first exacerbation in patients with moderate or severe asthma symptoms, as it allows disentangling of the effect of baseline covariates from the underlying base hazard rate. Known risk factors for exacerbations found to have a statistically significant effect on the base hazard rate, which alter the instantaneous risk of an event, were baseline ACQ-5, BMI, FEV_1p, smoking status and sex. Our analysis also reveals that seasonal variation affects the overall risk of exacerbation. Taken together with the concurrent effect of treatment, it becomes evident why interindividual differences cannot be ignored when defining an asthma management plan.

Whilst it may not yet be possible to define specific clinical phenotypes, these results show that physicians and prescribers should consider opportunities for interventions that maximize exacerbation risk reduction. Baseline characteristics (sex, uncontrolled asthma, overweight, active smoking, airflow obstruction [FEV1p]) need to be weighed when making clinical decisions about treatment for individual patients with moderate–severe asthma.

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 in the design of the study and interpretation of study data, drafting and critical revision of the manuscript; Ian D. Pavord, Guy Brusselle, Arzu Yorgancıoğlu, Chirag Teli, and Paulo M. Pitrez 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.

CONFLICT OF INTEREST STATEMENT

I.P. 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 organizing 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; G.B. has acted as a speaker/consultant for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi and Teva; A.Y. has received research grants from Novartis, MSD, AstraZeneca and Sanofi, and has acted as a speaker/consultant for AstraZeneca, Abdi İbrahim, GSK, Novartis, Chiesi and Bilim; P.M.P. has acted as a speaker/consultant for AstraZeneca, GSK, Novartis, Boehringer Ingelheim and Sanofi; S.O., C.T., A.PG. and O.D.P. are GSK employees and hold stocks/shares in GSK.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

TABLE A1 Overview of the studies identified for the proposed model-based meta-analysis. Protocol title is shown along with details regarding treatment type and duration, and device characteristics.

Study	Study title	Treatment arms	Dose titration/run-in	Dose maintenance	Comed albuterol/ salbutamol	Device
ADA109055 NCT00452699[50] *N*: 621 Duration: 52 weeks Visits: 15	A 52-week, randomized, double-blind, parallel-group study of fluticasone propionate/salmeterol DISKUS™ combination product (FSC) 250/50 mcg BID and fluticasone propionate (FP) DISKUS 250 mcg BID in treatment of subjects with asthma.	FP 250 mcg BID FP/SAL 250/50 mcg BID	FP 100 mcg BID (3 weeks)	FP 250 mcg BID FP/SAL 250/50 mcg BID	As needed	Diskus Inhaler
ADA109057 NCT00452348[51] *N*: 628 Duration: 52 weeks Visits: 15	A 52-week, randomized, double-blind, parallel-group study of fluticasone propionate/salmeterol DISKUS™ combination product (FSC) 250/50 mcg BID and fluticasone propionate (FP) DISKUS 250 mcg BID in treatment of subjects with asthma.	FP 250 mcg BID FP/SAL 250/50 mcg BID	FP 100 mcg BID (3 weeks)	FP 250 mcg BID FP/SAL 250/50 mcg BID	As needed	Diskus Inhaler
HZA113091 NCT01147848[52] *N*: 806 Duration: 24 weeks Visits: 4/5	A randomized, double-blind, double-dummy, parallel-group, multicentre study to assess efficacy and safety of fluticasone furoate (FF)/ GW642444 inhalation powder and fluticasone propionate (FP)/salmeterol inhalation powder in the treatment of persistent asthma in adults and adolescents.	FF/VI 100/25 mcg q.d. FP/SAL 250/50 mcg BID	FP 250 mcg BID (4 weeks)	FF/VI 100/25 mcg q.d. + Placebo Accuhaler Diskus FP/SAL 250/50 mcg BID + Placebo inhalation powder via NDPI	As needed	FF/VI via NDPI FP/SAL inhalation powder via Accuhaler/Diskus
HZA115150 NCT01706198[53] *N*: 4233 Duration: 52 weeks Visits: 5	A 12-month, open-label, randomized, effectiveness study to evaluate fluticasone furoate (FF,GW685698)/ vilanterol (VI/GW642444) inhalation powder delivered	Usual Care*, FF/VI	NA	FF/VI 100/25 mcg FF/VI 200/25 mcg	-	FF/VI via Ellipta inhaler

TABLE A1 (Continued)

Study	Study title	Treatment arms	Dose titration/run-in	Dose maintenance	Comed albuterol/ salbutamol	Device
	once daily via a novel dry powder inhaler compared with usual maintenance therapy in subjects with asthma.					
SAM40027[54] *N*: 3416 Duration: 52 weeks Visits: 7	Gaining Optimal Asthma Control (GOAL): A multicentre, stratified, randomized, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterol/fluticasone propionate combination DISKUS (ACCHUALER) dry powder inhaler compared with fluticasone propionate DISKUS (ACCUHALER)	FP BID FP/SAL BID	Step 1: FP/SAL 50/ 100 mcg BID or FP 100 mcg BID Step 2: FP/SAL 50/ 250 mcg BID or FP 250 mcg BID Step 3: FP/SAL 50/ 500 mcg BID or FP 500 mcg BID (until total control is achieved)	FP/SAL 50/100 mcg, 50/250, 50/500 BID FP 100, 250 or 500 mcg BID (+ 10-day oral prednisone, if needed)	As needed	Via dry powder inhaler
SAM40056 NCT00479739[55] *N*: 688 Duration: 52 weeks Visits: 6	A randomized, double-blind, double-dummy, 52-week, parallel-group study of a standard dosing regimen with fluticasone/salmeterol combination 50/250 mcg bid (via the DISKUS™/ ACCUHALER™ Inhaler) versus a symptom-driven, variable dosing regimen with formoterol/budesonide combination 4.5/160 mcg (via a breath-actuated dry powder reservoir inhaler) in adult asthmatics	FP/SAL 50/250 mcg BID BUD/FOR 4.5/160 mcg (varying dose)	Fixed doses (4 weeks) FP/SAL 50/250 mcg BID + placebo BADPI BUD/FOR 4.5/160 mcg + PLACEBO DISKUS BID	FP/SAL 50/250 mcg BID BUD/FOR 4.5/160 mcg (varying BADPI dosage based on Asthma Control Plan)	Inhaled salbutamol as needed	FP/SAL via Diskus Inhaler BUD/FOR via BADPI inhaler
SAM40065 NCT00920543[56] *N*: 449 Duration: 40 weeks Visits: 6	A multicentre, randomized, double-dummy, parallel-group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either	FP (dosage based on asthma severity and treatment strategy) FP/SAL (dosage based on asthma severity and treatment strategy)	Previous treatments (2 weeks)	FP/SAL 500/50 mcg or 250/ 50 mcg or 100/50 mcg FP 500 mcg or 250 mcg or 100 mcg (Dose adjustment every 8 weeks)	Albuterol inhalation as needed	Via Diskus Inhaler

(Continues)

TABLE A1 (Continued)

Study	Study title	Treatment arms	Dose titration/run-in	Dose maintenance	Comed albuterol/ salbutamol	Device
	fluticasone propionate/ salmeterol DISKUS BID or fluticasone propionate DISKUS BID (or placebo BID if asymptomatic)					
SAM40086 NCT01324362[57] *N*: 466 Duration: 40 weeks Visits: 6	As study SAM40065	FP, FP/SAL	As study SAM40065	As study SAM40065	As study SAM40065	As study SAM40065
SAS115359 NCT01475721[58] *N*: 11679 Duration: 26 weeks Visits: 4	A safety and efficacy study of inhaled fluticasone propionate/salmeterol combination versus inhaled fluticasone propionate in the treatment of adolescents and adult subjects with asthma	FP 100 mcg, 250 mcg or 500 mcg BID FP/SAL 100/50 mcg, 250/ 50 mcg or 500/50 mcg BID	Previous treatments (2 weeks)	FP/SAL 100/50 or FP 100 FP/SAL 250/50 or FP 250 FP/SAL 500/50 or FP 500 (based on control status)	NA	Via dry powder inhaler

Abbreviations: BMI, body mass index; BUD/FOR, budesonide-formoterol combination therapy; FP, fluticasone propionate as monotherapy; FP/SAL, fluticasone propionate in combination with salmeterol.
*Usual care arm included patients with different standard of care interventions. Only patients on BUD/FOR ($n = 399$) were retrieved for the purpose of the current analysis. Consequently the total number of patients receiving BUD/FOR combination therapy refers to SAM40056 ($n = 344$) and HZA115150 ($n = 399$).