SUPPLEMENTARY MATERIAL 2

Baseline characteristics and maintenance therapy choice on symptom control, reliever use, exacerbation risk in moderate–severe asthma: a clinical modelling and simulation study

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Development and evaluation of a Poisson model describing individual patterns of reliever medication intake in moderate-severe asthma.

Methods

Source data: The data available for the development of the Poisson model describing individual patterns of reliever medication use consisted of a subset of the studies selected for the implementation of the time-to-event model, which was used to characterise the risk of exacerbation in moderate to severe asthma patients. To ensure that a representative population, with as many patients as possible to describe interindividual patterns of reliever medication use, both the number of overnight occasions and total number of puffs over 24 hours were characterised. Four clinical trials met the inclusion criteria for the purpose of the current investigation (**Table S2_1**). 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.

In total, 3768 patients with accurate clinical and demographic baseline details, background treatment, (i.e., maintenance therapy) and regular records on reliever medication use were included in the analysis. The available data was subsequently split into a model building and an internal validation dataset. The model building dataset consisted of 74.2% of the individuals (n = 2795) from Studies SAM40040, HZA106829 and HZA106837. The remaining 25.8% of the individuals (n = 973) from Study HZA116863 were used for the purpose of external validation. No patients were excluded from the analysis except for those data records where details on reliever medication intake were missing.

Exacerbations, disease history, FEV1p, smoking habit and other relevant variables associated with asthma symptom control were evaluated as covariates on model parameters describing individual patterns of reliever medication use.

Poisson model parameterisation: The Poisson regression model was used to describe the reliever medication count data as previously described by van Dijkman and colleagues [1]. Briefly, the model is based on the Poisson parameter (called lambda (λ)), which represents both the mean and the variance of the counts. Lambda, the average number of occurrences per unit of time, was modelled as a function of a typical value (e.g., β_0), potentially with an inter-individual variance, adjusted for one or more covariates (e.g., baseline characteristics), represented by the coefficients β_1 (dependent on covariate x_i). The model was developed in a stepwise manner considering the effects estimated in the previous model, limitations of the dataset and the overall objectives of the current analysis (see **Figure S2_1**).

Exploratory data analysis was performed to identify additional covariates and are shown in **Figures S2_2**, **S2_3**, **S2_4** and **S2_5**. Following the structural model selection, demographic and clinical baseline covariates were investigated using a stepwise forward addition-backward elimination procedure. For standardisation 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. To ensure biological plausibility and prevent over-parameterisation, the evaluation of the demographic characteristics (e.g., BMI, body-surface area, or weight) was performed taking into account co-linearity. If a given covariate was identified as statistically significant, other descriptors displaying high co-linearity were excluded in the subsequent steps.

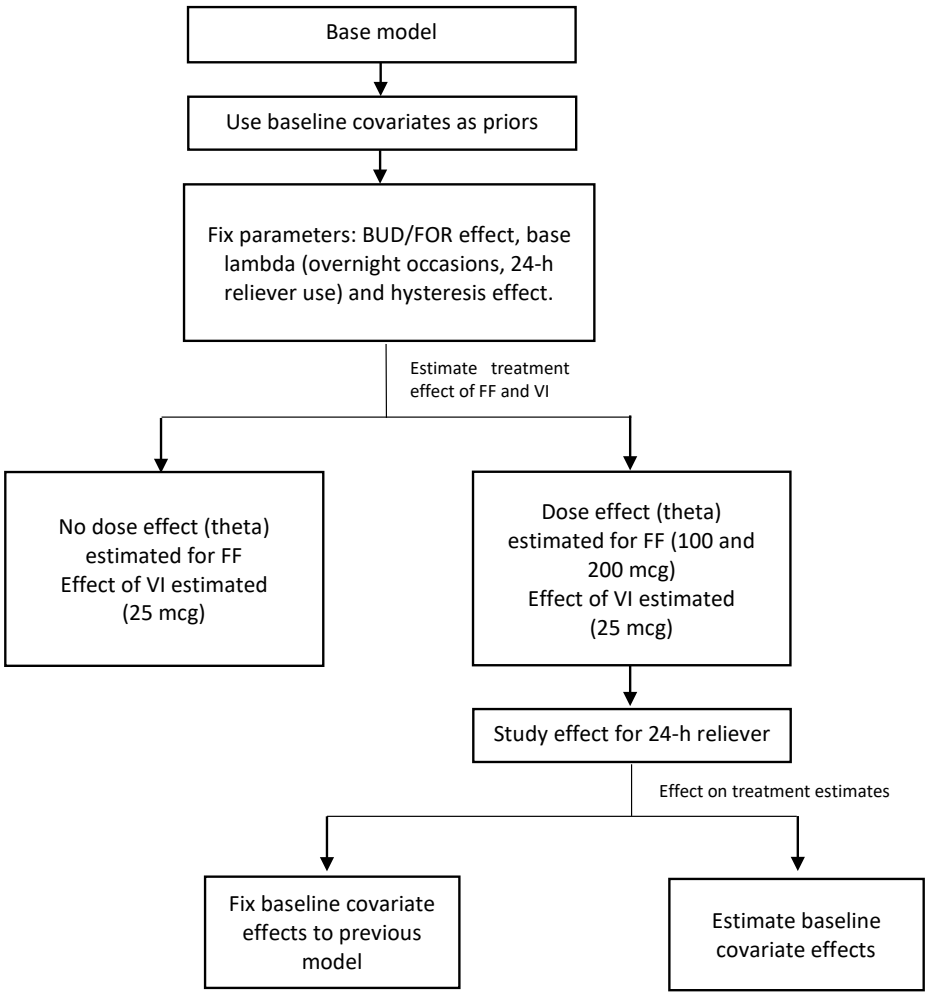


Figure S2_1: Poisson model development workflow including parameterisation of treatment and baseline covariate effects.

An important objective of the current analysis was to quantify the effect of FF and FF/VI treatment on reliever medication use. Since a larger population was identified in the previous analysis (n = 6212) [1] compared to the current study (n = 3768), it was assumed that the effect of disease-related or patient-specific baseline covariates was estimated with higher precision. Therefore, model parameter distributions from the previous analysis were used as informative priors. Medical history, in particular exacerbation history and disease duration were also considered as a potential factor affecting reliever use.

In addition to the aforementioned patient-specific (intrinsic) factors, extrinsic factors, including treatment were considered during model building in the previous analysis [1,2]. Of note is that in contrast to known seasonal differences in the risk of exacerbation [2], no consistent variation was observed in reliever use relative to season [1]. Therefore, seasonal variation was not included as a

covariate in this analysis. In addition, as with the previous analysis, 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 reliever use.

Treatment effect: There was only one study with overnight occasions count data following BUD/FOR treatment (SAM40040). Therefore, the effect of BUD/FOR, and base lambda for overnight occasion for SAM40040 were fixed to the final values estimated previously. The hysteresis effect was also fixed to previous values as there was only one study with a duration of 1 year in the present analysis.

For FF, there were two dose levels (100 µg and 200 µg o.d.) available in the dataset for 24-h reliever use and therefore modelled as a discrete effect. The effect of FF dose as a categorical variable was found to be significant and included in the final model. The additional effect of VI (25 µg) was estimated as an additional categorical variable.

Lastly, it was assumed that non-adherence to maintenance therapy and its effect on reliever use was negligible during the study period. A comparison between treatment arms was based on the mean and/or median dose level of ICS or ICS/LABA during the maintenance phase of treatment, taking into account the underlying dose-response relationships of the active moieties, where appropriate [3-5]. It should be emphasised that similar methodologies, aimed at characterising interindividual differences in disease processes, disease progression, and treatment response, have been applied elsewhere [2,6]. For completeness, an overview of the main assumptions supporting model parameterisation and analysis of reliever use data in patients with moderate-severe asthma symptoms is presented in **Table S2_2**.

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 added to the base model and considered statistically significant if the reduction in the objective function value (OFV) between the base and the more complex model was $\geq$ 3.84 (χ^2<0.05 for 1 degree of freedom, df). All significant covariates were then added simultaneously into a full model. Subsequently, each covariate was independently removed from the full model. The covariate was considered to be significantly correlated with the model parameter and retained in the final model if the increase in the OFV was $\geq$6.64 (χ^2<0.01 for 1 df).

VPCs were used to assess the adequacy of the parameter estimates of the final model, including the effects of statistically significant covariates. As standard goodness-of-fit plots, such as observed vs predicted data are not easily interpretable in the case of count data, two sets of VPCs were created. One set was based on population predictions, which allows the interpretation of the model to predict the impact of covariate effects (population-level parameters) alone. The second set of VPCs was based on the individual predictions for each study subject. Both kinds of VPCs were first created across individuals from all studies, separated by type of endpoint (puffs/24 h and overnight occasions), and stratified by symptom control level at baseline (i.e., ACQ-5 0 – <0.75, $\geq$0.75 – 1.5 and ≥1.5).

For each 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 mean observed and predicted counts were plotted over time along with the prediction intervals to visually assess the concordance between simulated and observed data. The final count model was assessed for its predictive performance to describe reliever use based on stratification by treatment and baseline covariates. External validation was performed against a new population (HZA116863, n = 973) which was not included in the model development phase. These patients received regular dosing FF/VI (100/25 or 200/25 μg o.d.).

The effect of fixing baseline demographic covariate estimates to the final values of the previous model was compared the model without fixing baseline covariate effects. This had minimal impact on the estimate of the treatment effects of FF and FF/VI, however it improved model predictions for FF and FF/VI.

Model development and evaluation were implemented in NONMEM v.7.3 using the Laplacian estimation method, as described elsewhere [7]. 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 data processing, including graphical and statistical summaries were performed in R (version 3.2.5) [8]. In addition, simulations of SABA counts based on the Poisson distribution were implemented using R and C++ code through the R package Rcpp [9]. The NONMEM control file of the final model and example dataset are provided as attachment to this supplementary file.

Table S2_1. Overview of the studies identified for the proposed model-based meta-analysis. Protocol title is shown along with details regarding treatment type, duration, dose, dosing regimen and device characteristics. These studies include treatment arms selected for model building and validation procedures.

Study	Study title	N*	Duration	Titration/Run-in	Treatment arms	Device
SAM40040	A twenty-four week, randomised, double-dummy, double-blind, parallel group study to compare the occurrence of exacerbations between SERETIDE DISKUS 50/250µg 1 inhalation bd and formoterol/budesonide Breath-Actuated Dry Powder Inhaler 4.5/160µg 2 inhalations bid in subjects with moderate to severe asthma.	691	24 weeks	Two-week run-in period	BUD/FOR 160/4.5 µg 2x b.i.d.	BADPI (Turbuhaler)
HZA106829	A randomised, double-blind, parallel group, multicentre study of fluticasone furoate/GW642444 inhalation powder, fluticasone furoate inhalation powder alone, and fluticasone propionate alone in the treatment of persistent asthma in adults and adolescents	376	24 weeks	Four-week run-in period	FF 200 µg o.d.	Diskus Inhaler
					FF/VI 200/25 µg o.d.	Diskus Inhaler
HZA106837	A long-term, randomized, double-blind, parallel group study of fluticasone furoate/GW642444 inhalation powder once-daily and fluticasone furoate inhalation powder once-daily in subjects with asthma	1728	52 weeks	Two-week run-in period	FF 100 µg o.d.	Diskus Inhaler
					FF/VI 100/25 µg o.d.	Diskus Inhaler
HZA116863	A randomised, double-blind, parallel group, multicentre study of fluticasone furoate/vilanterol 200/25 µg inhalation powder, fluticasone furoate/vilanterol 100/25 µg inhalation powder and fluticasone furoate 100 µg inhalation powder in the treatment of persistent asthma in adults and adolescents	973	12 weeks	Four-week run-in period	FF 100 µg o.d.	Diskus Inhaler
					FF/VI 100/25 µg o.d. 200/25 µg o.d.	Diskus Inhaler

*N represents the number of subjects included in the current data analysis

Table S2_2. Overview of the main assumptions supporting model parameterisation and analysis of reliever use data in patients with moderate-severe asthma symptoms**.**

Assumption	**Implications for model parameterisation and/or model interpretation**	**Notes**
Individual patient characteristics contribute the differences in reliever use frequency, irrespective of treatment or intervention.	Clinical and demographic baseline characteristics were evaluated as discrete or continuous covariates, affecting the frequency and extent of reliever use	As both overnight occasions and total number of puffs over the 24 h were collected, model parameterisation was based primarily on puffs/24 h to account for an eventual effect of circadian variation and random asthma triggers during day time.
As asthma symptom control achievement implies high degree of bronchoprotection, patients who achieve control should show a significant reduction in reliever use. Such a reduction may be biphasic, including a fast and a slow progressive decrease in over a wide time span.	This means that reliever use will vary for patients with different levels of symptom control. The magnitude of such an effect cannot be assessed in short term studies, despite a steep initial reduction in reliever medication use	
Data capture (i.e., number of overnight occasions or puffs over 24-h) from diary cards was accurate. Transcription errors, if occurred, were assumed to be random across treatment arms.	The observed number of occasions or puffs/24 h in each protocol are not affected by transcription errors. Random error estimates reflect not only model misspecification, but also any error in the recorded data	

Assumption	Implications for model parameterisation and/or model interpretation	Notes
When symptoms are under control, reliever use may occur in the presence of triggers, but are likely to be less frequent. Such an effect may be further modulated by treatment (i.e. drug=specific differences). In addition, a delay may be observed due to slow desensitisation to triggers and adaptative response to the anti-inflammatory effect of the underlying maintenance therapy.	This entails a delay to achieving the maximum effect of symptomatic interventions such as ICS monotherapy or ICS/LABA combination therapy, which may not be detectable immediately. This process is described by a hysteresis or adaptation mechanism.	This assumption reflects known differences in selectivity and intrinsic activity of the agonists on the desensitisation of β2-adrenoceptor-mediated response for airway smooth muscle relaxation, bronchodilation, and histamine release from mast cells in humans. For instance, it has been shown that treatment with formoterol causes a significant reduction in β-adrenoceptor density, whereas the effects of other β-agonists are not statistically significant.
Given the evidence that exacerbations and exacerbation history are associated with increased reliever use, as compared to patients who do not exacerbate, exacerbation events during the study were assumed to have minor effect on specific daily reliever use.	Irrespective of being a baseline covariate, exacerbation events or prior exacerbation history appears to have a persisting effect on the frequency and extent of reliever use. This apparent effect may be associated with other clinical and demographic baseline covariates known to determine an increased risk of exacerbation	As exacerbation history was not collected systematically across studies, a descriptive evaluation of the association between reliever use and exacerbation events was based on exacerbation events during the studies.

Assumption	Implications for model parameterisation and/or model interpretation	Notes
As the use of placebo intervention is not ethically acceptable. Initially, baseline estimates were derived using data from patients receiving ICS monotherapy.	Base lambda was estimated using data from patients receiving FF monotherapy. Given the limited dose levels included in the study, a theoretical estimate for a hypothetical dose of FF = 0 could not be derived directly, but inferred from estimates obtained with FP. All other treatments were estimated relative to this effect.	Whilst the use of a placebo control might have provided insight into the actual disease burden, treatment duration would have been too short to account for the hysteresis effect, which clearly affect reliever medication use.
The mean or median dose of ICS or ICS/LABA used in each treatment arm was considered representative of the treatment effect, irrespective of individual variation during maintenance therapy.	Given the symptomatic nature of the interventions and the known dose-exposure-response curves for inhaled corticosteroids, short-lasting variations in dose levels were considered to unlikely to alter the basal lambda.	As only two dose levels of FF were evaluated across the different studies, the effect of maintenance therapy on reliever medication use was treated as discrete covariates during model development.
ICS or ICS/LABA treatment effects were assumed to be independent from baseline characteristics. In addition, it was assumed that there is no interaction between drug-specific and patient-specific factors.	Baseline characteristics are defined as additive items, modifying the lambda parameter.	
Interindividual pharmacokinetic differences in reliever medication were assumed to have minor implications for its bronchodilatory activity. The frequency and number of puffs used was determined by the severity of symptoms (airway constriction).	Reliever exposure was not included as a source of variability in the model. Eventually, the effect of interindividual differences in drug exposure was captured by the residual error.	

Assumption	Implications for model parameterisation and/or model interpretation	Notes
Adherence to regular (maintenance) dosing across studies was assumed to be comparable given the similarity in patient population and protocol design. As such, it was treated as a constant random factor for the purposes of this analysis.	As adherence measurement was not standardised or eventually measured in the same way in all studies, the effect of adherence was not evaluated as a covariate during model development. If any, the effect of variable adherence was captured in the residual error.	This assumption implies that adherence to monotherapy and combination therapy are similar. During the exploratory analysis there was no evidence that patients on monotherapy behave differently from those on combination therapy.
Drop out and/or patient withdrawal during treatment were assumed to be random and non-informative, with minor or no effect on parameter estimates (baseline covariates or treatment).	It is unlikely that dropout or withdrawal affects parameter estimates, as the number of subjects dropping out prior to study completion was low. If any, the effect of drop-out and/or patient withdrawal was captured by the residual error.	
Given that there was only one dose level of vilanterol (VI), i.e., 25 µg, the effect of vilanterol was estimated based on the difference between FF 200 µg and FF/VI 200/25 µg. This effect was initially treated as constant across FF dose levels, including the effect of FF/VI at a 100/25 µg dose.	The effect of VI in combination with FF 100 µg is likely to be significantly greater than the estimated effect of VI in combination with FF 200 µg. The actual effect of VI may not be distinguishable from the anti-inflammatory activity of FF 200 µg.	The treatment arms included in the initial analysis data set consisted of FF 100 µg, FF 200 µg, FF/VI 100/25 and FF/VI 200/25 µg. In fact, 31.7% of the patients in the study population were treated with FF 100 µg , (monotherapy, Table S2_3. Study HZA116863, which was used as external validation data set also included a FF/VI 100/25 µg arm, but the study had a shorter treatment period than the minimum selected for the current analysis (12 weeks).

Results

The age of the subjects included in the population ranged from 18.0 to 82.0 years with a mean value of 46.7 years, whereas body weight ranged from 32.0 to 184.0 kg with a mean value of 78.0 kg. Mean observed symptom scores at baseline were 2.0 and 4.4 for ACQ-5 and AQLQ scores, respectively. Regarding lung function, as assessed by spirometry tests, FEV1 at baseline ranged from 0.7 to 5.6 L with a mean value of 2.15 L, while PEF ranged from 79.7 to 773.0 L/min, with a mean value of 347.0 L/min. Out of the patients reporting smoking history, the majority of patients reported to never have smoked (71.6%). A complete summary of the demographic and clinical baseline characteristics of subjects included in the analysis are presented in **Table S2_3** and **Table S2_4**. The distribution of the baseline characteristics per study are shown in **Figure S2_4**. The generalised pairs plot showing the relationship between the baseline demographics and clinical characteristics of the ITT population is displayed in **Figure S2_5**.

An initial exploratory analysis showed that individual patterns of 24-h reliever use were highly variable during the course of treatment (**Figure S2_2**). When stratified by baseline symptom control, there was a trend towards lower 24-h reliever use in subjects with well-controlled symptoms at baseline and higher 24-h reliever use for subjects with poor symptom control (**Figure S2_3**). There were also trends towards lower 24-h reliever use in subjects who have never smoked compared to former smokers, however there were no evident correlations between ACQ-5 and age, sex, BMI, or asthma duration (**Figure S2_5**).

Despite large inter and intra-individual variability, the final model was able to describe the patterns of 24-h reliever use in individual patients (**Figure S2_6**). The goodness-of-fit plots revealed acceptable correlations between observed data and model-predictions (**Figure S2_7** and **Figure S2_8**). Final model parameters are shown in **Table S2_5** and **Table S2_6**. A VPC of the total data set showed the observed data falls within the model predictions when stratified by treatment (**Figure S2_6**), indicating no bias, overfitting or other model mis-specifications. The VPC of the external validation dataset is shown in **Figure S2_9**.

The final model was used to generate heatmaps to extrapolate beyond the population used to develop the model (**Figure S2_10**). There was a trend higher 24-h reliever medication use for patients with higher BMI, longer asthma duration and for patients who had a history of smoking. Notably, smokers on average used 75.4% more reliever, compared to a never-smoker patient. Likewise, reliever use in former smokers was 42.3% higher than in patients who never smoked. Age and geographical ancestry were not found to significantly affect reliever use. By contrast, both combination therapies FF/VI and BUD/FOR were found to produce a significantly higher reduction in reliever use than FF monotherapy. Significant reductions in reliever use soon after initiation of the maintenance phase were observed with ICS/LABA combination therapy, with 74.9 % reduction relative to baseline being achieved after FF/VI 100/25 µg and 200/25 µg o.d.. Similarly, a 69.3% reduction was observed after BUD/FOR 320/9 µg b.i.d. Given the occurrence of a delayed effect (i.e., hysteresis), reliever use following FF/VI is further reduced up to 87.7% after 12 months, as compared to 85.4% following BUD/FOR.

Whilst the use of a Poisson model provided insight into individual patterns of reliever medication use, the approach we have used has some limitations. The main points of interest are summarised in **Table S2_7**.

Table S2_3. Demographic and clinical baseline characteristics of the patients included in this analysis stratified by treatment.

	BUD/FOR (N=691)	FF (N=1382)	FF/VI (N=1695)	Overall (N=3768)
Dataset				
Model Development	691 (100%)	1061 (76.8%)	1043 (61.5%)	2795 (74.2%)
External Validation	0 (0%)	321 (23.2%)	652 (38.5%)	973 (25.8%)
Treatment				
BUD/FOR 320/9 ug b.i.d	691 (100%)	0 (0%)	0 (0%)	691 (18.3%)
FF 100 ug o.d.	0 (0%)	1195 (86.5%)	0 (0%)	1195 (31.7%)
FF 200 ug o.d.	0 (0%)	187 (13.5%)	0 (0%)	187 (5.0%)
FF/VI 100/25 ug o.d.	0 (0%)	0 (0%)	1177 (69.4%)	1177 (31.2%)
FF/VI 200/25 ug o.d.	0 (0%)	0 (0%)	518 (30.6%)	518 (13.7%)
Sex				
Male	283 (41.0%)	456 (33.0%)	571 (33.7%)	1310 (34.8%)
Female	408 (59.0%)	926 (67.0%)	1124 (66.3%)	2458 (65.2%)
Age (y)				
Mean (SD)	47.0 (14.5)	46.5 (13.8)	47.0 (13.9)	46.8 (13.9)
Median [Min, Max]	48.0 [18.0, 82.0]	48.0 [18.0, 79.0]	48.0 [18.0, 82.0]	48.0 [18.0, 82.0]
Weight (kg)				
Mean (SD)	76.4 (16.4)	78.2 (18.8)	79.1 (19.4)	78.3 (18.7)
Median [Min, Max]	75.0 [40.0, 154]	76.0 [38.0, 166]	77.0 [32.0, 184]	76.0 [32.0, 184]
Height (cm)				
Mean (SD)	167 (10.2)	165 (10.2)	166 (9.93)	166 (10.0)
Median [Min, Max]	167 [140, 204]	164 [140, 201]	165 [136, 196]	165 [136, 204]
BMI (kg/m2)				
Mean (SD)	27.3 (5.43)	28.5 (6.05)	28.7 (6.27)	28.4 (6.06)
Median [Min, Max]	26.6 [17.4, 56.0]	27.5 [15.1, 55.8]	27.7 [14.8, 67.5]	27.5 [14.8, 67.5]
Asthma Duration (y)				
Mean (SD)	8.04 (5.20)	16.8 (13.7)	17.5 (14.0)	15.5 (13.2)
Median [Min, Max]	5.00 [2.00, 15.0]	13.0 [0, 70.0]	13.0 [0, 66.0]	12.0 [0, 70.0]
Smoking				
Never Smoked	437 (63.2%)	1003 (72.6%)	1259 (74.3%)	2699 (71.6%)
Current Smoker	72 (10.4%)	0 (0%)	0 (0%)	72 (1.9%)
Former Smoker	182 (26.3%)	192 (13.9%)	247 (14.6%)	621 (16.45%)
Missing	0 (0%)	187 (13.5%)	189 (11.2%)	376 (10.0%)
Observed ACQ5				
Mean (SD)	2.03 (0.952)	2.08 (0.890)	2.07 (0.898)	2.06 (0.911)
Median [Min, Max]	2.00 [0, 5.00]	2.00 [0, 5.00]	2.00 [0, 5.60]	2.00 [0, 5.60]
Missing	6 (0.9%)	508 (36.8%)	842 (49.7%)	1356 (36.0%)
ACT				
Mean (SD)	NA	14.1 (3.34)	13.8 (3.47)	13.9 (3.42)
Median [Min, Max]	NA	14.0 [6.00, 25.0]	14.0 [6.00, 24.0]	14.0 [6.00, 25.0]
Missing	691 (100%)	874 (63.2%)	854 (50.4%)	2419 (64.2%)
Calculated AQC5				
Mean (SD)	2.03 (0.952)	2.02 (0.846)	2.03 (0.852)	2.03 (0.869)
Median [Min, Max]	2.00 [0, 5.00]	2.00 [0, 5.00]	2.00 [0, 5.60]	2.00 [0, 5.60]
Missing	6 (0.9%)	0 (0%)	1 (0.1%)	7 (0.2%)
AQLQ				
Mean (SD)	NA	4.47 (1.01)	4.43 (1.03)	4.45 (1.02)
Median [Min, Max]	NA	4.48 [1.94, 6.66]	4.38 [1.55, 7.00]	4.41 [1.55, 7.00]

	BUD/FOR (N=691)	FF (N=1382)	FF/VI (N=1695)	Overall (N=3768)
Missing	691 (100%)	878 (63.5%)	857 (50.6%)	2426 (64.4%)
FEV1				
Mean (SD)	2.40 (0.851)	2.11 (0.643)	2.08 (0.625)	2.15 (0.689)
Median [Min, Max]	2.27 [0.750, 5.56]	1.99 [0.750, 4.55]	1.97 [0.700, 4.15]	2.03 [0.700, 5.56]
Missing	1 (0.1%)	3 (0.2%)	6 (0.4%)	10 (0.3%)
FEV1p				
Mean (SD)	78.1 (18.1)	68.0 (11.5)	67.0 (11.5)	69.4 (13.6)
Median [Min, Max]	76.9 [30.8, 143]	68.6 [40.1, 92.9]	67.4 [39.9, 99.0]	69.0 [30.8, 143]
Missing	1 (0.1%)	3 (0.2%)	6 (0.4%)	10 (0.3%)
PEF (L/min)				
Mean (SD)	386 (111)	334 (122)	322 (113)	347 (118)
Median [Min, Max]	379 [138, 770]	321 [81.3, 773]	311 [79.7, 749]	337 [79.7, 773]
Missing	0 (0%)	874 (63.2%)	854 (50.4%)	1728 (45.9%)

Table S2_4. Demographic and clinical baseline characteristics of the patient population included in the analysis stratified by study.

	SAM40040 (N=691)	HZA106829 (N=376)	HZA106837 (N=1728)	HZA116863 (N=973)	Overall (N=3768)
Dataset					
Model Development	691 (100%)	376 (100%)	1728 (100%)	0 (0%)	2795 (74.2%)
External Validation	0 (0%)	0 (0%)	0 (0%)	973 (100%)	973 (25.8%)
Treatment					
BUD/FOR 320/9 ug b.i.d	691 (100%)	0 (0%)	0 (0%)	0 (0%)	691 (18.3%)
FF 100 ug o.d.	0 (0%)	187 (49.7%)	0 (0%)	0 (0%)	187 (5.0%)
FF 200 ug o.d.	0 (0%)	189 (50.3%)	0 (0%)	329 (33.8%)	518 (13.7%)
FF/VI 100/25 ug o.d.	0 (0%)	0 (0%)	874 (50.6%)	321 (33.0%)	1195 (31.7%)
FF/VI 200/25 ug o.d.	0 (0%)	0 (0%)	854 (49.4%)	323 (33.2%)	1177 (31.2%)
Sex					
Male	283 (41.0%)	155 (41.2%)	500 (28.9%)	372 (38.2%)	1310 (34.8%)
Female	408 (59.0%)	221 (58.8%)	1228 (71.1%)	601 (61.8%)	2458 (65.2%)
Age (y)					
Mean (SD)	47.0 (14.5)	46.8 (13.6)	46.1 (13.8)	47.8 (13.8)	46.8 (13.9)
Median [Min, Max]	48.0 [18.0, 82.0]	48.0 [18.0, 74.0]	47.0 [18.0, 82.0]	48.0 [18.0, 82.0]	48.0 [18.0, 82.0]
Weight (kg)					
Mean (SD)	76.4 (16.4)	80.3 (17.8)	76.8 (19.0)	81.5 (19.4)	78.3 (18.7)
Median [Min, Max]	75.0 [40.0, 154]	78.6 [45.0, 149]	74.0 [32.0, 184]	79.0 [40.0, 177]	76.0 [32.0, 184]
Height (cm)					
Mean (SD)	167 (10.2)	168 (9.34)	164 (9.94)	167 (10.0)	166 (10.1)
Median [Min, Max]	167 [140, 204]	168 [142, 196]	164 [136, 201]	166 [141, 197]	165 [136, 204]
BMI (kg/m2)					
Mean (SD)	27.3 (5.43)	28.4 (5.94)	28.3 (6.16)	29.2 (6.24)	28.4 (6.06)
Median [Min, Max]	26.6 [17.4, 56.0]	27.5 [17.2, 52.2]	27.4 [14.8, 67.5]	28.1 [15.1, 55.1]	27.5 [14.8, 67.5]
Asthma Duration (y)					
Mean (SD)	8.04 (5.20)	15.9 (12.9)	16.6 (13.7)	18.7 (14.5)	15.5 (13.2)
Median [Min, Max]	5.00 [2.00, 15.0]	12.0 [0, 64.0]	13.0 [1.00, 70.0]	15.0 [0, 66.0]	12.0 [0, 70.0]
Smoking					
Never Smoked	437 (63.2%)	0 (0%)	1452 (84.0%)	810 (83.2%)	2699 (71.6%)
Current Smoker	72 (10.4%)	0 (0%)	0 (0%)	0 (0%)	72 (1.9%)
Former Smoker	182 (26.3%)	0 (0%)	276 (16.0%)	163 (16.8%)	621 (16.5%)
Missing	0 (0%)	376 (100%)	0 (0%)	0 (0%)	376 (10.0%)
Observed ACQ5					
Mean (SD)	2.03 (0.952)	NA (NA)	2.08 (0.894)	NA (NA)	2.06 (0.911)

	SAM40040 (N=691)	HZA106829 (N=376)	HZA106837 (N=1728)	HZA116863 (N=973)	Overall (N=3768)
Median [Min, Max]	2.00 [0, 5.00]	NA [NA, NA]	2.00 [0, 5.60]	NA [NA, NA]	2.00 [0, 5.60]
Missing	6 (0.9%)	376 (100%)	1 (0.1%)	973 (100%)	1356 (36.0%)
ACT					
Mean (SD)	NA (NA)	13.7 (3.32)	NA (NA)	14.0 (3.46)	13.9 (3.42)
Median [Min, Max]	NA [NA, NA]	14.0 [7.00, 25.0]	NA [NA, NA]	14.0 [6.00, 24.0]	14.0 [6.00, 25.0]
Missing	691 (100%)	0 (0%)	1728 (100%)	0 (0%)	2419 (70.1%)
Calculated AQC5					
Mean (SD)	2.03 (0.952)	2.00 (0.758)	2.08 (0.894)	1.95 (0.794)	2.03 (0.869)
Median [Min, Max]	2.00 [0, 5.00]	1.86 [0, 3.96]	2.00 [0, 5.60]	1.86 [0.126, 4.53]	2.00 [0, 5.60]
Missing	6 (0.9%)	0 (0%)	1 (0.1%)	0 (0%)	7 (0.2%)
AQLQ					
Mean (SD)	NA (NA)	4.41 (0.958)	NA (NA)	4.46 (1.05)	4.45 (1.02)
Median [Min, Max]	NA [NA, NA]	4.34 [1.97, 6.56]	NA [NA, NA]	4.47 [1.55, 7.00]	4.41 [1.55, 7.00]
Missing	691 (100%)	6 (1.6%)	1728 (100%)	1 (0.1%)	2426 (64.4%)
FEV1					
Mean (SD)	2.40 (0.851)	2.15 (0.662)	2.16 (0.644)	1.95 (0.580)	2.15 (0.689)
Median [Min, Max]	2.27 [0.750, 5.56]	2.05 [0.860, 4.55]	2.04 [0.700, 4.54]	1.87 [0.780, 4.02]	2.03 [0.700, 5.56]
Missing	1 (0.1%)	5 (1.3%)	0 (0%)	4 (0.4%)	10 (0.3%)
FEV1p					
Mean (SD)	78.1 (18.1)	66.5 (12.5)	70.9 (10.6)	61.7 (10.2)	69.4 (13.6)
Median [Min, Max]	76.9 [30.8, 143]	67.4 [40.1, 90.0]	71.3 [45.1, 99.0]	62.1 [39.9, 80.1]	69.0 [30.8, 143]
Missing	1 (0.1%)	5 (1.3%)	0 (0%)	4 (0.4%)	10 (0.3%)
PEF (L/min)					
Mean (SD)	386 (111)	329 (118)	NA (NA)	326 (116)	347 (118)
Median [Min, Max]	379 [138, 770]	315 [79.7, 773]	NA [NA, NA]	313 [88.3, 749]	337 [79.7, 773]
Missing	0 (0%)	0 (0%)	1728 (100%)	0 (0%)	1728 (45.9%)

Table S2_5. Parameter estimates of the final model describing reliever use in moderate-severe asthma patients. Basal reliever use count is described using FF monotherapy as reference treatment.

Parameter[1]	Value	SE	RSE[2]	95% CI from covariance step
Base lambda (log overnight occasions)[3]	-0.55 (FIXED)	-	-	-
Base lambda (log 24h puffs)[4]	1.28 (FIXED)	-	-	-
Effect BUD/FOR (b.i.d.)	-1.18 (FIXED)	-	-	-
Effect FF (100 µg o.d.)	-0.664	0.008	1.2%	-0.706 to -0.649
Effect FF (200 µg o.d.)	-1.13	0.020	1.8%	-1.170 to -1.090
Effect VI (25 µg o.d.)	-0.251	0.051	20.2%	-0.351 to -0.151
E_{MAX_T}	0.826 (FIXED)	-	-	-
ET_{50}	0.308 (FIXED)	-	-	-
Effect of ACQ-5	0.486	0.022	4.5%	0.444 to 0.529
Effect of BMI	0.0224	0.003	13.6%	0.016 to 0.028
Effect of asthma duration	0.013	0.002	14.3%	0.009 to 0.017
Effect of current smoking	0.562	0.071	12.7%	0.423 to 0.701
Effect of former smoker	0.353	0.024	6.9%	0.306 to 0.400
	Value	**SE**	**RSE (%)**	**Shrinkage (%)**
Ω_{base}	5.45	0.371	6.8	3%
Box-Cox transform	-0.231	0.008	20.2%	-0.247 to -0.215
Scaling factor (overnight occs to puffs/24h)[5]	0.624	0.024	3.8%	0.577 to 0.671

[1]All values on log scale except ET_{50} and ED_{50}

[2]Calculated based on normal-scale values.

[3] λ_{base} for overnight occasions was only available for SAM40040. Based on the previous model, the additional study effect of 0.563 (log overnight occasions) for SAM40040 was also incorporated in this model to improve model predictions.

[3] λ_{base} for puffs/24 h was different for study HZA106829 and HZA106837. Based on the previous model, the additional study effect of -1.215 (log 24-h reliever use) for HZA106837 was also incorporated in this model to improve model predictions.

[5]A single, scaled omega was used to characterise the variability of eta for both base lambda of overnight occasions and puffs/24h.

Table S2_6. Parameter estimates of the final model describing reliever use in moderate-severe asthma patients. Basal reliever count is described using FF monotherapy as reference treatment.

	Parameter	Value	Note
Baseline covariates	Base overnight occasions	0.58	Estimated population average base overnight occasions.
	Base puffs/24 h	3.60	Estimated population average base puffs/24 h. With the inclusion of study effect, the base puffs/24 h for HZA106837 was 1.07.
	ACQ-5 effect (% increase in reliever use per unit)	62.5%	Percentage change in reliever use for a 1 unit increase in ACQ-5 relative to the mean ACQ-5 score of 1.8
	Current smoker effect relative to Never Smoked (% increase in reliever use)	75.4%	Patients who are smokers at baseline have a 75.4 % higher reliever use compared to patients who have never smoked
	Former smoker effect relative to Never Smoked (% increase in reliever use)	42.3%	Patients who are former smokers have a 42.3 % higher reliever use compared to patients who have never smoked
	BMI effect (% increase in reliever use per kg/m^2)	2.22%	Percentage change in lambda for every 1 unit of change in BMI relative to the mean BMI of 26 kg/m^2
	Asthma duration effect (< 5, ≥5 -<10, ≥ 10 years)	6.7%, 13.8%	Patients who were diagnosed with asthma 5 or 10 years ago, have a higher reliever use compared to those patients recently diagnosed
	FF effect 100 µg o.d. 200 µg o.d. (% decrease in reliever use)	-48.5%, -67.7	Magnitude of the dose-dependent effect of treatment with FF monotherapy on reliever use relative to base lambda.
	VI effect (25 µg o.d.) (% decrease in reliever use)	-22.2%	Magnitude of the effect of treatment with VI monotherapy on reliever use relative to base lambda. The effect of FF/VI was assumed to be the sum of the two components on the base parameter (i.e., -74.9%). At twelve months after start of treatment, the effect of FF/VI 100 µg or 200 µg o.d. corresponds to a 87.7% reduction in reliever use
	BUD/FOR effect (% decrease in reliever use)	-69.3%	Magnitude of the effect of treatment with BUD/FOR combination therapy on reliever use relative to base lambda. At twelve months after start of treatment, this effect corresponds to a 85.4% reduction in reliever use
	Hysteresis effect at 3 months at 12 months	1.45 1.88	Fractional increase in treatment effect relative to the onset of therapy with FF, FF/VI or BUD/FOR.
	Hysteresis 50% effect time point (months)	3.7	At 3.7 months, one reaches 50% of the maximum effect that will be achieved on reliever use reduction. In fact, this parameter indicates that a 1.2 year study is required to assess near maximum (80%) reliever use reduction. This parameter indicates that maximum reduction in reliever use is detectable only in studies in which treatment lasts longer than 1 year

3.7

Figure S2_2. Exploratory graphs depicting the effect demographic and clinical baseline characteristics on the patterns of 24-h reliever use in moderate-severe asthma patients.

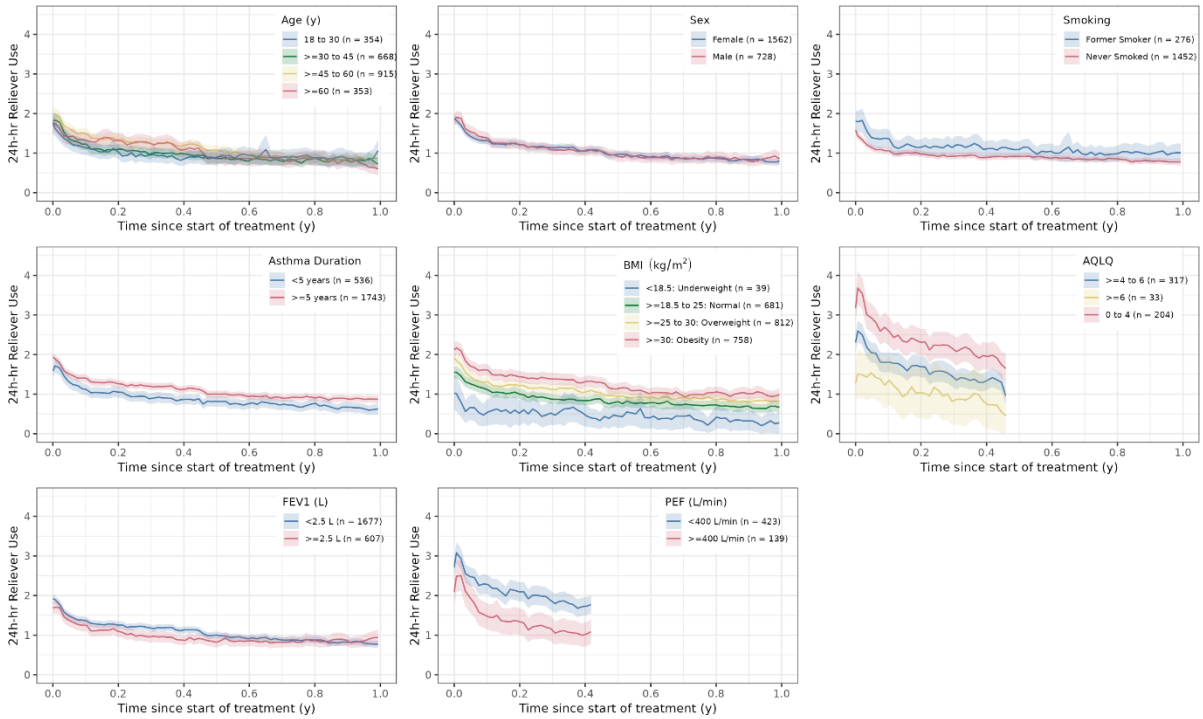


Figure S2_3. Observed reliever use (puffs/24 h and overnight occasions) over time in the overall population, stratified by symptom control level at baseline (ACQ-5) (left) and by occurrence of exacerbations (right). Mean patterns describe both exacerbating and non-exacerbating patients, with exacerbation defined as in the original study protocols: use of systemic corticosteroids for ≥3 days, OR in-patient hospitalization, OR emergency department visit due to asthma requiring systemic corticosteroids. These patterns of reliever use are associated with ICS and ICS/LABA doses according to individual response and/or protocol asthma control plan (FF: 100 and 200 µg once daily; FF/VI: 100/25 and 200/25 µg once daily). Legend in each panel indicates the number of patients in each category or group.

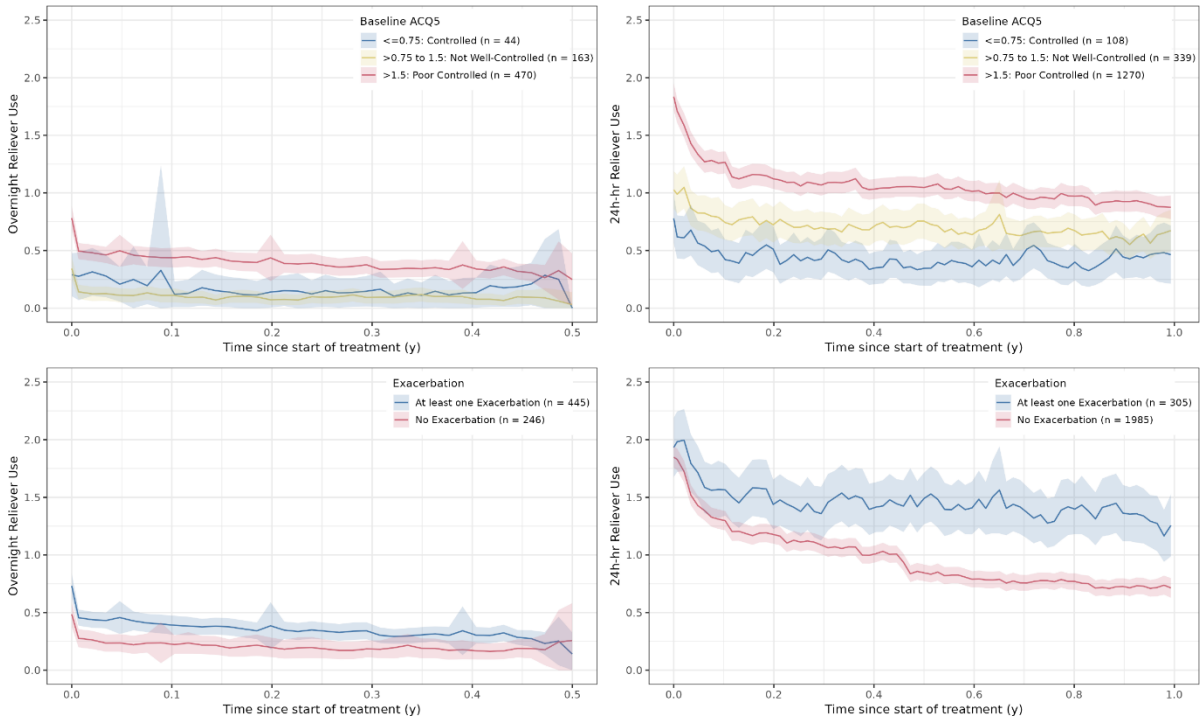


Figure S2_4. Distribution of baseline characteristics stratified by study. Number of distributions may vary in each panel as not all variables have been collected at baseline for all studies. ACQ-5 = asthma control questionnaire; BMI = body mass index, FEV_1 = forced expiratory volume 1 second, PEF = peak expiratory flow

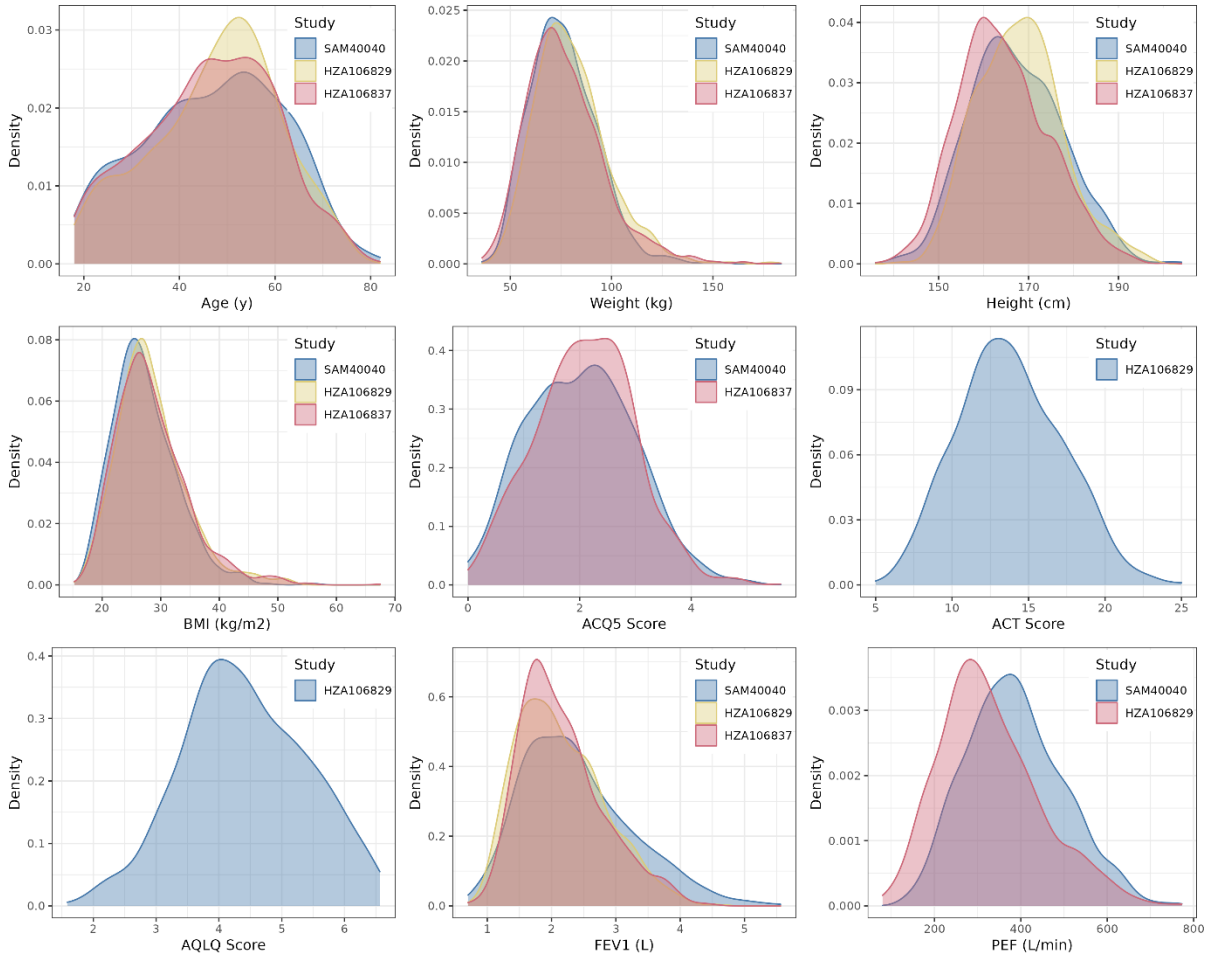


Figure S2_5. Generalised pairs plot describing the correlation matrix for available baseline characteristics across three studies used to develop the model (N=2795). ACQ5 – Asthma control questionnaire, AQLQ – Asthma quality of life questionnaire, BMI – Body mass index, FEV1 – Forced expiratory volume in the first second, Cort Use – prior use of inhaled corticosteroids, PEF – peak expiratory flow.

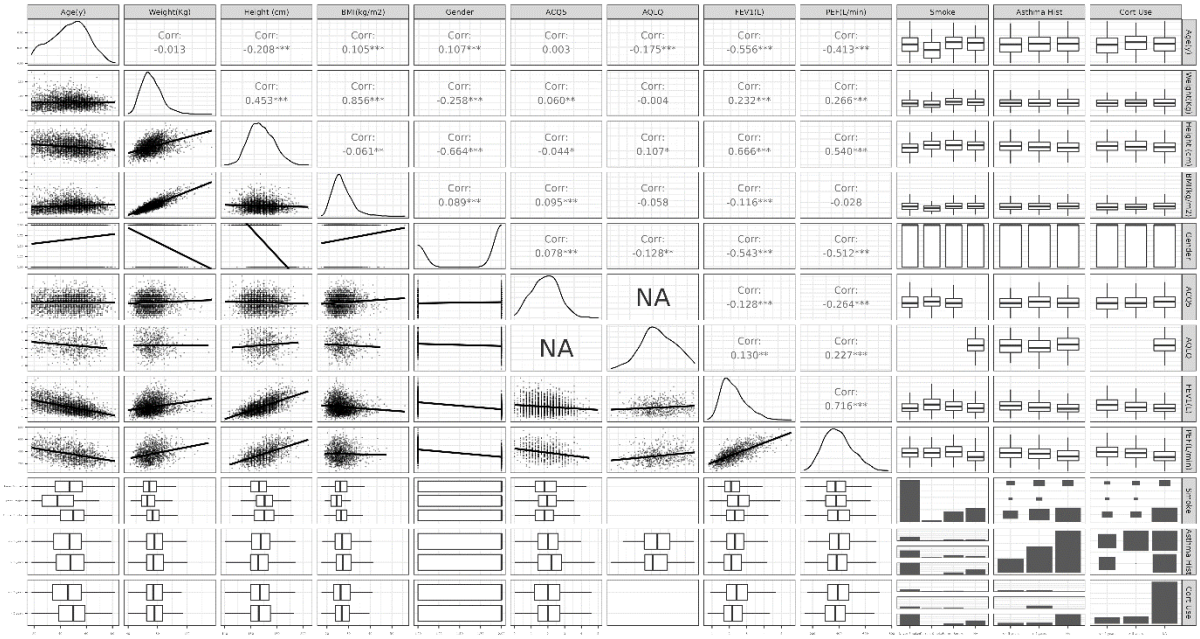


Figure S2_ 6. Visual-predictive check showing predicted overnight occasions (left panel) and puffs/24 h (right panel) over time stratified by treatment and symptom control at baseline. The solid line describes the average observed reliever use over the period of up to 12 months across the overall population. Shaded areas show the 95% prediction interval. "N" is the number of patients contributing to the profiles in each panel.

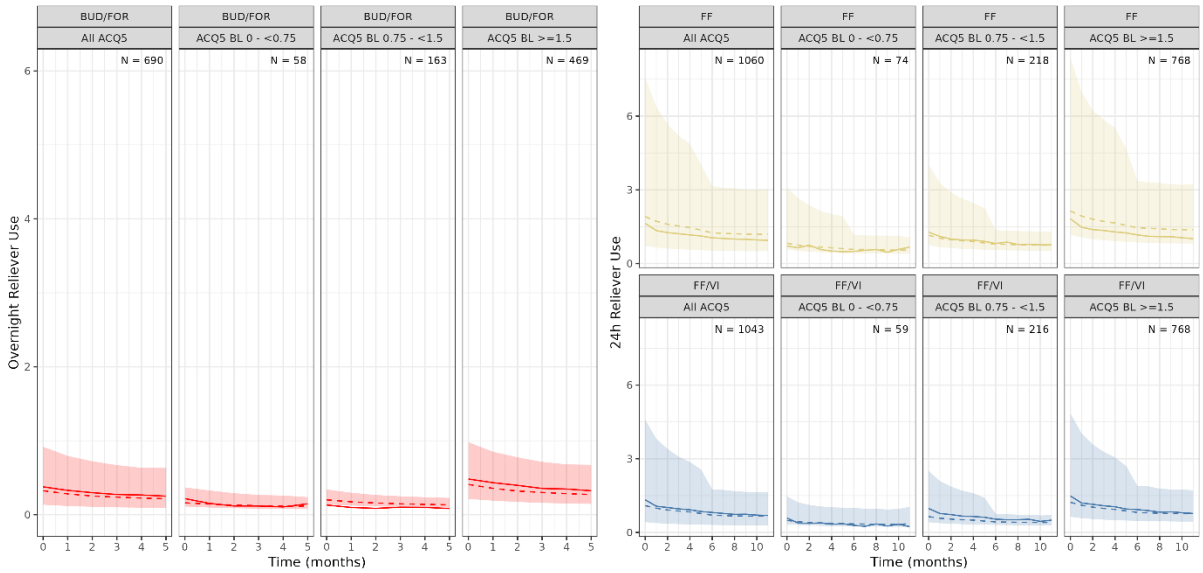


Figure S2_7. Visual predictive checks (VPCs) describing model predicted (dotted line) and observed (solid line) overnight occasions for study SAM40040 stratified by symptom control level (ACQ-5) at baseline. Shaded areas represent the 95% prediction interval. "N" is the number of patients contributing to the profiles in each panel. Deviations observed for the average population predicted overnight occasions in patients who are poorly controlled at baseline are eliminated by taking into account individual baseline differences in overnight occasions.

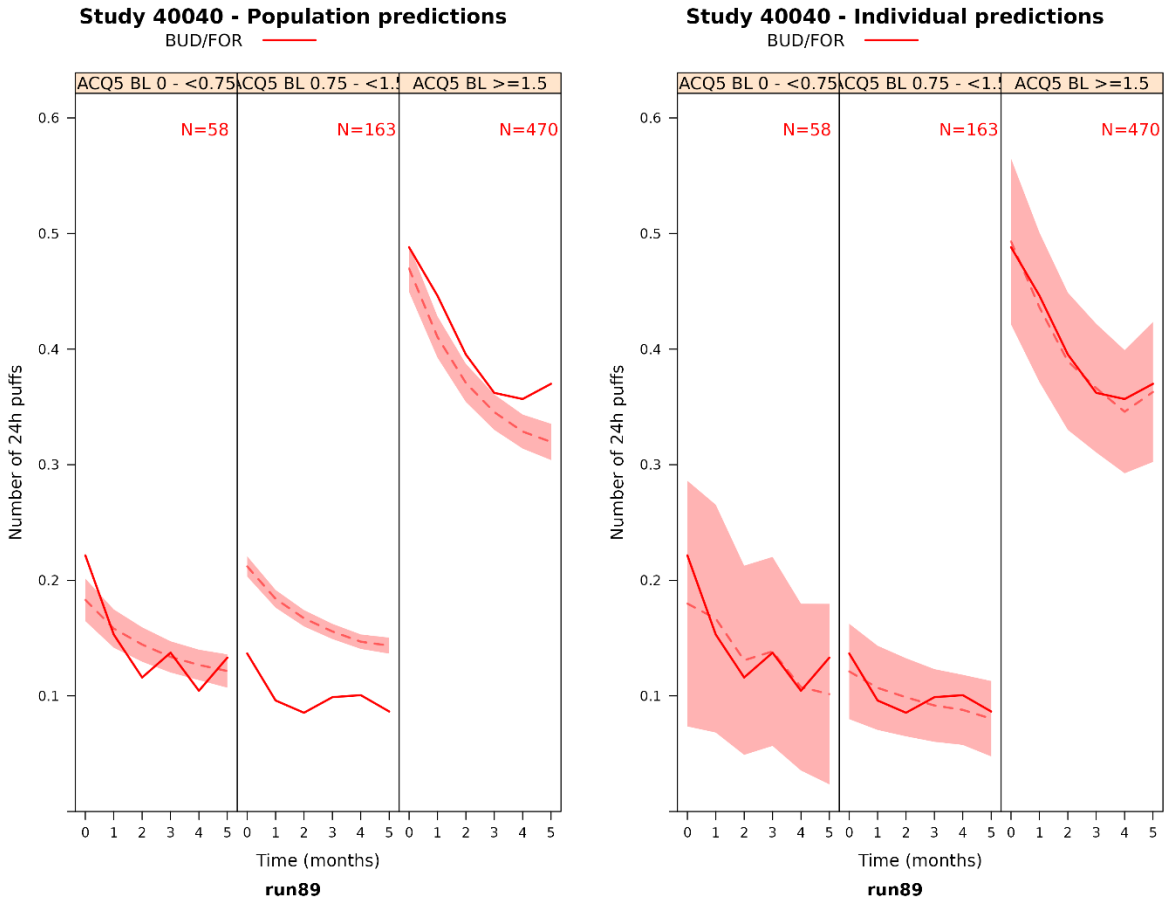


Figure S2_8. Visual predictive checks (VPCs) describing model predicted (dotted line) and observed (solid line) 24h reliever use for studies HZA106829 and HZA106837 stratified by symptom control level (ACQ-5) at baseline. Shaded areas represent the 95% prediction interval. "N" is the number of patients contributing to the profiles in each panel.

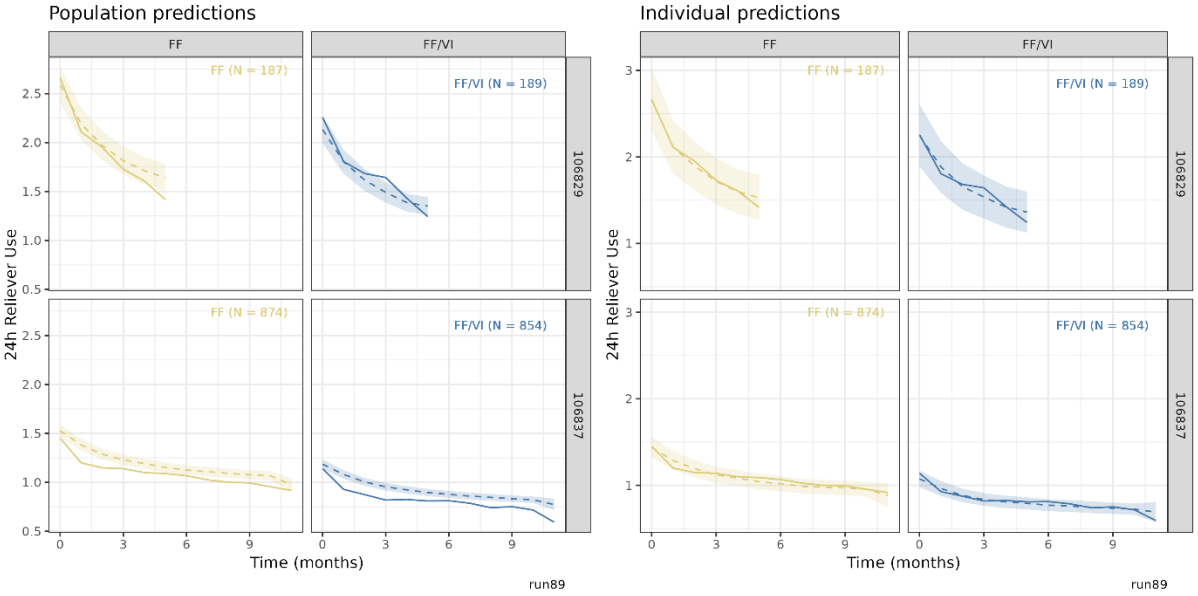


Figure S2_9. External validation of the Poisson model describing reliever use in patients with moderate-severe asthma symptoms (N=973). Visual-predictive checks (VPCs) show the mean observed (solid line) and predicted (dashed line) reliever use profiles along with the 95% prediction intervals (shaded area) stratified by treatment and symptom control level at baseline in study HZA116863. The number of puffs over the last 24 h (Y-axis) is depicted over the treatment period (maintenance therapy).

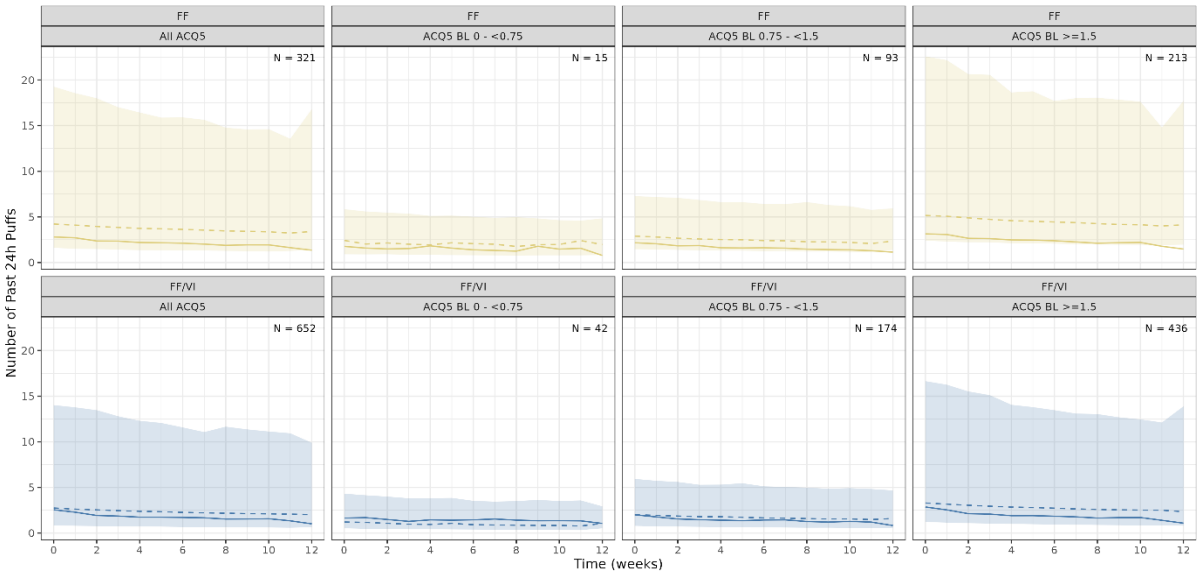
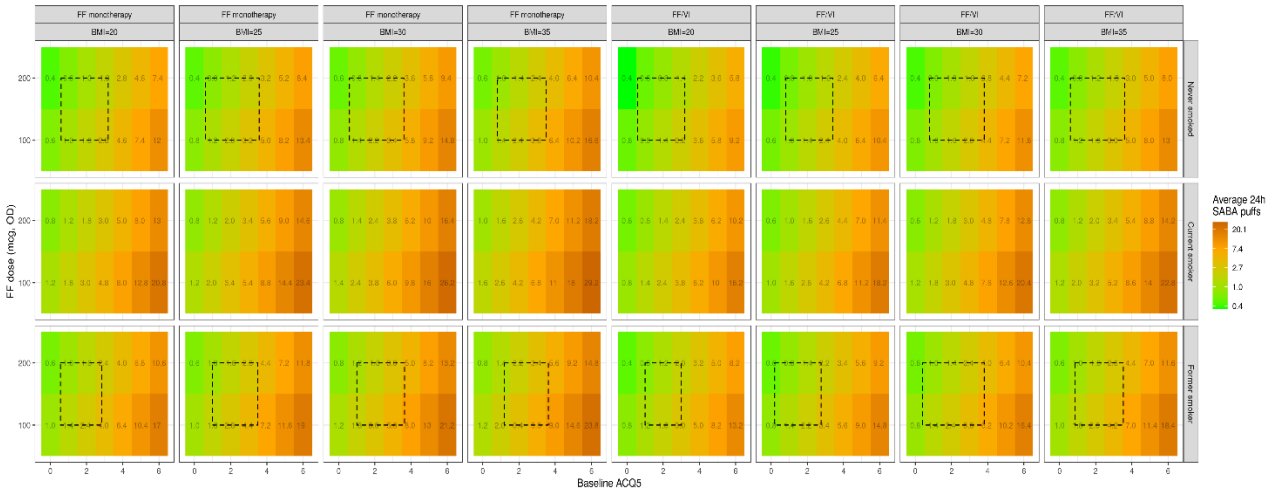


Figure S2_10. Heatmap of predicted puffs/24 h for **a**) varying baseline ACQ-5, smoking status and body mass index (BMI) vs. FF dose following monotherapy or combination with VI; **b**) varying baseline ACQ-5, BMI, smoking status and asthma duration following combination therapy with BUD/FOR or FF/VI.

A



B

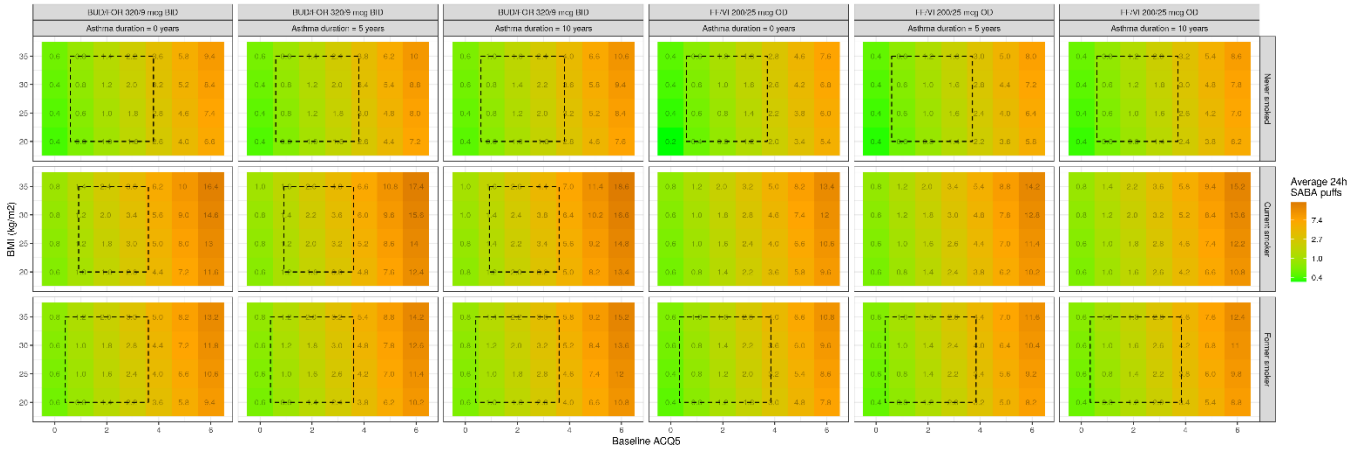


Table S2_7. Overview of limitations of the data and proposed modelling approach.

Data available for this analysis	As with any pharmacometrics approach, the predictive performance and generalisability of the model depends highly upon the data available and the clinical questions one aims to address. We have identified high-quality clinical trials in patients with moderate or severe asthma receiving different treatments, who were closely monitored for a period of at least 24 weeks and whose data included clinical and demographic baseline information, daily records on reliever medication use as well as longitudinal measures of symptom control and exacerbation events. Despite the high quality of the data, we acknowledge that the number of clinical trials that meet the inclusion criteria was limited. However, given the length of the study interventions and frequency of data collection, it is unlikely that eventual imbalance in the number of patients or in baseline characteristics of the patients assigned to the different treatment arms will result in bias or confounding.
Potential for selection bias	Selection bias is a common and valid concern when evaluating aggregated data. Nonetheless, we have used individual level patient data collected in trials that reflect typical protocol designs in moderate-severe asthma. Even if our analysis was limited to the available Phase III/IV clinical trials in which fluticasone furoate (FF), as monotherapy or in combination with vilanterol (VI), and budesonide/formoterol (BUD/FOR) were evaluated, the baseline characteristics of the patient population included in these studies reflect the interindividual variability observed in the published literature.
Missing data, protocol endpoints	Missing information on the start and end of treatment was imputed based on protocol treatment duration data (i.e. study visit dates and times). Patients were excluded if details on the treatment received were not available or the date and time of start and end of treatment could not be imputed with sufficient accuracy. Similarly, individual records were excluded if missing visit dates and times could not be imputed based on nominal visit dates and times. Values were also to be excluded from the analysis based on inconsistency or a documented error. On the other hand there were different protocol designs. Consequently, different endpoints have been used across studies, and as such, individual level data were not always available for the overall analysis population (e.g. baseline ACQ-5 measurements, ACQ-5 vs. ACT or ACQ-6). We have therefore attempted to minimise the use of imputation by converting ACT into ACQ-5 based on the underlying data distribution and category or level of symptom control.

Imputation procedures for missing baseline covariates	A sensitivity analysis was implemented to assess the impact of the working assumptions during model development and validation, including the potential effect of missing baseline covariates. The results from this analysis suggest that the missing covariate information does not have a significant effect on the final model parameter estimates. In addition, given the availability of data across a range of clinically relevant values we have assumed that parameter estimates obtained from the pooled database (n=3451) were unbiased and sufficiently precise to describe the effect of baseline covariates on reliever medication use in subsequent application of the model for simulation purposes.
Discriminating the effect of patient baseline characteristics from treatment	Whilst a Poisson model is a standard tool for the analysis of count data, we have considered the implications of overdispersion (i.e., where the variance is considerably greater than expected under an assumed distribution) and zero-inflation (i.e., where excessive zeros beyond what would be expected under a given probability distribution are observed) [10-12]. This assessment ensured that both covariate effects and interindividual random variation were adequately characterised. Moreover, the model was parameterised to disentangle the effect of different covariates, distinguishing patient and disease-related factors from drug-specific properties [6]. In addition, the availability of different dosing groups allowed for stratification of patients assigned to FF and FF/VI by dose level as a discrete variable, enabling the evaluation of treatment effect associated with the underlying maintenance therapy. Unfortunately, this was not possible for BUD/FOR combination therapy, as the tested dose levels during the study were limited. Consequently, estimates of the treatment effect for BUD/FOR were handled as a discrete covariate [13]. It is also worth highlighting that in the absence of data for BUD only, the estimates for the immediate effect of BUD/FOR on reliever use (i.e., initial steep reduction in reliever use) may not be interpreted in the same way as those obtained for FF/VI, for which FF monotherapy data was available. This is relevant when predicting the overall effect over 12 month, as the hysteresis observed in the data is assumed to be driven by the anti-inflammatory effect of corticosteroids. Finally, it should be noted that differences in ICS dose could be confounded by the effect of individual variation in inhalation procedures. Therefore, it has been assumed that at therapeutic doses, that the random variation in lung exposure to ICS has minor impact on the reliever medication use.
Treatment adherence and dropout	Another important point to consider is the duration of the studies (i.e., between 24 and 52 weeks). We have assumed that adherence to treatment would have been high, and interindividual differences in response are explained by patient characteristics, rather than variable treatment adherence [14, 15]. Dropout was not modelled as the number of patients who dropped out or withdrew from the studies was relatively low (~15%). These figures are in line with previously reported data in severe asthma [16,17]. In addition, it should be clear that we have only considered regular maintenance therapy, as the use of maintenance and reliever therapy (MART) was out of scope.
Apparent estimates of reliever use rate	We also acknowledge that the parameter estimates may not describe the true extent of reliever intake in the absence of maintenance therapy. Our parameterisation of the Poisson function was relative to the use of FF monotherapy. A placebo arm was not available in the clinical studies

at the start of maintenance therapy	included in this analysis, as it would have been ethically unacceptable to maintain patients on placebo for the duration of the study protocol. Moreover, estimates of reliever use obtained from a placebo arm in a much shorter study would lead to inaccurate extrapolation of results, among other things due to the hysteresis in the pattern of reliever medication use, which is observed relative to the start of treatment. It is also worth mentioning that we have attempted to assess the consistency of the estimated treatment effect relative to that of the baseline covariates which were identified as statistically significant in the final model. Additional steps were taken to assess the potential role of measured and unmeasured confounding. A propensity score matching was performed, which provided perfectly matched patients (FF, FF/VI an BUD/FOR). This subset of the overall population corroborated the findings, indicating that estimates of the effect of treatment on base lambda are unlikely to have been affected by confounding [18].
Apparent estimates of the mean effect of FF/VI 100/25 µg dose on reliever use during maintenance therapy	Given that there was only one dose level of vilanterol (VI), i.e., 25 µg, the effect of vilanterol was estimated based on the difference between FF 200 µg and FF/VI 200/25 µg. This effect was initially assumed to be constant across FF dose levels, including the effect of FF/VI at a 100/25 µg dose. However, previous reports have shown that the combination of long-acting inhaled β2-agonists with inhaled corticosteroids are not only additive, but the addition of a LABA to an inhaled corticosteroid was superior to administering twice as much of the inhaled corticosteroid [19,20]. Consequently, the effect of VI in combination with FF 100 µg is greater than the estimated effect of VI in combination with FF 200 µg. This is likely to be caused by the maximum (plateau) effect associated with the anti-inflammatory activity of FF 200 µg. Therefore, the mean effect of maintenance therapy with FF/VI 100/25 µg on reliever use, i.e., the covariate effect was fixed to the same value of the higher FF dose for subsequent use of the model in clinical trial simulations, including real-life clinical management scenarios. This imputation was required to avoid bias on the predicted effect of ICS/LABA maintenance therapy across the different scenarios

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APPENDIX 1: Poisson model control stream

```
$PROB POIS base model
$INPUT ID TIME TIM1 STUDYN SABAOCC1 SABAOCC4 EXEVENT DV FLG ICSDUR EXOCC IARACEN FDARACEN ICOUNTRY
ACTBL ACT AQLQBL AQLQ ACQ5BL EACQ5BL QACQ5BL ACQ5 TRTNUM FP BUDFORM FF VI SEXN AGEBL BMIBL WTBL
ASTHDUR FEV1 FEV1BL FEV1P FEV1PBL SMOKN ETHN FENOBL
$DATA ../DATASETS/SOURCE/relvar_countdata_v3.csv IGNORE=@ IGNORE=(STUDYN.EQ.40056)
IGNORE=(STUDYN.EQ.201378) IGNORE=(STUDYN.EQ.116863)

$PRIOR NWPRI NTHETA=20 NETA=1 NTHP=5
$PRED

BCTR=THETA(9)
IF(BCTR.EQ.0) BCTR=0.00000001

ET1=ETA(1)
ET2=ETA(1)*THETA(8)

ET1TR=((exp(ET1)**BCTR)-1)/BCTR
ET2TR=((exp(ET2)**BCTR)-1)/BCTR

ACQ5BL_C=QACQ5BL
IF(ACQ5BL_C.LE.0) ACQ5BL_C=1.8 ;in case of missing ACQ5BL

BMIBL_C=BMIBL
IF(BMIBL_C.LE.0) BMIBL_C=26

ASTHDUR_C=ASTHDUR
IF(ASTHDUR_C.LT.0) ASTHDUR_C=8.4

TIMY=TIM1/(24*365)
IF(STUDYN.EQ.40040)
TIMY=TIMY+14/365 ;RUN-IN period of 2 weeks

BASESM=0
IF(SMOKN.EQ.2) BASESM=THETA(4)
IF(SMOKN.EQ.3) BASESM=THETA(5)

ADDTH=0
IF(STUDYN.EQ.40040) ADDTH=-1 * THETA(7)  ;BASE SABAOCC1 EFFECT FOR 40040

ADDTH2=0
IF(STUDYN.EQ.106829) ADDTH2=0 ;BASE SABAOCC4 STUDY EFFECT
IF(STUDYN.EQ.106837) ADDTH2=THETA(18)  ;BASE SABAOCC4 STUDY EFFECT

BASE=THETA(17) + ADDTH +BASESM+THETA(1)*(ACQ5BL_C-1.8)+THETA(2)*(BMIBL_C-26)+THETA(3)*(ASTHDUR_C-
8.4)+ET1TR
IF(FLG.EQ.4) BASE=THETA(6) + ADDTH2 + BASESM+THETA(1)*(ACQ5BL_C-1.8)+THETA(2)*(BMIBL_C-
26)+THETA(3)*(ASTHDUR_C-8.4)+ET2TR

EMAX_T=THETA(13)
ET50=THETA(14)
EFF_T=(EMAX_T*TIMY)/(ET50+TIMY)

EMAX_FP=THETA(10)*(1+EFF_T)
EC50_FP=THETA(11)

EFF_FP=(EMAX_FP*FP)/(EC50_FP+FP)
;EFF_FP=EMAX_FP*FP
EFF_SALM=0
;IF(SALM.GT.0) EFF_SALM=THETA(16)

EFF_SYMB=0
SYMB=BUDFORM
IF(SYMB.GT.0) EFF_SYMB=THETA(12)*(1+EFF_T)

EFF_FF = 0
IF(FF.EQ.100) EFF_FF=THETA(19)*(1+EFF_T)
IF(FF.EQ.200) EFF_FF=THETA(20)*(1+EFF_T)
EC50_FF=THETA(15)

;EFF_FF =(EMAX_FF*FF/2)/(EC50_FF+FF/2)

EFF_VI=0
IF(VI.GT.0) EFF_VI=THETA(16)
```

```
LAMB=EXP(BASE+EFF_FP+EFF_SYMB+EFF_FF+EFF_VI)

ETTR=ET1TR
IF(FLG.EQ.4) ETTR=ET2TR
LAMBPOP=EXP(BASE+EFF_FP+EFF_SALM+EFF_SYMB+EFF_FF+EFF_VI-ETTR)

IF(LAMB.LE.0) LAMB=0.0000001

  ;Approximation of the factorial (log scale)
  ; In NM730 you can also use LFAC=GAMLN(DV+1.0)
 IF(DV.LE.1) THEN

LFAC=0
 ELSE

LFAC=DV*LOG(DV)-DV+LOG(DV*(1+4*DV*(1+2*DV)))/6+LOG(3.1415)/2
 ENDIF

  ;Logarithm of the Poisson distribution
 LPOI = -LAMB+DV*LOG(LAMB)-LFAC

  ;-2 Log Likelihood
 Y=-2*(LPOI)

$THETA
 5.65E-01   ;TH1 acq5bl ON base
 2.52E-02   ;TH2 BMIBL on BASE
 2.75E-02   ;TH3 ASTHDUR on BASE
 5.85E-01   ;TH4 SMOKE=2
 3.58E-01   ;TH5 SMOKE=3
(1.28 FIX) ;TH6 BASE SABAOCC4
(0.563) FIX ;TH7 40040 BASE SABAOCC1
(0, 0.611,2) ;TH8 Scaling ET1 to ET2
(-0.229) ;TH9 BOX-COX
(-5, -1.12,0) FIX  ;TH10 EMAX_FP
(0, 54.8) FIX ;TH11 EC50_FP
(-5, -1.18,0) FIX ;TH12 EMAX_SYMB
(0, 0.826,1) FIX  ;TH13 EMAX_T
(0, 0.307,1)  FIX ;TH14 ET50
(0 FIX)  ;TH15 EC50_FF
(-5, -0.291,0)  ;TH16 EMAX_VI
(-0.55 FIX)  ;TH17 BASE SABAOCC1
(0.67)  ;TH18 ADDTH2 SABAOCC4
(-5, -0.664,0)   ;TH19 100 EMAX_FF
(-5, -1.15,0)   ;TH20 200 EMAX_FF

$OMEGA
 5.6 ;BASE SABAOCC1

$THETA  ;PRIORS
 5.65E-01  FIX ;TH1 acq5bl ON base
 2.52E-02  FIX ;TH2 BMIBL on BASE
 2.75E-02  FIX ;TH3 ASTHDUR on BASE
 5.85E-01  FIX ;TH4 SMOKE=2
 3.58E-01  FIX ;TH5 SMOKE=3
;-3.93E-01  FIX ;TH6 BASE SABAOCC1
; 1.49E+00  FIX ;TH7 BASE SABAOCC4

$OMEGA BLOCK (5) FIX;PRIORS
9.99E-04
0  2.00E-05
0  0  2.10E-05
0  0  0  5.69E-03
0  0  0  0  6.69E-04

$ESTIM MAXEVAL=9999 METHOD=COND LAPLACE -2LL PRINT=10
$COV MATRIX=R
$TABLE ID TIME TIM1 STUDYN SABAOCC1 SABAOCC4 EXEVENT DV FLG TRTNUM ICSDUR ACTBL ACT AQLQBL AQLQ ACQ5BL
ACQ5 FP BUDFORM FF VI SEXN AGEBL BMIBL WTBL ASTHDUR EXOCC FEV1 FEV1BL FEV1P FEV1PBL SMOKN FENOBL LAMB
LAMBPOP LPOI BASE EFF_FP EFF_SYMB EFF_FF EFF_VI ACQ5BL_C QACQ5BL ET1 ET2

FILE=run89.tab NOAPPEND ONEHEADER NOPRINT FORMAT=s1PE11.5
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APPENDIX II: Poisson model input dataset example

SUBJIDN	TIME	TIM1	STUDYN	SABAOCC1	SABAOCC4	EXEVENT	DV	FLG	ICSDUR	EXOCC	IARACEN	FDARACEN	ICOUNTRY	ACTBL	ACT	AQLQBL	AQLQ	ACQ5BL	eACQ5BL	qACQ5BL	ACQ5	TRTNUM	FP	BUDFORM	FF	VI	SEXN	AGEBL	BMIBL	WTBL	ASTHDUR	FEV1	FEV1BL	FEV1P	FEV1PBL	SMOKN	ETHN	FENOBL
805	17.73333	0	106829	NA	0	0	0	4	NA	0	20	4	740	12	13	3.75	4.75	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	2.59	2.4	77.6	75	NA	2	NA
805	24	6.266667	106829	NA	3	0	3	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	48	30.26667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	72	54.26667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	96	78.26667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	120	102.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	144	126.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	168	150.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	192	174.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	216	198.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	240	222.2667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	264	246.2667	106829	NA	3	0	3	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	288	270.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	312	294.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	336	318.2667	106829	NA	4	0	4	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	377.25	359.5167	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	3.31	2.4	99.2	75	NA	2	NA
805	384	366.2667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	408	390.2667	106829	NA	5	0	5	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	432	414.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	456	438.2667	106829	NA	4	0	4	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	480	462.2667	106829	NA	6	0	6	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	504	486.2667	106829	NA	3	0	3	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	528	510.2667	106829	NA	4	0	4	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	552	534.2667	106829	NA	4	0	4	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	576	558.2667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	600	582.2667	106829	NA	3	0	3	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	624	606.2667	106829	NA	3	0	3	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	648	630.2667	106829	NA	6	0	6	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	672	654.2667	106829	NA	5	0	5	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	713.2	695.4667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	3.35	2.4	100.6	75	NA	2	NA
805	720	702.2667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	744	726.2667	106829	NA	4	0	4	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	768	750.2667	106829	NA	2	0	2	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	792	774.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	816	798.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	840	822.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	864	846.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	888	870.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	912	894.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	936	918.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA
805	960	942.2667	106829	NA	0	0	0	4	NA	0	20	4	740	12	NA	3.75	NA	NA	2.01	2.07	NA	3	0	0	200	25	1	63	28	75	9	NA	2.4	NA	75	NA	2	NA