Supplementary Material

Effect of individual patient characteristics and treatment choices on reliever medication use in moderate-severe asthma: a Poisson analysis of randomised clinical trials

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Identification, retrieval, and selection of studies from GSK's clinical study repository

Identification

Number of studies and enrolled patients with moderate-severe asthma identified from clinical trials within GSK's repository
(n studies = 17, n subjects = 24402)

Studies excluded *before screening*:
- experimental medicine studies
- Phase I studies in healthy subjects
- studies with a duration less than 24 weeks
- studies in which asthma was not the primary indication or condition, but a co-morbidity

Screening

Studies screened
(n studies = 17, n subjects = 24402)

Inclusion criteria:
- demographic and clinical baseline details
- treatment, dose and dosing regimens
- asthma symptom scores assessed during maintenance phase
- accurate records on exacerbation events
- individual longitudinal records on reliever medication use

Study data retrieval
(n studies = 5, n subjects = 6744)

Studies excluded
(n studies = 12, n patients = 17658)

Studies meeting the inclusion criteria
(n studies = 5, n subjects = 6744)

Subjects excluded due to lack of accurate demographic, treatment records, or baseline asthma symptom control scores (ACQ-5 or ACT) (n patients = 532)

Included

Studies selected for model development and evaluation (n =5)

Subjects included in the analysis (n = 6212)

Total number of records on maintenance therapy and reliever medication use
(n = 3,178,281 records)

Number of subjects per treatment:
FP (n=2077)
FP/SAL (n=3100)
BUD/FOR (n=1035)

Dose and dosing regimen:
FP: 100, 250 and 500 µg twice daily;
FP/SAL: 100/50, 250/50 and 500/50 µg twice daily;
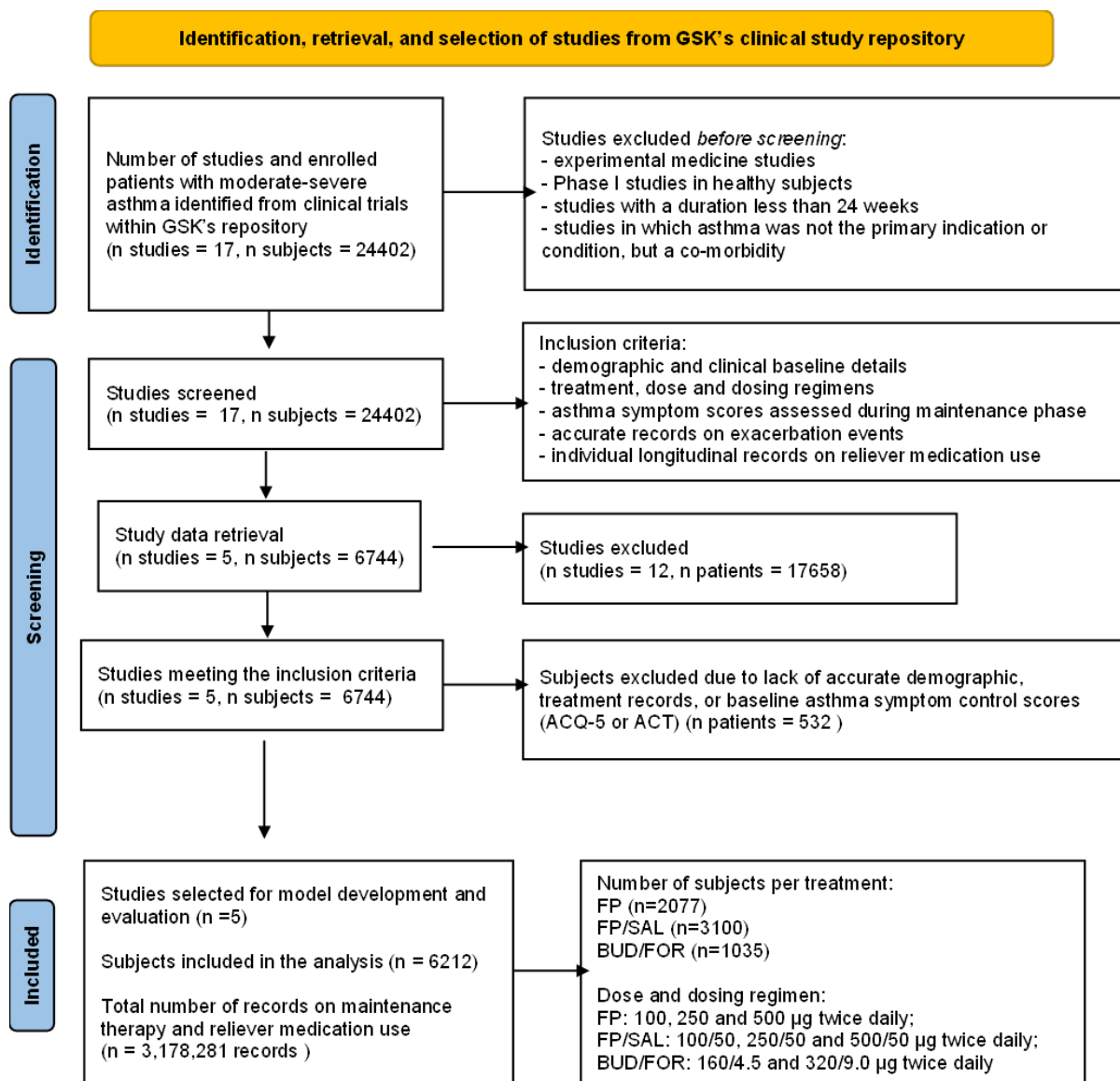BUD/FOR: 160/4.5 and 320/9.0 µg twice daily

Figure S1. Flow diagram describing the Identification, retrieval, and selection of studies from GSK's clinical study repository along with the inclusion and exclusion criteria.

ACQ-5= Asthma control questionnaire, ACT = Asthma control test , BUD/FOR – budesonide-formoterol, FP – fluticasone propionate, FP/SAL – fluticasone propionate-salmeterol

Poisson Model Parameterisation:

The model is based on a main parameter (i.e., the Poisson parameter) called lambda (λ), which represents both the mean and the variance of the counts. Here, we have modelled λ, the average number of occurrences per unit of time, 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).

Identification of potential covariates was undertaken during the exploratory analysis. Initially, reliever use data were stratified by symptom control level, as assessed by ACQ-5 and prior history of exacerbation or evidence of exacerbation during the treatment period. Such a stratification was deemed important to assess the long-term effects of symptom control and exacerbations on individual patterns of reliever use. These patient-specific factors were considered for further evaluation as covariates or described as interindividual variability in the base lambda parameter. Following the structural model selection, demographic and clinical baseline covariates were investigated using a stepwise forward addition-backward elimination procedure.

The following variables were available for investigation as covariates:

- Subject baseline demographics: age, race, body mass index, smoking status, sex.

- Baseline clinical characteristics: FEV_1, FEV_1p, PEF, ACQ-5, asthma duration, previous ICS use.

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.

In addition to the aforementioned patient-specific (intrinsic) factors, extrinsic factors were considered during model building. In contrast to previous findings on the influence of seasonal variation on the risk of exacerbations [1], no consistent variation was observed in reliever use relative to season following an initial graphical inspection of the data. Therefore, season was not included as a potential covariate in this analysis. Moreover, 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. Medical history, in particular exacerbation history and disease duration were also considered as a potential factor affecting reliever use.

In the end, maintenance therapy was evaluated, including dose level as a factor. Treatment was implemented either as a discrete effect (i.e., only one dose level), or as a sigmoidal Emax function when different doses levels were available (e.g., FP 100 µg, 250 µg and 500 µg). Given that none of the studies included in this analysis had a placebo arm, the base lambda (λ_{base}) was derived based on the extrapolation from the lowest FP dose level. Hence, estimates of λ obtained for the different treatments and conditions are relative to λ_{base}. In fact, a dose-response relationship could be estimated only for FP (as monotherapy or as part of the FP/SAL combination therapy), as this was the only treatment for which several dose levels were available. In addition, from an initial graphical exploration, it became apparent, after investigation of potential confounding (e.g., symptom severity), that the effect of reliever medication was also dependent on baseline reliever use, i.e. the more reliever was used at baseline, the larger the treatment effect. Consequently, treatment effect was modelled as a proportional effect relative to reliever use (additive on the log scale).

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 [2-4]. A detailed description of the dose response relationship, and its relevance for the dose range and dosing regimens included in these studies is provided later in this document (see **Dose-response relationship of inhaled corticosteroids**).

It should be emphasised that similar methodologies, aimed at characterising interindividual differences in disease processes, disease progression, and treatment response, have been applied elsewhere [1, 5]

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 ($\chi^2<0.05$ 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 ≥ 6.64 ($\chi^2<0.01$ for 1 df).

Whilst our initial plan was to perform model building with a subset of the population of all 5 studies and perform an internal validation step based on the remaining patients prior to implementing the external validation, during model building it became evident that all data were required to ensure successful runs and model stability. Hence, model performance was evaluated using visual predictive

checks (VPC) against the total patient population in the internal validation data set (data set 2). 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. A separate study was identified for the purpose of external validation. Study SAS115359:was a multicentre, randomised, double-blind trial, including patients with persistent moderate-severe asthma symptoms, who were assigned to receive either FP or FP/SAL for 26 weeks [6].

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 based on 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 (24-h puffs 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, which was not included in the model development phase. These patients received regular dosing FP/SAL (250/50 µg BID) or regular maintenance dose of BUD/FOR (160/4.5 µg BID), which could be increased by variable BUD/FOR 160/4.5 µg puffs up to 4 doses BID per day. The decision to increase the dose would be discussed with a physician and based on subjective symptoms of the patient ("BUD/FOR variable dosing").

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]. An example of the data set structure and NONMEM control stream file for the final model are included as an **Appendix** to this document.

Dose-response Relationships of Inhaled Corticosteroids

Even though it has been established that currently used ICS doses correspond to nearly maximum anti-inflammatory activity, the effect of dose level (in addition to treatment type) on reliever use was assumed to be significant. However, dose level was evaluated as a covariate only for FP due to data availability. As parameter estimates are based on FP, it is also important to highlight that we have applied the same principles endorsed by Beasley and colleagues [10], in that the current analysis does not rely on the terminology proposed by the Global Initiative for Asthma (GINA) guidelines. As underlined in their report, GINA's terminology classifies interventions into "low," "medium" and "high" doses of ICS to define daily maintenance doses of 100 to 250 µg, >250 to 500 µg and >500 µg, respectively, of fluticasone propionate or equivalent for adults with asthma. Specifically, the ICS dose that achieves 80%-90% of the maximum obtainable benefit is currently classified as a low dose, with the description of two higher dose levels, which in fact are associated with minor increase in ICS-related anti-inflammatory response [11, 12]. In this context, the "standard daily dose" can be defined as 200-250 µg of fluticasone propionate or equivalent, representing the dose at which approximately 80%-90% of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity.

There is a perception among prescribers that FP is equivalent to BUD at half the dose. Such a perception arises from the fact that FP is twice as potent as BUD in terms as GR binding affinity [13, 14]. Also, FP was launched as being twice as potent as beclomethasone dipropionate (BDP) and it was widely accepted at that time that BDP and BUD in metered dose inhalers (MDIs) were approximately equivalent on an mcg basis. Hence asthma treatment guidelines reflect dose equivalence as follows: BDP = BUD = FP/2. The problem is that the assumptions about dose equivalence were based on the original delivery devices, which were chlorofluorocarbon (CFC) MDIs and low efficiency dry-powder inhaler (DPIs). The Turbuhaler is a higher efficiency device and delivers about twice as much drug to the lungs compared to its original MDI, whereas the Diskus DPI is lower efficiency than the original CFC MDI. The net result is that BUD in the Turbuhaler is approximately equivalent to FP in the Diskus on a μg basis [15] .

RESULTS:

Model Validation

The internal validation step revealed that the model has acceptable performance when taking into account inter-individual differences in lambda. As shown in **Figure S5**, mean patterns of reliever use in patients receiving FP/SAL are well predicted, even though some variation is observed when stratifying the data by symptom control level at baseline. Interestingly, the use of a variable regimen in patients receiving BUD/FOR could not be described well by the model. Inspection of the VPC plots shows that reliever use in these patients remains higher than predicted by the model, suggesting that time-dependent maximum reduction in reliever observed following regular dosing may not be detected when the exposure to the underlying maintenance dose of ICS/LABA is variable. Such a deviation is not attributable to demographic or clinical baseline characteristics of the patients enrolled in this study (**Table S4**), which are similar to the population used for model development. The predictive performance of the model was further demonstrated by the external validation step, which

showed that the final model parameter estimates were sufficiently precise to describe reliever use in study SAS115359 (**Figure S6**).
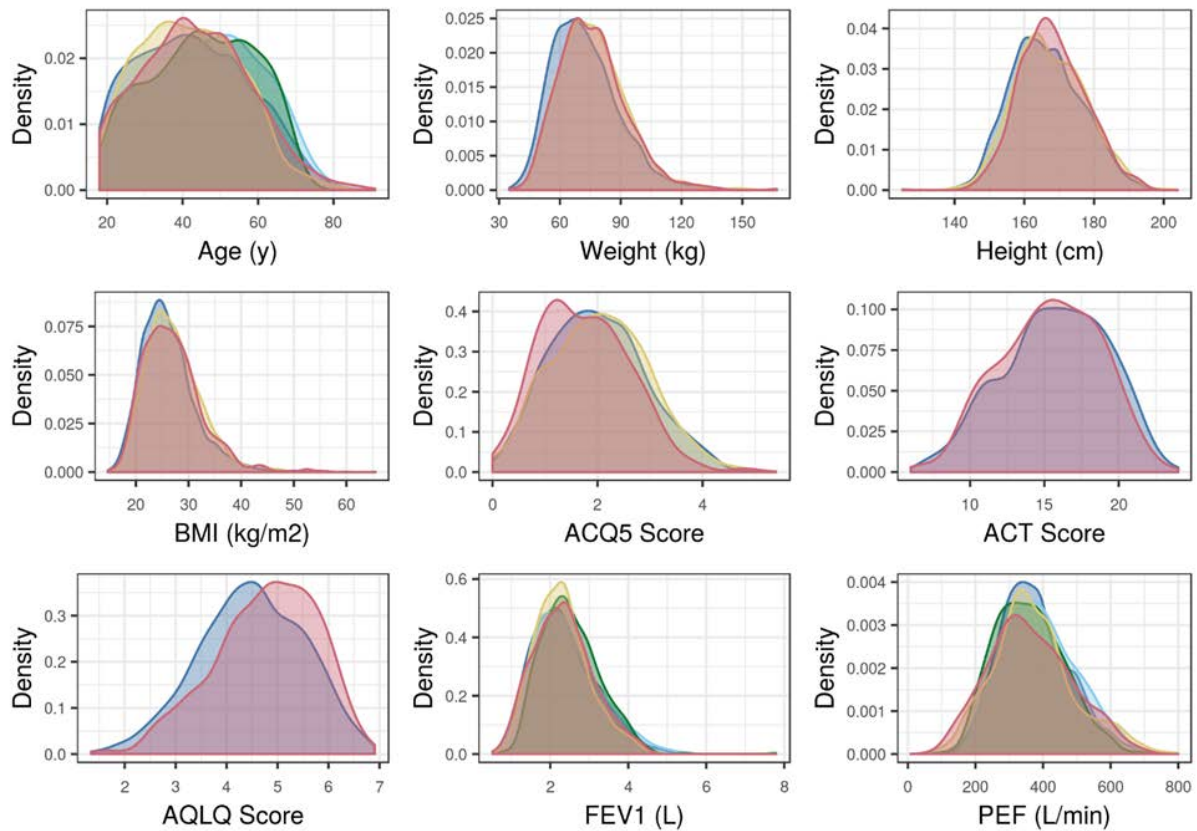
Figure S2. Distribution of baseline characteristics stratified by study (See Table 1 for details, N=6212). Number of distributions may vary in each panel as not all variables have been collected at baseline for all studies. ACQ-5 = asthma control questionnaire; BMI = body mass index, FEV_1 = forced expiratory volume 1 second, PEF = peak expiratory flow

Figure S3. Correlation matrix for available baseline characteristics across all five studies (N=6212).
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

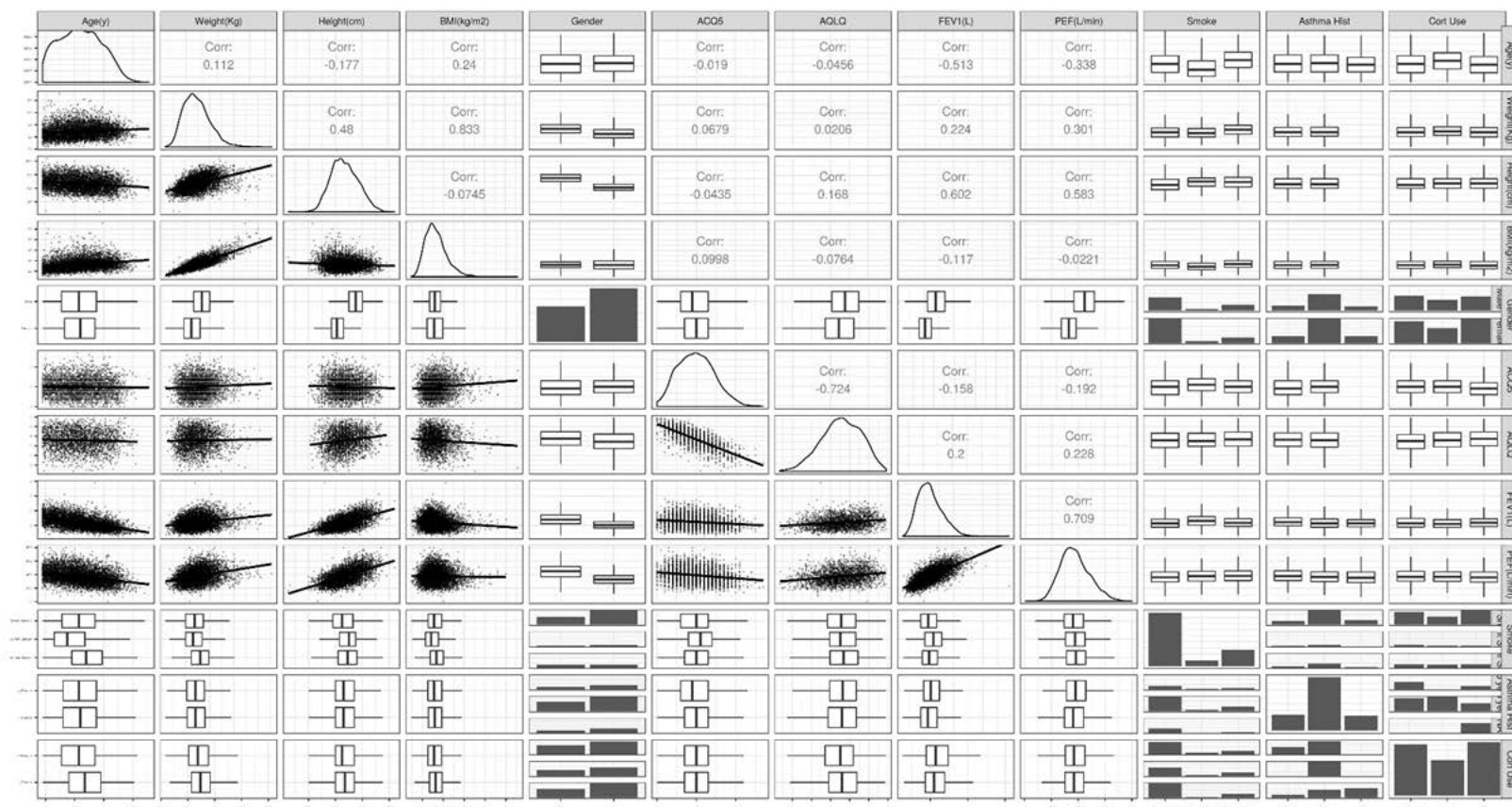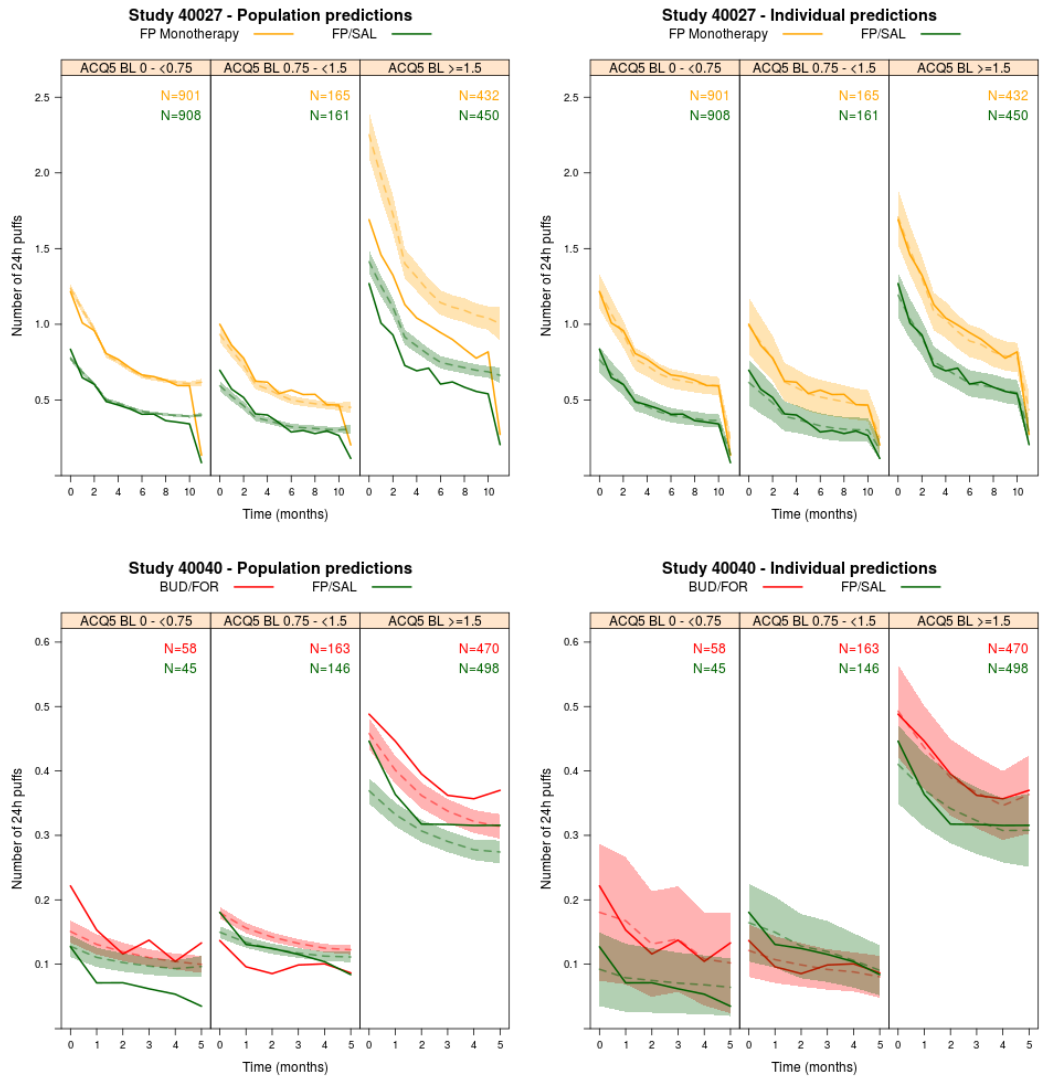**Figure S4.** Visual predictive checks (VPCs) describing model predicted (dotted line) and observed (solid line) 24 h puffs for studies SAM40027 (upper panel) and SAM40040 (lower panel) stratified by symptom control level (ACQ-5) at baseline. Shaded areas represent the 95% prediction interval. "N" is the number of patients contributing to the profiles in each panel. Deviations observed for the average population predicted 24h puffs in patients who are poorly controlled at baseline are eliminated by taking into account individual baseline differences in 24h puffs.

BUD/FOR – budesonide- formoterol, FP – fluticasone propionate, FP/SAL – fluticasone propionate-salmeterol
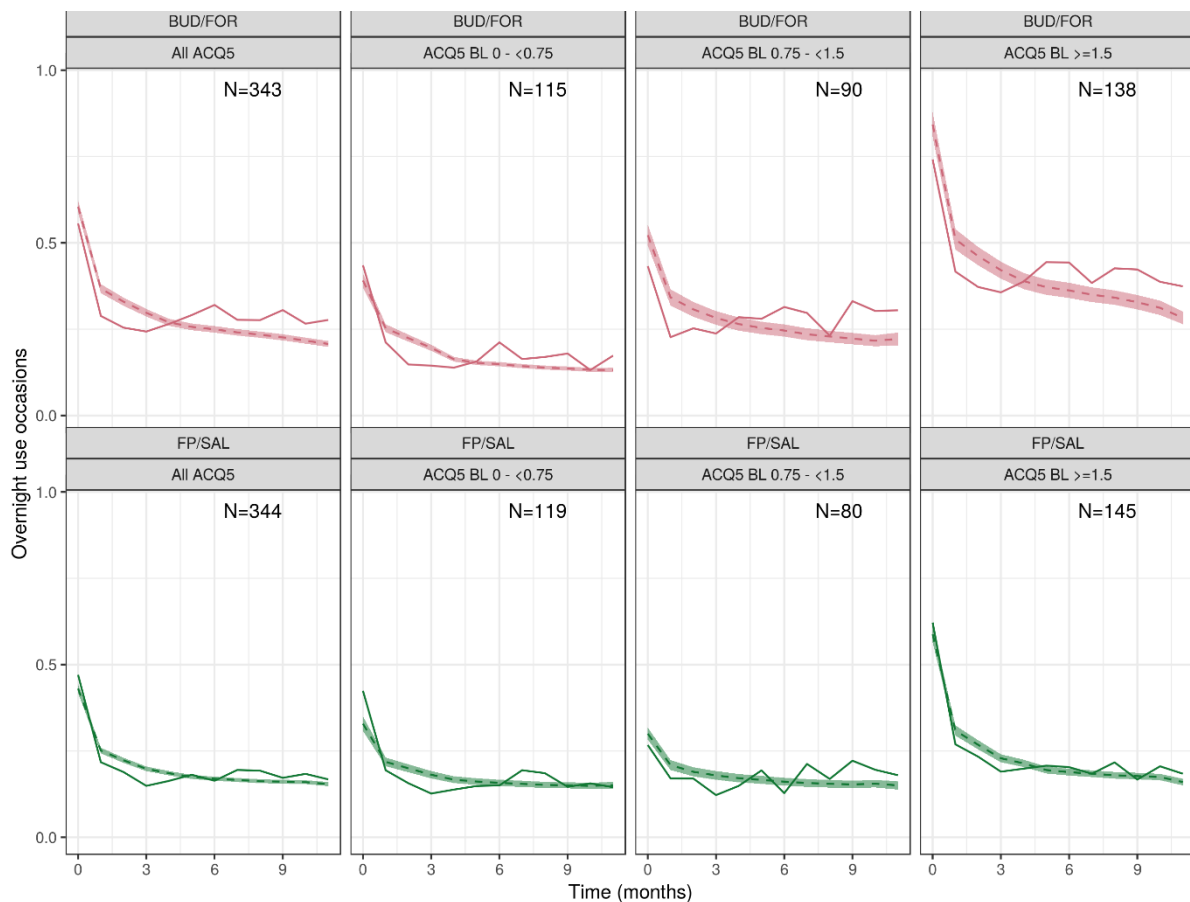
Figure S5. Internal validation focused on the FP/SAL treatment arm of study SAM40056. Average population observed (solid line) and predicted (dotted line) overnight reliever use following administration of regular maintenance dose FP/SAL (lower panel) or variable dosing BUD/FOR, as per protocol (upper panel). In addition to the total population, patterns of reliever use are 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. The differences between data and model performance following variable dosing of BUD/FOR suggest that maximum reduction in reliever use is not achieved with varying maintenance dosing regimen of ICS/LABA used in this study.

BUD/FOR – budesonide- formoterol, FP – fluticasone propionate, FP/SAL – fluticasone propionate-salmeterol, ICS/LABA – inhaled corticosteroid/long acting beta agonist
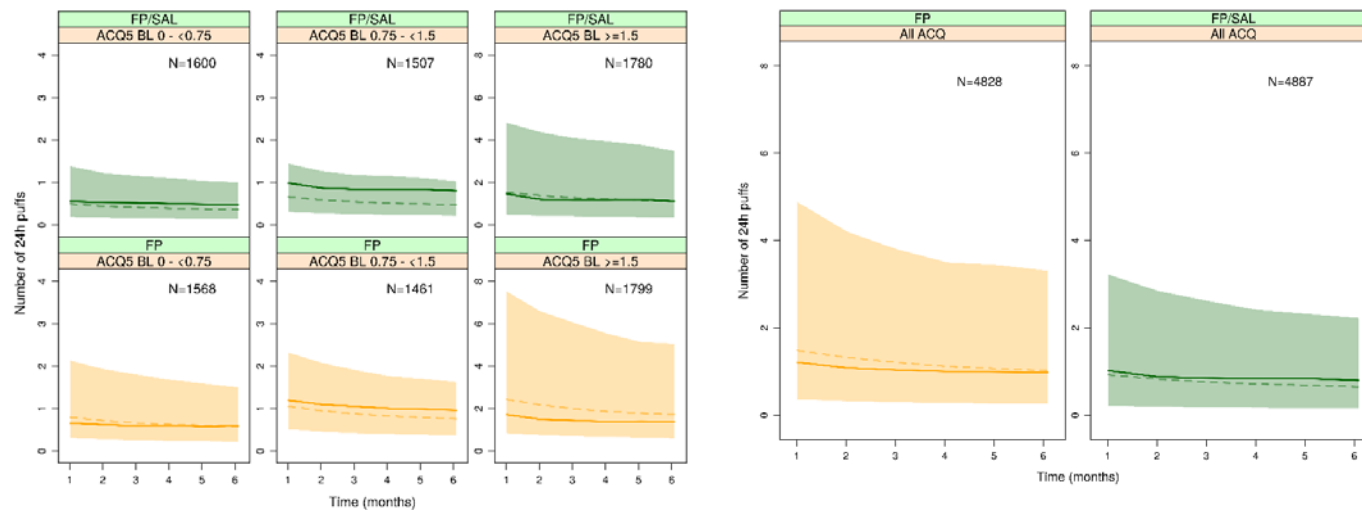
Figure S6. External validation of the Poisson model describing reliever use in patients with moderate-severe asthma symptoms (N=9715). Visual-predictive checks (VPCs) show the mean observed (solid line) and predicted (dashed line) reliever use profiles along with the 95% prediction intervals (shaded area) stratified by treatment and symptom control level at baseline in study SAS115359 (AUSTRI, NCT01475721) [6]. The number of puffs over the last 24 h (Y-axis) is depicted over the treatment period (maintenance therapy). See **Table S4** for details on the patient population baseline characteristics.

Standard validation procedures were implemented using final model parameter estimates. Baseline reliever use for patients the AUSTRI study was re-estimated (i.e., ~3 SABA puffs / 24h). ACQ-5 was derived from ACQ6 based on a linear correlation from model-building studies [ACQ-5 baseline = (ACQ-6 baseline – 0.1434)*1.0623]. Dosing regimens included in the studies were: FP Diskus 100 μg, 250 μg, and 500 μg bid (morning and evening); FP/SAL Diskus 100/50 μg, 250/50 μg, and 500/50 μg bid (morning and evening). Whilst the model predicts the data very well, this study also contributes to further understanding of the implications of the time delay to achieve maximum reduction in reliever use, which is overlooked when deriving annualised metrics based on short term studies. The observed and predicted mean reduction in cannisters per year between monotherapy and combination therapy was respectively, ~0.4 vs 0.8 (FP vs FP/SAL). Differences between observed and predicted mean reduction are partly caused by the annualization of the results based on data collected at 6 months. In addition, one needs to consider the absence of individual baseline data on reliever use, which imposes the assumption that maintenance therapy started at the same time for all patients, irrespective of symptom control status prior to inclusion into the studies.

ACQ5 – Asthma control questionnaire , BUD/FOR – budesonide- formoterol, FP – fluticasone propionate, FP/SAL – fluticasone propionate-salmeterol, ICS/LABA – inhaled corticosteroid/long acting beta agonis

Table S1. Demographic and clinical baseline characteristics of the patient population included in the analysis stratified by study (N=6212).

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Study	N	Age (y)	Weight (kg)	Height (cm)	BMI (Kg/m^2)	Female (%)	Male (%)	ACQ-5	ACT	ACQ-5*	AQLQ	FEV1 (L)	FEV1p (%)	PEF (L/min)
Mean (min-max)														
SAM40027	3049	42.9 (18-83)	72.4 (36-152)	166.2 (125-198)	26.1 (14.7-65.5)	59.9	40.1	2.0 (0-5.4)	NA	2.0 (0-5.4)	4.5 (1.3-6.9)	2.4 (0.5-6.2)	76.0 (20.5-147.6)	375.4 (102.9-799.8)
SAM40040	1380	46.3 (18-91)	76.3 (35-153.8)	167.5 (140-204)	27.2 (15.1-56.0)	57.3	42.7	2.0 (0-5.2)	NA	2.0 (0-5.2)	NA	2.4 (0.6-5.6)	78.2 (25.7-142.6)	391.0 (98.2-769.9)
SAM40056	688	45.3 (18-74)	76.1 (37-167)	168.1 (145-194)	26.9 (15.1-55.9)	61.0	39.0	1.8 (0.0-5.0)	NA	1.8 (0.0-5.0)	4.8 (1.5-6.8)	2.5 (0.8-7.8)	80.7 (40.1-376.3)	359.5 (82.7-688.2)
ADA109055	535	42.0 (18-80)	NA	NA	NA	67.5	32.5	NA	15.7 (7-24)	1.5 (0.2-3.9)	NA	2.3 (0.7-4.7)	72.0 (36.4-113.0)	371.2 (80.0-777.0)
ADA109057	560	43.3 (18-88)	NA	NA	NA	62.3	37.7	NA	15.4 (6-24)	1.6 (0.2-4.5)	NA	2.3 (0.6-4.4)	72.4 (33.0-122.0)	362.9 (71.0-704.0)
Median (5th – 95th percentile)														
SAM40027	3049	42 (21-68)	70 (50-101)	165 (150-183)	25.4 (19.1-35.7)	59.9	40.1	2 (0.6-3.6)	NA	2 (0.6-3.6)	4.5 (2.7-6.1)	2.2 (1.2-3.9)	76.4 (46.0-105.4)	363.8 (224.4-560.2)
SAM40040	1380	47 (22-69)	75 (53.0-104)	167 (152-185)	26.5 (19.8-36.4)	57.3	42.7	2 (0.6-3.6)	NA	2 (0.6-3.6)	NA	2.3 (1.3-4.0)	77.0 (51.6-109.9)	382.6 (222.4-588.2)
SAM40056	688	46 (22-66)	75 (52.5-105)	168 (154-184)	26.2 (19.8-37.0)	61.0	39.0	1.8 (0.6-3.2)	NA	1.8 (0.6-3.2)	4.9 (3.0-6.2)	2.5 (1.5-3.9)	80.9 (58.2-101.1)	351.4 (208.4-534.8)
ADA109055	535	41 (22-63)	NA	NA	NA	67.5	32.5	NA	16 (10-21)	1.45 (0.6-2.8)	NA	2.2 (1.3-3.6)	72.3 (51.4-95.9)	356.0 (186.3-604.0)
ADA109057	560	42 (20-67)	NA	NA	NA	62.3	37.7	NA	16 (10-21)	1.45 (0.6-2.8)	NA	2.3 (1.2-3.7)	72.7 (49.6-94.9)	353.0 (168.0-588.0)
Number of subjects (%)														
SAM40027	3049	3049 (100)	3048 (99.9)	3049 (100)	3048 (99.9)	1827	1222	1309 (42.9)	0 (0.0)	1309 (42.9)	1795 (58.9)	3019 (99.0)	3019 (99.0)	2998 (98.3)
SAM40040	1380	1380 (100)	1380 (100)	1380 (100)	1380 (100)	791	589	1369 (99.2)	0 (0.0)	1369 (99.2)	0 (0.0)	1378 (99.9)	1378 (99.9)	1380 (100)
SAM40056	688	688 (100)	688 (100)	688 (100)	688 (100)			498 (72.4)	0 (0.0)	498 (72.4)	567 (82.4)	687 (99.8)	687 (99.8)	688 (100)
ADA109055	535	535 (100)	0 (0.0)	0 (0.0)	0 (0.0)	361	174	0 (0.0)	535 (100)	535 (100)	0 (0.0)	535 (100)	535 (100)	474 (88.6)
ADA109057	560	560 (100)	0 (0.0)	0 (0.0)	0 (0.0)	349	211	0 (0.0)	559 (99.9)	559 (99.9)	0 (0.0)	560 (100)	560 (100)	494 (88.2)

*Combined ACQ-5 score of observed ACQ-5 scores and converted ACT to ACQ-5 score for studies where only ACT was measured.

Study	N	Smoking Status			Asthma Duration		Previous corticosteroid use	
		Current Smoker	Former Smoker	Never Smoked	<5 years	≥5 years	<5 years	≥5 years
N (%)								
SAM40027	3049	258 (8.5)	609 (20.0)	2182 (71.6)	697 (22.9)	2352 (77.1)	1593 (64.4)	881 (35.6)
SAM40040	1380	137 (9.9)	365 (26.4)	878 (63.6)	334 (24.2)	1046 (75.8)	684 (49.6)	696 (50.4)
SAM40056	688	44 (6.4)	173 (25.1)	471 (68.5)	161 (23.4)	527 (76.6)	NA	NA
ADA109055	535	0 (0.0)	102 (19.1)	433 (80.9)	NA	NA	NA	NA
ADA109057	560	1 (0.2)	114 (20.3)	445 (79.5)	NA	NA	NA	NA

Study	Treatment	N	Exacerbation	
			No Exacerbation	*At least 1 Exacerbation*
Number of subjects (%)				
SAM40027	FP	1518	1281 (0.8)	237 (0.2)
	FP/SALM	1531	1377 (0.9)	154 (0.1)
SAM40040	BUD/FORM	691	246 (35.6)	445 (64.4)
	FP/SALM	689	257 (37.3)	432 (62.7)
ADA109055	FP	280	222 (79.3)	58 (20.7)
	FP/SALM	255	226 (88.6)	29 (11.4)
ADA109057	FP	279	218 (78.1)	61 (21.9)
	FP/SALM	281	231 (82.2)	50 (17.8)
SAM40056	BUD/FORM	344	285 (82.8)	59 (17.2)
	FP/SALM	344	307 (89.2)	37 (10.8)

Further details on each study protocol can be found in the relevant publication or via the hyperlinks to the clinical study registry.

Study	Publication	Link to Clinical Study Register
SAM40027	Bateman ED, Bousquet J, Busse WW, et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma controL (GOAL) study. Allergy 2008;63(7):932–8.	https://www.gsk-studyregister.com/en/trial-details/?id=SAM40027
SAM40040	Dahl R, Chuchalin A, Gor D. EXCEL: a randomised trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. Resp Med 2006; 100: 1152-1162.	https://www.gsk-studyregister.com/en/trial-details/?id=SAM40040
ADA109055	Katial RK, Bernstein D, Prazma CM, Lincourt WR, Stempel DA. Long-term treatment with fluticasone propionate/salmeterol via Diskus improves asthma control versus fluticasone propionate alone. Allergy Asthma Proc. 2011; 32(2):127-36.	https://www.gsk-studyregister.com/en/trial-details/?id=ADA109055
ADA109057	Kerwin E, Prazma CM, Sutton L, Stempel DA. Safety and efficacy of long-term treatment with fluticasone propionate and salmeterol via DISKUS versus fluticasone propionate alone. Clin Res Reg Aff 2011; 28(1):14-21.	https://www.gsk-studyregister.com/en/trial-details/?id=ADA109057
SAM40056	FitzGerald JM, Boulet LP, Follows RM. The CONCEPT trial: a 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther. 2005; 27(4):393-406.	https://www.gsk-studyregister.com/en/trial-details/?id=SAM40056

ACQ-5= Asthma control questionnaire, ACT = Asthma control test, AQLQ = Asthma quality of life questionnaire, FEV1 = Forced expiratory volume in the first second, FEV1P = Predicted forced expiratory volume in the first second (%), PEF = Peak expiratory flow.

Table S1. Number and percentage of missing covariate data.

Baseline covariate	Study	N missing (total N)	Percentage imputed
BMI[1]	ADA109055	535 (535)	100%
	ADA109057	560 (560)	100%
	SAM40027	1 (3049)	<1%
	SAM40040	0 (1380)	0%
	SAM40056	0 (688)	0%
Asthma duration[2]	ADA109055	535 (535)	100%
	ADA109057	560 (560)	100%
	SAM40027	0 (3049)	0%
	SAM40040	0 (1380)	0%
	SAM40056	0 (688)	0%
ACQ-5[3]	ADA109055	0 (535)	0%
	ADA109057	1 (560)	<1%
	SAM40027	1752 (3049)	57%
	SAM40040	11 (1380)	<1%
	SAM40056	190 (688)	28%
Smoking status	ADA109055	0 (535)	0%
	ADA109057	0 (560)	0%
	SAM40027	0 (3049)	0%
	SAM40040	0 (1380)	0%
	SAM40056	0 (688)	0%

[1]Body mass index (BMI) was imputed based on the median of observed BMI values being 26 kg/m^2.
[2]Asthma duration was imputed based on the median of observed asthma duration being 8.4 years.
[3]Asthma control questionnaire (ACQ-5) was imputed based on asthma control test (ACT) in studies ADA109055 and ADA109057, for others the median value was used (ACQ-5 of1.8).

Table S3. 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 last 24 h puffs were collected, model parameterisation was based primarily on 24 h puffs 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 last 24-h puffs) from diary cards was accurate. Transcription errors, if occurred, were assumed to be random across treatment arms.	The observed number of occasions or 24h puffs 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	
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	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

adaptative response to the anti-inflammatory effect of the underlying maintenance therapy.		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.
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 FP monotherapy. Given the different dose levels included in the study, a theoretical estimate could be derived for a hypothetical dose of FP = 0. 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 or seasonal variation, 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.	
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.	
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 of the data 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 has an effect on 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.	

Table S4. Demographic and clinical baseline characteristics of the patient population used for the external validation step.

Study	N	Age (y)	Weight (kg)	Height (cm)	BMI (Kg/m^2)	Female (%)	Male (%)	ACQ-5	ACT	ACQ-5*	AQLQ	FEV1 (L)	FEV1p (%)	PEF (L/min)
Mean (min-max)														
SAS115359	9715	47.0 (18-91)	82 (30-239)	166 (120-206)	29.7 (9.4-78.4)	68.9	31.1	NA	NA	NA	NA	NA	NA	NA
Median (5th – 95th percentile)														
SAS115359	9715	48.0 (22-71)	79 (54-120)	165 (151-183)	28.5 (20.5-43.1)	68.9	31.1	NA	NA	NA	NA	NA	NA	NA
Number of subjects (%)														
SAS115359	9715	9715 (100)	9712 (99.9)	5601 (57.6)	9712 (99.9)	6691	3024	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Smoking Status (N=9714)			Asthma Duration (N=9715)		Previous corticosteroid use (N=0)	
Study	*Current Smoker*	*Former Smoker*	*Never Smoked*	*<5 years*	*≥5 years*	*<5 years*	*≥5 years*
N (%)							
SAS115359	503 (5.2)	1641 (16.9)	7570 (77.9)	1898 (19.5)	7817 (80.5)	NA	NA

Study	N	Treatment	Age (y)	Weight (kg)	Height (cm)	BMI (Kg/m^2)	Female (%)	Male (%)	ACQ-5	ACT	AQLQ	FEV1 (L)	FEV1p (%)	PEF (L/min)
Mean (min-max)														
SAS115359	4828	FP	47.0 (18-87)	81 (35-197)	166 (120-202)	29.7 (13.6-75.8)	69.6	30.4	NA	NA	NA	NA	NA	NA
	4887	FP/SALM	47.0 (18-91)	82 (30-239)	166 (128-206)	29.8 (9.4-78.4)	68.2	31.8	NA	NA	NA	NA	NA	NA
Median (5th – 95th percentile)														
SAS115359	4828	FP	48 (22-70)	79 (53-119)	165 (151-183)	28.5 (20.4-43.2)	69.6	30.4	NA	NA	NA	NA	NA	NA
	4887	FP/SALM	48 (21-71)	79 (54-122)	165 (151-183)	28.5 (20.6-43.1)	68.2	31.8	NA	NA	NA	NA	NA	NA

Abbreviations: ACQ-5 = Asthma control questionnaire, ACT = Asthma control test, AQLQ = Asthma quality of life questionnaire, FEV1 = Forced expiratory volume in the first second, FEV1P = Predicted forced expiratory volume in the first second (%), PEF = Peak expiratory flow.

Table S5. 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 propionate (FP), as monotherapy or in combination with salmeterol (SAL), 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 (**Table S2**). 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=6212) 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) [16-18]. 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 [5].
	In addition, the availability of different dosing groups allowed for stratification of patients assigned to FP and FP/SAL by dose level as a continuous 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 [19].
	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 [20, 21]. 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 [22,23]. 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 at the start of maintenance therapy	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 FP monotherapy. A placebo arm was not available in the clinical studies 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 (FP, FP/SAL 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 [24]

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APPENDIX I : Poisson model control stream

```
$PROB POIS base model
$INPUT ID TIME TIM1 STUDYN SABAOCC1 SABAOCC4 EXEVENT DV PDV1 PDV4 FLG PEFBL ICSDUR EXOCC IARACEN FDARACEN ICOUNTRY
ACTBL ACT AQLQBL AQLQ ACQ5BL ACQ5 TRTN TRTNUM FP SALM BUD FORM SEXN AGEBL BMIBL WTBL HTBL ASTHDUR FEV1 FEV1BL FEV1P
FEV1PBL SMOKN ETHN FENOBL
$DATA ../DATASETS/DERIVED/count_data_v5_MAIN.csv IGNORE=@
$PRED

BCTR=THETA(16)
IF(BCTR.EQ.0) BCTR=0.00000001

ET1=ETA(1)
ET2=ETA(1)*THETA(14)

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

ACQ5BL_C=ACQ5BL
ACTBL_C=ACTBL
IF(ACTBL_C.LT.0) ACTBL_C=15.5
IF(FLG.EQ.4) ACQ5BL_C= 6 + (-1.53932 * ((ACTBL_C-5)**0.45235))
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(12)
IF(SMOKN.EQ.3) BASESM=THETA(13)

ADDTH=0
IF(STUDYN.EQ.40027) ADDTH = THETA(15)
IF(STUDYN.EQ.40040) ADDTH = -1 * THETA(15)

BASE=THETA(1)+ADDTH+BASESM+THETA(9)*(ACQ5BL_C-1.8)+THETA(10)*(BMIBL_C-26)+THETA(11)*(ASTHDUR_C-8.4)+ET1TR
IF(FLG.EQ.4) BASE=THETA(2)+BASESM+THETA(9)*(ACQ5BL_C-1.8)+THETA(10)*(BMIBL_C-26)+THETA(11)*(ASTHDUR_C-8.4)+ET2TR

EMAX_T=THETA(7)*EXP(ETA(7))
ET50=THETA(8)*EXP(ETA(8))
EFF_T=(EMAX_T*TIMY)/(ET50+TIMY)

EMAX_FP=THETA(3)*(1+EFF_T)+ETA(3)
EC50_FP=THETA(4)*EXP(ETA(4))

EFF_FP=(EMAX_FP*FP)/(EC50_FP+FP)
;EFF_FP=EMAX_FP*FP
EFF_SALM=0
IF(SALM.GT.0) EFF_SALM=THETA(5)+ETA(5)

EFF_SYMB=0
SYMB=BUD+FORM
IF(SYMB.GT.0) EFF_SYMB=THETA(6)*(1+EFF_T)+ETA(6)

LAMB=EXP(BASE+EFF_FP+EFF_SALM+EFF_SYMB)

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

IF(LAMB.LE.0) LAMB=0.0000001

  ;Approximation of the factorial (log scale)
  ; In NM730 one 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
```

```
(0.01) ;BASE SABAOCC1
(1.7) ;BASE SABAOCC4
(-5, -1.42,0)  ;EMAX_FP
(0, 42.1)  ;EC50_FP
(-5, -0.75,0)  ;EMAX_SALM
(-5, -2.01,0)  ;EMAX_SYMB
(0, 0.625,1)  ;EMAX_T
(0, 0.33,1)  ;ET50
(0, 0.778,5)  ;acq5bl ON base
(0, 0.0304,5)  ;BMIBL on BASE
(0, 0.0455,1)  ;ASTHDUR on BASE
(0.7) ;SMOKE=2
(0.347)  ;SMOKE=3
(0, 0.694,2)  ;Scaling ET1 to ET2
(0.433) ;40040_40027
(-0.16) ;BOX-COX

$OMEGA
 3.71 ;BASE SABAOCC1
 0 FIX  ;BASE SABAOCC4
 0 FIX  ;EMAX_FP
 0 FIX  ;EC50_FP
 0 FIX  ;EMAX_SALM
 0 FIX  ;EMAX_SYMB
 0 FIX  ;EMAX_T
 0 FIX  ;ET50


$ESTIM MAXEVAL=9999 METHOD=COND LAPLACE -2LL PRINT=10
$COV
$TABLE ID TIME TIM1 STUDYN SABAOCC1 SABAOCC4 EXEVENT DV PDV1 PDV4 FLG PEFBL ICSDUR EXOCC IARACEN FDARACEN ICOUNTRY
ACTBL ACT AQLQBL AQLQ ACQ5BL ACQ5 TRTN TRTNUM FP SALM BUD FORM SEXN AGEBL BMIBL WTBL HTBL ASTHDUR FEV1 FEV1BL FEV1P
FEV1PBL SMOKN ETHN FENOBL LAMB LAMBPOP LPOI BASE EFF_FP EFF_SALM EFF_SYMB EFF_T ET1 ET2
FILE=run38.tab NOAPPEND ONEHEADER NOPRINT FORMAT=s1PE11.5
```

APPENDIX II: Poisson model input dataset example (first 100 lines)

```
ID TIME TIM1 STUDYN SABAOCC1 SABAOCC4 EXEVENT DV PDV1 PDV4 FLG PEFBL ICSDUR EXOCC IARACEN FDARACEN ICOUNTRY ACTBL ACT AQLQBL AQLQ ACQ5BL ACQ5 TRTN TRTNUM FP
SALM BUD FORM SEXN AGEBL BMIBL WTBL HTBL ASTHDUR FEV1 FEV1BL FEV1P FEV1PBL SMOKN ETHN FENOBL
1 510 0 109055 . 4 0 4 0 4 4 498 . 0 7 3 120 7 7 . . . . 3 19 250 0 0 0 2 33 . . . . 1.63 1.63 77.73 77.73 2 26 .
1 546 30 109055 . 2 0 2 . 2 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 564 48 109055 . 6 0 6 . 6 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 588 78 109055 . 3 0 3 . 3 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 612 96 109055 . 4 0 4 . 4 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 630 120 109055 . 5 0 5 . 5 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 654 144 109055 . 3 0 3 . 3 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 678 168 109055 . 2 0 2 . 2 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 702 192 109055 . 5 0 5 . 5 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 732 222 109055 . 3 0 3 . 3 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 750 240 109055 . 4 0 4 . 4 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 774 264 109055 . 1 0 1 . 1 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 798 288 109055 . 3 0 3 . 3 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
1 822 312 109055 . 2 0 2 . 2 4 498 . 0 7 3 120 7 . . . . . 3 19 250 0 0 0 2 33 . . . . 0 1.63 . 77.73 2 26 .
2 510 0 109055 . 4 0 4 . 4 4 302 . 0 7 3 120 13       . . . . 4 27 250 50 0 0 2 43 . . . . 2.36      67.23 1 8 .
2 534 24 109055 . 5 0 5 . 5 4 302 . 0 7 3 120 13 . . . . . 4 27 250 50 0 0 2 43 . . . . 0 2.36 . 67.23 1 8 .
2 564 48 109055 . 3 0 3 . 3 4 302 . 0 7 3 120 13 . . . . . 4 27 250 50 0 0 2 43 . . . . 0 2.36 . 67.23 1 8 .
2 582 72 109055 . 1 0 1 . 1 4 302 . 0 7 3 120 13 . . . . . 4 27 250 50 0 0 2 43 . . . . 0 2.36 . 67.23 1 8 .
2 606 96 109055 . 6 0 6 . 6 4 302 . 0 7 3 120 13 . . . . . 4 27 250 50 0 0 2 43 . . . . 0 2.36 . 67.23 1 8 .
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