SUPPLEMENTARY MATERIAL

A simulation study of the effect of clinical characteristics and treatment choice on reliever medication use, symptom control and exacerbation risk in moderate-severe asthma.

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Table S1. Demographic and clinical baseline characteristics of the patient population available for resampling, which was used across the different simulation scenarios, stratified by treatment. Summary statistics include medians (5^{th} - 95^{th} percentiles) along with the number of patients available in each category. Percentage values reported for smoking status and sex refer to the proportion of patients in each treatment arm.

	Variable	FP (N=7527)	BUD/FOR (N=1382)	FP/SAL (N=9032)	Total (N=17941)
Demographic characteristics	**Age (y)**	45 (21-69)	47 (22-70)	45.8 (21-69)	76.7 (52-116)
	Weight (kg)	77 (52-116.4)	77 (53-110)	76.4 (52-117)	165 (151-183)
	Height (cm)	165 (151-183)	167 (152-184.2)	165 (151.1-183)	27.5 (20-41.4)
	BMI (kg/m²)	27.6 (20-41.9)	27 (19.9-39.6)	27.5 (20-41.2)	2 (0.6-3.6)
	Female (%)	5041 (67%)	832 (60.2%)	5859 (64.9%)	11732 (65.4%)
	Baseline Smoking (N/F/C)	76/6/18	61/12/28	76/6/19	75/6/19
Symptom scores	**ACQ-5 score#**	1.64 (0.6-3.4)	1.8 (0.5-3.4)	1.8 (0.4-3.4)	1.64 (0.5-3.4)
	AQLQ score	4.6 (2.8-6.2)	5 (3-6.6)	4.7 (2.8-6.4)	4.7 (2.8-6.4)
Spirometry	**FEV1 (L)**	2.3 (1.3-3.9)	2.4 (1.3-3.9)	2.3 (1.2-3.8)	2.3 (1.3-3.9)
	FEV1p (%)	75.7 (49.1-102.4)	78.7 (53.1-107.4)	76.1 (49.3-102.3)	76.3 (49.7-103)
	PEF (L/min)	356.7 (215-571.4)	372 (217.1-569.4)	373 (219.4-579)	367.1 (216.9-576.6)
Medical history	**Asthma Duration**				
	< 6 mo	2 (0%)	2 (0%)	13 (0%)	40 (0%)
	≥ 6 mo to < 1 yr	364 (6%)	38 (4%)	380 (5%)	923 (5%)
	≥ 1 to 5 yrs	567 (9%)	102 (10%)	768 (9%)	1767 (9%)
	≥ 5 to 10 yrs	725 (11%)	118 (11%)	973 (12%)	2215 (12%)
	≥ 10 to 15 yrs	869 (13%)	153 (15%)	1081 (13%)	2564 (13%)
	≥ 15 to 20 yrs	1130 (17%)	200 (19%)	1381 (17%)	3373 (18%)
	≥ 20 to 25 yrs	1219 (19%)	209 (20%)	1530 (19%)	3459 (18%)
	≥ 25 yrs	1598 (25%)	219 (21%)	2107 (26%)	4811 (25%)
	Prev. cort.use				
	< 6 mo	92 (7%)	69 (8%)	162 (7%)	328 (7%)
	≥ 6 mo to < 1 yr	195 (16%)	74 (8%)	281 (13%)	561 (13%)
	≥ 1 to 5 yrs	502 (40%)	280 (32%)	831 (38%)	1632 (37%)
	≥ 5 to 10 yrs	265 (21%)	210 (24%)	454 (21%)	946 (22%)
	≥ 10 to 15 yrs	114 (9%)	111 (13%)	230 (11%)	463 (11%)
	≥ 15 to 20 yrs	37 (3%)	56 (6%)	86 (4%)	183 (4%)
	≥ 20 to 25 yrs	23 (2%)	25 (3%)	49 (2%)	101 (2%)
	≥ 25 yrs	14 (1%)	59 (7%)	96 (4%)	184 (4%)

BUD/FOR- budesonide-formoterol, FP – fluticasone propionate, FP/SAL – fluticasone propionate-salmeterol

Table S2. **A** Parameter estimates of the models describing reliever medication use, ACQ-5 scores and time to first exacerbation in patients with moderate-severe asthma . Basal estimates are derived using FP monotherapy as reference treatment. Adapted from van Dijkman et al., 2024 [1].

$E_{SAL\_base} = \theta 1$, $E_{BUD/FOR\_base} = \theta 2$, $E_{FP\_base} = \frac{Emax_{FP} * FP_{dose}}{ED50_{FP} + FP_{dose}}$, $E_{hysteresis} = \frac{Emax\_t * Time}{ET50 + Time}$

$E_{total} = (E_{FP\_base} + E_{SAL\_base} + E_{BUD/FOR\_base}) * E_{hysteresis}$

$Y = e^{(\lambda_{base} + \lambda_{ACQ5} + \lambda_{BMI} + \lambda_{ASTHDUR} + \lambda_{smoking} + E_{total} + \eta_{bc})}$

SE – standard error, RSE – relative standard error

θ	Parameter[1]	Value	SE	RSE (%)[2]
1	Base lambda (log overnight occasions)[3]	-0.55	0.314	57.10%
2	Base lambda (log puffs/24h)	1.28	0.304	23.80%
3	Emax FP	-1.12	0.304	27.10%
4	ED_{50} FP (µg BID)	54.8	19.7	35.90%
5	Effect SAL	-0.48	0.055	11.50%
6	Effect BUD/FOR	-1.18	0.388	32.90%
7	E_{MAX_T}	0.826	0.265	32.10%
8	ET_{50}	0.308	0.075	24.40%
9	Effect of ACQ-5	0.565	0.0316	5.60%
10	Effect of BMI	0.0252	0.0045	17.70%
11	Effect of Asthma duration	0.0275	0.0046	16.70%
12	Effect of current smoking	0.585	0.0754	12.90%
13	Effect of former smoker	0.358	0.0478	13.40%
		Value	**SE**	**RSE (%)**
	Ω_{base}	3.71	0.025	0.67
	Box-Cox transform	-0.192	0.0081	4.20%
	Scaling factor (overnight occs to puffs/24h)[4]	0.666	0.0182	2.70%

[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 can be taken as a generic value (parameter 1) or specified per study. λ_{base} SAM40027 was higher than that for SAM40040. This difference is explained by the fact that in SAM40040, patients were pre-treated (beclomethasone dipropionate doses 1000 - 2000 µg/d), in SAM40027 patients should not have used ICS for 6 months.

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

ACQ-5 – asthma control questionnaire, BMI – body mass index, BUD/FOR – budesonide/formoterol, FP – fluticasone propionate, SAL – salmeterol

B. Parameter estimates of the longitudinal model describing the individual ACQ-5 trajectories in patients with moderate-severe asthma. The model is parameterised as a turnover rate (kin/kout) that includes the effect of treatment with FP monotherapy, and FP/SAL and BUD/FOR combination therapy on ACQ-5. Baseline ACQ-5 (A0), rate of increase (Kin) and rate of decrease (Kout) were identified as the primary determinants of changes in individual ACQ-5 scores over time. Adapted from Singh et al., 2023 [2]. SE – standard error, RSE – relative standard error

$$\frac{d(ACQ5)}{dt} = k_{in} - k_{out} \cdot ACQ5 \qquad ACQ5(0) = baseline\ \text{ACQ5}$$

$$k_{in} = \theta_{kin} * \left(1 + \theta_{BUD/FOR}\right) * \left(1 + \theta_{FP/SAL}\right) * \left(1 + \theta_{previous\ smoker}\right) * \left(1 + \theta_{current\ smoker}\right) * \left(1 + (BMI - 26.26) * \theta_{BMI}\right) * \left(1 + (AGE - 41) * \theta_{Age}\right)$$

$$k_{out} = \theta_{kout} * \left(1 + \theta_{BUD/FOR}\right) * \left(1 + \theta_{FP/SAL}\right) * e^{\eta_{k_{out}}}$$

	Parameter	Estimate	SE	RSE (%)
Population parameters	ACQ-5 kin (θkin)	6.26	0.328	5.2%
	ACQ-5 kout rate (θkout)	12.4	0.464	3.7%
Age	Age effect (fractional increase in k_{in} per year)	0.00759	0.002	23.0%
BMI	BMI effect (fractional increase in k_{in} per kg/m^2)	0.0121	0.007	59.2%
Smoking	Former smoker relative to never smoked (fractional increase in k_{in})	0.271	0.063	21.6%
	Current smoker relative to never smoked (fractional increase in k_{in})	0.791	0.133	16.3%
Treatment	FP/SAL effect relative to FP (fractional increase in k_{in})	-0.2	0.079	29.7%
	BUD/FOR effect relative to FP (fractional increase in k_{in})	0.777	0.334	31.2%
	FP/SAL effect relative to FP (fractional increase in k_{out})	-0.355	0.052	13.2%
	BUD/FOR effect relative to FP (fractional increase in k_{out})	0.433	0.248	37.9%
Interindividual variability	Inter individual variability in k_{in} (ηk_{in})	2.45	0.122	4.8%
	Inter individual variability correlation between η_{kin} and ηk_{out}	1.76	0.097	5.2%
	Inter individual variability in k_{out} (ηk_{out})	1.68	0.093	5.3%
Residual error	Residual error	0.479	0.009	2.0%

ACQ-5 – asthma control questionnaire, BMI – body mass index, BUD/FOR – budesonide/formoterol, FP – fluticasone propionate, SAL – salmeterol

C. Parameter estimates of the final model describing the time-to-first exacerbation in patients with moderate-severe asthma. Basal hazard is described using FP monotherapy as reference treatment. Adapted from Oosterholt et al., 2023 [3]. SE – standard error, RSE – relative standard error

$$\text{Hazard} = \theta_{BASE} * \left(1 + \theta_{previos\ smoker}\right) * (1 + \theta_{current\ smoker}) * (1 + (BMI - 27.6) * \theta_{BMI}) * (1 + (FEV1P - 73) * \theta_{FEV1P}) * \left(1 + (ACQ5_{baseline} - 2) \cdot \theta_{ACQ5}\right) * (1 + \theta_{FEMALE}) * \left(1 + \theta_{\frac{BUD}{FORM}}\right) * \left(1 + \theta_{\frac{FP}{SAL}}\right) * e^{\theta_{amp} \cdot \sin(calendar\ time + \theta_{phase})}$$

Covariate	Parameter*	Estimate	SE	RSE(%)
	Base hazard (θ_{BASE})	0.188	0.0045	2.40%
ACQ-5	fHAZ $_{ACQ5}$ (fractional increase in hazard per unit ACQ5)	0.207	0.0629	30.40%
Sex	fHAZ $_{female}$ (fractional increase in hazard relative to male %)	0.327	0.0831	25.40%
BMI	fHAZ $_{BMI}$ (fractional increase in hazard per kg/m^2)	0.0279	0.007	25.20%
FEV_1 p%	fHAZ $_{FEV1p\%}$ (fractional change in hazard per % change in FEV_1p%)	-0.00834	0.002	24%
Smoking	fHAZ $_{current\ smoker}$ (fractional increase in hazard relative o never smoked)	0.51	0.121	23.70%
	fHAZ $_{former\ smoker}$ (fractional increase in hazard relative to never smoked)	0.268	0.0715	26.70%
Season	fHAZ $_{amplitude}$ (fractional change between season)	0.304	0.0006	0.20%
	Phase shift (years)	0.27	0.0006	0.20%
Treatment	fHAZ $_{BUD/FOR}$ (fractional increase in hazard relative to FP))	0.321	0.106	33%
	fHAZ $_{FP/SAL}$ (fractional increase in hazard relative to FP))	-0.308	0.0348	11.30%

ACQ-5 – asthma control questionnaire, BMI – body mass index, BUD/FOR – budesonide/formoterol, FEV1p% - percentage predicted forced expiratory volume in the first second, FP – fluticasone propionate, SAL – salmeterol

Table S3. Protocol design characteristics used for the simulation* of individual ACQ-5 trajectories, reliever medication use and time to first exacerbation after treatment with ICS monotherapy and ICS/LABA combination therapy.

Protocol characteristics	
Endpoints:	Endpoints evaluated were: 1) Change in ACQ-5 score at the end of treatment relative to baseline, 2) reduction in reliever medication at 12 months, relative to baseline , 3) time to first exacerbation; 4) (cumulative) incidence of exacerbation at 12 months and annualised exacerbation rate; 5) relative risk of exacerbation in patients treated with FP/SAL combination therapy, as compared to alternative treatments, namely ICS monotherapy and BUD/FOR combination therapy, 6) reduction in the number of SABA canisters per year.
Simulation scenarios	Simulation scenarios were used to evaluate the effect of different demographic and clinical baseline characteristics, as well as treatment choices (e.g. ICS, ICS/LABA) on symptom control scores, reliever medication use and time to first exacerbation in a virtual cohort of patients with moderate-severe asthma symptoms at baseline. To ensure simulations reflected the original clinical trial population, baseline characteristics from the available pooled population (**Table S2**) were randomly resampled and used as input in each simulation scenario. In addition, re-sampling of patients into each clinical trial scenario was performed taking into account the observed covariate distributions in the clinical studies. This ensured the creation of virtual cohorts which are representative the baseline characteristics of patients with moderate-severe asthma. Given the large sample size used across the different scenarios, along with the prior evidence of the predictive performance of the model, results from 500 trial replicates were assumed to be sufficiently accurate and precise to assess the statistical significance of eventual differences between treatment conditions. Confidence intervals from trial replicates based on resampling from the same patient pool were deemed appropriate to account for model parameter uncertainty. In an attempt to mimic clinical practice, a scenarios was implemented in which patients switch treatments. Aa parallel study design was used, i.e., each patient was randomised to one of the treatment arms at the beginning of the trial. The transition from ICS monotherapy to combination therapy in predefined study arms was based on ACQ-5 symptom level. Only non-responders to ICS monotherapy were assigned to combination therapy, as assessed by the ACQ-5 scores at the predefined visit (3 months). Treatment response (i.e. symptom control) was defined as ACQ-5 < 0.75. Consequently, a non-responder is a subject who shows a ACQ-5 ≥0.75 at 3 months e. Except for baseline values, which were resampled from the original patient pool, individual ACQ-5 values were derived by simulation using the longitudinal drµg-disease model developed previously [2]. In addition to symptom scores, reliever medication use and incidence of exacerbations were evaluated.
Baseline characteristics:	The patient population randomised into each simulation scenario was based on the inclusion and exclusion criteria used in previous studies (as shown in Table S1 in Oosterholt et al., 2023[3]).
Study visits	Simulation scenarios were based on typical clinical visits and included follow-up over a period of 12 months [4]. This period was used to avoid empirical extrapolation beyond the observation window considered for model development and validation, for which there is also supporting clinical trial data. Visits including ACQ-5 measurements were at study entry (baseline) and at 3, 6, 9 and 12 months after the start of treatment. Screening measurements were not included or considered for simulation purposes.

Treatment arms	For this analysis, patients were assumed to have undergone a washout period prior to the start of the intervention, with exception of the scenarios in which treatment switching is envisaged at predefined time points: **Scenario 1:** varying symptom control at baseline (ACQ-5) **Scenario 2:** varying body mass index at baseline **Scenario 3:** smoking habit at baseline **Scenario 4:** asthma history (i.e., time since diagnosis) **Scenario 5:** varying smoking habit at baseline **Scenario 6** treatment switch from ICS monotherapy to combination therapy. Only patients who do not achieve adequate symptom control switched to combination therapy at 3 months after initiation of treatment. Treatment assignment assumes an initial stepwise titration step followed by a maintenance phase. Regular dosing regimen was used across all scenarios: FP: 100, 250 and 500 µg twice daily; FP/SAL: 100/50, 250/50 and 500/50 µg twice daily; BUD/FOR: 100/6, 200/6, 400/12, 160/4.5 and 320/9 µg twice daily
Statistical methods:	Changes in symptom scores at the end of treatment were evaluated using a pairwise Wilcoxon Rank Sum test. In addition, the proportion of patients who transition from poorly controlled at baseline to not-well controlled and well-controlled at 12 months, and those not-well controlled at baseline to well-controlled at 12 months stratified by treatment. Similarly, reliever medication use at the end of treatment was assessed using a Poisson exact test. The total number of puffs/24 h was stratified by treatment and summarised in terms of canisters per year. Simulated exacerbations were described by Kaplan-Meier survival curves and analysed using a log-rank test with Bonferroni correction. In addition, the effect of baseline characteristics and treatment choices was assessed based on annualised exacerbation rates. Median estimates and 90% confidence intervals are presented in tabular format for results from trial replicates (n=500). The focus of the statistical analysis was to show the potential differences in treatment performance when considering immediate and long term effects of a treatment. In each scenario, the difference in the symptom levels, reliever medication use and incidence of exacerbation rate at 12 months was compared between patients in the reference arm and those whose were assigned to a group with different baseline characteristics and/or treatment. Assessment of the statistical significance of the differences between ICS monotherapy and ICS/LABA combination therapy, or between the different ICS/LABA combinations (i.e., FP/SAL vs. BUD/FOR) was based on a two-sided test with significance level α=0.05. As transition from monotherapy to FP/SAL or BUD/FOR, or in the case of combination therapy from BUD/FOR to FP/SAL (and vice-versa), was implemented by design, i.e., with transition defined at pre-specified times for each treatment arm, no additional statistical methods for adjustment of estimated treatment effect were used to correct for potential bias in estimates due to patients switching from their allocated treatment [5,6]. In addition to the incidence of exacerbations at month 12, the annualised exacerbation rate was also to be calculated, where appropriate. Given that the endpoints of the clinical trial simulations were only considered at the end of study, the hazard ratio was not estimated when summarising the results.
Sample size estimation	Additional sample size considerations were applied for the scenario 6, in which the differences between treatment arms were compared. Given the infrequency of exacerbation events in comparison to the

repeated ACQ-5 measurements and daily SABA data, calculations were based on a 90% power to detect a statistically significant difference in the risk of asthma exacerbations between two treatment arms, as defined for the comparison of survival curves [7]. Estimates of exacerbation incidence at month 12, were obtained from the supporting reports from the selected clinical trials from which the overall patient population was pooled, including data reported by de Roos and colleagues[8].

Number of events required to detect selected hazard ratios at various significance levels

Two-sided significance level	Power (%)	Hazard Ratio	Corresponding reduction	Number of Events required
0.05	90	0.7	30	337
0.01	90	0.65	35	331
0.001	90	0.6	40	334

Previous studies have shown improvements in asthma exacerbation incidence or rate of 17% to 45% for combination therapy versus ICS alone. For the current analysis, a reduction of at least 30% in exacerbation incidence between treatment arms was set as effect size. This figure is in line with improvement seen in previous clinical trials.

In order to calculate the approximate numbers of subjects to be randomised, the following assumptions were made: at least 20% of subjects in the reference or comparator arm would have at least one exacerbation within a year, and the total trial duration would be of 12 months. As drop out and loss of follow up do not apply in the evaluation of a virtual cohort, a sample size of 1100 patients per treatment arm is likely to provide at least 90% power to detect a hazard ratio of 0.7.

Effect of % of exacerbations in the reference or comparator treatment arm on sample size at a two-sided significance level of 0.05 and a power of 90%

% of subjects in the control arm with one of more exacerbations within a year	Number of Events Required to detect HR=0.70	Number of Subjects required per arm to detect HR=0.70
16	337	1364
18	337	1211
20	337	1088
22	337	988
24	337	904

Assumptions: and limitations	1. Parameter estimates from the Poisson, longitudinal and time-to-event models, which were obtained previously from a pooled patient database were assumed to be sufficiently precise to replicate the performance of the different treatments in a wider population, as observed in clinical practice or in real-life setting. However, we recognise that inclusion/exclusion criteria may not fully reflect the patient population with moderate to severe asthma symptoms that may be eligible for treatment with ICS and ICS/LABA in clinical practice. 2.Interindividual variability in pharmacokinetics was assumed to have a minor impact on treatment response, as the currently approved dose levels of ICS/LABA yield nearly maximum pharmacological effect. In fact, the parameter estimates describing the drµg-specific effect on reliever medication use, ACQ-5 symptom scores and base hazard reflects the mean and/or mode dose level of each treatment during the maintenance phase. 3. Given the primary aim of the analysis, all CTS scenarios were implemented under the assumption of constant adherence to treatment over the period of the study (i.e., 12 months). In real-life conditions, different adherence patterns may occur, depending on symptom severity and/or comorbidities [9], which may significantly alter the predicted differences across CTS scenarios. Based on randomisation principles, one would expect, however, that such an effect to occur randomly across the different treatment arms. Consequently, this assumption does not restrict the extrapolation of the findings to real-life settings. In fact, the implications of variable patterns of ICS and ICS/LABA use have been previously shown to be linked to different intrinsic properties of the active moieties [10]. 4. Given that the simulated scenarios were aimed to describe changes in symptom scores, reliever medication use, and exacerbation incidence over the period of 12 months, it was also assumed that variability due to incorrect device use was negligible, i.e., patients would have been trained on how to use each device correctly. 5. As drop-out in real clinical trials appears to be mostly non-informative (i.e., at random), treatment scenarios were implemented without dropout. 6. The reduction in puffs/24 h as well as the changes in ACQ-5 and cumulative incidence of exacerbations was not calculated beyond 12 months to ensure that simulation results could be supported by existing clinical data, i.e., the time span used in the analysis matches the duration of the longest clinical trial included in the development of the model. 7. The use of 500 trial replicates may seem excessive given the sample size in each treatment arm ($n \geq 1000$). However, this was deemed adequate to obtain reliable estimates of the 90%-confidence intervals of the survival function. 8. The assessment of treatment response at each visit using predicted ACQ-5 for each patient was based on the longitudinal model describing individual ACQ-5 trajectories. Whilst this does not represent a limitation, the predicted response does not include residual random variability, which may be relatively large in real life. As residual variation is random and 500 replicates have been used to evaluate the proposed scenarios, this should not alter the results obtained for the scenario in which the predicted symptom control level at 3 months is used to support treatment switch.

ICS dose-response relationships	To understand the effect of treatable traits, i.e. clinical and demographic baseline characteristics, on the risk of exacerbation, treatment effect was parameterised independently from baseline characteristics. In other words, the parameters describing the drμg-specific effects are not influenced by other model parameters. However, as the dose of ICS has not been identified as covariate in the model, the comparison between treatment arms was performed using the mean and/or mode dose level used during the maintenance phase of treatment. This was based on the underlying dose-response relationships of the active moieties (i.e. FP, BUD) included in this study [11-13]. As it has been established that currently used ICS doses correspond to the maximum or nearly maximum pharmacological effect, the effect of dose level variation on the base hazard during the maintenance phase was assumed to be minor [14,15]. In fact, here we have applied the same principles endorsed by Beasley and colleagues [16], in that the current analysis does not rely on the terminology proposed by the Global Initiative for Asthma (GINA) guidelines. As highlighted in their report, GINA's terminology which is not evidence-based, 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 are associated with minor increase in ICS-related anti-inflammatory response [17]. 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. Unfortunately, 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 [18,19]. 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 μg 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 drμg to the lungs compared to its original MDI, whereas the Diskus DPI is lower efficiency that the original CFC MDI [20-22]. The net result is that BUD in the Turbuhaler is approximately equivalent to FP in the Diskus on an μg basis [12]. These considerations provide support for the comparison of the mode (250 μg FP and 200 μg BUD) or mean (281 μg FP and 255 μg BUD) doses used across the different studies.

* Clinical trial simulations were implemented in NONMEM version 7.3 (Icon Development Solutions, MD, USA) based on the time to event, longitudinal and Poisson models describing the first exacerbation along with individual ACQ-5 trajectories and patterns of reliever medication use over a period of 12 months. All required data manipulation, including graphical and statistical summaries were performed in R (v. 4.1.3)

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Scenario 1 – Effect of ACQ-5 scores at baseline and treatment choice on symptom control, reliever medication use and risk of exacerbation at 12 months

Table S4. Upper panel shows the clinical and demographic baseline characteristics of the simulated population (n=1500, 500 iterations) stratified by symptom control level and treatment. Lower panels summarises the statistical significance level of the different comparisons after 12 months; *p*-values take into account the Bonferroni correction for multiplicity.

Asthma Control	Treatment	Age (y)	BMI (Kg/m2)	Baseline ACQ-5	Asthma history (y) [% missing]	Baseline Smoking (N/C/F)	Female %	Baseline FEV1p (%)
Well Controlled	FP	48.0 (24.0-71.0)	26.2 (19.8-37.0)	0.4 (0.0-0.6)	12.5 (3.0-30.0) [29]	76/1/23	60.1	77.3 (54.5-103.8)
	FP/SAL	48.0 (24.0-71.0)	26.2 (19.6-36.9)	0.4 (0.0-0.6)	12.5 (0.8-30.0) [30]	76/1/23	60	77.3 (54.5-103.8)
	BUD/FOR	48.0 (24.0-71.0)	26.2 (19.6-37.0)	0.4 (0.0-0.6)	12.5 (0.8-30.0) [29]	76/1/22	60	77.3 (54.2-103.8)
Not Well Controlled	FP	46.0 (21.0-69.7)	26.3 (20.2-37.5)	1.2 (0.8-1.4)	12.5 (3.0-30.0) [27]	75/3/22	60.4	77.0 (51.8-102.4)
	FP/SAL	46.0 (21.0-69.9)	26.3 (20.2-37.5)	1.2 (0.8-1.4)	12.5 (3.0-30.0) [27]	75/3/22	60.2	77.0 (51.8-102.3)
	BUD/FOR	46.0 (21.0-70.0)	26.3 (20.2-37.3)	1.2 (0.8-1.4)	12.5 (3.0-30.0) [27]	74/3/22	60.4	77.0 (51.8-102.3)
Poor Control	FP	49.0 (23.0-70.0)	27.5 (20.2-40.3)	2.4 (1.6-3.6)	12.5 (3.0-30.0) [35]	75/4/21	63.6	71.8 (46.7-97.8)
	FP/SAL	49.0 (23.0-70.0)	27.5 (20.2-40.3)	2.4 (1.6-3.6)	12.5 (3.0-30.0) [35]	75/4/21	63.6	71.9 (46.7-97.9)
	BUD/FOR	49.0 (23.0-70.0)	27.5 (20.2-40.3)	2.4 (1.6-3.6)	12.5 (3.0-30.0) [35]	75/4/21	63.6	71.9 (46.7-97.8)

ACQ-5 - statistical significance (p value with Bonferroni correction)

Treatment	Asthma Control	BUD/FOR, Not Well Controlled	BUD/FOR, Poor Control	BUD/FOR, Well Controlled	FP, Not Well Controlled	FP, Poor Control	FP, Well Controlled	FP/SAL, Not Well Controlled	FP/SAL, Poor Control
BUD/FOR	BUD/FOR, Poor Control	1 (2.83e-03-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	BUD/FOR, Well Controlled	1 (2.06e-01-1.00e+00)	0.12 (1.06e-04-1.00e+00)	NA	NA	NA	NA	NA	NA
FP	FP, Not Well Controlled	1 (7.45e-02-1.00e+00)	1 (3.74e-01-1.00e+00)	1 (2.61e-03-1.00e+00)	NA	NA	NA	NA	NA
	FP, Poor Control	<0.01 (1.08e-10-1.60e-02)	0.06 (4.89e-05-1.00e+00)	<0.01 (4.44e-13-6.77e-04)	<0.01 (3.06e-07-9.71e-01)	NA	NA	NA	NA
	FP, Well Controlled	1 (3.28e-02-1.00e+00)	<0.05 (3.52e-06-1.00e+00)	1 (3.23e-01-1.00e+00)	0.16 (7.28e-05-1.00e+00)	<0.01 (1.73e-16-3.31e-05)	NA	NA	NA
FP/SAL	FP/SAL, Not Well Controlled	<0.01 (9.44e-15-1.08e-04)	<0.01 (9.52e-23-2.71e-10)	<0.01 (2.24e-11-5.88e-03)	<0.01 (2.05e-20-5.56e-08)	<0.01 (1.47e-38-2.76e-22)	<0.01 (3.74e-10-7.90e-02)	NA	NA
	FP/SAL, Poor Control	<0.05 (4.16e-06-1.00e+00)	<0.01 (6.93e-12-2.19e-03)	0.29 (4.62e-04-1.00e+00)	<0.01 (7.88e-10-3.19e-02)	<0.01 (1.29e-23-2.48e-11)	1 (7.26e-03-1.00e+00)	0.12 (2.58e-04-1.00e+00)	NA
	FP/SAL, Well Controlled	<0.01 (6.84e-21-5.95e-09)	<0.01 (1.13e-30-4.07e-16)	<0.01 (4.86e-18-4.03e-06)	<0.01 (1.08e-28-8.19e-14)	<0.01 (3.50e-48-7.13e-29)	<0.01 (1.99e-16-5.26e-05)	1 (1.05e-02-1.00e+00)	<0.01 (4.78e-09-9.76e-02)

Reliever medication use - statistical significance (p value with Bonferroni correction)

Treatment	Asthma Control	BUD/FOR, Not Well Controlled	BUD/FOR, Poor Control	BUD/FOR, Well Controlled	FP, Not Well Controlled	FP, Poor Control	FP, Well Controlled	FP/SAL, Not Well Controlled	FP/SAL, Poor Control
BUD/FOR	Not Well Controlled	1 (1.00e+00 - 1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	Poor Control	<0.01 (9.03e-187 - 7.78e-111)	1 (1.00e+00 - 1.00e+00)	NA	NA	NA	NA	NA	NA
	Well Controlled	<0.01 (1.72e-33 - 5.41e-11)	<0.01 (0.00e+00 - 1.85e-228)	1 (1.00e+00 - 1.00e+00)	NA	NA	NA	NA	NA
FP	Not Well Controlled	<0.01 (2.06e-48 - 3.39e-17)	<0.01 (1.02e-69 - 1.38e-22)	<0.01 (4.30e-133 - 7.16e-79)	1 (1.00e+00 - 1.00e+00)	NA	NA	NA	NA
	Poor Control	<0.01 (0.00e+00 - 2.22e-322)	<0.01 (9.52e-110 - 2.96e-39)	<0.01 (0.00e+00 - 2.22e-322)	<0.01 (2.40e-283 - 3.91e-166)	1 (1.00e+00 - 1.00e+00)	NA	NA	NA
	Well Controlled	1 (3.37e-02 - 1.00e+00)	<0.01 (2.53e-189 - 2.58e-113)	<0.01 (7.19e-33 - 5.63e-10)	<0.01 (2.03e-51 - 6.90e-19)	<0.01 (0.00e+00 - 2.22e-322)	1 (1.00e+00 - 1.00e+00)	NA	NA
FP/SAL	Not Well Controlled	1 (7.09e-04 - 1.00e+00)	<0.01 (2.70e-200 - 2.36e-124)	<0.01 (1.62e-28 - 2.53e-08)	<0.01 (3.52e-59 - 1.90e-23)	<0.01 (0.00e+00 - 2.22e-322)	1 (3.26e-03 - 1.00e+00)	1 (1.00e+00 - 1.00e+00)	NA
	Poor Control	<0.01 (7.11e-160 - 1.75e-88)	0.92 (6.69e-09 - 1.00e+00)	<0.01 (1.10e-294 - 5.17e-197)	<0.01 (6.14e-53 - 4.81e-15)	<0.01 (9.19e-134 - 1.05e-54)	<0.01 (6.23e-164 - 1.14e-95)	<0.01 (2.00e-175 - 4.76e-102)	1 (1.00e+00 - 1.00e+00)
	Well Controlled	<0.01 (4.93e-41 - 1.28e-16)	<0.01 (0.00e+00 - 3.67e-244)	1 (6.37e-03 - 1.00e+00)	<0.01 (2.32e-146 - 4.65e-89)	<0.01 (0.00e+00 - 2.22e-322)	<0.01 (2.93e-40 - 6.28e-14)	<0.01 (8.54e-35 - 1.01e-11)	<0.01 (2.22e-310 - 4.56e-215)

Exacerbations - statistical significance (p value with Bonferroni correction)

Treatment	Asthma Control	FP, Well Controlled	FP, Not Well Controlled	FP, Poor Control	FP/SAL, Well Controlled	FP/SAL, Not Well Controlled	FP/SAL, Poor Control	BUD/FOR, Well Controlled	BUD/FOR, Not Well Controlled
FP	Not Well Controlled	0.52 (1.56e-03-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	Poor Control	<0.01 (3.28e-16-3.96e-06)	<0.01 (1.23e-08-2.02e-01)	NA	NA	NA	NA	NA	NA
FP/SAL	Well Controlled	<0.05 (3.83e-06-1.00e+00)	<0.01 (7.00e-13-5.06e-04)	<0.01 (5.85e-31-3.96e-17)	NA	NA	NA	NA	NA
	Not Well Controlled	1 (5.43e-02-1.00e+00)	<0.01 (8.54e-07-1.00e+00)	<0.01 (3.40e-22-9.00e-10)	1 (6.96e-03-1.00e+00)	NA	NA	NA	NA
	Poor Control	0.58 (2.19e-03-1.00e+00)	1 (1.00e+00-1.00e+00)	<0.01 (3.25e-08-8.15e-02)	<0.01 (2.40e-12-4.49e-04)	<0.01 (6.16e-07-5.82e-01)	NA	NA	NA
BUD/FOR	Well Controlled	0.09 (1.34e-04-1.00e+00)	1 (6.79e-01-1.00e+00)	<0.01 (6.52e-07-9.51e-01)	<0.01 (1.87e-14-5.53e-05)	<0.01 (1.84e-08-1.54e-01)	1 (1.00e+00-1.00e+00)	NA	NA
	Not Well Controlled	<0.01 (4.91e-12-2.26e-03)	<0.05 (3.68e-05-1.00e+00)	1 (1.28e-01-1.00e+00)	<0.01 (9.84e-26-1.58e-12)	<0.01 (5.15e-17-9.70e-07)	<0.05 (1.64e-05-1.00e+00)	0.21 (2.90e-04-1.00e+00)	NA
	Poor Control	<0.01 (6.77e-33-7.32e-18)	<0.01 (9.10e-22-5.56e-10)	<0.01 (1.11e-06-7.78e-01)	<0.01 (1.48e-53-7.88e-35)	<0.01 (2.07e-41-1.03e-24)	<0.01 (7.52e-22-2.45e-10)	<0.01 (6.91e-20-1.59e-08)	<0.01 (7.06e-10-1.41e-02)

Scenario 2 – Effect of body mass index at baseline and treatment choice on symptom control, reliever medication use and risk of exacerbation at 12 months

Table S5. Upper panel shows the clinical and demographic baseline characteristics of the simulated population (n=1500, 500 iterations) stratified by treatment and body mass index range (i.e. normal, overweight, obese, and extreme obese). Lower panels summarises the statistical significance level of the different comparisons after 12 months; *p*-values take into account the Bonferroni correction for multiplicity.

BMI arm	Treatment	Age (y)	BMI (Kg/m2)	Baseline ACQ-5	Asthma history (y) [% missing]	Baseline Smoking (N/C/F)	Female %	Baseline FEV1p (%)
Normal	FP	43.0 (20.1-70.0)	22.9 (19.4-24.8)	2.0 (0.6-3.4)	12.5 (0.8-30.0) [26]	74/7/19	62.7	75.5 (49.7-103.0)
	FP/SAL	43.0 (20.2-70.0)	22.8 (19.4-24.8)	2.0 (0.6-3.4)	12.5 (0.8-30.0) [26]	74/7/20	62.8	75.4 (49.7-102.7)
	BUD/FOR	43.0 (20.2-70.0)	22.9 (19.4-24.8)	2.0 (0.6-3.4)	12.5 (0.8-30.0) [26]	74/7/20	62.7	75.6 (49.6-102.9)
Overweight	FP	51.0 (25.0-70.0)	27.4 (25.3-29.7)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	75/3/23	55.5	73.0 (47.4-98.2)
	FP/SAL	50.0 (25.0-70.0)	27.4 (25.3-29.7)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	75/3/23	55.4	73.0 (47.4-98.4)
	BUD/FOR	50.8 (25.0-70.0)	27.4 (25.3-29.7)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	74/3/23	55.4	73.0 (47.1-98.2)
Obese	FP	51.0 (27.0-70.0)	32.0 (30.1-34.6)	2.2 (0.6-3.6)	12.5 (3.0-30.0) [38]	75/2/23	65.2	71.9 (48.9-97.1)
	FP/SAL	51.0 (27.0-70.0)	32.0 (30.1-34.6)	2.2 (0.6-3.6)	12.5 (3.0-30.0) [38]	75/2/23	65.2	71.9 (48.9-97.1)
	BUD/FOR	51.0 (27.0-70.0)	32.0 (30.1-34.6)	2.2 (0.6-3.6)	12.5 (3.0-30.0) [38]	75/2/23	65.3	71.9 (48.9-97.1)
Extreme obese	FP	49.0 (27.0-68.0)	38.7 (35.3-50.7)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [45]	78/2/21	78.8	71.0 (47.0-94.4)
	FP/SAL	49.0 (27.0-68.0)	38.7 (35.3-50.7)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [45]	78/2/21	78.6	71.0 (47.0-94.4)
	BUD/FOR	49.0 (27.0-68.0)	38.7 (35.3-50.7)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [45]	78/2/21	78.9	71.0 (47.0-94.3)

ACQ-5 - statistical significance (p value with Bonferroni correction)

Treatment	Arm	BUD/FOR, Extremely obese	BUD/FOR, Normal	BUD/FOR, Obese	BUD/FOR, Overweight	FP, Extremely obese	FP, Normal	FP, Obese	FP, Overweight	FP/SAL, Extremely obese	FP/SAL, Normal	FP/SAL, Obese
BUD/FOR	Normal	<0.01 (6.60e-17-4.30e-06)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Obese	1 (2.67e-03-1.00e+00)	<0.01 (2.61e-09-5.29e-02)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Overweight	<0.01 (1.54e-08-4.14e-01)	0.34 (5.01e-04-1.00e+00)	1 (1.41e-02-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA
FP	Extremely obese	1 (4.48e-03-1.00e+00)	<0.01 (6.19e-27-3.28e-13)	<0.01 (1.15e-08-1.99e-01)	<0.01 (4.62e-16-1.48e-05)	NA	NA	NA	NA	NA	NA	NA
	Normal	<0.01 (9.20e-09-8.62e-02)	0.73 (2.49e-03-1.00e+00)	0.79 (1.58e-03-1.00e+00)	1 (1.00e+00-1.00e+00)	<0.01 (4.25e-17-2.28e-06)	NA	NA	NA	NA	NA	NA
	Obese	1 (1.00e+00-1.00e+00)	<0.01 (1.05e-17-5.63e-07)	0.81 (9.84e-04-1.00e+00)	<0.01 (1.72e-08-2.40e-01)	1 (5.47e-03-1.00e+00)	<0.01 (1.25e-09-1.08e-01)	NA	NA	NA	NA	NA
	Overweight	1 (9.62e-03-1.00e+00)	<0.01 (2.45e-10-2.14e-02)	1 (1.00e+00-1.00e+00)	0.63 (1.62e-03-1.00e+00)	<0.01 (6.49e-08-2.86e-01)	0.24 (8.06e-04-1.00e+00)	1 (7.75e-03-1.00e+00)	NA	NA	NA	NA
FP/SAL	Extremely obese	<0.01 (1.20e-12-8.69e-04)	1 (1.85e-01-1.00e+00)	<0.05 (4.50e-06-1.00e+00)	1 (5.53e-02-1.00e+00)	<0.01 (1.47e-22-6.16e-10)	1 (1.01e-01-1.00e+00)	<0.01 (6.47e-14-3.97e-04)	<0.01 (4.19e-07-1.00e+00)	NA	NA	NA
	Normal	<0.01 (1.08e-45-2.00e-28)	<0.01 (1.74e-12-1.47e-03)	<0.01 (1.91e-33-2.20e-18)	<0.01 (2.81e-23-2.19e-10)	<0.01 (2.76e-62-2.44e-41)	<0.01 (1.14e-22-7.19e-10)	<0.01 (5.26e-49-7.00e-30)	<0.01 (9.72e-36-3.85e-19)	<0.01 (1.17e-16-1.69e-06)	NA	NA
	Obese	<0.01 (9.22e-22-1.14e-09)	1 (8.73e-01-1.00e+00)	<0.01 (1.90e-12-4.26e-04)	<0.01 (2.94e-06-1.00e+00)	<0.01 (3.32e-33-1.49e-17)	<0.05 (6.46e-06-1.00e+00)	<0.01 (8.53e-23-7.16e-10)	<0.01 (1.27e-13-3.00e-04)	1 (5.18e-03-1.00e+00)	<0.01 (2.56e-09-1.06e-01)	NA
	Overweight	<0.01 (8.82e-33-1.08e-16)	0.11 (5.53e-05-1.00e+00)	<0.01 (1.28e-20-5.68e-09)	<0.01 (1.50e-12-2.20e-03)	<0.01 (4.89e-45-6.24e-27)	<0.01 (1.67e-11-3.50e-03)	<0.01 (8.72e-33-1.95e-17)	<0.01 (2.68e-22-1.34e-09)	<0.01 (9.43e-08-6.79e-01)	0.29 (3.46e-04-1.00e+00)	1 (8.67e-03-1.00e+00)

Reliever medication use - statistical significance (p value with Bonferroni correction)

Treatment	Arm	BUD/FOR, Normal	BUD/FOR, Overweight	BUD/FOR, Obese	BUD/FOR, Extremely obese	FP, Normal	FP, Overweight	FP, Obese	FP, Extremely obese	FP/SAL, Normal	FP/SAL, Overweight	FP/SAL, Obese	FP/SAL, Extremely obese
BUD/FOR	Normal	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Overweight	<0.01 (1.97e-19-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Obese	<0.01 (2.70e-60-4.07e-14)	<0.01 (1.89e-25-8.50e-01)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Extremely obese	<0.01 (5.28e-140-8.07e-59)	<0.01 (2.10e-85-5.82e-24)	<0.01 (4.74e-42-8.33e-03)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA
FP	Normal	<0.01 (3.66e-80-1.61e-24)	<0.01 (9.77e-38-5.49e-05)	0.39 (3.62e-10-1.00e+00)	<0.01 (4.17e-25-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	Overweight	<0.01 (8.12e-141-3.11e-65)	<0.01 (2.83e-91-5.14e-28)	<0.01 (2.90e-42-7.73e-04)	1 (1.66e-07-1.00e+00)	<0.01 (8.14e-26-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA
	Obese	<0.01 (3.26e-256-5.75e-140)	<0.01 (7.06e-177-7.98e-83)	<0.01 (7.91e-118-1.06e-32)	<0.01 (1.95e-43-2.86e-02)	<0.01 (1.85e-85-1.31e-22)	<0.01 (4.63e-38-1.33e-01)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA
	Extremely obese	<0.01 (0.00e+00-6.35e-265)	<0.01 (0.00e+00-1.15e-191)	<0.01 (4.94e-251-1.92e-108)	<0.01 (5.17e-145-3.15e-41)	<0.01 (1.35e-213-8.26e-92)	<0.01 (2.24e-134-4.21e-43)	<0.01 (5.41e-58-2.94e-05)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA
FP/SAL	Normal	1 (5.92e-07-1.00e+00)	<0.01 (1.42e-28-5.01e-02)	<0.01 (5.32e-71-1.42e-20)	<0.01 (2.84e-162-3.23e-72)	<0.01 (7.21e-92-2.06e-32)	<0.01 (7.17e-164-7.73e-77)	<0.01 (4.74e-292-1.38e-158)	<0.01 (0.00e+00-5.17e-295)	1 (1.00e+00-1.00e+00)	NA	NA	NA
	Overweight	<0.05 (5.48e-11-1.00e+00)	1 (1.55e-07-1.00e+00)	<0.01 (5.85e-37-6.07e-04)	<0.01 (2.43e-106-3.56e-36)	<0.01 (3.62e-50-1.44e-11)	<0.01 (2.06e-110-3.09e-39)	<0.01 (1.91e-212-1.52e-101)	<0.01 (0.00e+00-5.61e-213)	<0.01 (1.38e-18-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA
	Obese	<0.01 (1.78e-45-2.07e-06)	<0.01 (5.01e-16-1.00e+00)	0.84 (1.91e-11-1.00e+00)	<0.01 (4.85e-57-2.32e-07)	<0.01 (1.14e-17-1.00e+00)	<0.01 (1.05e-56-7.47e-08)	<0.01 (1.20e-139-2.34e-46)	<0.01 (2.45e-290-2.21e-132)	<0.01 (6.31e-59-2.17e-11)	<0.01 (1.72e-26-1.00e+00)	1 (1.00e+00-1.00e+00)	NA
	Extremely obese	<0.01 (2.44e-119-3.37e-46)	<0.01 (1.09e-70-1.18e-17)	<0.01 (1.34e-26-1.00e+00)	0.29 (1.76e-14-1.00e+00)	<0.01 (5.60e-17-1.00e+00)	0.37 (2.59e-12-1.00e+00)	<0.01 (1.95e-58-8.77e-07)	<0.01 (1.93e-170-2.60e-54)	<0.01 (1.03e-135-1.25e-55)	<0.01 (5.74e-85-6.25e-24)	<0.01 (3.91e-43-5.29e-02)	1 (1.00e+00-1.00e+00)

Exacerbations - statistical significance (p value with Bonferroni correction)

Treatment	Arm	FP, Normal	FP, Overweight	FP, Obese	FP, Extremely obese	FP/SAL, Normal	FP/SAL, Overweight	FP/SAL, Obese	FP/SAL, Extremely obese	BUD/FOR, Normal	BUD/FOR, Overweight	BUD/FOR, Obese
FP	Normal	1 (2.62e-02-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Obese	<0.01 (1.18e-07-5.73e-01)	1 (2.52e-03-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Overweight	<0.01 (3.77e-18-1.75e-07)	<0.01 (1.02e-11-2.91e-03)	0.07 (3.99e-05-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA
FP/SAL	Extremely obese	<0.01 (4.03e-06-1.00e+00)	<0.01 (2.22e-11-2.64e-03)	<0.01 (1.37e-20-3.98e-09)	<0.01 (6.87e-36-1.48e-20)	NA	NA	NA	NA	NA	NA	NA
	Normal	1 (4.95e-03-1.00e+00)	<0.01 (4.32e-07-4.55e-01)	<0.01 (8.64e-15-2.30e-05)	<0.01 (4.25e-28-1.03e-14)	1 (1.33e-01-1.00e+00)	NA	NA	NA	NA	NA	NA
	Obese	1 (1.00e+00-1.00e+00)	1 (5.23e-03-1.00e+00)	<0.01 (1.02e-08-1.83e-01)	<0.01 (1.05e-19-1.24e-08)	<0.05 (1.95e-05-1.00e+00)	1 (1.35e-02-1.00e+00)	NA	NA	NA	NA	NA
	Overweight	0.71 (2.44e-03-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (5.01e-02-1.00e+00)	<0.01 (1.39e-09-4.65e-02)	<0.01 (3.02e-14-9.27e-05)	<0.01 (8.23e-09-8.82e-02)	0.25 (5.37e-04-1.00e+00)	NA	NA	NA	NA
BUD/FOR	Extremely obese	<0.05 (2.87e-05-1.00e+00)	1 (5.73e-02-1.00e+00)	1 (6.12e-01-1.00e+00)	<0.01 (4.41e-07-9.65e-01)	<0.01 (2.82e-17-6.05e-07)	<0.01 (6.89e-12-1.36e-03)	<0.01 (9.69e-06-1.00e+00)	1 (7.27e-01-1.00e+00)	NA	NA	NA
	Normal	<0.01 (5.91e-11-4.66e-03)	<0.05 (2.15e-06-1.00e+00)	1 (2.98e-01-1.00e+00)	1 (1.58e-02-1.00e+00)	<0.01 (1.83e-26-8.66e-13)	<0.01 (2.78e-19-3.21e-08)	<0.01 (2.17e-12-1.12e-03)	0.15 (2.45e-04-1.00e+00)	1 (1.21e-02-1.00e+00)	NA	NA
	Obese	<0.01 (1.06e-20-1.85e-09)	<0.01 (7.25e-14-5.84e-05)	<0.01 (7.61e-07-1.00e+00)	1 (1.00e+00-1.00e+00)	<0.01 (7.76e-39-1.24e-23)	<0.01 (1.42e-31-9.31e-18)	<0.01 (1.73e-22-2.87e-10)	<0.01 (1.11e-11-2.57e-03)	<0.01 (3.36e-09-8.31e-02)	0.47 (6.66e-04-1.00e+00)	NA
	Overweight	<0.01 (1.24e-39-1.26e-22)	<0.01 (5.30e-30-6.62e-15)	<0.01 (3.87e-19-1.97e-07)	<0.01 (1.26e-07-4.88e-01)	<0.01 (3.57e-63-1.83e-41)	<0.01 (5.21e-54-1.53e-33)	<0.01 (8.26e-41-8.16e-24)	<0.01 (8.78e-27-1.53e-12)	<0.01 (1.79e-22-7.27e-10)	<0.01 (2.64e-14-1.05e-04)	<0.05 (3.32e-06-1.00e+00)

Scenario 3 – Effect of asthma history and treatment choice on symptom control, reliever medication use and risk of exacerbation at 12 months

Table S6. Upper panel shows the clinical and demographic baseline characteristics of the simulated population (n=1500, 500 iterations) stratified by treatment and asthma history. Lower panels summarises the statistical significance level of the different comparisons after 12 months; *p*-values take into account the Bonferroni correction for multiplicity.

Asthma history (y)	Treatment	Age (y)	BMI (Kg/m2)	Baseline ACQ-5	Asthma history (y) [% missing]	Baseline Smoking (N/C/F)	Female %	Baseline FEV1p (%)
<5	FP	44.3 (22.0-69.0)	26.6 (19.8-37.6)	2.0 (0.4-3.4)	3 (0.8-3.0) [0]	70/7/23	64.3	77.9 (54.9-107.4)
	FP/SAL	44.1 (22.0-69.0)	26.6 (19.9-37.6)	2.0 (0.4-3.4)	3 (0.8-3.0) [0]	70/7/23	64.3	77.9 (54.9-107.4)
	BUD/FOR	44.6 (22.0-69.0)	26.6 (19.8-37.6)	2.0 (0.4-3.4)	3 (0.8-3.0) [0]	69/7/23	64.3	77.8 (54.9-107.4)
≥5 - <10	FP	47.0 (21.0-67.0)	26.7 (20.1-39.1)	2.0 (0.8-3.6)	7.5 (7.5-7.5) [0]	75/5/20	67	75.5 (52.8-103.4)
	FP/SAL	47.0 (21.0-67.0)	26.7 (20.1-39.5)	2.0 (0.8-3.4)	7.5 (7.5-7.5) [0]	75/5/20	66.9	75.6 (52.8-102.5)
	BUD/FOR	47.0 (21.0-67.0)	26.8 (20.1-39.1)	2.0 (0.8-3.4)	7.5 (7.5-7.5) [0]	75/5/21	66.9	75.6 (52.8-102.5)
≥10 - < 20	FP	44.0 (19.0-68.0)	26.2 (19.4-37.0)	2.0 (0.6-3.6)	12.5 (12.5-17.5) [0]	71/7/22	64.9	75.9 (52.9-103.9)
	FP/SAL	44.0 (19.0-68.0)	26.2 (19.4-37.0)	2.0 (0.6-3.6)	12.5 (12.5-17.5) [0]	71/8/22	64.8	75.8 (52.9-103.8)
	BUD/FOR	44.0 (19.0-68.0)	26.1 (19.4-37.0)	2.0 (0.6-3.6)	12.5 (12.5-17.5) [0]	71/7/22	65	75.8 (52.8-103.8)
≥20	FP	45.0 (25.0-69.0)	27.1 (20.2-38.9)	2.0 (0.6-3.6)	30 (22.5-30.0) [0]	73/4/23	58.7	73.5 (50.8-98.9)
	FP/SAL	45.0 (25.0-69.0)	27.0 (20.2-38.8)	2.0 (0.6-3.6)	30 (22.5-30.0) [0]	73/4/23	58.6	73.4 (50.8-98.8)
	BUD/FOR	45.0 (25.0-69.0)	27.1 (20.2-38.9)	2.0 (0.6-3.6)	30 (22.5-30.0) [0]	72/4/23	58.5	73.5 (50.8-99.0)

ACQ-5 - statistical significance (p value with Bonferroni correction)

		BUD/FOR, <5	BUD/FOR,≥10 - < 20	BUD/FOR,≥20	BUD/FOR,≥5 - <10	FP, <5	FP,≥10 - < 20	FP,≥20	FP,≥5 - <10	FP/SAL, <5	FP/SAL,≥10 - < 20	FP/SAL,≥20
BUD/FOR	≥10 - < 20	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥20	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥5 - <10	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA
FP	<5	1 (1.29e-03-1.00e+00)	0.18 (1.42e-04-1.00e+00)	1 (1.93e-03-1.00e+00)	0.57 (8.65e-04-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	≥10 - < 20	1 (2.14e-02-1.00e+00)	0.61 (1.44e-03-1.00e+00)	1 (6.31e-03-1.00e+00)	1 (3.63e-03-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA
	≥20	1 (3.99e-03-1.00e+00)	0.18 (1.55e-04-1.00e+00)	1 (8.67e-04-1.00e+00)	0.53 (1.06e-03-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA
	≥5 - <10	1 (3.11e-03-1.00e+00)	0.19 (2.11e-04-1.00e+00)	1 (1.30e-03-1.00e+00)	0.52 (5.86e-04-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA
FP/SAL	<5	<0.01 (1.59e-13-1.00e-03)	<0.01 (3.03e-10-2.28e-02)	<0.01 (6.95e-13-1.59e-03)	<0.01 (5.38e-12-3.36e-03)	<0.01 (3.14e-22-2.91e-09)	<0.01 (9.16e-21-4.59e-08)	<0.01 (8.07e-22-1.25e-09)	<0.01 (2.38e-22-1.84e-09)	NA	NA	NA
	≥10 - < 20	<0.01 (8.09e-15-9.70e-05)	<0.01 (2.54e-12-3.88e-03)	<0.01 (3.38e-14-1.89e-04)	<0.01 (1.18e-13-8.97e-04)	<0.01 (4.69e-24-7.05e-11)	<0.01 (1.69e-22-1.88e-09)	<0.01 (3.51e-24-4.98e-11)	<0.01 (6.16e-24-3.96e-11)	1 (9.19e-01-1.00e+00)	NA	NA
	≥20	<0.01 (2.63e-13-1.66e-03)	<0.01 (4.52e-11-1.84e-02)	<0.01 (5.59e-13-3.41e-03)	<0.01 (5.23e-12-4.97e-03)	<0.01 (1.83e-22-2.39e-09)	<0.01 (1.17e-20-1.48e-08)	<0.01 (2.35e-22-1.16e-09)	<0.01 (1.08e-22-2.26e-09)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA
	≥5 - <10	<0.01 (4.73e-13-7.01e-04)	<0.01 (9.84e-11-2.07e-02)	<0.01 (2.16e-13-1.21e-03)	<0.01 (1.11e-12-5.34e-03)	<0.01 (3.82e-23-2.43e-09)	<0.01 (1.11e-20-1.80e-08)	<0.01 (2.04e-22-7.09e-10)	<0.01 (2.31e-22-1.35e-09)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)

Reliever medication use - statistical significance (p value with Bonferroni correction)

Treatment	Arm	BUD/FOR, <5	BUD/FOR, ≥5 - <10	BUD/FOR, ≥10 - < 20	BUD/FOR, ≥20	FP, <5	FP, ≥5 - <10	FP, ≥10 - < 20	FP, ≥20	FP/SAL, <5	FP/SAL, ≥5 - <10	FP/SAL, ≥10 - < 20	FP/SAL, ≥20
BUD/FOR	<5	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥5 - <10	<0.01 (4.37e-20-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥10 - < 20	<0.01 (1.87e-59-2.71e-13)	<0.01 (3.00e-27-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥20	<0.01 (2.89e-198-1.60e-97)	<0.01 (2.23e-130-1.30e-55)	<0.01 (3.67e-71-1.04e-17)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA
FP	<5	<0.01 (4.81e-74-1.83e-17)	<0.01 (5.32e-34-8.66e-03)	1 (9.17e-09-1.00e+00)	<0.01 (6.76e-64-6.70e-12)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	≥5 - <10	<0.01 (6.33e-134-5.54e-60)	<0.01 (1.22e-90-9.88e-24)	<0.01 (9.09e-38-7.88e-02)	<0.01 (1.12e-23-1.00e+00)	<0.01 (6.11e-29-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA
	≥10 - < 20	<0.01 (4.24e-250-1.16e-131)	<0.01 (1.61e-176-5.59e-80)	<0.01 (1.54e-109-3.45e-28)	0.06 (2.13e-17-1.00e+00)	<0.01 (7.49e-93-7.30e-23)	<0.01 (2.58e-41-2.63e-02)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA
	≥20	<0.01 (0.00e+00-3.85e-322)	<0.01 (0.00e+00-1.39e-267)	<0.01 (6.97e-319-7.99e-177)	<0.01 (1.59e-147-1.30e-46)	<0.01 (5.46e-302-3.02e-159)	<0.01 (5.39e-207-7.72e-86)	<0.01 (4.03e-109-1.51e-25)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA
FP/SAL	<5	1 (1.68e-06-1.00e+00)	<0.01 (2.88e-24-9.14e-02)	<0.01 (5.40e-71-8.64e-21)	<0.01 (7.44e-218-1.78e-115)	<0.01 (1.04e-85-1.46e-25)	<0.01 (5.14e-155-3.63e-69)	<0.01 (4.55e-269-1.75e-142)	<0.01 (0.00e+00-3.85e-322)	1 (1.00e+00-1.00e+00)	NA	NA	NA
	≥5 - <10	<0.05 (2.33e-12-1.00e+00)	1 (1.34e-07-1.00e+00)	<0.01 (3.27e-38-1.28e-03)	<0.01 (3.46e-152-1.65e-65)	<0.01 (3.72e-46-2.47e-07)	<0.01 (1.40e-105-5.09e-31)	<0.01 (9.85e-201-1.30e-91)	<0.01 (0.00e+00-1.54e-299)	<0.01 (1.48e-18-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA
	≥10 - < 20	<0.01 (5.92e-49-1.80e-07)	<0.01 (2.33e-19-1.00e+00)	0.6 (4.38e-11-1.00e+00)	<0.01 (2.15e-91-1.06e-24)	0.06 (1.79e-14-1.00e+00)	<0.01 (1.26e-48-1.32e-05)	<0.01 (2.26e-130-2.93e-41)	<0.01 (0.00e+00-4.14e-190)	<0.01 (4.07e-57-2.51e-12)	<0.01 (2.03e-26-5.27e-01)	1 (1.00e+00-1.00e+00)	NA
	≥20	<0.01 (3.31e-168-2.83e-81)	<0.01 (4.33e-111-9.39e-40)	<0.01 (1.47e-58-2.50e-08)	0.6 (2.60e-13-1.00e+00)	<0.01 (4.33e-46-1.07e-04)	0.23 (3.37e-12-1.00e+00)	<0.01 (3.82e-25-1.00e+00)	<0.01 (6.44e-177-1.03e-58)	<0.01 (2.99e-186-8.61e-97)	<0.01 (1.06e-125-8.77e-52)	<0.01 (3.44e-68-3.45e-15)	1 (1.00e+00-1.00e+00)

Exacerbations - statistical significance (p value with Bonferroni correction)

		FP, <5	FP,≥5 - <10	FP,≥10 - < 20	FP,≥20	FP/SAL, <5	FP/SAL,≥5 - <10	FP/SAL,≥10 - < 20	FP/SAL,≥20	BUD/FOR, <5	BUD/FOR,≥5 - <10	BUD/FOR,≥10 - < 20
FP	≥10 - < 20	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥20	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	≥5 - <10	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA	NA
FP/SAL	<5	<0.01 (1.11e-07-1.00e+00)	<0.01 (2.73e-09-2.25e-01)	<0.01 (1.02e-07-3.15e-01)	<0.01 (1.34e-08-1.97e-01)	NA	NA	NA	NA	NA	NA	NA
	≥10 - < 20	<0.05 (3.35e-06-1.00e+00)	<0.01 (9.72e-08-9.63e-01)	<0.01 (1.62e-06-9.29e-01)	<0.01 (3.93e-07-6.85e-01)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA
	≥20	<0.01 (1.32e-06-1.00e+00)	<0.01 (6.83e-08-2.50e-01)	<0.01 (4.19e-07-6.92e-01)	<0.01 (3.07e-08-3.76e-01)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA
	≥5 - <10	<0.05 (1.28e-05-1.00e+00)	<0.01 (1.84e-07-3.09e-01)	<0.01 (1.16e-06-5.42e-01)	<0.01 (6.68e-07-3.73e-01)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA
BUD/FOR	<5	<0.01 (5.20e-06-1.00e+00)	0.09 (9.66e-05-1.00e+00)	<0.05 (3.27e-05-1.00e+00)	0.07 (1.39e-04-1.00e+00)	<0.01 (1.58e-19-8.21e-08)	<0.01 (6.89e-18-7.68e-07)	<0.01 (9.60e-19-1.46e-07)	<0.01 (9.97e-18-1.84e-07)	NA	NA	NA
	≥10 - < 20	<0.01 (2.44e-07-3.89e-01)	<0.05 (5.14e-06-1.00e+00)	<0.01 (1.69e-06-1.00e+00)	<0.01 (8.77e-06-1.00e+00)	<0.01 (3.66e-22-2.37e-09)	<0.01 (2.51e-20-1.02e-08)	<0.01 (3.62e-21-5.21e-09)	<0.01 (3.99e-20-7.24e-09)	1 (1.00e+00-1.00e+00)	NA	NA
	≥20	<0.01 (1.83e-06-1.00e+00)	<0.05 (4.38e-05-1.00e+00)	<0.05 (1.92e-05-1.00e+00)	<0.05 (3.60e-05-1.00e+00)	<0.01 (1.64e-20-1.40e-08)	<0.01 (1.29e-18-1.52e-07)	<0.01 (5.73e-20-4.33e-08)	<0.01 (1.69e-18-5.95e-08)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	NA
	≥5 - <10	<0.01 (2.78e-07-4.85e-01)	<0.05 (6.60e-06-1.00e+00)	<0.01 (2.00e-06-1.00e+00)	<0.05 (5.13e-06-1.00e+00)	<0.01 (1.79e-21-2.31e-09)	<0.01 (1.69e-20-3.31e-08)	<0.01 (2.18e-20-1.56e-09)	<0.01 (1.59e-19-6.03e-09)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)	1 (1.00e+00-1.00e+00)

Scenario 4 – Effect of smoking habit and treatment choice on symptom control, reliever medication use and risk of exacerbation at 12 months

Table S7. Upper panel shows the clinical and demographic baseline characteristics of the simulated population (n=1500, 500 iterations) stratified by treatment and smoking habit (non-smoker, former smoker and current smoker). Lower panels summarises the statistical significance level of the different comparisons after 12 months; *p*-values take into account the Bonferroni correction for multiplicity.

Smoking habit	Treatment	Age (y)	BMI (Kg/m2)	Baseline ACQ-5	Asthma history (y) [% missing]	Baseline Smoking (N/C/F)	Female %	Baseline FEV1p (%)
Current smoker	FP	34.0 (19.5-60.0)	24.2 (19.0-35.4)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [0]	0/100/0	58.2	79.2 (54.6-105.7)
	FP/SAL	34.0 (19.5-60.0)	24.2 (19.1-35.4)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [0]	0/100/0	57.8	79.0 (54.6-105.7)
	BUD/FOR	34.0 (19.5-60.0)	24.2 (19.1-35.4)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [0]	0/100/0	58.6	79.0 (54.6-105.7)
Former smoker	FP	51.0 (27.0-70.0)	27.5 (20.5-39.1)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [30]	0/0/100	49.9	73.7 (48.2-99.8)
	FP/SAL	51.0 (27.0-70.0)	27.5 (20.6-39.1)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [30]	0/0/100	50.2	73.8 (48.5-99.8)
	BUD/FOR	51.0 (27.0-70.0)	27.5 (20.6-39.1)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [30]	0/0/100	50.2	73.8 (48.5-99.8)
Never smoked	FP	48.0 (22.0-70.0)	27.2 (20.2-39.9)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [36]	100/0/0	66.5	73.1 (48.1-98.8)
	FP/SAL	48.0 (22.0-70.0)	27.2 (20.2-39.8)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [36]	100/0/0	66.6	73.2 (48.1-98.7)
	BUD/FOR	48.0 (22.0-70.0)	27.2 (20.2-39.9)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [36]	100/0/0	66.4	73.2 (48.0-98.8)

ACQ-5 - statistical significance (p value with Bonferroni correction)

Treatment	Smoking status	BUD/FOR, Current smoker	BUD/FOR, Former smoker	BUD/FOR, Never smoked	FP, Current smoker	FP, Former smoker	FP, Never smoked	FP/SAL, Current smoker	FP/SAL, Former smoker
BUD/FOR	Former smoker	<0.01 (1.93e-16-2.06e-06)	NA	NA	NA	NA	NA	NA	NA
	Never smoked	<0.01 (5.61e-63-6.28e-41)	<0.01 (7.31e-23-7.94e-11)	NA	NA	NA	NA	NA	NA
FP	Current smoker	1 (5.36e-03-1.00e+00)	<0.01 (9.81e-25-2.15e-11)	<0.01 (2.57e-77-1.88e-53)	NA	NA	NA	NA	NA
	Former smoker	<0.01 (1.99e-10-2.91e-02)	1 (6.56e-03-1.00e+00)	<0.01 (2.98e-33-5.12e-18)	<0.01 (3.44e-17-2.03e-06)	NA	NA	NA	NA
	Never smoked	<0.01 (7.69e-47-4.90e-28)	<0.01 (6.40e-13-4.02e-04)	0.26 (5.10e-04-1.00e+00)	<0.01 (1.06e-60-1.75e-38)	<0.01 (2.42e-21-2.41e-09)	NA	NA	NA
FP/SAL	Current smoker	<0.01 (1.41e-15-5.20e-04)	1 (3.50e-01-1.00e+00)	<0.01 (3.35e-26-5.19e-13)	<0.01 (2.65e-23-4.83e-09)	1 (4.57e-02-1.00e+00)	<0.01 (3.72e-16-2.37e-05)	NA	NA
	Former smoker	<0.01 (1.70e-47-8.34e-29)	<0.01 (3.40e-13-2.78e-04)	0.53 (6.09e-04-1.00e+00)	<0.01 (3.58e-61-1.17e-37)	<0.01 (3.00e-22-1.91e-09)	1 (1.00e+00-1.00e+00)	<0.01 (2.65e-17-4.94e-06)	NA
	Never smoked	<0.01 (1.18e-106-1.96e-79)	<0.01 (9.70e-55-3.15e-35)	<0.01 (1.60e-12-5.54e-04)	<0.01 (3.63e-124-1.39e-95)	<0.01 (1.45e-70-1.74e-47)	<0.01 (1.42e-23-5.50e-11)	<0.01 (9.05e-60-2.89e-39)	<0.01 (1.24e-22-4.51e-10)

Reliever medication use - statistical significance (p value with Bonferroni correction)

Treatment	Smoking status	BUD/FOR, Current smoker	BUD/FOR, Former smoker	BUD/FOR, Never smoked	FP, Current smoker	FP, Former smoker	FP, Never smoked	FP/SAL, Current smoker	FP/SAL, Former smoker
BUD/FOR	Current smoker	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	Former smoker	<0.01 (1.10e-77-8.40e-06)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA	NA
	Never smoked	<0.01 (7.32e-214-8.26e-76)	<0.01 (7.28e-71-9.92e-18)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA
FP	Current smoker	<0.01 (2.93e-221-2.59e-30)	<0.01 (2.22e-322-1.04e-144)	<0.01 (0.00e+00-2.22e-322)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA
	Former smoker	<0.01 (1.88e-36-1.00e+00)	<0.01 (4.62e-127-5.70e-36)	<0.01 (5.35e-292-3.05e-157)	<0.01 (2.82e-112-2.22e-10)	1 (1.00e+00-1.00e+00)	NA	NA	NA
	Never smoked	<0.01 (1.09e-55-7.13e-02)	0.43 (2.22e-10-1.00e+00)	<0.01 (7.47e-86-8.68e-28)	<0.01 (2.22e-322-4.45e-124)	<0.01 (1.90e-100-4.32e-27)	1 (1.00e+00-1.00e+00)	NA	NA
FP/SAL	Current smoker	<0.01 (2.94e-30-1.00e+00)	<0.01 (7.14e-56-6.30e-02)	<0.01 (3.22e-185-1.76e-60)	<0.01 (3.13e-249-1.17e-46)	<0.01 (1.89e-56-1.00e+00)	<0.01 (4.13e-40-1.00e+00)	1 (1.00e+00-1.00e+00)	NA
	Former smoker	<0.01 (3.20e-92-3.64e-12)	0.44 (7.60e-11-1.00e+00)	<0.01 (2.73e-54-9.81e-10)	<0.01 (0.00e+00-2.16e-181)	<0.01 (1.64e-145-4.36e-50)	<0.01 (3.18e-17-1.00e+00)	<0.01 (1.08e-74-5.37e-06)	1 (1.00e+00-1.00e+00)
	Never smoked	<0.01 (1.60e-237-1.20e-92)	<0.01 (3.03e-82-1.61e-26)	1 (1.49e-06-1.00e+00)	<0.01 (0.00e+00-2.22e-322)	<0.01 (2.49e-319-1.54e-184)	<0.01 (4.07e-101-2.12e-39)	<0.01 (8.07e-205-6.37e-81)	<0.01 (5.50e-65-1.86e-17)

Exacerbations - statistical significance (p value with Bonferroni correction)

Treatment	Smoking status	BUD/FOR, Current smoker	BUD/FOR, Former smoker	BUD/FOR, Never smoked	FP, Current smoker	FP, Former smoker	FP, Never smoked	FP/SAL, Current smoker	FP/SAL, Former smoker
FP	Former smoker	1 (2.90e-02-1.00e+00)	NA	NA	NA	NA	NA	NA	NA
	Never smoked	<0.01 (3.79e-07-1.00e+00)	0.62 (1.34e-03-1.00e+00)	NA	NA	NA	NA	NA	NA
FP/SAL	Current smoker	<0.01 (2.98e-10-1.13e-01)	<0.05 (8.55e-06-1.00e+00)	1 (1.93e-01-1.00e+00)	NA	NA	NA	NA	NA
	Former smoker	<0.01 (6.84e-14-6.99e-04)	<0.01 (1.36e-08-1.76e-01)	0.84 (3.58e-03-1.00e+00)	1 (1.27e-01-1.00e+00)	NA	NA	NA	NA
	Never smoked	<0.01 (4.36e-21-2.20e-08)	<0.01 (6.88e-15-1.96e-05)	<0.01 (1.59e-07-2.57e-01)	<0.05 (3.42e-05-1.00e+00)	1 (9.18e-03-1.00e+00)	NA	NA	NA
BUD/FOR	Current smoker	<0.01 (1.72e-08-1.00e+00)	<0.01 (7.62e-12-9.37e-03)	<0.01 (2.52e-20-2.51e-08)	<0.01 (9.29e-26-1.93e-10)	<0.01 (2.77e-30-1.41e-14)	<0.01 (8.37e-42-3.60e-23)	NA	NA
	Former smoker	0.44 (5.74e-04-1.00e+00)	<0.01 (1.01e-06-1.00e+00)	<0.01 (3.38e-14-6.17e-05)	<0.01 (2.23e-17-7.08e-07)	<0.01 (1.92e-22-3.36e-10)	<0.01 (8.57e-32-8.38e-18)	1 (3.97e-02-1.00e+00)	NA
	Never smoked	1 (5.76e-01-1.00e+00)	1 (1.24e-01-1.00e+00)	<0.05 (2.76e-06-1.00e+00)	<0.01 (1.93e-08-8.26e-02)	<0.01 (5.98e-12-1.88e-03)	<0.01 (8.15e-20-4.82e-08)	<0.01 (3.01e-08-6.64e-01)	0.26 (6.70e-04-1.00e+00)

Scenario 5 – Effect of smoking cessation and treatment choice on symptom control, reliever medication use and risk of exacerbation at 12 months

Table S8. Upper panel shows the clinical and demographic baseline characteristics of the simulated population (n=1500, 500 iterations) stratified by treatment and smoking cessation (current smoker vs former smoker). Lower panels summarises the statistical significance level of the different comparisons after 12 months; *p*-values take into account the Bonferroni correction for multiplicity.

Arm	Treatment	Age (y)	BMI (Kg/m2)	Baseline ACQ-5	Asthma history (y) [% missing]	Baseline Smoking (N/C/F)	Female %	Baseline FEV1p (%)
Current smoker	FP	48.0 (23.0-70.0)	27.2 (20.2-39.6)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	0/100/0	62.7	73.4 (48.2-99.5)
	FP/SAL	48.0 (23.0-70.0)	27.2 (20.2-39.6)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	0/100/0	62.8	73.4 (48.4-99.4)
	BUD/FOR	48.0 (23.0-70.0)	27.1 (20.2-39.5)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	0/100/0	62.7	73.4 (48.2-99.3)
Former smoker	FP	48.0 (23.0-70.0)	27.2 (20.2-39.6)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	0/100/0	62.8	73.4 (48.2-99.2)
	FP/SAL	48.0 (23.0-70.0)	27.2 (20.2-39.6)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	0/100/0	62.7	73.4 (48.4-99.5)
	BUD/FOR	48.0 (23.0-70.0)	27.2 (20.2-39.6)	2.0 (0.6-3.4)	12.5 (3.0-30.0) [33]	0/100/0	62.7	73.4 (48.4-99.2)

ACQ-5 - statistical significance (p value with Bonferroni correction)

Treatment	Arm	BUD/FOR, Current smoker	BUD/FOR, Former smoker	FP, Current smoker	FP, Former smoker	FP/SAL, Current smoker
BUD/FOR	Former smoker	<0.01 (4.07e-34-4.25e-19)	NA	NA	NA	NA
FP	Current smoker	1 (3.53e-02-1.00e+00)	<0.01 (2.80e-42-3.14e-26)	NA	NA	NA
	Former smoker	<0.01 (3.71e-23-2.92e-11)	0.15 (5.62e-04-1.00e+00)	<0.01 (1.04e-30-1.95e-16)	NA	NA
FP/SAL	Current smoker	<0.01 (1.83e-15-1.60e-05)	<0.01 (1.17e-08-7.56e-02)	<0.01 (5.90e-21-2.25e-09)	0.76 (3.34e-03-1.00e+00)	NA
	Former smoker	<0.01 (1.52e-71-1.57e-49)	<0.01 (1.37e-13-1.11e-04)	<0.01 (4.52e-85-6.04e-61)	<0.01 (6.77e-23-3.09e-11)	<0.01 (1.72e-32-3.51e-18)

Reliever medication use - statistical significance (p value with Bonferroni correction)

Treatment	Arm	BUD/FOR, Current smoker	BUD/FOR, Former smoker	FP, Current smoker	FP, Former smoker	FP/SAL, Current smoker	FP/SAL, Former smoker
BUD/FOR	Current smoker	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA	NA
	Former smoker	<0.01 (6.53e-44-5.55e-05)	1 (1.00e+00-1.00e+00)	NA	NA	NA	NA
FP	Current smoker	<0.01 (3.24e-158-2.80e-51)	<0.01 (4.61e-281-1.09e-137)	1 (1.00e+00-1.00e+00)	NA	NA	NA
	Former smoker	<0.01 (4.97e-45-2.11e-03)	<0.01 (2.55e-122-8.61e-40)	<0.01 (2.25e-69-2.27e-06)	1 (1.00e+00-1.00e+00)	NA	NA
FP/SAL	Current smoker	0.15 (5.14e-11-1.00e+00)	<0.01 (7.06e-31-2.77e-01)	<0.01 (1.51e-180-7.50e-69)	<0.01 (2.55e-62-5.44e-10)	1 (1.00e+00-1.00e+00)	NA
	Former smoker	<0.01 (6.48e-57-2.19e-11)	0.33 (4.18e-10-1.00e+00)	<0.01 (1.47e-307-9.83e-156)	<0.01 (3.74e-144-7.65e-54)	<0.01 (2.64e-44-1.48e-04)	1 (1.00e+00-1.00e+00)

Exacerbations - statistical significance (p value with Bonferroni correction)

Treatment	Arm	FP, Current smoker	FP, Former smoker	FP/SAL, Current smoker	FP/SAL, Former smoker	BUD/FOR, Current smoker
FP	Former smoker	0.26 (8.13e-04-1.00e+00)	NA	NA	NA	NA
FP/SAL	Current smoker	<0.01 (8.64e-10-8.98e-03)	0.18 (6.71e-04-1.00e+00)	NA	NA	NA
	Former smoker	<0.01 (1.90e-16-6.85e-07)	<0.01 (8.30e-09-3.18e-02)	0.5 (4.61e-03-1.00e+00)	NA	NA
BUD/FOR	Current smoker	<0.01 (4.98e-08-1.94e-01)	<0.01 (6.01e-15-1.36e-05)	<0.01 (2.55e-25-6.95e-13)	<0.01 (3.97e-35-6.82e-20)	NA
	Former smoker	1 (1.66e-02-1.00e+00)	<0.01 (3.38e-07-2.54e-01)	<0.01 (5.85e-15-6.74e-06)	<0.01 (2.20e-22-3.94e-11)	0.22 (4.66e-04-1.00e+00)

Scenario 6 – Effect of step-up to combination therapy and treatment choice on symptom control, reliever medication use and risk of exacerbation at 12 months

Table S9. Upper panel shows the clinical and demographic baseline characteristics of the simulated population (n=1500, 500 iterations) stratified by treatment (FP NR= FO non-responder). Lower panels summarises the statistical significance level of the different comparisons after 12 months; *p*-values take into account the Bonferroni correction for multiplicity.

Arm	Age (y)	BMI (Kg/m2)	Baseline ACQ-5	Asthma history (y) [% missing]	Baseline Smoking (N/C/F)	Female %	Baseline FEV1p (%)
FP (R)	46.0 (22.0-69.0)	26.5 (19.8-38.3)	1.8 (0.4-3.2)	12.5 (3.0-30.0) [31]	81/2/17	62.4	74.5 (50.0-100.6)
FP (NR) > BUD/FOR	49.0 (23.0-70.0)	27.5 (20.3-40.1)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [34]	72/5/23	62.7	72.9 (47.8-98.9)
FP (NR) > FP/SAL	49.0 (23.0-70.0)	27.5 (20.3-40.1)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [34]	72/5/23	62.8	72.9 (47.8-98.9)
FP (NR) > FP (500 µg)	49.0 (23.0-70.0)	27.5 (20.3-40.1)	2.2 (0.8-3.6)	12.5 (3.0-30.0) [34]	72/5/23	62.9	72.9 (47.7-98.9)

ACQ-5 - statistical significance (p value with Bonferroni correction)

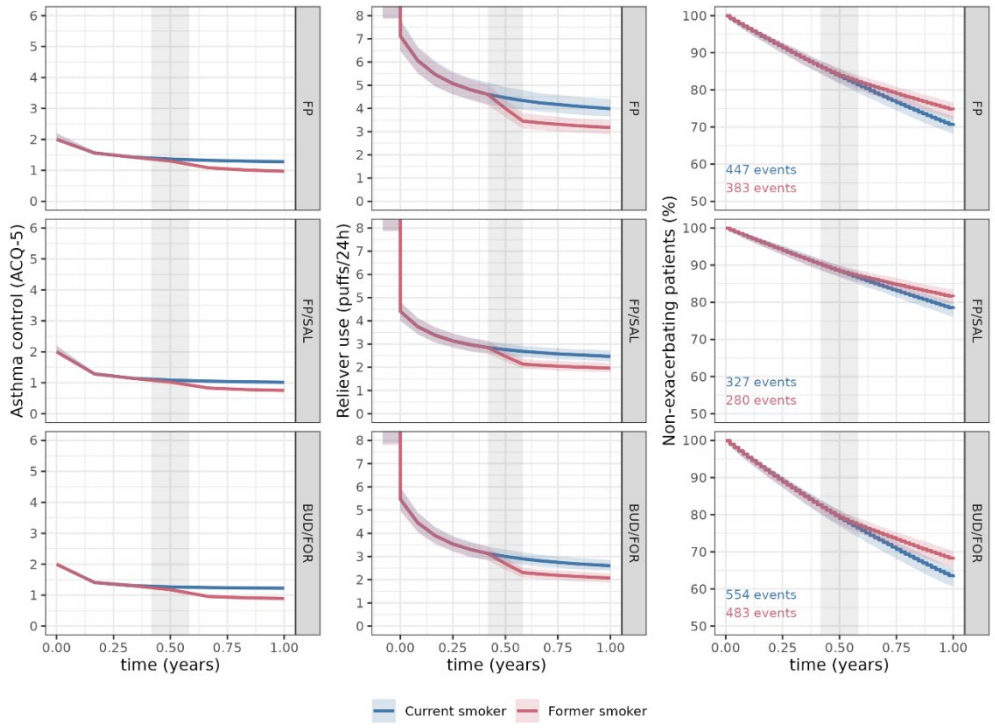
	FP (R)	FP (NR) > BUD/FOR	FP (NR) > FP/SAL
FP (NR) > BUD/FOR	<0.01 (0.00e+00-0.00e+00)	NA	NA
FP (NR) > FP/SAL	<0.01 (0.00e+00-0.00e+00)	<0.01 (4.44e-50-5.11e-30)	NA
FP (NR) > FP (500 µg)	<0.01 (0.00e+00-0.00e+00)	<0.01 (9.04e-14-1.31e-04)	<0.01 (1.31e-102-1.79e-73)

Reliever medication use - statistical significance (p value with Bonferroni correction)

Treatment	FP (NR) > BUD/FOR	FP (NR) > FP (500 µg)	FP (NR) > FP/SAL	FP (R)
FP (NR) > BUD/FOR	1 (1.00e+00-1.00e+00)	NA	NA	NA
FP (NR) > FP (500 µg)	<0.01 (2.87e-121-5.47e-82)	1 (1.00e+00-1.00e+00)	NA	NA
FP (NR) > FP/SAL	<0.01 (1.34e-05-4.14e-01)	<0.01 (3.84e-172-3.91e-111)	1 (1.00e+00-1.00e+00)	NA
FP (R)	<0.01 (4.94e-323-1.81e-292)	<0.01 (2.67e-67-2.06e-26)	<0.01 (4.94e-323-4.94e-323)	1 (1.00e+00-1.00e+00)

Exacerbations - statistical significance (p value with Bonferroni correction)

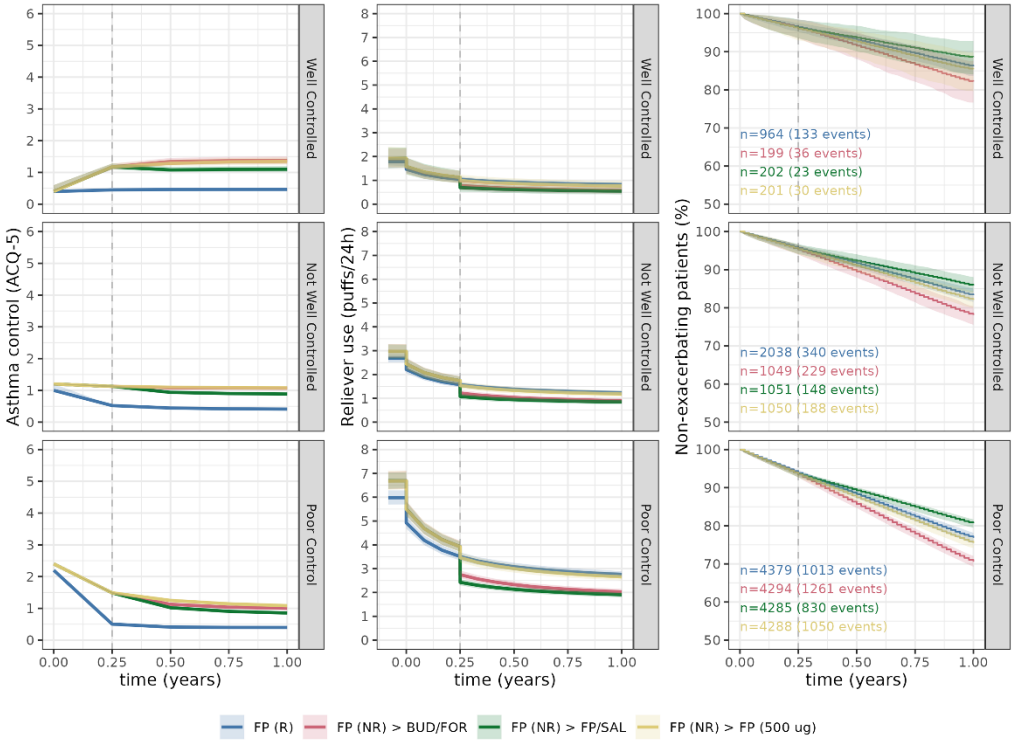
	FP (R)	FP (NR) > BUD/FOR	FP (NR) > FP/SAL
FP (NR) > BUD/FOR	<0.01 (1.05e-29-1.70e-15)	NA	NA
FP (NR) > FP/SAL	<0.05 (8.64e-05-1.00e+00)	<0.01 (8.37e-39-5.44e-22)	NA
FP (NR) > FP (500 µg)	<0.01 (2.14e-07-2.15e-01)	<0.01 (3.24e-12-1.06e-03)	<0.01 (9.49e-14-6.92e-05)



		Asthma control (ACQ-5)			Reliever use (puffs/24h)			Annualised exacerbating rate (%)		
Treatment	**Arm**	Median	95% Confidence interval		Mean	95% Confidence interval		Median	95% Confidence interval	
FP	Current smoker	1.28	1.22	1.34	3.99	3.65	4.40	70.3	68.1	72.9
	Former smoker	0.97	0.92	1.01	3.18	2.89	3.49	74.5	72.2	76.6
FP/SAL	Current smoker	1.02	0.97	1.06	2.47	2.24	2.71	78.3	76.2	80.2
	Former smoker	0.75	0.71	0.79	1.96	1.79	2.17	81.4	79.6	83.4
BUD/FOR	Current smoker	1.23	1.17	1.28	2.60	2.39	2.84	63.2	60.7	65.5
	Former smoker	0.89	0.85	0.94	2.07	1.88	2.27	68.0	65.7	70.3

Figure S1. Effect of smoking cessation on symptom control score, reliever medication use (puffs/24h) and exacerbation risk. Treatment arms (n=1500 each, 500 iterations) include: FP (250 µg b.i.d., arm1), FP/SAL (250/50 µg b.i.d., arm2), BUD/FOR (200/6 b.i.d, arm3).. Parameter estimates describing treatment effect correspond to that of the mean dose during the maintenance phase. It should be highlighted that despite comparable reduction in reliever medication use after 12 months on combination therapy with ICS/LABA, FP/SAL results in a significantly lower ACQ-5 scores (*p< 0.01*) and lower exacerbation rate (*p< 0.01*) than BUD/FOR. These findings suggest that exposure to airway irritants, such as tobacco smoking increases airway inflammation, and that persistent airway inflammation has long term consequences (i.e., epithelial damage and repair). Of note are also the significant differences between treatment choices. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. Further details on the clinical and demographic baseline characteristics of the simulated population and an overview of the statistical significance level of the comparison between different groups and treatment arms at 12 months are summarised in **Table S8**.

ACQ-5 – asthma control questionnaire, BMI – body mass index, BUD/FOR – budesonide/formoterol, FP – fluticasone propionate, ICS- inhaled corticosteroid, LABA- long-acting beta agonist, SAL – salmeterol



		Asthma control (ACQ-5)			Reliever use (puffs/24h)			Annualised exacerbating rate (%)		
Arm		Median	95% Confidence interval		Mean	95% Confidence interval		Median	95% Confidence interval	
FP (R)	Well Controlled	0.47	0.49	0.45	0.82	0.92	0.73	86.2	83.7	88.4
	Not Well Controlled	0.41	0.42	0.40	1.24	1.31	1.14	83.3	81.5	85.0
	Poor Control	0.40	0.41	0.39	2.76	2.89	2.63	76.9	75.4	78.2
FP (NR) > BUD/FOR	Well Controlled	1.37	1.50	1.26	0.57	0.73	0.44	82.2	76.7	87.6
	Not Well Controlled	1.07	1.12	1.03	0.90	1.01	0.80	78.1	75.6	80.4
	Poor Control	1.00	1.02	0.98	2.02	2.14	1.91	70.6	69.3	72.1
FP (NR) > FP/SAL	Well Controlled	1.10	1.20	1.02	0.55	0.71	0.41	88.6	84.1	92.8
	Not Well Controlled	0.89	0.92	0.85	0.85	0.94	0.76	85.9	83.9	88.0
	Poor Control	0.85	0.87	0.83	1.91	2.01	1.80	80.7	79.5	81.7
FP (NR) > FP (500 ug)	Well Controlled	1.35	1.47	1.25	0.77	0.99	0.59	85.4	79.7	89.8
	Not Well Controlled	1.08	1.12	1.04	1.18	1.32	1.07	82.1	80.0	84.4
	Poor Control	1.08	1.11	1.06	2.66	2.82	2.51	75.5	74.2	76.8

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

Figure S2. Results from Scenario 6 following stratification by AQC-5 score at baseline. The effect of increased ICS dose and transition to ICS/ LABA combination therapy is assessed in patients who do not achieve adequate symptom control on ICS monotherapy. Curves in each panel depict the median (symptom scores, exacerbation events) or mean (reliever use) profiles in each treatment arm. The lower panel summarises the response to treatment after 12 months. Treatment arms (n = 8000 each, 500 iterations) include FP (250 µg b.i.d.), FP (500 µg b.i.d.), FP/SAL (250/50 µg b.i.d.), BUD/FOR (200/6 µg b.i.d.). Parameter estimates describing the treatment effect correspond to that of the mean dose during the maintenance phase. Despite comparable reduction in reliever medication use after 12 months on combination therapy with ICS/LABA, FP/SAL results in significantly lower ACQ-5 scores and exacerbation rate than BUD/ FOR (p < 0.01). It is worth noting that a difference of 10.1% is observed in the annualised exacerbation rate for patients with ACQ-5>1.5 at baseline who switch to combination therapy [i.e., BUD/FOR (29.40%) vs FP/SAL (19.34%)]. This difference corresponds to approximately 34.2% less events after switching to FP/SAL vs. BUD/FOR (i.e. 830 vs 1261 exacerbations in a population at risk of ~ 4290 patients).

ACQ-5 asthma control questionnaire, BMI body mass index, BUD/FOR budesonide/formoterol, FP fluticasone propionate, FP(NR) non-responder to FP monotherapy, FP(R) responder to FP monotherapy, ICS inhaled corticosteroid, LABA long-acting beta agonist, SAL salmeterol