Supplementary Material

Understanding the clinical implications of individual patient characteristics and treatment choice on the risk of exacerbation in asthma patients with moderate-severe symptoms

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

Baseline characteristic	FP	FP/SAL	BUD/FOR
BMI			
Not available	*NA* [n=561]	*NA* [n=543]	*NA* [n=8]
Underweight (<18.5)	17.7 (16.2-18.4) [n=121]	17.6 (15.2-18.4) [n=133]	18 (16.6-18.4) [n=11]
Normal weight (18.5 - <25)	22.7 (19.4-24.8) [n=2122]	22.7 (19.3-24.8) [n=2327]	22.8 (19.6-24.9) [n=226]
Overweight (25 - <30)	27.4 (25.3-29.7) [n=2231]	27.4 (25.2-29.6) [n=2404]	27.5 (25.3-29.7) [n=256]
Obese (30 - <35)	32 (30.1-34.7) [n=1363]	32 (30.1-34.7) [n=1428]	32.1 (30.1-34.6) [n=142]
Severely obese (≥35)	39 (35.3-52.1) [n=1092]	38.9 (35.4-51) [n=1214]	39.5 (35.2-52.7) [n=100]
Smoking status			
Not available	6.6% [n=491]	3.1% [n=250]	0.3% [n=2]
Never smoked	71.4% [n=5349]	74.2% [n=5970]	58% [n=431]
Former smoker	16.8% [n=1259]	17.4% [n=1397]	28.9% [n=215]
Current smoker	5.2% [n=391]	5.4% [n=432]	12.8% [n=95]
Sex			
Male	33% [n=2471]	34.4% [n=2765]	38.8% [n=288]
Female	67% [n=5019]	65.6% [n=5284]	61.2% [n=455]
ACQ-5*			
Not available	*NA* [n=6828]	*NA* [n=7137]	*NA* [n=492]
Well controlled (≤0.75)	0.4 (0-0.6) [n=45]	0.4 (0-0.6) [n=61]	0.6 (0-0.6) [n=22]
Not well controlled (>0.75-≤1.5)	1.2 (0.8-1.4) [n=169]	1.2 (0.8-1.4) [n=246]	1.2 (0.8-1.4) [n=90]
Poorly controlled (>1.5)	2.4 (1.6-3.8) [n=448]	2.4 (1.6-3.8) [n=605]	2.2 (1.6-3.2) [n=139]
ACT**			
Not available	*NA* [n=6923]	*NA* [n=7100]	*NA* [n=344]
Well controlled (≥20)	21 (20 – 23) [n=83]	21 (20 – 25) [n=255]	21 (20 – 24) [n=119]
Not well controlled (≥16-<20)	17 (16 – 19) [n=234]	18 (16 – 19) [n=321]	18 (16 – 19) [n=122]
Poorly controlled (<16)	13 (9 – 15) [n=264]	13 (8 – 15) [n=383]	12 (7.8 – 15) [n=158]
FEV1p			
Not available	*NA* [n=4921]	*NA* [n=5033]	*NA* [n=400]
<50%	44.5 (32.7-49.7) [n=147]	45.3 (34.4-49.6) [n=199]	44.8 (41.4-48.2) [n=2]
50% - <80%	68.6 (53.4-78.8) [n=1428]	68.2 (53-78.9) [n=1665]	72.3 (55.1-79.3) [n=159]
≥80%	89.3 (80.8-111.2) [n=994]	88.3 (80.7-109.8) [n=1152]	87 (80.6-105.7) [n=182]

** A total of 1825 patients had symptom control level assessed at baseline using ACQ-5. The largest group of patients were those with poorly controlled asthma (>65%). While there were very few patients at the upper end of ACQ-5 above 4: 84% of patients had an ACQ-5 score < 3 and 98% of patients had a ACQ-5 score <4.*

***In some studies, symptom control was assessed by the asthma control test (ACT) (n=2283). ACQ-5 was not measured in this group of patients.*

Table S2: Overview of the studies available for pooling of patient data with moderate to severe asthma, which were used to generate the demographic and clinical baseline characteristics of the virtual patient cohorts used across the different simulation scenarios. Protocol title is shown along with details regarding treatment type and duration, and device characteristics.

Study	Study title	N	Duration	Visits	Treatment arms	Dose Titration/Run-in	Dose Maintenance	Comed Albuterol/ salbutamol	Device
ADA109055 NCT00452699 [1]	A 52-week, randomised, double-blind, parallel-group study of fluticasone propionate/salmeterol DISKUS™ combination product (FSC) 250/50 mcg BID and fluticasone propionate (FP) DISKUS 250 mcg BID in treatment of subjects with asthma.	621	52 weeks	15	FP 250 mcg BID FP/SAL 250/50 mcg BID	FP 100 mcg BID (3 weeks)	FP 250 mcg BID FP/SAL 250/50 mcg BID	As needed	Diskus Inhaler
ADA109057 NCT00452348 [2]	A 52-week, randomised, double-blind, parallel-group study of fluticasone propionate/salmeterol DISKUS™ combination product (FSC) 250/50 mcg BID and fluticasone propionate (FP) DISKUS 250 mcg BID in treatment of subjects with asthma.	628	52 weeks	15	FP 250 mcg BID FP/SAL 250/50 mcg BID	FP 100 mcg BID (3 weeks)	FP 250 mcg BID FP/SAL 250/50 mcg BID	As needed	Diskus Inhaler
HZA113091 NCT01147848 [3]	A randomised, double-blind, double-dummy, parallel-group, multicentre study to assess efficacy and safety of fluticasone furoate (FP)/GW642444 inhalation powder and fluticasone propionate (FP)/salmeterol inhalation powder in the treatment of persistent asthma in adults and adolescents.	806	24 weeks	4/5	FF/VI 100/25 mcg o.d. FP/SAL 250/50 mcg BID	FP 250 mcg BID (4 weeks)	FF/VI 100/25 mcg o.d. + Placebo Accuhaler Diskus FP/SAL 250/50 mcg BID + Placebo Inhalation Powder via NDPI	As needed	FF/VI via NDPI FP/SAL Inhalation Powder via Accuhaler/Diskus
HZA115150 NCT01706198 [4]	A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF,GW685698)/vilanterol (VI/GW642444) inhalation powder delivered once daily via a novel dry powder inhaler compared with usual maintenance therapy in subjects with asthma.	4233	52 weeks	5	Usual Care*, FF/VI	NA	FF/VI 100/25 mcg FF/VI 200/25 mcg	-	FF/VI via Ellipta inhaler
SAM40027 [5]	Gaining Optimal Asthma Control (GOAL): A multicentre, stratified, randomised, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterol/fluticasone propionate combination DISKUS (ACCHUALER) dry powder inhaler compared with fluticasone propionate DISKUS (ACCUHALER)	3416	52 weeks	7	FP BID FP/SAL BID	Step 1: FP/SAL 50/100 mcg BID or FP 100 mcg BID Step 2: FP/SAL 50/250 mcg BID or FP 250 mcg BID Step 3: FP/SAL 50/500 mcg BID or FP 500 mcg BID (until Total control is achieved)	FP/SAL 50/100 mcg, 50/250, 50/500 BID FP 100, 250 or 500 mcg BID (+ 10-day oral prednisone if needed)	As needed	Via dry powder inhaler
SAM40056 NCT00479739 [6]	A randomised, double-blind, double-dummy, 52-week, parallel-group study of a standard dosing regimen with fluticasone/salmeterol combination 50/250 mcg bid (via the DISKUS™/ACCUHALER™ Inhaler) versus a symptom-driven, variable dosing regimen with formoterol/budesonide combination 4.5/160 mcg (via a breath-actuated dry powder reservoir inhaler) in adult asthmatics.	688	52 weeks	6	FP/SAL 50/250 mcg BID BUD/FOR 4.5/160 mcg (varying dose)	Fixed doses (4 weeks) FP/SAL 50/250 mcg BID + placebo BADPI BUD/FOR 4.5/160 mcg + PLACEBO DISKUS BID	FP/SAL 50/250 mcg BID BUD/FOR 4.5/160 mcg (varying BADPI dosage based on Asthma Control Plan)	Inhaled Salbutamol As needed	FP/SAL via Diskus Inhaler BUD/FOR via BADPI inhaler
SAM40065 NCT00920543 [7]	A multicentre, randomised, double-dummy, parallel-group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol DISKUS BID or fluticasone propionate DISKUS BID (or placebo BID if asymptomatic).	449	40 weeks	6	FP (dosage based on Asthma severity and treatment strategy) FP/SAL (dosage based on Asthma severity and treatment strategy)	Previous treatments (2 weeks)	FP/SAL 500/50 mcg or 250/50 mcg or 100/50 mcg FP 500 mcg or 250 mcg or 100 mcg (Dose adjustment every 8 weeks)	Albuterol inhalation as needed	Via Diskus Inhaler
SAM40086 NCT01324362 [8]	As study SAM40065	466	40 weeks	6	FP, FP/SAL	As study SAM40065	As study SAM40065	As study SAM40065	As study SAM40065
SAS115359 NCT01475721 [9]	A safety and efficacy study of inhaled fluticasone propionate/salmeterol combination versus inhaled fluticasone propionate in the treatment of adolescents and adult subjects with asthma.	11679	26 weeks	4	FP 100 mcg, 250 mcg or 500 mcg BID FP/SAL 100/50 mcg, 250/50 mcg or 500/50 mcg BID	Previous treatments (2 weeks)	FP/SAL 100/50 or FP 100 FP/SAL 250/50 or FP 250 FP/SAL 500/50 or FP 500 (Based on control status)	NA	Via dry powder inhaler

* Usual care arm included patients with different standard of care interventions. Only patients on BUD/FOR (n=399) were retrieved for the purpose of the current analysis. Consequently the total number of patients receiving BUD/FOR combination therapy refers to SAM40056 (n=344) and HZA115150 (n=399). Further details on each study protocol can be found in the references and hyperlinks below:

[1] Anderson WH, Koshy BT, Huang L, Mosteller M, Stinnett SW, Condreay LD, Ortega H. Genetic analysis of asthma exacerbations. Ann Allergy Asthma Immunol 2013; 110(6): 416–22.e2.
[2] GSK. A 12-month study comparing fluticasone propionate/salmeterol (ADVAIR) Diskus combination product 250/50mcg twice daily to fluticasone propionate (FLOVENT) Diskus 250 mcg twice daily in symptomatic patients with asthma. 2016. http://clinicaltrials.gov/ct/show/NCT00452348. Last accessed: 03/01/23.
[3] Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest 2013; 144(4): 1222–29.
[4] Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, Jones R, Collier S, Lay-Flurrie J, Frith L, Jacques L, Fletcher JL, Harvey C, Svedsater H, Leather D. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet 2017; 390(10 109): 2247–55.
[5] GSK. A Multicentre, stratified, randomised, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterol/fluticasone propionate combination Diskus (Accuhaler) dry powder inhaler compared with fluticasone propionate Diskus alone in adults and adolescents. 2018. https://www.gsk-studyregister.com/en/trial-details/?id=SAM40027. Last accessed: 03/01/23.
[6] Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol/budesonide adjustable maintenance dosing: impact on health-related quality of life. Respir Res 2007; 8(1): 46.
[7] GSK. A multicenter, randomized, double-blind, parallel Group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus twice daily or fluticasone propionate Diskus twice daily (or placebo BID if asymptomatic). 2016. https://clinicaltrials.gov/ct2/show/NCT00920543. Last accessed: 03/01/23
[8] GSK. A multicenter, randomized, double-blind, parallel group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus twice daily or fluticasone propionate Diskus twice daily (or placebo twice daily if asymptomatic). 2016. https://clinicaltrials.gov/ct2/show/NCT01324362. Last accessed: 03/01/23.
[9] Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, Buaron KS, Pascoe SJ. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med 2016; 374(19): 1822–30.

Table S3: Parameter estimates of the longitudinal model describing the individual ACQ-5 trajectories in moderate-severe asthma patients. 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.

$$\frac{d(ACQ5)}{dt} = k_{in} - k_{out} \cdot ACQ5 \quad \text{Eq. 1}$$

$$ACQ5(0) = baseline\ \text{ACQ5} \quad \text{Eq. 2}$$

$$k_{in} = \theta_{kin} * \left(1 + \theta_{BUD/FOR}\right) * \left(1 + \theta_{FP/SAL}\right) * \left(1 + \theta_{previous\ smoker}\right) * \left(1 + \theta_{current\ smoker}\right) * \left(1 + (BMI - 26.26) * \theta_{BMI}\right) * \left(1 + (AGE - 41) * \theta_{Age}\right) * e^{\eta_{k_{in}}} \quad \text{Eq. 3}$$

$$k_{out} = \theta_{kout} * \left(1 + \theta_{BUD/FOR}\right) * \left(1 + \theta_{FP/SAL}\right) * e^{\eta_{k_{out}}} \quad \text{Eq. 4}$$

	Parameter	Estimate	SE	RSE (%)	Bootstrap median (5^{th} – 95^{th} percentiles)
Population parameter	ACQ-5 kin (θkin)	6.26	0.328	5.2%	6.3 (6.0 - 6.9)
	ACQ-5 kout rate (θkout)	12.4	0.464	3.7%	12.4 (11.9 - 13.4)
Age	Age effect (fractional increase in k_{in} per year)	0.00759	0.002	23.0%	0.0069 (0.0045 - 0.0097)
BMI	BMI effect (fractional increase in k_{in} per kg/m^2)	0.0121	0.007	59.2%	0.014 (-0.001 - 0.022)
Smoking	Former smoker relative to never smoked (fractional increase in k_{in})	0.271	0.063	21.6%	0.29 (0.20 - 0.40)
	Current smoker relative to never smoked (fractional increase in k_{in})	0.791	0.133	16.3%	0.82 (0.59 - 1.05)
Treatment	FP/SAL effect relative to FP (fractional increase in k_{in})	-0.2	0.079	29.7%	-0.25 (-0.42 - -0.17)
	BUD/FOR effect relative to FP (fractional increase in k_{in})	0.777	0.334	31.2%	0.97 (0.68 - 1.74)
	FP/SAL effect relative to FP (fractional increase in k_{out})	-0.355	0.052	13.2%	-0.38 (-0.49 - -0.33)
	BUD/FOR effect relative to FP (fractional increase in k_{out})	0.433	0.248	37.9%	0.60 (0.38 - 1.18)
Interindividual variability	Inter individual variability in k_{in} (ηk_{in})	2.45	0.122	4.8%	2.51 (2.38 - 2.76)
	Inter individual variability correlation between η_{kin} and ηk_{out}	1.76	0.097	5.2%	1.83 (1.72 - 2.02)
	Inter individual variability in k_{out} (ηk_{out})	1.68	0.093	5.3%	1.75 (1.63 - 1.93)
Residual error	Residual error	0.479	0.009	2.0%	0.48 (0.46 - 0.49)

Further details on the development and evaluation are summarised in the appendix.

Table S4: Protocol design characteristics used for the simulation* of time to first exacerbation and individual ACQ-5 trajectories after treatment with ICS monotherapy and ICS/LABA combination therapy.

Protocol characteristics	
Endpoints:	Endpoints evaluated were: 1) time to first exacerbation; 2) (cumulative) incidence of exacerbation at 12 months and at different time points relative to the start of treatment; 3) increase in the time to exacerbation following ICS/LABA combination therapy; 4) 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
Simulation scenarios	Simulation scenarios were used to evaluate the effect of different demographic and clinical baseline characteristics, as well as different interventions on the time to first exacerbation and symptom control level in a virtual cohort of asthma patients with moderate-severe symptoms at baseline. Differences or changes in the underlying hazard describing the risk of exacerbation were summarised primarily using the cumulative incidence of events (i.e., exacerbations) at 12 months. 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 observed in the available clinical studies. This ensured the creation of virtual cohorts which are representative the population distribution in typical clinical trials including 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, two scenarios were implemented in which patients switch treatments. In the first setting, the effect of ICS/LABA combination therapy was assessed in four parallel arms. In two arms all patients were switched from BUD/FOR to FP/SAL (and vice versa) at 4 and 6 months after the start of treatment [1], irrespective of symptom control level at the time of switching. In the second setting, a 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 drug-disease model developed previously (see **Appendix** for details). In addition to the incidence of events, Kaplan-Meier curves and relative risk of exacerbation were also evaluated.
Baseline characteristics:	The patient population randomised into each simulation scenario was based on the inclusion and exclusion criteria used in previous studies **[Table S2**].
Study visits	Simulation scenarios were based on typical clinical visits and included follow-up over a period of 12 months. 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:** sex differences **Scenario 4:** varying airway function at baseline as assessed by FEV_1 **Scenario 5:** varying smoking habit at baseline **Scenario 6:** varying season at start of treatment **Scenario 7:** ICS/LABA treatment switch at 4 and 6 months after start of therapy, irrespective of symptom control level **Scenario 8:** 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:	Simulated events (exacerbations) were described by Kaplan-Meier survival curves and analysed using a log-rank test with Bonferroni correction. Survival curves are a standard way to represent the occurrence of an event over a predefined observation window. In the context of this analysis, survival refers to the proportion of patients who have not had an exacerbation. Median estimates and 90% confidence intervals are presented in tabular format for results from trial replicates (n=500). On the other hand, where applicable, graphical summaries are also described as those obtained in a single trial, i.e., only point estimates are shown without confidence intervals to ensure direct comparison with data arising from a prospective study protocol. The primary objective of the statistical analysis in each scenario was to compare the difference in the incidence of exacerbation rate at 12 months 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 [2,3]. In addition to the incidence of exacerbations at month 12, relative risk and time to reach comparable incidence at 12 months following different interventions were 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 scenarios 7 and 8, in which the differences between treatment arms were compared. 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 [4]. 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[5]. *Number of events required to detect selected hazard ratios at various significance levels* 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%*
Assumptions: and limitations	1. Parameter estimates from the final time-to-event and longitudinal models, which were obtained from the 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 asthma patient population with moderate to severe symptoms that is 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 drug-specific effect on the 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 [6], 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.

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

% 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

	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 [7]. 4. Given that the simulated scenarios were aimed to describe 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 cumulative incidence 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 drug-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 [8-10]. 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 [11,12]. In fact, here we have applied the same principles endorsed by Beasley and colleagues [13], 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 [14]. 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 [15,16]. 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 that the original CFC MDI [17-19]. The net result is that BUD in the Turbuhaler is approximately equivalent to FP in the Diskus on an mcg basis [9]. 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 model and longitudinal model describing individual ACQ-5 trajectories (Table S3). Exacerbation events were simulated for each scenario along with ACQ-5 response over a period of 12 months. All required data manipulation, including graphical and statistical summaries were performed in R (v. 3.1.1)

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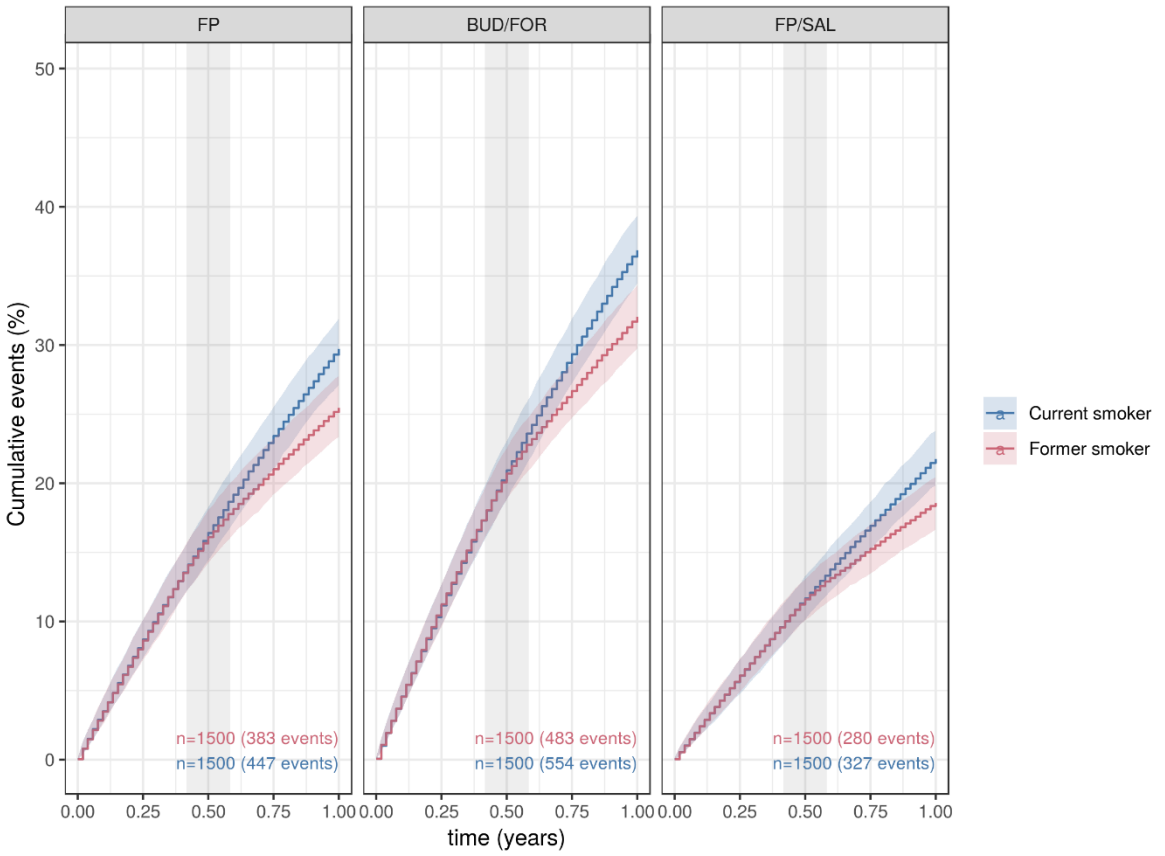
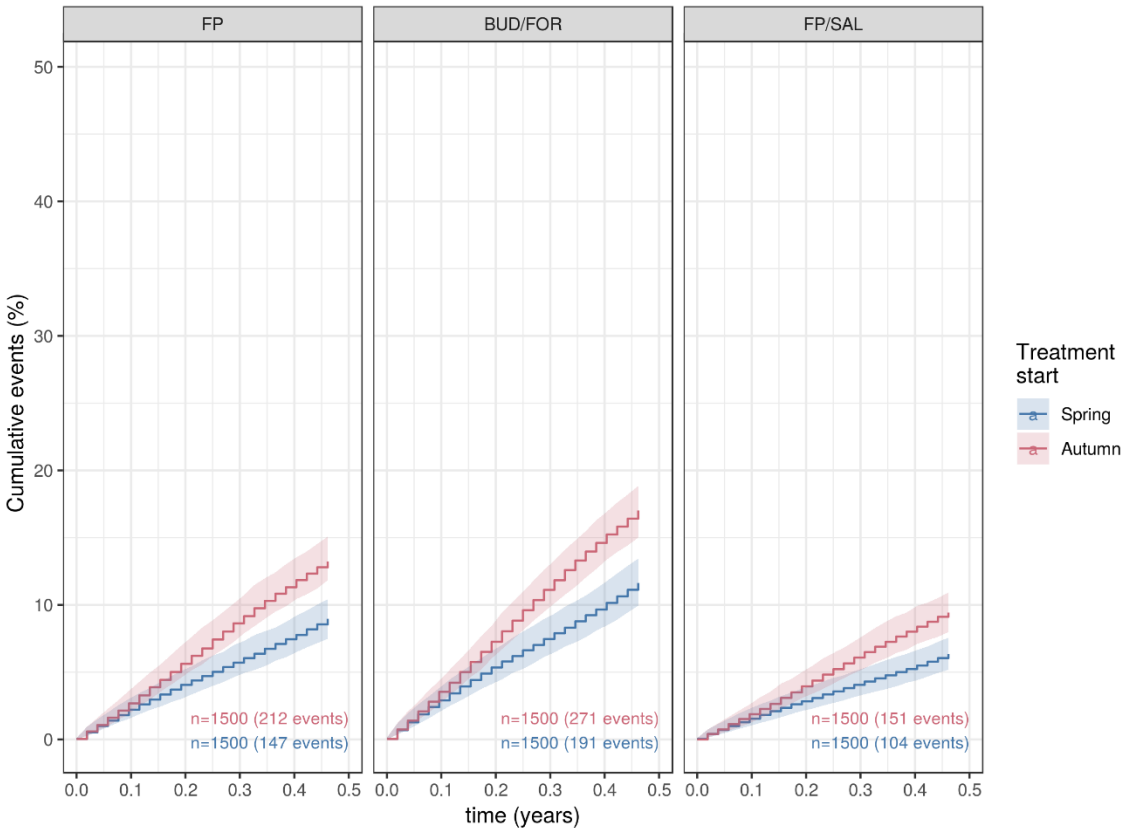
Figure S1: (Scenario 5). Effect of smoking habit and treatment on exacerbation risk. Patients were stratified by baseline smoking status according to the following categories: current smoker, former smoker and never smoker. The upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with 95% of all simulated curve are within the shaded area. Lower panel: Cumulative incidence after 1 year (median and 95% prediction interval). Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S9.



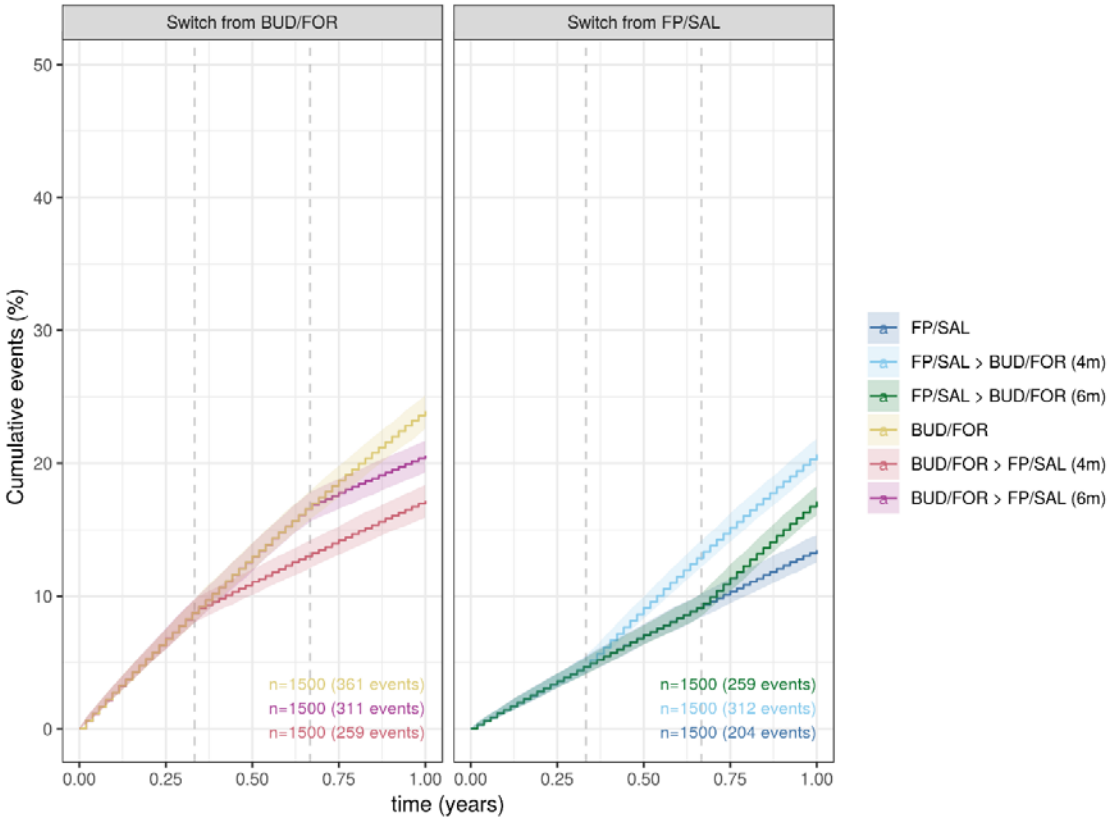
Cumulative incidence at 1 year	Current smoker	Former smoker
FP	29.7% (27.1% - 31.9%)	25.5% (23.4% - 27.8%)
BUD/FOR	36.8% (34.5% - 39.3%)	32% (29.7% - 34.3%)
FP/SAL	21.7% (19.8% - 23.8%)	18.6% (16.6% - 20.4%)

Figure S2: (Scenario 6). Effect of seasonal variation and treatment on exacerbation risk. Patients were stratified according to the season of year at the start of treatment. The upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 6 months. In contrast to the other simulation scenarios describing exacerbation events over 1 year, the effect of seasonal variation is maximum at approximately 6 months from the start of treatment. This illustrates the potential heterogeneity in clinical trial results obtained from treatment follow up over a period of 20 to 24 weeks. Solid lines represent the median simulated curve with 95% of all simulated curve are within the shaded area. Lower panel: Cumulative incidence after 6 months (median and 95% prediction interval). Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S10.



Cumulative incidence after 6 months	Autumn	Spring
FP	13.5% (11.4% - 15.6%)	9.4% (7.4% - 11.5%)
BUD/FOR	17.5% (15.3% - 19.6%)	12.2% (10.3% - 14%)
FP/SAL	9.6% (7.6% - 11.5%)	6.7% (5.3% - 8.4%)

Figure S3: (Scenario 7). Effect of treatment switch on exacerbation risk. In this scenario, patients randomised to BUD/FOR or FP/SAL switch to FP/SAL or BUD/FOR, respectively after 4 and 6 months after start of therapy, irrespective of symptom control level*. The upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with 95% of all simulated curve are within the shaded area. Lower panel: Cumulative incidence after 1 year (median and 95% prediction interval). Demographic characteristics of the virtual cohorts along with the statistical significance levels of the differences between strata and treatment are summarised in Table S11.



FP/SAL	FP/SAL > BUD/FOR (4m)	FP/SAL > BUD/FOR (6m)	BUD/FOR	BUD/FOR > FP/SAL (4m)	BUD/FOR > FP/SAL (6m)
13.5% (12.5% - 14.6%)	20.6% (19.5% - 21.8%)	17.1% (16.1% - 18.3%)	23.9% (22.6% - 25.1%)	17.2% (15.9% - 18.3%)	20.6% (19.3% - 21.7%)

Whilst expert panels recommend visits to a clinician about every six months for patients whose asthma is under control and more often for patients whose asthma is uncontrolled or has severe persistent asthma (see Table S4, reference [1]), the choice of two specific intervals in this scenario is aimed to illustrate likely real-life conditions, which require patient to seek medical advice on their asthma management. Even though clinical management according to GINA guidelines includes a stepwise approach, including recommendations for changes to ICS/LABA dose, it has been assumed that any titration steps have been implemented at the start of treatment. These simulations show that compared to patients who remain on BUD/FOR, exacerbation risk is significantly reduced when patients on BUD/FOR are switched to FP/SAL at 4 or 6 months after the initiation of therapy.

Scenario 1 – Effect of symptom control level and treatment choice on the risk of exacerbation.

Table S5: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by symptom control level and treatment. Lower panel summarises the statistical significance level of the different comparisons.

Asthma Control	Treatment	ACQ-5 score	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)	Female (%)
Well Controlled (ACQ-5≤0.75)	**BUD/FOR**	0.4 (0.0-0.6)	26.2 (19.6-37.0)	77.3 (54.2-103.8)	(76.1/22.4/1.5)	60.0
	FP	0.4 (0-0.6)	26.2 (19.8-37.0)	77.3 (54.5-103.8)	(75.8/22.7/1.4)	60.1
	FP/SAL	0.4 (0.0-0.6)	26.2 (19.6-36.9)	77.3 (54.5-103.8)	(76.0/22.5/1.5)	60.0
Not Well Controlled (ACQ-5 >0.75-≤1.5)	**BUD/FOR**	1.2 (0.8-1.4)	26.3 (20.2-37.3)	77.0 (51.8-102.3)	(74.5/22.4/3.1)	60.4
	FP	1.2 (0.8-1.4)	26.3 (20.2-37.5)	77.0 (51.8-102.4)	(74.5/22.2/3.3)	60.0
	FP/SAL	1.2 (0.8-1.4)	26.3 (20.2-37.5)	77.0 (51.8-102.3)	(74.6/22.3/3.2)	60.2
Poor Controlled (ACQ-5 >1.5)	**BUD/FOR**	2.4 (1.6-3.6)	27.5 (20.2-40.3)	71.9 (46.7-97.8)	(74.6/21.0/4.4)	63.6
	FP	2.4 (1.6-3.6)	27.5 (20.2-40.3)	71.8 (46.7-97.8)	(74.8/20.8/4.4)	63.6
	FP/SAL	2.4 (1.6-3.6)	27.5 (20.2-40.3)	71.9 (46.7-97.9)	(74.8/20.8/4.4)	63.6

P values	**Well Controlled, BUD/FOR**	**Well Controlled, FP**
Well Controlled, FP	1.00e-03** (1.02e-06-1.00e-03)	
Well Controlled, FP/SAL	1.05e-13** (4.43e-19-1.05e-13)	1.95e-05** (5.08e-09-1.95e-05)
	Not Well Controlled, BUD/FOR	**Not Well Controlled, FP**
Not Well Controlled, FP	1.41e-03** (1.03e-06-1.41e-03)	
Not Well Controlled, FP/SAL	9.04e-12** (2.82e-17-9.04e-12)	1.76e-04** (3.86e-08-1.76e-04)
	Poor Control, BUD/FOR	**Poor Control, FP**
Poor Control, FP	3.50e-05** (5.46e-09-3.50e-05)	
Poor Control, FP/SAL	2.17e-17** (4.89e-24-2.17e-17)	1.07e-05** (1.63e-09-1.07e-05)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles. Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

Scenario 2 – Effect of body mass index and treatment choice on the risk of exacerbation.

Table S6: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and body mass index range (i.e. normal, overweight, obese, and extreme obese). Lower panel summarises the statistical significance level of the different comparisons.

Treatment	BMI	ACQ-5	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)	Female (%)
BUD/FOR	Normal	2.0 (0.6-3.4)	22.9 (19.4-24.8)	75.6 (49.6-102.9)	73.7/19.5/6.7	62.7
	Overweight	2.0 (0.6-3.4)	27.4 (25.3-29.7)	73.0 (47.1-98.2)	74.4/22.8/2.8	55.4
	Obese	2.2 (0.6-3.6)	32.0 (30.1-34.6)	71.9 (48.9-97.1)	74.8/23/2.2	65.3
	Extremely Obese	2.2 (0.8-3.6)	38.7 (35.3-50.7)	71.0 (47.0-94.3)	77.5/20.6/1.9	78.9
FP	Normal	2.0 (0.6-3.4)	22.9 (19.4-24.8)	75.5 (49.7-103.0)	73.8/19.5/6.8	62.7
	Overweight	2.0 (0.6-3.4)	27.4 (25.3-29.7)	73.0 (47.4-98.2)	74.5/22.6/2.8	55.5
	Obese	2.2 (0.6-3.6)	32.0 (30.1-34.6)	71.9 (48.9-97.1)	74.7/23/2.3	65.2
	Extremely Obese	2.2 (0.8-3.6)	38.7 (35.3-50.7)	71.0 (47.0-94.4)	77.6/20.6/1.8	78.8
FP/SAL	Normal	2.0 (0.6-3.4)	22.8 (19.4-24.8)	75.4 (49.7-102.7)	73.7/19.5/6.8	62.8
	Overweight	2.0 (0.6-3.4)	27.4 (25.3-29.7)	73 (47.4-98.4)	74.6/22.5/2.8	55.4
	Obese	2.2 (0.6-3.6)	32.0 (30.1-34.6)	71.9 (48.9-97.1)	74.9/22.8/2.2	65.2
	Extremely Obese	2.2 (0.8-3.6)	38.7 (35.3-50.7)	71.0 (47.0-94.4)	77.5/20.6/1.8	78.6

P values	Normal, BUD/FOR	Normal, FP
Normal, FP	3.59e-02* (2.87e-05-1.00e+00)	
Normal, FP/SAL	1.93e-11** (2.82e-17-6.05e-07)	5.11e-03** (4.03e-06-1.00e+00)
	Overweight, BUD/FOR	**Overweight, FP**
Overweight, FP	1.74e-02* (2.15e-06-1.00e+00)	
Overweight, FP/SAL	2.44e-13** (2.78e-19-3.21e-08)	1.61e-03** (4.32e-07-4.55e-01)
	Obese, BUD/FOR	**Obese, FP**
Obese, FP	4.58e-03** (7.61e-07-1.00e+00)	
Obese, FP/SAL	1.35e-15** (1.73e-22-2.87e-10)	2.30e-04** (1.02e-08-1.83e-01)
	Extremely obese, BUD/FOR	**Extremely obese, FP**
Extremely obese, FP	7.22e-04** (1.26e-07-4.88e-01)	
Extremely obese, FP/SAL	2.95e-19** (8.78e-27-1.53e-12)	3.80e-05** (1.39e-09-4.65e-02)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles. Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

Scenario 3 – Effect of sex and treatment choice on the risk of exacerbation.

Table S7: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and sex, as assessed by predicted forced expiratory volume in the first second. Lower panel summarises the statistical significance level of the different comparisons.

Treatment	Sex	ACQ-5	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)
BUD/FOR	Female	2.0 (0.6-3.4)	26.9 (20.8-36.0)	72.5 (46.7-97.9)	(66.9/28.7/4.4)
	Male	2.0 (0.6-3.6)	27.5 (19.8-41.1)	74.1 (49.5-100.7)	(79.3/17.0/3.6)
FP	Female	2.0 (0.6-3.4)	26.9 (20.7-36.1)	72.6 (46.8-97.9)	(67.1/28.5/4.3)
	Male	2.0 (0.6-3.6)	27.4 (19.8-41.1)	74.0 (49.6-100.7)	(79.2/17.1/3.7)
FP/SAL	Female	2.0 (0.6-3.4)	26.8 (20.7-36.0)	72.6 (46.8-97.9)	(67.2/28.5/4.3)
	Male	2.0 (0.6-3.6)	27.5 (19.8-41.1)	74.1 (49.5-100.6)	(79.3/17.0/3.7)

P values	Male, BUD/FOR	Male, FP	Male, FP/SAL	Female, BUD/FOR	Female, FP
Male, FP	5.15e-04** (3.44e-07-6.61e-02)				
Male, FP/SAL	1.66e-13** (9.47e-20-1.01e-08)	7.18e-05** (1.45e-08-1.93e-02)			
Female, BUD/FOR	5.54e-05** (2.38e-08-2.61e-02)	1.01e-13** (4.28e-19-5.93e-09)	3.43e-29** (2.13e-37-1.59e-22)		
Female, FP	5.59e-01 (5.15e-02-9.59e-01)	4.50e-04** (1.94e-07-4.43e-02)	4.81e-14** (1.54e-19-4.54e-09)	1.08e-04** (6.17e-08-2.30e-02)	
Female, FP/SAL	9.25e-06** (8.45e-10-3.37e-03)	3.04e-01 (1.09e-02-9.34e-01)	3.41e-03** (6.55e-06-1.42e-01)	4.82e-17** (1.87e-23-7.16e-12)	4.82e-06** (2.32e-09-3.78e-03)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles. Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

Scenario 4 – Effect of lung function and treatment choice on the risk of exacerbation.

Table S8: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and lung function, as assessed by predicted forced expiratory volume in the first second. Lower panel summarises the statistical significance level of the different comparisons.

Treatment	FEV1p (baseline)	ACQ-5	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)	Female (%)
BUD/FOR	<50%	2.4 (1.0-3.8)	27.8 (20.2-39.6)	44.5 (31.6-49.6)	(75.7/22.2/2.1)	55.8
	50-80%	2.0 (0.6-3.4)	27.5 (20.2-40.2)	68.0 (52.8-78.8)	(75.9/20.9/3.2)	62.2
	>80%	1.8 (0.6-3.2)	26.4 (20.0-38.7)	87.8 (80.7-109.0)	(72.4/21.9/5.7)	64.7
FP	<50%	2.4 (1.0-3.8)	27.8 (20.2-39.6)	44.5 (31.6-49.6)	(75.8/22.2/2.0)	55.9
	50-80%	2.0 (0.6-3.4)	27.5 (20.2-40.1)	68.0 (52.8-78.8)	(75.9/20.9/3.2)	62.2
	>80%	1.8 (0.6-3.2)	26.4 (20.0-38.6)	87.8 (80.7-109.1)	(72.3/22.0/5.7)	64.6
FP/SAL	<50%	2.4 (1.0-3.8)	27.8 (20.3-40.0)	44.5 (31.7-49.6)	(76.0/22.0/2.0)	56.1
	50-80%	2.0 (0.6-3.4)	27.5 (20.2-40.2)	68.0 (52.8-78.8)	(75.8/21.1/3.1)	62.3
	>80%	1.8 (0.6-3.2)	26.4 (20.1-38.7)	87.8 (80.7-109.0)	(72.4/22.0/5.7)	64.7

P values	>80%, BUD/FOR	>80%, FP
>80%, FP	3.95e-04** (2.34e-07-7.14e-02)	
>80%, FP/SAL	1.09e-13** (8.91e-20-1.97e-08)	1.33e-04** (1.83e-08-1.48e-02)
	50-80%, BUD/FOR	**50-80%, FP**
50-80%, FP	1.30e-04** (3.44e-08-3.48e-02)	
50-80%, FP/SAL	7.23e-17** (4.13e-23-1.51e-11)	5.65e-06** (1.04e-09-3.29e-03)
	<50%, BUD/FOR	**<50%, FP**
<50%, FP	4.73e-05** (1.92e-09-2.39e-02)	
<50%, FP/SAL	2.17e-19** (4.67e-28-1.16e-12)	6.16e-07** (1.39e-11-9.42e-04)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles. Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

Scenario 5 – Effect of smoking status and treatment choice on the risk of exacerbation.

Table S9: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and smoking status at baseline. Lower panel summarises the statistical significance level of the different comparisons.

Treatment	Smoking Status	ACQ-5 score	BMI (Kg/m^2)	FEV1p (%)	Female (%)
BUD/FOR	**Current**	2.0 (0.6-3.4)	27.1 (20.2-39.5)	73.4 (48.2-99.3)	62.7
	Former	2.0 (0.6-3.4)	27.2 (20.2-39.6)	73.4 (48.4-99.2)	62.7
FP	**Current**	2.0 (0.6-3.4)	27.2 (20.2-39.6)	73.4 (48.2-99.5)	62.7
	Former	2.0 (0.6-3.4)	27.2 (20.2-39.6)	73.4 (48.2-99.2)	62.8
FP/SAL	**Current**	2.0 (0.6-3.4)	27.2 (20.2-39.6)	73.4 (48.4-99.4)	62.8
	Former	2.0 (0.6-3.4)	27.2 (20.2-39.6)	73.4 (48.4-99.5)	62.7

P values	Current smoker BUD/FOR	Former smoker BUD/FOR	Current smoker FP	Former smoker FP	Current smoker FP/SAL
Former smoker BUD/FOR	5.05e-01 (5.90e-02-9.50e-01)				
Current smoker FP	1.03e-02* (3.82e-03-1.68e-02)	7.02e-01 (4.34e-01-9.70e-01)			
Former smoker FP	1.63e-08** (1.63e-09-3.10e-08)	6.90e-04** (1.69e-04-1.21e-03)	1.50e-01 (1.53e-02-2.84e-01)		
Current smoker FP/SAL	1.72e-15** (1.72e-16-3.27e-15)	2.61e-08** (2.98e-09-4.92e-08)	3.92e-05** (3.93e-06-7.45e-05)	6.01e-01 (4.26e-01-7.76e-01)	
Former smoker FP/SAL	1.35e-25** (1.36e-26-2.56e-25)	2.51e-14** (2.51e-15-4.77e-14)	9.77e-12** (9.81e-13-1.86e-11)	5.77e-04** (8.33e-05-1.07e-03)	3.80e-01 (1.69e-01-5.90e-01)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles. Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

Scenario 6 – Effect of season and treatment choice on the risk of exacerbation.

Table S10: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment arm and season at start of treatment. Lower panel summarises the statistical significance level of the different comparisons.

Treatment	Treatment start	ACQ-5	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)	Female (%)
BUD/FOR	Spring	2 (0.6-3.4)	27.1 (20.3-38.9)	73.2 (48-99)	73.1/22.9/4	50
	Autumn	2 (0.6-3.4)	27.1 (20.3-39.1)	73.2 (48-99)	73.1/22.9/4	50
FP	Spring	2 (0.6-3.4)	27.1 (20.3-39.1)	73.3 (48-99.1)	73.2/22.8/4	50
	Autumn	2 (0.6-3.4)	27.1 (20.3-39)	73.3 (48-99)	73.2/22.9/4	49.9
FP/SAL	Spring	2 (0.6-3.4)	27.1 (20.3-39.1)	73.3 (48-99.1)	73.1/22.9/4	50
	Autumn	2 (0.6-3.4)	27.1 (20.3-39.1)	73.3 (48-99)	73.2/22.8/4	50.1

P values	Autumn BUD/FOR	Spring BUD/FOR	Autumn FP	Spring FP	Autumn FP/SAL
Spring BUD/FOR	1.06e-03** (7.88e-07-7.85e-02)				
Autumn FP	1.36e-02* (6.54e-05-3.93e-01)	3.36e-01 (9.46e-03-9.41e-01)			
Spring FP	1.59e-07** (3.50e-12-1.80e-04)	3.67e-02* (1.53e-04-6.13e-01)	2.92e-03** (3.75e-06-2.37e-01)		
Autumn FP/SAL	2.14e-07** (7.88e-12-5.12e-04)	6.27e-02 (2.90e-04-6.35e-01)	6.05e-03** (9.33e-06-3.15e-01)	4.77e-01 (2.57e-02-9.58e-01)	
Spring FP/SAL	1.94e-13** (1.10e-18-4.91e-09)	2.45e-05** (1.09e-08-9.43e-03)	5.09e-07** (4.00e-11-1.22e-03)	2.83e-02* (1.48e-04-6.59e-01)	1.78e-02* (5.88e-05-5.67e-01)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles . Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

Scenario 7–Effect of treatment switch to FP/SAL on the risk of exacerbation.

Table S11: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment. Lower panel summarises the statistical significance level of the different comparisons.

Asthma Control	ACQ-5	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)	Female (%)
FP/SAL	1.2 (0.2-3)	26.7 (20-38.3)	75.5 (51-102.2)	75/22/3	61.4
FP/SAL → BUD/FOR (4m)	1.2 (0.2-3)	26.7 (20-38.3)	75.5 (51.1-102.4)	75.1/21.9/3	61.3
FP/SAL → BUD/FOR (6m)	1.2 (0.2-3.0)	26.7 (20-38.4)	75.5 (51-101.9)	75/21.9/3.1	61.2
BUD/FOR	1.2 (0.2-3.0)	26.7 (20-38.3)	75.5 (51.1-102)	75/22/3	61.3
BUD/FOR → FP/SAL (4m)	1.2 (0.2-3)	26.7 (20-38.3)	75.6 (51.1-102.3)	74.9/22/3	61.4
BUD/FOR → FP/SAL (6m)	1.2 (0.2-3)	26.7 (20-38.4)	75.5 (51.1-101.8)	75.1/21.8/3	61.3

P values	BUD/FOR	BUD/FOR → FP/SAL (4m)	BUD/FOR → FP/SAL (6m)	FP/SAL	FP/SAL → BUD/FOR (4m)
BUD/FOR → FP/SAL (4m)	2.76e-13** (1.52e-19-1.48e-07)				
BUD/FOR → FP/SAL (6m)	6.44e-03** (2.61e-06-9.58e-01)	7.86e-04** (6.01e-08-3.38e-01)			
FP/SAL	5.86e-36** (5.74e-45-1.16e-27)	1.07e-05** (2.90e-10-1.03e-02)	1.03e-18** (2.91e-26-1.06e-12)		
FP/SAL → BUD/FOR (4m)	5.65e-04** (1.20e-07-2.27e-01)	3.83e-03** (1.44e-06-8.38e-01)	1.00e+00 (2.00e-01-1.00e+00)	1.38e-17** (8.92e-25-3.47e-11)	
FP/SAL → BUD/FOR (6m)	7.31e-16** (9.34e-23-7.83e-10)	1.00e+00 (2.37e-01-1.00e+00)	3.66e-05** (6.75e-10-2.44e-02)	7.00e-05** (5.84e-09-4.62e-02)	1.91e-04** (3.09e-08-1.54e-01)

Median Log rank p value over 500 iterations. Values between parentheses are the 5th and 95th percentiles. Asterisks indicate *p*-value < 0.05 (*) or < 0.01 (**)

→ *indicates the treatment to which the patient is switched*

Scenario 8 – Effect of switch to combination therapy on the risk of exacerbation.

Table S12: Not-in-Trial Simulations (NITS). Treatment switch from monotherapy to ICS/LABA combination therapy. Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by symptom control level at baseline. Lower panel summarises the statistical significance level of the different comparisons.

Baseline asthma control	Treatment	ACQ-5	BMI (Kg/m^2)	FEV1p (%)	Smoking Status (N/F/C%)	Female (%)
Well Controlled (ACQ-5≤0.75)	FP (NR) → FP/SAL	0.4 (0-0.6)	25.5 (19.3-37)	2.3 (1.1-3.8)	65.1/29.1/5.9	63.6
	FP (R)	0.4 (0-0.6)	24.7 (19.1-37)	2.5 (1.3-3.9)	77.7/20/2.3	64.6
	FP (NR) → BUD/FOR	0.4 (0-0.6)	25.5 (19.3-37)	2.3 (1.2-3.7)	64.3/29.6/6	63.5
Not Well Controlled (ACQ-5 >0.75-≤1.5)	FP (NR) → FP/SAL	1.2 (0.8-1.4)	26 (20.3-36.2)	2.5 (1.4-4)	63.5/27.8/8.7	54.6
	FP (R)	1 (0.8-1.4)	24.9 (20-34.7)	2.6 (1.5-4)	76.2/19.7/4.1	56.6
	FP (NR) → BUD/FOR	1.2 (0.8-1.4)	26 (20.3-36.3)	2.5 (1.4-3.9)	63.5/27.9/8.6	54.8
Poor Controlled (ACQ-5 >1.5)	FP (NR) → FP/SAL	2.4 (1.6-3.8)	26.7 (19.9-38.8)	2.3 (1.3-3.9)	61.5/27.8/10.8	61.1
	FP (R)	2.2 (1.6-3.6)	26.2 (19.8-37.4)	2.4 (1.4-3.9)	73.4/21.1/5.5	61.1
	FP (NR) → BUD/FOR	2.4 (1.6-3.8)	26.7 (19.9-38.8)	2.3 (1.3-3.9)	61.5/27.8/10.7	61.0

FP(NR) – non-responder to ICS monotherapy with FP; FP(R) - responder to ICS monotherapy with FP, as assessed by ICQ-5 level at 3 months after the start of treatment. → indicates the treatment to which the patient is switched

P values	NWC, FP (NR) → BUD/FOR	NWC, FP (NR) → FP/SAL	NWC, FP (R)	PC, FP (NR) → BUD/FOR	PC, FP (NR) → FP/SAL	PC, FP (R)	WC, FP (NR) → BUD/FOR	WC, FP (NR) → FP/SAL
NWC, FP (NR) → FP/SAL	7.40e-05** (1.35e-09-9.86e-02)							
NWC, FP (R)	2.73e-02* (4.09e-05-1.00e+00)	1.00e+00 (1.87e-02-1.00e+00)						
PC, FP (NR) → BUD/FOR	4.13e-06** (8.58e-11-6.23e-03)	1.03e-23** (3.03e-30-9.26e-18)	6.56e-21** (3.67e-27-1.23e-14)					
PC, FP (NR) → FP/SAL	1.00e+00 (9.61e-02-1.00e+00)	4.84e-04** (1.30e-07-1.93e-01)	1.96e-01 (1.39e-03-1.00e+00)	2.16e-19** (2.13e-27-1.55e-12)				
PC, FP (R)	1.00e+00 (1.60e-01-1.00e+00)	6.64e-09** (1.41e-13-6.10e-05)	1.28e-05** (1.15e-09-1.47e-02)	2.33e-06** (9.09e-11-7.93e-03)	6.31e-02 (3.40e-05-1.00e+00)			
WC, FP (NR) → BUD/FOR	1.00e+00 (1.84e-01-1.00e+00)	1.00e+00 (1.98e-02-1.00e+00)	1.00e+00 (7.83e-01-1.00e+00)	8.32e-03** (1.49e-05-1.00e+00)	1.00e+00 (8.75e-01-1.00e+00)	1.00e+00 (4.16e-02-1.00e+00)		
WC, FP (NR) → FP/SAL	5.72e-02 (2.35e-04-1.00e+00)	1.00e+00 (7.91e-01-1.00e+00)	1.00e+00 (7.58e-02-1.00e+00)	2.76e-06** (1.18e-09-1.80e-03)	1.79e-01 (2.10e-03-1.00e+00)	6.83e-03** (2.68e-05-8.13e-01)	1.00e+00 (2.36e-02-1.00e+00)	
WC, FP (R)	5.16e-03** (4.53e-06-8.51e-01)	1.00e+00 (1.00e+00-1.00e+00)	1.00e+00 (6.58e-02-1.00e+00)	1.90e-12** (1.04e-17-9.05e-09)	4.31e-02* (5.80e-05-1.00e+00)	8.02e-05** (1.02e-08-2.95e-02)	1.00e+00 (2.31e-02-1.00e+00)	1.00e+00 (7.44e-01-1.00e+00)

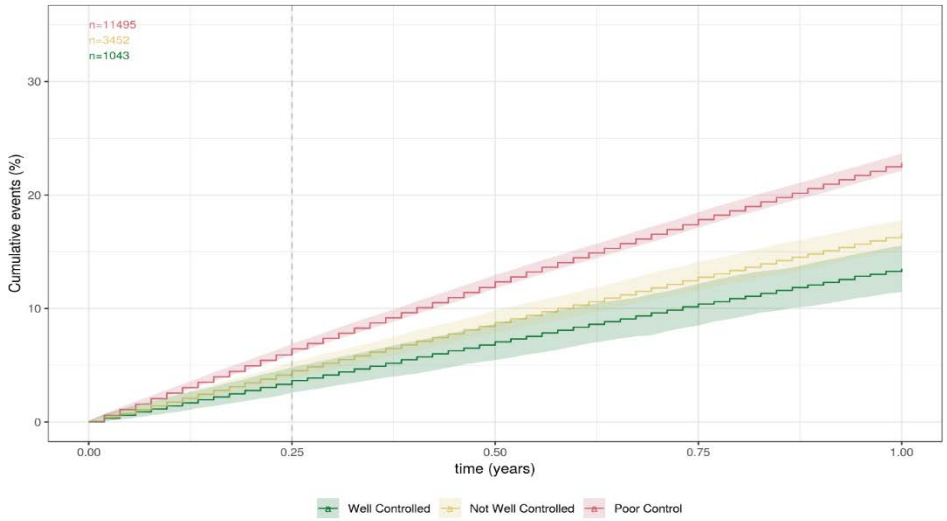
NWC – Not well controlled(ACQ-5 >0.75-≤1.5), PC – Poorly controlled(ACQ-5 >1.5), WC – Well controlled(ACQ-5 ≤0.75). Values between parentheses are 95% confidence intervals. p-value < 0.05 (*) or < 0.01 (**)

Asthma symptom control levels are defined based on baseline ACQ-5. A non-responder (NR) to initial treatment with ICS monotherapy is defined as subject who has not reached a minimum ACQ-5 score of 0.75 within the first 3 months on treatment. A responder (R) to treatment is defined by a ACQ-5 score below 0.75 within the first 3 months on treatment. → indicates the treatment to which the patient is switched

FP- fluticasone propionate; FP/SAL - fluticasone propionate + salmeterol combination therapy. BUD/FOR – budesonide + formoterol combination therapy. Statistical significance is indicated by asterisks.ACQ-5 – asthma control questionnaire, BMI – body mass index, FEV1p – Predicted forced expiratory volume in one second (%). Smoking status at baseline: N – non-smoker, F – former smoker, C – current smoker

Sub scenario 8a

Figure S4: Upper panel shows the cumulative incidence of exacerbations stratified by baseline asthma control level, irrespective of treatment choice. Subjects not achieving symptom control (NR, i.e. those classified as not-well controlled [ACQ-5 >0.75-≤1.5] or poorly controlled [ACQ-5 >1.5] at 3 months after initiation of ICS monotherapy) switch to combination therapy (BUD/FOR or FP/SAL). Responders to monotherapy progress with the same treatment over the period of 12 months. Patients remaining on monotherapy (FP) have generally lower ACQ-5 baseline values. Patients who are well controlled at baseline are more likely to remain on ICS monotherapy (FP). Lower panels show the cumulative incidence of exacerbation at each visit up to 12 months after the start of treatment.



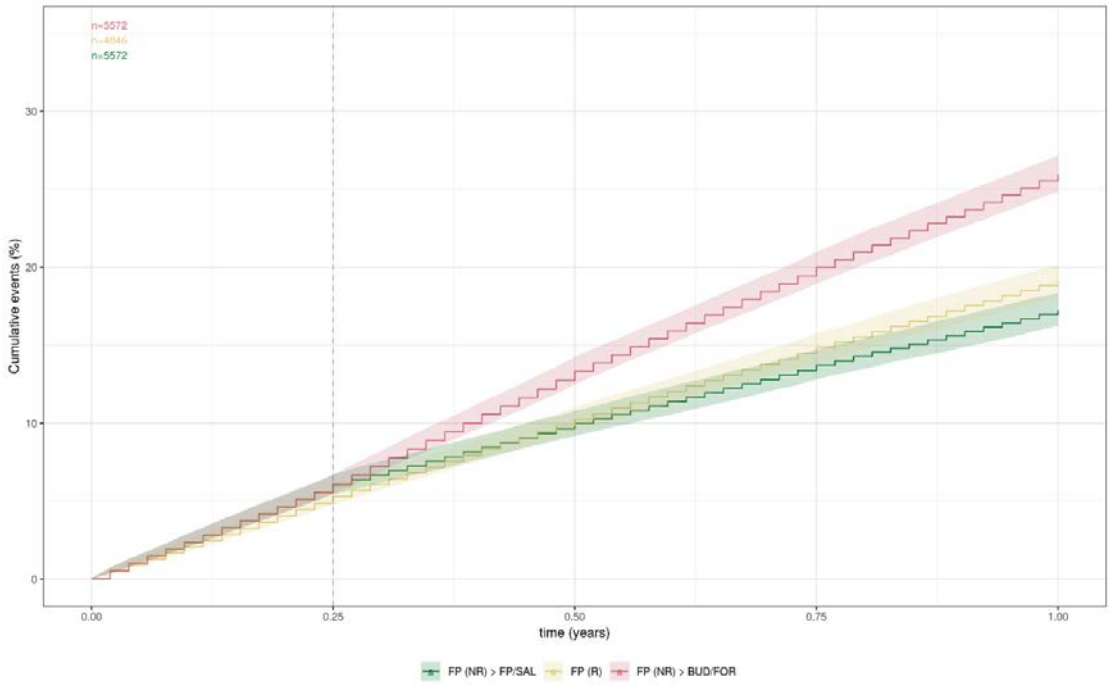
At time (months)	Well Controlled	Not Well Controlled	Poor Control
3	3.6% (2.6% - 4.8%)	4.5% (3.8% - 5.2%)	6.4% (6% - 6.9%)
6	7.1% (5.5% - 8.7%)	8.8% (7.9% - 9.8%)	12.3% (11.8% - 12.9%)
9	10.4% (8.5% - 12.2%)	12.8% (11.6% - 14.1%)	17.8% (17.1% - 18.5%)
12	13.5% (11.4% - 15.5%)	16.5% (15.2% - 17.8%)	22.8% (22.1% - 23.6%)

P values	Well Controlled	Not Well Controlled
Not Well Controlled	1.98e-02* (1.26e-04-3.95e-01)	
Poor Control	8.67e-12** (2.74e-16-2.93e-08)	4.35e-15** (5.80e-21-2.22e-10)

Values between parentheses are 95% confidence intervals. Asterisks indicate p-value < 0.05 (*) or < 0.01 (**) Symptom control level defined according to the following categories: well controlled (ACQ-5 ≤0.75), not well controlled (ACQ-5 >0.75-≤1.5) or poorly controlled (ACQ-5 >1.5). FP- fluticasone propionate; FP/SAL – fluticasone propionate + salmeterol combination therapy. BUD/FOR – budesonide + formoterol combination therapy. Statistical significance is indicated by asterisks. ACQ-5 – asthma control questionnaire. It is evident from the summary tables that incidence of events (i.e., moderate or severe exacerbations) is significantly lower in patients to are well controlled or not-well controlled, as compared to those who are poorly controlled at 12 months. This difference appears to persist throughout the course of treatment.

Sub-scenario 8b

Figure S5: Upper panel shows the cumulative incidence of exacerbations stratified by treatment. Subjects not achieving symptom control (NR, i.e. those classified as not-well controlled [ACQ-5 >0.75-≤1.5] or poorly controlled [ACQ-5 >1.5] at 3 months after initiation of ICS monotherapy) switch to combination therapy (BUD/FOR or FP/SAL). Responders to monotherapy progress with the same treatment over the period of 12 months. Patients remaining on monotherapy (FP) have generally lower ACQ-5 baseline values.). Lower panels show the cumulative incidence of exacerbation at each visit up to 12 months after the start of treatment.



At time (months)	FP (NR) → FP/SAL	FP ®	FP (NR) → BUD/FOR
3	6% (5.4% - 6.7%)	5.3% (4.8% - 5.9%)	6.1% (5.4% - 6.7%)
6	10% (9.2% - 10.8%)	10.2% (9.4% - 11%)	13.3% (12.5% - 14.2%)
9	13.7% (12.8% - 14.7%)	14.9% (13.9% - 15.8%)	20% (18.9% - 21%)
12	17.2% (16.2% - 18.3%)	19.2% (18.1% - 20.1%)	26% (24.8% - 27.1%)

P values	FP (NR) → FP/SAL	FP (R)
FP (R)	4.40e-02* (2.68e-04-1.00e+00)	
FP (NR) → BUD/FOR	3.93e-27** (6.02e-36-1.28e-19)	1.19e-15** (1.63e-21-1.47e-10)

Values between parentheses are 95% confidence intervals. Asterisks indicate p-value < 0.05 (*) or < 0.01 (**)

FP- fluticasone propionate; FP/SAL - fluticasone propionate + salmeterol combination therapy. BUD/FOR – budesonide + formoterol combination therapy. Statistical significance is indicated by asterisks.ACQ-5 – asthma control questionnaire

Figure S6: Visual predictive check showing Kaplan–Meier survival estimate over time of the overall patient population, including the EXCEL study, stratified by treatment. Survival (y-axis) indicates the proportion of patients who have not had an event; at time zero the survival rate is 100% (i.e., no patient has experienced an exacerbation). The solid line describes the observed time-to-first exacerbation over the period of 12 months. Shaded areas show the model-predicted 95% confidence intervals of the survival. The slope of survival curve for patients treated with FP is used as reference for comparing the effect of combination therapy. "At risk" refers to the number of patients in each stratum, "No. of events" is the number of observed exacerbations.

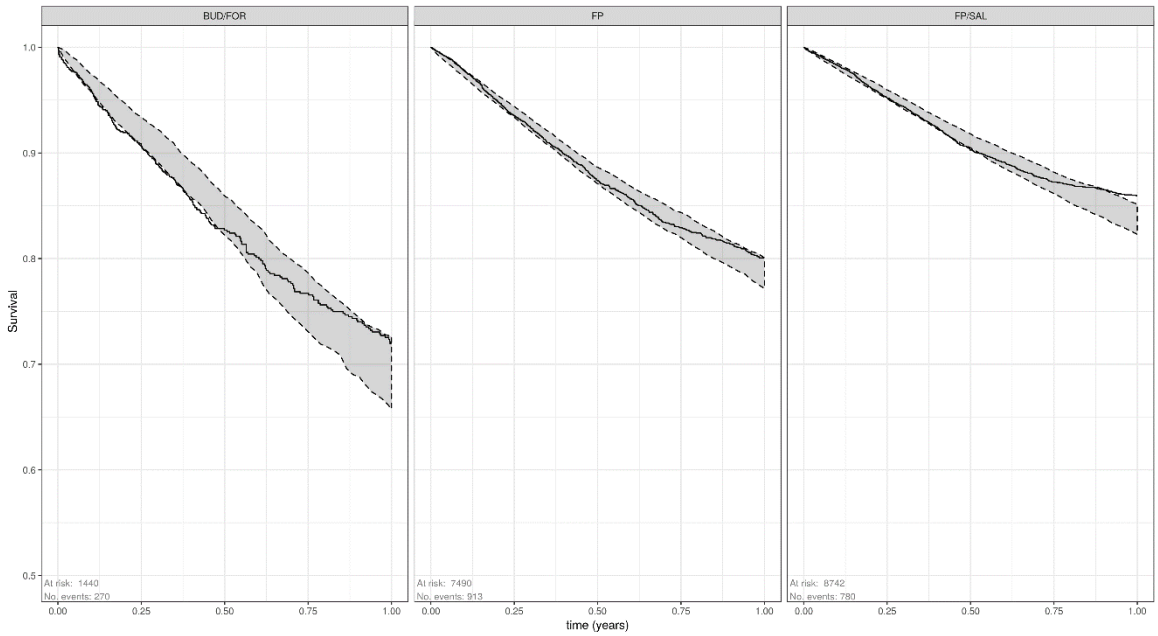
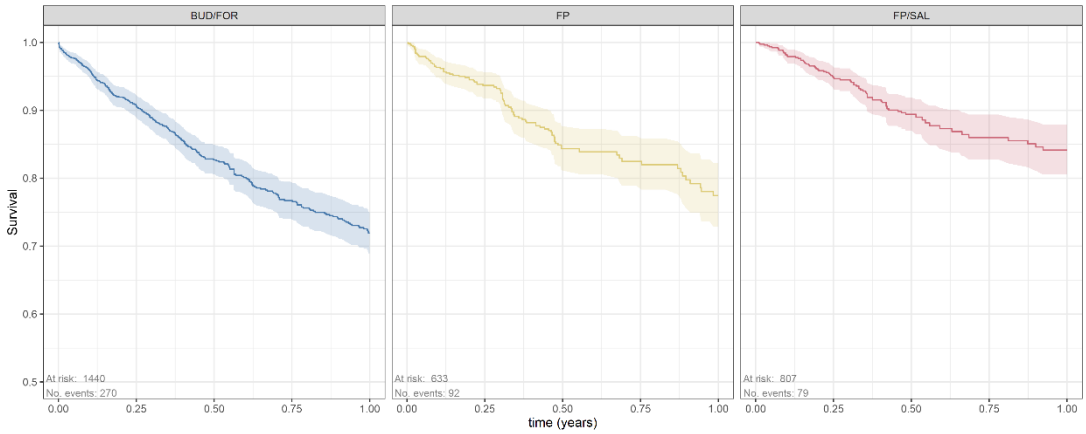


Figure S7: Kaplan–Meier survival estimate over time stratified by treatment for perfectly matched asthma patients with moderate to severe symptoms, using propensity score matching, as implemented in R (MatchIt Package). Survival (y-axis) indicates the proportion of patients who have not had an event; at time zero the survival rate is 100% (i.e., no patient has experienced an exacerbation). The solid line describes the observed time-to-first exacerbation over the period of 12 months. Shaded areas show the 95% confidence intervals of the survival. "At risk" refers to the number of patients in each stratum, "No. of events" is the number of observed exacerbations. A comparison of the incidence of exacerbations using a log-rank test showed that differences between treatments (FP vs. FP/SAL and BUD/FOR vs. FP/SAL) are statistically significant ($p<0.05$ and $p<0.001$, respectively).



The observed Kaplan-Meier survival curves were subsequently analysed using a Cox proportional hazard model, with a nonlinear least square function (nls) in R. The hazard of each treatment was estimated relative to FP/SAL. This step was implemented to explore the potential effect of unmeasured confounding using the E-value, which is an alternative approach to sensitivity analyses for unmeasured confounding in observational studies. The E-value indicates how strong the unmeasured confounding should be to refute the observed results. Based on the estimated hazard ratio for BUD/FOR [1.85 (95% CI: 1.44, 2.37)], the E-value associated with the treatment differences (i.e., FP/SAL vs BUD/FOR) was 2.42, with a confidence interval of 1.89. This strongly suggests that the observed differences are unlikely to be explained by confounding and consequently can be assigned to the treatment.

APPENDIX

Development and evaluation of the longitudinal model describing the time course of ACQ-5 in moderate-severe asthma patients.

Methods

Source data: The data used for the development of a longitudinal model describing individual ACQ-5 trajectories consisted of a subset of the studies available for the implementation of the time-to-event model used to characterise the risk of exacerbation in moderate to severe asthma patients. For minimise the use of imputation for missing data variable, only those studies that had longitudinal ACQ-5 data available at baseline and throughout the course of treatment were included in the current analysis. Two studies out of the 9 clinical trials (SAM40027 and SAM40056) met the inclusion criteria. SAM40027 contained patients receiving either FP or FP/SAL, whilst SAM40056 contained patients receiving either BUD/FOR or FP/SAL.

The available data was subsequently split into a model building and an internal validation dataset. The model building dataset consisted of 70% of the individuals, randomly sampled from the total population. The remaining 30% of the individuals were used for the purpose of internal validation. External validation was subsequently performed using data from two additional studies, which were not included in analysis dataset: SAM40040 and HZA106837. Consistency and generalisability of the model were assessed using study HZA106837, which only included FF and FF/VI treatment arms. No data was excluded from the longitudinal ACQ-5 modelling analysis except for those data records where ACQ-5 details were missing.

Exacerbations, prior ICS, SABA use, FEV1 and other relevant variables associated with asthma symptom control were evaluated as covariates on model parameters describing individual trajectories. Model performance was assessed by statistical and graphical diagnostic measures.

Model parameterisation: A longitudinal model based on first-order rates and turnover concepts (Equations 5, 6 and 7) has been used to describe the individual trajectory and time course of ACQ-5 following initiation of the treatment. This approach has been used across different therapeutic areas when the apparent delay between exposure or drug concentration and effect is due more to a delayed or slow pharmacodynamic or pathophysiological process than biophase equilibration, i.e., the time required to reach equilibrium in the lung. The observed effect is considered a dynamic process. Asthma control, treatment effect and any other relevant covariates were parameterised relative to baseline symptoms (Equation 8). This parameterisation assumes that a patient's baseline measurements immediately prior to the start of treatment reflects their disease state and eventually rate of progression.

$$\frac{d(ACQ5)}{dt} = k_{in} - k_{out} \cdot ACQ5 \qquad \text{Eq. 5}$$

$$ACQ5(0) = baseline\ ACQ5 \qquad \text{Eq. 6}$$

$$k_{out} = \frac{ACQ5(0)}{k_{in_{baseline}}} \qquad \text{Eq. 7}$$

$$k_{in} = k_{in_{baseline}} + Eff_{trt} + Eff_{cov} \qquad \text{Eq. 8}$$

The term d(ACQ5)/dt in Eq. 1 represents the rate of change in ACQ-5, whereas the term *ACQ5* refers to the hypothetical input in the compartment of the ordinary differential equation at any given time point. *ACQ5*(0) represents the input in this compartment at time = 0. k_{in} and k_{out} describe the rate of increase or reduction in symptoms according to the selected clinical scale. The effect of treatment (Eff_{trt}) and relevant baseline covariates (Eff_{cov}) are parameterised in terms of changes to the baseline symptom rate constant.

Without any treatment or covariate effects, the base model (Eq. 8) describes a stationary condition, in which symptoms variation is random. Consequently, the analysis was based on the assumption of no significant disease progression during the course of clinical trial.

This parameterisation was identified as the best one to describe the available data. Alternative parameterisation based on suitable distributions has also been tested (e.g. Gompertz function), but no significant time-dependent changes were identified (e.g., a placebo effect). Carry over from run in effect was considered to be minimal as the analysis focused on the maintenance phase of the treatment. The impact of continuous and categorical covariates on ACQ-5 was examined by visual inspection, and formally using the forward/backward approach (PsN SCM routine). Final model performance was assessed using Visual Predictive Checks (VPC). VPCs were based on 200 replications of the dataset. VPCs were created for the model fit, internal validation, external validation, and total data datasets. External validation included the assessment of treatment effects for additional drugs, namely, fluticasone furoate (FF) and FF-vilanterol (VI) combination therapy. The treatment effect parameter was (re)estimated for these interventions (with all other parameter fixed) before VPC simulations were performed. A bootstrap of the model was performed with 2000 samples on the final model based on the total data set.

The final model described the changes in ACQ-5 scores over time taking into account the effect of treatment with FP monotherapy, FP/SAL and BUD/FOR combination therapy. The parameterisation included baseline ACQ-5 (A0), rate of increase (Kin) and rate of decrease (Kout) in symptoms.

$$\frac{d(ACQ5)}{dt} = k_{in} - k_{out} \cdot ACQ5 \qquad \text{Eq. 9}$$

$$ACQ5(0) = baseline\ ACQ5 \qquad \text{Eq. 10}$$

$$k_{in} = \theta_{kin} * \left(1 + \theta_{BUD/FORM}\right) * (1 + \theta_{FP}) * \left(1 + \theta_{prevoius\ smoker}\right) * (1 + \theta_{current\ smoker}) * (1 + (BMI - 26.26) * \theta_{BMI}) * \left(1 + (AGE - 41) * \theta_{Age}\right) * e^{\eta_{k_{in}}} \qquad \text{Eq. 11}$$

$$k_{out} = \theta_{kout} * \left(1 + \theta_{BUD/FORM}\right) * (1 + \theta_{FP}) * e^{\eta_{k_{out}}} \qquad \text{Eq. 12}$$

Exponential random effects were used to describe between-subject variability in baseline ACQ-5 and maximum effects of FP, FP/SAL and BUD/FOR on ACQ-5. An exponential residual error model was used to describe the intra-individual variability.

Modelling development and evaluation were based on analytical solution and $PRED options in NONMEM v.7.3 using the FOCE-I estimation method. The analysis was run on the Model-based Analyses Platform (MAP), a validated analysis platform entirely hosted on Amazon Web Services (AWS). The platform runs NONMEM 7.3 through gFortran compiler and Perl-speaks-NONMEM (PsN)

4.6.0. All required data manipulation, including graphical and statistical summaries were performed in R (version 3.2.5).

Results

1,825 patients with accurate clinical and demographic baseline details were included in the final data set. The age of the subjects included in the population ranged from 18.0 to 82.0 years with a mean value of 42.4 years, whereas body weight ranged from 37.0 to 167.0 kg with a mean value of 76.2 kg. Mean symptom scores at baseline were 1.9 and 4.7 for ACQ-5 and AQLQ scores, respectively. Regarding lung function, as assessed by spirometry tests, FEV1 at baseline ranged from 0.6 to 5.3 L with a mean value of 2.5 L, while PEF ranged from 137.1 to 799.8.0 L/min, with a mean value of 391.1 L/min. Out of the patients reporting smoking history, the majority of patients reported to never have smoked (66.0%). A complete summary of the demographic and clinical baseline characteristics of subjects included in the analysis are presented in **Table S13**. The distribution of the baseline characteristics per study are shown in **Figure S8**. The generalised pairs plot showing the relationship between the baseline demographics and clinical characteristics of the ITT population is displayed in **Figure S9**.

An initial exploratory analysis showed that individual ACQ-5 trajectories were highly variable during the course of treatment. When stratified by baseline symptom control, there was a trend towards lower ACQ-5 scores in subjects with well-controlled symptoms at baseline and higher ACQ-5 scores for subjects with poor symptom control (**Figure S10**). However, there was large overlap in the median ACQ-5 scores by treatment, indicating that there are other factors influencing symptom control (**Figure S11**). There were also clear trends towards lower ACQ-5 scores in subjects who have never smoked compared to current and former smokers, however there were no evident correlations between ACQ-5 and age, sex, BMI, or asthma duration (**Figure S12**). As expected, there was a trend towards lower ACQ-5 scores with higher baseline AQLQ scores (i.e.,, better quality of life). No correlations or trends were observed for baseline previous ICS use duration, FEV1, FEV1P and PEF with ACQ5 score (**Figure S13**). No seasonal effect was observed for ACQ-5 scores (**Figure S14**).

The goodness-of-fit for the final model was adequate (**Figure S15**, **Figure S16**). Final model parameters are shown for completeness once more along with bootstrap results in **Table S14**. A VPC of the total data set showed the observed data falls within the model predictions (**Figure S17**). Moreover, the VPCs of the model fit, internal and external validation sets (**Figure S18**, **Figure S19** and **Figure S20**, respectively) showed no bias, overfitting or other model misspecifications. The NONMEM control file and output results for the final model are provided as attachment to this supplementary file.

Table S13: Baseline demographic and clinical characteristics of the pooled patient population included in the modelling of individual ACQ-5 trajectories.

	Variable	Mean (min – max)	Median* (5th – 95th percentiles)	N (%)[a]
Demographic Charact-eristics	Age (y)	42.4 (18.0 – 82.0)	41.0 (21.0 – 67.1)	1825 (100%)
	Weight (kg)	76.2 (37.0 – 167.0)	74.0 (52.0 – 107.4)	1824 (99.9%)
	Height (cm)	167.7 (142.0 – 194.0)	167.0 (152.0 – 185.0)	1825 (100%)
	BMI (kg/m^2)	27.0 (15.1 – 65.5)	26.2 (19.9 – 37.5)	1824 (99.9%)
	Gender N (%) Female Male	-	Female 1091 (59.8%)	1825 (100%) 1091 (59.8%) 734 (40.2%)
	Smoke habit Current smoker Former smoker Never smoked	-	Never smoked 1204 (66.0%)	1825 (~100%) 151 (~8.3%) 470 (~25.7%) 1204 (~66.0%)
	Race (Geographic ancestry)	NA	NA	NA
Clinical Scales (Symptom scores)	ACQ-5 score	1.9 (0.0 – 5.4)	1.8 (0.6 – 3.6)	1825 (100%)
	AQLQ score	4.7 (1.3 – 6.9)	4.8 (2.9 – 6.2)	1586 (86.9%)
Spirometry	FEV1 (L)	2.5 (0.6 – 5.3)	2.4 (1.4 – 3.9)	1799 (98.6%)
	FEV1p (%)	78.7 (28.6 – 130.0)	79.5 (51.4 – 104.7)	1799 (98.6%)
	PEF (L/min)	391.1 (137.1 – 799.8)	382.9 (233.6 – 579.8)	1774 (97.2%)
Biomarkers	EOS (%)	NA (NA – NA)	NA (NA – NA)	NA (NA – NA)
	FeNO (ppb)	NA (NA – NA)	NA (NA – NA)	NA (NA – NA)
Medical History	Asthma Duration <6 months ≥6 months < 1 year ≥1 year < 5 years ≥5 years < 10 years ≥10 years < 15 years ≥15 years < 20 years ≥20 years < 25 years ≥25 years	–	≥25 years 510 (27.9%)	1825 (100%) 1 (0.05%) 46 (2,5%) 280 (15.3%) 270 (14.8%) 257 (14.1%) 242 (13.3%) 219 (12.0%) 510 (27.9%)
	Previous Inhaled corticosteroid <6 months ≥6 months < 1 year ≥1 year < 5 years ≥5 years < 10 years ≥10 years < 15 years ≥15 years < 20 years ≥20 years < 25 years ≥25 years	–	≥1 year < 5 years 380 (~33.5%)	1133 (62.1%) 77 (6.8%) 140 (12.4%) 380 (33.5%) 263 (23.2%) 162 (14.3%) 58 (5.1%) 31 (2.7%) 22 (1.9%)

Abbreviations: N = Number of available records (%), ACQ = Asthma Control Questionnaire, ACT = Asthma Control Test, AQLQ = Asthma Quality of Life Questionnaire, FEV1 = Forced Expiratory Volume in one Second, FEV1P = Predicted Forced Expiratory Volume in one Second (%), PEF = Peak Expiratory Flow, EOS = Eosinophils (%), FeNO = Fractional exhaled nitric oxide, NA= not available.

* For categorical variables the Mode is shown instead of the median (5th - 95th percentiles).

a. Total number of subjects 1825. The patient population comprised all adult subjects with age ≥ 18 years.

Figure S8: Distribution of baseline demographics, clinical scales, and spirometry measures by study protocol.

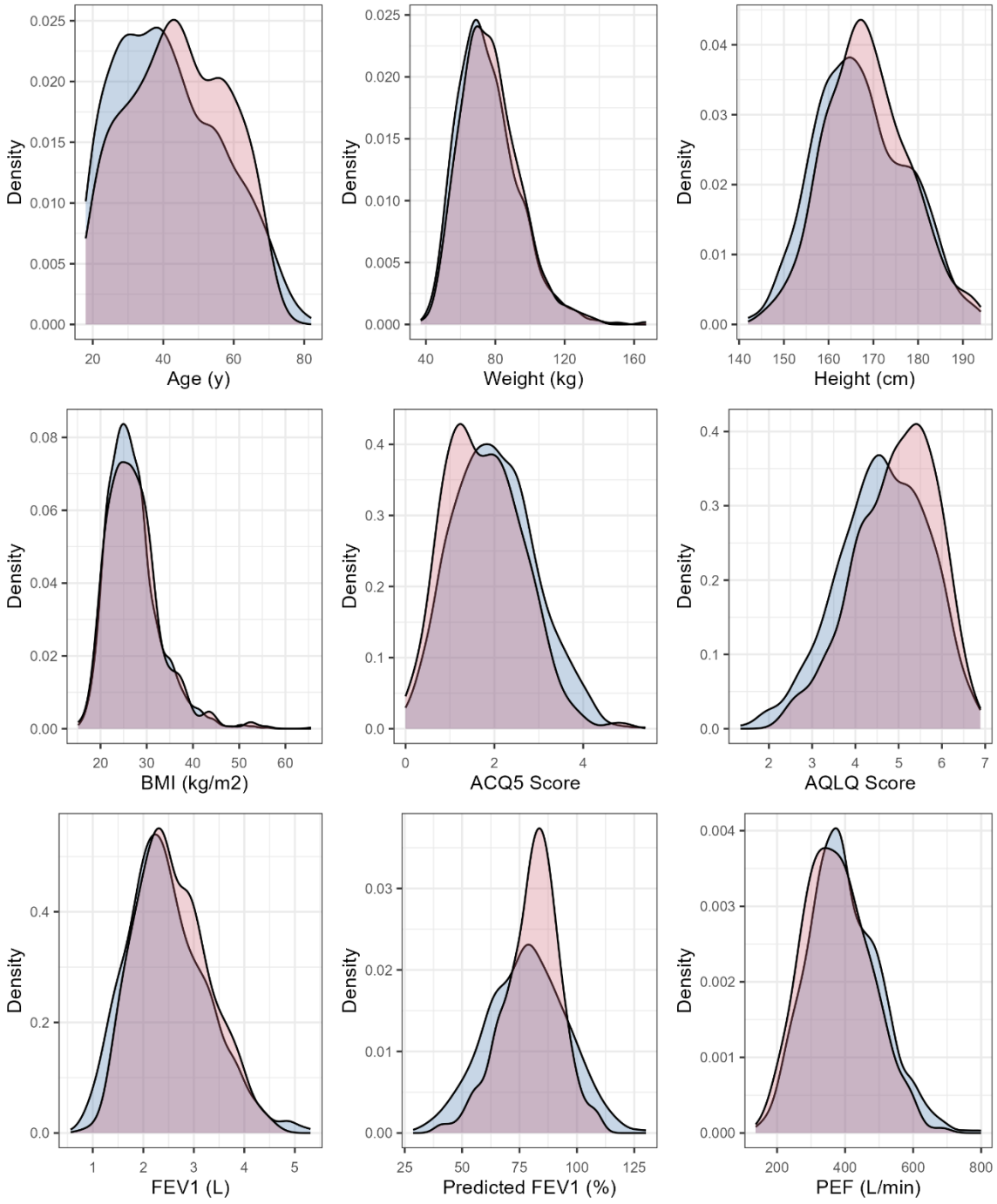


Figure S9: Generalised pairs plot. Panels show the correlations between the main demographics and clinical characteristics at baseline, which were tested during model development. Solid circles indicate individual observed values for each variable. The black solid line is a general linear function and is used to identify trends. Each column and row indicate a different variable. The value of the Pearson correlation index is shown for each pairwise comparison.

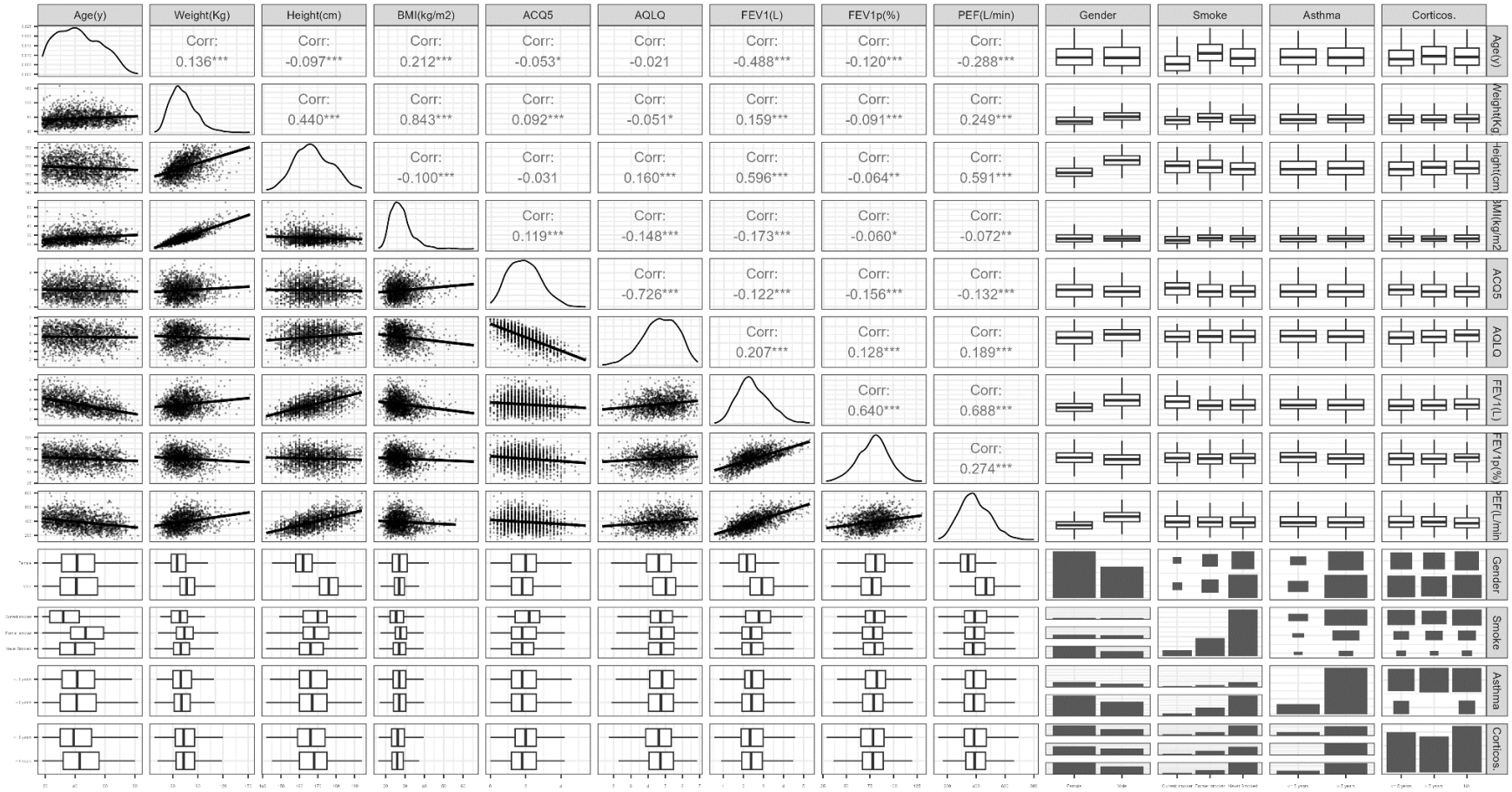


Figure S10: ACQ-5 score stratified by baseline ACQ-5. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles.

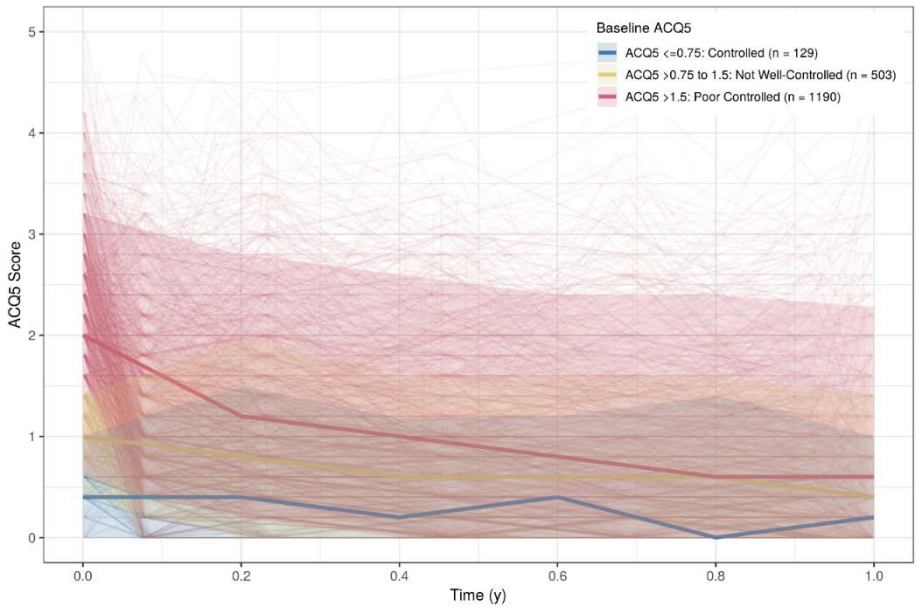


Figure S11: ACQ-5 scores stratified by treatment. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles.

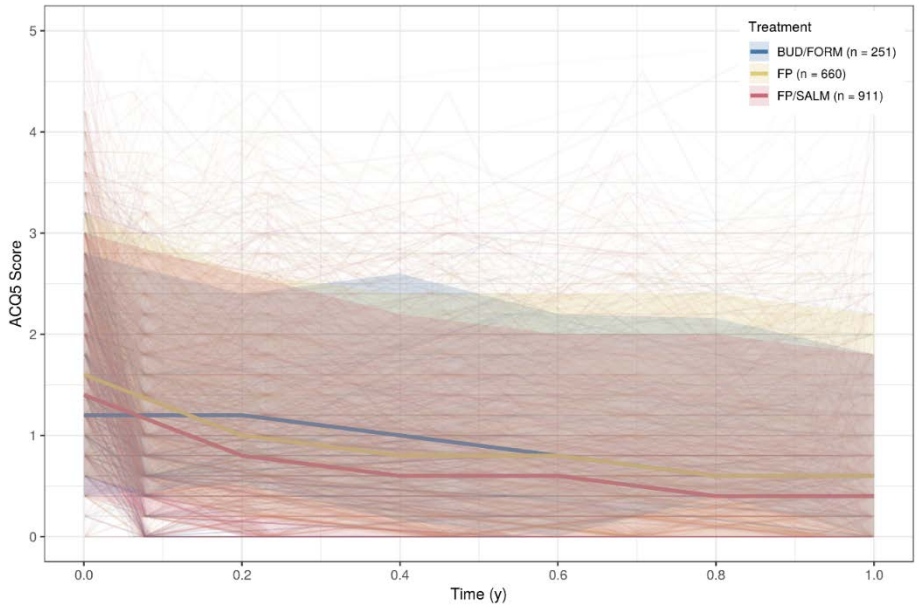


Figure S12*:* ACQ-5 scores stratified by baseline demographic characteristics. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles. No race covariate data available for longitudinal ACQ5 data set.

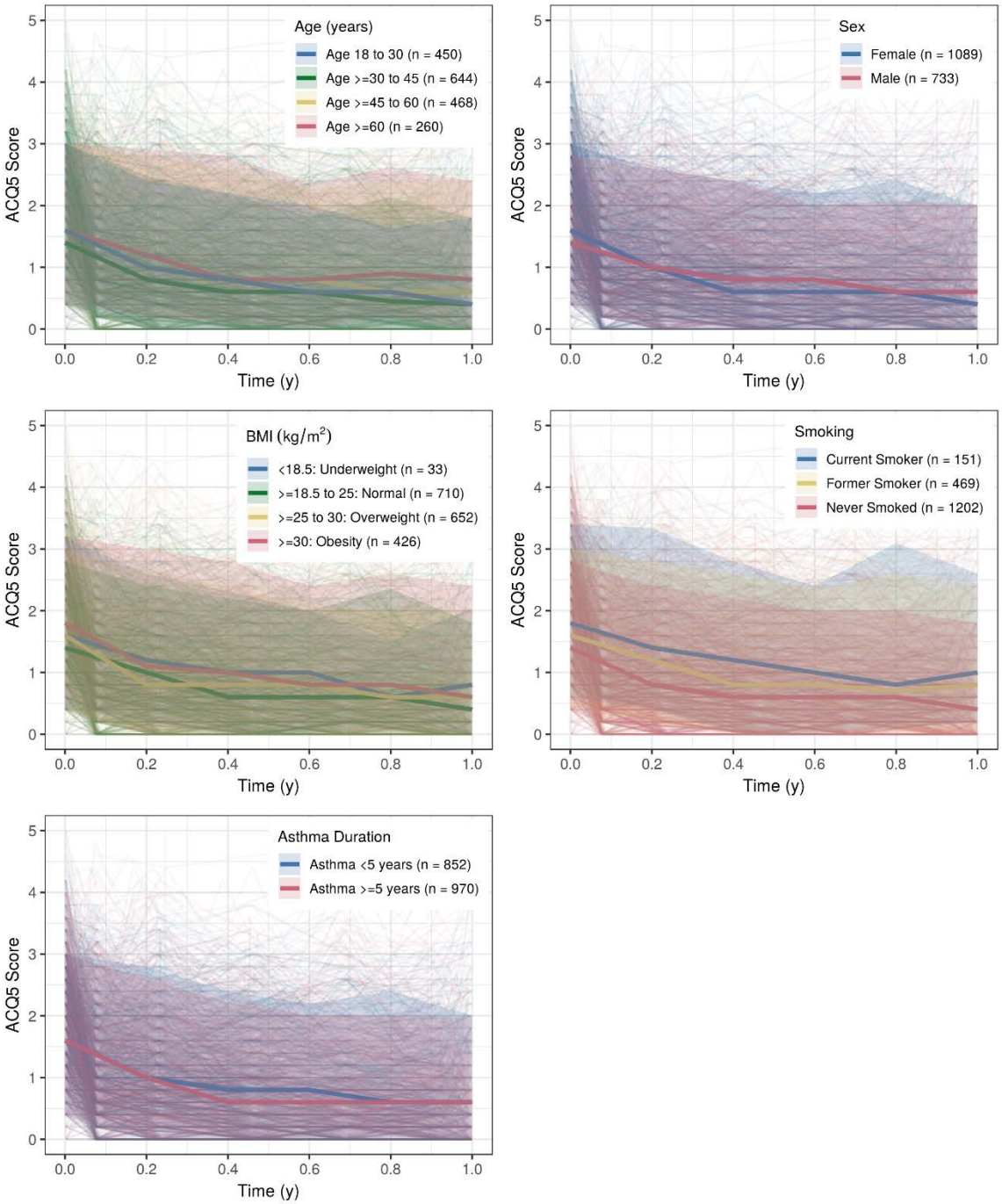


Figure S13: ACQ-5 scores stratified by baseline clinical covariates. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles.

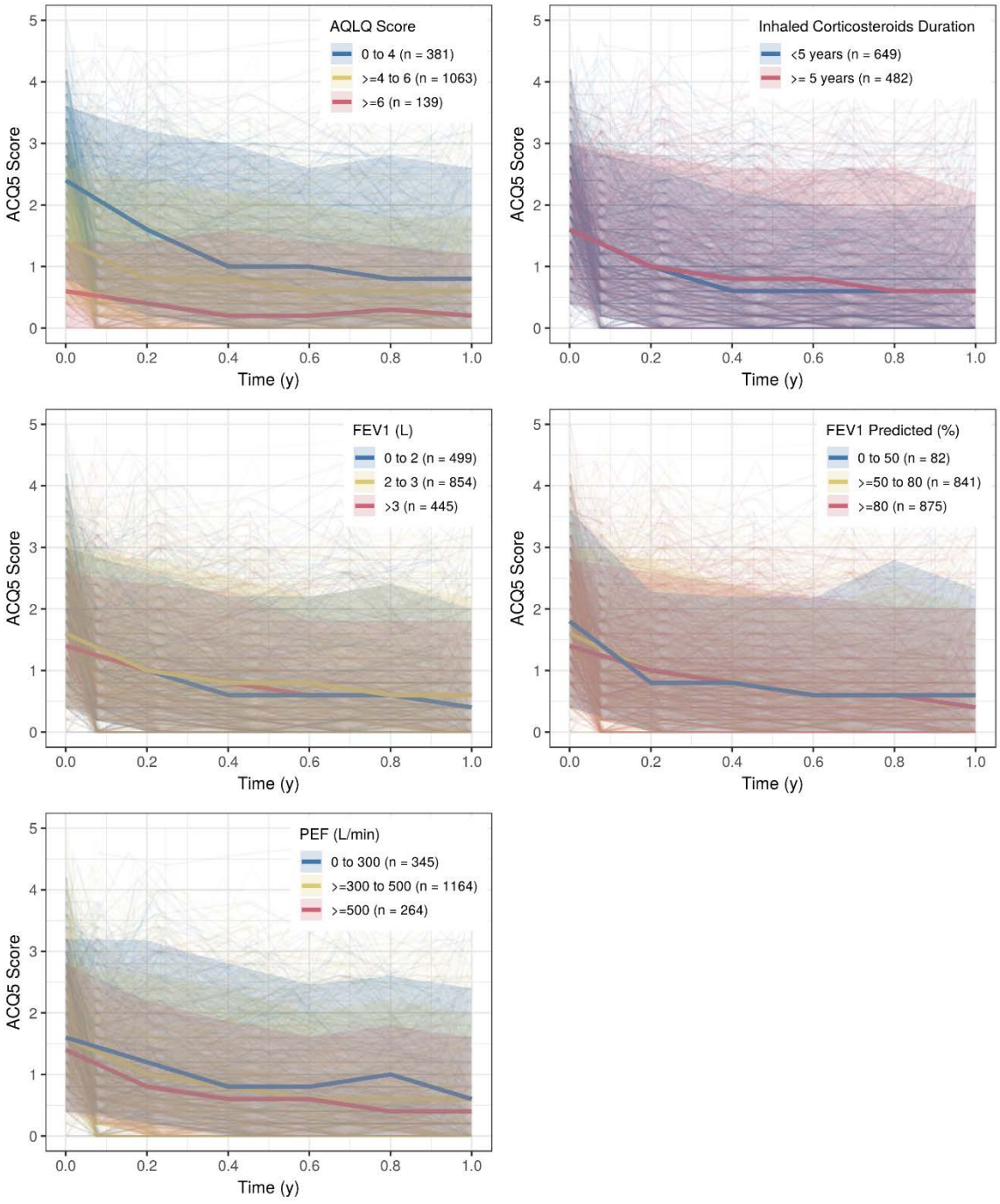


Figure S14: Lack of seasonal effect of individual ACQ-5 trajectories. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th-90th percentiles.

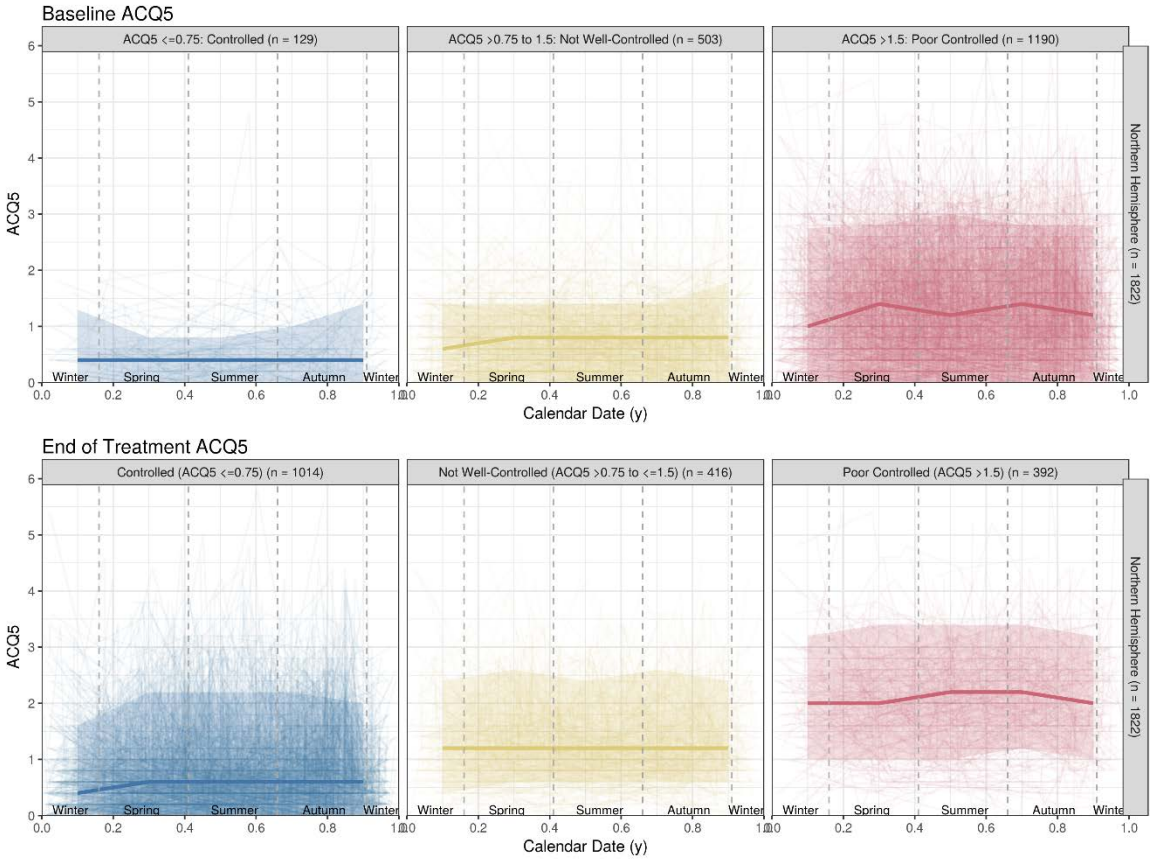


Table S14: Parameter estimates of the longitudinal model describing the individual ACQ-5 trajectories in moderate-severe asthma patients. The model is parameterised as a turnover rate (kin/kout) that includes the effect of treatment with FP monotherapy, and FP/SAL and BUD/FOR combination therapy on ACQ-5 (equations 9-12). The use of a turnover rates is recommended when describing pharmacodynamic processes which are associated with an apparent delay between drug exposure and effect, rather than pharmacokinetic equilibration [1-3]. 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.

	Parameter	Estimate	SE	RSE (%)	Bootstrap median (5^{th} – 95^{th} percentiles)
Population parameter	ACQ-5 kin (θkin)	6.26	0.328	5.2%	6.3 (6.0 - 6.9)
	ACQ-5 kout rate (θkout)	12.4	0.464	3.7%	12.4 (11.9 - 13.4)
Age	Age effect (fractional increase in k_{in} per year)	0.00759	0.002	23.0%	0.0069 (0.0045 - 0.0097)
BMI	BMI effect (fractional increase in k_{in} per kg/m^2)	0.0121	0.007	59.2%	0.014 (-0.001 - 0.022)
Smoking	Former smoker relative to never smoked (fractional increase in k_{in})	0.271	0.063	21.6%	0.29 (0.20 - 0.40)
	Current smoker relative to never smoked (fractional increase in k_{in})	0.791	0.133	16.3%	0.82 (0.59 - 1.05)
Treatment	FP/SAL effect relative to FP (fractional increase in k_{in})	-0.2	0.079	29.7%	-0.25 (-0.42 - -0.17)
	BUD/FOR effect relative to FP (fractional increase in k_{in})	0.777	0.334	31.2%	0.97 (0.68 - 1.74)
	FP/SAL effect relative to FP (fractional increase in k_{out})	-0.355	0.052	13.2%	-0.38 (-0.49 - -0.33)
	BUD/FOR effect relative to FP (fractional increase in k_{out})	0.433	0.248	37.9%	0.60 (0.38 - 1.18)
Interindividual variability	Inter individual variability in k_{in} (ηk_{in})	2.45	0.122	4.8%	2.51 (2.38 - 2.76)
	Inter individual variability correlation between η_{kin} and ηk_{out}	1.76	0.097	5.2%	1.83 (1.72 - 2.02)
	Inter individual variability in k_{out} (ηk_{out})	1.68	0.093	5.3%	1.75 (1.63 - 1.93)
Residual error	Residual error	0.479	0.009	2.0%	0.48 (0.46 - 0.49)

[1] Nagashima R, O'Reilly RA, Levy G. Kinetics of pharmacologic effects in man: the anticoagulant action of warfarin. Clin Pharmacol Ther. 1969; 10: 22–35.

[2] Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm. 1993; 21: 457–478.

[3] Upton RN, Mould DR. Basic concepts in population modeling, simulation, and model-based drug development: part 3-introduction to pharmacodynamic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2014; 3(1):e88.

Figure S15: Goodness-of-fit plots. Time is shown in years. Colours indicate study, SAM40027 is represented by blue and SAM40056 is represented by red dots. Blue lines in the top two panels depict a linear model fit. Blue lines in the bottom two panels are a loess regression line. Minor trends in the trend lines were not deemed to be clinically relevant.

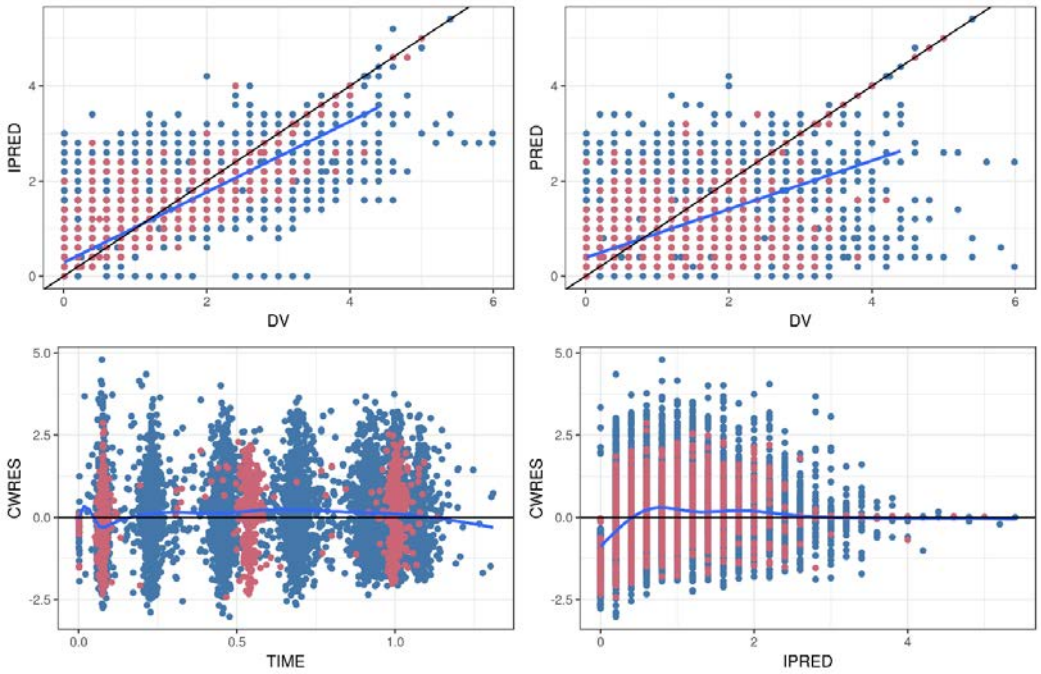


Figure S16: Randomly selected individual ACQ-5 trajectories over the period of up to 12 months. Black dots are observed ACQ-5 scores. Dashed red lines and solid blue lines depict the population predicted (PRED)and individual predicted values (IPRED), respectively.

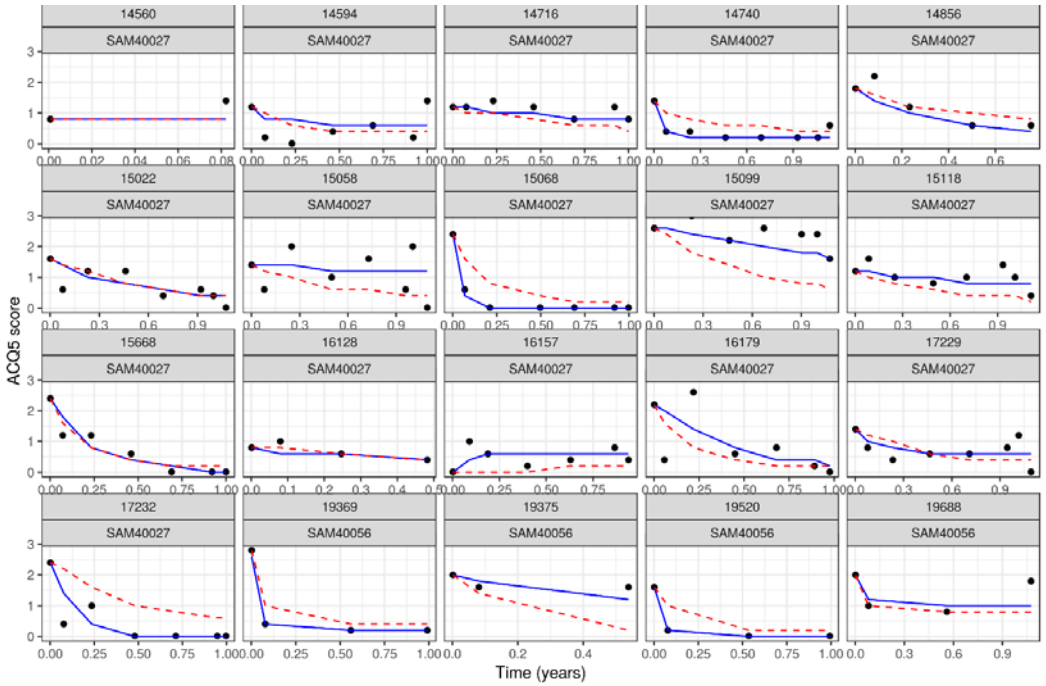


Figure S17: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories. Blue shaded area depicts the 5th and 95th percentiles of the model predictions. Dashed and solid red lines are the 5th and 95th percentiles and median of the observed ACQ-5 scores, respectively. Blue solid lines are the median model predicted ACQ-5 scores. Black dots are individual observed ACQ-5 scores.

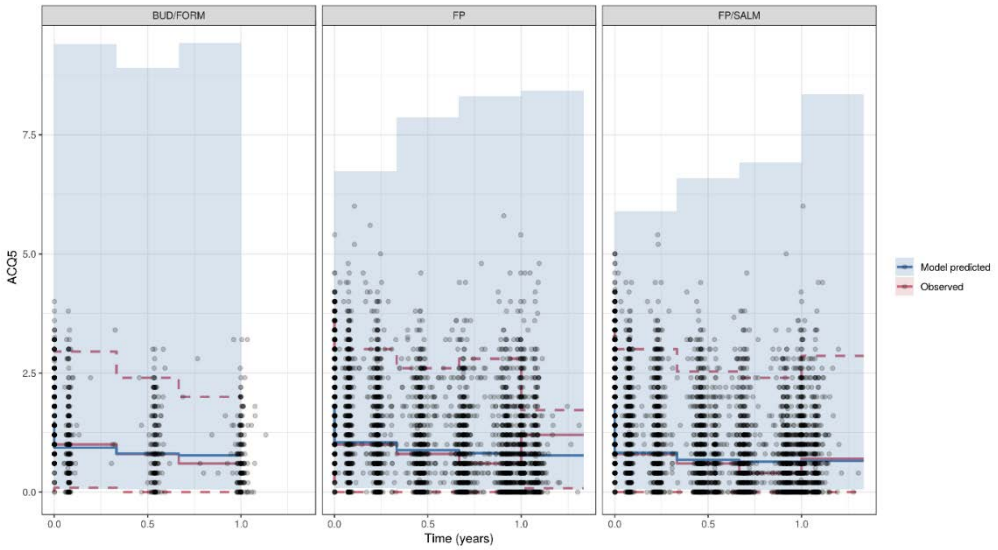


Figure S18: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories. Panels depict model performance for randomly selected subset of the population (i.e., 70% of the available data). Blue shaded area depicts the 5th and 95th percentiles of the model predictions. Dashed and solid red lines are the 5th and 95th percentiles and median of the observed ACQ-5 scores, respectively. Blue solid lines are the median model predicted ACQ-5 scores. Black dots are individual observed ACQ-5 scores.

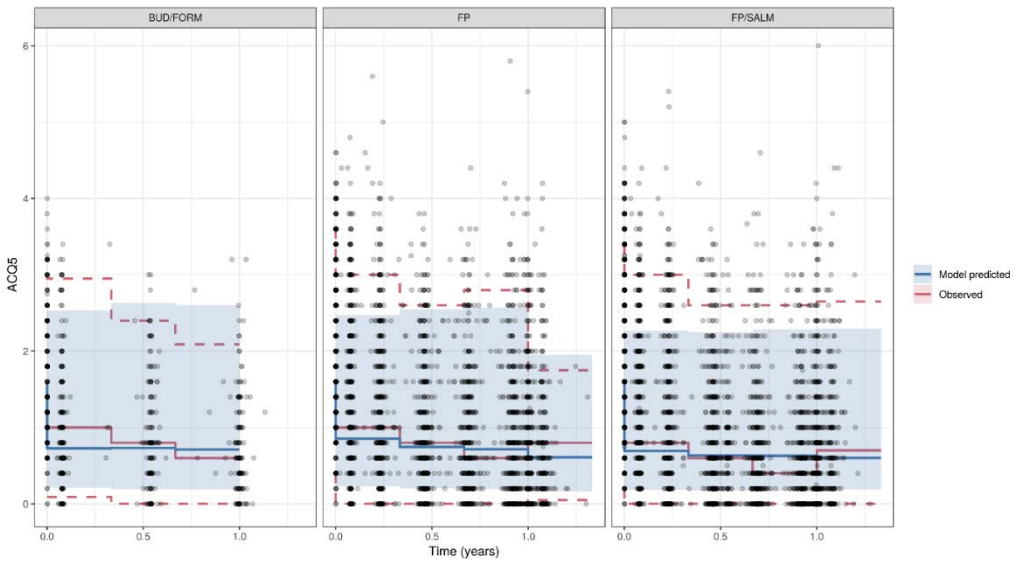


Figure 19: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories. Panels depict model performance for the internal validation subset (i.e., 30% of the available data). Blue shaded area depicts the 5th and 95th percentiles of the model predictions. Dashed and solid red lines are the 5th and 95th percentiles and median of the observed ACQ-5 scores, respectively. Blue solid lines are the median model predicted ACQ-5 scores. Black dots are individual observed ACQ-5 scores.

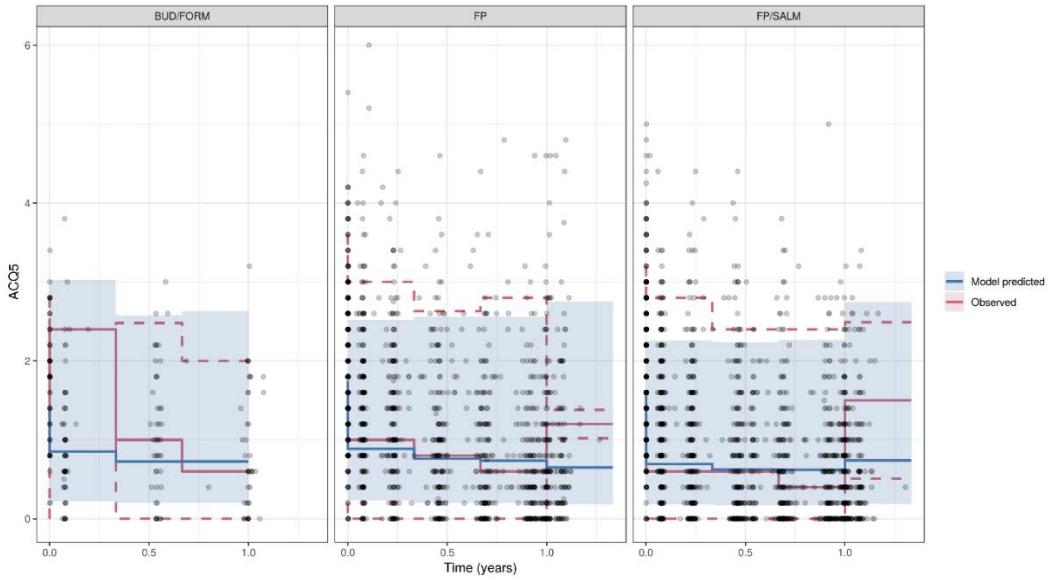
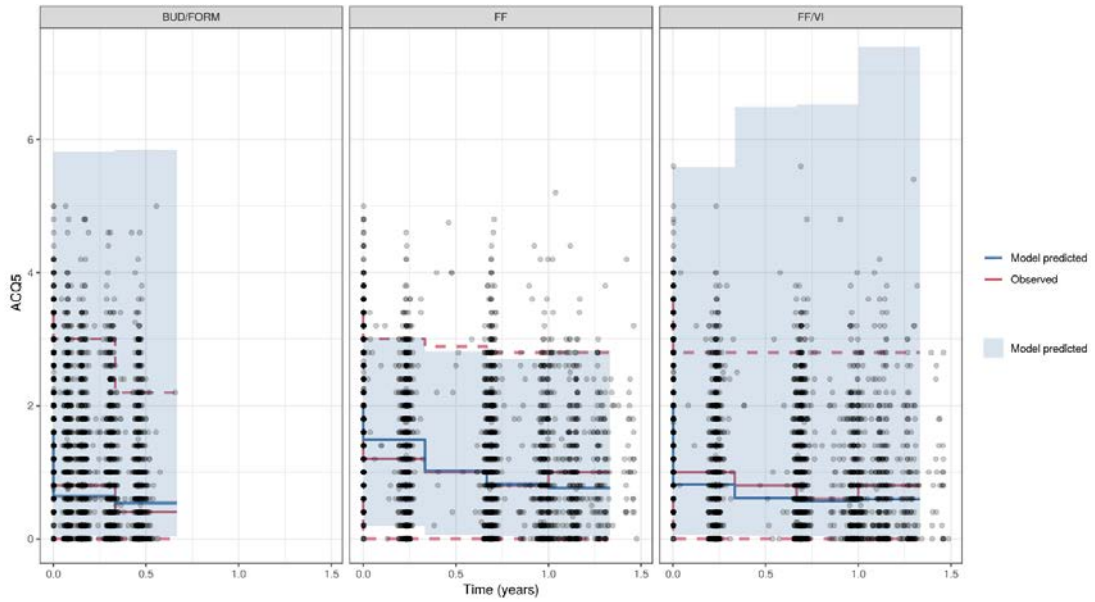


Figure 20: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories. Panels depict model performance for the external validation studies (SAM40040 and HZA106837), which were not include in the model development phase. Blue shaded area depicts the 5th and 95th percentiles of the model predictions. Dashed and solid red lines are the 5th and 95th percentiles and median of the observed ACQ-5 scores, respectively. Blue solid lines are the median model predicted ACQ-5 scores. Black dots are individual observed ACQ-5 scores.



Attachment

NONMEM control file final model

```
$PROBLEM    ACQ-5 long
$INPUT     ID ODV OBASE AMT CMT MDV EVID ACQ5 TIME ACQ5BL AQLQBL AQLQ STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL
FEV1BL FEV1PBL RACEC SET2 SET3 SET4 SET5 FLAG BASE DV
$DATA      ACQAQLQ_9.txt IGNORE=@ IGNORE=(BASE.LT.0) IGNORE=(FLAG.EQ.2)  IGNORE=(SET5.EQ.0)  IGNORE=(STUDYN.EQ.205715)
           IGNORE=(STUDYN.EQ.40040) IGNORE=(STUDYN.EQ.106837)
$PRED

;;; KOUTTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E+01) KOUTTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.1.9000E+01) KOUTTRTNUM = ( 1 + THETA(10))
IF(TRTNUM.EQ.5.0000E+00) KOUTTRTNUM = ( 1 + THETA(11))
;;; KOUTTRTNUM-DEFINITION END

;;; KOUT-RELATION START
KOUTCOV=KOUTTRTNUM
;;; KOUT-RELATION END


;;; KINTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E+01) KINTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.1.9000E+01) KINTRTNUM = ( 1 + THETA(8))
IF(TRTNUM.EQ.5.0000E+00) KINTRTNUM = ( 1 + THETA(9))
;;; KINTRTNUM-DEFINITION END


;;; KINSMOKN-DEFINITION START
IF(SMOKN.EQ.1.0000E+00) KINSMOKN = 1  ; Most common
IF(SMOKN.EQ.3.0000E+00) KINSMOKN = ( 1 + THETA(6))
IF(SMOKN.EQ.2.0000E+00) KINSMOKN = ( 1 + THETA(7))
;;; KINSMOKN-DEFINITION END


;;; KINBMIBL-DEFINITION START
KINBMIBL = ( 1 + THETA(5)*(BMIBL - 26.26))
;;; KINBMIBL-DEFINITION END


;;; KINAGEBL-DEFINITION START
KINAGEBL = ( 1 + THETA(4)*(AGEBL - 41))
;;; KINAGEBL-DEFINITION END

;;; KIN-RELATION START
KINCOV=KINAGEBL*KINBMIBL*KINSMOKN*KINTRTNUM
;;; KIN-RELATION END


  TVKIN   = THETA(1) * EXP(ETA(1))

TVKIN = KINCOV*TVKIN
  TVKOUT   = THETA(2) * EXP(ETA(2))

TVKOUT = KOUTCOV*TVKOUT

  KIN = TVKIN
 KOUT = TVKOUT

 PACQ5  =  ((EXP(-KOUT * TIME)*(BASE * KOUT + KIN*(EXP(KOUT * TIME) - 1)))/KOUT)
 IPRED =  PACQ5
    W1 = SQRT(THETA(3)**2)
     Y = IPRED + W1*EPS(1)

$THETA
 (0,6.89772) ;
 (0,10.62) ;
 (0,0.487261) ;
 (-0.024,-2.4E-05,0.043) ; KINAGEBL1
 (-0.025,-2.5E-05,0.090) ; KINBMIBL1
 (-1,-0.001,5) ; KINSMOKN1
 (-1,-0.001,5) ; KINSMOKN2
 (-1,-0.001,5) ; KINTRTNUM1
 (-1,-0.001,5) ; KINTRTNUM2
 (-1,-0.001,5) ; KOUTTRTNUM1
 (-1,-0.001,5) ; KOUTTRTNUM2

$OMEGA  BLOCK(2)
 0.661156
 0.302055 0.574912



$SIGMA  1  FIX  ; Proportional error PK
$ESTIMATION METHOD=1 INTER MAXEVAL=99999 NOABORT SIG=1 PRINT=1 POSTHOC
$COVARIANCE
$TABLE ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC
ICSDURC SMOKN TRTNUM FLAG IPRED ONEHEADER NOPRINT
FORMAT=s1PE11.5 FILE=table281.txt
```

NONMEM output file final model

```
$PROBLEM    ACQ-5 long
$INPUT      ID ODV OBASE AMT CMT MDV EVID ACQ5 TIME ACQ5BL AQLQBL AQLQ
            STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN
            BMIBL FEV1BL FEV1PBL RACEC SET2 SET3 SET4 SET5 FLAG BASE
            DV
$DATA      ../../ACQAQLQ_9.txt IGNORE=@ IGNORE=(BASE.LT.0)
            IGNORE=(FLAG.EQ.2) IGNORE=(SET5.EQ.0)
            IGNORE=(STUDYN.EQ.205715) IGNORE=(STUDYN.EQ.40040)
            IGNORE=(STUDYN.EQ.106837)

$PRED

;;; KOUTTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E+01) KOUTTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.1.9000E+01) KOUTTRTNUM = ( 1 + THETA(10))
IF(TRTNUM.EQ.5.0000E+00) KOUTTRTNUM = ( 1 + THETA(11))
;;; KOUTTRTNUM-DEFINITION END

;;; KOUT-RELATION START
KOUTCOV=KOUTTRTNUM
;;; KOUT-RELATION END


;;; KINTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E+01) KINTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.1.9000E+01) KINTRTNUM = ( 1 + THETA(8))
IF(TRTNUM.EQ.5.0000E+00) KINTRTNUM = ( 1 + THETA(9))
;;; KINTRTNUM-DEFINITION END


;;; KINSMOKN-DEFINITION START
IF(SMOKN.EQ.1.0000E+00) KINSMOKN = 1  ; Most common
IF(SMOKN.EQ.3.0000E+00) KINSMOKN = ( 1 + THETA(6))
IF(SMOKN.EQ.2.0000E+00) KINSMOKN = ( 1 + THETA(7))
;;; KINSMOKN-DEFINITION END


;;; KINBMIBL-DEFINITION START
KINBMIBL = ( 1 + THETA(5)*(BMIBL - 26.26))
;;; KINBMIBL-DEFINITION END


;;; KINAGEBL-DEFINITION START
KINAGEBL = ( 1 + THETA(4)*(AGEBL - 41))
;;; KINAGEBL-DEFINITION END

;;; KIN-RELATION START
KINCOV=KINAGEBL*KINBMIBL*KINSMOKN*KINTRTNUM
;;; KIN-RELATION END




  TVKIN   = THETA(1) * EXP(ETA(1))

TVKIN = KINCOV*TVKIN
  TVKOUT   = THETA(2) * EXP(ETA(2))

TVKOUT = KOUTCOV*TVKOUT

  KIN = TVKIN
 KOUT = TVKOUT

 PACQ5  =  ((EXP(-KOUT * TIME)*(BASE * KOUT + KIN*(EXP(KOUT * TIME) - 1)))/KOUT)
 IPRED =  PACQ5
    W1 = SQRT(THETA(3)**2)
     Y = IPRED + W1*EPS(1)

$THETA  (0,6.26207999348608) ;
 (0,9.68028101150034) ;
 (0,0.482748057155104) ;
 (-0.024,-2.19076278905144E-05,0.043) ; KINAGEBL1
 (-0.025,-2.59874394519405E-05,0.090) ; KINBMIBL1
 (-1,-0.000941183372913202,5) ; KINSMOKN1
 (-1,-0.000937289898269643,5) ; KINSMOKN2
 (-1,-0.00108835365688897,5) ; KINTRTNUM1
 (-1,-0.00102329174963748,5) ; KINTRTNUM2
 (-1,-0.000993075595754862,5) ; KOUTTRTNUM1
 (-1,-0.00100077784171613,5) ; KOUTTRTNUM2
$OMEGA  BLOCK(2)
 0.661233793949875
 0.313029818086115 0.580302137774261

$SIGMA  1  FIX  ; Proportional error PK
$ESTIMATION METHOD=1 INTER MAXEVAL=99999 NOABORT SIG=1 PRINT=1 POSTHOC
$COVARIANCE
$TABLE      ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC ICSDURC
            SMOKN TRTNUM FLAG IPRED ONEHEADER NOPRINT FORMAT=s1PE11.5
```

```
            FILE=table281.txt


NM-TRAN MESSAGES

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1

 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

License Registered to: GlaxoSmithKline
Expiration Date:    14 MAY 2022
Current Date:        6 MAR 2022
Days until program expires :  68
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0
 ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
 CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
 AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
 PERFORMED BY NOUS INFOSYSTEMS.

 PROBLEM NO.:         1
 PK
0DATA CHECKOUT RUN:              NO
 DATA SET LOCATED ON UNIT NO.:    2
 THIS UNIT TO BE REWOUND:        NO
 NO. OF DATA RECS IN DATA SET:    12436
 NO. OF DATA ITEMS IN DATA SET:  31
 ID DATA ITEM IS DATA ITEM NO.:   1
 DEP VARIABLE IS DATA ITEM NO.:  31
 MDV DATA ITEM IS DATA ITEM NO.:  6
0LABELS FOR DATA ITEMS:
 ID ODV OBASE AMT CMT MDV EVID ACQ5 TIME ACQ5BL AQLQBL AQLQ STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL
 FEV1BL FEV1PBL RACEC SET2 SET3 SET4 SET5 FLAG BASE DV
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
 KIN KOUT IPRED
0FORMAT FOR DATA:
 (1(3E21.0/),1E21.0)

 TOT. NO. OF OBS RECS:    10611
 TOT. NO. OF INDIVIDUALS:   1825
0LENGTH OF THETA:  11
0DEFAULT THETA BOUNDARY TEST OMITTED:    NO
0OMEGA HAS BLOCK FORM:
  1
  1  1
0DEFAULT OMEGA BOUNDARY TEST OMITTED:    NO
0SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION:   1
0DEFAULT SIGMA BOUNDARY TEST OMITTED:    NO
0INITIAL ESTIMATE OF THETA:
 LOWER BOUND    INITIAL EST    UPPER BOUND
  0.0000E+00     0.6262E+01     0.1000E+07
  0.0000E+00     0.9680E+01     0.1000E+07
  0.0000E+00     0.4827E+00     0.1000E+07
 -0.2400E-01    -0.2191E-04     0.4300E-01
 -0.2500E-01    -0.2599E-04     0.9000E-01
 -0.1000E+01    -0.9412E-03     0.5000E+01
 -0.1000E+01    -0.9373E-03     0.5000E+01
 -0.1000E+01    -0.1088E-02     0.5000E+01
 -0.1000E+01    -0.1023E-02     0.5000E+01
 -0.1000E+01    -0.9931E-03     0.5000E+01
 -0.1000E+01    -0.1001E-02     0.5000E+01
0INITIAL ESTIMATE OF OMEGA:
 BLOCK SET NO.   BLOCK                                                    FIXED
       1                                                                   NO
                  0.6612E+00
                  0.3130E+00   0.5803E+00
0INITIAL ESTIMATE OF SIGMA:
 0.1000E+01
0SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE
0COVARIANCE STEP OMITTED:        NO
 EIGENVLS. PRINTED:              NO
 SPECIAL COMPUTATION:            NO
 COMPRESSED FORMAT:              NO
 SIGDIGITS ETAHAT (SIGLO):                  -1
 SIGDIGITS GRADIENTS (SIGL):                -1
 RELATIVE TOLERANCE (TOL):                  -1
 ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY (ATOL): -1
 EXCLUDE COV FOR FOCE (NOFCOV):              NO
 RESUME COV ANALYSIS (RESUME):               NO
0TABLES STEP OMITTED:    NO
 NO. OF TABLES:           1
 SEED NUMBER (SEED):    11456
 RANMETHOD:
 MC SAMPLES (ESEED):    300
 WRES SQUARE ROOT TYPE:           EIGENVALUE
0-- TABLE   1 --
 PRINTED:                NO
 HEADERS:               ONE
 FILE TO BE FORWARDED:   NO
 FORMAT:                s1PE11.5
 LFORMAT:
 RFORMAT:
0USER-CHOSEN ITEMS:
```

```
 ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC ICSDURC SMOKN TRTNUM FLAG IPRED
1


 #TBLN:      1
 #METH: First Order Conditional Estimation with Interaction

 ESTIMATION STEP OMITTED:                 NO
 ANALYSIS TYPE:                           POPULATION
 CONDITIONAL ESTIMATES USED:              YES
 CENTERED ETA:                            NO
 EPS-ETA INTERACTION:                     YES
 LAPLACIAN OBJ. FUNC.:                    NO
 NO. OF FUNCT. EVALS. ALLOWED:            99999
 NO. OF SIG. FIGURES REQUIRED:            1
 INTERMEDIATE PRINTOUT:                   YES
 ESTIMATE OUTPUT TO MSF:                  NO
 ABORT WITH PRED EXIT CODE 1:             NO
 IND. OBJ. FUNC. VALUES SORTED:           NO
 NUMERICAL DERIVATIVE
       FILE REQUEST (NUMDER):             NONE
 MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
 ETA HESSIAN EVALUATION METHOD (ETADER):  0
 INITIAL ETA FOR MAP ESTIMATION (MCETA):  0
 SIGDIGITS FOR MAP ESTIMATION (SIGLO):    100
 GRADIENT SIGDIGITS OF
       FIXED EFFECTS PARAMETERS (SIGL):   100
 EXCLUDE TITLE (NOTITLE):                 NO
 EXCLUDE COLUMN LABELS (NOLABEL):         NO
 NOPRIOR SETTING (NOPRIOR):               OFF
 NOCOV SETTING (NOCOV):                   OFF
 DERCONT SETTING (DERCONT):               OFF
 ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY(ATOL):-100
 FINAL ETA RE-EVALUATION (FNLETA):        ON
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
       IN SHRINKAGE (ETASTYPE):           NO
 NON-INFL. ETA CORRECTION (NONINFETA):    OFF
 FORMAT FOR ADDITIONAL FILES (FORMAT):    S1PE12.5
 PARAMETER ORDER FOR OUTPUTS (ORDER):     TSOL
 ADDITIONAL CONVERGENCE TEST (CTYPE=4)?:  NO
 EM OR BAYESIAN METHOD USED:                NONE


 THE FOLLOWING LABELS ARE EQUIVALENT
 PRED=PREDI
 RES=RESI
 WRES=WRESI
 IWRS=IWRESI
 IPRD=IPREDI
 IRS=IRESI

 MONITORING OF SEARCH:


0ITERATION NO.:    0    OBJECTIVE VALUE:  -169.085693959215        NO. OF FUNC. EVALS.:  13
 CUMULATIVE NO. OF FUNC. EVALS.:       13
 NPARAMETR:  6.2621E+00  9.6803E+00  4.8275E-01 -2.1908E-05 -2.5987E-05 -9.4118E-04 -9.3729E-04 -1.0884E-03 -1.0233E-03 -9.9308E-04
            -1.0008E-03  6.6123E-01  3.1303E-01  5.8030E-01
 PARAMETER:  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01
             1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01
 GRADIENT:   1.1454E+02  5.1739E+02 -6.6459E+02 -8.1044E+01  2.3592E+01 -1.3777E+02 -9.3808E+01 -7.8098E+01 -7.0667E+01  4.7793E+02
             2.1694E+00 -3.5199E+02 -1.0694E+03 -2.8887E+02

0ITERATION NO.:    1    OBJECTIVE VALUE:  -222.775779648485        NO. OF FUNC. EVALS.:  15
 CUMULATIVE NO. OF FUNC. EVALS.:       28
 NPARAMETR:  6.2193E+00  9.3854E+00  5.0232E-01  5.2745E-05 -5.3552E-05  5.9363E-03  3.7416E-03  2.8053E-03  2.4995E-03 -2.4559E-02
            -1.1088E-03  6.8966E-01  5.2409E-01  8.4557E-01
 PARAMETER:  9.3152E-02  6.9068E-02  1.3973E-01  1.0485E-01  9.8590E-02  1.0824E-01  1.0561E-01  1.0467E-01  1.0422E-01  7.1427E-02
             9.9870E-02  1.2104E-01  1.6394E-01  1.1727E-01
 GRADIENT:   5.7788E+01  4.6469E+02  7.7889E+02 -9.6828E+01  9.4679E+00 -1.7143E+02 -1.1139E+02 -8.8999E+01 -8.4916E+01  4.1375E+02
             2.9044E+01 -5.5799E+02  4.4075E+02 -3.8710E+02

0ITERATION NO.:    2    OBJECTIVE VALUE:  -249.792888175797        NO. OF FUNC. EVALS.:  15
 CUMULATIVE NO. OF FUNC. EVALS.:       43
 NPARAMETR:  6.2051E+00  9.2135E+00  4.8699E-01  1.1218E-04 -6.0910E-05  1.1660E-02  7.4516E-03  5.7664E-03  5.3240E-03 -3.7932E-02
            -2.0706E-03  7.2097E-01  4.7853E-01  7.7891E-01
 PARAMETER:  9.0853E-02  5.0578E-02  1.0874E-01  1.0870E-01  9.8213E-02  1.1506E-01  1.1004E-01  1.0821E-01  1.0760E-01  5.4964E-02
             9.8715E-02  1.4325E-01  1.4640E-01  1.3267E-01
 GRADIENT:   2.8959E+02  2.5376E+02 -2.2895E+02 -8.2546E+01  1.7205E+01 -9.7494E+01 -8.5471E+01  1.6234E+01 -6.1428E+01  3.3207E+02
             7.3174E-01 -4.8455E+02 -1.9784E+02 -2.5062E+02

0ITERATION NO.:    3    OBJECTIVE VALUE:  -314.466127091640        NO. OF FUNC. EVALS.:  14
 CUMULATIVE NO. OF FUNC. EVALS.:       57
 NPARAMETR:  5.5058E+00  8.0268E+00  5.0110E-01  7.4087E-04 -2.0875E-04  5.6508E-02  4.3870E-02  6.3327E-03  3.1683E-02 -1.6380E-01
            -4.2431E-03  1.1580E+00  7.8571E-01  1.1319E+00
 PARAMETER: -2.8703E-02 -8.7308E-02  1.3730E-01  1.4921E-01  9.0627E-02  1.6746E-01  1.5287E-01  1.0889E-01  1.3878E-01 -1.0993E-01
             9.6101E-02  3.8019E-01  1.8967E-01  2.6311E-01
 GRADIENT:   7.7397E+02 -3.7076E+02  1.1726E+03 -3.4040E+01  1.2136E+01  1.0199E+02 -1.0899E+01  2.8753E+02 -5.6903E+00 -1.9203E+01
            -4.1262E+01 -3.2650E+01 -1.0087E+03  2.4632E+02

0ITERATION NO.:    4    OBJECTIVE VALUE:  -359.362583578070        NO. OF FUNC. EVALS.:  14
 CUMULATIVE NO. OF FUNC. EVALS.:       71
```

```
 NPARAMETR:  5.0516E+00  7.6599E+00  4.8719E-01  1.0483E-03 -2.8573E-04  7.3460E-02  6.0993E-02 -3.3706E-03  4.3910E-02 -2.1539E-01
            -3.7476E-03  1.4385E+00  1.1662E+00  1.6056E+00
 PARAMETER: -1.1481E-01 -1.3409E-01  1.0915E-01  1.6886E-01  8.6664E-02  1.8682E-01  1.7260E-01  9.7256E-02  1.5302E-01 -1.8356E-01
            9.6698E-02  4.8862E-01  2.5260E-01  3.1182E-01
 GRADIENT:   7.6252E+02 -2.1093E+02  4.0244E+02 -3.3081E+01  6.9571E+00  1.0538E+02 -3.0844E+00  2.9821E+02 -1.4887E+01  2.6918E+01
            -1.9134E+01 -2.6976E+02  6.0002E+01  3.4254E+02

0ITERATION NO.:    5    OBJECTIVE VALUE:  -398.915988443168       NO. OF FUNC. EVALS.:  14
 CUMULATIVE NO. OF FUNC. EVALS.:       85
 NPARAMETR:  4.2524E+00  7.3373E+00  4.7473E-01  1.4622E-03 -3.8603E-04  8.4995E-02  8.1508E-02 -3.7629E-02  6.0065E-02 -2.7604E-01
            -2.4198E-03  1.9981E+00  1.5087E+00  1.8292E+00
 PARAMETER: -2.8703E-01 -1.7712E-01  8.3258E-02  1.9516E-01  8.1487E-02  1.9985E-01  1.9592E-01  5.5453E-02  1.7164E-01 -2.7557E-01
            9.8295E-02  6.5291E-01  2.7726E-01  3.3400E-01
 GRADIENT:   1.0982E+03  1.3174E+02 -2.2028E+02 -2.3927E+01  3.7638E+00  8.6269E+01  1.0280E+00  2.4816E+02 -2.8132E+01  1.9030E+02
            1.7041E+00 -3.6114E+01 -3.8659E+02  3.8698E+02

0ITERATION NO.:    6    OBJECTIVE VALUE:  -398.915988443168       NO. OF FUNC. EVALS.:  27
 CUMULATIVE NO. OF FUNC. EVALS.:      112
 NPARAMETR:  4.2524E+00  7.3373E+00  4.7473E-01  1.4622E-03 -3.8603E-04  8.4995E-02  8.1508E-02 -3.7629E-02  6.0065E-02 -2.7604E-01
            -2.4198E-03  1.9981E+00  1.5087E+00  1.8292E+00
 PARAMETER: -2.8703E-01 -1.7712E-01  8.3258E-02  1.9516E-01  8.1487E-02  1.9985E-01  1.9592E-01  5.5453E-02  1.7164E-01 -2.7557E-01
            9.8295E-02  6.5291E-01  2.7726E-01  3.3400E-01
 GRADIENT:   2.3418E+02 -5.2004E+02 -4.3686E+02 -5.8980E+01 -1.2399E+01 -4.7930E+01 -4.8911E+01  1.4053E+02 -4.8456E+01 -2.0158E+02
            -1.2090E+01 -3.6114E+01 -3.8659E+02  3.8698E+02

0ITERATION NO.:    7    OBJECTIVE VALUE:  -468.333127868072       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      137
 NPARAMETR:  4.8657E+00  9.5702E+00  4.7245E-01  3.3243E-03 -1.9274E-05  3.0700E-01  2.0131E-01  1.7918E-03  1.5931E-01 -2.4890E-01
            -1.9414E-02  3.1698E+00  2.0100E+00  1.8368E+00
 PARAMETER: -1.5231E-01  8.8559E-02  7.8431E-02  3.1160E-01  1.0034E-01  4.3223E-01  3.2563E-01  1.0346E-01  2.8144E-01 -2.3361E-01
            7.7722E-02  8.8366E-01  2.9327E-01  2.3166E-01
 GRADIENT:   2.5227E+02 -4.3635E+02 -3.3934E+02 -3.1982E+01  6.0150E+00  6.5574E+01 -4.7945E+01  1.1083E+02  8.6790E+00 -1.3002E+02
            -5.6745E+01  8.0117E+02 -1.7754E+03  3.1588E+02

0ITERATION NO.:    8    OBJECTIVE VALUE:  -513.620282393144       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      162
 NPARAMETR:  5.6855E+00  1.0930E+01  4.8130E-01  5.0487E-03  2.8821E-04  5.0118E-01  3.3088E-01  5.4976E-02  2.4662E-01 -2.5722E-01
            -3.1869E-02  2.6978E+00  1.7862E+00  1.6089E+00
 PARAMETER:  3.4133E-03  2.2140E-01  9.7004E-02  4.1724E-01  1.1600E-01  6.1300E-01  4.5543E-01  1.6588E-01  3.7225E-01 -2.4634E-01
            6.2460E-02  8.0304E-01  2.8250E-01  9.3107E-02
 GRADIENT:   4.5764E+02 -6.3617E+02  7.4229E+01 -6.1981E+00  4.3091E+01  1.9699E+02 -3.7892E+01  2.2055E+02  5.4235E+01 -2.3811E+02
            -1.0883E+02  5.0295E+02 -1.2656E+03  1.3883E+01

0ITERATION NO.:    9    OBJECTIVE VALUE:  -528.821657154060       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      187
 NPARAMETR:  5.8032E+00  1.1555E+01  4.8409E-01  5.5223E-03  2.3224E-04  5.3482E-01  3.7459E-01  6.1554E-02  2.6466E-01 -2.5687E-01
            -2.6471E-02  2.5266E+00  1.6481E+00  1.5149E+00
 PARAMETER:  2.3893E-02  2.7707E-01  1.0278E-01  4.4597E-01  1.1316E-01  6.4267E-01  4.9715E-01  1.7343E-01  3.9042E-01 -2.4580E-01
            6.9093E-02  7.7025E-01  2.6935E-01  1.0884E-01
 GRADIENT:   3.4207E+02 -4.4811E+02  2.9840E+02 -6.6717E-01  3.4611E+01  1.8057E+02 -3.9075E+01  1.8465E+02  4.4833E+01 -1.7286E+02
            -9.3673E+01  4.6310E+02 -1.4260E+03  7.8115E+01

0ITERATION NO.:   10    OBJECTIVE VALUE:  -554.616384972036       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      212
 NPARAMETR:  6.2344E+00  1.2011E+01  4.8310E-01  9.3695E-03 -1.4918E-03  4.0760E-01  9.5953E-01 -8.6657E-02  3.8451E-01 -3.2401E-01
            1.2252E-01  2.5315E+00  1.6387E+00  1.4608E+00
 PARAMETER:  9.5573E-02  3.1569E-01  1.0072E-01  6.7678E-01  2.3362E-02  5.2805E-01  9.8691E-01 -6.5203E-03  5.0659E-01 -3.5317E-01
            2.4158E-01  7.7122E-01  2.6755E-01  6.1448E-02
 GRADIENT:   3.8262E+02 -5.1454E+02  1.7749E+02  2.2941E+01 -2.6638E+01  1.3752E+02  4.0101E+01  1.8357E+02  3.6762E+01 -2.0128E+02
            -7.1191E+01  4.7710E+02 -1.4174E+03  4.4794E-01

0ITERATION NO.:   11    OBJECTIVE VALUE:  -566.780987147228       NO. OF FUNC. EVALS.:  27
 CUMULATIVE NO. OF FUNC. EVALS.:      239
 NPARAMETR:  6.2108E+00  1.1857E+01  4.8225E-01  1.0619E-02  1.6484E-03  4.1747E-01  1.0889E+00 -2.0135E-01  5.1698E-01 -3.5269E-01
            1.6346E-01  2.4761E+00  1.6228E+00  1.4798E+00
 PARAMETER:  9.1785E-02  3.0282E-01  9.8973E-02  7.5142E-01  1.8367E-01  5.3719E-01  1.0833E+00 -1.6301E-01  6.2709E-01 -4.0191E-01
            2.8584E-01  7.6017E-01  2.6790E-01  8.1228E-02
 GRADIENT:   3.5192E+02 -4.9041E+02  1.5791E+02  3.9063E+01  2.2199E+00  1.4054E+02  4.6106E+01  1.0955E+02  5.9623E+01 -1.2815E+02
            -9.7034E+01  3.9795E+02 -1.2487E+03  2.8824E+01

0ITERATION NO.:   12    OBJECTIVE VALUE:  -574.109371359085       NO. OF FUNC. EVALS.:  26
 CUMULATIVE NO. OF FUNC. EVALS.:      265
 NPARAMETR:  6.1214E+00  1.2095E+01  4.8082E-01  1.1001E-02  3.6624E-03  4.1027E-01  1.1367E+00 -2.3025E-01  5.7813E-01 -4.0429E-01
            2.2298E-01  2.4800E+00  1.6183E+00  1.4704E+00
 PARAMETER:  7.7276E-02  3.2268E-01  9.6007E-02  7.7424E-01  2.7958E-01  5.3053E-01  1.1183E+00 -2.0541E-01  6.8035E-01 -4.9457E-01
            3.4812E-01  7.6096E-01  2.6695E-01  7.9068E-02
 GRADIENT:   3.0846E+02 -4.5350E+02  5.7188E+01  4.1655E+01 -3.6076E+00  1.2758E+02  4.5828E+01  1.4270E+02  4.2977E+01 -1.9289E+02
            -7.2483E+01  3.9352E+02 -1.2736E+03  2.6245E+01

0ITERATION NO.:   13    OBJECTIVE VALUE:  -575.394602128977       NO. OF FUNC. EVALS.:  46
 CUMULATIVE NO. OF FUNC. EVALS.:      311             RESET HESSIAN, TYPE I
 NPARAMETR:  5.9350E+00  1.2232E+01  4.8041E-01  1.0816E-02  3.5651E-03  2.6668E-01  7.8413E-01 -3.1588E-01  4.7831E-01 -3.5799E-01
            3.8152E-01  2.3256E+00  1.6504E+00  1.5816E+00
 PARAMETER:  4.6361E-02  3.3394E-01  9.5155E-02  7.6317E-01  2.7506E-01  3.9234E-01  8.5064E-01 -3.3958E-01  5.9268E-01 -4.1112E-01
            5.0375E-01  7.2882E-01  2.8113E-01  7.4211E-02
 GRADIENT:  -1.4784E+02  1.8791E+03  2.8646E+02  2.1076E+02 -1.8091E+00  1.8179E+02  1.8573E+02  2.2909E+02 -1.9228E-01  9.3877E+02
            1.4150E+02 -4.0100E+02  5.5867E+02 -1.2113E+02

0ITERATION NO.:   14    OBJECTIVE VALUE:  -575.394602128977       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      336
 NPARAMETR:  5.9350E+00  1.2232E+01  4.8041E-01  1.0816E-02  3.5651E-03  2.6668E-01  7.8413E-01 -3.1588E-01  4.7831E-01 -3.5799E-01
            3.8152E-01  2.3256E+00  1.6504E+00  1.5816E+00
```

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 PARAMETER:  4.6361E-02  3.3394E-01  9.5155E-02  7.6317E-01  2.7506E-01  3.9234E-01  8.5064E-01 -3.3958E-01  5.9268E-01 -4.1112E-01
             5.0375E-01  7.2882E-01  2.8113E-01  7.4211E-02
 GRADIENT:  -5.0495E+02  4.7899E+02  7.4998E+01  4.5078E+01 -2.0103E+01 -1.0752E+02 -3.6415E+01 -2.3333E+02 -7.6122E+01  2.7254E+02
             6.9007E+01 -4.0100E+02  5.5867E+02 -1.2113E+02

0ITERATION NO.:   15    OBJECTIVE VALUE:  -608.895347142775       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      361
 NPARAMETR:  6.0665E+00  1.2177E+01  4.8040E-01  1.0817E-02  3.6765E-03  3.5267E-01  1.1164E+00 -2.3675E-01  5.8420E-01 -3.7512E-01
             3.2499E-01  2.3759E+00  1.6508E+00  1.5638E+00
 PARAMETER:  6.8275E-02  3.2946E-01  9.5117E-02  7.6323E-01  2.8024E-01  4.7635E-01  1.1035E+00 -2.1513E-01  6.8556E-01 -4.4134E-01
             4.4981E-01  7.3951E-01  2.7822E-01  8.1917E-02
 GRADIENT:   2.1793E+01 -1.0972E+02  4.2526E+01  4.1464E+01 -1.1569E+01  4.2636E+01  3.2913E+01  2.1190E+01 -3.5040E+00 -3.2372E+01
            -1.2497E+01  5.8012E-01 -3.5180E+02  1.4702E+01

0ITERATION NO.:   16    OBJECTIVE VALUE:  -615.428368693332       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      386
 NPARAMETR:  6.1242E+00  1.2305E+01  4.7983E-01  1.0207E-02  3.9934E-03  3.1234E-01  7.7765E-01 -2.0628E-01  6.7545E-01 -3.6461E-01
             3.5227E-01  2.3938E+00  1.6845E+00  1.6031E+00
 PARAMETER:  7.7739E-02  3.3989E-01  9.3940E-02  7.2677E-01  2.9491E-01  4.3745E-01  8.4546E-01 -1.7015E-01  7.6244E-01 -4.2271E-01
             4.7604E-01  7.4327E-01  2.8283E-01  8.2996E-02
 GRADIENT:  -3.2094E+01 -3.3403E+01  1.1329E+01  3.9882E+01 -1.3379E+01  2.2197E+01 -2.9305E-01  8.4860E+00  5.6793E+00 -1.1735E+01
            -1.4723E+01 -2.5121E+01 -2.8305E+02  1.7213E+01

0ITERATION NO.:   17    OBJECTIVE VALUE:  -618.097330619074       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      411
 NPARAMETR:  6.2043E+00  1.2356E+01  4.7944E-01  9.3349E-03  4.4362E-03  2.5869E-01  7.0608E-01 -1.9422E-01  6.9171E-01 -3.6288E-01
             4.1326E-01  2.4206E+00  1.7279E+00  1.6483E+00
 PARAMETER:  9.0732E-02  3.4404E-01  9.3134E-02  6.7471E-01  3.1522E-01  3.8433E-01  7.8756E-01 -1.5275E-01  7.7586E-01 -4.1966E-01
             5.3337E-01  7.4883E-01  2.8850E-01  7.9615E-02
 GRADIENT:  -8.6575E+01  1.6314E+01 -1.1817E+01  2.7350E+01 -1.4750E+01 -1.6515E+01 -1.4384E+01  1.1639E+01 -2.1480E+01 -1.6527E+01
             1.2046E+01 -1.0948E+02  4.1731E+00 -4.7930E+00

0ITERATION NO.:   18    OBJECTIVE VALUE:  -620.021188720949       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      436
 NPARAMETR:  6.2667E+00  1.2382E+01  4.7928E-01  8.7412E-03  4.7734E-03  2.3617E-01  6.9578E-01 -1.9970E-01  7.3947E-01 -3.5759E-01
             4.2815E-01  2.4511E+00  1.7565E+00  1.6722E+00
 PARAMETER:  1.0073E-01  3.4613E-01  9.2788E-02  6.3926E-01  3.3057E-01  3.6153E-01  7.7911E-01 -1.6062E-01  8.1485E-01 -4.1041E-01
             5.4711E-01  7.5509E-01  2.9145E-01  7.7888E-02
 GRADIENT:  -9.1326E+01  2.6210E+01 -2.2692E+01  1.7768E+01 -1.6006E+01 -3.0699E+01 -1.3955E+01 -4.4840E+00 -1.3857E+01  4.8881E+00
             6.0237E+00 -9.9881E+01  7.0493E+00 -7.2346E+00

0ITERATION NO.:   19    OBJECTIVE VALUE:  -624.613807571676       NO. OF FUNC. EVALS.:  44
 CUMULATIVE NO. OF FUNC. EVALS.:      480             RESET HESSIAN, TYPE I
 NPARAMETR:  6.2622E+00  1.2323E+01  4.7893E-01  8.0572E-03  1.6918E-02  2.6334E-01  7.4637E-01 -1.9832E-01  7.7054E-01 -3.6047E-01
             4.1958E-01  2.4365E+00  1.7589E+00  1.6845E+00
 PARAMETER:  1.0001E-01  3.4134E-01  9.2059E-02  5.9838E-01  8.2641E-01  3.8900E-01  8.2033E-01 -1.5863E-01  8.3988E-01 -4.1545E-01
             5.3921E-01  7.5211E-01  2.9273E-01  7.9419E-02
 GRADIENT:   3.7692E+02  1.3880E+03  1.5255E+02  1.5881E+02  8.2925E+01  3.0416E+02  2.1884E+02  2.4545E+02  1.0729E+02  6.6446E+02
             6.7109E+01 -1.0230E+02  9.6798E+00  1.0591E+01

0ITERATION NO.:   20    OBJECTIVE VALUE:  -624.613807571676       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      505
 NPARAMETR:  6.2622E+00  1.2323E+01  4.7893E-01  8.0572E-03  1.6918E-02  2.6334E-01  7.4637E-01 -1.9832E-01  7.7054E-01 -3.6047E-01
             4.1958E-01  2.4365E+00  1.7589E+00  1.6845E+00
 PARAMETER:  1.0001E-01  3.4134E-01  9.2059E-02  5.9838E-01  8.2641E-01  3.8900E-01  8.2033E-01 -1.5863E-01  8.3988E-01 -4.1545E-01
             5.3921E-01  7.5211E-01  2.9273E-01  7.9419E-02
 GRADIENT:   6.1753E+00 -8.5453E+01 -6.0264E+01  2.3211E+01  1.4565E+01  9.3798E+00 -4.2718E+00  2.9576E+01  4.0659E+00 -3.4474E+01
            -1.6034E+01 -1.0230E+02  9.6798E+00  1.0591E+01

0ITERATION NO.:   21    OBJECTIVE VALUE:  -626.634252670872       NO. OF FUNC. EVALS.:  25
 CUMULATIVE NO. OF FUNC. EVALS.:      530
 NPARAMETR:  6.2627E+00  1.2356E+01  4.7903E-01  7.5895E-03  1.2051E-02  2.7073E-01  7.9120E-01 -2.0013E-01  7.7731E-01 -3.5453E-01
             4.3328E-01  2.4489E+00  1.7634E+00  1.6844E+00
 PARAMETER:  1.0010E-01  3.4409E-01  9.2267E-02  5.7038E-01  6.3849E-01  3.9639E-01  8.5627E-01 -1.6124E-01  8.4530E-01 -4.0509E-01
             5.5181E-01  7.5465E-01  2.9271E-01  7.9391E-02
 GRADIENT:  -1.7156E+01 -5.2788E+01 -4.8964E+01  9.1972E+00 -1.6497E+00  3.6153E-01  3.9890E+00  1.2940E+01  2.1600E+00 -1.1862E+01
            -1.0981E+01 -7.9902E+01 -3.9527E+01  1.2649E+01

0ITERATION NO.:   22    OBJECTIVE VALUE:  -626.634252670872       NO. OF FUNC. EVALS.:  30
 CUMULATIVE NO. OF FUNC. EVALS.:      560
 NPARAMETR:  6.2627E+00  1.2356E+01  4.7903E-01  7.5895E-03  1.2051E-02  2.7073E-01  7.9120E-01 -2.0013E-01  7.7731E-01 -3.5453E-01
             4.3328E-01  2.4489E+00  1.7634E+00  1.6844E+00
 PARAMETER:  1.0010E-01  3.4409E-01  9.2267E-02  5.7038E-01  6.3849E-01  3.9639E-01  8.5627E-01 -1.6124E-01  8.4530E-01 -4.0509E-01
             5.5181E-01  7.5465E-01  2.9271E-01  7.9391E-02
 GRADIENT:   2.5502E+01  1.2615E+02 -4.8719E+01  5.9412E-01 -1.8171E+00  4.3108E+00 -3.0264E+00  1.9451E+01 -4.0708E+00 -4.9810E-01
            -6.0574E+00  1.0753E+02 -2.2209E+02 -1.3227E+02

 #TERM:
0MINIMIZATION SUCCESSFUL
 HOWEVER, PROBLEMS OCCURRED WITH THE MINIMIZATION.
 REGARD THE RESULTS OF THE ESTIMATION STEP CAREFULLY, AND ACCEPT THEM ONLY
 AFTER CHECKING THAT THE COVARIANCE STEP PRODUCES REASONABLE OUTPUT.
 NO. OF FUNCTION EVALUATIONS USED:      560
 NO. OF SIG. DIGITS IN FINAL EST.:  1.0

 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

 ETABAR:         1.0923E-01  4.6877E-02
 SE:             2.2869E-02  1.7276E-02
 N:                    1825        1825
```

```
 P VAL.:         1.7872E-06  6.6593E-03

 ETAshrink(%):   3.7554E+01  4.3118E+01
 EBVshrink(%):   3.5812E+01  3.6812E+01
 EPSshrink(%):   8.2715E+00

 #TERE:
 Elapsed estimation time in seconds:   154.39
0R MATRIX ALGORITHMICALLY SINGULAR
 AND ALGORITHMICALLY NON-POSITIVE-SEMIDEFINITE
0R MATRIX IS OUTPUT 0COVARIANCE STEP ABORTED --->  BOOTSTRAPPING USED TO DERIVE 90% CI OF PARAMETER ESTIMATES

 Elapsed covariance time in seconds:   213.84
1


 ********************************************************************************************************************
 ********************                                                                        ********************
 ********************              FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION       ********************
 #OBJT:***************                      MINIMUM VALUE OF OBJECTIVE FUNCTION               ********************
 ********************                                                                        ********************
 ********************************************************************************************************************


 #OBJV:*****************************************     -626.634       ***************************************************
1
 ********************************************************************************************************************
 ********************                                                                        ********************
 ********************              FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION       ********************
 ********************                           FINAL PARAMETER ESTIMATE                     ********************
 ********************                                                                        ********************
 ********************************************************************************************************************


 THETA - VECTOR OF FIXED EFFECTS PARAMETERS   *********

        TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH 9      TH10      TH11

        6.26E+00  1.24E+01  4.79E-01  7.59E-03  1.21E-02  2.71E-01  7.91E-01 -2.00E-01  7.77E-01 -3.55E-01  4.33E-01


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

            ETA1      ETA2

 ETA1
+        2.45E+00

 ETA2
+        1.76E+00  1.68E+00


 SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****

            EPS1

 EPS1
+        1.00E+00

1


 OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS  *******

            ETA1      ETA2

 ETA1
+        1.56E+00

 ETA2
+        8.68E-01  1.30E+00


 SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS  ***

            EPS1

 EPS1
+        1.00E+00


1
 ********************************************************************************************************************
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********************                                                                                    ********************
********************              FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION                    ********************
********************                                   R MATRIX                                         ********************
********************                                                                                    ********************
************************************************************************************************************************


           TH 1      TH 2      TH 3      TH 4      TH 5      TH 6      TH 7      TH 8      TH 9      TH10      TH11      OM11
            OM12      OM22      SG11

 TH 1
+       1.98E+02

 TH 2
+      -2.68E+01  2.49E+01

 TH 3
+       1.08E+03  2.26E+01  9.35E+04

 TH 4
+       1.58E+03  2.35E+02 -1.16E+05  6.26E+05

 TH 5
+       1.41E+03 -1.11E+02 -1.62E+03 -1.69E+04  4.85E+04

 TH 6
+       6.94E+01 -3.68E+01 -1.33E+02  2.36E+03  5.42E+02  1.19E+03

 TH 7
+       1.79E+01 -9.02E+00 -3.76E+01 -7.70E+02 -1.15E+02  6.65E-12  6.39E+01

 TH 8
+       3.13E+02 -1.05E+02 -4.15E+02 -1.09E+04  4.67E+02  1.81E+02  5.31E+01  2.09E+03

 TH 9
+       2.36E+01 -1.23E+01  6.67E+00  2.99E+02  5.03E+01  4.41E+01  1.34E+01  0.00E+00  7.98E+01

 TH10
+      -2.02E+02  1.42E+02  6.13E+02  5.07E+03 -5.62E+02 -3.61E+02 -7.07E+01 -1.97E+03 -5.76E-12  2.71E+03

 TH11
+      -2.52E+01  1.69E+01 -1.10E+02 -9.29E+02 -2.49E+02 -5.71E+01 -9.79E+00  0.00E+00 -1.06E+02  0.00E+00  1.50E+02

 OM11
+       7.11E+01 -1.97E+01  1.05E+03  2.05E+03  1.16E+03  9.59E+01  3.20E+01  2.49E+02  3.74E+01 -2.29E+02  1.11E+01  1.15E+03

 OM12
+      -1.01E+02  2.01E+01 -2.04E+03 -6.16E+03 -2.00E+03 -1.15E+02 -5.38E+01 -2.94E+02 -4.49E+01  2.37E+02 -4.95E+01 -2.36E+03
         5.27E+03

 OM22
+       3.02E+01 -3.44E+00  1.19E+03  3.50E+03  6.82E+02  2.22E+01  2.00E+01  4.42E+01  5.68E+00 -3.70E+01  3.07E+01  1.21E+03
        -2.93E+03  1.84E+03

 SG11
+       ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... ......... .........
         ......... ......... .........

 #CPUT: Total CPU Time in Seconds,      191.980
```