Supplementary Material 3

Influence of baseline characteristics and maintenance therapy on symptom control, reliever use and exacerbation risk: lessons learned from a modelling study in moderate–severe asthma

Pierluigi Paggiaro[1], Gabriel Garcia[2], Nicolas Roche[3,4], Manish Verma[5], Shalini Girotra[6], Maximilian Plank[7,8], Sean Oosterholt[9], Janna K. Duong[10], Anurita Majumdar[6], Oscar Della Pasqua[9,11]

[1]University of Pisa, Pisa, Italy; [2]Respiratory Research Center, CEPIR, La Plata, Argentina; [3]Hôpital Cochin, Paris, France; [4]Université Paris Cité, Paris, France; [5]GSK, Mumbai, India; [6]GSK, Singapore; [7]GSK, Munich, Germany; [8]University of Newcastle, Newcastle, Australia; [9]GSK, Brentford, UK; [10]GSK, Sydney, Australia; [11]University College London, London, UK

Corresponding author:

Prof. Oscar Della Pasqua
Address: 79 New Oxford St, London WC1A 1DG, UK
E-mail: odp72514@gsk.com

Development and evaluation of a time to event model describing the time to the first exacerbation in moderate-severe asthma.

Methods

Data source: The data used for this analysis were obtained from nine clinical trials (HZA106829, HZA106837, HZA106839, HZA113091, HZA115150, SAM40040, HZA116492, SAM40056, 201378). The selection of these data was based on the requirement to have accurate individual patient exacerbation event records, clinical, and demographic baseline details (**Table S3_1**). Exacerbation definitions for each study can be found in the Appendix **Table S3_5.** In order to account for seasonal variation in asthma symptoms and exacerbations, studies were included in which treatment lasted for at least 6 months. For studies where ACT was measured instead of ACQ-5, the scores were converted from ACT to ACQ-5. Finally, the analysis population was only to include patients aged 18 years or older with accurate treatment records. Patients in studies that allowed a change of therapy were kept in the data set up to the point at which their treatment switched; this only applied to changes in drug, not for changes in dose or frequency. It includes 1144 observed exacerbation events (first only) from 6765 patients who were randomised to receive FF (n = 1063), FF/VI (n = 4328) or BUD/FOR (n = 1374) over a period of up to 1 year. All patients enrolled into the selected clinical trials have given informed consent for participation. The terms of consent include the scope of the investigation presented here.

Analysis population: The mean age was 47.3 years old with a range of 18.0 – 91.0 years old. The majority have never smoked (58.1%). An overview of the baseline demographic and clinical characteristics of the pooled patient population included in the analysis is summarised in **Table S3_2**. Histograms describing the distribution of relevant baseline clinical and demographic characteristics were used to assess the homogeneity of the patient population across the different studies. A summary of the distributions stratified by study and treatment arm is shown in the Appendix **Figures S3_11** and **S3_12**, respectively.

Given that the individual studies did not record the same baseline variables, individual covariate values were imputed where missing (60.5% baseline ACQ-5, 0.6% baseline BMI, 11.5% smoking status, 33.3% FEV_{1p}, 72.2% PEF, 53.5% asthma duration and 89.7% previous use of inhaled corticosteroids), where appropriate. For continuous covariates, missing values for an individual patient were imputed as the median value for the study population while for categorical covariates the most frequent value was used. In contrast, missing information on the treatment initiation and ending were imputed based on protocol treatment initiation and ending (i.e., relative to reported study visit dates and times). Patients were excluded if details on the treatment received were not available or the date and time of treatment initiation and ending could not be imputed. Similarly, individual records were excluded if missing visit dates and times could not be imputed based on protocol visit dates and times. Values were also to be excluded from the analysis based on inconsistency or a documented error. The absence of the clinical event of interest (i.e., exacerbation) was not treated as missing data. If exacerbations did not occur within the observation window defined in the original study protocol, the information from these patients was right censored to the maximum time or duration of the study.

Table S3_1: Overview of the studies identified for the proposed model-based meta-analysis. Protocol title is shown along with details regarding treatment type and duration, device characteristics and the purpose of the study data during model building and validation procedures.

Study	Name	Study title	Duration	N (ITT)	Treatment arms	Device
HZA106829		HZA106829: A Randomised, Double-Blind, Parallel Group Multicentre Study of **FF/VI** Inhalation Powder, **FF** Inhalation Powder Alone, and **FP** alone in the treatment of persistent asthma in adults and adolescents. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=106829	24 weeks	197	FF/VI 200 mcg/25 mcg OD	NDPI + Placebo DISKUS/ACCU
				194	FF 200 mcg OD	NDPI + Placebo DISKUS/ACCU
				195	FP 500 mcg BD	DISKUS/ACCUH+ placebo NDPI
HZA106837		A long-term, Randomized, Double-blind, Parallel Group study of **FF/VI** Inhalation Powder OD and **FF** Inhalation Powder Once-Daily in subjects with asthma. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=106837	≥24 weeks ≤76 weeks	1009	FF/VI 100/25 mcg OD	NDPI
				1010	FF 100 mcg OD	NDPI
HZA106839		A Randomized, Double-Blind, Double Dummy, Active Comparator, Parallel Group, Multicenter study to evaluate the safety of OD **FF/VI** Inhalation Powder for 52 weeks in adolescent and adult subjects with asthma. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=106839	52 weeks	201	FF/VI 100/25 mcg OD	NDPI + Placebo DISKUS/ACCU
				202	FF/VI 200/25 mcg OD	NDPI + Placebo DISKUS/ACCU
				100	FP 500 mcg BD	DISKUS/ACCU + Placebo NDPI
HZA113091		A randomised, double-blind, double-dummy, parallel-group, multicentre study to assess efficacy and safety **of FF/VI** Inhalation Powder and **FP/SALM** Inhalation Powder in the treatment of persistent asthma in adults and adolescents. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=113091	24 weeks	403	FF/VI 100/25 mcg o.d.	NDPI + Placebo ACCU/DISKUS
				403	FP/SALM 250/50 mcg BID	ACCU/DISKUS + Placebo NDPI
HZA115150	SLS	A 12-month, open label, randomised, effectiveness study to evaluate **FF/VI** Inhalation Powder delivered once daily via a novel dry powder inhaler compared with **usual maintenance therapy** in subjects with asthma. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=115150	52 weeks	2114	FF/VI 100/25 or 200/25 mcg	Ellipta inhaler
				2119	Usual treatments (FP/SALM , BUD/FORM, FP)	NA
SAM40040		A 24 week, randomised, double-dummy, double-blind, parallel group study to compare the occurrence of exacerbations between **SERETIDE DISKUS** 50/250 mcg 1 inhalation BD and **FORM/BUD** Breath-Actuated Dry Powder Inhaler 4.5/160 mcg 2 inhalations BD in subjects with moderate to severe asthma. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=SAM40040	24 weeks	694	FP/SALM 250/50 mcg BID	DISKUS inhaler
				697	BUD/FORM 160/4.5 mcg BID	BADPI
HZA116492		A 6-month, open label, randomised, efficacy study to evaluate **FF/VI** inhalation powder delivered OD via the dry powder inhaler Ellipta compared with **usual ICS/LABA** maintenance therapy delivered by dry powder inhaler in subjects with persistent asthma More details at: https://www.gsk-studyregister.com/en/trial-details/?id=116492	24 weeks	210	FF/VI 100/25 mcg or 200/25 mcg OD	Ellipta
				210	ICS/LABAs[1]	DPI DISKUS or DPI Turbuhaler
SAM40056	CONCEPT	A randomised, double-blind, double-dummy, 52-week, parallel-group study of a standard dosing regimen with **SALM/FP** combination 50/250 mcg bid (via the DISKUS™ /ACCUHALER™ Inhaler) versus a symptom-driven, variable dosing regimen with **FORM/BUD** combination 4.5/160 mcg (via a breath-actuated dry powder reservoir inhaler) in adult asthmatics. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=SAM40056	52 weeks	344	FP/SALM 250/50 mcg BID (Varying regimen)[2]	DISKUS Inhaler + Placebo BADPI
				344	BUD/FORM 160/4.5 mcg BID (Varying regimen)[2]	BADPI + Placebo DISKUS

201378		A randomized, double-blind, double-dummy, parallel group, multicentre study of OD **FF/VI** 100/25 inhalation powder, BID **FP/SALM** 250/50 inhalation powder, and BID **FP** 250 inhalation powder in the treatment of persistent asthma in adults and adolescents already adequately controlled on BID ICS and LABA. More details at: https://www.gsk-studyregister.com/en/trial-details/?id=201378	24 weeks	504	FF/VI 100/25 OD	RELVAR ELLIPTA
				501	FP/SALM 250/50 BID	DISKUS/ACCUHALER
				499	FP 250 BID	DISKUS/ACCUHALER

Time-to-event model development: A previously developed time-to-event was used as the basis for the modelling development. Previously estimated covariate effects were used as priors ($PRIOR routine in NONMEM) for the current analysis. Priors were not used for the treatment effects. Details on the assumptions supporting this investigation and implications for model development are presented in the Appendix **Table S3_6**.

The available data were randomly split into two subsets to ensure evaluation of the predictive performance of the model. An overview of the data sets is shown **Figure S3_1**. Data sets for internal validation were based on a random selection of 30% of subjects from the total population pool. Concomitant medication and co-morbidities or concurrent medical conditions were not accounted for as covariates. The rationale for the exclusion of these variables from the covariate analysis is based on the fact that concomitant drugs and concurrent conditions allowed in the protocols were not expected to have a direct effect on the risk of exacerbation.

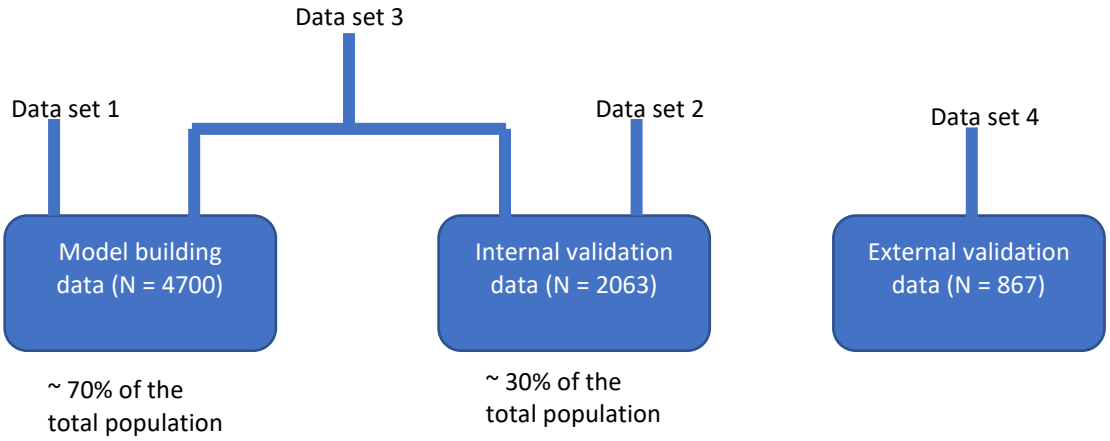


Figure S3_1: Diagram describing the different data sets used for model building (data set 1), internal validation (data set 2), and final data analysis (data set 3, N = 6763). Data set 3 comprises the total patient population from studies HZA106829, HZA106837, HZA106839, HZA113091, HZA115150, SAM40040, HZA116492, SAM40056, 201378 used for this analysis. External validation was aimed at the assessment of model consistency and estimation of drug-specific differences. Therefore, data set 4 included data from asthma patients enrolled into study HZA115150, who were treated with either beclomethasone and formoterol combination therapy or beclomethasone monotherapy. Data from these patients were not used for model development or internal validation.

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

To ensure appropriate interpretation of the results, final model estimates were presented as hazard ratios. For continuous covariates, the hazard ratio (**Eq. 1**) was calculated as the exponent of the coefficient of each parameter in the model. The hazard ratio for exacerbation was defined as follows:

$$\frac{e^{\beta(x+1)}}{e^{\beta x}} = e^{\beta} \qquad \textbf{(Eq. 1)}$$

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

For categorical variables the hazard ratio (**Eq. 2**) for an individual in any group or category is relative to an individual in the first group or category. It is defined by the exponential of α_j, where the parameter α is the logarithm of the relative hazard. The hazard function was calculated as follows:

$$h_j(t) = e^{\alpha_j} \cdot h_0(t) \qquad \textbf{(Eq. 2)}$$

Given that the use of a placebo-controlled arm is unethical in this type of trial, data from patients randomised to FF monotherapy were used as reference group for the purposes of estimating the effect of treatment on the hazard ratio. Furthermore, as interindividual differences in the therapeutic dose levels achieved during titration and maintenance phases of the trials are expected to have minor effect on exacerbation risk, dose levels were not considered as a separate covariate factor. An overview of the modelling workflow is depicted below in **Figure S3_2.**

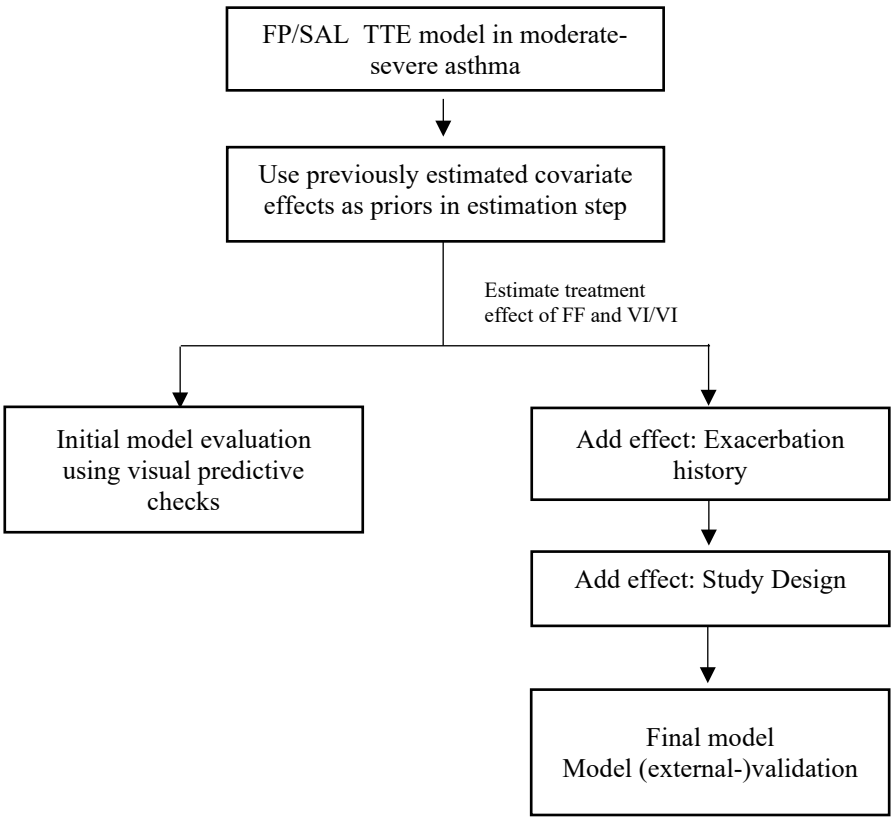


Figure S3_2: Flowchart of the steps for model development and validation.

Model evaluation and predictive performance: Comparison of hierarchical models was based on the likelihood ratio test and standard error of the parameter estimates. Covariate model building was conducted in a stepwise manner and the likelihood ratio was used to test the effect of each covariate on model parameters with a significance level of 0.01. In the stepwise forward addition procedure, each covariate was individually included in the base model and if the reduction in the objective function value (OFV) between the base and more complex model was $\geq$3.84 (χ^2<0.5 for 1 degree of freedom, df) then the covariate was considered statistically significant. All significant covariates were then added simultaneously into a full model. Subsequently, each covariate was independently removed from the full model. If the increase in the OFV was $\geq$6.64 (χ^2<0.01 for 1 df), the covariate was considered to be significantly correlated with the model parameter and retained in the final model. It is worth mentioning that this analysis was implemented under the assumption that there is no statistically significant interaction between baseline covariates and treatment effect. In fact, there is no reason to believe that pharmacological effects would depend on or correlate with any of the baseline covariates included in the model.

Internal validation procedures were implemented by splitting the full data set into an index data set (comprising ~70% of the data) and a reference data set (comprising of the remaining portion of the data). Individual empirical Bayes estimates obtained from the index data set were then used to predict the reference data. The average relative error and average relative variance (mean square error) were used to assess the precision of parameter estimates and robustness of the model obtained with the model building data set.

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

Modelling development and evaluation were implemented in NONMEM v.7.3 using the Laplacian estimation method. The analysis was run on the Model-based Analyses Platform (MAP), a validated analysis platform entirely hosted on Amazon Web Services (AWS). The platform runs NONMEM 7.3 through gFortran compiler and Perl-speaks-NONMEM (PsN) 4.6.0. All required data manipulation, including graphical and statistical summaries performed in R (version 4.1.3).

Results

Demographics and baseline characteristics: The age of the subjects across all studies included in the current analysis ranged from 18 to 91 years. In the subset of patients who have had symptom control level and airway function measured at baseline, the median ACQ-5 score (including ACT to ACQ-5 converted scores) and FEV_{1p} were 1.73 and 75.1%, respectively. Immediately prior to treatment

initiation, 28.8% of the patients had been diagnosed with asthma between >1 and ≤20 years, whilst 11% had a history of asthma for more than 25 years. A summary of demographic and clinical baseline characteristics stratified by treatment is presented in **Table S3_2**.

No correlations or interactions were found between demographic and baseline clinical characteristics, other than those due to the known co-linearity between variables for instance height and FEV_1 (See **Figure S3_3**).

Time-to-event model building and validation: An exponential hazard model was found to best describe the time-to-first exacerbation in the overall patient population and across subgroups following stratification by treatment and baseline covariates. The final model consisted of a baseline hazard term and the associated covariate coefficients. All parameters were well estimated with good precision (RSE ≤40%) and without statistically significant correlations between parameters.

At completion of the stepwise forward inclusion and backward exclusion procedures, the following additional baseline covariates showed statistical significance (χ^2<0.01) and were included into the final model, namely: study type (efficacy or safety) and study design (run-in period). All covariates were found to significantly contribute to the underlying base hazard, independently of pharmacological treatment effect.

Table S3_2: Demographic and clinical baseline characteristics of the patients included in this analysis stratified by treatment. Summary statistics include means (standard deviations) and medians (range) along with the number of patients with missing values in each category.

	BUD/FOR (N=1374)	FF (N=1063)	FF/VI (N=4328)	Overall (N=6765)
Age (y)				
Mean (SD)	46.7 (14.9)	46.3 (13.7)	47.8 (15.0)	47.3 (14.8)
Median [Min, Max]	47.0 [18.0,88.0]	48.0 [18.0, 79.0]	48.0 [18.0, 91.0]	48.0 [18.0, 91.0]
Weight (kg)				
Mean (SD)	78.6 (18.4)	77.6 (19.1)	79.9 (19.4)	79.3 (19.2)
Median [Min, Max]	77.0 [37.0, 197]	75.0 [38.0, 166]	78.0 [32.0, 218]	77.0 [32.0, 218]
Missing	4 (0.3%)	0 (0%)	21 (0.5%)	25 (0.4%)
Height (cm)				
Mean (SD)	168 (9.95)	165 (10.2)	166 (10.1)	166 (10.1)
Median [Min, Max]	167 [131, 204]	164 [140, 201]	165 [130, 196]	165 [130, 204]
Missing	6 (0.4%)	0 (0%)	27 (0.6%)	33 (0.5%)
BMI (Kg/m2)				
Mean (SD)	28.0 (6.20)	28.4 (6.09)	28.9 (6.44)	28.7 (6.35)
Median [Min, Max]	27.0 [15.8, 69.4]	27.4 [17.0, 55.8]	27.9 [14.8, 67.5]	27.6 [14.8, 69.4]
Missing	6 (0.4%)	0 (0%)	32 (0.7%)	38 (0.6%)
Baseline ACQ-5				
Mean (SD)	1.95 (0.928)	2.07 (0.891)	2.07 (0.898)	2.03 (0.908)
Median [Min, Max]	2.00 [0, 5.00]	2.00 [0, 5.00]	2.00 [0, 5.60]	2.00 [0, 5.60]
Missing	432 (31.4%)	187 (17.6%)	3471 (80.2%)	4090 (60.5%)
Baseline qACQ-5*				
Mean (SD)	1.83 (0.941)	2.05 (0.870)	1.60 (0.943)	1.73 (0.946)
Median [Min, Max]	1.80 [0, 5.00]	2.00 [0, 5.00]	1.45 [0, 6.00]	1.64 [0, 6.00]
Missing	99 (7.2%)	0 (0%)	811 (18.7%)	910 (13.5%)
Baseline ACT				
Mean (SD)	16.4 (4.34)	14.0 (3.45)	16.6 (4.33)	16.4 (4.32)
Median [Min, Max]	17.0 [6.00, 25.0]	14.0 [7.00, 25.0]	17.0 [5.00, 25.0]	17.0 [5.00, 25.0]
Missing	1041 (75.8%)	876 (82.4%)	1668 (38.5%)	3585 (53.0%)
Baseline AQLQ				

	BUD/FOR (N=1374)	FF (N=1063)	FF/VI (N=4328)	Overall (N=6765)
Mean (SD)	4.94 (1.08)	4.48 (0.992)	5.22 (1.21)	5.14 (1.19)
Median [Min, Max]	5.03 [1.50, 6.94]	4.47 [1.97, 6.53]	5.38 [1.13, 7.00]	5.27 [1.13, 7.00]
Missing	754 (54.9%)	880 (82.8%)	1215 (28.1%)	2849 (42.1%)
Baseline FEV1				
Mean (SD)	2.44 (0.804)	2.16 (0.649)	2.32 (0.751)	2.31 (0.747)
Median [Min, Max]	2.35 [0.75, 5.56]	2.04 [0.75, 4.55]	2.20 [0.70, 5.81]	2.19 [0.70, 5.81]
Missing	335 (24.4%)	1 (0.1%)	1918 (44.3%)	2254 (33.3%)
Baseline FEV1P				
Mean (SD)	78.7 (16.5)	70.2 (11.0)	75.7 (15.4)	75.1 (15.0)
Median [Min, Max]	78.7 [30.8, 143]	70.8 [40.1, 92.9]	75.3 [34.0, 155]	74.7 [30.8, 155]
Missing	335 (24.4%)	1 (0.1%)	1918 (44.3%)	2254 (33.3%)
Baseline PEF				
Mean (SD)	378 (108)	334 (124)	386 (122)	377 (116)
Median [Min, Max]	372 [138, 770]	319 [81.3, 773]	369 [79.7, 833]	365 [79.7, 833]
Missing	333 (24.2%)	876 (82.4%)	3675 (84.9%)	4884 (72.2%)
Baseline Feno				
Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Median [Min, Max]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]
Missing	1374 (100%)	1063 (100%)	4328 (100%)	6765 (100%)
Sex				
Male	825 (60.0%)	737 (69.3%)	2735 (63.2%)	4297 (63.5%)
Female	549 (40.0%)	326 (30.7%)	1593 (36.8%)	2468 (36.5%)
Baseline Smoking (N/F/C)				
Never smoked	836 (60.8%)	736 (69.2%)	2358 (54.5%)	3930 (58.1%)
Former smoker	377 (27.4%)	140 (13.2%)	984 (22.7%)	1501 (22.2%)
Current smoker	159 (11.6%)	0 (0%)	400 (9.2%)	559 (8.3%)
Missing	2 (0.1%)	187 (17.6%)	586 (13.5%)	775 (11.5%)
Previous Inhaled Corticosteroids				
< 6 months	45 (3.3%)	0 (0%)	0 (0%)	45 (0.7%)
>= 6 months to < 1 year	57 (4.1%)	0 (0%)	0 (0%)	57 (0.8%)
>= 1 to 5 years	230 (16.7%)	0 (0%)	0 (0%)	230 (3.4%)
>= 5 to 10 years	184 (13.4%)	0 (0%)	0 (0%)	184 (2.7%)

	BUD/FOR (N=1374)	FF (N=1063)	FF/VI (N=4328)	Overall (N=6765)
>= 10 to 15 years	98 (7.1%)	0 (0%)	0 (0%)	98 (1.4%)
>= 15 to 20 years	48 (3.5%)	0 (0%)	0 (0%)	48 (0.7%)
>= 20 to 25 years	17 (1.2%)	0 (0%)	0 (0%)	17 (0.3%)
>= 25 years	18 (1.3%)	0 (0%)	0 (0%)	18 (0.3%)
Missing	677 (49.3%)	1063 (100%)	4328 (100%)	6068 (89.7%)
Asthma Duration				
< 6 months	2 (0.1%)	0 (0%)	3 (0.1%)	5 (0.1%)
>= 6 months to < 1 year	38 (2.8%)	62 (5.8%)	52 (1.2%)	152 (2.2%)
>= 1 to 5 years	200 (14.6%)	148 (13.9%)	187 (4.3%)	535 (7.9%)
>= 5 to 10 years	209 (15.2%)	171 (16.1%)	237 (5.5%)	617 (9.1%)
>= 10 to 15 years	153 (11.1%)	119 (11.2%)	168 (3.9%)	440 (6.5%)
>= 15 to 20 years	118 (8.6%)	99 (9.3%)	140 (3.2%)	357 (5.3%)
>= 20 to 25 years	102 (7.4%)	77 (7.2%)	117 (2.7%)	296 (4.4%)
>= 25 years	219 (15.9%)	200 (18.8%)	325 (7.5%)	744 (11.0%)
Missing	333 (24.2%)	187 (17.6%)	3099 (71.6%)	3619 (53.5%)
Exacerbation History				
Zero previous exacerbations	752 (54.7%)	182 (17.1%)	1022 (23.6%)	1956 (28.9%)
One previous exacerbation	168 (12.2%)	5 (0.5%)	170 (3.9%)	343 (5.1%)
More than one previous exacerbation	121 (8.8%)	0 (0%)	10 (0.2%)	131 (1.9%)
Missing	333 (24.2%)	876 (82.4%)	3126 (72.2%)	4335 (64.1%)

Baseline covariates were parameterised as proportional terms to base hazard parameter, i.e., that estimated for patients receiving FF monotherapy. This approach was necessary due to the ethical limitations associated with the use of a placebo arm for at least 6 months. It can be assumed that model structure and imputed covariate effects associated with the base hazard are sufficiently precise to disentangle the contribution of patient- and disease-related factors from the effect of the intervention across the different treatment arms. Treatment-specific terms were added to the model to characterise the changes associated with combination therapy. They were all parameterised as proportional to the base hazard rate. Final parameter estimates are summarised in **Table S3_3**.

The final estimates for base hazard rates correspond to an incidence of 14.4% events per year. The effect of parameter estimates for baseline covariate factors and treatments shown in **Table S3_3** can be interpreted as follows: starting from the median value of the covariate factor an increase or decrease of 1 unit in the covariate results, respectively in a percentage increase or reduction in the

baseline hazard of the magnitude of the parameter point estimate. For instance, for every unit increase (i.e., kg/m^2) in baseline BMI relative to the median BMI of 28.7 kg/m^2, the instantaneous risk of an exacerbation increases by 2.66%. Hence, a patient with baseline BMI value of 33.7 (i.e., 5 units higher than the median value) will have an instantaneous risk of exacerbation that is 13.3% higher than a patient with median BMI of 28.7 kg/m^2. Similarly, for every unit increase in ACQ-5, the instantaneous risk of an exacerbation increases by 16.8% whereas a unit reduction in FEV_{1p} increases the instantaneous risk by approximately 1.06% relative to a median FEV_{1p} of 74.7%. Interestingly, smoking is associated with an increase of 39.4% in the instantaneous risk, as compared to a patient who never smoked, and females were found to have a 32.4% higher risk of exacerbation relative to male patients. It is also worth mentioning that age and geographical ancestry were not associated with statistically significant differences in the risk of exacerbation. Given the wide age range and geographical ancestry of the patients included in this analysis, this may be explained by the correlation between age and FEV_{1p} and other baseline covariates, such as BMI.

In a comparable manner, the use of combination therapy FF/VI was found to significantly reduce the base hazard rate. These results mean that at any point in time, the risk of exacerbation is 22.9% lower patients receiving FF/VI, as compared to patients receiving FF alone. This effect was independent of the actual base hazard rate, i.e., irrespective of the contribution of baseline patient characteristics to the instantaneous risk of exacerbation.

The VPCs (**Figure S3_4**) showed that the observed TTE rate fell within the 95% confidence intervals of the simulated values, as depicted by the shaded area. Based on the VPCs, the final model was deemed to have acceptable predictive performance to describe the time-to-first exacerbation in this pool of patients with moderate or severe asthma symptoms. Overall model performance was also evaluated by comparing predicted and observed events after stratification by the selected baseline covariates. Of interest is how symptom control level at baseline is associated with the risk of exacerbation (**Figure S3_5**). An assessment of the generalisability of the model and accuracy of the estimates of the effect of clinical and demographic baseline characteristics was performed using an external validation data set. A sensitivity analysis showing the impact of missing covariates on parameter estimates can be found in the Appendix **Table S3_2.**

Relationship between symptom control level and other clinical and demographic baseline covariates and the risk and incidence of exacerbations: The effect of variable symptom control on overall risk of exacerbation was further characterised in terms of relative risk (RR). Using well controlled patients on FF monotherapy as reference, the relative risk was calculated using the available data and model predicted exacerbations (**Figure S3_6, Table S3_4**). The shift in relative risk highlights the impact of variable symptom control on the risk of exacerbation. These results also show that risk reduction is also drug/treatment specific: adding VI to FF as combination therapy counteracts the increase in relative risk that is observed with symptom control deterioration (i.e., RR ranges between 0.86 and 1.12 for FF monotherapy vs. 0.66 and 0.90 for FF/VI combination therapy). Further evaluation of the inferences regarding differences in treatment response was performed using propensity score matching (**Figure S3_7**).

In addition to baseline ACQ-5, it is important to assess the overall impact of other contributing factors on the changes in base hazard. Even though no interaction has been identified between baseline covariates and treatment effect during model development, the magnitude of the effect of baseline characteristics (i.e., treatable traits) will differ per patient across the population. Such an overview can be obtained using simulations and subsequently stratifying the results by treatment arm and symptom control level at baseline, as assessed by ACQ-5. These simulations are summarised as heat maps in **Figure S3_8** and **Figure S3_9**, where the yearly incidence of events for patients with varying baseline ACQ-5, BMI, FEV_{1p}, smoking status and sex. To understand the impact and magnitude of the effect of concurrent factors on the risk of exacerbation, **Figure S3_10** summarises the relative change in the probability of an exacerbation within the first year of treatment with combination therapy for both male and female patients who have never smoked, previously smoked or are current smokers and have a BMI of 20 kg/m^2.

It is important to highlight that even though LABA have been associated with symptomatic relief, our results suggest that the use of FF/VI combination therapy appears to modify the base hazard relative to FF alone, irrespective of the magnitude of the effect of other demographic and clinical baseline covariates. In fact, based on the heat maps, it becomes evident that FF/VI combination therapy effectively reduced the risks associated with known risk factors such as higher BMI or lower FEV_{1p}.

Table S3_3: Parameter estimates of the final model describing the time-to-first exacerbation in moderate-severe asthma patients. Basal hazard is described using FF monotherapy as reference treatment.

$$\text{Hazard} = \theta_{BASE} * \left(1 + \theta_{previous\ smoker}\right) * (1 + \theta_{current\ smoker}) * (1 + (BMI - 27.6) * \theta_{BMI}) * (1 + (FEV1P - 73) * \theta_{FEV1P}) * \left(1 + (ACQ5_{baseline} - 1.74) \cdot \theta_{ACQ5}\right) * (1 + \theta_{FEMALE}) * \left(1 + \theta_{\frac{BUD}{FORM}}\right) * \left(1 + \theta_{\frac{FF}{VI}}\right) * e^{\theta_{amp} \cdot \sin(calendar\ time + \theta_{phase})} * (1 + \theta_{SAFETY}) * (1 + Prev.Exacerbations * \theta_{EXAHIST}) * \left(1 + \frac{\theta_{Run-in\ Max} * time^{gamma}}{\theta_{Run\ in\ 50}{}^{gamma} + time^{gamma}}\right)$$

Description	Estimates	SE	RSE%	Bootstrap median (5th/95th percentiles)	What the parameter means
BASE hazard (FF)	0.156	0.013	8.1	0.156 (0.136-0.177)	Estimated population average base hazard
BMI effect (percentage increase in hazard per kg/m2)	+2.66%	0.002	7.8	0.026 (0.023-0.030)	Percentage change in hazard for every 1 unit of change in BMI relative to a BMI of 27.6 kg/m2
Estimated ACQ-5 at baseline effect (percentage increase in hazard per point)	+16.8%	0.026	15.4	0.168 (0.123-0.210)	Percentage change in hazard for every 1 unit of change in ACQ-5 relative to the median ACQ-5 score of 1.74
Current smoker effect relative to Never Smoked (percentage increase in hazard)	+39.4%	0.061	15.3	0.399 (0.293-0.494)	Patients smoking at baseline have a 39.4% higher hazard compared to patients who have never smoked
Former smoker effect relative to Never Smoked (percentage increase in hazard)	+31.2%	0.033	10.5	0.314 (0.261-0.367)	Patients who used to smoke but don't at baseline have a 31.2% higher hazard compared to patients who have never smoked
FEV1p at baseline effect (percentage change in hazard per %)	-1.06%	0.001	7.0	-0.011 (-0.012--0.010)	Percentage change in hazard for every 1 unit of change in FEV1p relative to an FEV1p of 74.7%
Female effect relative to male (percentage increase in hazard)	+32.4%	0.015	4.6	0.323 (0.298-0.348)	Female patients have a 32.4% higher hazard compared to male patients.
Exacerbation history	+53.5%	0.176	31.5	0.554 (0.292-0.859)	Percentage change in hazard for every previous exacerbation relative to no previous exacerbation history
Season effect amplitude (percentage change in hazard relative to between seasons [winter/summer])	+36%/-26%	0.00023	0.1	0.305 (0.305-0.305)	At the peak and crest of the sine wave the change in hazard is +36% in winter and -26% in summer
Season effect Phase shift (years)	0.27	0.00015	0.1	0.274 (0.273-0.274)	Shift in sine wave resulting in a crest at the end of December and a trough in beginning of July.
BUD/FORM effect relative to FF (percentage increase in hazard)	+61.7%	0.182	28.9	0.619 (0.350-0.945)	Patients receiving the combination of BUD/FORM have a 61.7% higher hazard than patients receiving FF alone.

FF/VI effect relative to FF (percentage change in hazard)	-22.9%	0.089	39.4	-0.232 (-0.366--0.069)	Patients receiving the combination of FF/VI have a 22.9% lower hazard than patients receiving FF alone.
Safety study effect (percentage change in hazard)	-70.8%	0.051	7.3	-0.708 (-0.788--0.618)	Percentage change in hazard for studies where exacerbations are a safety endpoint relative to an efficacy endpoint
Maximum run in effect (percentage change in hazard)	+310%	0.582	18.4	3.122 (2.299-4.142)	Percentage change in hazard for studies without run-in period at the start of the study.
Time of 50% run-in effect (weeks)	*4 (fixed)*	*fixed*	*fixed*	*fixed*	Time at which the run-in effect is 50% of the maximum effect
Gamma	0.469	0.128	27.2	0.469 (0.251-0.678)	Shape parameter of run-in effect

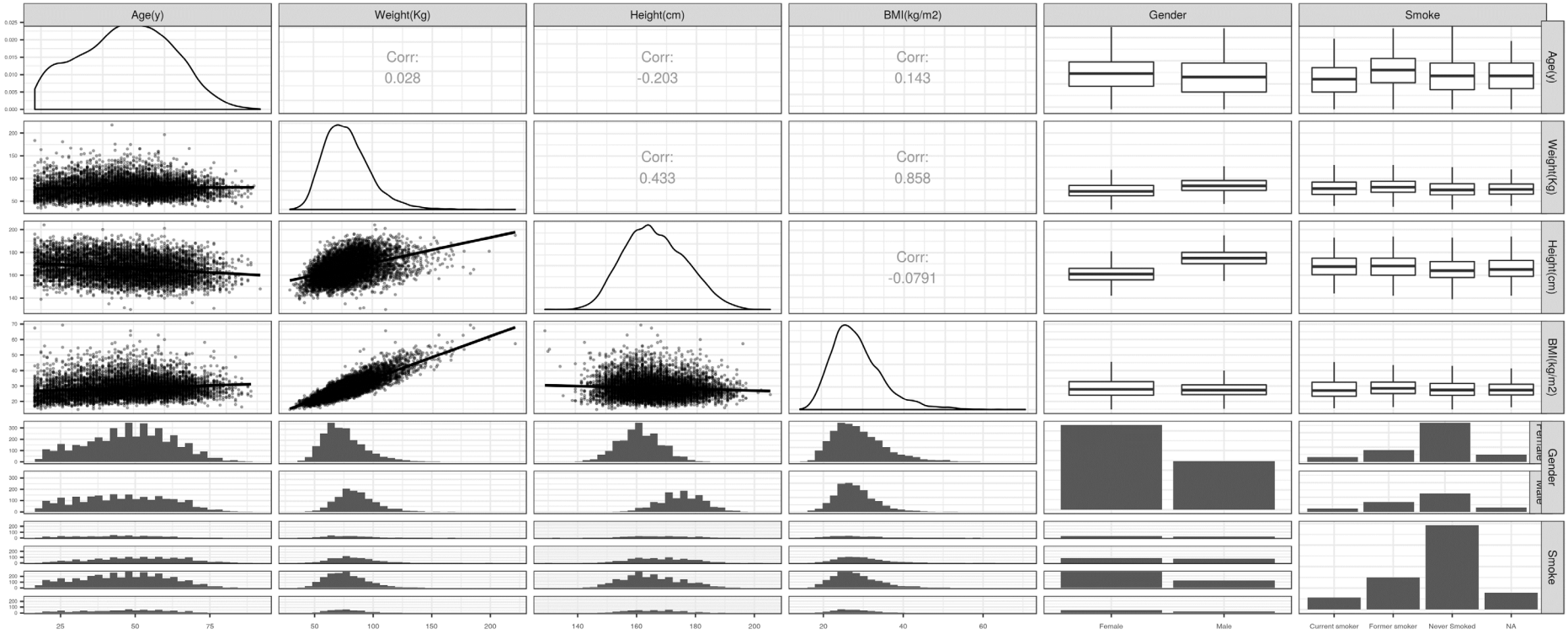
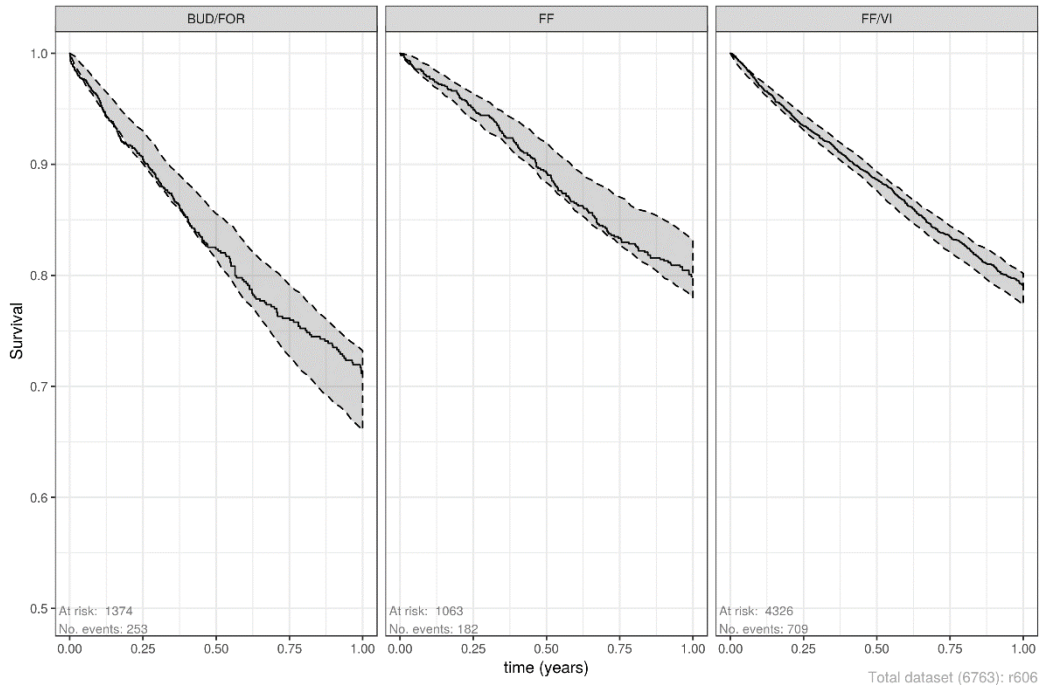


Figure S3_3: Correlation matrix for available baseline characteristics.



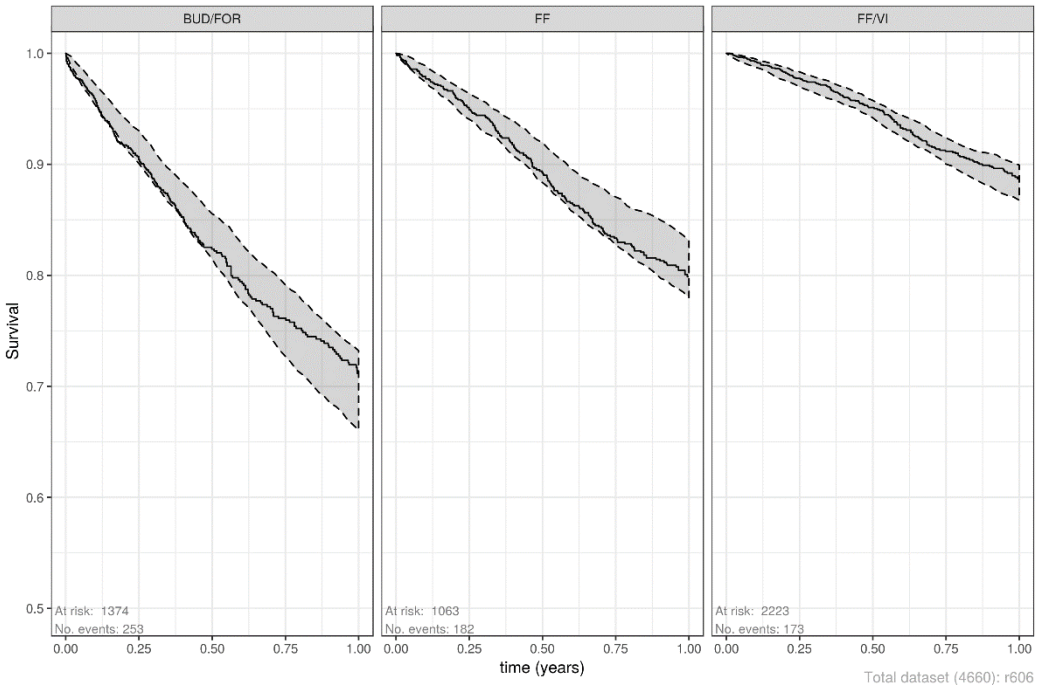


Figure S3_4: Visual-predictive check showing Kaplan–Meier survival estimate over time stratified by treatment. Survival (Y-axis) indicates the proportion of patients who have not had an event; at time zero the survival is 100% (i.e., no patient has experienced an exacerbation). The solid line describes 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 FF 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. Upper panel includes all studies, lower panel excludes studies with a treatment run-in effect.

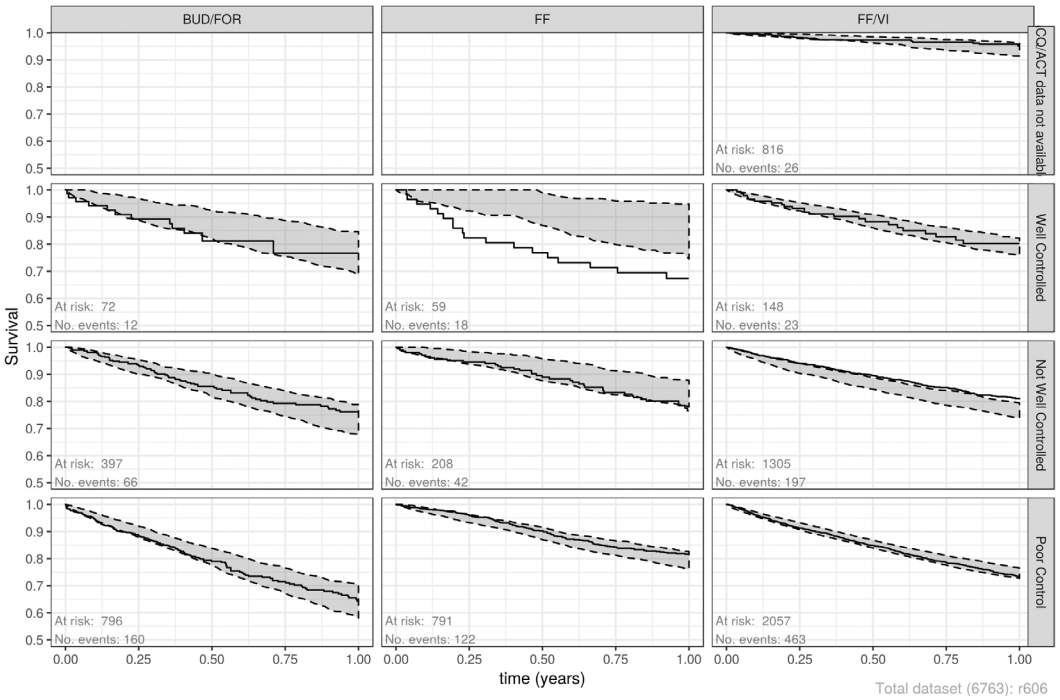


Figure S3_5: Visual-predictive check (VPC) showing Kaplan–Meier survival estimate over time stratified by treatment and symptom control level at baseline. Survival (Y-axis) indicates the proportion of patients who have not had an event; at time zero the survival is 100%. The solid line describes the observed time-to-first exacerbation over the period of 12 months across the overall population. Shaded areas show the model-predicted 95% confidence intervals of the survival. "At risk" refers to the number of patients in each stratum, "No. of events" is the number of observed exacerbations. To assess the potential effect of missing covariates, the VPC was implemented in such a way that baseline ACQ-5 values were omitted for 50% of the subjects who had complete baseline covariate information. The panels show the predicted survival for subjects whose baseline covariate data had been omitted during the parameter estimation step, but included into the data set for the VPC simulations. This diagnostics suggests that missing covariates and imputation procedures (i.e., centring to population point estimate) used for those with missing baseline covariates does not lead to observable bias in the estimated covariate effect. Results correspond, respectively, to scenarios 1 in **Table S5**.

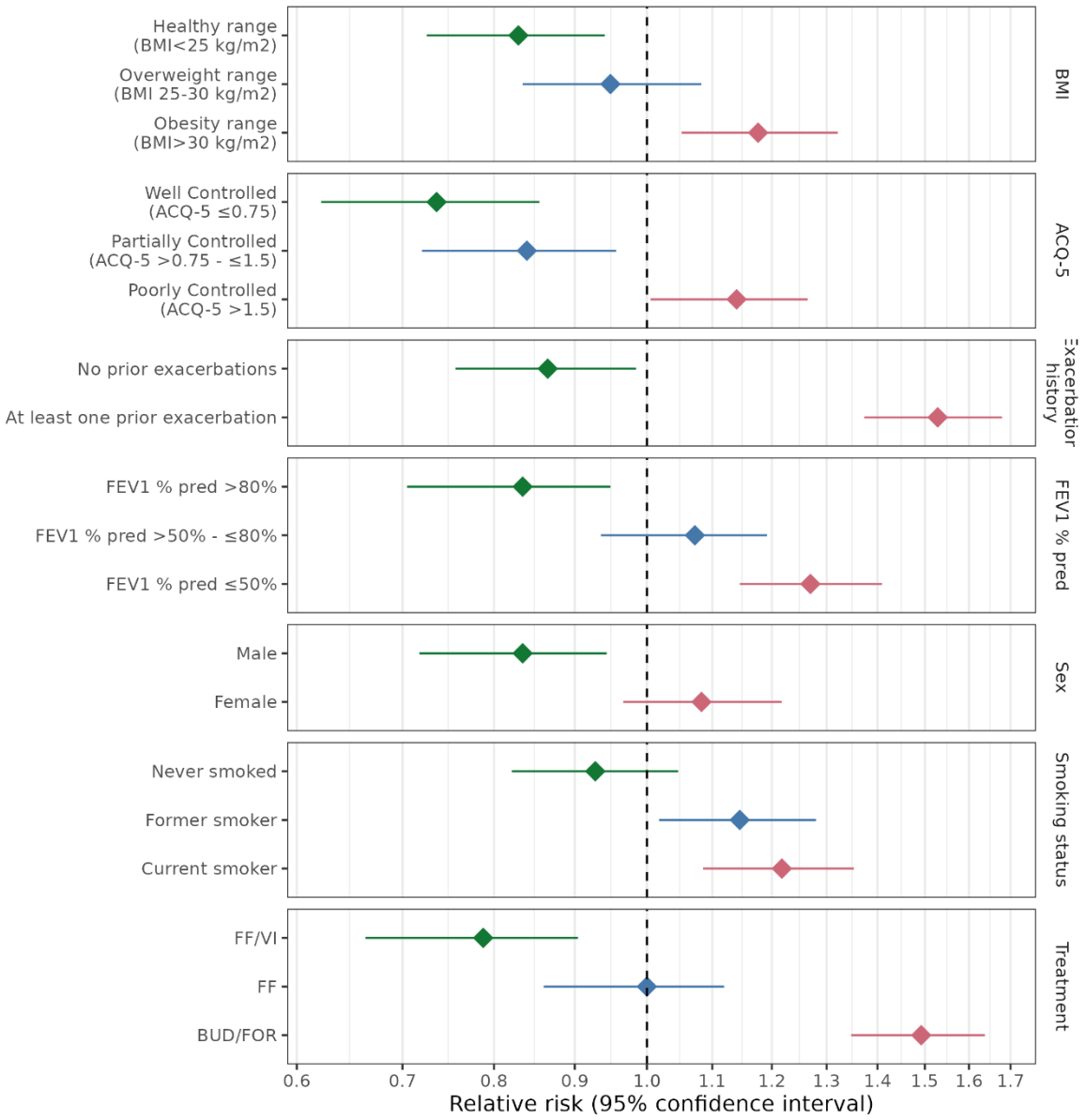


Figure S3_6: Model predicted relative risk (RR). The dashed line depicts the reference value (i.e., RR = 1) associated with patients receiving FF monotherapy. Bars are the 95% prediction intervals (N = 1000 per arm and level of control, 500 iterations. The changes in RR show that baseline symptom control level has a significant effect on the risk of exacerbation, and that this effect is independent of treatment choice. Most importantly also shows that risk reduction is drug-specific: adding VI to FF as combination therapy counteracts the effect of symptom control deterioration.

Table S3_4: RR and corresponding 95% confidence intervals calculated from the Kaplan-Meier estimates from the simulated data summarised in tabular format, along with the p-value comparing each category to FF.

Variable	Subcategory	Relative risk (95% CI)	P value
ACQ-5	Poorly Controlled (ACQ-5 >1.5)	1.14(1.01-1.26)	<0.01
	Partially Controlled (ACQ-5 >0.75 - ≤1.5)	0.84(0.72-0.96)	<0.01
	Well Controlled (ACQ-5 ≤0.75)	0.74(0.62-0.85)	<0.01
BMI	Overweight range (BMI 25-30 kg/m2)	0.95(0.83-1.08)	<0.01
	Healthy range (BMI<25 kg/m2)	0.83(0.73-0.94)	<0.01
	Obesity range (BMI>30 kg/m2)	1.18(1.05-1.32)	<0.01
FEV1p	FEV1 % pred >80%	0.83(0.7-0.95)	<0.01
	FEV1 % pred >50% - ≤80%	1.07(0.94-1.19)	<0.01
	FEV1 % pred ≤50%	1.27(1.15-1.41)	<0.01
Exacerbation history	No prior exacerbations	0.87(0.76-0.98)	<0.01
	At least one prior exacerbation	1.53(1.37-1.68)	<0.01
Sex	Male	0.83(0.72-0.94)	<0.01
	Female	1.08(0.97-1.22)	<0.01
Smoking history	Former smoker	1.15(1.02-1.28)	<0.01
	Never smoked	0.93(0.82-1.05)	<0.01
	Current smoker	1.22(1.09-1.35)	<0.01
Treatment	BUD/FOR	1.49(1.35-1.64)	<0.01
	FF	1(0.86-1.12)	1
	FF/VI	0.79(0.66-0.9)	<0.01

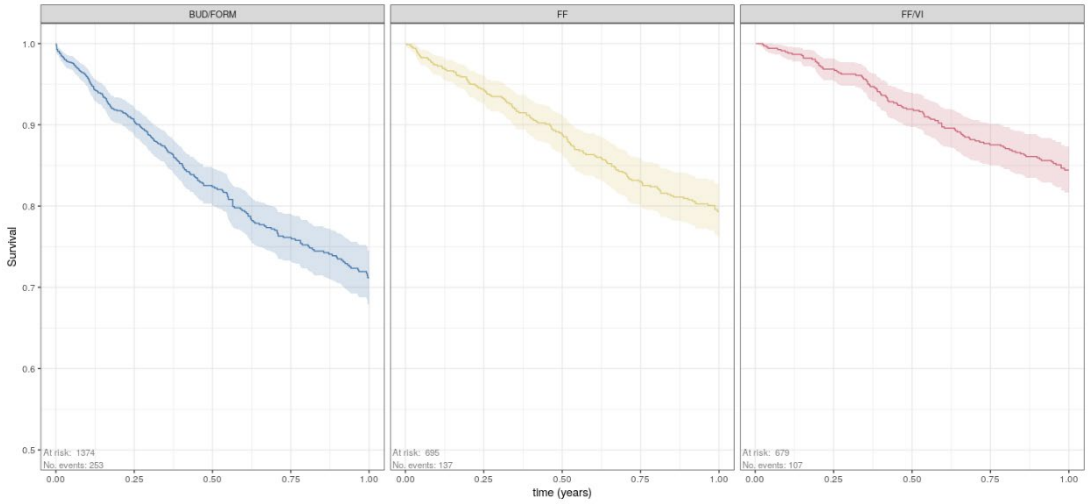


Figure S3_1: Kaplan–Meier survival estimate over time stratified by treatment for perfectly matched asthma patients with moderate to severe symptoms, using propensity score matching, as implemented in R (MatchIt Package). Survival (Y-axis) indicates the proportion of patients who have not had an event; 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 (FF vs. FF/VI and BUD/FOR vs. FF/VI) are statistically significant ($p<0.05$ and $p<0.001$, respectively). 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 [2.05 (95% CI: 1.63, 2.59)], the E-value associated with the treatment differences (i.e., FF/VI vs BUD/FOR) was 3.53, with a confidence interval of 2.65. This strongly suggests that the observed differences are unlikely to be explained by confounding and consequently can be assigned to the treatment.

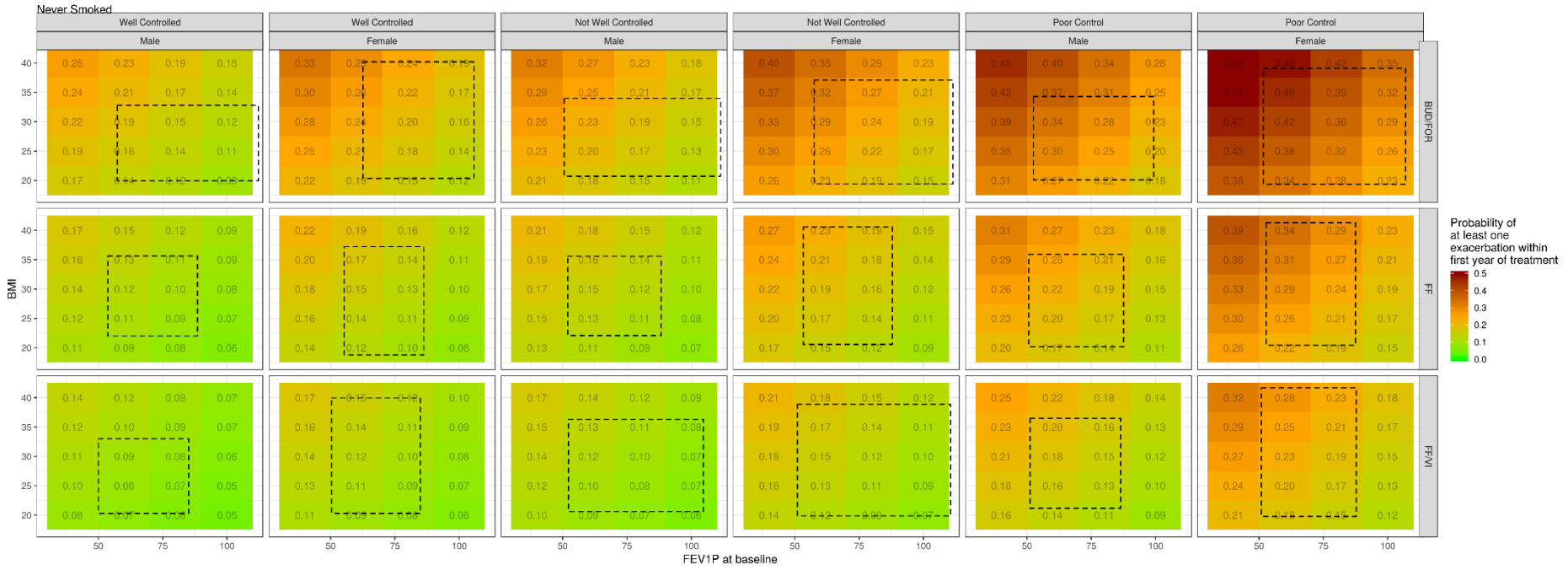


Figure S3_8: Heat map showing the probability of at least one exacerbation within the first year of treatment for patients receiving monotherapy, or combination therapy. Colour gradient from green to red reflects the change in the incidence of exacerbations in patients with varying level of symptom control, BMI or FEV_{1p} at baseline. Predicted risk is stratified for male and female patients who have never smoked. The midpoint for the colour gradient was set to 0.25, which corresponds to the point estimate of the base hazard rate after FF treatment. Exacerbation incidence estimates were calculated not only taking into account the observed covariate distributions (dotted solid lines) but also included covariate values across a clinically relevant range.

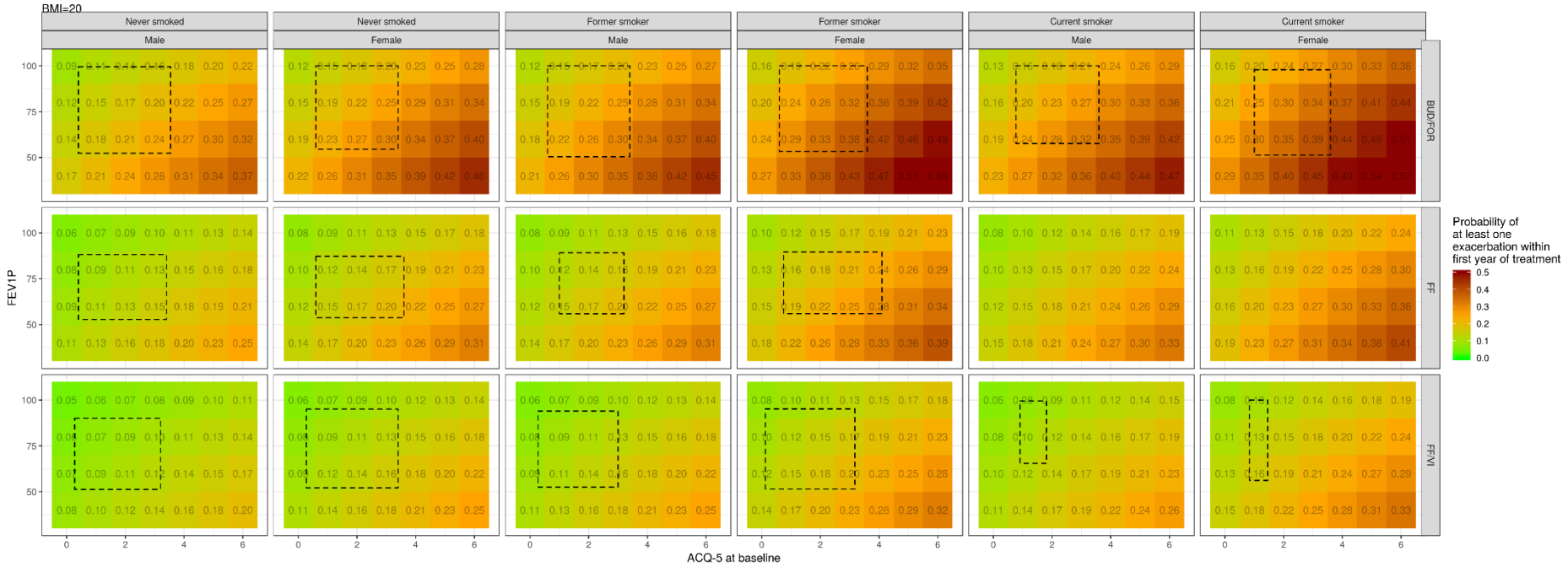


Figure S3_9: Heat map showing the probability of at least one exacerbation within the first year of treatment for patients receiving monotherapy, or combination therapy. Colour gradient from green to red reflects the change in the incidence of exacerbations in patients with varying level of symptom control or FEV_{1p} at baseline. Predicted risk is stratified for male and female patients who have never smoked, previously smoked or are current smokers and have a BMI of 20 kg/m^2. The midpoint for the colour gradient was set to 0.25, which corresponds to the point estimate of the base hazard rate after FF treatment. Exacerbation incidence estimates were calculated not only taking into account the observed covariate distributions (dotted solid lines) but also included covariate values across a clinically relevant range.

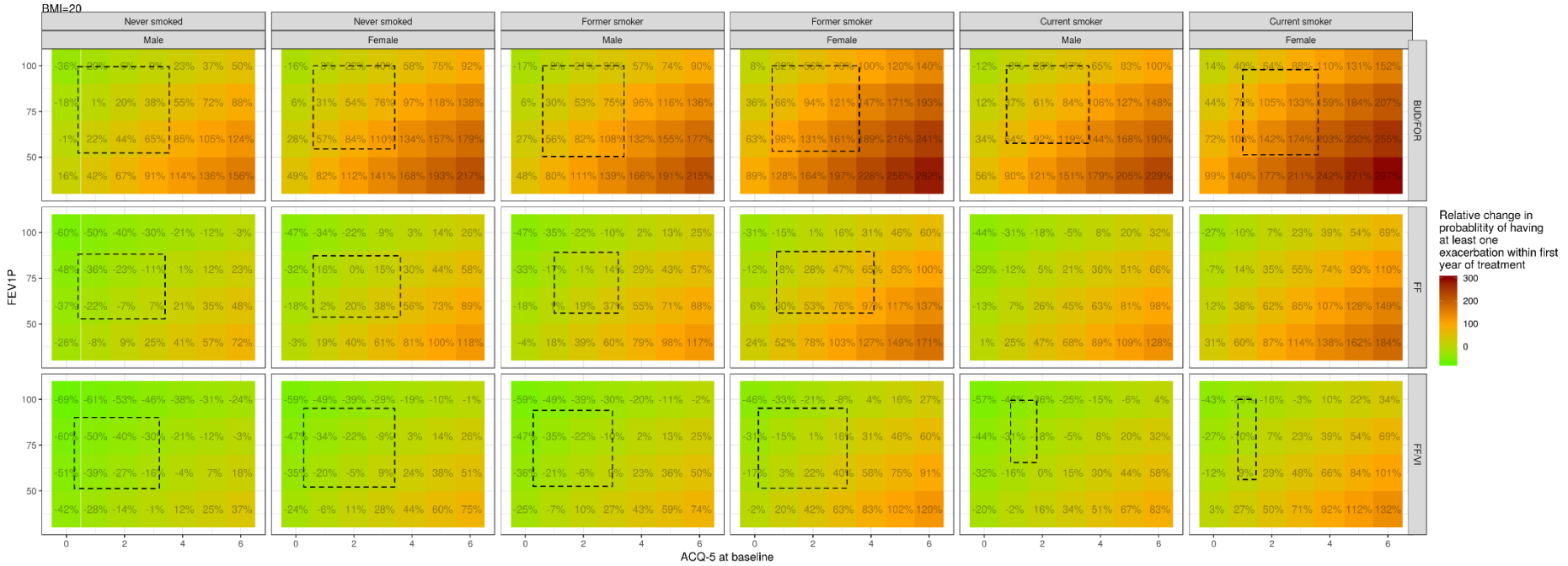


Figure S3_10: Heat map showing the relative change in the probability of an exacerbation within the first year of treatment for patients receiving monotherapy or combination therapy. Colour gradient from green to red reflects the change in the relative probability of an exacerbation in patients with varying levels of symptom control or FEV_{1p} at baseline. Relative changes in probability are shown for male and female patients who have never smoked, previously smoked or are current smokers and have a BMI of 20 kg/m^2. The midpoint for the colour gradient was set to 100%, which corresponds to the point estimate of the base hazard rate after FF treatment. Exacerbation incidence estimates were calculated not only taking into account the observed covariate distributions (dotted solid lines) but also included covariate values across a clinically relevant range.

Appendix

Figure S3_11: Distribution of baseline characteristics stratified by study. Number of distributions may vary in each panel as not all variables have been collected at baseline for all studies. ACQ-5 = asthma control questionnaire; BMI = body mass index, FEV_1 = forced expiratory volume 1 second, PEF = peak expiratory flow.

Figure S3_12: Distribution of baseline characteristics stratified by treatment. Number of patients may vary in each panel as a different number of patients have been evaluated across treatment arms. Bar charts show patients within a category (e.g., male/female) as a percentage of the total number of patients within a treatment arm. ACQ-5 = asthma control questionnaire; BMI = body mass index.

116 **Table S3_5:** Exacerbation definition and related inclusion/exclusion criteria

Study	Exacerbation inclusion/exclusion criteria	Exacerbation definition
113091	Exclusion criteria: Asthma exacerbation requiring hospitalisation within 12 weeks prior to Visit 1.	(Severe) Deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-subject hospitalisation or emergency department visit that required systemic corticosteroids between Visits 1 and 2.
115150	Exacerbations not mentioned.	(Severe) Deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or antibiotics, an in-subject hospitalisation, or emergency department visit that required systemic corticosteroids or antibiotics.
SAM40040		Moderate: Deterioration of asthma requiring oral corticosteroids for 7-10 days Severe: Deterioration of asthma requiring hospital admission
SAM 40056	Exclusion criteria: Had an acute asthma exacerbation of reversible airways obstruction requiring hospitalisation within 4 weeks prior to Visit 1.	Deterioration in asthma requiring treatment with oral corticosteroids or hospital admission.
HZA106829		Severe: Deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids
HZA106837		Severe: Deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroid
HZA106839		Severe: Deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids
HZA116492		Deterioration of asthma requiring the use of systemic corticosteroids 4 (tablets, suspension, or injection) with or without antibiotics, an inpatient hospitalisation, or emergency department visit due to asthma that required systemic corticosteroids or antibiotics
201378		Type 1: Requires oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation) Type 2: Requires hospitalisation

117

Table S3_6: Overview of limitations of the data and proposed modelling approach.

Data available for this analysis	As with any pharmacometrics approach, model predictive performance and generalisability depends highly upon the data available and the clinical questions one aims to address. We have identified high-quality clinical trials in moderate or severe asthma patients receiving different treatments, who were closely monitored for a period of at least 6 months and whose data included clinical and demographic baseline information as well as longitudinal measures of response.
Protocol endpoints, missing data	Given that different protocol designs and clinical endpoints have been used across protocols, individual level data were not always available for the overall analysis population (e.g. baseline ACQ-5 measurements, ACQ-5 vs. ACT). We have therefore attempted to minimise the use of imputation during model development. Instead, emphasis was given to information that could be extracted from the available data. This imposed the assumption of representativeness of the subsets of the patient population included in the final data analysis. The only exception where missing covariates were replaced with data was with the conversion of ACT to ACQ-5. However, this was not imputed but converted, as both scales include similar questions, and capture the same dimensions of the disease. ACQ-5 was preferred as metrics of symptom control because it does not include reliever medication use, which was analysed separately.
Imputation procedures for missing baseline covariates	A sensitivity analysis was implemented to assess the impact of the working assumptions during model development and validation, including the potential effect of missing values at baseline for ACQ-5 and FEV1p (Table S3_7). The results from this analysis suggest that the missing covariate information does not have a significant effect on the final model parameter estimates. In addition, we have assumed that parameter estimates obtained from the pooled database (n=6765) were sufficiently precise to describe the contribution of baseline covariates to the risk of exacerbation.
Discriminating the effect of patient baseline characteristics from treatment effect	Whilst a parametric TTE model is a standard tool for the analysis of survival data, it can be parameterised to disentangle the effect of the underlying disease, patient-related factors, and drug-specific properties [1, 2]. Here, the assessment of treatment was implemented as a discrete covariate, without stratification by dose level, even though up and down-titration have been used across the different protocols. [3, 4]. As differences in dose may be further confounded by the effect of individual variation in inhalation procedures, it has been assumed that at therapeutic doses, the variation in lung exposure to ICS will have minor impact on the risk of future exacerbations.
Treatment adherence and dropout	Another important point to consider is the limited duration of the studies. We have assumed that adherence to treatment would have been high, and interindividual differences in response are explained by patient characteristics, rather than variable treatment adherence [5, 6]. Dropout was not modelled as the number of patients who dropped out or withdrew from the studies was very low (< 10%). These figures are in line with reported data in severe asthma [7].
Apparent estimates of base hazard	We also acknowledge that parameter estimates do not describe the absolute risk of an exacerbation associated with the natural course of the disease. Our parameterisation of the base hazard was relative to the use of FF monotherapy. It would have been ethically unacceptable to maintain patients on placebo for this period of time and estimates of base hazard obtained from much shorter studies including a placebo arm would lead to inaccurate extrapolation of results, among other things due to the effect of seasonal variation.

1. Lim HS. Brief introduction to parametric time to event model. Transl Clin Pharmacol. 2021; 29(1):1–5.
2. Kasai H, Mori Y, Ose A, Shiraki M, Tanigawara Y. Prediction of fracture risk from early-stage bone markers in patients with osteoporosis treated with once-yearly administered zoledronic acid. J Clin Pharmacol. 2021; 61(5):606–13.
3. Beasley R, Harper J, Bird G, Maijers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma. Time for a new therapeutic dose terminology. Am J Respir Crit Care Med. 2019; 199(12):1471–77.
4. Rice-McDonald G, Bowler S, Staines G, Mitchell C. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. Intern Med J. 2005; 35(12):693–8.
5. Musuamba FT, Teutonico D, Maas HJ, et al. Prediction of disease progression, treatment response and dropout in chronic obstructive pulmonary disease (COPD). Pharm Res. 2015; 32(2):617–27.
6. Wraight JM, Cowan JO, Flannery EM, Town GI, Taylor DR. Adherence to asthma self-management plans with inhaled corticosteroid and oral prednisone: A descriptive analysis. Respirology. 2002; 7(2):133–9.
7. Lombardi C, Bagnasco D, Caruso C, et al. Analysis of the drop-out rate in patients receiving mepolizumab for severe asthma in real life. Pulm Pharmacol Ther. 2019; 54:87–89.

Table S3_3: Results of an analysis of model sensitivity to missing baseline ACQ-5 and FEV_{1p} values.

Parameter	Final model	RSE of final model estimate	Scenario 1: 50% of subjects with baseline ACQ-5 values set to missing[1]	Scenario 2: 50% of subjects with baseline FEV1p values set to missing[3]	Scenario 3: Model without baseline ACQ-5 effect[4]	Scenario 4: Model without baseline FEV1p effect[5]
Base hazard (FF)	**0.156**	***2.0%***	0.161	0.16	0.167	0.162
FF/VI effect relative to FF	**-0.229**	***14.0%***	-0.226	-0.23	-0.235	-0.23
BUD/FORM effect relative to FF	**0.617**	***19.8%***	0.562	0.551	0.49	0.509
BMI effect	**0.0266**	***4.4%***	0.0272	0.0271	0.0273	0.0274
ACQ5 at baseline effect	**0.168**	***12.0%***	0.154	0.174	-	0.177
Current smoker effect relative to Never Smoked	**0.394**	***20.5%***	0.419	0.396	0.444	0.394
Former smoker effect relative to Never Smoked	**0.312**	***16.8%***	0.31	0.309	0.312	0.306
FEV1p at baseline effect	**-0.0106**	***14.7%***	-0.0107	-0.00934	-0.0108	-
Female effect relative to male	**0.324**	***7.3%***	0.321	0.324	0.321	0.325
Season effect amplitude	**0.305**	***0.1%***	0.305	0.305	0.305	0.305
Season effect Phase shift	**0.274**	***0.2%***	0.274	0.274	0.274	0.274
Safety study effect	**-0.708**	***6.7%***	-0.72	-0.716	-0.729	-0.721
Exacerbation history	**0.535**	***27.1%***	0.561	0.543	0.619	0.519
Maximum run in effect	**3.1**	***7.9%***	2.8	2.96	2.59	2.85
Time of 50% run-in effect (weeks)	**4 (fixed)**	**-**	**4 (fixed)**	**4 (fixed)**	**4 (fixed)**	**4 (fixed)**
Gamma	**0.468**	***9.1%***	0.503	0.467	0.525	0.469

1. 50% of the subjects who had baseline ACQ-5 had their values randomly set to missing
2. 50% of the subjects who had baseline FEV1p had their values randomly set to missing
3. ACQ-5 covariate effect was removed from the final model, despite having been identified as a statistically significant covariate
4. FEV1p covariate effect was removed from the final model, despite having been identified as a statistically significant covariate

TTE estimation control stream

```
$SIZES      MAXIDS=38000 LVR=35
$PROBLEM    Relvar
$INPUT      ID DV TIME OCC RACQ5BL STUDYN FPFF AGEBL ASTHDURC ICSDURC SMOKN TRTNUM
TRTNUM2 ACQ5BLC SEXN BMIBL PEFBL FEV1BL FEV1PBL
            RACEC ACQ_Q6BL ACQ_Q7BL ACTBL SH EXAHIST EACQ5BL ACQ5BL TRTNO
TRTNOCSUM EVID MDV YY TRTID SET1 SET2 SET3 SET4 SET5 SET6 SET7 SET8

$DATA       total.nm.v17.txt IGNORE=@ IGNORE=(SET4.EQ.0)
            IGNORE=(STUDYN.EQ.205715)
            IGNORE=(STUDYN.EQ.116863)
            IGNORE=(TRTNUM.EQ.8) IGNORE=(TRTNUM.EQ.12) IGNORE=(TRTNUM.EQ.10)


$SUBROUTINE ADVAN=6 TOL=1
$PRIOR NWPRI NTHETA=19 NETA=1 NTHP=11
$MODEL      COMP=(HAZARD)
$PK

  IF(NEWIND.NE.2) TP=0


BASE = THETA(17) + ETA(1)

;Safety effect
IF (STUDYN.EQ.106839) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.113091) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.116863) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.106829) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.201378) BASE = BASE * (1 + THETA(12))

;Run-in effect
RUNIN = 0
IF (STUDYN.EQ.115150.AND.TRTNUM.EQ.9) RUNIN = 1
IF (STUDYN.EQ.116492) RUNIN = 1
RUNHALF = THETA(14)
RUNMAX = THETA(15)
GAM = THETA(16)

;Treatment effect
IF (TRTNUM.EQ.7) BASE = BASE ;FF
IF (TRTNUM.EQ.5) BASE = BASE * (1 + THETA(19))  ;BUD/FORM
IF (TRTNUM.EQ.9) BASE = BASE * (1 + THETA(18)) ;FF/VI

;BMI effect
IF (BMIBL.GE.0) BASE = BASE * (1+ (BMIBL-27.6)*THETA(4))

;ACQ-5 effect
IF (ACQ5BL.GE.0) BASE = BASE * (1 + (ACQ5BL-1.74)*THETA(5))

;Smoking status effect
IF (SMOKN.EQ.2) BASE = BASE * (1 + THETA(6))
IF (SMOKN.EQ.3) BASE = BASE * (1 + THETA(7))

;FEV1p effect
IF (FEV1PBL.GE.0) BASE = BASE * (1 + (FEV1PBL-74.7)*THETA(8))

;Exacerbation history effect
```

```
IF (EXAHIST.GE.0) BASE = BASE * (1 + EXAHIST*THETA(13))

;Sex effect
IF (SEXN.EQ.2) BASE = BASE * (1 + THETA(9))

;Season effect
AMP = THETA(10)
PHASE = THETA(11)

;Southern hemisphere
IF(SH.EQ.1) PHASE = PHASE + 0.5
CIRCEFF = EXP(AMP * SIN((TIME+YY+PHASE)*(3.141593*2)))

IF (BASE.LT.0) BASE = 0

$DES
  DEL=1E-6
  DADT(1) = BASE * EXP(AMP * SIN((T+YY+PHASE)*(3.141593*2))) * (1 + RUNIN *
(RUNMAX + (((-1 * RUNMAX) * (T**GAM))/(RUNHALF**GAM + T**GAM))))


$ERROR
  DEL1=1E-6
  IF(NEWIND.NE.2) OLDCHZ=0
  CHZ = A(1)-OLDCHZ
  OLDCHZ = A(1)
  SUR = EXP(-CHZ)

   HAZNOW=BASE * EXP(AMP * SIN((TIME+YY+PHASE)*(3.141593*2))) * (1 + RUNIN *
(RUNMAX + (((-1 * RUNMAX) * (TIME**GAM))/(RUNHALF**GAM + TIME**GAM))))

  IF(DV.EQ.0) Y=SUR ;censored event
  IF(DV.EQ.1) Y=SUR*HAZNOW ;event
  IF(DV.EQ.1) TP = 0

$THETA
(0, 0.188) FIX; BASE_FP
(0.452) FIX; BUD/FOR
(-0.361) FIX; FP/SAL
(0, 0.0282) ; BMI_BASE
(0.118) ; ACQ_BASE
(0.527) ; SMOK2_BASE
(0.326) ; SMOK3_BASE
(-0.00988) ; FEV1_BASE
(0.307) ; SEX_BASE
(0, 0.305) ; AMP
(0.274) ; PHASE
(-0.796) ; Safety
(0,0.5) ; EXAHIST
;(0,0.5) ; 115150_runin
(0,0.07692308) FIX; RUNHALF
(0, 1) ; RUNMAX
(0,2) ; GAM

(0, 0.188) ; BASE_FF
(-0.361) ; FF/VI
(0.452) ; BUD/FOR

$OMEGA 0 FIX
```

```
$THETA ;PRIORS
(0, 0.188) FIX ; FP_BASE 205715
(0.322)    FIX ; DRUG1_BASE
(-0.308)   FIX ; DRUG2_BASE
(0, 0.0278) FIX; BMI_BASE
(0.207)     FIX ; ACQ_BASE
(0.509)     FIX ; SMOK2_BASE
(0.268)     FIX ; SMOK3_BASE
(-0.00837)  FIX ; FEV1_BASE
(0.326)     FIX ; SEX_BASE
(0, 0.305)  FIX ; AMP
(0.274)     FIX ; PHASE

$OMEGA BLOCK (11) FIX;PRIORS
  2.03E-05
  5.64E-05  1.12E-02
  6.73E-05  8.45E-04  1.21E-03
  2.48E-05  1.03E-04  1.10E-04  4.93E-05
 -1.74E-05  1.15E-04 -2.28E-06 -3.16E-05  3.95E-03
  8.00E-05 -1.60E-03 -4.25E-04  1.02E-04 -3.93E-04  1.47E-02
 -4.86E-05 -1.65E-03 -6.17E-04 -5.76E-05  8.89E-06  8.14E-04  5.11E-03
 -3.43E-06 -2.84E-05 -1.56E-05 -3.36E-06  1.38E-05 -2.65E-05 -1.90E-06  3.99E-06
 -3.22E-04 -1.85E-03 -1.73E-03 -4.99E-04  3.51E-04 -1.67E-03  5.07E-04  6.42E-05
6.91E-03
  7.44E-07  2.67E-06  2.70E-06  2.73E-06 -1.60E-06 -1.78E-05 -4.33E-06  1.33E-07 -
1.49E-05  3.73E-07
 -3.51E-07 -7.55E-06 -2.50E-06 -9.29E-08 -1.24E-06 -1.90E-06  6.28E-07  6.93E-07
7.22E-06  1.05E-07  4.11E-07

$ESTIMATION METHOD=COND MAXEVAL=99999 LAPLACE LIKE PRINT=1 NSIG=3
$COV MATRIX=R
$TABLE ID DV TIME OCC EVID ACQ5BL ACQ5BLC RACQ5BL ACTBL SEXN STUDYN BASE
TRTNUM TRTNUM2 FPFF SMOKN BMIBL FEV1PBL BMIBL AGEBL
NOPRINT NOAPPEND ONEHEADER FORMAT=s1PE11.5
FILE=table604.txt
```

TTE simulation control stream

```
$SIZES      MAXIDS=38000 LVR=35
$PROBLEM    Relvar
$INPUT      ID DV TIME EXOCC RACQ5BL STUDYN FPFF AGEBL ASTHDURC
            ICSDURC SMOKN TRTNUM TRTNUM2 ACQ5BLC SEXN BMIBL PEFBL
            FEV1BL FEV1PBL RACEC ACQ_Q6BL ACQ_Q7BL ACTBL SH EXAHIST
            EACQ5BL ACQ5BL TRTNO TRTNOCSUM YY EVID MDV TRTID SET1 SET2 SET3
            SET4 SET5 SET6 SET7 SET8 MAX
$DATA      total.nm.VPC.v18.txt IGNORE=@ IGNORE=(SET4.EQ.0)
            IGNORE=(STUDYN.EQ.205715) IGNORE=(STUDYN.EQ.116863)
            IGNORE=(TRTNUM.EQ.8) IGNORE=(TRTNUM.EQ.12)
            IGNORE=(TRTNUM.EQ.10)


$SUBROUTINE ADVAN=6 TOL=1
$MODEL      COMP=(HAZARD)
$PK

  IF(NEWIND.NE.2) TP=0

BASE = THETA(17) + ETA(1)

;Safety effect
IF (STUDYN.EQ.106839) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.113091) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.116863) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.106829) BASE = BASE * (1 + THETA(12))
IF (STUDYN.EQ.201378) BASE = BASE * (1 + THETA(12))

;Run-in effect
RUNIN = 0
IF (STUDYN.EQ.115150.AND.TRTNUM.EQ.9) RUNIN = 1
IF (STUDYN.EQ.116492) RUNIN = 1
RUNHALF = THETA(14)
RUNMAX = THETA(15)
GAM = THETA(16)

;Treatment effect
IF (TRTNUM.EQ.7) BASE = BASE ;FF
IF (TRTNUM.EQ.5) BASE = BASE * (1 + THETA(19))  ;BUD/FORM
IF (TRTNUM.EQ.9) BASE = BASE * (1 + THETA(18)) ;FF/VI

;BMI effect
IF (BMIBL.GE.0) BASE = BASE * (1+ (BMIBL-27.6)*THETA(4))

;ACQ-5 effect
IF (ACQ5BL.GE.0) BASE = BASE * (1 + (ACQ5BL-1.74)*THETA(5))

;Smoking status effect
IF (SMOKN.EQ.2) BASE = BASE * (1 + THETA(6))
IF (SMOKN.EQ.3) BASE = BASE * (1 + THETA(7))

;FEV1p effect
IF (FEV1PBL.GE.0) BASE = BASE * (1 + (FEV1PBL-74.7)*THETA(8))

;Exacerbation history effect
IF (EXAHIST.GE.0) BASE = BASE * (1 + EXAHIST*THETA(13))
```

```
;Sex effect
IF (SEXN.EQ.2) BASE = BASE * (1 + THETA(9))

;Season effect
AMP = THETA(10)
PHASE = THETA(11)

;Southern hemisphere
IF(SH.EQ.1) PHASE = PHASE + 0.5
CIRCEFF = EXP(AMP * SIN((TIME+YY+PHASE)*(3.141593*2)))

IF (BASE.LT.0) BASE = 0

$DES
  DEL=1E-6
  DADT(1) = BASE * EXP(AMP * SIN((T+YY+PHASE)*(3.141593*2))) * (1 + RUNIN *
(RUNMAX + (((-1 * RUNMAX) * (T**GAM))/(RUNHALF**GAM + T**GAM))))

$ERROR
  DEL1=1E-6
  IF(NEWIND.NE.2) OLDCHZ=0
  CHZ = A(1)-OLDCHZ
  OLDCHZ = A(1)
  SUR = EXP(-CHZ)

   HAZNOW=BASE * EXP(AMP * SIN((TIME+YY+PHASE)*(3.141593*2))) * (1 + RUNIN *
(RUNMAX + (((-1 * RUNMAX) * (TIME**GAM))/(RUNHALF**GAM + TIME**GAM))))

  IF(DV.EQ.0) Y=SUR ;censored event
  IF(DV.EQ.1) Y=SUR*HAZNOW ;event
  IF(DV.EQ.1) TP = 0

  ITER= IREP
  IF(ICALL.EQ.4) THEN ; for simulation
   CALL RANDOM (2,R)
   DV=0
   RTTE = 0
   IF(MAX.EQ.1) RTTE = 1 ; for the censored observation at 480 min
   IF(R.GT.SUR) THEN
      DV=1
      RTTE = 1
   ENDIF
  ENDIF

$THETA
(0, 0.188) FIX ; BASE_FP
(0.452) FIX ; BUD/FOR
(-0.361) FIX ; FP/SAL
(0, 0.0266) ; BMI_BASE
(0.168) ; ACQ_BASE
(0.395) ; SMOK2_BASE
(0.312) ; SMOK3_BASE
(-0.0106) ; FEV1_BASE
(0.324) ; SEX_BASE
(0, 0.305) ; AMP
(0.274) ; PHASE
(-0.708) ; Safety
(0, 0.535) ; EXAHIST
(0, 0.0769) FIX ; RUNHALF
```

```
(0, 3.1) ; RUNMAX
(0, 0.469) ; GAM
(0, 0.156) ; BASE_FF
(-0.229) ; FF/VI
(0.617) ; BUD/FOR

$OMEGA 0 FIX

$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=100
$TABLE ID DV TIME ACQ5BL ACTBL RACQ5BL STUDYN YY SH CIRCEFF TRTNUM ITER SMOKN
BMIBL FEV1PBL RTTE NOPRINT NOAPPEND ONEHEADER FORMAT=s1PE11.5 FILE=table606.txt
```

TTE model input dataset example

ID	EXEVENT	TIME	EXOCCACQ5BL	STUDYN	FPFF	AGEBL	ASTHDUR	CICSDUR	CSMOK	NTRTNUM	TRTNUM2	ACQ5BL	CSEX	N	BMIBL	PEFBL	FEV1BL	FEV1PBL	RACE	CACQ_Q6BL	ACQ_Q7BL	ACTBL	SH	EXAHIST	eACQ5BL	qACQ5BL	TRTNO	TRTNOCSUM	EVID	MDV	YY	ID2	SET1	SET2	SET3	SET4	SET5	SET6	SET7	SET8
1	.	0	0	-999	106829	0	41.31	15	14	2	7	2	1	1	24.60926309.2308	3.12	72.73	1	-999	-999	-999	0	-999	-999	-999	1	1	3	1	0.469176	27	1	0	1	1	1	1	1	1
1	0	0.460274	0	-999	106829	0	41.31	15	14	2	7	2	1	1	24.60926309.2308	3.12	72.73	1	-999	-999	-999	0	-999	-999	-999	1	1	0	0	0.469176	27	1	0	1	1	1	1	1	1
2	.	0	0	-999	106829	0	35.87	.	14	2	7	2	1	1	29.52775279.8571	2.22	89.9	1	-999	-999	-999	0	0	-999	-999	1	1	3	1	0.080139	27	1	0	1	1	1	1	1	1
2	0	0.446575	0	-999	106829	0	35.87	.	14	2	7	2	1	1	29.52775279.8571	2.22	89.9	1	-999	-999	-999	0	0	-999	-999	1	1	0	0	0.080139	27	1	0	1	1	1	1	1	1
3	.	0	0	-999	115150	0	33.24	3	.	-999	9	2	3	2	21.45357437.1429	3.27	59.55852	.	-999	-999	-999	0	2	-999	-999	1	1	3	1	-0.58566	27	1	0	1	1	1	1	1	1
3	0	0.155394	0	-999	115150	0	33.24	3	.	-999	9	2	3	2	21.45357437.1429	3.27	59.55852	.	-999	-999	-999	0	2	-999	-999	1	1	0	0	-0.58566	27	1	0	1	1	1	1	1	1
4	.	0	0	-999	106839	0	47.02	4	5	-999	9	2	0	1	50.31118439.0241	3.87	66.4	.	-999	-999	-999	0	4	-999	-999	1	1	3	1	-0.62117	27	1	0	1	1	1	1	1	1
4	0	0.457534	0	-999	106839	0	47.02	4	5	-999	9	2	0	1	50.31118439.0241	3.87	66.4	.	-999	-999	-999	0	4	-999	-999	1	1	0	0	-0.62117	27	1	0	1	1	1	1	1	1
5	.	0	0	-999	40040	0	72	13	14	3	7	2	3	2	33.30499419.2514	3.98	67.5	1	-999	-999	-999	0	0	-999	-999	1	1	3	1	-0.53647	27	1	0	1	1	1	1	1	1
5	0	0.460274	0	-999	40040	0	72	13	14	3	7	2	3	2	33.30499419.2514	3.98	67.5	1	-999	-999	-999	0	0	-999	-999	1	1	0	0	-0.53647	27	1	0	1	1	1	1	1	1
6	.	0	0	-999	40056	0	38.92	2	15	3	5	2	0	1	34.21436	457.5	1.65	79.38596	4	-999	-999	-999	0	15	-999	-999	1	1	3	1	0.150685	27	1	0	1	1	1	1	1	1
6	0	0.457534	0	-999	40056	0	38.92	2	15	3	5	2	0	1	34.21436	457.5	1.65	79.38596	4	-999	-999	-999	0	15	-999	-999	1	1	0	0	0.150685	27	1	0	1	1	1	1	1	1
7	.	0	0	-999	40040	0	64.51	3	4	-999	9	2	3	2	32.95068582.7143	2.46	80.1	4	-999	-999	-999	0	3	-999	-999	1	1	3	1	-0.12877	27	1	0	1	1	1	1	1	1
7	0	0.460274	0	-999	40040	0	64.51	3	4	-999	9	2	3	2	32.95068582.7143	2.46	80.1	4	-999	-999	-999	0	3	-999	-999	1	1	0	0	-0.12877	27	1	0	1	1	1	1	1	1
8	.	0	0	-999	40056	0	53.2	13	1	2	9	2	0	1	26.30362	336	1.22	57.65125	3	-999	-999	-999	0	3	-999	-999	1	1	3	1	-0.33894	27	1	0	1	1	1	1	1	1
8	0	0.457534	0	-999	40056	0	53.2	13	1	2	9	2	0	1	26.30362	336	1.22	57.65125	3	-999	-999	-999	0	3	-999	-999	1	1	0	0	-0.33894	27	1	0	1	1	1	1	1	1
9	.	0	0	-999	106839	0	19.2	5	13	2	5	2	2	2	21.46915430.7143	2.62	125	3	-999	-999	-999	0	12	-999	-999	1	1	3	1	-0.64308	27	1	0	1	1	1	1	1	1
9	0	0.456836	0	-999	106839	0	19.2	5	13	2	5	2	2	2	21.46915430.7143	2.62	125	3	-999	-999	-999	0	12	-999	-999	1	1	0	0	-0.64308	27	1	0	1	1	1	1	1	1
10	.	0	0	-999	106837	0	39	15	4	3	7	2	3	1	29.04	536.4286	2.93	119.9336	3	-999	-999	-999	0	4	-999	-999	1	1	3	1	-0.41569	27	1	0	1	1	1	1	1	1
10	0	0.460274	0	-999	106837	0	39	15	4	3	7	2	3	1	29.04	536.4286	2.93	119.9336	3	-999	-999	-999	0	4	-999	-999	1	1	0	0	-0.41569	27	1	0	1	1	1	1	1	1
11	.	0	0	-999	201378	0	87	3	5	2	5	2	3	2	29.83119318.7143	3.61	67.96117	1	-999	-999	-999	0	15	-999	-999	1	1	3	1	0.048206	27	1	0	1	1	1	1	1	1
11	0	0.424658	0	-999	201378	0	87	3	5	2	5	2	3	2	29.83119318.7143	3.61	67.96117	1	-999	-999	-999	0	15	-999	-999	1	1	0	0	0.048206	27	1	0	1	1	1	1	1	1