SUPPLEMENTARY MATERIAL 1

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

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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. To ensure that a representative population, with as many patients as possible to describe interindividual variability and heterogeneity in symptom trajectories, studies that did not measure ACQ-5 but did measure ACT had their ACT scores converted to ACQ-5, based on the underlying score distributions and clinical status at baseline (i.e., well controlled, not-well controlled or poorly controlled). Nine clinical trials met the inclusion criteria. All patients enrolled into the selected clinical trials have given informed consent for participation. The terms of consent include the scope of the investigation presented here.

In total, 7,593 patients with accurate clinical and demographic baseline details were selected for the purposes of the current investigation. The available data was subsequently split into a model building and an internal validation data set. The model building data set 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. 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, reliever medication use, FEV_1 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: Given the availability of a longitudinal model previously developed for the evaluation of fluticasone propionate (FP) alone and in combination with salmeterol (SAL), which included drug- and disease-specific parameters, model development consisted in further characterisation of the influence of covariates and estimation of drug specific effects. Prior parameter distributions associated with individual differences in symptom trajectories (i.e., clinical and demographic baseline covariates) were evaluated during model building.

In brief, the longitudinal model is based on first-order rates and turnover concepts (Equations 1, 2 and 3) [1]. This approach has been applied in 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 [2-4]. The observed effect is considered a dynamic process. Asthma control, treatment effect and any other relevant covariates were parameterised relative to baseline symptoms (Equation 4). 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.

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

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

$$k_{out} = \frac{ACQ5(0)}{k_{in_{baseline}}} \quad \text{Eq. 3}$$

$$k_{in} = k_{in_{baseline}} + Eff_{trt} + Eff_{cov} \quad \text{Eq. 4}$$

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 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. 4) 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 phase was considered to be minimal as the analysis focused on the maintenance phase of the treatment.

The final model described the changes in ACQ-5 scores over time (Eq. 1 , Eq 2) taking into account the effect of treatment with FF monotherapy, FF/VI and BUD/FOR combination therapy. The parameterisation included baseline ACQ-5 (A_0), rate of increase (K_{in}) and rate of decrease (K_{out}) in symptoms.

$$k_{in} = \theta_{kin} * \left(1 + \theta_{BUD/FORM}\right) * \left(1 + \theta_{FF/VI}\right) * \left(1 + \theta_{previous\ smoker}\right) * \left(1 + \theta_{current\ smoker}\right) * \left(1 + (BMI - 26.26) * \theta_{BMI}\right) * \left(1 + (AGE - 41) * \theta_{Age}\right) * e^{\eta_{k_{in}}} \quad \text{Eq. 5}$$

$$k_{out} = \theta_{kout} * \left(1 + \theta_{BUD/FORM}\right) * \left(1 + \theta_{FF/VI}\right) * e^{\eta_{k_{out}}} \quad \text{Eq. 6}$$

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

In addition, in order to facilitate the clinical interpretation of the rate constant parameters, k_{in} and k_{out} have been re-parameterised as T_{50}, i.e., time associated with half of the final (maximum) shift in ACQ-5 scores and ACQ-5_{Tmax}, which represents the final (maximum) shift in symptoms and occurs at approximately 5 times the T_{50} (**Figure S1_1**, eqs. 7 and 8).

$$T_{50} = \frac{\ln 2}{k_{out}} \quad \text{Eq. 7}$$

$$ACQ5_{\ T_{max}} = \frac{k_{in}}{k_{out}} \quad \text{Eq. 8}$$

For clarity, a list of assumptions supporting the analysis and model parameterisation can be found in **Table S1_4.**

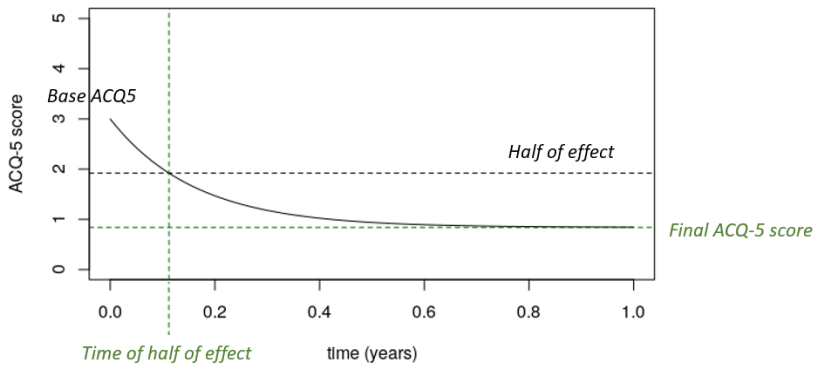

Figure S1_1: Modelling of individual symptom trajectories. Assessment of the clinical implications of an indirect response model describing symptom scores. Parameterisation of the time course of ACQ-5 scores based on the time to reach half of the maximum effect, along with estimates of the maximum, final effect, provide insight into the onset of action as well as on the magnitude of symptom improvement.

Model Evaluation and Predictive Performance: As indicated in the previous section, model development steps were limited to model refinement, assuming potentially different parameter estimates for drug effects, along with re-estimation of disease-related covariate effects based on informative priors. 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). Comparison of hierarchical models was based on the likelihood ratio test and standard error of the parameter estimates. The effect of additional covariates was assessed 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 >3.84 (χ^2<0.05 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 >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 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. The internal validation steps were considered as failed if an average relative

error and average relative variance (mean square error) ≥30% was observed for at least one of the model parameters.

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. VPCs were based on 200 replicates of the original data set along with the 95% prediction intervals. VPCs were created for the model fit, internal validation, and total datasets. A bootstrap of the model was performed with 2000 samples on the final model based on the total data set. The observed symptom trajectories were plotted over time along with the prediction intervals to visually assess the concordance between simulated and observed data. The final longitudinal model was assessed for its predictive performance to describe the individual symptom score trajectories based on stratification by baseline symptom control level and treatment.

Modelling development and evaluation were based on analytical solution and $PRED options in NONMEM v.7.5 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 7.5 through gFortran compiler and Perl-speaks-NONMEM (PsN) 5.3.0. All required data manipulation, including graphical and statistical summaries were performed in R (version 4.1.3). The NONMEM control file and output results for the final model are provided as attachment to this supplementary file.

Results

The age of the patients included in the population ranged from 18.0 to 91.0 years with a mean value of 48.3 years, whereas body weight ranged from 32.0 to 218.0 kg with a mean value of 80.2 kg. Mean symptom scores at baseline were 2.0 and 4.9 for ACQ-5 and AQLQ scores, respectively. Regarding lung function, as assessed by spirometry tests, FEV_1 at baseline ranged from 0.6 to 5.8 L with a mean value of 2.15 L, while PEF ranged from 79.9 to 773.0 L/min, with a mean value of 345.0 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 S1_1 and Table S1_2**. The distribution of the baseline characteristics per study are shown in **Figure S1_2**. The generalised pairs plot showing the relationship between the baseline demographics and clinical characteristics of the ITT population is displayed in **Figure S1_3**.

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 S1_4**). However, there was large overlap in the median ACQ-5 scores by treatment, indicating that there are other factors influencing symptom control (**Figure S1_5**). 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 S1_6**). As expected, there was a trend towards lower ACQ-5 scores with higher baseline AQLQ scores (i.e., better quality of life).

Despite large inter and intraindividual variability, the final model was able to describe the time course of symptom scores in individual patients. The goodness-of-fit plots revealed acceptable correlations between observed data and model-predictions, but residual variability remained relatively high even after inclusion of the selected covariates. Final model parameters are shown along with bootstrap

results in **Table S1_3**. A VPC of the total data set showed the observed data falls within the model predictions (**Figure S1_7, Figure S1_8 and Figure S1_9**), indicating no bias or other model mis-specifications. A sample of the individual model predictions, along with the observed ACQ-5 scores is shown in (**Figure S1_10**), **Figure S1_11** shows the predictive performance of the model to describe individual measurements over time.

It is worth noting that the proposed parameterisation showed important differences in drug-specific properties, which can lead to misinterpretation of clinical trial findings. First, it became evident that stabilisation of symptom scores requires time and maximum treatment response may not be reached within 12 weeks, which represents the duration of many studies in moderate-severe asthma. Here we have shown that while treatment with BUD/FOR leads to a significant, strong reduction on base time to T_{50}, but had minor effect on the base final (maximum) AQC-5 score. By contrast FF/VI, acts on both parameters, it reduces T_{50} and produces a large shift in the final ACQ-5 scores.

Table S1_1: Demographic and clinical baseline characteristics of the pooled patient population included in the modelling of individual ACQ-5 trajectories.

	BUD/FOR (N=1314)	FF (N=1348)	FF/VI (N=4931)	Overall (N=7593)
Age (y)				
Mean (SD)	46.8 (15.0)	46.5 (13.8)	49.2 (14.8)	48.3 (14.7)
Median [Min, Max]	47.0 [18.0, 88.0]	48.0 [18.0, 79.0]	50.0 [18.0, 91.0]	49.0 [18.0, 91.0]
Weight (kg)				
Mean (SD)	79.0 (18.6)	78.2 (18.8)	81.0 (19.6)	80.2 (19.3)
Median [Min, Max]	78.0 [37.0, 197]	76.0 [38.0, 166]	79.0 [32.0, 218]	78.0 [32.0, 218]
Missing	6 (0.5%)	0 (0%)	20 (0.4%)	26 (0.3%)
Height (cm)				
Mean (SD)	167 (10.0)	165 (10.2)	166 (10.0)	166 (10.0)
Median [Min, Max]	167 [131, 204]	164 [140, 201]	165 [130, 196]	165 [130, 204]
Missing	8 (0.6%)	0 (0%)	27 (0.5%)	35 (0.5%)
BMI (Kg/m2)				
Mean (SD)	28.2 (6.22)	28.5 (6.01)	29.2 (6.46)	28.9 (6.36)
Median [Min, Max]	27.1 [15.8, 69.4]	27.6 [15.1, 55.8]	28.3 [14.8, 67.5]	27.9 [14.8, 69.4]
Missing	9 (0.7%)	0 (0%)	31 (0.6%)	40 (0.5%)
Baseline ACQ-5				
Mean (SD)	1.96 (0.933)	2.07 (0.890)	2.05 (0.840)	2.03 (0.879)
Median [Min, Max]	2.00 [0, 5.00]	2.00 [0, 5.00]	2.00 [0, 5.60]	2.00 [0, 5.60]
Missing	391 (29.8%)	492 (36.5%)	3281 (66.5%)	4164 (54.8%)
Baseline qACQ-5*				
Mean (SD)	1.81 (0.945)	2.02 (0.840)	1.71 (0.917)	1.78 (0.916)
Median [Min, Max]	1.80 [0, 5.00]	2.00 [0, 5.00]	1.64 [0, 6.00]	1.80 [0, 6.00]

	BUD/FOR (N=1314)	FF (N=1348)	FF/VI (N=4931)	Overall (N=7593)
Baseline ACT				
Mean (SD)	16.5 (4.33)	14.0 (3.35)	16.1 (4.31)	15.9 (4.27)
Median [Min, Max]	17.0 [6.00, 25.0]	14.0 [6.00, 25.0]	16.0 [5.00, 25.0]	16.0 [5.00, 25.0]
Missing	923 (70.2%)	856 (63.5%)	1650 (33.5%)	3429 (45.2%)
Baseline AQLQ				
Mean (SD)	5.01 (1.10)	4.47 (1.01)	4.88 (1.13)	4.86 (1.13)
Median [Min, Max]	5.16 [1.50, 6.94]	4.50 [1.94, 6.66]	4.94 [1.13, 7.00]	4.91 [1.13, 7.00]
Missing	705 (53.7%)	860 (63.8%)	858 (17.4%)	2423 (31.9%)
Baseline FEV1				
Mean (SD)	2.44 (0.814)	2.11 (0.642)	2.09 (0.686)	2.15 (0.711)
Median [Min, Max]	2.34 [0.790, 5.56]	1.99 [0.750, 4.55]	1.98 [0.603, 5.81]	2.04 [0.603, 5.81]
Missing	393 (29.9%)	3 (0.2%)	1895 (38.4%)	2291 (30.2%)
Baseline FEV1P				
Mean (SD)	78.6 (16.7)	68.0 (11.5)	68.6 (14.2)	70.2 (14.6)
Median [Min, Max]	78.6 [30.8, 143]	68.5 [40.1, 92.9]	68.7 [24.1, 155]	70.1 [24.1, 155]
Missing	393 (29.9%)	3 (0.2%)	1895 (38.4%)	2291 (30.2%)
Baseline PEF				
Mean (SD)	383 (108)	334 (122)	327 (110)	345 (114)
Median [Min, Max]	376 [138, 770]	321 [81.3, 773]	317 [79.7, 749]	336 [79.7, 773]
Missing	391 (29.8%)	856 (63.5%)	3293 (66.8%)	4540 (59.8%)
FeNO (ppb)				
Mean (SD)	NA (NA)	NA (NA)	25.8 (21.4)	25.8 (21.4)
Median [Min, Max]	NA [NA, NA]	NA [NA, NA]	19.0 [5.00, 193]	19.0 [5.00, 193]
Missing	1314 (100%)	1348 (100%)	4186 (84.9%)	6848 (90.2%)
Sex				
Male	787 (59.9%)	905 (67.1%)	3089 (62.6%)	4781 (63.0%)
Female	527 (40.1%)	443 (32.9%)	1842 (37.4%)	2812 (37.0%)
Baseline Smoking (N/F/C)				
Never smoked	774 (58.9%)	993 (73.7%)	3256 (66.0%)	5023 (66.2%)
Former smoker	376 (28.6%)	184 (13.6%)	1087 (22.0%)	1647 (21.7%)
Current smoker	162 (12.3%)	0 (0%)	395 (8.0%)	557 (7.3%)
Missing	2 (0.2%)	171 (12.7%)	193 (3.9%)	366 (4.8%)
Previous Inhaled Corticosteroids				
< 6 months	44 (3.3%)	0 (0%)	0 (0%)	44 (0.6%)
>= 6 months to < 1 year	52 (4.0%)	0 (0%)	0 (0%)	52 (0.7%)

	BUD/FOR (N=1314)	FF (N=1348)	FF/VI (N=4931)	Overall (N=7593)
>= 1 year to 5 years	226 (17.2%)	0 (0%)	0 (0%)	226 (3.0%)
>= 5 years to 10 years	182 (13.9%)	0 (0%)	0 (0%)	182 (2.4%)
>= 10 years to 15 years	95 (7.2%)	0 (0%)	0 (0%)	95 (1.3%)
>= 15 years to 20 years	46 (3.5%)	0 (0%)	0 (0%)	46 (0.6%)
>= 20 years to 25 years	17 (1.3%)	0 (0%)	0 (0%)	17 (0.2%)
>= 25 years	18 (1.4%)	0 (0%)	0 (0%)	18 (0.2%)
Missing	634 (48.2%)	1348 (100%)	4931 (100%)	6913 (91.0%)
Asthma Duration				
< 6 months	1 (0.1%)	10 (0.7%)	11 (0.2%)	22 (0.3%)
>= 6 months to < 1 year	32 (2.4%)	70 (5.2%)	66 (1.3%)	168 (2.2%)
>= 1 to 5 years	174 (13.2%)	190 (14.1%)	269 (5.5%)	633 (8.3%)
>= 5 to 10 years	191 (14.5%)	217 (16.1%)	377 (7.6%)	785 (10.3%)
>= 10 to 15 years	132 (10.0%)	160 (11.9%)	249 (5.0%)	541 (7.1%)
>= 15 to 20 years	106 (8.1%)	146 (10.8%)	197 (4.0%)	449 (5.9%)
>= 20 to 25 years	87 (6.6%)	107 (7.9%)	179 (3.6%)	373 (4.9%)
>= 25 years	200 (15.2%)	277 (20.5%)	510 (10.3%)	987 (13.0%)
Missing	391 (29.8%)	171 (12.7%)	3073 (62.3%)	3635 (47.9%)
Exacerbation History				
Zero previous exacerbations	647 (49.2%)	411 (30.5%)	1118 (22.7%)	2176 (28.7%)
One previous exacerbation	162 (12.3%)	71 (5.3%)	586 (11.9%)	819 (10.8%)
More than one previous exacerbation	114 (8.7%)	10 (0.7%)	139 (2.8%)	263 (3.5%)
Missing	391 (29.8%)	856 (63.5%)	3088 (62.6%)	4335 (57.1%)

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 (5^{th} - 95^{th} percentiles).

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

Table S1_2: Demographic and clinical baseline characteristics of the pooled patient population included in the modelling of individual ACQ-5 trajectories stratified by study.

	40040 (N=680)	40056 (N=243)	106829 (N=351)	106837 (N=1696)	113091 (N=368)	115150 (N=2271)	116492 (N=203)	116863 (N=971)	205715 (N=810)	Overall (N=7593)
Treatment										
BUD/FOR	680 (100%)	243 (100%)	0 (0%)	0 (0%)	0 (0%)	391 (17.2%)	0 (0%)	0 (0%)	0 (0%)	1314 (17.3%)
FF	0 (0%)	0 (0%)	171 (48.7%)	856 (50.5%)	0 (0%)	0 (0%)	0 (0%)	321 (33.1%)	0 (0%)	1348 (17.8%)
FF/VI	0 (0%)	0 (0%)	180 (51.3%)	840 (49.5%)	368 (100%)	1880 (82.8%)	203 (100%)	650 (66.9%)	810 (100%)	4931 (64.9%)
Age (y)										
Mean (SD)	47.2 (14.5)	43.4 (13.5)	46.6 (13.7)	46.2 (13.8)	46.3 (13.9)	49.5 (16.1)	49.4 (14.5)	47.8 (13.8)	53.6 (13.2)	48.3 (14.7)
Median [Min, Max]	48.0 [18.0, 82.0]	42.4 [18.7, 74.0]	48.0 [18.0, 74.0]	47.0 [18.0, 82.0]	47.0 [18.0, 79.0]	50.0 [18.0, 91.0]	51.0 [19.0, 75.0]	48.0 [18.0, 82.0]	55.0 [19.0, 85.0]	49.0 [18.0, 91.0]
Weight (kg)										
Mean (SD)	76.4 (16.4)	77.1 (17.6)	79.8 (17.5)	76.8 (19.0)	75.3 (19.4)	84.0 (20.2)	81.0 (17.9)	81.5 (19.4)	81.3 (18.8)	80.2 (19.3)
Median [Min, Max]	75.0 [40.0, 154]	75.0 [37.0, 167]	78.5 [45.0, 149]	74.0 [32.0, 184]	72.9 [39.5, 155]	82.0 [38.0, 218]	78.0 [50.0, 140]	79.0 [40.0, 177]	79.7 [40.0, 156]	78.0 [32.0, 218]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (1.1%)	0 (0%)	0 (0%)	0 (0%)	26 (0.3%)
Height (cm)										
Mean (SD)	167 (10.2)	168 (9.47)	168 (9.65)	164 (9.90)	163 (10.7)	167 (10.1)	167 (9.37)	167 (10.0)	166 (9.45)	166 (10.0)
Median [Min, Max]	167 [140, 204]	168 [147, 193]	168 [142, 196]	163 [136, 201]	163 [140, 193]	167 [130, 196]	167 [145, 191]	166 [141, 197]	165 [134, 195]	165 [130, 204]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (1.5%)	0 (0%)	0 (0%)	0 (0%)	35 (0.5%)
BMI (Kg/m2)										
Mean (SD)	27.3 (5.41)	27.2 (6.04)	28.1 (5.64)	28.4 (6.17)	28.0 (6.26)	30.0 (6.84)	29.1 (5.82)	29.2 (6.24)	29.3 (6.19)	28.9 (6.36)
Median [Min, Max]	26.6 [17.4, 56.0]	26.3 [15.8, 55.9]	27.4 [17.2, 51.5]	27.5 [14.8, 67.5]	26.9 [17.0, 52.5]	28.7 [15.6, 69.4]	28.7 [19.3, 52.1]	28.1 [15.1, 55.1]	28.4 [17.3, 60.4]	27.9 [14.8, 69.4]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	40 (1.8%)	0 (0%)	0 (0%)	0 (0%)	40 (0.5%)
Baseline ACQ-5										

	40040 (N=680)	40056 (N=243)	106829 (N=351)	106837 (N=1696)	113091 (N=368)	115150 (N=2271)	116492 (N=203)	116863 (N=971)	205715 (N=810)	Overall (N=7593)
Mean (SD)	2.03 (0.956)	1.74 (0.829)	NA (NA)	2.08 (0.893)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	2.02 (0.777)	2.03 (0.879)
Median [Min, Max]	2.00 [0, 5.00]	1.80 [0, 4.00]	NA [NA, NA]	2.00 [0, 5.60]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	2.00 [0, 4.60]	2.00 [0, 5.60]
Missing	0 (0%)	0 (0%)	351 (100%)	0 (0%)	368 (100%)	2271 (100%)	203 (100%)	971 (100%)	0 (0%)	4164 (54.8%)
Baseline ACQ-5*										
Mean (SD)	2.03 (0.956)	1.74 (0.829)	1.99 (0.737)	2.08 (0.893)	1.03 (0.796)	1.48 (0.934)	1.24 (0.284)	1.93 (0.771)	2.02 (0.777)	1.78 (0.916)
Median [Min, Max]	2.00 [0, 5.00]	1.80 [0, 4.00]	1.84 [0.03, 3.89]	2.00 [0, 5.60]	0.921 [0.0317, 6.00]	1.26 [0.03,6.00]	1.26 [0.76, 2.81]	1.84 [0.17, 4.46]	2.00 [0, 4.60]	1.80 [0, 6.00]
Baseline ACT										
Mean (SD)	NA (NA)	NA (NA)	13.7 (3.33)	NA (NA)	18.8 (4.16)	16.4 (4.41)	17.2 (1.55)	14.0 (3.46)	NA (NA)	15.9 (4.27)
Median [Min, Max]	NA [NA, NA]	NA [NA, NA]	14.0 [7.00, 25.0]	NA [NA, NA]	19.0 [5.00, 25.0]	17.0 [5.00, 25.0]	17.0 [10.0, 20.0]	14.0 [6.00, 24.0]	NA [NA, NA]	16.0 [5.00, 25.0]
Missing	680 (100%)	243 (100%)	0 (0%)	1696 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	810 (100%)	3429 (45.2%)
Baseline AQLQ										
Mean (SD)	NA (NA)	4.90 (0.922)	4.41 (0.956)	NA (NA)	5.34 (1.11)	5.02 (1.19)	5.01 (0.893)	4.46 (1.05)	4.83 (1.01)	4.86 (1.13)
Median [Min, Max]	NA [NA, NA]	4.94 [2.28,6.81]	4.34 [1.97, 6.56]	NA [NA, NA]	5.56 [1.13, 7.00]	5.19 [1.31, 7.00]	4.94 [2.66, 7.00]	4.47 [1.55, 7.00]	4.90 [1.90, 7.00]	4.91 [1.13, 7.00]
Missing	680 (100%)	25 (10.3%)	6 (1.7%)	1696 (100%)	9 (2.4%)	0 (0%)	4 (2.0%)	1 (0.1%)	2 (0.2%)	2423 (31.9%)
Baseline FEV1										
Mean (SD)	2.39 (0.851)	2.56 (0.686)	2.16 (0.664)	2.15 (0.643)	1.98 (0.638)	NA (NA)	2.78 (0.893)	1.95 (0.580)	2.00 (0.678)	2.15 (0.711)
Median [Min, Max]	2.27 [0.79, 5.56]	2.48 [1.28, 4.50]	2.06 [0.86, 4.55]	2.04 [0.70, 4.54]	1.87 [0.70, 4.03]	NA [NA, NA]	2.63 [0.93, 5.81]	1.87 [0.78, 4.02]	1.92 [0.60, 4.86]	2.04 [0.60, 5.81]
Missing	1 (0.1%)	1 (0.4%)	5 (1.4%)	0 (0%)	2 (0.5%)	2271 (100%)	6 (3.0%)	3 (0.3%)	2 (0.2%)	2291 (30.2%)
Baseline FEV1P										

	40040 (N=680)	40056 (N=243)	106829 (N=351)	106837 (N=1696)	113091 (N=368)	115150 (N=2271)	116492 (N=203)	116863 (N=971)	205715 (N=810)	Overall (N=7593)
Mean (SD)	78.1 (18.1)	80.1 (11.6)	66.5 (12.4)	70.9 (10.6)	67.5 (11.8)	NA (NA)	89.1 (19.8)	61.7 (10.2)	67.5 (15.0)	70.2 (14.6)
Median [Min, Max]	76.6 [30.8, 143]	81.2 [41.1, 109]	67.3 [40.1, 90.0]	71.3 [45.1, 99.0]	69.8 [40.4, 87.8]	NA [NA, NA]	89.0 [34.0, 155]	62.1 [39.9, 80.1]	68.7 [24.1, 108]	70.1 [24.1, 155]
Missing	1 (0.1%)	1 (0.4%)	5 (1.4%)	0 (0%)	2 (0.5%)	2271 (100%)	6 (3.0%)	3 (0.3%)	2 (0.2%)	2291 (30.2%)
Baseline PEF										
Mean (SD)	386 (111)	375 (97.6)	330 (119)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	326 (116)	331 (106)	345 (114)
Median [Min, Max]	379 [138, 770]	363 [153, 688]	315 [79.7, 773]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	313 [88.3, 749]	324 [87.0, 723]	336 [79.7, 773]
Missing	0 (0%)	0 (0%)	0 (0%)	1696 (100%)	368 (100%)	2271 (100%)	203 (100%)	0 (0%)	2 (0.2%)	4540 (59.8%)
Sex										
Male	402 (59.1%)	149 (61.3%)	205 (58.4%)	1214 (71.6%)	235 (63.9%)	1331 (58.6%)	142 (70.0%)	600 (61.8%)	503 (62.1%)	4781 (63.0%)
Female	278 (40.9%)	94 (38.7%)	146 (41.6%)	482 (28.4%)	133 (36.1%)	940 (41.4%)	61 (30.0%)	371 (38.2%)	307 (37.9%)	2812 (37.0%)
Baseline Smoking (N/F/C)										
Never smoked	427 (62.8%)	141 (58.0%)	0 (0%)	1432 (84.4%)	291 (79.1%)	1115 (49.1%)	136 (67.0%)	808 (83.2%)	673 (83.1%)	5023 (66.2%)
Former smoker	181 (26.6%)	82 (33.7%)	0 (0%)	264 (15.6%)	77 (20.9%)	696 (30.6%)	47 (23.2%)	163 (16.8%)	137 (16.9%)	1647 (21.7%)
Current smoker	72 (10.6%)	20 (8.2%)	0 (0%)	0 (0%)	0 (0%)	445 (19.6%)	20 (9.9%)	0 (0%)	0 (0%)	557 (7.3%)
Missing	0 (0%)	0 (0%)	351 (100%)	0 (0%)	0 (0%)	15 (0.7%)	0 (0%)	0 (0%)	0 (0%)	366 (4.8%)
FeNO (ppb)										
Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	25.8 (21.4)	25.8 (21.4)
Median [Min, Max]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	19.0 [5.00, 193]	19.0 [5.00, 193]
Missing	680 (100%)	243 (100%)	351 (100%)	1696 (100%)	368 (100%)	2271 (100%)	203 (100%)	971 (100%)	65 (8.0%)	6848 (90.2%)
Eosinophil (%)										

	40040 (N=680)	40056 (N=243)	106829 (N=351)	106837 (N=1696)	113091 (N=368)	115150 (N=2271)	116492 (N=203)	116863 (N=971)	205715 (N=810)	Overall (N=7593)
Mean (SD)	NA (NA)	NA (NA)	0.267 (0.217)	0.300 (0.262)	NA (NA)	NA (NA)	NA (NA)	0.300 (0.318)	0.316 (0.257)	0.300 (0.273)
Median [Min, Max]	NA [NA, NA]	NA ¶[NA, NA]	0.210 [0, 1.51]	0.230 [0, 2.98]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	0.220 [0, 5.41]	0.250 [0, 1.61]	0.230 [0, 5.41]
Missing	680 (100%)	243 (100%)	38 (10.8%)	88 (5.2%)	368 (100%)	2271 (100%)	203 (100%)	76 (7.8%)	56 (6.9%)	4023 (53.0%)

Figure S1_2: Distribution of demographic and clinical baseline characteristics stratified by study.

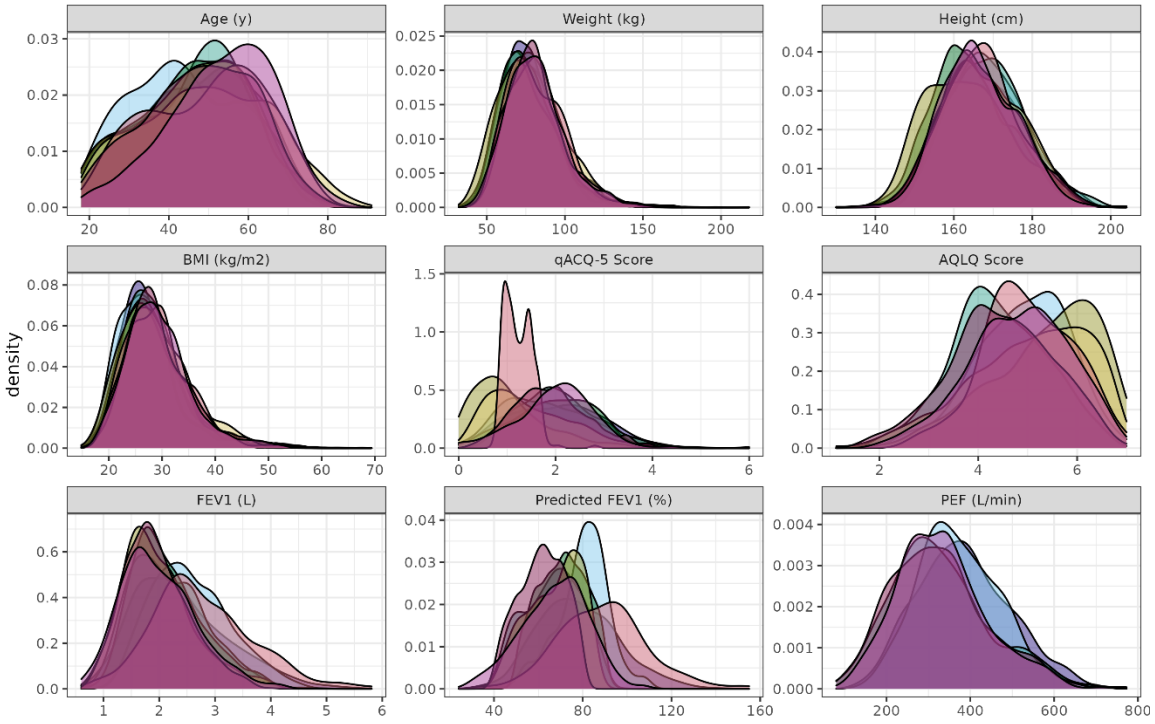

Figure S1_3*:* Generalised pairs plot. Panels show the correlations between the main demographics and clinical characteristics at baseline, which were tested during model development. Solid circles indicate individual observed values for each variable. The black solid line is a general linear function 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.

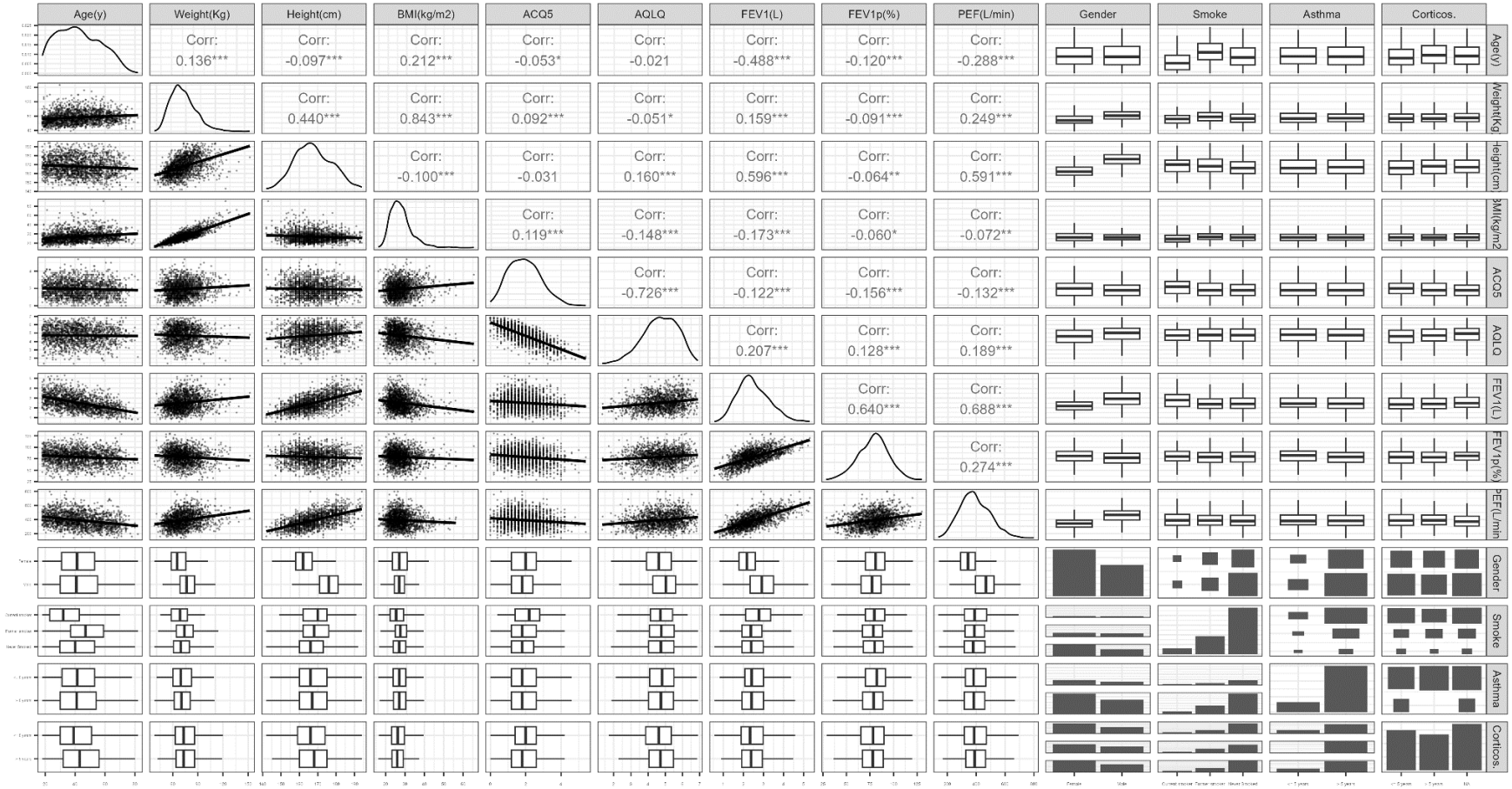

Figure S1_4: ACQ-5 score trajectories stratified by baseline asthma symptom ACQ-5. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles.

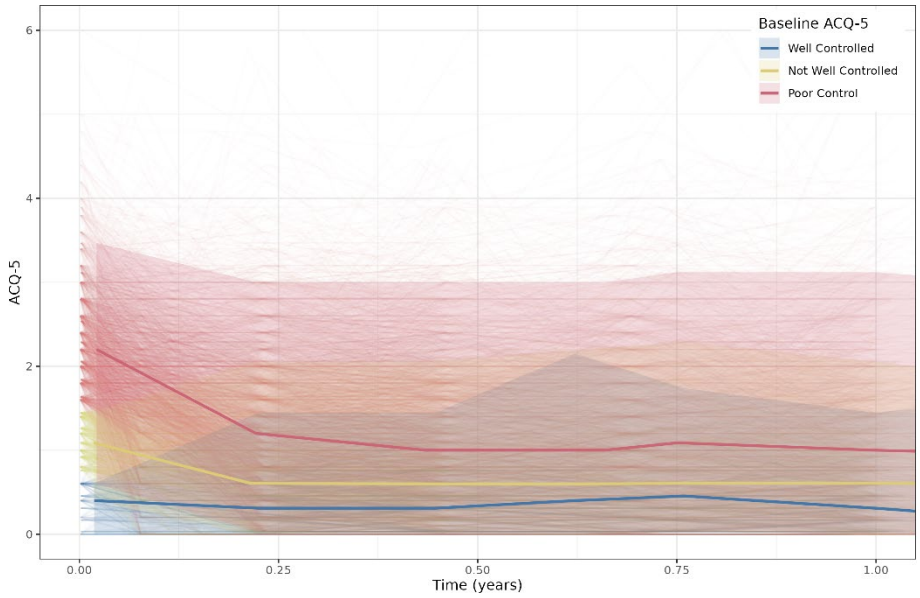

Figure 1: ACQ-5 score trajectories stratified by treatment. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles.

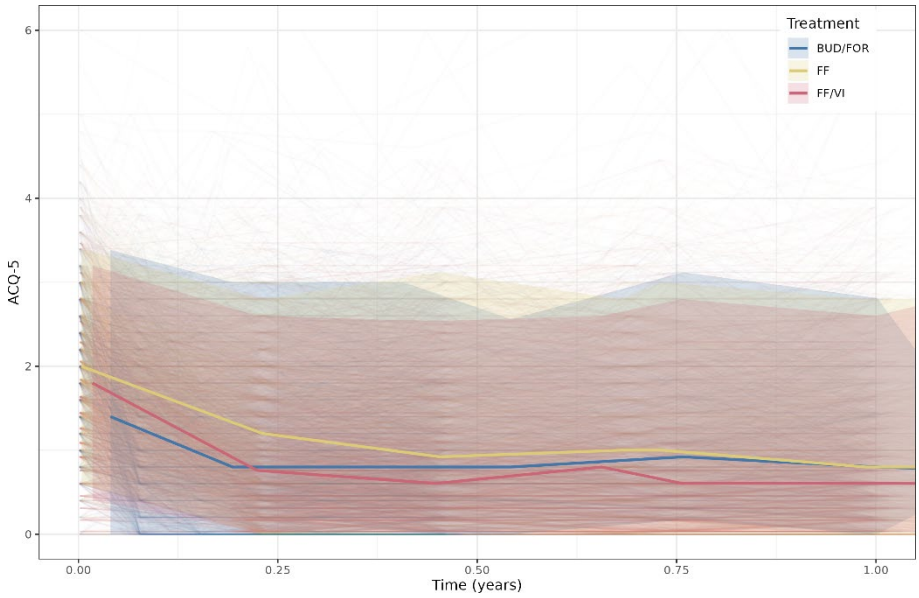

Figure S1_6*:* ACQ-5 scores stratified by demographic baseline characteristics. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, 10th -90th percentiles. No race covariate data available for longitudinal ACQ5 data set.

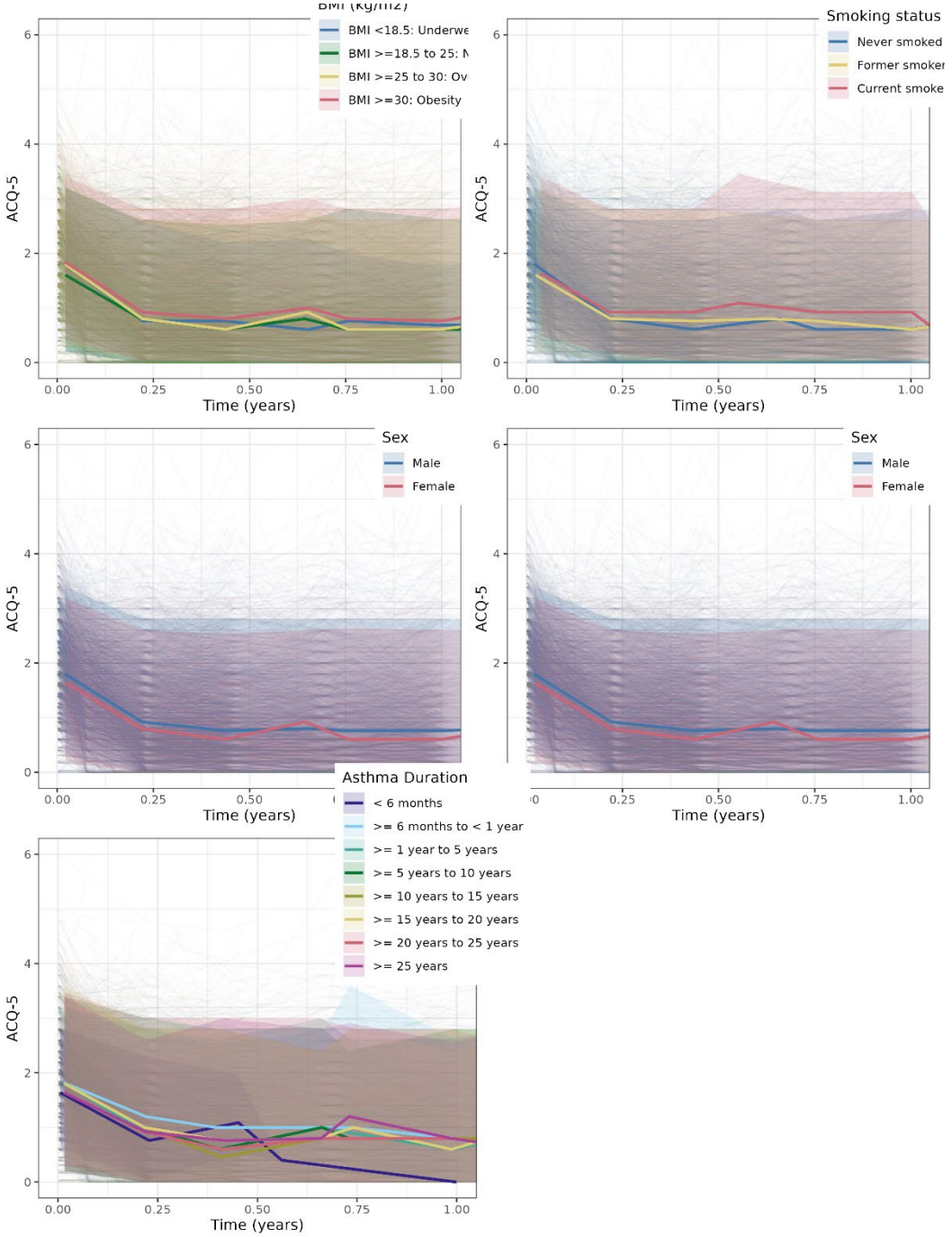

Table S1_3: Parameter estimates of the longitudinal model describing the individual ACQ-5 trajectories in moderate-severe asthma patients. The model is parameterised as a turnover rate (k_{in}/k_{out}) that includes the effect of treatment with FF monotherapy, and FF/VI and BUD/FOR combination therapy on ACQ-5 (equations 1–4). 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 [2–4]. Baseline ACQ-5, rate of increase (K_{in}) and rate of decrease (K_{out}) were identified as the primary determinants of changes in individual ACQ-5 scores over time but have been parameterised as time corresponding to half of the final ACQ-5, and final (maximum) shift in ACQ-5 score (equations 7–8).

	Parameter	Estimate	SE	RSE (%)	Bootstrap median (5^{th} – 95^{th} percentiles)
Population parameters	Base T_{50} – time at half of the max shift [years]	0.11	0.01	6	0.11 (0.11 - 0.13)
	Base maximum shift ACQ-5 [score]	0.87	0.02	2.6	0.86 (0.82 - 0.89)
Age	Age effect (fractional increase in ACQ-5 score at T_{max} per year)	0.005	0.0007	13.1	0.006 (0.004 - 0.007)
BMI	BMI effect (fractional increase in final ACQ-5 score per kg/m^2)	0.016	0.0019	11.6	0.016 (0.013 - 0.019)
Smoking	Former smoker relative to never smoked (fractional increase in final ACQ-5 score)	0.009	0.0257	286.4	0.008 (-0.033 - 0.053)
	Current smoker relative to never smoked (fractional increase in final ACQ-5 score)	0.339	0.0464	13.7	0.337 (0.264 - 0.419)
	BUD/FOR effect relative to FF (fractional increase in final ACQ-5 score)	-0.094	0.0347	36.9	-0.09 (-0.144 - -0.03)
	FF/VI effect relative to FF (fractional increase in final ACQ-5 score)	-0.251	0.0224	8.9	-0.244 (-0.271 - -0.199)
	BUD/FOR effect relative to FF (fractional increase in T_{50})	-0.684	0.0312	4.6	-0.661 (-0.686 - -0.593)
	FF/VI effect relative to FF (fractional increase in T_{50})	-0.243	0.0501	20.6	-0.25 (-0.379 - -0.222)
Interindividual variability	Inter individual variability in k_{in} (ηk_{in})	1.63	0.102	6.3	1.71 (1.56 - 1.89)
	Inter individual variability correlation between η_{kin} and ηk_{out}	1.4	0.0921	6.6	1.46 (1.35 - 1.64)
	Inter individual variability in k_{out} (ηk_{out})	1.64	0.120	7.4	1.69 (1.55 - 1.94)
Residual error	Residual error	0.45	0.0057	1.3	0.45 (0.44 - 0.46)

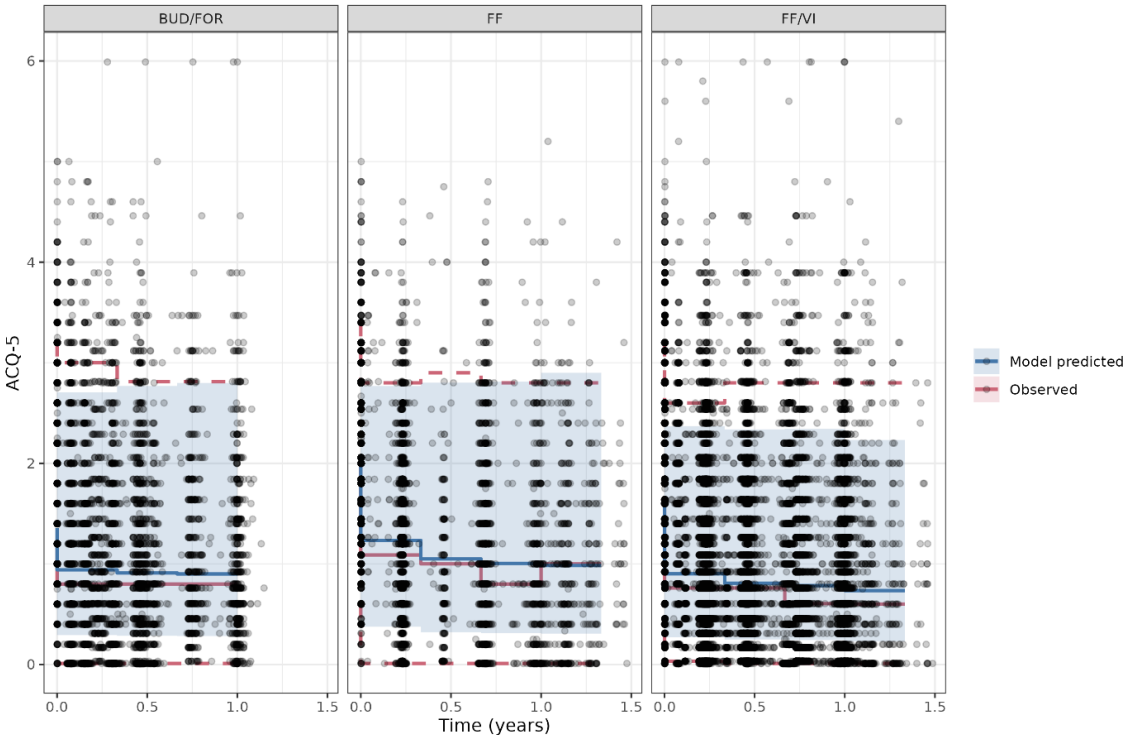

Figure S1_7: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories. Blue shaded area depicts the 5th and 95th percentiles of the model predictions. Dashed and solid red lines are the 5th and 95th percentiles and median of the observed ACQ-5 scores, respectively. Blue solid lines are the median model predicted ACQ-5 scores. Black dots are individual observed ACQ-5 scores.

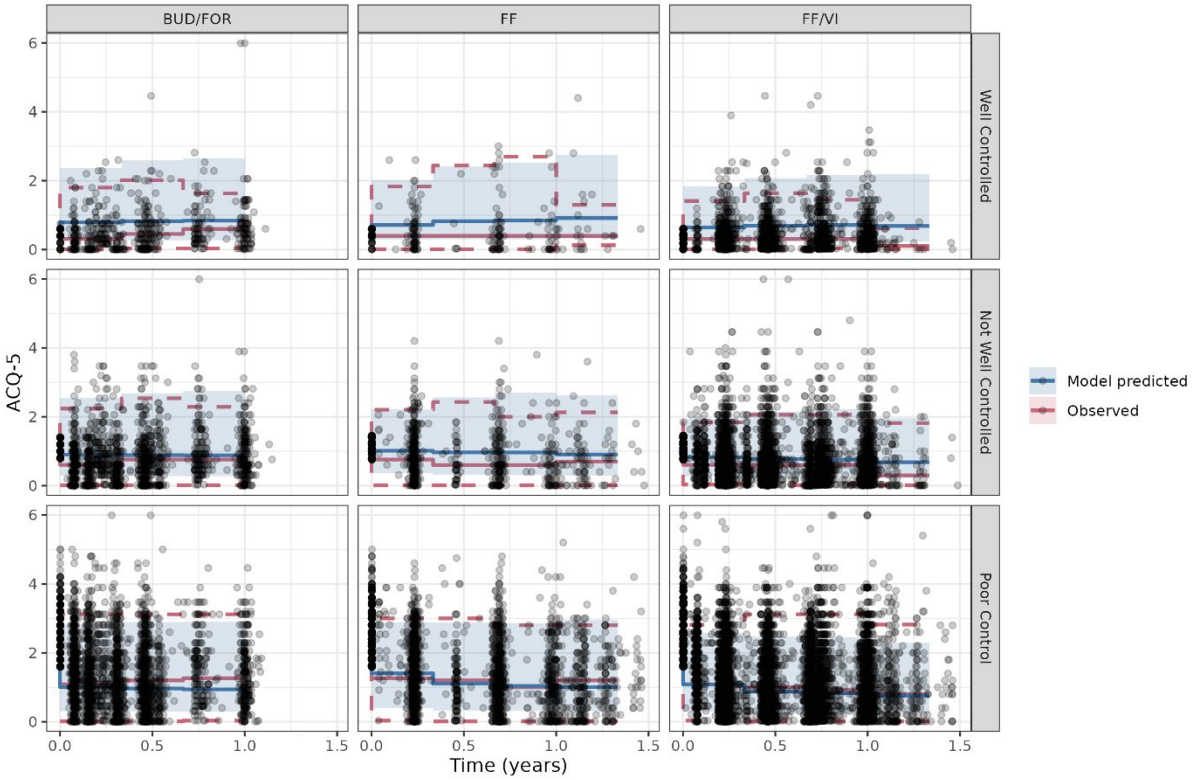

Figure S1_8: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories, stratified by symptom control level at baseline. Panels depict model performance for randomly selected subset of the population (i.e., 70% of the available data). Blue shaded area depicts the 5th 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.

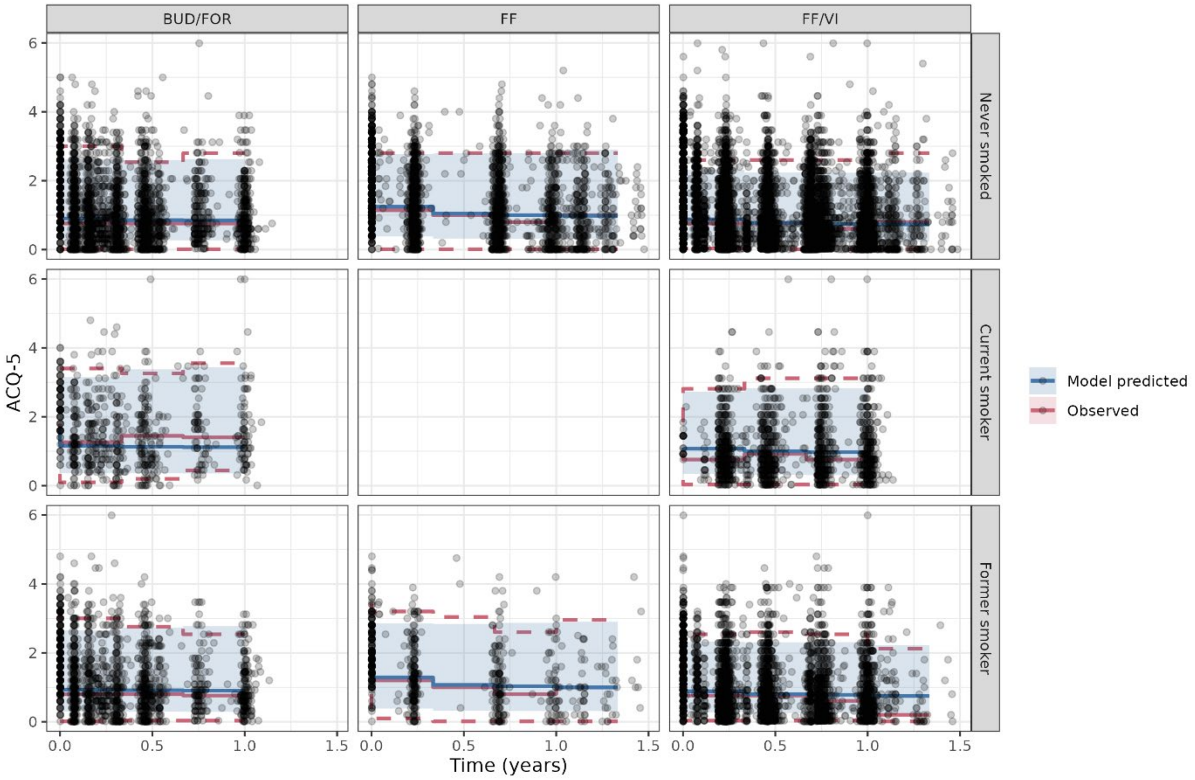

Figure S1_9: Visual predictive check of the longitudinal model describing individual ACQ-5 trajectories, stratified by smoking status at baseline. Panels depict model performance for the internal validation subset (i.e., 30% of the available data). Blue shaded area depicts the 5th and 95th percentiles 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.

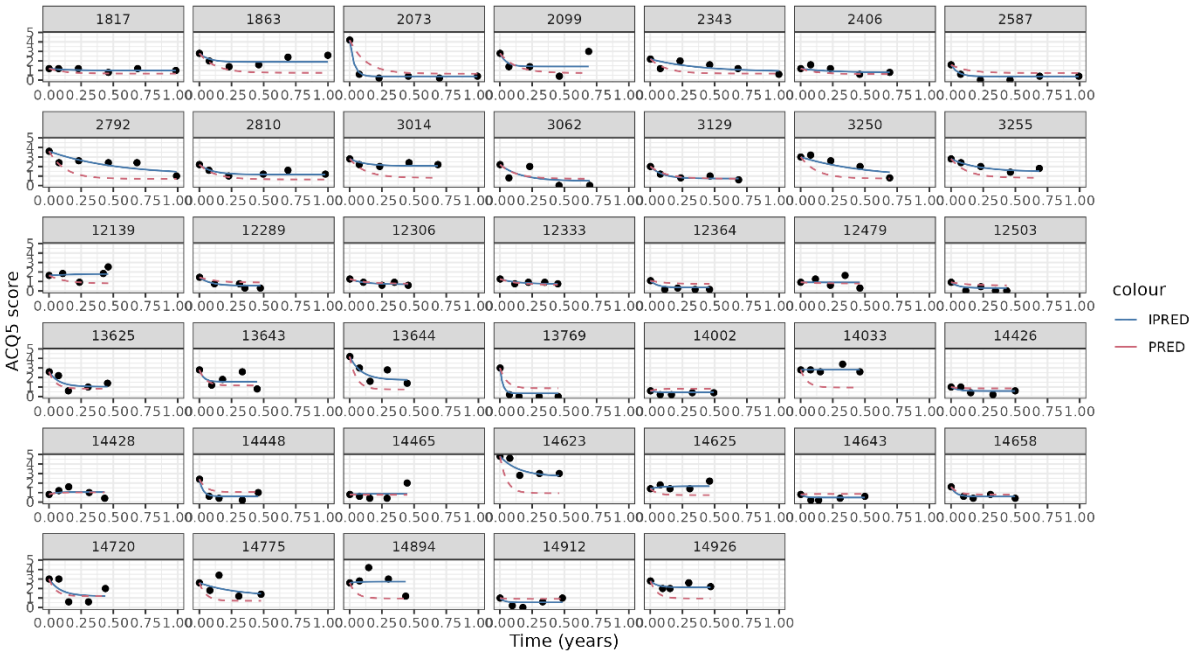

Figure S1_10: Randomly selected individual ACQ-5 trajectories over the period of up to 12 months. Black dots are observed ACQ-5 scores. Dashed red lines and solid blue lines depict the population predicted (PRED)and individual predicted values (IPRED), respectively.

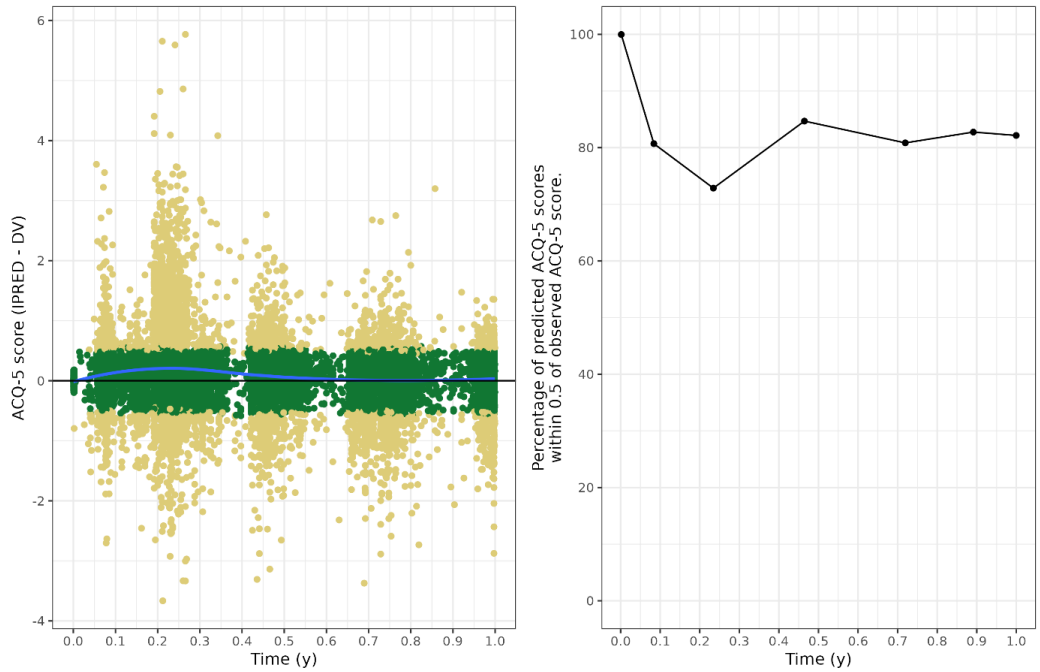

Figure S1_11: Goodness-of-fit plot of the longitudinal model describing individual ACQ-5 measurements. Left panel shows the data included in the model, green dots are measurements that were predicted within 0.5 points of the measured ACQ-5 score, i.e., the minimal clinically important difference. Right panel shows that despite the relatively large unexplained variability in the data, on average around 80% of predicted values were between 0 and <0.5 points from the measured scores.

Table S1_4: Overview of the main assumptions supporting model parameterisation and analysis of the ACQ-5 over time in asthma patients with moderate-severe symptoms**.**

Assumption	Implications for model parameterisation and/or model interpretation	Notes
A patient whose asthma symptoms are under control also has a significant reduction in future risk	This implies that short fluctuations in symptom control level influences instantaneous risk and reliever medication use.	
Individual patient characteristics contribute the differences in symptom control, irrespective of treatment or intervention.	Clinical and demographic baseline characteristics were evaluated as discrete or continuous covariates, and found to affect individual symptom trajectories .	As biomarker data (e.g. FeNO and eosinophil counts) were limited, they were not evaluated as baseline covariates in this population. Similarly, diary cards on reliever medication use were not collected in all studies. Therefore reliever medication use was modelled separately, including ACQ-5 as a baseline covariate in that model.
The measurement of asthma symptoms through ACQ-5 or ACT captures similar aspects of the condition, even though ACT does incorporate information on reliever use (item 4 of the test). Conversion of the scales (ACT to ACQ-5) provides an accurate description of the symptoms at individual patient level.	The conversion of scales was based on the score distributions within each category, i.e., well controlled, not-well controlled, and poorly controlled. This allowed for accurate matching of the patients across the different scales. However, goodness-of-fit plots revealed higher variability in studies which ACT scores were converted to ACQ-5.	Patient symptom distribution at baseline and during the course of treatment appears to be comparable across studies, allowing for pooling of the data the purpose of this analysis.
When exacerbations or triggers can affect symptom scores. Such an event may have prolonged duration,	This implies that intraindividual as well as interindividual fluctuations in symptom trajectory	Exploratory analysis showed that patients who have prior history of

which outlasts the period of exposure to a trigger or exacerbation..	may have a time-varying component associated with trigger and exacerbation events, which are not always recorded in a clinical study. Such fluctuations may need to be treated as residual, unexplained variability.	exacerbations show higher ACQ-5 levels throughout the course of treatment. This variation in symptoms is further affected by treatment (i.e. drug=specific differences).
As the use of placebo intervention is not ethically acceptable, individual symptom trajectories are not available. Baseline estimates describing symptom trajectory will be associated with the severity and level of control at the start of treatment using data from patients receiving ICS monotherapy.	Base Kin and Kout were estimated using data from patients receiving FF monotherapy. All other treatments were estimated relative to this effect.	Whilst the use of a placebo control might have provided insight into the actual disease burden, treatment duration would have been too short to account for the effect of extrinsic factors, such as seasonal differences. In addition, the use of placebo would have been confounded by the effect of reliever medication, which would be significantly higher in the absence of ICS or ICS/LABA maintenance therapy.
The mean or median dose of ICS or ICS/LABA used in each treatment arm was considered representative of the treatment effect, irrespective of individual variation during titration and/or maintenance phase.	Given the symptomatic nature of the interventions and the known dose-exposure-response curves for inhaled corticosteroids, short-lasting variations in dose levels were therefore not considered as a baseline covariate.	This assumption applies to currently available ICS and ICS/LABA combinations when considering regular dosing and comparable symptom severity range (moderate-severe asthma)
Treatment effect is assumed to be independent from baseline characteristics. In addition, it is assumed that there is no interaction between drug-specific and patient-specific factors.	Baseline characteristics are defined as additive items, modifying the basal rates (Kin and Kout), under the assumption that patients are at steady-state condition, and disease is not progressing	

	within the treatment period (i.e., minor net variation in Kin/Kout)	
Interindividual pharmacokinetic differences are assumed to have minor implications for pharmacodynamics and other clinical endpoints, as the doses used in Phase 3 and 4 protocols are associated with the upper part of the dose-exposure-response curve.	Drug exposure was not included as a source of variability in the model. Eventually, the effect of interindividual differences in drug exposure were captured by the residual error.	
Adherence to regular (maintenance) dosing was assumed to be comparable across studies given the similarity in patient population and protocol designs. As such, it was treated as a constant random factor for the purposes of this analysis.	As adherence measurement was not standardised or eventually measured in the same way in all studies, the effect of adherence was not evaluated as a covariate during model development. If any, the effect of variable adherence was captured in the residual error.	
Drop out and/or patient withdrawal during treatment were assumed to be random and non-informative, with minor or no effect on parameter estimates (baseline covariates or treatment).	It is unlikely that dropout or withdrawal has an effect on parameter estimates, as the number of subjects who may have dropped out was very low. If any, the effect of drop-out and/or patient withdrawal was captured by the residual error.	

References

1. Oosterholt S, Pavord ID, Brusselle G, et al. Modelling Asthma TrEatment Responses (MASTER): Effect of individual patient characteristics on the risk of exacerbation in moderate or severe asthma: A time-to-event analysis of randomized clinical trials. Br J Clin Pharmacol. 2023; 89(11):3273–3290
2. 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.
3. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm. 1993; 21:457–478.
4. 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.

Attachment

NONMEM control file final model

```
$SIZES      MAXIDS=15000 LVR=35
$PROBLEM    ACQ5
$INPUT      ID TIME ACQ5 EACQ5 QACQ5 ACQ5BL EACQ5BL QACQ5BL STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL PEFBL FEV1BL
FEV1PBL RACEC SH EXAHIST NHASEX TRTNO TRTNOCSUM YDAY AMT EAMT QAMT CMT MDV EVID YY SET1 SET2 SET3 OBASE DV2 EBASE EDV2 BASE DV
$DATA      ACQ_v5.txt IGNORE=@ IGNORE=(BASE.LT.0) IGNORE=(SET1.EQ.0) ;IGNORE=(ID.GE.1502)

$PRIOR NWPRI NTHETA=17 NETA=2 NTHP=11 NETP=0

$PRED

;;; KOUTTRTNUM-DEFINITION START
IF(TRTNUM.EQ.7) KOUTTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.5) KOUTTRTNUM = ( 1 + THETA(14)) ;BUD/FOR
IF(TRTNUM.EQ.9) KOUTTRTNUM = ( 1 + THETA(15)) ;FF/VI
;;; KOUTTRTNUM-DEFINITION END

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


;;; KINTRTNUM-DEFINITION START
IF(TRTNUM.EQ.7) KINTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.5) KINTRTNUM = ( 1 + THETA(12))
IF(TRTNUM.EQ.9) KINTRTNUM = ( 1 + THETA(13))
;;; 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))
IF(BMIBL.EQ.-999) KINBMIBL = 1

;;; KINBMIBL-DEFINITION END


;;; KINAGEBL-DEFINITION START
KINAGEBL = ( 1 + THETA(4)*(AGEBL - 41))
IF(KINAGEBL.EQ.-999) KINAGEBL = 1

;;; KINAGEBL-DEFINITION END

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

  TVKIN   = THETA(16) * EXP(ETA(1))

TVKIN = KINCOV*TVKIN
  TVKOUT   = THETA(17) * EXP(ETA(2))

TVKOUT = KOUTCOV*TVKOUT

  KIN = TVKIN
 KOUT = TVKOUT

  KEXP = (KOUT * TIME)
 IF(KEXP.GT.300) KEXP = 300

ITER = IREP
 PACQ5  =  ((EXP(-KEXP)*(BASE * KOUT + KIN*(EXP(KEXP) - 1)))/KOUT)

; 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)  FIX; KIN_FP
 (0,10.62)    FIX; KOUT_FP
 (0,0.487261) ; ERR2
 (-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
 (-1,-0.001,5) ; KINTRTNUM5_BUDFOR
 (-1,-0.001,5) ; KINTRTNUM9_FFVI
 (-1,-0.001,5) ; KOUTTRTNUM5_BUDFOR
 (-1,-0.001,5) ; KOUTTRTNUM9_FFVI

 (0,6.89772)  ; KIN_FF
 (0,10.62)    ; KOUT_FF
```

```
$OMEGA  BLOCK(2)
 0.661156  ;   IIV KIN0
 0.302055 0.574912  ;    IIV KIN

$THETA ;PRIORS
 6.26E+00 FIX ; KIN0
 1.24E+01 FIX ; KIN
 4.79E-01 FIX ; ERR2
 7.59E-03 FIX ; KINAGEBL1
 1.21E-02 FIX ; KINBMIBL1
 2.71E-01 FIX ; KINSMOKN1
 7.91E-01 FIX ; KINSMOKN2
-2.00E-01 FIX ; KINTRTNUM1
 7.77E-01 FIX ; KINTRTNUM2
-3.55E-01 FIX ; KOUTTRTNUM1
 4.33E-01 FIX ; KOUTTRTNUM2

$OMEGA  ;PRIORS
 1.98E+02 FIX
 2.49E+01 FIX
 9.35E+04 FIX
 6.26E+05 FIX
 4.85E+04 FIX
 1.19E+03 FIX
 6.39E+01 FIX
 2.09E+03 FIX
 7.98E+01 FIX
 2.71E+03 FIX
 1.50E+02 FIX

$SIGMA  1  FIX  ; Proportional error PK


$ESTIMATION METHOD=1 INTER MAXEVAL=99999 NOABORT SIG=1 PRINT=1 POSTHOC
$COVARIANCE MATRIX=R
$TABLE ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC OBASE DV2 ACQ5
ICSDURC SMOKN BMIBL TRTNUM IPRED ONEHEADER NOPRINT
FORMAT=s1PE11.5 FILE=table27.txt
```

NONMEM output file final model

```
$SIZES      MAXIDS=15000 LVR=35
$PROBLEM    PK
$INPUT      ID TIME ACQ5 EACQ5 QACQ5 ACQ5BL EACQ5BL QACQ5BL STUDYN
            AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL
            PEFBL FEV1BL FEV1PBL RACEC SH EXAHIST NHASEX TRTNO
            TRTNOCSUM YDAY AMT EAMT QAMT CMT MDV EVID YY SET1 SET2
            SET3 OBASE DV2 EBASE EDV2 BASE DV
$DATA      ../../ACQ_v5.txt IGNORE=@ IGNORE=(BASE.LT.0)
            IGNORE=(SET1.EQ.0)
 ;IGNORE=(ID.GE.1502)
$PRIOR      NWPRI NTHETA=17 NETA=2 NTHP=11 NETP=0
$PRED

;;; KOUTTRTNUM-DEFINITION START
IF(TRTNUM.EQ.7) KOUTTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.5) KOUTTRTNUM = ( 1 + THETA(14)) ;BUD/FOR
IF(TRTNUM.EQ.9) KOUTTRTNUM = ( 1 + THETA(15)) ;FF/VI
;;; KOUTTRTNUM-DEFINITION END

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


;;; KINTRTNUM-DEFINITION START
IF(TRTNUM.EQ.7) KINTRTNUM = 1  ; Most common
IF(TRTNUM.EQ.5) KINTRTNUM = ( 1 + THETA(12))
IF(TRTNUM.EQ.9) KINTRTNUM = ( 1 + THETA(13))
;;; 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))
IF(BMIBL.EQ.-999) KINBMIBL = 1

;;; KINBMIBL-DEFINITION END


;;; KINAGEBL-DEFINITION START
KINAGEBL = ( 1 + THETA(4)*(AGEBL - 41))
IF(KINAGEBL.EQ.-999) KINAGEBL = 1

;;; KINAGEBL-DEFINITION END

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


  TVKIN   = THETA(16) * EXP(ETA(1))

TVKIN = KINCOV*TVKIN
  TVKOUT   = THETA(17) * EXP(ETA(2))

TVKOUT = KOUTCOV*TVKOUT

  KIN = TVKIN
 KOUT = TVKOUT

  KEXP = (KOUT * TIME)
 IF(KEXP.GT.300) KEXP = 300

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

$THETA  (0,6.89772) FIX ; KIN_FP
 (0,10.62) FIX ; KOUT_FP
 (0,0.46492639552867) ; ERR2
 (-0.024,-2.48594844834209E-05,0.043) ; KINAGEBL1
 (-0.025,-2.57382908487947E-05,0.090) ; KINBMIBL1
 (-1,-0.0010224934250172,5) ; KINSMOKN1
 (-1,-0.00099852101736436,5) ; KINSMOKN2
 (-1,-0.0010444751184808,5) ; KINTRTNUM1
 (-1,-0.000998443301658929,5) ; KINTRTNUM2
 (-1,-0.000903844569403114,5) ; KOUTTRTNUM1
 (-1,-0.000984467500811321,5) ; KOUTTRTNUM2
 (-1,-0.000996183843619948,5) ; KINTRTNUM5_BUDFOR
 (-1,-0.000927490232389732,5) ; KINTRTNUM9_FFVI
 (-1,-0.000904137612111725,5) ; KOUTTRTNUM5_BUDFOR
 (-1,-0.00107230268290533,5) ; KOUTTRTNUM9_FFVI
 (0,7.48694066348737) ; KIN_FF
 (0,9.70887804733805) ; KOUT_FF


$THETA  6.26E+00 FIX ; KIN0
 1.24E+01 FIX ; KIN
```

```
 4.79E-01 FIX ; ERR2
 7.59E-03 FIX ; KINAGEBL1
 1.21E-02 FIX ; KINBMIBL1
 2.71E-01 FIX ; KINSMOKN1
 7.91E-01 FIX ; KINSMOKN2
 -2.00E-01 FIX ; KINTRTNUM1
 7.77E-01 FIX ; KINTRTNUM2
 -3.55E-01 FIX ; KOUTTRTNUM1
 4.33E-01 FIX ; KOUTTRTNUM2
 ;PRIORS
$OMEGA  BLOCK(2)
 0.672737179365174  ;   IIV KIN0
 0.287320354136999 0.527296202538603  ;    IIV KIN
$OMEGA  1.98E+02  FIX
 2.49E+01  FIX
 9.35E+04  FIX
 6.26E+05  FIX
 4.85E+04  FIX
 1.19E+03  FIX
 6.39E+01  FIX
 2.09E+03  FIX
 7.98E+01  FIX
 2.71E+03  FIX
 1.50E+02  FIX
  ;PRIORS
$SIGMA  1  FIX  ; Proportional error PK
$ESTIMATION METHOD=1 INTER MAXEVAL=99999 NOABORT SIG=1 PRINT=1 POSTHOC
$COVARIANCE MATRIX=R
$TABLE      ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC OBASE
            DV2 ACQ5 ICSDURC SMOKN BMIBL TRTNUM IPRED ONEHEADER
            NOPRINT FORMAT=s1PE11.5 FILE=table27.txt


NM-TRAN MESSAGES

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1

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

 (WARNING  40) $THETA INCLUDES A NON-FIXED INITIAL ESTIMATE CORRESPONDING TO
 A THETA THAT IS NOT USED IN ABBREVIATED CODE.
 THIS WARNING APPLIES TO THE FOLLOWING THETAS:
 THETA      8
 THETA      9
 THETA     10
 THETA     11

 (WARNING  41) NON-FIXED PARAMETER ESTIMATES CORRESPONDING TO UNUSED
 PARAMETERS MAY CAUSE THE COVARIANCE STEP TO FAIL.

Note: Analytical 2nd Derivatives are constructed in FSUBS but are never used.
      You may insert $ABBR DERIV2=NO after the first $PROB to save FSUBS construction and compilation time


License Registered to: GlaxoSmithKline UK
Expiration Date:    14 MAY 2024
Current Date:        7 MAY 2024
  **** WARNING!!! Days until program expires :   7 ****
  **** CONTACT idssoftware@iconplc.com FOR RENEWAL ****
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.5.1
 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:    27172
 NO. OF DATA ITEMS IN DATA SET:  43
 ID DATA ITEM IS DATA ITEM NO.:   1
 DEP VARIABLE IS DATA ITEM NO.:  43
 MDV DATA ITEM IS DATA ITEM NO.: 32
0LABELS FOR DATA ITEMS:
 ID TIME ACQ5 EACQ5 QACQ5 ACQ5BL EACQ5BL QACQ5BL STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL PEFBL
 FEV1BL FEV1PBL RACEC SH EXAHIST NHASEX TRTNO TRTNOCSUM YDAY AMT EAMT QAMT CMT MDV EVID YY SET1 SET2 SET3 OBASE DV2 EBASE
 EDV2 BASE DV
0(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
 KIN KOUT IPRED
0FORMAT FOR DATA:
 (14(3E21.0/),1E21.0)

 TOT. NO. OF OBS RECS:    27172
 TOT. NO. OF INDIVIDUALS:     7593
0LENGTH OF THETA:  28
0DEFAULT THETA BOUNDARY TEST OMITTED:    NO
0OMEGA HAS BLOCK FORM:
  1
  1  1
  0  0  2
  0  0  0  3
  0  0  0  0  4
  0  0  0  0  0  5
  0  0  0  0  0  0  6
  0  0  0  0  0  0  0  7
  0  0  0  0  0  0  0  0  8
  0  0  0  0  0  0  0  0  0  9
```

```
  0  0  0  0  0  0  0  0  0  0 10
  0  0  0  0  0  0  0  0  0  0  0 11
  0  0  0  0  0  0  0  0  0  0  0  0 12
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
  0.6898E+01     0.6898E+01     0.6898E+01
  0.1062E+02     0.1062E+02     0.1062E+02
  0.0000E+00     0.4649E+00     0.1000E+07
 -0.2400E-01    -0.2486E-04     0.4300E-01
 -0.2500E-01    -0.2574E-04     0.9000E-01
 -0.1000E+01    -0.1022E-02     0.5000E+01
 -0.1000E+01    -0.9985E-03     0.5000E+01
 -0.1000E+01    -0.1044E-02     0.5000E+01
 -0.1000E+01    -0.9984E-03     0.5000E+01
 -0.1000E+01    -0.9038E-03     0.5000E+01
 -0.1000E+01    -0.9845E-03     0.5000E+01
 -0.1000E+01    -0.9962E-03     0.5000E+01
 -0.1000E+01    -0.9275E-03     0.5000E+01
 -0.1000E+01    -0.9041E-03     0.5000E+01
 -0.1000E+01    -0.1072E-02     0.5000E+01
  0.0000E+00     0.7487E+01     0.1000E+07
  0.0000E+00     0.9709E+01     0.1000E+07
  0.6260E+01     0.6260E+01     0.6260E+01
  0.1240E+02     0.1240E+02     0.1240E+02
  0.4790E+00     0.4790E+00     0.4790E+00
  0.7590E-02     0.7590E-02     0.7590E-02
  0.1210E-01     0.1210E-01     0.1210E-01
  0.2710E+00     0.2710E+00     0.2710E+00
  0.7910E+00     0.7910E+00     0.7910E+00
 -0.2000E+00    -0.2000E+00    -0.2000E+00
  0.7770E+00     0.7770E+00     0.7770E+00
 -0.3550E+00    -0.3550E+00    -0.3550E+00
  0.4330E+00     0.4330E+00     0.4330E+00
0INITIAL ESTIMATE OF OMEGA:
 BLOCK SET NO.   BLOCK                                                          FIXED
       1                                                                         NO
                 0.6727E+00
                 0.2873E+00   0.5273E+00
       2                                                                         YES
                 0.1980E+03
       3                                                                         YES
                 0.2490E+02
       4                                                                         YES
                 0.9350E+05
       5                                                                         YES
                 0.6260E+06
       6                                                                         YES
                 0.4850E+05
       7                                                                         YES
                 0.1190E+04
       8                                                                         YES
                 0.6390E+02
       9                                                                         YES
                 0.2090E+04
      10                                                                         YES
                 0.7980E+02
      11                                                                         YES
                 0.2710E+04
      12                                                                         YES
                 0.1500E+03
0INITIAL ESTIMATE OF SIGMA:
 0.1000E+01
0SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE
0COVARIANCE STEP OMITTED:        NO
 R MATRIX SUBSTITUTED:          YES
 S MATRIX SUBSTITUTED:           NO
 EIGENVLS. PRINTED:              NO
 COMPRESSED FORMAT:              NO
 GRADIENT METHOD USED:     NOSLOW
 SIGDIGITS ETAHAT (SIGLO):                  -1
 SIGDIGITS GRADIENTS (SIGL):                -1
 EXCLUDE COV FOR FOCE (NOFCOV):              NO
 Cholesky Transposition of R Matrix (CHOLROFF):0
 KNUTHSUMOFF:                                -1
 RESUME COV ANALYSIS (RESUME):               NO
 SIR SAMPLE SIZE (SIRSAMPLE):
 NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
 PRECONDTIONING CYCLES (PRECOND):        0
 PRECONDTIONING TYPES (PRECONDS):        TOS
 FORCED PRECONDTIONING CYCLES (PFCOND):0
 PRECONDTIONING TYPE (PRETYPE):        0
 FORCED POS. DEFINITE SETTING DURING PRECONDITIONING: (FPOSDEF):0
 SIMPLE POS. DEFINITE SETTING: (POSDEF):-1
0TABLES STEP OMITTED:    NO
 NO. OF TABLES:           1
 SEED NUMBER (SEED):    11456
 NPDTYPE:    0
 INTERPTYPE:    0
 RANMETHOD:             3U
 MC SAMPLES (ESAMPLE):    300
 WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE
0-- TABLE   1 --
0RECORDS ONLY:    ALL
04 COLUMNS APPENDED:    YES
 PRINTED:                NO
 HEADERS:               ONE
```

```
 FILE TO BE FORWARDED:   NO
 FORMAT:                 s1PE11.5
 IDFORMAT:
 LFORMAT:
 RFORMAT:
 FIXED_EFFECT_ETAS:
0USER-CHOSEN ITEMS:
 ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC OBASE DV2 ACQ5 ICSDURC SMOKN BMIBL TRTNUM IPRED
0
 PRIOR SUBROUTINE USER-SUPPLIED
1


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

 ESTIMATION STEP OMITTED:                 NO
 ANALYSIS TYPE:                           POPULATION
 NUMBER OF SADDLE POINT RESET ITERATIONS:      0
 GRADIENT METHOD USED:               NOSLOW
 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
 NOPRIOR SETTING (NOPRIOR):                 0
 NOCOV SETTING (NOCOV):                     OFF
 DERCONT SETTING (DERCONT):                 OFF
 FINAL ETA RE-EVALUATION (FNLETA):          1
 EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
       IN SHRINKAGE (ETASTYPE):             NO
 NON-INFL. ETA CORRECTION (NONINFETA):      0
 RAW OUTPUT FILE (FILE): psn.ext
 EXCLUDE TITLE (NOTITLE):                   NO
 EXCLUDE COLUMN LABELS (NOLABEL):           NO
 FORMAT FOR ADDITIONAL FILES (FORMAT):      S1PE12.5
 PARAMETER ORDER FOR OUTPUTS (ORDER):       TSOL
 KNUTHSUMOFF:                               0
 INCLUDE LNTWOPI:                           NO
 INCLUDE CONSTANT TERM TO PRIOR (PRIORC):   NO
 INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO
 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:  -592.266445323248        NO. OF FUNC. EVALS.:  17
 CUMULATIVE NO. OF FUNC. EVALS.:       17
 NPARAMETR:  4.6493E-01 -2.4859E-05 -2.5738E-05 -1.0225E-03 -9.9852E-04 -1.0445E-03 -9.9844E-04 -9.0384E-04 -9.8447E-04 -9.9618E-04
            -9.2749E-04 -9.0414E-04 -1.0723E-03  7.4869E+00  9.7089E+00  6.7274E-01  2.8732E-01  5.2730E-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  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01
 GRADIENT:   1.6223E+03 -2.3419E+02 -1.8205E+02  1.4429E+02 -1.4769E+02  1.6239E-04 -1.6203E-02  2.2092E-04 -4.7878E-03 -1.3267E+02
             1.1264E+03  1.5985E+02  1.4179E+02  1.0494E+03  1.6667E+03  9.4431E+02 -6.5756E+03  3.9818E+02

0ITERATION NO.:    1    OBJECTIVE VALUE:  -759.133670014752        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:       35
 NPARAMETR:  4.4804E-01  5.7452E-05  5.5550E-05 -3.7601E-03  1.8098E-03 -1.0445E-03 -9.9814E-04 -9.0385E-04 -9.8438E-04  1.5263E-03
            -2.2142E-02 -3.9369E-03 -3.7625E-03  7.3098E+00  9.3467E+00  6.4437E-01  7.0299E-01  1.1643E+00
 PARAMETER:  6.2993E-02  1.0534E-01  1.0415E-01  9.6709E-02  1.0337E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0303E-01
             7.4304E-02  9.6354E-02  9.6766E-02  7.6062E-02  6.1979E-02  7.8459E-02  2.5000E-01  9.0917E-02
 GRADIENT:  -2.0037E+03 -5.0299E+02 -3.3804E+02 -1.4820E+02 -3.7512E+02  1.6239E-04 -1.6203E-02  2.2092E-04 -4.7878E-03 -4.3103E+02
             4.3518E+02  4.6153E+02  4.5162E+02 -5.1009E+02  2.4475E+03 -1.0951E+03  1.2611E+03 -1.7562E+03

0ITERATION NO.:    2    OBJECTIVE VALUE:  -786.053156502830        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:       53
 NPARAMETR:  4.8347E-01  3.5284E-04  3.0809E-04  9.2560E-04  1.3757E-02 -1.0445E-03 -9.9762E-04 -9.0386E-04 -9.8423E-04  1.5261E-02
            -3.5596E-02 -1.8415E-02 -1.7933E-02  7.4529E+00  8.5169E+00  7.0027E-01  5.9243E-01  9.5520E-01
 PARAMETER:  1.3910E-01  1.2445E-01  1.1699E-01  1.0234E-01  1.1762E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.1940E-01
             5.7774E-02  7.8823E-02  7.9611E-02  9.5437E-02 -3.0989E-02  1.2006E-01  2.0210E-01  1.5762E-01
 GRADIENT:   4.5275E+03 -4.4381E+01 -1.1556E+02  4.9042E+02 -6.1540E+01  1.6239E-04 -1.6203E-02  2.2092E-04 -4.7878E-03  2.4416E+02
             2.0134E+03 -2.1808E+02 -1.1758E+03  2.7310E+03 -8.9648E+02 -2.4688E+02 -1.1434E+03  1.6199E+02

0ITERATION NO.:    3    OBJECTIVE VALUE:  -815.194372451707        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:       71
 NPARAMETR:  4.6368E-01  7.6056E-04  7.1065E-04 -5.6657E-03  3.1087E-02 -1.0445E-03 -9.9654E-04 -9.0387E-04 -9.8390E-04  2.6861E-02
```

```
           -1.0171E-01 -3.1486E-02 -6.1769E-03  7.0210E+00  7.7608E+00  7.9230E-01  5.4682E-01  9.1195E-01
 PARAMETER:  9.7316E-02  1.5066E-01  1.3727E-01  9.4413E-02  1.3805E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.3309E-01
           -2.6281E-02  6.2816E-02  9.3857E-02  3.5748E-02 -1.2396E-01  1.8179E-01  1.7537E-01  2.3929E-01
 GRADIENT:   1.9133E+03  6.0078E+01 -6.1343E+01  5.0951E+02  3.4259E+01  1.6239E-04 -1.6203E-02  2.2092E-04 -4.7878E-03  5.1304E+02
             1.7659E+03 -4.9049E+02 -8.6883E+02  3.0150E+03 -8.2219E+02  5.2039E+02 -4.3563E+03  1.2856E+03

0ITERATION NO.:    4    OBJECTIVE VALUE:  -874.652855321865        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:       89
 NPARAMETR:  4.6239E-01  1.1174E-03  1.0776E-03 -1.2996E-02  4.6177E-02 -1.0445E-03 -9.9549E-04 -9.0388E-04 -9.8360E-04  3.3254E-02
           -1.6028E-01 -3.9304E-02  2.5757E-03  6.5655E+00  7.1185E+00  8.6645E-01  6.8496E-01  1.1396E+00
 PARAMETER:  9.4536E-02  1.7345E-01  1.5556E-01  8.5551E-02  1.5562E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.4058E-01
           -1.0512E-01  5.3158E-02  1.0437E-01 -3.1338E-02 -2.1035E-01  2.2652E-01  2.1006E-01  2.9542E-01
 GRADIENT:   1.9558E+03  3.9924E+01 -7.4625E+01  4.0306E+02  2.3326E+01  1.6239E-04 -1.6203E-02  2.2092E-04 -4.7878E-03  5.8832E+02
             1.2826E+03 -5.5445E+02 -4.7634E+02  2.5442E+03  2.9654E+02  1.8452E+02 -2.8285E+03  1.7348E+03

0ITERATION NO.:    5    OBJECTIVE VALUE:  -874.652855321865        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      137
 NPARAMETR:  4.6239E-01  1.1174E-03  1.0776E-03 -1.2996E-02  4.6177E-02 -1.0445E-03 -9.9549E-04 -9.0388E-04 -9.8360E-04  3.3254E-02
           -1.6028E-01 -3.9304E-02  2.5757E-03  6.5655E+00  7.1185E+00  8.6645E-01  6.8496E-01  1.1396E+00
 PARAMETER:  9.4536E-02  1.7345E-01  1.5556E-01  8.5551E-02  1.5562E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.4058E-01
           -1.0512E-01  5.3158E-02  1.0437E-01 -3.1338E-02 -2.1035E-01  2.2652E-01  2.1006E-01  2.9542E-01
 GRADIENT:   1.4267E+03 -7.5441E+01 -1.1037E+02  2.5298E+02 -1.0208E+02  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8179E-03  3.9015E+02
             8.3794E+02 -7.2140E+02 -9.4964E+02  1.5872E+03 -1.9991E+03  1.8452E+02 -2.8285E+03  1.7348E+03

0ITERATION NO.:    6    OBJECTIVE VALUE:  -922.281998853205        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      185
 NPARAMETR:  4.7043E-01  1.5375E-03  1.4615E-03 -8.9671E-03  6.6318E-02 -1.0445E-03 -9.9442E-04 -9.0390E-04 -9.8328E-04  3.5819E-02
           -1.7010E-01 -2.0848E-02  2.2907E-02  6.6139E+00  7.3188E+00  9.5749E-01  6.9415E-01  1.0669E+00
 PARAMETER:  1.1177E-01  2.0012E-01  1.7450E-01  9.0428E-02  1.7876E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.4358E-01
           -1.1878E-01  7.5856E-02  1.2853E-01 -2.3983E-02 -1.8260E-01  2.7648E-01  2.0251E-01  2.6584E-01
 GRADIENT:   2.8644E+03 -1.1994E+02 -1.3445E+02  1.6223E+02 -1.2082E+02  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8179E-03  3.5058E+02
             4.6581E+02 -6.7513E+02 -5.0859E+02  1.0549E+03 -1.3407E+03  6.6541E+02 -4.0779E+03  1.5412E+03

0ITERATION NO.:    7    OBJECTIVE VALUE:  -1120.70084067395        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:      232
 NPARAMETR:  4.6138E-01  4.1132E-03  3.7940E-03  2.8668E-02  1.9050E-01 -1.0446E-03 -9.8853E-04 -9.0398E-04 -9.8153E-04  6.7073E-02
           -1.8592E-01  6.8571E-02  8.3683E-02  7.6375E+00  7.7144E+00  1.5240E+00  1.1708E+00  1.3716E+00
 PARAMETER:  9.2337E-02  3.6035E-01  2.8568E-01  1.3524E-01  3.1442E-01  1.0000E-01  1.0001E-01  1.0000E-01  1.0000E-01  1.7962E-01
           -1.4109E-01  1.8122E-01  1.9853E-01  1.1992E-01 -1.2995E-01  5.0887E-01  2.7072E-01  1.7735E-01
 GRADIENT:   1.7858E+03  1.2610E+02 -5.1351E+01  4.8255E+02  4.5417E+01  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8179E-03  6.5936E+02
             9.5916E+02 -9.2039E+02 -9.6022E+02  2.3211E+03 -2.5494E+03  1.2450E+03 -3.9167E+03  7.4975E+02

0ITERATION NO.:    8    OBJECTIVE VALUE:  -1149.53745552925        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:      279
 NPARAMETR:  4.5985E-01  6.8191E-03  7.0643E-03  3.0004E-02  3.3781E-01 -1.0447E-03 -9.7954E-04 -9.0410E-04 -9.7886E-04 -6.4296E-03
           -1.6027E-01  3.2845E-01  1.0855E-01  7.7384E+00  7.8290E+00  1.7631E+00  1.3522E+00  1.5560E+00
 PARAMETER:  8.9017E-02  5.2437E-01  4.3193E-01  1.3681E-01  4.6218E-01  1.0000E-01  1.0002E-01  1.0000E-01  1.0001E-01  9.3460E-02
           -1.0511E-01  4.5304E-01  2.2629E-01  1.3304E-01 -1.1521E-01  5.8174E-01  2.9070E-01  2.2454E-01
 GRADIENT:   1.9418E+03  2.6326E+02  1.6337E+01  3.9173E+02  1.0770E+02  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8179E-03 -1.0620E+02
             1.4843E+03 -7.1881E+01 -1.4493E+03  2.0824E+03 -2.1537E+03  1.5686E+03 -4.1322E+03  1.5656E+03

0ITERATION NO.:    9    OBJECTIVE VALUE:  -1223.54085345271        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      327
 NPARAMETR:  4.6223E-01  9.1206E-03  1.0651E-02  2.9120E-02  4.9135E-01 -1.0448E-03 -9.6902E-04 -9.0424E-04 -9.7574E-04  2.1248E-02
           -2.0484E-01  4.9611E-01  2.2531E-01  7.7834E+00  7.2861E+00  1.5263E+00  1.2377E+00  1.5233E+00
 PARAMETER:  9.4180E-02  6.6211E-01  5.8219E-01  1.3577E-01  6.0432E-01  1.0000E-01  1.0004E-01  1.0000E-01  1.0001E-01  1.2648E-01
           -1.6824E-01  6.0845E-01  3.5059E-01  1.3883E-01 -1.8707E-01  5.0963E-01  2.8598E-01  2.2522E-01
 GRADIENT:   2.1508E+03  3.4571E+02  5.2682E+01  3.3030E+02  1.7520E+02  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8179E-03 -8.4455E+01
             1.0319E+03 -8.3303E+01 -9.5430E+02  1.8751E+03 -1.9027E+03  7.8228E+02 -2.4907E+03  1.4033E+03

0ITERATION NO.:   10    OBJECTIVE VALUE:  -1285.51398873382        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:      374
 NPARAMETR:  4.6204E-01  1.0168E-02  1.9339E-02  2.1069E-02  7.1513E-01 -1.0451E-03 -9.3321E-04 -9.0472E-04 -9.6511E-04  3.8383E-01
           -1.6457E-01  6.8873E-01  1.3262E-01  6.3851E+00  7.0719E+00  1.4800E+00  1.1953E+00  1.4811E+00
 PARAMETER:  9.3783E-02  7.2463E-01  9.1623E-01  1.2630E-01  7.9504E-01  9.9999E-02  1.0008E-01  9.9999E-02  1.0002E-01  5.0592E-01
           -1.1108E-01  7.7326E-01  2.5270E-01 -5.9201E-02 -2.1692E-01  4.9423E-01  2.8048E-01  2.2133E-01
 GRADIENT:   2.1190E+03  3.8322E+02  1.6588E+02  2.9195E+02  3.2614E+02  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8178E-03  8.7039E+01
             1.0703E+03 -2.1172E+02 -1.0802E+03  1.6366E+03 -1.7332E+03  6.7295E+02 -2.2458E+03  1.2619E+03

0ITERATION NO.:   11    OBJECTIVE VALUE:  -1303.04554755876        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      422
 NPARAMETR:  4.6166E-01  9.0302E-03  2.2059E-02  3.1953E-02  6.4812E-01 -1.0454E-03 -9.0803E-04 -9.0506E-04 -9.5764E-04  5.6747E-01
           -1.7767E-01  8.9190E-01  1.5629E-01  6.1259E+00  6.6960E+00  1.6128E+00  1.3205E+00  1.6224E+00
 PARAMETER:  9.2950E-02  6.5671E-01  1.0150E+00  1.3909E-01  7.3966E-01  9.9999E-02  1.0011E-01  9.9999E-02  1.0003E-01  6.7112E-01
           -1.2942E-01  9.3515E-01  2.7826E-01 -1.0063E-01 -2.7153E-01  5.3718E-01  2.9683E-01  2.4547E-01
 GRADIENT:   2.2477E+03  3.1813E+02  1.8366E+02  2.9957E+02  2.6794E+02  1.5855E-04 -1.6235E-02  2.1763E-04 -4.8178E-03  1.6247E+02
             8.4691E+02 -2.7157E+02 -8.9691E+02  1.5250E+03 -1.6719E+03  7.6602E+02 -2.1079E+03  1.5540E+03

0ITERATION NO.:   12    OBJECTIVE VALUE:  -1314.85808582946        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      470
 NPARAMETR:  4.6200E-01  8.0793E-03  2.4055E-02  3.7827E-02  5.7147E-01 -1.0456E-03 -8.7854E-04 -9.0545E-04 -9.4889E-04  7.8067E-01
           -1.6373E-01  1.1318E+00  1.6849E-01  6.3578E+00  6.8755E+00  1.5176E+00  1.2362E+00  1.5382E+00
 PARAMETER:  9.3680E-02  5.9989E-01  1.0864E+00  1.4595E-01  6.7458E-01  9.9999E-02  1.0014E-01  9.9998E-02  1.0004E-01  8.4794E-01
           -1.0991E-01  1.1147E+00  2.9128E-01 -6.3471E-02 -2.4507E-01  5.0676E-01  2.8646E-01  2.3615E-01
 GRADIENT:   2.2188E+03  3.0610E+02  2.1959E+02  3.5870E+02  2.4003E+02  1.5855E-04 -1.6234E-02  2.1763E-04 -4.8177E-03  1.9609E+02
             9.1869E+02 -2.8590E+02 -9.4242E+02  1.6832E+03 -1.7205E+03  6.9933E+02 -2.2015E+03  1.5250E+03

0ITERATION NO.:   13    OBJECTIVE VALUE:  -1318.70866640927        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      518
 NPARAMETR:  4.6212E-01  8.0270E-03  2.3159E-02 -8.0858E-03  5.5991E-01 -1.0459E-03 -8.5761E-04 -9.0573E-04 -9.4268E-04  9.1475E-01
           -1.5968E-01  1.2645E+00  1.7200E-01  6.4142E+00  6.8610E+00  1.5117E+00  1.2311E+00  1.5335E+00
 PARAMETER:  9.3937E-02  5.9677E-01  1.0545E+00  9.1493E-02  6.6459E-01  9.9998E-02  1.0017E-01  9.9998E-02  1.0005E-01  9.5284E-01
           -1.0430E-01  1.2100E+00  2.9501E-01 -5.4643E-02 -2.4719E-01  5.0481E-01  2.8584E-01  2.3589E-01
 GRADIENT:   2.2282E+03  2.9384E+02  2.0586E+02  2.5024E+02  2.4897E+02  1.5855E-04 -1.6234E-02  2.1763E-04 -4.8177E-03  2.1425E+02
             9.0245E+02 -3.0183E+02 -9.3044E+02  1.7051E+03 -1.7241E+03  7.0192E+02 -2.2300E+03  1.5482E+03

0ITERATION NO.:   14    OBJECTIVE VALUE:  -1321.74237218182        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      566
 NPARAMETR:  4.6217E-01  8.3162E-03  2.1605E-02 -2.8223E-03  5.5182E-01 -1.0461E-03 -8.3605E-04 -9.0602E-04 -9.3628E-04  1.0425E+00
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           -1.5512E-01  1.3862E+00  1.7356E-01  6.3619E+00  6.8396E+00  1.4958E+00  1.2184E+00  1.5255E+00
 PARAMETER:  9.4052E-02  6.1406E-01  9.9868E-01  9.7837E-02  6.5757E-01  9.9998E-02  1.0020E-01  9.9997E-02  1.0006E-01  1.0492E+00
           -9.7996E-02  1.2955E+00  2.9666E-01 -6.2840E-02 -2.5031E-01  4.9953E-01  2.8438E-01  2.3789E-01
 GRADIENT:   2.2245E+03  3.0501E+02  1.8596E+02  2.6633E+02  2.4239E+02  1.5855E-04 -1.6234E-02  2.1763E-04 -4.8176E-03  2.2928E+02
            8.7998E+02 -3.1543E+02 -9.1048E+02  1.6921E+03 -1.6897E+03  6.9869E+02 -2.2622E+03  1.5885E+03

0ITERATION NO.:   15    OBJECTIVE VALUE:  -1322.36532666723        NO. OF FUNC. EVALS.:  49
 CUMULATIVE NO. OF FUNC. EVALS.:      615
 NPARAMETR:  4.6216E-01  7.7540E-03  2.0990E-02  5.5200E-03  5.9296E-01 -1.0463E-03 -8.1459E-04 -9.0631E-04 -9.2991E-04  1.0707E+00
           -1.5170E-01  1.4233E+00  1.8039E-01  6.3813E+00  6.8423E+00  1.4927E+00  1.2174E+00  1.5272E+00
 PARAMETER:  9.4024E-02  5.8043E-01  9.7642E-01  1.0784E-01  6.9303E-01  9.9998E-02  1.0022E-01  9.9997E-02  1.0007E-01  1.0700E+00
           -9.3299E-02  1.3212E+00  3.0388E-01 -5.9785E-02 -2.4992E-01  4.9849E-01  2.8446E-01  2.3903E-01
 GRADIENT:   2.2281E+03  2.7449E+02  1.7582E+02  2.7331E+02  2.7094E+02  1.5855E-04 -1.6234E-02  2.1763E-04 -4.8176E-03  2.3413E+02
            8.7664E+02 -3.2181E+02 -9.0195E+02  1.6989E+03 -1.6859E+03  6.9137E+02 -2.2646E+03  1.6057E+03

0ITERATION NO.:   16    OBJECTIVE VALUE:  -1411.41257035333        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      663
 NPARAMETR:  4.5805E-01  6.6445E-03  1.4142E-02 -3.7710E-03  4.8509E-01 -1.1001E-03  4.7121E-03 -9.8024E-04  7.0748E-04  2.6595E+00
            3.8960E-02  2.8884E+00  3.7729E-01  5.8722E+00  6.5998E+00  1.5132E+00  1.2862E+00  1.6078E+00
 PARAMETER:  8.5104E-02  5.1387E-01  7.2057E-01  9.6696E-02  5.9872E-01  9.9933E-02  1.0684E-01  9.9908E-02  1.0203E-01  2.1576E+00
            1.4716E-01  2.3211E+00  4.9986E-01 -1.4293E-01 -2.8600E-01  5.0530E-01  2.9848E-01  2.2018E-01
 GRADIENT:   1.4722E+03  1.4565E+02  4.1420E+01  1.4727E+02  1.9777E+02  1.5850E-04 -1.6190E-02  2.1757E-04 -4.8057E-03  1.0063E+02
            4.2886E+02 -2.9187E+02 -4.5128E+02  1.0893E+03 -8.6232E+02  2.8012E+02 -1.3259E+03  1.3457E+03

0ITERATION NO.:   17    OBJECTIVE VALUE:  -1468.88610223135        NO. OF FUNC. EVALS.:  58
 CUMULATIVE NO. OF FUNC. EVALS.:      721             RESET HESSIAN, TYPE I
 NPARAMETR:  4.5596E-01  6.1437E-03  1.3749E-02 -1.4395E-02  4.2271E-01 -4.5752E-02  6.5798E-01 -7.2280E-02  1.8998E-01  2.5821E+00
            2.7527E-02  2.9221E+00  3.8572E-01  5.7877E+00  6.6464E+00  1.4978E+00  1.2926E+00  1.6152E+00
 PARAMETER:  8.0521E-02  4.8371E-01  7.0533E-01  8.3853E-02  5.4209E-01  4.5313E-02  7.4790E-01  1.1707E-02  3.1386E-01  2.1037E+00
            1.3379E-01  2.3458E+00  5.0779E-01 -1.5743E-01 -2.7896E-01  5.0020E-01  3.0149E-01  2.0561E-01
 GRADIENT:   1.6445E+03  3.8593E+02  2.1551E+02  1.1199E+02  5.9309E+02  1.2196E-04 -2.2440E-03  1.6649E-04 -2.9263E-03  1.0846E+03
            4.9258E+02  7.7976E+02  2.2175E+03  1.9102E+03  3.6834E+03  2.0491E+01 -6.7398E+02  9.5171E+02

0ITERATION NO.:   18    OBJECTIVE VALUE:  -1493.18218840203        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:      739
 NPARAMETR:  4.5458E-01  5.3737E-03  1.2128E-02 -1.8795E-02  3.1217E-01 -6.3252E-02  7.1366E-01 -9.9491E-02  2.5502E-01  2.1721E+00
            2.0188E-02  2.6693E+00  3.4800E-01  5.7054E+00  6.5023E+00  1.4973E+00  1.2954E+00  1.6148E+00
 PARAMETER:  7.7492E-02  4.3716E-01  6.4155E-01  7.8501E-02  4.3735E-01  2.3342E-02  7.9383E-01 -2.3413E-02  3.8069E-01  1.8255E+00
            1.2515E-01  2.1643E+00  4.7205E-01 -1.7174E-01 -3.0088E-01  5.0005E-01  3.0220E-01  2.0002E-01
 GRADIENT:   1.3528E+03  3.2652E+02  1.5380E+02  1.1624E+02  3.8850E+02  1.0681E-04 -4.3469E-04  1.4700E-04 -2.1258E-03  1.1740E+03
            5.5946E+02  9.7758E+02  1.9538E+03  1.9483E+03  3.9395E+03  1.0160E+02 -8.5663E+02  8.6887E+02

0ITERATION NO.:   19    OBJECTIVE VALUE:  -1495.39551907989        NO. OF FUNC. EVALS.:  19
 CUMULATIVE NO. OF FUNC. EVALS.:      758
 NPARAMETR:  4.5421E-01  5.1643E-03  1.1760E-02 -2.0265E-02  2.8963E-01 -6.8146E-02  7.1718E-01 -1.0712E-01  2.7063E-01  2.0267E+00
            1.7511E-02  2.5639E+00  3.3742E-01  5.6786E+00  6.4534E+00  1.4966E+00  1.2963E+00  1.6153E+00
 PARAMETER:  7.6689E-02  4.2445E-01  6.2687E-01  7.6710E-02  4.1523E-01  1.7137E-02  7.9670E-01 -3.3413E-02  3.9634E-01  1.7284E+00
            1.2198E-01  2.0910E+00  4.6190E-01 -1.7645E-01 -3.0844E-01  4.9979E-01  3.0248E-01  1.9837E-01
 GRADIENT:   1.3312E+03  2.8144E+02  1.4704E+02  6.9911E+01  3.4200E+02  1.0264E-04 -3.1793E-04  1.4167E-04 -1.9219E-03  1.1640E+03
            5.9071E+02  1.0658E+03  1.8623E+03  1.9198E+03  4.0292E+03 -1.7238E+01 -4.7346E+02  7.8277E+02

0ITERATION NO.:   20    OBJECTIVE VALUE:  -1495.39551907989        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      806
 NPARAMETR:  4.5421E-01  5.1643E-03  1.1760E-02 -2.0265E-02  2.8963E-01 -6.8146E-02  7.1718E-01 -1.0712E-01  2.7063E-01  2.0267E+00
            1.7511E-02  2.5639E+00  3.3742E-01  5.6786E+00  6.4534E+00  1.4966E+00  1.2963E+00  1.6153E+00
 PARAMETER:  7.6689E-02  4.2445E-01  6.2687E-01  7.6710E-02  4.1523E-01  1.7137E-02  7.9670E-01 -3.3413E-02  3.9634E-01  1.7284E+00
            1.2198E-01  2.0910E+00  4.6190E-01 -1.7645E-01 -3.0844E-01  4.9979E-01  3.0248E-01  1.9837E-01
 GRADIENT:   7.9571E+02 -3.9130E+01 -5.9014E+01 -1.0745E+02 -5.1337E+01  9.9337E-05 -1.7863E-03  1.3905E-04 -2.1622E-03 -1.1603E+02
            5.4754E+01 -6.6362E+01 -1.2911E+02 -5.4032E+01  1.9208E+02 -1.7238E+01 -4.7346E+02  7.8277E+02

0ITERATION NO.:   21    OBJECTIVE VALUE:  -1520.99620276250        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:      854
 NPARAMETR:  4.5039E-01  5.6140E-03  1.4327E-02  4.2852E-03  3.4342E-01 -1.4662E-01  9.8717E-01 -2.2834E-01  5.7947E-01  2.2836E+00
            1.2833E-02  2.6918E+00  3.4995E-01  5.6919E+00  6.4109E+00  1.4989E+00  1.3095E+00  1.6111E+00
 PARAMETER:  6.8227E-02  4.5171E-01  7.2772E-01  1.0636E-01  4.6758E-01 -8.6193E-02  1.0078E+00 -2.0278E-01  6.8145E-01  1.9003E+00
            1.1643E-01  2.1801E+00  4.7391E-01 -1.7411E-01 -3.1504E-01  5.0056E-01  3.0533E-01  1.7181E-01
 GRADIENT:  -3.3172E+01  3.8539E+01  1.7772E+00  4.3400E+01  2.7594E+01  3.7413E-05  7.0723E-03  6.2910E-05  2.2921E-03  6.3567E+00
            1.3416E+02 -1.8956E+02 -2.1466E+02  3.8368E+02 -2.6121E+02 -9.3008E+01 -2.6000E+02  4.7118E+02

0ITERATION NO.:   22    OBJECTIVE VALUE:  -1522.31824721656        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:      901
 NPARAMETR:  4.4910E-01  5.6698E-03  1.5219E-02  1.0636E-02  3.5576E-01 -1.7879E-01  8.3612E-01 -2.7808E-01  6.1521E-01  2.3688E+00
            8.6289E-03  2.8163E+00  3.5906E-01  5.6752E+00  6.4093E+00  1.5025E+00  1.3168E+00  1.6093E+00
 PARAMETER:  6.5372E-02  4.5509E-01  7.6203E-01  1.1394E-01  4.7937E-01 -1.3085E-01  8.9184E-01 -2.7888E-01  7.1194E-01  1.9577E+00
            1.1143E-01  2.2688E+00  4.8260E-01 -1.7706E-01 -3.1529E-01  5.0176E-01  3.0667E-01  1.5897E-01
 GRADIENT:  -3.0761E+02  2.5627E+01  6.1706E+00  2.5839E+01  2.3054E+01  1.4417E-05  1.9501E-03  3.6139E-05  2.8889E-03 -1.4865E+01
            1.3217E+01 -1.7348E+02 -9.8693E+01  2.0205E+02 -6.4558E+01 -1.8246E+02 -3.8947E+01  2.4239E+02

0ITERATION NO.:   23    OBJECTIVE VALUE:  -1530.15169532238        NO. OF FUNC. EVALS.:  56
 CUMULATIVE NO. OF FUNC. EVALS.:      957             RESET HESSIAN, TYPE I
 NPARAMETR:  4.5034E-01  5.5266E-03  1.4788E-02  1.0121E-03  3.4584E-01 -2.1506E-01  7.7354E-01 -4.0032E-01  3.3264E-01  2.3605E+00
            1.0737E-02  2.7383E+00  3.6354E-01  5.6397E+00  6.4092E+00  1.5743E+00  1.3755E+00  1.6374E+00
 PARAMETER:  6.8113E-02  4.4642E-01  7.4551E-01  1.0244E-01  4.6989E-01 -1.8301E-01  8.4225E-01 -4.8729E-01  4.5719E-01  1.9522E+00
            1.1394E-01  2.2131E+00  4.8686E-01 -1.8332E-01 -3.1531E-01  5.2511E-01  3.1295E-01  1.3692E-01
 GRADIENT:   4.4828E+02  3.2774E+02  2.4072E+02  1.3642E+02  4.5764E+02 -5.7684E-06  1.5932E-03 -1.2959E-05 -1.0688E-03  1.1883E+03
            3.3763E+02  9.0971E+02  2.1945E+03  2.0631E+03  4.2102E+03 -2.7191E+02  3.2243E+02 -8.2162E+01

0ITERATION NO.:   24    OBJECTIVE VALUE:  -1538.33857786192        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:      975
 NPARAMETR:  4.5009E-01  5.1771E-03  1.3766E-02 -7.5024E-03  3.0059E-01 -2.1333E-01  7.6315E-01 -3.9564E-01  3.4473E-01  2.1342E+00
            9.1260E-03  2.5010E+00  3.3750E-01  5.5847E+00  6.2930E+00  1.5911E+00  1.3792E+00  1.6318E+00
 PARAMETER:  6.7573E-02  4.2523E-01  7.0600E-01  9.2197E-02  4.2602E-01 -1.8047E-01  8.3392E-01 -4.7865E-01  4.6882E-01  1.8002E+00
            1.1202E-01  2.0477E+00  4.6198E-01 -1.9313E-01 -3.3359E-01  5.3041E-01  3.1212E-01  1.3776E-01
 GRADIENT:   4.1772E+02  3.1694E+02  2.2103E+02  1.5261E+02  3.9228E+02 -4.6858E-06  1.2356E-03 -1.1195E-05 -8.9467E-04  1.2795E+03
            5.3776E+02  1.0328E+03  1.8918E+03  2.4166E+03  4.1038E+03 -1.6859E+02  1.4023E+02 -1.6894E+01

0ITERATION NO.:   25    OBJECTIVE VALUE:  -1538.71061984482        NO. OF FUNC. EVALS.:  18
 CUMULATIVE NO. OF FUNC. EVALS.:      993
 NPARAMETR:  4.4988E-01  4.8657E-03  1.2910E-02 -1.6241E-02  2.6555E-01 -2.1202E-01  7.5573E-01 -3.9189E-01  3.5414E-01  1.9076E+00
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            6.7591E-03  2.2450E+00  3.1702E-01  5.5257E+00  6.1903E+00  1.6008E+00  1.3819E+00  1.6294E+00
 PARAMETER:  6.7109E-02  4.0630E-01  6.7248E-01  8.1610E-02  3.9128E-01 -1.7856E-01  8.2795E-01 -4.7177E-01  4.7781E-01  1.6490E+00
            1.0920E-01  1.8743E+00  4.4217E-01 -2.0374E-01 -3.5006E-01  5.3345E-01  3.1179E-01  1.3792E-01
 GRADIENT:   3.7745E+02  2.9747E+02  2.0027E+02  1.5630E+02  3.3716E+02 -3.8695E-06  9.8156E-04 -9.7610E-06 -7.5749E-04  1.3529E+03
            6.5355E+02  1.1434E+03  1.6704E+03  2.6829E+03  4.0475E+03 -1.0526E+02  5.2004E+01  2.0683E+00

0ITERATION NO.:   26    OBJECTIVE VALUE:  -1538.71061984482        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:     1040
 NPARAMETR:  4.4988E-01  4.8657E-03  1.2910E-02 -1.6241E-02  2.6555E-01 -2.1202E-01  7.5573E-01 -3.9189E-01  3.5414E-01  1.9076E+00
            6.7591E-03  2.2450E+00  3.1702E-01  5.5257E+00  6.1903E+00  1.6008E+00  1.3819E+00  1.6294E+00
 PARAMETER:  6.7109E-02  4.0630E-01  6.7248E-01  8.1610E-02  3.9128E-01 -1.7856E-01  8.2795E-01 -4.7177E-01  4.7781E-01  1.6490E+00
            1.0920E-01  1.8743E+00  4.4217E-01 -2.0374E-01 -3.5006E-01  5.3345E-01  3.1179E-01  1.3792E-01
 GRADIENT:  -1.6765E+02 -1.7060E+01 -2.8120E+01 -2.5533E+01 -4.2888E+01 -7.8209E-06 -6.0703E-04 -1.4684E-05 -1.0933E-03  7.5138E+00
            1.6094E+02 -1.8836E+02 -3.0119E+02  3.5193E+02 -4.1637E+02 -1.0526E+02  5.2004E+01  2.0683E+00

0ITERATION NO.:   27    OBJECTIVE VALUE:  -1544.96822588137        NO. OF FUNC. EVALS.:  56
 CUMULATIVE NO. OF FUNC. EVALS.:     1096             RESET HESSIAN, TYPE I
 NPARAMETR:  4.5037E-01  4.9780E-03  1.4063E-02 -1.1611E-02  2.9936E-01 -2.0294E-01  7.6557E-01 -3.5913E-01  4.2441E-01  1.9119E+00
           -2.9604E-03  2.2284E+00  3.3557E-01  5.4523E+00  6.2338E+00  1.5961E+00  1.4021E+00  1.6655E+00
 PARAMETER:  6.8180E-02  4.1313E-01  7.1751E-01  8.7230E-02  4.2481E-01 -1.6535E-01  8.3586E-01 -4.1320E-01  5.4365E-01  1.6519E+00
            9.7557E-02  1.8631E+00  4.6012E-01 -2.1713E-01 -3.4305E-01  5.3198E-01  3.1681E-01  1.3500E-01
 GRADIENT:   4.3713E+02  2.3303E+02  1.9270E+02  4.9752E+01  3.4823E+02  1.8719E-06  1.3186E-03  3.3894E-06  3.1379E-04  1.3199E+03
            1.8251E+02  1.1533E+03  2.1129E+03  2.1794E+03  4.5361E+03 -2.3386E+02  3.7547E+02 -1.8725E+02

0ITERATION NO.:   28    OBJECTIVE VALUE:  -1544.96822588137        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:     1143
 NPARAMETR:  4.5037E-01  4.9780E-03  1.4063E-02 -1.1611E-02  2.9936E-01 -2.0294E-01  7.6557E-01 -3.5913E-01  4.2441E-01  1.9119E+00
           -2.9604E-03  2.2284E+00  3.3557E-01  5.4523E+00  6.2338E+00  1.5961E+00  1.4021E+00  1.6655E+00
 PARAMETER:  6.8180E-02  4.1313E-01  7.1751E-01  8.7230E-02  4.2481E-01 -1.6535E-01  8.3586E-01 -4.1320E-01  5.4365E-01  1.6519E+00
            9.7557E-02  1.8631E+00  4.6012E-01 -2.1713E-01 -3.4305E-01  5.3198E-01  3.1681E-01  1.3500E-01
 GRADIENT:  -1.0736E+02 -7.8531E+01 -4.7548E+01 -1.2688E+02 -5.5657E+01 -1.8961E-06 -3.0104E-04 -1.5808E-06 -1.1214E-04 -8.3275E+00
           -2.5505E+02 -1.7112E+02  1.3401E+02 -2.3684E+02  2.5673E+02 -2.3386E+02  3.7547E+02 -1.8725E+02

0ITERATION NO.:   29    OBJECTIVE VALUE:  -1547.55802232493        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:     1190
 NPARAMETR:  4.5042E-01  5.0889E-03  1.4524E-02 -3.3271E-03  3.0858E-01 -2.0242E-01  7.6642E-01 -3.5895E-01  4.2459E-01  1.9061E+00
            1.9165E-03  2.2549E+00  3.2843E-01  5.4674E+00  6.2178E+00  1.6187E+00  1.4055E+00  1.6572E+00
 PARAMETER:  6.8311E-02  4.1988E-01  7.3536E-01  9.7230E-02  4.3384E-01 -1.6460E-01  8.3654E-01 -4.1290E-01  5.4380E-01  1.6480E+00
            1.0341E-01  1.8809E+00  4.5323E-01 -2.1436E-01 -3.4562E-01  5.3901E-01  3.1535E-01  1.3834E-01
 GRADIENT:  -4.0704E+01 -3.0417E+01 -1.6829E+01 -4.5274E+01 -2.4945E+01 -1.5542E-06 -2.7440E-04 -1.5089E-06 -1.0966E-04 -6.5473E+00
           -2.6436E+01 -1.7418E+02 -1.0877E+02  7.0431E+01 -9.6600E+01 -1.6578E+02  2.5467E+02 -5.0703E+01

0ITERATION NO.:   30    OBJECTIVE VALUE:  -1549.29735908153        NO. OF FUNC. EVALS.:  61
 CUMULATIVE NO. OF FUNC. EVALS.:     1251             RESET HESSIAN, TYPE I
 NPARAMETR:  4.5065E-01  5.2193E-03  1.6555E-02 -4.8926E-03  3.1600E-01 -2.0197E-01  7.6808E-01 -3.5828E-01  4.2602E-01  1.9111E+00
            2.9079E-04  2.2448E+00  3.2956E-01  5.4588E+00  6.2175E+00  1.6248E+00  1.4049E+00  1.6513E+00
 PARAMETER:  6.8802E-02  4.2779E-01  8.1273E-01  9.5345E-02  4.4108E-01 -1.6396E-01  8.3788E-01 -4.1172E-01  5.4512E-01  1.6513E+00
            1.0146E-01  1.8741E+00  4.5432E-01 -2.1594E-01 -3.4568E-01  5.4090E-01  3.1462E-01  1.3804E-01
 GRADIENT:   5.4244E+02  3.1852E+02  3.0333E+02  1.5353E+02  4.0950E+02  2.4863E-06  1.4052E-03  3.7449E-06  3.3918E-04  1.3537E+03
            4.6668E+02  1.1379E+03  1.8639E+03  2.6217E+03  4.2030E+03 -1.2600E+02  1.4552E+02 -1.9676E+01

0ITERATION NO.:   31    OBJECTIVE VALUE:  -1549.29735908153        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:     1298
 NPARAMETR:  4.5065E-01  5.2193E-03  1.6555E-02 -4.8926E-03  3.1600E-01 -2.0197E-01  7.6808E-01 -3.5828E-01  4.2602E-01  1.9111E+00
            2.9079E-04  2.2448E+00  3.2956E-01  5.4588E+00  6.2175E+00  1.6248E+00  1.4049E+00  1.6513E+00
 PARAMETER:  6.8802E-02  4.2779E-01  8.1273E-01  9.5345E-02  4.4108E-01 -1.6396E-01  8.3788E-01 -4.1172E-01  5.4512E-01  1.6513E+00
            1.0146E-01  1.8741E+00  4.5432E-01 -2.1594E-01 -3.4568E-01  5.4090E-01  3.1462E-01  1.3804E-01
 GRADIENT:  -9.8947E-01 -9.5800E+00  2.1815E+01 -2.7426E+01 -1.2126E+01 -1.2615E-06 -2.2248E-04 -1.2249E-06 -8.8904E-05  1.1532E+01
            1.0025E+01 -1.9174E+02 -1.4129E+02  1.6235E+02 -1.8655E+02 -1.2600E+02  1.4552E+02 -1.9676E+01

0ITERATION NO.:   32    OBJECTIVE VALUE:  -1549.45570816314        NO. OF FUNC. EVALS.:  57
 CUMULATIVE NO. OF FUNC. EVALS.:     1355             RESET HESSIAN, TYPE I
 NPARAMETR:  4.5073E-01  5.2686E-03  1.6422E-02 -2.7151E-03  3.2038E-01 -2.0156E-01  7.6964E-01 -3.5764E-01  4.2736E-01  1.9119E+00
           -1.2251E-02  2.2385E+00  3.3173E-01  5.4406E+00  6.2228E+00  1.6243E+00  1.4021E+00  1.6470E+00
 PARAMETER:  6.8992E-02  4.3079E-01  8.0771E-01  9.7966E-02  4.4533E-01 -1.6336E-01  8.3912E-01 -4.1062E-01  5.4635E-01  1.6519E+00
            8.6339E-02  1.8699E+00  4.5641E-01 -2.1927E-01 -3.4483E-01  5.4075E-01  3.1406E-01  1.3820E-01
 GRADIENT:   5.8100E+02  2.9208E+02  2.8138E+02  1.1191E+02  3.9721E+02  2.7519E-06  1.4587E-03  4.0105E-06  3.6040E-04  1.3536E+03
            2.7130E+02  1.1410E+03  2.0423E+03  2.4102E+03  4.4286E+03 -1.5803E+02  2.1047E+02 -6.4888E+01

0ITERATION NO.:   33    OBJECTIVE VALUE:  -1550.42613109575        NO. OF FUNC. EVALS.:  19
 CUMULATIVE NO. OF FUNC. EVALS.:     1374
 NPARAMETR:  4.5060E-01  5.1416E-03  1.5913E-02 -4.6713E-03  3.0807E-01 -2.0170E-01  7.6799E-01 -3.5798E-01  4.2648E-01  1.8521E+00
           -2.0475E-02  2.1792E+00  3.2280E-01  5.3821E+00  6.1797E+00  1.6292E+00  1.4038E+00  1.6467E+00
 PARAMETER:  6.8700E-02  4.2307E-01  7.8846E-01  9.5611E-02  4.3335E-01 -1.6357E-01  8.3780E-01 -4.1120E-01  5.4555E-01  1.6119E+00
            7.6339E-02  1.8302E+00  4.4777E-01 -2.3008E-01 -3.5176E-01  5.4225E-01  3.1395E-01  1.3873E-01
 GRADIENT:   5.7279E+02  2.5828E+02  2.5456E+02  7.7622E+01  3.6102E+02  2.6584E-06  1.4020E-03  3.8700E-06  3.4649E-04  1.3465E+03
            1.9358E+02  1.1764E+03  2.0697E+03  2.3711E+03  4.6192E+03 -1.6403E+02  2.2099E+02 -8.7799E+01

0ITERATION NO.:   34    OBJECTIVE VALUE:  -1550.42613109575        NO. OF FUNC. EVALS.:  48
 CUMULATIVE NO. OF FUNC. EVALS.:     1422
 NPARAMETR:  4.5060E-01  5.1416E-03  1.5913E-02 -4.6713E-03  3.0807E-01 -2.0170E-01  7.6799E-01 -3.5798E-01  4.2648E-01  1.8521E+00
           -2.0475E-02  2.1792E+00  3.2280E-01  5.3821E+00  6.1797E+00  1.6292E+00  1.4038E+00  1.6467E+00
 PARAMETER:  6.8700E-02  4.2307E-01  7.8846E-01  9.5611E-02  4.3335E-01 -1.6357E-01  8.3780E-01 -4.1120E-01  5.4555E-01  1.6119E+00
            7.6339E-02  1.8302E+00  4.4777E-01 -2.3008E-01 -3.5176E-01  5.4225E-01  3.1395E-01  1.3873E-01
 GRADIENT:   2.9666E+01 -6.2645E+01 -1.4478E+01 -1.0099E+02 -5.0446E+01 -1.0839E-06 -2.2536E-04 -1.0997E-06 -8.2209E-05 -4.6440E+00
           -2.5191E+02 -1.7446E+02  1.1633E+02 -2.1332E+02  1.9767E+02 -1.6403E+02  2.2099E+02 -8.7799E+01

0ITERATION NO.:   35    OBJECTIVE VALUE:  -1552.32549957862        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:     1469
 NPARAMETR:  4.5059E-01  5.1803E-03  1.5950E-02 -2.1593E-03  3.1029E-01 -2.0162E-01  7.6835E-01 -3.5785E-01  4.2677E-01  1.8524E+00
           -9.6004E-03  2.1921E+00  3.2207E-01  5.3895E+00  6.1770E+00  1.6365E+00  1.4062E+00  1.6463E+00
 PARAMETER:  6.8679E-02  4.2543E-01  7.8987E-01  9.8634E-02  4.3551E-01 -1.6345E-01  8.3809E-01 -4.1097E-01  5.4581E-01  1.6121E+00
            8.9548E-02  1.8388E+00  4.4707E-01 -2.2871E-01 -3.5221E-01  5.4447E-01  3.1379E-01  1.3975E-01
 GRADIENT:   3.3643E+01 -3.5573E+01 -1.1809E+00 -5.8987E+01 -3.3914E+01 -1.0296E-06 -2.1405E-04 -1.0448E-06 -7.8082E-05 -7.2644E+00
           -9.4756E+01 -1.7254E+02 -4.2924E+01 -2.0925E+01 -1.2112E+01 -1.1479E+02  1.2304E+02 -2.3936E+01

0ITERATION NO.:   36    OBJECTIVE VALUE:  -1553.42971303228        NO. OF FUNC. EVALS.:  58
 CUMULATIVE NO. OF FUNC. EVALS.:     1527             RESET HESSIAN, TYPE I
 NPARAMETR:  4.5074E-01  5.4591E-03  1.6121E-02  8.9842E-03  3.3853E-01 -2.0084E-01  7.7179E-01 -3.5661E-01  4.2947E-01  1.8678E+00
```

```
           -1.1204E-02  2.1652E+00  3.2071E-01  5.3898E+00  6.1643E+00  1.6295E+00  1.3991E+00  1.6395E+00
 PARAMETER:  6.9005E-02  4.4233E-01  7.9634E-01  1.1197E-01  4.6287E-01 -1.6233E-01  8.4085E-01 -4.0881E-01  5.4829E-01  1.6224E+00
             8.7608E-02  1.8207E+00  4.4575E-01 -2.2865E-01 -3.5427E-01  5.4235E-01  3.1288E-01  1.3998E-01
 GRADIENT:   5.8016E+02  3.4622E+02  2.9222E+02  2.2402E+02  4.4753E+02  3.2091E-06  1.5329E-03  4.4462E-06  3.9388E-04  1.4020E+03
             4.5239E+02  1.1445E+03  1.8337E+03  2.8181E+03  4.2313E+03 -7.4365E+01  1.4305E+01  2.6134E+01

0ITERATION NO.:   37    OBJECTIVE VALUE:  -1553.42971303228        NO. OF FUNC. EVALS.:  47
 CUMULATIVE NO. OF FUNC. EVALS.:     1574
 NPARAMETR:  4.5074E-01  5.4591E-03  1.6121E-02  8.9842E-03  3.3853E-01 -2.0084E-01  7.7179E-01 -3.5661E-01  4.2947E-01  1.8678E+00
            -1.1204E-02  2.1652E+00  3.2071E-01  5.3898E+00  6.1643E+00  1.6295E+00  1.3991E+00  1.6395E+00
 PARAMETER:  6.9005E-02  4.4233E-01  7.9634E-01  1.1197E-01  4.6287E-01 -1.6233E-01  8.4085E-01 -4.0881E-01  5.4829E-01  1.6224E+00
             8.7608E-02  1.8207E+00  4.4575E-01 -2.2865E-01 -3.5427E-01  5.4235E-01  3.1288E-01  1.3998E-01
 GRADIENT:   3.7108E+01  8.5828E+00  1.7512E+01  2.1711E+01  8.7319E+00 -5.1479E-07 -1.0651E-04 -5.2248E-07 -3.8848E-05  4.6457E+01
             1.7380E+00 -2.2416E+02 -1.3649E+02  2.1809E+02 -2.6276E+02 -7.4365E+01  1.4305E+01  2.6134E+01

0ITERATION NO.:   38    OBJECTIVE VALUE:  -1553.42971303228        NO. OF FUNC. EVALS.:  38
 CUMULATIVE NO. OF FUNC. EVALS.:     1612
 NPARAMETR:  4.5074E-01  5.4591E-03  1.6121E-02  8.9842E-03  3.3853E-01 -2.0084E-01  7.7179E-01 -3.5661E-01  4.2947E-01  1.8678E+00
            -1.1204E-02  2.1652E+00  3.2071E-01  5.3898E+00  6.1643E+00  1.6295E+00  1.3991E+00  1.6395E+00
 PARAMETER:  6.9005E-02  4.4233E-01  7.9634E-01  1.1197E-01  4.6287E-01 -1.6233E-01  8.4085E-01 -4.0881E-01  5.4829E-01  1.6224E+00
             8.7608E-02  1.8207E+00  4.4575E-01 -2.2865E-01 -3.5427E-01  5.4235E-01  3.1288E-01  1.3998E-01
 GRADIENT:  -5.1568E+01 -2.1987E+00  9.8596E+00  2.5928E+01 -2.7208E+00 -5.1477E-07 -1.0651E-04 -5.2248E-07 -3.8848E-05  2.8709E+01
             8.3993E+01 -1.2693E+01 -7.2356E+01  2.2108E+02 -1.3731E+02  4.6493E+01  6.9368E+01  5.9371E+01

 #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:     1612
 NO. OF SIG. DIGITS IN FINAL EST.:  1.2

 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:         5.3464E-02  8.1565E-03
 SE:             6.1288E-03  6.6094E-03
 N:                    7593        7593

 P VAL.:         2.7373E-18  2.1717E-01

 ETASHRINKSD(%)  5.8164E+01  5.5021E+01
 ETASHRINKVR(%)  8.2497E+01  7.9769E+01
 EBVSHRINKSD(%)  5.7209E+01  4.5288E+01
 EBVSHRINKVR(%)  8.1689E+01  7.0065E+01
 RELATIVEINF(%)  1.9279E+01  5.7288E+01
 EPSSHRINKSD(%)  1.2017E+01
 EPSSHRINKVR(%)  2.2590E+01


 TOTAL DATA POINTS NORMALLY DISTRIBUTED (N):        27172
 N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION:    49938.795648474734
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT:   -1553.4297130322757
 OBJECTIVE FUNCTION VALUE WITH CONSTANT:       48385.365935442460
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

 TOTAL EFFECTIVE ETAS (NIND*NETA):                          15186

 PRIOR CONSTANT TO OBJECTIVE FUNCTION:    96.804979879007576
 OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT:   -1553.4297130322757
 OBJECTIVE FUNCTION VALUE WITH CONSTANT:      -1456.6247331532682
 REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

 #TERE:
 Elapsed estimation  time in seconds:   358.98
0R MATRIX ALGORITHMICALLY SINGULAR
 AND ALGORITHMICALLY NON-POSITIVE-SEMIDEFINITE
0COVARIANCE STEP ABORTED
 Elapsed covariance  time in seconds:   194.38
 Elapsed postprocess time in seconds:     0.51
1


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

```
 #OBJV:********************************************    -1553.430       **************************************************
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      TH12
          TH13      TH14      TH15      TH16      TH17

         6.90E+00  1.06E+01  4.51E-01  5.46E-03  1.61E-02  8.98E-03  3.39E-01 -2.01E-01  7.72E-01 -3.57E-01  4.29E-01  1.87E+00
         -1.12E-02  2.17E+00  3.21E-01  5.39E+00  6.16E+00


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

         ETA1      ETA2

 ETA1
+        1.63E+00

 ETA2
+        1.40E+00  1.64E+00


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

         EPS1

 EPS1
+        1.00E+00

1


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

         ETA1      ETA2

 ETA1
+        1.28E+00

 ETA2
+        8.56E-01  1.28E+00


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

         EPS1

 EPS1
+        1.00E+00

 Elapsed finaloutput time in seconds:     1.10
 #CPUT: Total CPU Time in Seconds,      558.715
```