## Supplementary Material

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

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

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

* A total of 1825 patients had symptom control level assessed at baseline using ACQ-5. The largest group of patients were those with poorly controlled asthma (>65\%). While there were very few patients at the upper end of ACQ-5 above 4: 84\% of patients had an ACQ-5 score $<3$ and $98 \%$ of patients had a ACQ-5 score <4.
${ }^{* *}$ In some studies, symptom control was assessed by the asthma control test (ACT) ( $n=2283$ ). ACQ-5 was not measured in this group of patients.

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

| Study | Study title | N | Duration | Visits | Treatmentars | $\begin{gathered} \text { Dose } \\ \text { Titration/Run-in } \end{gathered}$ | Dose Maintenance | Comed Albuterol/ salbutamol | Device |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| ADA109055 <br> NCT00452699 <br> [1] | A 52 -week, randomised, doubleblind, paralle-group study of futicasone propionate/salmetero DISKUS ${ }^{T M}$ combination product (FSC) 250150 mcg BID and fluticasone propionate (FP) DISKUS 250 mcg BID in treatment of subjects with asthma. | 621 | 52 weeks | 15 | FP 250 mcg BID FP/SAL $250 / 50 \mathrm{mcg}$ BID | FP 100 mcg BID ( 3 weeks) | FP 250 mcg BID FP/SAL $250 / 50 \mathrm{mcg}$ BID | As needed | Diskus Inhaler |
| ADA109057 NCT00452348 [2] | A 52 -week, randomised, double-blind, paralle-group study of futicasone propionate/salmeterol DISKUS ${ }^{\text {TM }}$ combination product (FSC) 250150 mcg BID and fluticasone propionate (FP) DISKUS 250 mcg BID in treatment of sujjects with asthma. | 628 | 52 weeks | 15 | FP 250 mcg BID FP/SAL $250 / 50 \mathrm{mcg}$ BID | FP 100 mcg BID ( 3 weeks) | FP 250 mcg BID FPISAL $250 / 50 \mathrm{mcg}$ BID | As needed | Diskus Inhaler |
| HZA113091 <br> NCT01147848 <br> [3] | A randomised, double-blind, double-dummy, paralle-group, multicentre study to assess eficacy and safety of fluticasone furoate (FF)/GW642444 inhalation powder and fluticasone propionate (FP)/salmeterol inhalation powder in the teatment of persistent asthma in adults and addescents. | 806 | 24 weeks | $4 / 5$ | FF/VI 100/25 mcg o.d. FP/SAL $250 / 50 \mathrm{mcg}$ BID | FP 250 mcg BID (4 weeks) | FF/VI 100/25 mcg o.d. +Placebo Accuhaler Diskus FP/SAL $250 / 50 \mathrm{mcg}$ BID + Placebo Inhalation Powder via NDPI | As needed | FF/VI via NDPI FP/SAL Inhalation Powder via Accuhaler/Diskus |
| HZA115150 NCT01706198 [4] | A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF,GW685698)/vilanterd (VI/GW642444) inhalation powder delivered once daly via a novel dry powder inhaler compared with usual maintenance therapy in subjects with asthma | 4233 | 52 weeks | 5 | Usual Care*, $\ddagger$ / V I | NA | FF/VI 100/25 mcg FF/VI 200/25 mcg | - | FFNV via Ellipta inhaler |
| SAM40027 <br> [5] | Gaining Optimal Asthma Control (GOAL): Amulticentre, stratified, randomised, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterolffluticasone propionate combination DISKUS(ACCHUALER) dry powder inhaler compared with fluticasone propionate DISKUS (ACCUHALER) | 3416 | 52 weeks | 7 | FP BID FP/SAL BID | Step 1: FP/SAL 50/100 mcg BID or FP 100 mcg BID <br> Step 2: FP/SAL 50/250 mcg BID or FP 250 mcg BID <br> Step 3: FP/SAL 501500 mcg BID or FP 500 mcg BID (until Total control is achieved) | FP/SAL $50 / 100 \mathrm{mcg}, 50 / 250,50500$ BID <br> FP 100, 250 or 500 mcg BID <br> ( +10 -day oral prednisone if needed) | As needed | Via dry powder inhaler |
| SAM40056 <br> NCT00479739 <br> [6] | A randomised, double-blind, double-dummy, 52-week, parallel-group study of a standard dosing regimen with fluticasonelsalmeterol combination $50 / 250 \mathrm{mcg}$ bid (via the DISKUS ${ }^{T M} / A C C U H A L E R^{T M}$ Inhaler) versus a symptom-driven, variable dosing regimen with formoterol/budesonide combination 4.5160 mcg (via a breath-actuated dry powder reservoir inhaler) in adult asthmatics. | 688 | 52 weeks | 6 | FP/SAL $50 / 250 \mathrm{mcg}$ BID BUD/FOR 4.51160 mcg (vanying dose) | Fixed doses (4 weeks) <br> FP/SAL 50/250 mcg BID + placbo BADPI <br> BUD/FOR $4.5160 \mathrm{mcg}+$ <br> PLACEBO DISKUS BID | FP/SAL $50 / 250 \mathrm{mcg}$ BID BUD/FOR 4.5160 mcg (varying BADPI dosage based on Asthma Control Plan) | Inhaled Salbutamol As needed | FPISAL via Diskus Inhaler BUD/FOR via BADPI inhaler |
| SAM40065 <br> NCT00920543 <br> [7] | A multicentre, randomised, double-dummy, paralle-group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term teatment in addescents and adults receiving eitherffuticasone propionate/salmetero DISKUS BID or fluicasone propionate DISKUS BD (or placebo BID if asymptomatic). | 449 | 40 weeks | 6 | FP (dosage based on Asthma severity and treatment strategy) <br> FP/SAL (dosage based on Asthma severity and treatment strategy) | Previous treatments (2 weeks) | FP/SAL $500 / 50 \mathrm{mcg}$ or $250 / 50 \mathrm{mcg}$ or $100 / 50 \mathrm{mcg}$ <br> FP 500 mcg or 250 mcg or 100 mcg (Dose adjustment every 8 weeks) | Abuterol inhalation as needed | Via Diskus Inhaler |
| SAM40086 NCT01324362 [8] | As study SAM40065 | 466 | 40 weeks | 6 | FP, FP/SAL | As study SAM40065 | As study SAM40065 | As study SAM40065 | As study SAM40065 |
| SAS115359 <br> NCT01475721 <br> [9] | A safety and efficacy study of inhaled flucicasone propion atelsalmeterol combination versus inhaled fluticasone propionate in the reatment of addescents and adult subjects with asthma. | 11679 | 26 weeks | 4 | FP $100 \mathrm{mcg}, 250 \mathrm{mcg}$ or 500 mcg BID <br> FP/SAL $100 / 50 \mathrm{mcg}, 25050$ mcg or $500,50 \mathrm{mcg}$ BID | Previous treatments (2 weeks) | FP/SAL 100/50 or P 100 FP/SAL 250/50 or P 250 FP/SAL $500 / 50$ or P 500 (Based on control status) | NA | Via dry powder inhaler |

* Usual care arm included patients with different standard of care interventions. Only patients on BUD/FOR ( $\mathrm{n}=399$ ) were retrieved for the purpose of the current analysis. Consequently, the total number of patients receiving BUD/FOR combination therapy refers to SAM $40056(n=344)$ and HZA115150 ( $n=399$ ). Further details on each study protocol can be found in the references and hyperlinks below:
[1] Anderson WH, Koshy BT, Huang L, Mosteller M, Stinnett SW, Condreay LD, Ortega H. Genetic analysis of asthma exacerbations. Ann Allergy Asthma Immunol 2013; 110(6): 416-22.e2.
[2] GSK. A 12-month study comparing fluticasone propionate/salmeterol (ADVAIR) Diskus combination product $250 / 50 \mathrm{mcg}$ twice daily to fluticasone propionate (FLOVENT) Diskus 250 mcg twice daily in symptomatic patients with asthma. 2016. http://clinicaltrials.gov/ct/show/NCT00452348. Last accessed: 03/01/23
[3] Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest 2013; 144(4): 1222-29.
[4] Woodcock A, Vestbo J, Bakerly ND, New J, Gibson JM, McCorkindale S, Jones R, Collier S, Lay-Flurrie J, Frith L, Jacques L, Fletcher JL, Harvey C, Svedsater H, Leather D. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet 2017; 390(10 109): 2247-55.
[5] GSK. A Multicentre, stratified, randomised, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterol/fluticasone propionate combination Diskus (Accuhaler) dry powder inhaler compared with fluticasone propionate Diskus alone in adults and adolescents. 2018. https://www.gsk-studyregister.com/en/trial-details/?id=SAM40027. Last accessed 03/01/23.
[6] Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol/budesonide adjustable maintenance dosing: impact on health-related quality of life. Respir Res 2007; 8(1): 46.
[7] GSK. A multicenter, randomized, double-blind, parallel Group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus twice daily or fluticasone propionate Diskus twice daily (or placebo BID if asymptomatic). 2016. https://clinicaltrials.gov/ct2/show/NCT00920543. Last accessed: 03/01/23
[8] GSK. A multicenter, randomized, double-blind, parallel group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus twice daily or fluticasone propionate Diskus twice daily (or placebo twice daily if asymptomatic). 2016. https://clinicaltrials.gov/ct2/show/NCT01324362. Last accessed: 03/01/23.
[9] Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, Buaron KS, Pascoe SJ. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med 2016; 374(19): 1822-30.

Table S3: Parameter estimates of the longitudinal model describing the individual ACQ-5 trajectories in moderate-severe asthma patients. The model is parameterised as a turnover rate (kin/kout) that includes the effect of treatment with FP monotherapy, and FP/SAL and BUD/FOR combination therapy on ACQ-5. Baseline ACQ-5 (AO), rate of increase (Kin) and rate of decrease (Kout) were identified as the primary determinants of changes in individual ACQ-5 scores over time.
$\frac{d(A C Q 5)}{d t}=k_{\text {in }}-k_{\text {out }} \cdot A C Q 5$
Eq. 1
ACQ5(0) = baseline ACQ5
Eq. 2
$k_{\text {in }}=\theta_{\text {kin }} *\left(1+\theta_{B U D / F O R}\right) *\left(1+\theta_{F P / S A L}\right) *\left(1+\theta_{\text {previous smoker }}\right) *$
$\left(1+\theta_{\text {current smoker }}\right) *\left(1+(B M I-26.26) * \theta_{B M I}\right) *(1+(A G E-41) *$
Eq. 3
$\left.\theta_{\text {Age }}\right) * e^{\eta_{k_{\text {in }}}}$
$k_{\text {out }}=\theta_{\text {kout }} *\left(1+\theta_{\text {BUD } / F O R}\right) *\left(1+\theta_{F P / S A L}\right) * e^{\eta_{k_{\text {out }}}}$
Eq. 4
$\left.\begin{array}{|l|l|l|l|l|l|}\hline & \text { Parameter } & \text { Estimate } & \text { SE } & \text { RSE (\%) } & \begin{array}{l}\text { Bootstrap median } \\ \text { (5 }\end{array} \text { - } 5^{\text {th }} \text { percentiles) }\end{array}\right]$

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

Table S4: Protocol design characteristics used for the simulation* of time to first exacerbation and individual ACQ-5 trajectories after treatment with ICS monotherapy and ICS/LABA combination therapy.
$\left.\left.\begin{array}{|l|l|}\hline \text { Protocol characteristics } \\ \hline \text { Endpoints: } & \begin{array}{l}\text { Endpoints evaluated were: 1) time to first exacerbation; 2) (cumulative) incidence of exacerbation at } 12 \\ \text { months and at different time points relative to the start of treatment; 3) increase in the time to } \\ \text { exacerbation following ICS/LABA combination therapy; 4) relative risk of exacerbation in patients treated } \\ \text { with FP/SAL combination therapy, as compared to alternative treatments, namely ICS monotherapy and } \\ \text { BUD/FOR combination therapy }\end{array} \\ \hline \text { Simulation } \\ \text { scenarios } & \begin{array}{l}\text { Simulation scenarios were used to evaluate the effect of different demographic and clinical baseline } \\ \text { characteristics, as well as different interventions on the time to first exacerbation and symptom control } \\ \text { level in a virtual cohort of asthma patients with moderate-severe symptoms at baseline. Differences or } \\ \text { changes in the underlying hazard describing the risk of exacerbation were summarised primarily using the } \\ \text { cumulative incidence of events (i.e., exacerbations) at 12 months. }\end{array} \\ \hline \text { Study visits } & \begin{array}{l}\text { To ensure simulations reflected the original clinical trial population, baseline characteristics from the } \\ \text { available pooled population (Table S2) were randomly resampled and used as input in each simulation } \\ \text { scenario. In addition, re-sampling of patients into each clinical trial scenario was performed taking into }\end{array} \\ \text { account the observed covariate distributions observed in the available clinical studies. This ensured the } \\ \text { creation of virtual cohorts which are representative the population distribution in typical clinical trials } \\ \text { including patients with moderate-severe asthma. Given the large sample size used across the different } \\ \text { scenarios, along with the prior evidence of the predictive performance of the model, results from 500 trial } \\ \text { replicates were assumed to be sufficiently accurate and precise to assess the statistical significance of } \\ \text { eventual differences between treatment conditions. Confidence intervals from trial replicates based on } \\ \text { resampling from the same patient pool were deemed appropriate to account for model parameter } \\ \text { uncertainty. } \\ \text { characteristics: }\end{array} \right\rvert\, \begin{array}{l}\text { Simulation scenarios were based on typical clinical visits and included follow-up over a period of 12 } \\ \text { months. This period was used to avoid empirical extrapolation beyond the observation window considered } \\ \text { for model development and validation, for which there is also supporting clinical trial data. Visits including } \\ \text { ACQ-5 measurements were at study entry (baseline) and at 3, 6, 9 and 12 months after the start of } \\ \text { treatment. Screening measurements were not included or considered for simulation purposes. }\end{array}\right\}$

| Treatment <br> arms | For this analysis, patients were assumed to have undergone a washout period prior to the start of the <br> intervention, with exception of the scenarios in which treatment switching is envisaged at predefined time <br> points: <br> Scenario 1: varying symptom control at baseline (ACQ-5) <br> Scenario 2: varying body mass index at baseline <br> Scenario 3: sex differences <br> Scenario 4: varying airway function at baseline as assessed by FEV ${ }_{1}$ <br> Scenario 5: varying smoking habit at baseline <br> Scenario 6: varying season at start of treatment <br> Scenario 7: ICS/LABA treatment switch at 4 and 6 months after start of therapy, irrespective of symptom <br> control level <br> Scenario 8: treatment switch from ICS monotherapy to combination therapy. Only patients who do not <br> achieve adequate symptom control switched to combination therapy at 3 months after initiation of <br> treatment. |
| :--- | :--- |
| Treatment assignment assumes an initial stepwise titration step followed by a maintenance phase. Regular <br> dosing regimen was used across all scenarios: <br> FP: 100, 250 and 500 mcg twice daily; <br> FP/SAL: 100/50, 250/50 and 500/50 mcg twice daily; <br> BUD/FOR: 100/6, 200/6, 400/12, 160/4.5 and 320/9 mcg twice daily |  |
| Statistical |  |
| methods: | Simulated events (exacerbations) were described by Kaplan-Meier survival curves and analysed using a <br> log-rank test with Bonferroni correction. Survival curvesare a standard way to represent the occurrence <br> of an event over a predefined observation window. In the context of this analysis, survival refers to the <br> proportion of patients who have not had an exacerbation. Median estimates and $90 \%$ confidence intervals <br> are presented in tabular format for results from trial replicates (n=500). On the other hand, where <br> applicable, graphical summaries are also described as those obtained in a single trial, i.e., only point <br> estimates are shown without confidence intervals to ensure direct comparison with data arising from a <br> prospective study protocol. |
| Sample |  |
| estimation |  |



|  | Consequently, this assumption does not restrict the extrapolation of the findings to real-life settings. In fact, the implications of variable patterns of ICS and ICS/LABA use have been previously shown to be linked to differentintrinsic properties of the active moieties [7]. <br> 4. Given that the simulated scenarios were aimed to describe exacerbation incidence over the period of 12 months, it was also assumed that variability due to incorrect device use was negligible, i.e., patients would have been trained on how to use each device correctly. <br> 5. As drop-out in real clinical trials appears to be mostly non-informative (i.e., at random), treatment scenarios were implemented without dropout. <br> 6. The cumulative incidence was not calculated beyond 12 months to ensure that simulation results could be supported by existing clinical data, i.e., the time span used in the analysis matches the duration of the longest clinical trial included in the development of the model. <br> 7. The use of 500 trial replicates may seem excessive given the sample size in each treatment arm ( $n \geq 1000$ ). However, this was deemed adequate to obtain reliable estimates of the $90 \%$-confidence intervals of the survival function. <br> 8. The assessment of treatment response at each visit using predicted ACQ-5 for each patient was based on the longitudinal model describing individual ACQ-5 trajectories. Whilst this does not represent a limitation, the predicted response does not include residual random variability, which may be relatively large in real life. As residual variation is random and 500 replicates have been used to evaluate the proposed scenarios, this should not alter the results obtained for the scenario in which the predicted symptom control level at 3 months is used to support treatment switch. |
| :---: | :---: |
| ICS doseresponse relationships | To understand the effect of treatable traits, i.e. clinical and demographic baseline characteristics, on the risk of exacerbation, treatment effect was parameterised independently from baseline characteristics. In other words, the parameters describing the drug-specific effects are not influenced by other model parameters. However, as the dose of ICS has not been identified as covariate in the model, the comparison between treatment arms was performed using the mean and/or mode dose level used during the maintenance phase of treatment. This was based on the underlying dose-response relationships of the active moieties (i.e. FP, BUD) included in this study [8-10]. As it has been established that currently used ICS doses correspond to the maximum or nearly maximum pharmacological effect, the effect of dose level variation on the base hazard during the maintenance phase was assumed to be minor [11,12]. In fact, here we have applied the same principles endorsed by Beasley and colleagues [13], in that the current analysis does not rely on the terminology proposed by the Global Initiative for Asthma (GINA) guidelines. As highlighted in their report, GINA's terminology which is not evidence-based, classifies interventions into "low," "medium" and "high" doses of ICS to define daily maintenance doses of 100 to $250 \mu \mathrm{~g}$, >250 to 500 $\mu \mathrm{g}$ and $>500 \mu \mathrm{~g}$, respectively, of fluticasone propionate or equivalent for adults with asthma. Specifically, the ICS dose that achieves $80 \%-90 \%$ of the maximum obtainable benefit is currently classified as a low dose, with the description of two higher dose levels, which are associated with minor increase in ICSrelated anti-inflammatory response [14]. In this context, the "standard daily dose" can be defined as 200$250 \mu \mathrm{~g}$ of fluticasone propionate or equivalent, representing the dose at which approximately $80 \%-90 \%$ of the maximum achievable therapeutic benefit of ICS is obtained in adult asthma across the spectrum of severity. <br> Unfortunately, there is a perception among prescribers that FP is equivalent to BUD at half the dose. Such a perception arises from the fact that FP is twice as potent as BUD in terms as GR binding affinity [15,16]. Also, FP was launched as being twice as potent as beclomethasone dipropionate (BDP) and it was widely accepted at that time that BDP and BUD in metered dose inhalers (MDIs) were approximately equivalent on an mcg basis. Hence asthma treatment guidelines reflect dose equivalence as follows: BDP = BUD = FP/2. The problem is that the assumptions about dose equivalence were based on the original delivery devices, which were chlorofluorocarbon (CFC) MDIs and low efficiency dry-powder inhaler (DPIs). The |

Turbuhaler is a higher efficiency device and delivers about twice as much drug to the lungs compared to its original MDI, whereas the Diskus DPI is lower efficiency that the original CFC MDI [17-19]. The net result is that BUD in the Turbuhaler is approximately equivalent to FP in the Diskus on an mcg basis [9]. These considerations provide support for the comparison of the mode ( $250 \mu \mathrm{gFP}$ and $200 \mu \mathrm{~g}$ BUD) or mean (281 $\mu \mathrm{g}$ FP and $255 \mu \mathrm{~g}$ BUD) doses used across the different studies.

* Clinical trial simulations were implemented in NONMEM version 7.3 (Icon Development Solutions, MD, USA) based on the time to event model and longitudinal model describing individual ACQ-5 trajectories (Table S3). Exacerbation events were simulated for each scenario along with ACQ-5 response over a period of 12 months. All required data manipulation, including graphical and statistical summaries were performed in $R$ (v. 3.1.1)
[1] Centers for Disease Control and Prevention. Asthma-related physician office visits. https://www.cdc.gov/asthma/asthma stats/asthma-related-physician-visits.html\#print (Last reviewed: December 12, 2022)
[2] Branson M, Whitehead $J$ (2002) Estimating a treatment effect in survival studies in which patients switch treatment. Stats Med. 21(17): 2449-2463.
[3] Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ (2011) Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. BMC Med Res Methodol. 11:4.
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Figure S1: (Scenario 5). Effect of smoking habit and treatment on exacerbation risk. Patients were stratified by baseline smoking status according to the following categories: current smoker, former smoker and never smoker. The upper panel shows the percentage of subjects with at least 1 exacerbation event over the period of 12 months. Solid lines represent the median simulated curve with $95 \%$ of all simulated curve are within the shaded area. Lower panel: Cumulative incidence after 1 year (median and 95\% prediction interval).


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

Figure S2: (Scenario 6). Effect of seasonal variation and treatment on exacerbation risk. Patients were stratified according to the season of year at the start of treatment. The upper panel shows the percentage of subjects with at least 1 exacerbation event of the period of 6 months. In contrast to the other simulation scenarios describing exacerbation events over 12 months, the effect of seasonal variation is maximum at approximately 6 months from the start of treatment. This illustrates the potential heterogeneity in clinical trial results obtained from treatment follow up over a period of 20 to 24 weeks. Solid lines represent the median simulated curve with $95 \%$ of all simulated curve are within the shaded area. Lower panel: Cumulative incidence after 1 year (median and 95\% prediction interval).


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

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


| FPISAL | $\begin{aligned} & \text { FP/SAL > BUD/FOR } \\ & (4 \mathrm{~m}) \end{aligned}$ | $\begin{aligned} & \text { FP/SAL > BUD/FOR } \\ & (6 \mathrm{~m}) \end{aligned}$ | BUD/FOR | $\begin{aligned} & \text { BUD/FOR }>\text { FP/SAL } \\ & (4 \mathrm{~m}) \end{aligned}$ | $\begin{aligned} & \text { BUD/FOR > FP/SAL } \\ & (6 \mathrm{~m}) \end{aligned}$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 13.5\% (12.5\% - 14.6\%) | 20.6\% (19.5\% - 21.8\%) | $17.1 \%$ (16.1\% - 18.3\%) | 23.9\% (22.6\% - 25.1\%) | 17.2\% (15.9\% - 18.3\%) | 20.6\% (19.3\% - 21.7 |

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

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

Table S51: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by symptom control level and treatment. Lower panel summarises the statistical significance level of the different comparisons.

| Asthma Control | Treatment | ACQ-5 <br> score | $\begin{gathered} \mathrm{BMI} \\ \left(\mathrm{Kg} / \mathrm{m}^{2}\right) \end{gathered}$ | FEV1p <br> (\%) | Smoking Status (N/F/C\%) | Female <br> (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Well Controlled (ACQ-5 50.75 ) | BUD/FOR | $\begin{gathered} 0.4 \\ (0.0-0.6) \end{gathered}$ | $\begin{gathered} \hline 26.2 \\ (19.6-37.0) \end{gathered}$ | $\begin{gathered} \hline 77.3 \\ (54.2-103.8) \end{gathered}$ | (76.1/22.4/1.5) | 60.0 |
|  | FP | $\begin{gathered} 0.4 \\ (0-0.6) \end{gathered}$ | $\begin{gathered} 26.2 \\ (19.8-37.0) \end{gathered}$ | $\begin{gathered} 77.3 \\ (54.5-103.8) \end{gathered}$ | (75.8/22.7/1.4) | 60.1 |
|  | FP/SAL | $\begin{gathered} 0.4 \\ (0.0-0.6) \end{gathered}$ | $\begin{gathered} 26.2 \\ (19.6-36.9) \end{gathered}$ | $\begin{gathered} 77.3 \\ (54.5-103.8) \end{gathered}$ | (76.0/22.5/1.5) | 60.0 |
| Not Well Controlled (ACQ-5 >0.75- $\leq 1.5$ ) | BUD/FOR | $\begin{gathered} 1.2 \\ (0.8-1.4) \end{gathered}$ | $\begin{gathered} 26.3 \\ (20.2-37.3) \end{gathered}$ | $\begin{gathered} 77.0 \\ (51.8-102.3) \end{gathered}$ | (74.5/22.4/3.1) | 60.4 |
|  | FP | $\begin{gathered} 1.2 \\ (0.8-1.4) \end{gathered}$ | $\begin{gathered} 26.3 \\ (20.2-37.5) \end{gathered}$ | $\begin{gathered} 77.0 \\ (51.8-102.4) \end{gathered}$ | (74.5/22.2/3.3) | 60.0 |
|  | FP/SAL | $\begin{gathered} 1.2 \\ (0.8-1.4) \end{gathered}$ | $\begin{gathered} 26.3 \\ (20.2-37.5) \end{gathered}$ | $\begin{gathered} 77.0 \\ (51.8-102.3) \end{gathered}$ | (74.6/22.3/3.2) | 60.2 |
| Poor Controlled(ACQ-5 >1.5) | BUD/FOR | $\begin{gathered} 2.4 \\ (1.6-3.6) \end{gathered}$ | $\begin{gathered} 27.5 \\ (20.2-40.3) \end{gathered}$ | $\begin{gathered} 71.9 \\ (46.7-97.8) \end{gathered}$ | (74.6/21.0/4.4) | 63.6 |
|  | FP | $\begin{gathered} 2.4 \\ (1.6-3.6) \end{gathered}$ | $\begin{gathered} 27.5 \\ (20.2-40.3) \end{gathered}$ | $\begin{gathered} 71.8 \\ (46.7-97.8) \end{gathered}$ | (74.8/20.8/4.4) | 63.6 |
|  | FP/SAL | $\begin{gathered} 2.4 \\ (1.6-3.6) \end{gathered}$ | $\begin{gathered} 27.5 \\ (20.2-40.3) \end{gathered}$ | $\begin{gathered} 71.9 \\ (46.7-97.9) \end{gathered}$ | (74.8/20.8/4.4) | 63.6 |


| $P$ values | Well Controlled, BUD/FOR | Well Controlled, FP |
| :---: | :---: | :---: |
| Well Controlled, FP | $\begin{aligned} & 1.00 \mathrm{e}-03^{* *} \\ & (1.02 \mathrm{e}-06-1.00 \mathrm{e}-03) \end{aligned}$ |  |
| Well Controlled, FP/SAL | $\begin{aligned} & 1.05 \mathrm{e}-13^{* *} \\ & (4.43 \mathrm{e}-19-1.05 \mathrm{e}-13) \end{aligned}$ | $\begin{aligned} & 1.95 \mathrm{e}-05^{* *} \\ & \text { (5.08e-09-1.95e-05) } \end{aligned}$ |
| $P$ values | Not Well Controlled, BUD/FOR | Not Well Controlled, FP |
| Not Well Controlled, FP | $\begin{aligned} & 1.41 \mathrm{e}-03^{* *} \\ & \text { (1.03e-06-1.41e-03) } \end{aligned}$ |  |
| Not Well Controlled, FP/SAL | $\begin{aligned} & 9.04 \mathrm{e}-12^{* *} \\ & (2.82 \mathrm{e}-17-9.04 \mathrm{e}-12) \end{aligned}$ | $\begin{aligned} & 1.76 \mathrm{e}-04^{* *} \\ & (3.86 \mathrm{e}-08-1.76 \mathrm{e}-04) \end{aligned}$ |
| $P$ values | Poor Control, BUD/FOR | Poor Control, FP |
| Poor Control, FP | $\begin{aligned} & 3.50 \mathrm{e}-05^{* *} \\ & (5.46 \mathrm{e}-09-3.50 \mathrm{e}-05) \end{aligned}$ |  |
| Poor Control, FP/SAL | $\begin{aligned} & 2.17 \mathrm{e}-17^{* *} \\ & \text { (4.89e-24-2.17e-17) } \end{aligned}$ | $\begin{aligned} & 1.07 \mathrm{e}-05^{* *} \\ & \text { (1.63e-09-1.07e-05) } \end{aligned}$ |

Median Log rank p value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$ percentiles. Asterisks indicate $p$-value $<0.05\left(^{*}\right)$ or $<0.01\left(^{* *}\right)$

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

Table S62: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and body mass index range (i.e. normal, overweight, obese, and extreme obese). Lower panel summarises the statistical significance level of the different comparisons.

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


|  | FP, Extremely obese | FP, Normal | FP, Obese |
| :--- | :--- | :--- | :--- |
| FP, Normal | $4.77 \mathrm{e}-11^{* *}$ <br> $(5.78 \mathrm{e}-12-8.96 \mathrm{e}-11)$ |  |  |
| FP, Obese | $1.08 \mathrm{e}-02^{*}$ |  |  |
| $(1.52 \mathrm{e}-03-2.00 \mathrm{e}-02)$ |  |  |  |

Median Log rankp value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$
percentiles. Asterisks indicate $p$-value $<0.05\left(^{*}\right)$ or $<0.01\left(^{* *}\right)$

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

Table S73: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and sex, as assessed by predicted forced expiratory volume in the first second. Lower panel summarises the statistical significance level of the different comparisons.

| Treatment | Sex |  | ACQ-5 | BMI (Kg/m ${ }^{2}$ ) | FEV1p (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | \(\left.\begin{array}{c}Smoking Status <br>

(N/F/C\%)\end{array}\right]\)

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

Median Log rank $p$ value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$ percentiles. Asterisks indicate $p$-value $<0.05\left(^{*}\right)$ or $<0.01\left(^{* *}\right)$

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

Table S84: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and lung function, as assessed by predicted forced expiratory volume in the first second. Lower panel summarises the statistical significance level of the different comparisons.

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


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

Median Log rankp value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$ percentiles. Asterisks indicate $p$-value $<0.05\left(^{*}\right)$ or $<0.01$ (**)

Scenario 5 - Effect of smoking status at baseline and treatment choice on the risk of exacerbation.

Table S95: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment and smoking status at baseline. Lower panel summarises the statistical significance level of the different comparisons.

| Treatment | Smoking <br> Status | ACQ-5 score | $\begin{gathered} \mathrm{BMI} \\ \left(\mathrm{Kg} / \mathrm{m}^{2}\right) \end{gathered}$ | FEV1p (\%) | Female (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| BUD/FOR | Current | $\begin{gathered} 2.0 \\ (0.6-3.4) \end{gathered}$ | $\begin{gathered} 27.1 \\ (20.2-39.5) \end{gathered}$ | $\begin{gathered} 73.4 \\ (48.2-99.3) \end{gathered}$ | 62.7 |
|  | Former | $\begin{gathered} 2.0 \\ (0.6-3.4) \end{gathered}$ | $\begin{gathered} 27.2 \\ (20.2-39.6) \end{gathered}$ | $\begin{gathered} 73.4 \\ (48.4-99.2) \end{gathered}$ | 62.7 |
| FP | Current | $\begin{gathered} 2.0 \\ (0.6-3.4) \end{gathered}$ | $\begin{gathered} 27.2 \\ (20.2-39.6) \end{gathered}$ | $\begin{gathered} 73.4 \\ (48.2-99.5) \end{gathered}$ | 62.7 |
|  | Former | $\begin{gathered} 2.0 \\ (0.6-3.4) \end{gathered}$ | $\begin{gathered} 27.2 \\ (20.2-39.6) \end{gathered}$ | $\begin{gathered} 73.4 \\ (48.2-99.2) \end{gathered}$ | 62.8 |
| FP/SAL | Current | $\begin{gathered} 2.0 \\ (0.6-3.4) \end{gathered}$ | $\begin{gathered} 27.2 \\ (20.2-39.6) \end{gathered}$ | $\begin{gathered} 73.4 \\ (48.4-99.4) \end{gathered}$ | 62.8 |
|  | Former | $\begin{gathered} 2.0 \\ (0.6-3.4) \end{gathered}$ | $\begin{gathered} 27.2 \\ (20.2-39.6) \end{gathered}$ | $\begin{gathered} 73.4 \\ (48.4-99.5) \end{gathered}$ | 62.7 |


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

Median Log rank p value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$ percentiles. Asterisks indicate $p$-value $<0.05\left(^{*}\right)$ or $<0.01\left(^{* *}\right)$

## Scenario 6 - Effect of season a nd treatment choice on the risk of exacerbation.

Table S10:6 Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment arm and season at start of treatment. Lower panel summarises the statistical significance level of the different comparisons.

| Treatment | Treatment start | ACQ-5 | $\begin{aligned} & \mathrm{BMI} \\ & \left(\mathrm{Kg} / \mathrm{m}^{2}\right) \end{aligned}$ | FEV1p <br> (\%) | Smoking Status (N/F/C\%) | Female <br> (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| BUD/FOR | Spring | 2 (0.6-3.4) | 27.1 (20.3-38.9) | 73.2 (48-99) | 73.1/22.9/4 | 50 |
|  | Autumn | 2 (0.6-3.4) | 27.1 (20.3-39.1) | 73.2 (48-99) | 73.1/22.9/4 | 50 |
| FP | Spring | 2 (0.6-3.4) | 27.1 (20.3-39.1) | 73.3 (48-99.1) | 73.2/22.8/4 | 50 |
|  | Autumn | 2 (0.6-3.4) | 27.1 (20.3-39) | 73.3 (48-99) | 73.2/22.9/4 | 49.9 |
| FP/SAL | Spring | 2 (0.6-3.4) | 27.1 (20.3-39.1) | 73.3 (48-99.1) | 73.1/22.9/4 | 50 |
|  | Autumn | 2 (0.6-3.4) | 27.1 (20.3-39.1) | 73.3 (48-99) | 73.2/22.8/4 | 50.1 |


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

Median Log rank p value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$ percentiles. Asterisks indicate $p$-value $<0.05\left(^{*}\right)$ or $<0.01\left(^{* *}\right)$

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

Table S117: Upper panel shows the clinical and demographic baseline characteristics of the simulated population stratified by treatment. Lower panel summarises the statistical significance level of the different comparisons.

| Asthma Control | ACQ-5 | $\begin{gathered} \mathrm{BMI} \\ \left(\mathrm{Kg} / \mathrm{m}^{2}\right) \end{gathered}$ | FEV1p (\%) | Smoking Status (N/F/C\%) | Female <br> (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| FP/SAL | $\begin{gathered} \hline 1.2 \\ (0.2-3) \end{gathered}$ | $\begin{gathered} 26.7 \\ (20-38.3) \end{gathered}$ | $\begin{gathered} 75.5 \\ (51-102.2) \end{gathered}$ | 75/22/3 | 61.4 |
| FP/SAL > BUD/FOR (4m) | $\begin{gathered} 1.2 \\ (0.2-3) \end{gathered}$ | $\begin{gathered} 26.7 \\ (20-38.3) \end{gathered}$ | $\begin{gathered} 75.5 \\ (51.1-102.4) \end{gathered}$ | 75.1/21.9/3 | 61.3 |
| FP/SAL > BUD/FOR (6m) | $\begin{gathered} 1.2 \\ (0.2-3.0) \end{gathered}$ | $\begin{gathered} 26.7 \\ (20-38.4) \end{gathered}$ | $\begin{gathered} 75.5 \\ (51-101.9) \end{gathered}$ | 75/21.9/3.1 | 61.2 |
| BUD/FOR | $\begin{gathered} 1.2 \\ (0.2-3.0) \end{gathered}$ | $\begin{gathered} 26.7 \\ (20-38.3) \end{gathered}$ | $\begin{gathered} 75.5 \\ (51.1-102) \end{gathered}$ | 75/22/3 | 61.3 |
| BUD/FOR > FP/SAL (4m) | $\begin{gathered} 1.2 \\ (0.2-3) \end{gathered}$ | $\begin{gathered} 26.7 \\ (20-38.3) \end{gathered}$ | $\begin{gathered} 75.6 \\ (51.1-102.3) \end{gathered}$ | 74.9/22/3 | 61.4 |
| BUD/FOR > FP/SAL (6m) | $\begin{gathered} 1.2 \\ (0.2-3) \end{gathered}$ | $\begin{gathered} 26.7 \\ (20-38.4) \end{gathered}$ | $\begin{gathered} 75.5 \\ (51.1-101.8) \end{gathered}$ | 75.1/21.8/3 | 61.3 |


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

Median Log rankp value over 500 iterations. Values between parentheses are the $5^{\text {th }}$ and $95^{\text {th }}$ percentiles. Asterisks indicate $p$-value $<0.05$ ( $^{*}$ ) or $<0.01\left(^{* *}\right)$

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

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

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

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

| P values | $\begin{aligned} & \text { NWC, } \\ & \text { FP }(\text { NR }) \rightarrow \text { BUD/FOR } \end{aligned}$ | $\begin{aligned} & \text { NWC, } \\ & \text { FP (NR) } \rightarrow \text { FPISAL } \end{aligned}$ | NWC, <br> FP (R) | $\begin{aligned} & \text { PC, } \\ & \text { FP }(N R) \rightarrow \text { BUD/FOR } \end{aligned}$ | $\begin{aligned} & \text { PC, } \\ & \text { FP (NR) } \rightarrow \text { FPISAL } \end{aligned}$ | $\begin{aligned} & \mathrm{PC}, \\ & \mathrm{FP}(\mathrm{R}) \end{aligned}$ | $\begin{aligned} & \text { WC, } \\ & \text { FP }(\text { NR }) \rightarrow \text { BUD/FOR } \end{aligned}$ | $\begin{aligned} & \text { WC, } \\ & \text { FP }(\text { NR }) \rightarrow \text { FPISAL } \end{aligned}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\begin{aligned} & \text { NWC, } \\ & \text { FP }(\text { NR }) \rightarrow \text { FPISAL } \end{aligned}$ | $\begin{aligned} & \text { 7.40e-05** } \\ & (1.35 \mathrm{e}-09-9.86 \mathrm{e}-02) \end{aligned}$ |  |  |  |  |  |  |  |
| NWC, <br> FP (R) | $\begin{aligned} & 2.73 \mathrm{e}-02^{*} \\ & (4.09 \mathrm{e}-05-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (1.87 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ |  |  |  |  |  |  |
| $\begin{aligned} & \text { PC, } \\ & \text { FP }(N R) \rightarrow \text { BUD/FOR } \end{aligned}$ | $\begin{aligned} & 4.13 \mathrm{e}-06^{* *} \\ & (8.58 \mathrm{e}-11-6.23 \mathrm{e}-03) \end{aligned}$ | $\begin{aligned} & \text { 1.03e-23** } \\ & \text { (3.03e-30-9.26e-18) } \end{aligned}$ | $\begin{aligned} & 6.56 \mathrm{e}-21^{* *} \\ & (3.67 \mathrm{e}-27-1.23 \mathrm{e}-14) \end{aligned}$ |  |  |  |  |  |
| $\begin{aligned} & \text { PC, } \\ & \text { FP }(N R) \rightarrow \text { FPISAL } \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (9.61 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 4.84 \mathrm{e}-044^{* *} \\ & (1.30 \mathrm{e}-07-1.93 \mathrm{e}-01) \end{aligned}$ | $\begin{aligned} & 1.96 \mathrm{e}-01 \\ & (1.39 \mathrm{e}-03-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 2.16 e-19 * * \\ & (2.13 \mathrm{e}-27-1.55 \mathrm{e}-12) \end{aligned}$ |  |  |  |  |
| $\begin{aligned} & \mathrm{PC}, \\ & \mathrm{FP}(\mathrm{R}) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (1.60 \mathrm{e}-01-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 6.64 \mathrm{e}-09 * * \\ & (1.41 \mathrm{e}-13-6.10 \mathrm{e}-05) \end{aligned}$ | $\begin{aligned} & 1.28 \mathrm{e}-05^{\star *} \\ & (1.15 \mathrm{e}-09-1.47 \mathrm{e}-02) \end{aligned}$ | $\begin{aligned} & 2.33 \mathrm{e}-06 * * \\ & (9.09 \mathrm{e}-11-7.93 \mathrm{e}-03) \end{aligned}$ | $\begin{aligned} & 6.31 \mathrm{e}-02 \\ & (3.40 \mathrm{e}-05-1.00 \mathrm{e}+00) \end{aligned}$ |  |  |  |
| $\begin{aligned} & \text { WC, } \\ & \text { FP }(N R) \rightarrow \text { BUD/FOR } \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (1.84 \mathrm{e}-01-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (1.98 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (7.83 \mathrm{e}-01-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 8.32 \mathrm{e}-03 * * \\ & (1.49 \mathrm{e}-05-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (8.75 \mathrm{e}-01-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (4.16 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ |  |  |
| $\begin{aligned} & \text { WC, } \\ & \text { FP }(N R) \rightarrow \text { FPISAL } \end{aligned}$ | $\begin{aligned} & 5.72 \mathrm{e}-02 \\ & (2.35 \mathrm{e}-04-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (7.91 \mathrm{e}-01-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (7.58 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 2.76 \mathrm{e}-06 * * \\ & (1.18 \mathrm{e}-09-1.80 \mathrm{e}-03) \end{aligned}$ | $\begin{aligned} & 1.79 \mathrm{e}-01 \\ & (2.10 \mathrm{e}-03-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 6.83 e-03^{* *} \\ & (2.68 e-05-8.13 e-01) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (2.36 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ |  |
| $\begin{aligned} & \text { WC, } \\ & \text { FP (R) } \end{aligned}$ | $\begin{aligned} & 5.16 \mathrm{e}-03^{* *} \\ & (4.53 \mathrm{e}-06-8.51 \mathrm{e}-01) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (1.00 \mathrm{e}+00-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (6.58 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.90 \mathrm{e}-12^{* *} \\ & (1.04 \mathrm{e}-17-9.05 \mathrm{e}-09) \end{aligned}$ | $\begin{aligned} & 4.31 \mathrm{e}-02^{*} \\ & (5.80 \mathrm{e}-05-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 8.02 \mathrm{e}-05 * * \\ & (1.02 \mathrm{e}-08-2.95 \mathrm{e}-02) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (2.31 \mathrm{e}-02-1.00 \mathrm{e}+00) \end{aligned}$ | $\begin{aligned} & 1.00 \mathrm{e}+00 \\ & (7.44 \mathrm{e}-01-1.00 \mathrm{e}+00) \end{aligned}$ |

NWC - Not well controlled(ACQ-5>0.75-51.5), PC - Poorly controlled(ACQ-5>1.5), WC - Well controlled(ACQ-5 $\leq 0.75)$. Values between parentheses are $95 \%$ confidence intervals. $p$-value $<0.05$ (*) or $^{( } \mathbf{0 . 0 1}$ ( $\left.^{* *}\right)$

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

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

## Sub scenario 8a

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


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


| P values | Well Controlled | Not Well Controlled |
| :--- | :--- | :--- |
| Not Well Controlled | $1.98 \mathrm{e}-02^{*}(1.26 \mathrm{e}-04-3.95 \mathrm{e}-01)$ |  |
| Poor Control | $8.67 \mathrm{e}-12^{* *}(2.74 \mathrm{e}-16-2.93 \mathrm{e}-08)$ | $4.35 \mathrm{e}-15^{* *}(5.80 \mathrm{e}-21-2.22 \mathrm{e}-10)$ |

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

## Sub-scenario 8b

Figure S5: Upper panel shows the cumulative incidence of exacerbations stratified by treatment. Subjects not achieving symptom control (NR, i.e. those classified as not-well controlled [ACQ-5 >0.75s1.5] or poorly controlled [ACQ-5 >1.5] at 3 months after initiation of ICS monotherapy) switch to combination therapy (BUD/FOR or FP/SAL). Responders to monotherapy progress with the same treatment over the period of 12 months. Patients remaining on monotherapy (FP) have generally lower ACQ-5 baseline values. ). Lower panels show the cumulative incidence of exacerbation at each visit up to 12 months after the start of treatment.


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


| P values | FP (NR) $\rightarrow$ FP/SAL | FP (R) |
| :--- | :--- | :--- |
| FP (R) | $4.40 \mathrm{e}-02^{*}(2.68 \mathrm{e}-04-1.00 \mathrm{e}+00)$ |  |
| FP (NR) $\rightarrow$ BUD/FOR | $3.93 \mathrm{e}-27^{* *}(6.02 \mathrm{e}-36-1.28 \mathrm{e}-19)$ | $1.19 \mathrm{e}-15^{* *}(1.63 \mathrm{e}-21-1.47 \mathrm{e}-10)$ |

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

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

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




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


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

APPENDIX

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

## Methods

Source data: The data used for the development of a longitudinal model describing individual ACQ-5 trajectories consisted of a subset of the studies available for the implementation of the time-to-event model used to characterise the risk of exacerbation in moderate to severe asthma patients. For minimise the use of imputation for missing data variable, only those studies that had longitudinal ACQ5 data available at baseline and throughout the course of treatment were included in the current analysis. Two studies out of the 9 clinical trials (SAM40027 and SAM40056) met the inclusion criteria. SAM40027 contained patients receiving either FP or FP/SAL, whilst SAM40056 contained patients receiving either BUD/FOR or FP/SAL.

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

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

Model parameterisation: A longitudinal model based on first-order rates and turnover concepts (Equations 5, 6 and 7) has been used to describe the individual trajectory and time course of ACQ-5 following initiation of the treatment. This approach has been used across different therapeutic areas when the apparent delay between exposure or drug concentration and effect is due more to a delayed or slow pharmacodynamic or pathophysiological process than biophase equilibration, i.e., the time required to reach equilibrium in the lung. The observed effect is considered a dynamic process. Asthma control, treatment effect and any other relevant covariates were parameterised relative to baseline symptoms (Equation 8). This parameterisation assumes that a patient's baseline measurements immediately prior to the start of treatment reflects their disease state and eventually rate of progression.
$\frac{d(A C Q 5)}{d t}=k_{\text {in }}-k_{\text {out }} \cdot A C Q 5$
ACQ5(0) = baseline ACQ5
$k_{\text {out }}=\frac{\operatorname{ACQ5(0)}}{k_{\text {in }_{\text {baseline }}}}$
$k_{\text {in }}=k_{\text {in }_{\text {baseline }}}+E f f_{\text {trt }}+E f f_{\text {cov }}$

Eq. 5

Eq. 6

Eq. 7

Eq. 8

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

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

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

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

$$
\begin{equation*}
\frac{d(A C Q 5)}{d t}=k_{\text {in }}-k_{\text {out }} \cdot A C Q 5 \tag{Eq. 9}
\end{equation*}
$$

$$
\begin{equation*}
\text { ACQ5 }(0)=\text { baseline } A C Q 5 \tag{Eq. 10}
\end{equation*}
$$

$$
k_{\text {in }}=\theta_{\text {kin }} *\left(1+\theta_{\text {BUD/FORM }}\right) *\left(1+\theta_{F P}\right) *\left(1+\theta_{\text {prevoius smoker }}\right) *
$$

$$
\begin{equation*}
\left(1+\theta_{\text {current smoker }}\right) *\left(1+(B M I-26.26) * \theta_{B M I}\right) *(1+(A G E-41) * \tag{Eq. 11}
\end{equation*}
$$

$\left.\theta_{A g e}\right) * e^{\eta_{k_{i n}}}$

$$
\begin{equation*}
k_{\text {out }}=\theta_{\text {kout }} *\left(1+\theta_{\text {BUD } / F O R M}\right) *\left(1+\theta_{F P}\right) * e^{\eta_{k_{\text {out }}}} \tag{Eq. 12}
\end{equation*}
$$

$k_{\text {out }}=\theta_{\text {kout }} *\left(1+\theta_{\text {BUD } / F O R M}\right) *\left(1+\theta_{F P}\right) * e^{\eta_{k_{\text {out }}}}$

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

Modelling development and evaluation were based on analytical solution and \$PRED options in NONMEM v.7.3 using the FOCE-I estimation method. The analysis was run on the Model-based Analyses Platform (MAP), a validated analysis platform entirely hosted on Amazon Web Services (AWS). The platform runs NONMEM 7.3 through gFortran compiler and Perl-speaks-NONMEM (PsN)
4.6.0. All required data manipulation, including graphical and statistical summaries were performed in $R$ (version 3.2.5).

Results

1,825 patients with accurate event records, clinical and demographic baseline details were included in the final data set. The age of the subjects included in the population ranged from 18.0 to 82.0 years with a mean value of 42.4 years, whereas body weight ranged from 37.0 to 167.0 kg with a mean value of 76.2 kg . Mean symptom scores at baseline were 1.9 and 4.7 for ACQ-5 and AQLQ scores, respectively. Regarding lung function, as assessed by spirometry tests, FEV1 at baseline ranged from 0.6 to 5.3 L with a mean value of 2.5 L , while PEF ranged from 137.1 to $799.8 .0 \mathrm{~L} / \mathrm{min}$, with a mean value of $391.1 \mathrm{~L} / \mathrm{min}$. Out of the patients reporting smoking history, the majority of patients reported to never have smoked (66.0\%). A complete summary of the demographic and clinical baseline characteristics of subjects included in the analysis are presented in Table S13. The distribution of the baseline characteristics per study are shown in Figure S8. The generalised pairs plot showing the relationship between the baseline demographics and clinical characteristics of the ITT population is displayed in Figure S9.

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

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

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

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

Abbreviations: $\mathrm{N}=$ 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 ( $5^{\text {th }}-95^{\text {th }}$ percentiles).
a. Total number of subjects 1825 . The patient population comprised all adult subjects with age $\geq 18$ years.

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


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


Figure S10: ACQ-5 scores stratified by treatment. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, $10^{\text {th }}-90^{\text {th }}$ percentiles.


Figure 1: ACQ-5 score stratified by baseline ACQ-5. Thin solid lines, individual ACQ-5 trajectories; thick solid line, median ACQ-5; shaded area, $10^{\text {th }}-90^{\text {th }}$ percentiles.


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


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


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


Table S14：Parameter estimates of the longitudinal model describing the individual ACQ－5 trajectories in moderate－severe asthma patients．The model is parameterised as a turnover rate（kin／kout）that includes the effect of treatment with FP monotherapy，and FP／SAL and BUD／FOR combination therapy on ACQ－5（equations 9－12）．The use of a turnover rates is recommended when describing pharmacodynamic processes which are associated with an apparent delay between drug exposure and effect，rather than pharmacokinetic equilibration［1－3］．Baseline ACQ－5（A0），rate of increase（Kin） and rate of decrease（Kout）were identified as the primary determinants of changes in individual ACQ－ 5 scores over time．

|  | Parameter | Estimate | SE | RSE（\％） | Bootstrap median （ $5^{\text {th }}-95^{\text {th }}$ percentiles） |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | ACQ－5 kin（ $\theta$ kin） | 6.26 | 0.328 | 5．2\％ | 6.3 （6．0－6．9） |
|  | ACQ－5 kout rate（ $\theta$ kout） | 12.4 | 0.464 | 3．7\％ | 12.4 （11．9－13．4） |
| 哭 | Age effect <br> （fractional increase in $k_{\text {in }}$ peryear） | 0.00759 | 0.002 | 23．0\％ | 0.0069 （0．0045－0．0097） |
| $\sum_{\infty}$ | BMI effect （fractional increase in $\mathrm{k}_{\mathrm{in}}$ per $\mathrm{kg} / \mathrm{m}^{2}$ ） | 0.0121 | 0.007 | 59．2\％ | 0.014 （－0．001－0．022） |
| $\begin{aligned} & \text { 咢 } \\ & \text { 言 } \\ & \text { E } \end{aligned}$ | Former smoker relative to never smoked （fractional increase in $\mathrm{k}_{\mathrm{in}}$ ） | 0.271 | 0.063 | 21．6\％ | 0.29 （0．20－0．40） |
|  | Currentsmoker relative to never smoked （fractional increase in $\mathrm{k}_{\text {in }}$ ） | 0.791 | 0.133 | 16．3\％ | 0.82 （0．59－1．05） |
| $\begin{aligned} & \stackrel{\rightharpoonup}{\stackrel{\rightharpoonup}{\omega}} \\ & \stackrel{E}{⿷ 匚} \\ & \ddot{H} \end{aligned}$ | FP／SAL effect relative to FP （fractional increase in $\mathrm{k}_{\text {in }}$ ） | －0．2 | 0.079 | 29．7\％ | －0．25（－0．42－－0．17） |
|  | BUD／FOR effect relative to FP （fractional increase in $\mathrm{k}_{\text {in }}$ ） | 0.777 | 0.334 | 31．2\％ | 0.97 （0．68－1．74） |
|  | FP／SAL effect relative to FP （fractional increase in $\mathrm{k}_{\text {out }}$ ） | －0．355 | 0.052 | 13．2\％ | －0．38（－0．49－－0．33） |
|  | BUD／FOR effect relative to FP （fractional increase in $\mathrm{k}_{\text {out }}$ ） | 0.433 | 0.248 | 37．9\％ | 0.60 （0．38－1．18） |
|  | Inter individual variability in $\mathrm{k}_{\text {in }}\left(\eta \mathrm{k}_{\text {in }}\right.$ ） | 2.45 | 0.122 | 4．8\％ | 2.51 （2．38－2．76） |
|  | Inter individual variabilitycorrelation between $\eta_{\text {kin }}$ and $\eta k_{\text {out }}$ | 1.76 | 0.097 | 5．2\％ | 1.83 （1．72－2．02） |
|  | Inter individual variability in $\mathrm{k}_{\text {out }}\left(\eta \mathrm{k}_{\text {out }}\right.$ ） | 1.68 | 0.093 | 5．3\％ | 1.75 （1．63－1．93） |
|  | Residual error | 0.479 | 0.009 | 2．0\％ | 0.48 （0．46－0．49） |

［1］Nagashima R，O＇Reilly RA，Levy G．Kinetics of pharmacologic effects in man：the anticoagulant action of warfarin．Clin Pharmacol Ther．1969；10：22－35．
［2］Dayneka NL，Garg V，Jusko WJ．Comparison of four basic models of indirect pharmacodynamic responses．J Pharmacokinet Biopharm．1993；21：457－478．
［3］Upton RN，Mould DR．Basic concepts in population modeling，simulation，and model－based drug development：part 3－introduction to pharmacodynamic modeling methods．CPT Pharmacometrics Syst Pharmacol．2014；3（1）：e88．

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


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


Page 39 of 49

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


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


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


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


## Attachment

## NONMEM control file final model

\$PROBLEM ACQ-5 long
\$INPUT ID ODV OBASE AMT CMT MDV EVID ACQ5 TIME ACQ5BL AQLQBL AQLQ STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL
FEV1BL FEV1PBL RACEC SET2 SET3 SET4 SET5 FLAG BASE DV
\$DATA ACQAQLQ9.txt IGNORE=@ IGNORE=(BASE.LT.0) IGNORE=(FLAG.EQ.2) IGNORE=(SET5.EQ.0) IGNORE=(STUDYN.EQ.205715) IGNORE=(STUDYN.EQ.40040) IGNORE=(STUDYN.EQ.106837)
\$PRED
; ; ; KOUTTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E +01) KOUTTRTNUM = 1 ; Most common
IF(TRTNUM.EQ.1.9000E +01) KOUTTRTNUM $=(1+$ THETA(10))
IF(TRTNUM.EQ.5.0000E +00) KOUTTRTNUM $=(1+$ THETA(11) $)$
;; ; KOUTTRTNUM-DEFINITION END
;; ; KOUT-RELATION START
KOUTCOV=KOUT TRTNUM
; ; KOUT-RELATION END
; ; KINTRTNUM-DEFINI TION START
IF(TRTNUM.EQ.2.7000E +01) KINTRTNUM = 1 ; Most common
IF(TRTNUM.EQ.1.9000E +01) KINTRTNUM = ( $1+$ THETA(8))
IF(TRTNUM.EQ.5.0000E +00) KINTRTNUM $=(1+$ THETA(9) $)$
;; KINTRTNUM-DEFINITION END
; ; ; KINSMOKN-DEFINIT ION 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-DEFINIT ION END
;;; KINBMIBL-DEFINIT ION START
KINBMIBL $=(1+$ THETA(5)*(BMIBL - 26.26))
;;; KINBMIBL-DEFINITION END
;;; KINAGEBL-DEFINIT ION START
KINAGEBL = ( $1+$ THETA(4)*(AGEBL - 41))
;;; KINAGEBL-DEFINITION END
;; K KIN-RELATION START
KINCOV=KINAG EBL*KINBMIBL*KINSMOKN*KINTRTNUM
;; ; KIN-RELATION END

TVKIN $=\operatorname{THETA}(1) * \operatorname{EXP}(E T A(1))$
TVKIN $=$ KINCOV*TVKIN
TVKOUT $=$ THETA(2) $* \operatorname{EXP}(\operatorname{ETA}(2))$
TVKOUT $=$ KOUTCOV*TVKOUT

```
KIN = TVKIN
KOUT = TVKOUT
PACQ5 = ((EXP(-KOUT * TIME)*(BASE * KOUT + KIN*(EXP(KOUT * TIME) - 1)))/KOUT)
IPRED = PACQ5
    W1 = SQRT(THETA(3)**2)
    Y = IPRED + W1*EPS(1)
$THETA
(0,6.89772) ;
(0,10.62) ;
(0,0.487261)
(-0.024,-2.4E-05,0.043) ; KINAGEBL1
(-0.025,-2.5E-05,0.090) ; KINBMIBL1
(-1,-0.001,5) ; KINSMOKN1
(-1,-0.001, 5) ; KINSMOKN2
(-1,-0.001,5) ; KINTRTNUM1
(-1,-0.001,5) ; KINTRTNUM2
(-1,-0.001,5) ; KOUTTRTNUM1
(-1,-0.001,5) ; KOUTTRTNUM2
$OMEGA BLOCK(2)
0.661156
0.302055 0.574912
```

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

## NONMEM output file final model

\$PROBLEM ACO-5 long
\$INPUT ID ODV OBASE AMT CMT MDV EVID ACQ5 TIME ACQ5BL AQLQBL AQLQ STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN bMIBL FEV1BL FEV1PBL RACEC SET2 SET3 SET4 SET5 FLAG BASE DV
./../ACQAQLQ 9.txt IGNORE=@ IGNORE=(BASE.LT.0)
IGNORE=(FLAG.EQ. 2) IGNORE=(SET5. EQ.0)
IGNORE=(STUDYN.EQ. 205715) IGNORE = (STUDYN .EQ.40040) IGNORE=(STUDYN.EQ.106837)
\$PRED
; ; KOUTTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E +01) KOUTTRTNUM = 1 ; Most common
IF(TRTNUM.EQ.1.9000E +01 ) KOUTTRTNUM $=(1+$ THETA(10) $)$
IF(TRTNUM.EQ.5.0000E +00) KOUTTRTNUM $=(1+$ THETA(11) $)$
;;; KOUTTRTNUM-DEFINITION END
; ; KOUT-RELATION START
KOUTCOV=KOUT TRTNUM
;;; KOUT-RELATION END
;;; KINTRTNUM-DEFINITION START
IF(TRTNUM.EQ.2.7000E +01) KINTRTNUM = 1 ; Most common
IF(TRTNUM.EQ.1.9000E +01 ) KINTRTNUM $=(1+$ THETA(8) $)$
IF(TRTNUM.EQ.5.0000E + 00) KINTRTNUM $=(1+$ THETA(9) $)$
;;; KINTRTNUM-DEFINI TION END
;; ; KINSMOKN-DEFINIT ION START
IF(SMOKN.EQ. 1.0000E+00) KINSMOKN = 1 ; Most common
IF (SMOKN.EQ. 3.0000E+00) KINSMOKN $=(1+$ THE TA(6) $)$
IF(SMOKN.EQ. 2.0000E+00) KINSMOKN $=(1+$ THETA(7) $)$
;;; KINSMOKN-DEFINITION END
; ; ; KINBMIBL -DEFINIT ION START
KINBMIBL $=(1+$ THETA(5)*(BMIBL - 26.26))
;;; KINBMIBL -DEFINIT ION END
;; ; KINAGEBL-DEFINIT ION START
KINAGEBL $=(1+$ THETA(4)*(AGEBL - 41))
;;; KINAGEBL-DEFINITION END
; ; ; KIN-RELATION START
KINCOV=KINAG EBL*KINBMIBL*KINSMOKN*KINTRTNUM
;;; KIN-RELATION END

TVKIN $=\operatorname{THETA}(1) * \operatorname{EXP}(E T A(1))$

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

TVKOUT $=$ KOUTCOV*TVKOUT
KIN $=$ TVKIN
KOUT $=$ TVKOUT

IPRED $=$ PACQ5
W1 $=$ SQRT(THETA(3)**2)
$Y=$ IPRED + W1*EPS(1)
\$THETA (0,6.26207999348608) ;
(0,9.68028101150034) ;
(0,0.482748057155104) ;
(-0.024, -2. 19076278905144E-05,0.043) ; KINAGEBL1
(-0.025,-2. $59874394519405 \mathrm{E}-05,0.090)$; KINBMIBL1
(-1, -0.000941183372913202,5) ; KINSMOKN1
(-1,-0.000937289898269643,5) ; KINSMOKN2
(-1,-0.00108835365688897,5) ; KINTR TNUM1
( $-1,-0.00102329174963748,5$ ) ; KINTR TNUM2
( $-1,-0.000993075595754862,5$ ) ; KOUT TRTNUM1
$(-1,-0.00100077784171613,5)$; KOUTT RTNUM2
\$OMEGA BLOCK(2)
0.661233793949875
0.3130298180861150 .580302137774261
\$SIGMA 1 FIX ; Proportional error PK
\$ESTIMATION METHOD=1 INTER MAXEVAL=99999 NOABORT SIG=1 PRINT=1 POSTHOC
\$COVARIANCE
\$TABLE ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC ICSDURC
SMOKN TRTNUM FLAG IPRED ONEHEADER NOPRINT FORMAT=s1PE11.5

## NM-TRAN MESSAGES

WARNINGS AND ERRORS (IF ANY) FOR PROBLEM 1
(WARNING 2) NM-TRAN INFERS THAT THE DATA ARE POPULATION
Note: The following floating-point exceptions are signalling: IEEE_INVALID_FLAG IEEE_DIVIDE_BY_ZERO
License Registered to: GlaxoSmithKline
Expiration Date: 14 MAY 2022
Current Date: 6 MAR 2022
Days until program expires : 68
1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0
ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUT IONS,
AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
PERFORMED BY NOUS INFOSYSTEMS.

## PROBLEM NO.

PK
ODATA CHECKOUT RUN: NO
DATA SET LOCATED ON UNIT NO.: 2
THIS UNIT TO BE REWOUND: NO
NO. OF DATA RECS IN DATA SET: 12436
NO. OF DATA ITEMS IN DATA SET: 31
ID DATA ITEM IS DATA ITEM NO.: 1
DEP VARIABLE IS DATA ITEM NO.: 31
MDV DATA ITEM IS DATA ITEM NO.: 6
OLABELS FOR DATA ITEMS:
ID ODV OBASE AMT CMT MDV EVID ACQ5 TIME ACQ5BL AQLQBL AQLQ STUDYN AGEBL ASTHDURC ICSDURC SMOKN TRTNUM ACQ5BLC SEXN BMIBL
FEV1BL FEV1PBL RACEC SET2 SET3 SET4 SET5 FLAG BASE DV
$\theta$ (NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
KIN KOUT IPRED
OFORMAT FOR DATA
(1(3E21.0/) , 1E21.0)
TOT. NO. OF OBS RECS: 10611
TOT. NO. OF INDIVIDUALS: 1825
OLENGTH OF THETA: 11
ODEFAULT THETA BOUNDARY TEST OMITTED: NO OOMEGA HAS BLOCK FORM:
$\begin{array}{ll}1 & \\ 1 & 1\end{array}$
ODEFAULT OMEGA BOUNDARY TEST OMITTED: NO
OSIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1
ODEFAULT SIGMA BOUNDARY TEST OMITTED: NO
OINITIAL EST IMATE OF THETA

| LOWER BOUND | INIT IAL EST | UPPER BOUND |
| ---: | ---: | ---: |
| $0.0000 E+00$ | $0.6262 E+01$ | $0.1000 \mathrm{E}+07$ |
| $0.0000 \mathrm{E}+00$ | $0.9680 \mathrm{E}+01$ | $0.1000 \mathrm{E}+07$ |
| $0.0000 \mathrm{E}+00$ | $0.4827 \mathrm{E}+00$ | $0.1000 \mathrm{E}+07$ |
| $-0.2400 \mathrm{E}-01$ | $-0.2191 \mathrm{E}-04$ | $0.4300 \mathrm{E}-01$ |
| $-0.2500 \mathrm{E}-01$ | $-0.2599 \mathrm{E}-04$ | $0.9000 \mathrm{E}-01$ |
| $-0.1000 \mathrm{E}+01$ | $-0.9412 \mathrm{E}-03$ | $0.5000 \mathrm{E}+01$ |
| $-0.1000 \mathrm{E}+01$ | $-0.9373 \mathrm{E}-03$ | $0.5000 \mathrm{E}+01$ |
| $-0.1000 \mathrm{E}+01$ | $-0.1088 \mathrm{E}-02$ | $0.5000 \mathrm{E}+01$ |
| $-0.1000 \mathrm{E}+01$ | $-0.1023 \mathrm{E}-02$ | $0.5000 \mathrm{E}+01$ |
| $-0.1000 \mathrm{E}+01$ | $-0.9931 \mathrm{E}-03$ | $0.5000 \mathrm{E}+01$ |
| $-0.1000 \mathrm{E}+01$ | $-0.1001 \mathrm{E}-02$ | $0.5000 \mathrm{E}+01$ |

INITIAL ESTIMATE OF OMEGA
BLOCK SET NO. BLOCK

INITIAL ESTIMATE OF SIGMA:
$0.1000 E+01$
OSIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE
OCOVARIANCE STEP OMITTED:
NO
EIGENVLS. PRINTED
NO
SPECIAL COMPUTATION
NO
NO
COMPRESSED FORMAT:
SIGDIGITS ETAHAT (SIGLO):
SIGDIGITS GRADIENTS (SIGL):
$-1$
RELATIVE TOLERANCE (TOL):
ABSOLUTE TOLERANCE-ADVAN 9, 13 ONLY (ATOL): -1
EXCLUDE COV FOR FOCE (NOFCOV): N
RESUME COV ANALYSIS (RESUME):
OTABLES STEP OMITTED: NO
NO. OF TABLES:
NO
SEED NUMBER (SEED): 11456
RANMETHOD:
MC SAMPLES (ESEED): 300
WRES SQUARE ROOT TYPE:
E IGENVALUE
0 -- TABLE 1 -
PRINTED: NO
HEADERS: ONE
FILE TO BE FORWARDED: NO
FORMAT: s1PE11.5

RFORMAT

OUSER-CHOSEN ITEMS:
ID TIME DV MDV BASE STUDYN KIN KOUT AGEBL ASTHDURC ICSDURC SMOKN TRTNUM FLAG IPRED
\#TBLN: 1
\#METH: First Order Conditional Estimation with Interaction

| ESTIMATION STEP OMI TTED: | NO |
| :--- | :--- |
| ANALYSIS TYPE: | POPULATION |
| CONDITIONAL ESTIMATES USED: | YES |
| CENTERED ETA: | NO |
| EPS-ETA INT ERACTION : | 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 ESTIMAT ION (MCE TA): | 0 |
| SIGDIGITS FOR MAP ESTIMATION (SIGLO): | 100 |
| GRADIENT SIGDIGITS OF |  |
| FIXED EFFECTS PARAMETERS (SIGL): | 100 |
| EXCLUDE TIT LE (NOTITLE): | NO |
| EXCLUDE COLUMN LABE LS (NOLABEL): | NO |
| NOPRIOR SETTING (NOPRIOR): | OFF |
| NOCOV SETTING (NOCOV): | OF F |
| DERCONT SETTING (DE RCONT): | OFF |
| ABSOLUTE TOLERANCE-ADVAN 9, 13 ONLY(ATOL):-100 |  |
| FINAL ETA RE-EVALUATION (FNLETA): | ON |
| EXCLUDE NON -INFLUENTIAL (NON-INFL.) ETAS |  |
| IN SHRINKAGE (ETASTYPE): | NO |
| NON-INFL. ETA CORRECTION (NONINFETA): | OFF |
| FORMAT FOR ADDITIONAL FILES (FORMAT): | S1PE12.5 |
| PARAMETER ORDER FOR OUTPUTS (ORDER): | TSOL |
| ADDITIONAL CONVERGENCE TEST (CTYPE=4)?: | NO |
| EM OR BAYES IAN METHOD USED: | NONE |

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

OITERATION NO.: 0 OBJECTIVE VALUE: -169.085693959215
CUMULATIVE NO. OF FUNC. EVALS.: 13
NPARAMETR: $6.2621 \mathrm{E}+00 \quad 9.6803 \mathrm{E}+00 \quad 4.8275 \mathrm{E}-01$-2.1908E-05 -1.0008E-03 $\quad 6.6123 \mathrm{E}-01 \quad 3.1303 \mathrm{E}-01 \quad 5.8030 \mathrm{E}-01$
PARAMETER: $1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01$
TRADTENT: $1.0000 \mathrm{E}-011.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01 \quad 1.0000 \mathrm{E}-01$ $\begin{array}{rrrrr}1.0000 \mathrm{E}-01 & 1.0000 \mathrm{E}-01 & 1.0000 \mathrm{E}-01 & 1.0000 \mathrm{E}-01 \\ 1.1454 \mathrm{E}+02 & 5.1739 \mathrm{E}+02 & -6.6459 \mathrm{E}+02 & -8.1044 \mathrm{E}+01\end{array}$ $\begin{array}{llll}1.1694 E \\ 2.00 & -3.5199 E+02 & -1.0694 E & +03 \\ -2.8887 E\end{array}$

OITERATION NO.: 1 OBJECTIVE VALUE: -222.775779648485
CUMULATIVE NO. OF FUNC. EVALS.: 28 五
NPARAMETR: $\quad 6.2193 \mathrm{E}+0010.3854 \mathrm{E}+00 \quad 5.0232 \mathrm{E}-01 \quad 5.2745 \mathrm{E}-05$
$\begin{array}{lrrrrr} & -1.1088 E-03 & 6.8966 E-01 & 5.2409 \mathrm{E}-01 & 8.455 & \\ \text { PARAMETER: } & 9.3152 \mathrm{E}-02 & 6.9068 \mathrm{E}-02 & 1.3973 \mathrm{E}-01 & 1.0485 \mathrm{E}-01\end{array}$ $\begin{array}{cccc}9.3152 \mathrm{E}-02 & 6.9068 \mathrm{E}-02 & 1.3973 \mathrm{E}-01 & 1.0485 \mathrm{E}-01 \\ 9.9870 \mathrm{E}-02 & 1.2104 \mathrm{E}-01 & 1.6394 \mathrm{E}-01 & 1.1727 \mathrm{E}-01\end{array}$
GRADIENT: $\quad 5.7788 \mathrm{E}+01 \quad 4.6469 \mathrm{E}+02 \quad 7.7889 \mathrm{E}+02-9.6828 \mathrm{E}+01$ $2.9044 \mathrm{E}+01-5.5799 \mathrm{E}+02 \quad 4.4075 \mathrm{E}+02-3.8710 \mathrm{E}+02$


OITERATION NO.: 4 OBJECTIVE VALUE: -359.362583578070 NO. OF FUNC. EVALS.: 14

CUMULATIVE NO. OF FUNC. EVALS.: 71
NPARAMETR: $5.0516 \mathrm{E}+00 \quad 7.6599 \mathrm{E}+00 \quad 4.8719 \mathrm{E}-01 \quad 1.0483 \mathrm{E}-03-2.8573 \mathrm{E}-04 \quad 7.3460 \mathrm{E}-02 \quad 6.0993 \mathrm{E}-02 \quad-3.3706 \mathrm{E}-03 \quad 4.3910 \mathrm{E}-02$-2.1539E-01 $-3.7476 \mathrm{E}-03 \quad 1.4385 \mathrm{E}+00 \quad 1.1662 \mathrm{E}+00 \quad 1.6056 \mathrm{E}+00$
PARAMETER: $-1.1481 \mathrm{E}-01-1.3409 \mathrm{E}-01 \quad 1.0915 \mathrm{E}-01 \quad 1.6886 \mathrm{E}-01 \quad 8.6664 \mathrm{E}-02 \quad 1.8682 \mathrm{E}-01 \quad 1.7260 \mathrm{E}-01 \quad 9.7256 \mathrm{E}-02 \quad 1.5302 \mathrm{E}-01-1.8356 \mathrm{E}-01$ $\begin{array}{lllll}9.6698 \mathrm{E}-02 & 4.8862 \mathrm{E}-01 & 2.5260 \mathrm{E}-01 & 3.1182 \mathrm{E}-01\end{array}$ GRADIENT: $\quad 7.6252 \mathrm{E}+02-2.1093 \mathrm{E}+02 \quad 4.0244 \mathrm{E}+02-3.3081 \mathrm{E}+01$ $-1.9134 \mathrm{E}+01-2.6976 \mathrm{E}+02 \quad 6.0002 \mathrm{E}+01 \quad 3.4254 \mathrm{E}+02$

OITERATION NO.: 5 OBJECTIVE VALUE: -398.915988443168 CUMULATIVE NO. OF FUNC. EVALS.: 85
$\begin{array}{lllll}\text { NPARAMETR: } & 4.2524 \mathrm{E}+00 & 7.3373 \mathrm{E}+00 & 4.7473 \mathrm{E}-01 & 1.4622 \mathrm{E}-03\end{array}$ $-2.4198 \mathrm{E}-03 \quad 1.9981 \mathrm{E}+00 \quad 1.5087 \mathrm{E}+00 \quad 1.8292 \mathrm{E}+00$
PARAMETER: $-2.8703 \mathrm{E}-01-1.7712 \mathrm{E}-01 \quad 8.3258 \mathrm{E}-02 \quad 1.9516 \mathrm{E}-01$ $\begin{array}{lllll}\text { 9.8295E-02 } & 6.5291 E-01 & 2.7726 E-01 & 3.3400 E-01\end{array}$ $1.0982 \mathrm{E}+03 \quad 1.3174 \mathrm{E}+02-2.2028 \mathrm{E}+02-2.3927 \mathrm{E}+01$ $1.7041 \mathrm{E}+00-3.6114 \mathrm{E}+01-3.8659 \mathrm{E}+02 \quad 3.8698 \mathrm{E}+02$

OITERATION NO.: 6 OBJECTIVE VALUE: -398.915988443168 CUMULATIVE NO. OF FUNC. EVALS.: 112 NPARAMETR: $4.2524 \mathrm{E}+00 \quad 7.3373 \mathrm{E}+00 \quad 4.7473 \mathrm{E}-01 \quad 1.4622 \mathrm{E}-03$ $-2.4198 \mathrm{E}-03 \quad 1.9981 \mathrm{E}+00 \quad 1.5087 \mathrm{E}+00 \quad 1.8292 \mathrm{E}+00$ PARAMETER: $-2.8703 \mathrm{E}-01-1.7712 \mathrm{E}-01 \quad 8.3258 \mathrm{E}-02 \quad 1.9516 \mathrm{E}-01$ $\begin{array}{llll}9.8295 \mathrm{E}-02 & 6.5291 \mathrm{E}-01 & 2.7726 \mathrm{E}-01 & 3.3400 \mathrm{E}-01\end{array}$
GRADIENT: $\quad 2.3418 \mathrm{E}+02-5.2004 \mathrm{E}+02-4.3686 \mathrm{E}+02-5.8980 \mathrm{E}+01-1.2399 \mathrm{E}+01-4.7930 \mathrm{E}+01-4.8911 \mathrm{E}+01 \quad 1.4053 \mathrm{E}+02-4.8456 \mathrm{E}+01-2.0158 \mathrm{E}+02$ $-1.2090 \mathrm{E}+01 \quad-3.6114 \mathrm{E}+01 \quad-3.8659 \mathrm{E}+02 \quad 3.8698 \mathrm{E}+02$


```
    3.8152E-01 2.3256E+00 1.6504E+00 1.5816E+00
PARAMETER: 4.6361E-02 3.3394E-01 9.5155E-02 7.6317E-01
    5.0375E-01 7.2882E-01 2.8113E-01 7.4211E-02
GRADIENT: -5.0495E+02 4.7899E+02 7.4998E+01 4.5078E+01
    6.9007E+01 -4.0100E+02 5.5867E+02 -1.2113E+02
OITERATION NO.: }15\mathrm{ OBJECTIVE VALUE: -608.895347142775
CUMULATIVE NO. OF FUNC. EVALS.: }36
NPARAMETR: 6.0665E+00 1.2177E+01 4.8040E-01 1.0817E-02
        3.2499E-01 
PARAMETER: }\begin{array}{lllll}{3.2499E-01 }&{2.3759E+00 1.655-02}&{3.2946E-01}&{9.5117E-02 }&{7.6323E-01}
4.4981E-01 7.3951E-01 2.7822E-01 8.1917E-02
GRADIENT: 2.1793E+01 -1.0972E+02 4.2526E+01 4.1464E+01 -1.1569E+01 4.2636E+01 3.2913E+01 2.1190E+01 -3.5040E+00 -3.2372E+01
    -1.2497E+01 5.8012E-01 -3.5180E+02 1.4702E+01
OITERATION NO.: 16 OBJECTIVE VALUE: -615.428368693332
CUMULATIVE NO. OF FUNC. EVALS.: }38
CUMULATIVE NO. OF FUNC. EVALS.: 
        3.5227E-01 2.3938E+00 1.6845E+00 1.6031E+00
PARAMETER: 7.7739E-02 3.3989E-01 9.3940E-02 7.2677E-01
        4.7604E-01 7.4327E-01 2.8283E-01 8.2996E-02
GRADIENT: 
OITERATION NO.: 17 OBJECTIVE VALUE: -618.097330619074
CUMULATIVE NO. OF FUNC. EVALS.: 411
NPARAMETR: 6.2043E+00 1.2356E+01 4.7944E-01 9.3349E-03
        4.1326E-01 2.4206E+00 1.7279E+00 1.6483E+00
PARAMETER: 9.0732E-02 3.4404E-01 9.3134E-02 6.7471E-01
5.3337E-01 7.4883E-01 2.8850E-01 7.9615E-02
GRADIENT: -8.6575E+01 1.6314E+01 -1.1817E+01 2.7350E+01
    1.2046E+01-1.0948E+02 4.1731E+00 -4.7930E+00
OITERATION NO.: 18 OBJECTIVE VALUE: -620.021188720949
CUMULATIVE NO. OF FUNC. EVALS.: 436
NPARAMETR: 6.2667E+00 1.2382E+01 
    4.2815E-01 
PARAMETER: 1.0073E-01 
5.4711E-01 7.5509E-01 2.9145E-01 7.7888E-02
GRADIENT: -9.1326E+01 2.6210E+01 -2.2692E+01 1.7768E+01 -1.6006E+01 -3.0699E+01 -1.3955E+01 -4.4840E+00 -1.3857E+01 4.8881E+00
    6.0237E+00 -9.9881E+01 7.0493E+00-7.2346E+00
OITERATION NO.: 19 OBJECTIVE VALUE: -624.613807571676
CUMULATIVE NO. OF FUNC. NO. OF FUNC. EVALS.: 44
```



```
    4.1958E-01 2.4365E+00 1.7589E+00 1.6845E+00
PARAMETER: 1.0001E-01 3.4134E-01 9.2059E-02 5.9838E-01 8.2641E-01 3.8900E-01 8.2033E-01 -1.5863E-01 8.3988E-01 -4.1545E-01
5.3921E-01 7.5211E-01 2.9273E-01 7.9419E-02
GRADIENT: }\begin{array}{lllllllllllll}{0.7692E+02 1.3880E+03 1.5255E+02 1.5881E+02 }&{8.2925E+01}&{3.0416E+02}&{2.1884E+02}&{2.4545E+02}&{1.0729E+02}&{6.6446E+02}
    6.7109E+01 -1.0230E+02 9.6798E+00 1.0591E+01
OITERATION NO.: 20 OBJECTIVE VALUE: -624.613807571676
CUMULATIVE NO. OF FUNC. EVALS.: 505 
NPARAMETR: 6.2622E+00 1.2323E+01 4.7893E-01 8.0572E-03
        4.1958E-01 2.4365E+00 1.7589E+00 1.6845E+00
MARAMETER: }\begin{array}{llllll}{4.1958E-01}&{2.4365E+00}&{1.7589E+00}&{1.6845E+00}\\{\mathrm{ 1.0001E-01 }}&{3.4134E-01}&{9.2059E-02}&{5.9838E-01}
PARAMETER: 1.0001E-01 3.4134E-01 9.2059E-02 5.9838E-01 
GRADIENT: 5.3921E-01 7.5211E-01 2.9273E-01 7.9419E-02
GRADIENT: 
    -1.6034E+01 -1.0230E+02 9.6798E+00 1.0591E+01
OITERATION NO.: 21 OBJECTIVE VALUE: -626.634252670872
CUMULATIVE NO. OF FUNC. EVALS.: }53
```



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        llll
PARAMETER: 1.0010E-01 3.4409E-01 9.2267E-02 5.7038E-01
5.5181E-01 7.5465E-01 2.9271E-01 7.9391E-02
    -1.0981E+01 -7.9902E+01 -3.9527E+01 1.2649E+01
OITERATION NO.: 22 OBJECTIVE VALUE: -626.634252670872
CUMULATIVE NO. OF FUNC. EVALS.: }56
NPARAMETR: 6.2627E+00 1.2356E+01 4.7903E-01 7.5895E-03 1.2051E-02 2.7073E-01 7.9120E-01 -2.0013E-01 7.7731E-01 -3.5453E-01
        4.3328E-01 2.4489E+00 1.7634E+00 1.6844E+00
PARAMETER: 1.0010E-01 3.4409E-01 9.2267E-02 5.7038E-01 6.3849E-01 3.9639E-01 8.5627E-01 -1.6124E-01 8.4530E-01 -4.0509E-01
F.5181E-01 7.5465E-01 2.9271E-01 7.9391E-02
GRADIENT: 
    -6.0574E+00 1.0753E+02 -2.2209E+02 -1.3227E+02
\#TERM:
OMINIMIZATION SUCCESSFUL
HOWEVER, PROBLEMS OCCURRED WITH THE MINIMIZATION.
REGARD THE RESULTS OF THE ESTIMATION STEP CAREFULLY, AND ACCEPT THEM ONLY
AFTER CHECK ING THAT THE COVARIANCE STEP PRODUCES REASONABLE OUTPUT.
NO. OF FUNCTION EVALUATIONS USED: 560
NO. OF SIG. DIGITS IN FINAL EST.: 1.0
```

etabar is the arithmetic mean of the eta-estimates,
and the p-value is given for the null hypothesis that the true mean is 0.

| ETABAR: | $1.0923 \mathrm{E}-01$ | $4.6877 \mathrm{E}-02$ |
| :--- | ---: | ---: |
| SE: | $2.2869 \mathrm{E}-02$ | $1.7276 \mathrm{E}-02$ |
| $\mathrm{~N}:$ | 1825 | 1825 |


| P VAL.: | $1.7872 \mathrm{E}-06$ | $6.6593 \mathrm{E}-03$ |  |
| :--- | :--- | :--- | :--- |
|  |  |  |  |
| ETAshrink(\%): | $3.7554 \mathrm{E}+01$ | $4.3118 \mathrm{E}+01$ |  |
| EBVshrink(\%): | $3.5812 \mathrm{E}+01$ | $3.6812 \mathrm{E}+01$ |  |
| EPSshrink(\%): | $8.2715 \mathrm{E}+00$ |  |  |
|  |  |  |  |
| \#TERE: |  |  |  |
| Elapsed est imation time in seconds: | 154.39 |  |  |
| OR MATRIX AL GORITHMICALLY SINGULAR |  |  |  |
| AND ALGORITHMICALLY NON-POSITIVE-SEMIDEFINITE |  |  |  |
| OR MATRIX IS OUTPUT |  |  |  |
| OCOVARIANCE STEP ABORTED |  |  |  |
| Elapsed covariance time in seconds: | 213.84 |  |  |
| 1 |  |  |  |



THETA - VECTOR OF FIXED EFFECTS PARAMETERS *********
$\begin{array}{lllllllllll}\text { TH } 1 & \text { TH } 2 & \text { TH } 3 & \text { TH } 4 & \text { TH } 5 & \text { TH } 6 & \text { TH } 7 & \text { TH } 8 & \text { TH } 9 & \text { TH10 }\end{array}$ $6.26 \mathrm{E}+00 \quad 1.24 \mathrm{E}+01 \quad 4.79 \mathrm{E}-01 \quad 7.59 \mathrm{E}-03 \quad 1.21 \mathrm{E}-02 \quad 2.71 \mathrm{E}-01 \quad 7.91 \mathrm{E}-01 \quad-2.00 \mathrm{E}-01 \quad 7.77 \mathrm{E}-01-3.55 \mathrm{E}-01 \quad 4.33 \mathrm{E}-01$

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

|  | ETA1 | ETA2 |
| :--- | ---: | ---: |
| ETA1 |  |  |
| + | $2.45 \mathrm{E}+00$ |  |
| + ETA2 |  |  |
| + | $1.76 \mathrm{E}+00$ | $1.68 \mathrm{E}+0$ |

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

EPS1
EPS1
$+\quad 1.00 \mathrm{E}+00$
1

OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS $* * * * * * *$
ETA1 ETA2

ETA1
$+\quad 1.56 \mathrm{E}+00$
ETA2
$+\quad 8.68 \mathrm{E}-01 \quad 1.30 \mathrm{E}+00$

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

## EPS1

EPS1
$+\quad 1.00 \mathrm{E}+00$


```
TH 1
\(+\quad 1.98 \mathrm{E}+02\)
\(+\begin{array}{lll}\text { TH } 2 & -2.68 \mathrm{E}+01 & 2.49 \mathrm{E}+01\end{array}\)
TH 3
\(+\quad 1.08 \mathrm{E}+03 \quad 2.26 \mathrm{E}+01 \quad 9.35 \mathrm{E}+04\)
\(\begin{array}{lllll}\text { TH } 4 & 1.58 \mathrm{E}+03 & 2.35 \mathrm{E}+02 & -1.16 \mathrm{E}+05 & 6.26 \mathrm{E}+05\end{array}\)
TH 5
\(+\quad 1.41 \mathrm{E}+03-1.11 \mathrm{E}+02-1.62 \mathrm{E}+03-1.69 \mathrm{E}+04 \quad 4.85 \mathrm{E}+04\)
TH 6
\(+\quad 6.94 \mathrm{E}+01-3.68 \mathrm{E}+01-1.33 \mathrm{E}+02 \quad 2.36 \mathrm{E}+03 \quad 5.42 \mathrm{E}+02 \quad 1.19 \mathrm{E}+03\)
\(\begin{array}{llllllll}\text { TH } 7 \\ + & 1.79 \mathrm{E}+01 & -9.02 \mathrm{E}+00 & -3.76 \mathrm{E}+01 & -7.70 \mathrm{E}+02 & -1.15 \mathrm{E}+02 & 6.65 \mathrm{E}-12 & 6.39 \mathrm{E}+01\end{array}\)
TH 8
\(\begin{array}{llllllllll}\text { TH } 9 & & 2.36 \mathrm{E}+01 & -1.23 \mathrm{E}+01 & 6.67 \mathrm{E}+00 & 2.99 \mathrm{E}+02 & 5.03 \mathrm{E}+01 & 4.41 \mathrm{E}+01 & 1.34 \mathrm{E}+01 & 0.00 \mathrm{E}+00\end{array} \quad 7.98 \mathrm{E}+01\)
TH10
\(+\quad-2.02 \mathrm{E}+021.42 \mathrm{E}+02 \quad 6.13 \mathrm{E}+02 \quad 5.07 \mathrm{E}+03-5.62 \mathrm{E}+02-3.61 \mathrm{E}+02-7.07 \mathrm{E}+01-1.97 \mathrm{E}+03-5.76 \mathrm{E}-12 \quad 2.71 \mathrm{E}+03\)
TH11
\(+\quad-2.52 \mathrm{E}+01 \quad 1.69 \mathrm{E}+01-1.10 \mathrm{E}+02-9.29 \mathrm{E}+02-2.49 \mathrm{E}+02-5.71 \mathrm{E}+01 \quad-9.79 \mathrm{E}+00 \quad 0.00 \mathrm{E}+00-1.06 \mathrm{E}+02 \quad 0.00 \mathrm{E}+00 \quad 1.50 \mathrm{E}+02\)
OM11
\(+\underset{5.27}{-1.01 \mathrm{E}+02} 2.01 \mathrm{E}+01-2.04 \mathrm{E}+03-6.16 \mathrm{E}+03-2.00 \mathrm{E}+03-1.15 \mathrm{E}+02 \quad-5.38 \mathrm{E}+01-2.94 \mathrm{E}+02-4.49 \mathrm{E}+01 \quad 2.37 \mathrm{E}+02-4.95 \mathrm{E}+01 \quad-2.36 \mathrm{E}+03\)
OM22
\(+\quad 3.02 \mathrm{E}+01-3.44 \mathrm{E}+00 \quad 1.19 \mathrm{E}+03 \quad 3.50 \mathrm{E}+03 \quad 6.82 \mathrm{E}+02 \quad 2.22 \mathrm{E}+01 \quad 2.00 \mathrm{E}+01 \quad 4.42 \mathrm{E}+01 \quad 5.68 \mathrm{E}+00-3.70 \mathrm{E}+01 \quad 3.07 \mathrm{E}+01 \quad 1.21 \mathrm{E}+03\) \(-2.93 \mathrm{E}+03 \quad 1.84 \mathrm{E}+03\)
SG11```

