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ARTICLE

Population repeated time-to-event analysis of exacerbations in asthma patients: A novel approach for predicting asthma exacerbations based on biomarkers, spirometry, and diaries/questionnaires

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Abstract

Identification of covariates, including biomarkers, spirometry, and diaries/questionnaires, that predict asthma exacerbations would allow better clinical predictions, shorter phase II trials and inform decisions on phase III design, and/or initiation (go/no-go). The objective of this work was to characterize asthma-exacerbation hazard as a function of baseline and time-varying covariates. A repeated time-to-event (RTTE) model for exacerbations was developed using data from a 52-week phase IIb trial, including 502 patients with asthma randomized to placebo or 70 mg, 210 mg, or 490 mg astegolimab every 4 weeks. Covariate analysis was performed for 20 baseline covariates using the full random effects modeling approach, followed by time-varying covariate analysis of nine covariates using the stepwise covariate model (SCM) building procedure. Following the SCM, an astegolimab treatment effect was explored. Diary-based symptom score (difference in objective function value [dOFV] of −83.7) and rescue medication use (dOFV = −33.5), and forced expiratory volume in 1 s (dOFV = −14.9) were identified as significant time-varying covariates. Of note, time-varying covariates become more useful with more frequent measurements, which should favor the daily diary scores over others. The most influential baseline covariates were exacerbation history and diary-based symptom score (i.e., symptom score was important as both time-varying and baseline covariate). A (nonsignificant) astegolimab treatment effect was included in the final model because the limited data set did not allow concluding the remaining effect size as irrelevant. Without time-varying

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covariates, the treatment effect was statistically significant ($p < 0.01$). This work demonstrated the utility of a population RTTE approach to characterize exacerbation hazard in patients with severe asthma.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

For early-stage asthma trials, decisions can be guided by changes in biomarkers, spirometry, or diaries/questionnaires, instead of asthma exacerbations (which is often the registrational end point). As exacerbations are rare events, exacerbation-based end points require longer treatment duration and larger studies. Knowing which biomarkers, spirometry, and/or diaries/questionnaires are relevant predictors of asthma exacerbations could benefit decision making for asthma trials.

WHAT QUESTION DID THIS STUDY ADDRESS?

Based on several baseline and time-varying covariates, available from a phase IIb study, we explored relevant predictors for asthma exacerbations, using repeated time-to-event (RTTE) modeling.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study determined that exacerbation history, diary-based symptom score, diary-based rescue medication use, and FEV1 are relevant predictors of exacerbations. Treatments improving these end points should also produce a better outcome in exacerbations.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The presented model has the potential for decision making within asthma drug development to be more efficient. The RTTE model allows realistic simulations of different subpopulations, study designs, etc., which can further tailor studies to efficiently address questions on exacerbations.

INTRODUCTION

Asthma is a chronic respiratory condition associated with allergic airway inflammation primarily affecting pediatric to middle-aged adult patients and estimated to affect over 300 million people worldwide.[1,2] The standard of care treatments of asthma are anti-inflammatory medications and bronchodilators, which control symptoms in most patients. However, 20–40% of patients with asthma are estimated to have persistent symptoms despite controller medications and are categorized as having moderate-to-severe asthma.[3–6] Asthma patients can experience recurrent acute episodes of asthma exacerbations, defined as new or increased asthma symptoms (wheezing, coughing, dyspnea, chest tightness, and/or nighttime awakenings due to these symptoms) resulting in use of systemic corticosteroids and/or hospitalization.[7] Patients with moderate-to-severe asthma have a higher risk of exacerbation, hospitalization, and death, and have a substantially impaired quality of life. Therefore, there is an unmet medical need for new effective treatments to reduce the frequency and severity of asthma exacerbations.

Annualized asthma exacerbation rate (exacerbations/year) is conventionally used as the registrational end point in clinical trials for novel asthma treatments.[7–11] Although reduction of exacerbations are clinically meaningful, there are drawbacks to this end point, because asthma exacerbations rarely occur and thus require long treatment duration (typically 52 weeks) and large sample size to achieve sufficient power to show differences between treatment arms. In addition, there are limitations in the traditional methods of analyzing asthma exacerbation data. For example, analysis of asthma exacerbation rate ignores features of time between each event and time-to-first exacerbation analysis accounts for the time feature but ignores data from subsequent exacerbation events.

In early-stage clinical development for moderate-to-severe asthma treatments, go/no go decisions can be guided by changes in biomarkers, spirometry, or diaries/questionnaires, instead of asthma exacerbations. Forced expiratory volume in 1 s (FEV1) or fractional exhaled nitric oxide are typical examples of such end points and indicate degree of airway obstruction and airway inflammation, respectively. Knowing which of these biomarkers, spirometry, and

diaries/questionnaires are the most relevant predictors of asthma exacerbation hazard could benefit decision making for earlystage asthma trials. Furthermore, if the relationship between the most relevant predictors and asthma exacerbations were to be quantified by a pharmacometric approach, it would allow predictions of asthma exacerbations from early-stage data, help planning and designing of later-stage trials, and, consequently, accelerate drug development in this area. Repeated time-to-event (RTTE) analysis is a pharmacometric approach that can handle repeated event data (i.e., the event can occur several times per individual), has been applied to analyze event data in other therapeutic areas,[12–15] and was expected to be useful for analyzing asthma-exacerbation event data.

The objective of this work was to characterize the hazard of asthma exacerbations as a function of both baseline covariates (including e.g., demographics, biomarkers, spirometry, and diaries/questionnaires measured at screening/baseline) and time-varying covariates (including time-varying biomarkers, spirometry, and diaries/questionnaires) using an RTTE analysis approach. To our knowledge, this is the first RTTE model published for any respiratory indication. An overall goal with this analysis was to better understand how biomarkers, spirometry, and diaries/questionnaires impact exacerbation hazard. This goal was met by developing a population RTTE model for asthma exacerbations using clinical data from a recent large dose-ranging phase IIb study investigating astegolimab, a human monoclonal immunoglobulin G2 that targets suppression of tumorigenicity 2 receptor and blocks IL-33 signaling.

METHODS

Patient data and study design

The analysis dataset consisted of all subjects randomized in the Zenyatta study, a double-blind, placebo-controlled fixed-dose phase IIb study of astegolimab in patients with uncontrolled severe asthma (GB39242, clinicaltrials.gov identifier: NCT02918019).[16] Patients were on inhaled corticosteroid therapy (≥500 μg fluticasone propionate or equivalent) plus greater than or equal to 1 additional controller medication. Patients were required to have a history of greater than or equal to 1 asthma exacerbation within 12 months prior to screening. The study was approved by an ethics committee or institutional review board at each trial site and carried out in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice. Informed consent was obtained from all subjects.

Data from 502 patients with asthma, randomized to subcutaneously administered placebo ($n = 127$) or astegolimab as 70 mg ($n = 127$), 210 mg ($n = 126$) or 490 mg ($n = 122$) every 4 weeks for 52 weeks, were included in the analysis. Visits were scheduled on weeks 2, 4, and then every 4 weeks until week 52. Note that one single-blind dose of placebo started at run-in period (2 weeks prior to randomization). In this work, start of the randomized treatment period is used as the reference timepoint. The study recorded asthma exacerbations which could occur repeatedly, on any day, except that a new exacerbation could not occur until after the previous event had ended. Start of exacerbation events was the dependent variable for the present analysis, ignoring event duration. The data were censored at the end of the randomized treatment period at the individual patient level. An asthma exacerbation was defined as new or increased asthma symptoms that resulted in either hospitalization or an emergency department visit with administration of systemic corticosteroid treatment or treatment with systemic corticosteroids for greater than or equal to 3 days or a long-acting depot corticosteroid preparation with a therapeutic effectiveness of greater than or equal to 3 days. Several biomarkers, spirometry, and diaries/questionnaires were measured throughout the study, of which 20 were explored as baseline covariates (Table 1) and nine as time-varying covariates (Table 2). In addition to these covariates, astegolimab trough concentration (C_{trough}) was derived using the tabular output from a two-compartment population pharmacokinetic model, developed on the same patients (data on file). If the time since the last dose greater than or equal to 56 days, then C_{trough} was set to a half of lower limit of quantification (LLOQ/2; LLOQ = 0.15 μg/ml), which was relevant after missing two consecutive planned doses (occurred for 2.9% of patients on active treatment). Because the tabular output did not include predictions for observations below LLOQ, imputation by LLOQ/2 required less effort than predicting actual values and was considered fit-for-purpose.

Graphical exploration

An exploratory graphical analysis was performed to guide model development, including Kaplan–Meier plots of time-to-first, second, and third exacerbations (data on file). Changes in time-varying covariates versus time until next exacerbation were also plotted, in patients with greater than or equal to 1 exacerbation. Trends were assessed using smooths including 95% confidence intervals (CIs).

TABLE 1 Summary of baseline covariate statistics, stratified by dose arm

Covariate	Description	Available data points, *n* (%)		Dose group				
				Placebo	70 mg	210 mg	490 mg	All
n	Number of subjects			127	127	126	122	502
BWPEF (L/min)	Baseline peak expiratory flow, average of baseline and 6 preceding days	501 (99.8)	Mean (SD)	282 (115)	285 (102)	281 (114)	295 (97.9)	286 (107)
BWPFEV1 (%)	Baseline forced expiratory volume in 1 second, % of normal, average of run-in and baseline	498 (99.2)	Mean (SD)	57.9 (9.66)	58.0 (9.35)	60.1 (10.0)	59.1 (9.70)	58.8 (9.70)
BACQ5	Baseline asthma control questionnaire−5 (score 0–5)	500 (99.6)	Mean (SD)	2.79 (0.752)	2.73 (0.660)	2.81 (0.859)	2.77 (0.821)	2.77 (0.774)
BAQLQS	Baseline asthma quality of life questionnaire (score −1 to −7)	497 (99.0)	Mean (SD)	4.24 (1.03)	4.25 (0.852)	4.38 (0.984)	4.21 (0.863)	4.27 (0.934)
BWFENO (ppb)	Baseline fraction exhaled nitric oxide, average of run-in and baseline	496 (98.8)	Mean (SD)	29.5 (23.9)	27.4 (24.8)	28.9 (24.6)	29.5 (23.6)	28.8 (24.2)
BWSST2 (μg/ml)	Baseline soluble ST2, average of run-in and baseline	472 (94.0)	Mean (SD)	13.8 (6.69)	16.8 (23.7)	14.3 (10.6)	13.6 (8.24)	14.6 (14.0)
EXAHIST	Subjects' history of exacerbations in the past year	502 (100)	Mean (SD)	1.35 (0.596)	1.32 (0.576)	1.45 (0.711)	1.47 (0.805)	1.40 (0.678)
BEOS (cells/μL)	Baseline blood eosinophils	424 (84.5)	Mean (SD)	276 (314)	259 (220)	245 (210)	243 (198)	256 (240)
Age (years)		502 (100)	Mean (SD)	51.4 (12.2)	52.4 (11.9)	52.5 (12.0)	51.4 (12.0)	51.9 (12.0)
Weight (kg)		502 (100)	Mean (SD)	79.5 (13.8)	79.4 (15.4)	79.1 (13.8)	78.8 (14.2)	79.2 (14.3)
Height (cm)		502 (100)	Mean (SD)	168 (8.71)	168 (10.1)	167 (9.94)	168 (8.76)	168 (9.41)
BMI (kg/m^2)	Body mass index	502 (100)	Mean (SD)	28.3 (4.18)	28.0 (4.38)	28.4 (4.05)	27.9 (4.19)	28.1 (4.20)
BWSYM	Baseline diary-based symptom score, average of baseline and 6 preceding days (score 0–10)	500 (99.6)	Mean (SD)	3.69 (2.03)	3.70 (1.80)	4.07 (2.18)	3.88 (1.88)	3.84 (1.98)
BWRELI	Baseline diary-based short-acting rescue medication use, average of baseline and 6 preceding days (possible values 0–1)	501 (99.8)	Mean (SD)	0.593 (0.361)	0.623 (0.349)	0.672 (0.344)	0.675 (0.367)	0.641 (0.356)
BWAWAK	Baseline diary-based symptom awakening, average of baseline and 6 preceding days (possible values 0–1)	501 (99.8)	Mean (SD)	0.493 (0.411)	0.503 (0.391)	0.585 (0.390)	0.596 (0.392)	0.544 (0.398)
Sex	Male		*n* (%)	45 (35)	46 (36)	36 (29)	43 (35)	170 (34)
	Female		*n* (%)	82 (65)	81 (64)	90 (71)	79 (65)	332 (66)
Race	White		*n* (%)	107 (84)	105 (83)	108 (86)	102 (84)	422 (84)
	Black, African American, Asian, American Indian or Alaska native, multiple, and other		*n* (%)	20 (16)	22 (17)	18 (14)	20 (16)	80 (17)

(Continues)

TABLE 1 (Continued)

Covariate	Description	Available data points, *n* (%)	Dose group				
			Placebo	70 mg	210 mg	490 mg	All
Ethnicity	Hispanic or Latino	*n* (%)	18 (14)	19 (15)	15 (12)	14 (11)	66 (13)
	Not Hispanic or Latino	*n* (%)	109 (86)	108 (85)	110 (87)	108 (89)	435 (87)
Genotype	IL1RL1 positive	*n* (%)	45 (35)	57 (45)	61 (48)	67 (55)	230 (46)
	IL1RL1 negative	*n* (%)	73 (57)	58 (46)	54 (43)	47 (39)	232 (46)
Region	Asia, Central and Eastern Europe or Latin America	*n* (%)	86 (68)	84 (66)	90 (72)	82 (67)	342 (68)
	North America, missing, Western Europe or rest of World	*n* (%)	41 (33)	43 (33)	36 (28)	40 (33)	160 (32)

Model development

Model development started by exploring different baseline hazard parameterizations, including time-varying Weibull and Gompertz distributions (based on time since randomization), and an exponential (constant hazard) distribution. These models were re-investigated on the final model. Interindividual variability (IIV) was explored on the hazard as log-normal and Box-Cox distributions. Dropout modeling was not performed (dropout was <10%).

A baseline-covariate analysis was performed using Full Random Effects Modeling (FREM),[17–19] including 20 covariates (Table 1). Baseline covariates were entered into the dataset as observed variables, and their distributions were modeled as random effects. A full covariance matrix between random effects for parameters and covariates was estimated together with the other model components.

After FREM, a visit-effect was investigated by exploring a difference in the hazard when approaching (or getting past) the planned time of a visit compared to in-between visits. An "outpatient time ratio" (RATOUT, Equation 1) was derived, ranging between 0 and 1, and tested as a covariate. Zero signifies the beginning of an outpatient period (defined as 0.8 days after finishing a planned visit) and 1 means on-going visit, or overdue for a visit. RATOUT was defined as:

$$\mathrm{RATOUT}(t) = \begin{cases} \dfrac{\mathrm{TSLV}(t)}{\mathrm{TUNV}(t)+\mathrm{TSLV}(t)}, & \text{if } \mathrm{TSLV}(t) > 0.8 \text{ days} \\ 1, & \text{if } \mathrm{TSLV}(t) \le 0.8 \text{ days} \end{cases} \quad (1)$$

where TSLV is the time since last visit and TUNV is the time until the next planned visit. RATOUT was set to 1 until 0.8 days after a visit, ensuring that RATOUT = 1 for exacerbations occurring on the same date as an actual visit. The visit-effect was included on the hazard through ROCOV, according to Equations 2 and 3:

$$h(t) = \begin{cases} h(\ldots)\cdot e^{\mathrm{ROCOV(t)}}, & \text{if } t_{\mathrm{exac}} > 8 \text{ days} \\ 0, & \text{if } t_{\mathrm{exac}} \le 8 \text{ days} \end{cases} \quad (2)$$

$$\mathrm{ROCOV}(t) = \begin{cases} \theta_{\mathrm{RO}} \cdot -0.1, & \text{if } \mathrm{RATOUT}(t) \le 0.9 \\ \theta_{\mathrm{RO}} \cdot (1-0.1), & \text{if } \mathrm{RATOUT}(t) > 0.9 \end{cases} \quad (3)$$

where t_{exac} is the time since most recent exacerbation, θ_{RO} is the coefficient for the visit-effect, and h(...) is a placeholder for other components of the model (e.g., baseline hazard and time-varying covariates). This led to higher hazards when RATOUT > 0.9. This implementation converts the

TABLE 2 Summary of time-varying covariate statistics, drug exposure and outcome at 52 weeks after randomization

Covariate	Description	Scheduled timepoints for measurements[a]	Summary measure[b]	Dose group				
				Placebo	70 mg	210 mg	490 mg	All
DAQLQS	Asthma quality of life questionnaire, absolute change from baseline	Weeks 24, 52	Mean (SD)	0.742 (1.09)	0.862 (1.01)	0.785 (1.04)	0.861 (1.01)	0.812 (1.04)
DFENO (ppb)	Fraction exhaled nitric oxide, absolute change from baseline	Weeks 2, 4, 12, 24, 36, 52	Mean (SD)	−2.34 (21.0)	−0.875 (19.7)	−2.14 (25.2)	−2.87 (23.8)	−2.05 (22.4)
RFEV1	Forced expiratory volume in 1 second, ratio versus baseline	Weeks 2 and 4 and monthly until week 52	Mean (SD)	1.06 (0.212)	1.06 (0.153)	1.09 (0.186)	1.10 (0.215)	1.08 (0.193)
LREOS	Blood eosinophils, log-ratio versus baseline	Weeks 2 and 4 and monthly until week 52	Mean (SD)	−0.0457 (0.566)	−0.300 (0.881)	−0.366 (0.704)	−0.337 (0.774)	−0.258 (0.746)
LRST2	Soluble ST2, log-ratio versus baseline	Weeks 2, 8, 12 and 36	Mean (SD)	−0.0326 (0.334)	2.92 (0.803)	3.17 (0.693)	3.20 (0.577)	2.29 (1.51)
DSYM	Diary-based symptom score, absolute change from baseline	Daily, included as 4-day average	Mean (SD)	−1.10 (1.50)	−1.46 (1.70)	−1.22 (1.95)	−1.48 (1.83)	−1.31 (1.75)
RPEF	Peak expiratory flow, ratio versus baseline	Daily, included as 4-day average	Mean (SD)	1.00 (0.231)	1.06 (0.264)	1.07 (0.339)	1.05 (0.226)	1.04 (0.269)
DRELI	Diary-based short-acting rescue medication use, absolute change from baseline	Daily, included as 4-day average	Mean (SD)	−0.209 (0.357)	−0.283 (0.345)	−0.224 (0.368)	−0.315 (0.414)	−0.257 (0.373)
DAWAK	Diary-based symptom awakening, absolute change from baseline	Daily, included as 4-day average	Mean (SD)	−0.202 (0.373)	−0.209 (0.409)	−0.233 (0.416)	−0.267 (0.438)	−0.227 (0.409)
C_{trough} (μg/ml)[c]	Model-predicted astegolimab trough concentration	Weeks 4, 8, 12, 24, 36, 48 and 52[e]	Mean (SD)	0 (0)	6.00 (2.87)	23.1 (11.4)	52.3 (28.1)	19.9 (25.1)
Number of asthma exacerbation events[d]	Total number of exacerbations during randomized treatment period	Daily	Sum	92	58	61	50	261

[a]Relative to time since first dose (i.e., randomization).

[b]Except for outcome (number of exacerbations), the mean (SD) change from baseline at the end-of treatment visit (52 weeks after start of randomized treatment).

[c]Explored after stepwise covariate model.

[d]Asthma exacerbations were the dependent variable, treated as a repeated time-to-event variable and was not tested as a covariate.

[e]Refers to timepoints where drug concentrations were to be measured, which were used to predict astegolimab trough concentration, using a population pharmacokinetic model.

time between visits into a relative variable applicable regardless of the interval between visits (which varied throughout the study). The model included an 8-day delay to implement a convention of phase III trials (e.g., refs. 8,11) where exacerbations less than or equal to 7 days apart are treated as a single exacerbation, and adding 1 day which was considered the minimum duration between exacerbations. Note that for the Zenyatta study, there was no defined minimum duration between two exacerbations (but the shortest observed interval between exacerbation events were 10 days).

Subsequently, a stepwise covariate model (SCM) building procedure[20–22] was performed for the nine exploratory time-varying covariates (Table 2) included in the dataset as the difference from baseline, ratio versus (of) baseline or log-ratio versus baseline, based on the observed data. The dataset was discretized into 3–4 day intervals. The variables collected daily were explored as the average in each interval. If time-varying covariates were unavailable at a given timepoint, last observation carry forward was applied. If the corresponding baseline value was missing (Table 1 reports missingness), the time-varying covariate was imputed with the median change for placebo. In the first stage, the nine potentially useful covariates were investigated (forward inclusion) and included into the model one-by-one, based on a significance level of $p < 0.01$. In the second stage, included covariates were formally tested by removal from the model (backward elimination) where covariates were retained only if they were significant at $p < 0.001$. The time-varying covariate-parameter relationships were implemented as linear models, according to Equation 4:

$$\begin{aligned} \mathrm{EffCov}_{m,ij} &= \left(\mathrm{Cov}_{m,ij} - \mathrm{Cov}_{m,\mathrm{ref}}\right) \cdot \theta_m \\ \mathrm{RESP}_{ij}(t) &= \sum_{m=1}^{n} \mathrm{EffCov}_{m,ij} \end{aligned} \tag{4}$$

where $\mathrm{Cov}_{m,ij}$ is the individual change in covariate m, for subject i at time-point t_j. $\mathrm{Cov}_{m,\mathrm{ref}}$ is a reference covariate value for covariate m, around which the covariate was centered: the median change in placebo patients, at 6 months. The θ_m is the coefficient for covariate m. The sum of the contribution of the selected time-varying covariates (RESP_{ij}) was included on the hazard, h, on the log-hazard scale according to Equation 5:

$$h(t) = h(\ldots) \cdot e^{\mathrm{RESP}_{ij}(t)} \tag{5}$$

where $h(...)$ is a placeholder for other functions on the hazard.

Following SCM, model finalizations were performed. This included exposure-response evaluation based on time-varying C_{trough}. This was performed after inclusion of significant covariates among the nine covariates tested in the SCM. Exposure was included through $\mathrm{RESP}_{\mathrm{Exp}}$ on the log-hazard ratio scale as in Equation 6:

$$\mathrm{RESP}_{\mathrm{exp}}(t) = \begin{cases} 0, & \text{if } C_{\mathrm{trough}}(t) < \mathrm{LLOQ} \\ \theta_{\mathrm{exp}}, & \text{if } C_{\mathrm{trough}}(t) \geq \mathrm{LLOQ} \end{cases} \tag{6}$$

where θ_{Exp} is the change in hazard for C_{trough} greater than or equal to 0.15 μg/ml (LLOQ). Linear and log-linear exposure-response models were also tested.

A Markov element was investigated to describe the lower hazard during the weeks/days after onset of an asthma exacerbation event, defined by a time-dependent return to the baseline hazard according to Equation 7:

$$h(t) = \begin{cases} h(\ldots) \cdot \left(1 - e^{-\frac{\log(2)}{t_{1/2,\mathrm{Markov}}} \cdot (t_{\mathrm{exac}} - t_{\mathrm{lag}})}\right), & \text{if } t_{\mathrm{exac}} > 8 \text{ days} \\ 0, & \text{if } t_{\mathrm{exac}} \leq 8 \text{ days} \end{cases} \tag{7}$$

where $t_{½,\ \mathrm{Markov}}$ is a half-life for the recovery of the hazard and t_{lag} is a lag-time of 7 days. Note that with t_{lag} set to 7 days, the hazard starts well above zero as soon as the 8-day delay period following an exacerbation has passed.

Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the final model. These included investigation of exposure-response prior to performing an SCM, and performing an SCM only on the placebo subjects.

Model selection and evaluation

Models were selected based on differences in the objective function value (dOFV) where for a more complicated model to be retained it generally had to provide a significant improvement over the contending model ($p < 0.05$ [dOFV = −3.84], whereas for the SCM for time-varying covariates, a stricter value of $p < 0.001$ [dOFV = −10.83] was used, to compensate for type I error inflation). The final model was evaluated using Kaplan–Meier visual predictive checks (VPCs) for time-to-first, second, and third exacerbations, and using posterior predictive checks (PPCs) for the weighted average exacerbation rate (total exacerbations/total duration of follow-up in the randomized treatment period, per treatment arm). Parameter uncertainties were assessed using the covariance step in NONMEM (using MATRIX = R).

Software details

The analysis was performed using NONMEM 7.3.0,[23] using Monte Carlo importance sampling for estimation. Plotting and processing of NONMEM output were performed using R 3.5.3.[24] VPCs, FREM, and SCM were run using PsN 4.9.0.[20,21] Xpose 4.6.0 was used as an aid in model assessment.[25]

RESULTS

Graphical exploration

The graphical exploration for changes in time-varying covariates versus time until next exacerbation suggests that peak expiratory flow (PEF), diary-based symptom score, rescue medication use, nighttime awakenings, and FEV1 had relevant trends 10–20 days prior to an exacerbation event (Figure 1). However, note that the CIs should be interpreted with caution because some subjects contributed several data points.

Model development

The final model included a Weibull parameterization for the baseline hazard. The shape parameter was positive, indicating an increase in hazard over time (on top of changes from time-varying covariates). A Markovian element of lower hazard following an exacerbation was included, with a time-dependent return to the baseline hazard. A visit-effect predicted higher hazard just prior to and during visits or when overdue for a visit. The influence on the hazard from the baseline covariates are visualized in Figure 2; baseline symptom score and history of asthma exacerbations were most influential. Symptom score, short-acting rescue medication use, and FEV1 were selected as time-varying covariates. Exposure was included as a step function, although not significant

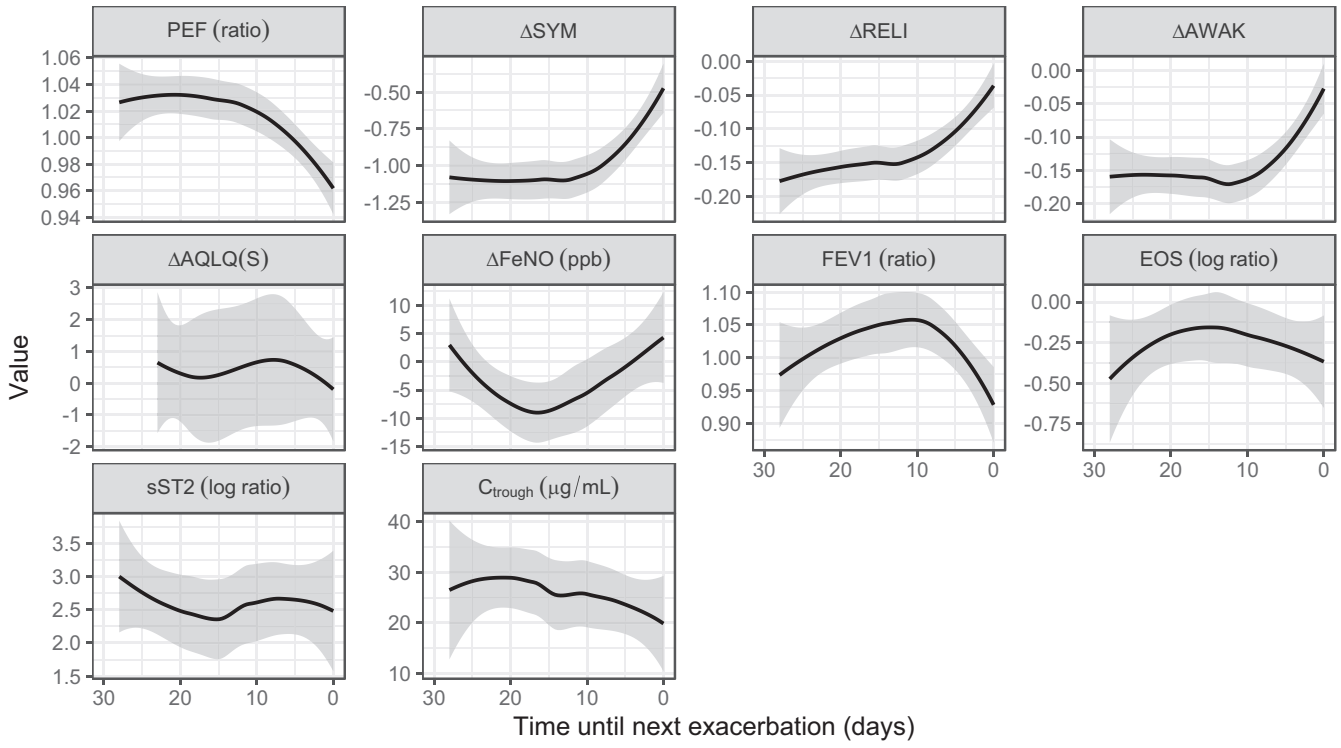
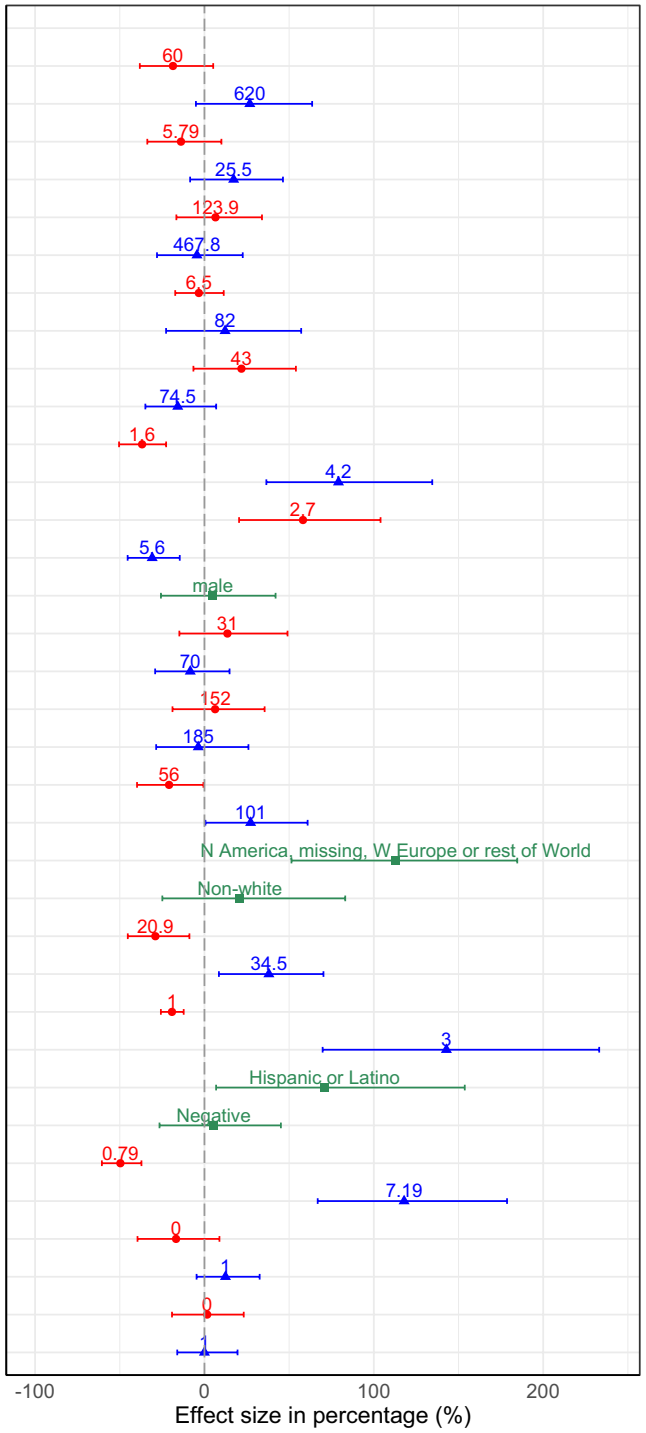


FIGURE 1 Observed changes from baseline in time-varying covariates versus time until next exacerbation for the analysis dataset. The solid lines are loess smooths. The values are shown as absolute (delta) change from baseline, or as the ratio or log-ratio of baseline. PEF, SYM, RELI, and AWAK are shown for 4-day average values. The plot includes measurements from patients with at least one exacerbation. Measurements earlier than 32 days after the first dose are not included in the plot and for AQLQS, where measurements earlier than 172 days have been excluded. Measurements earlier than 29 days before each exacerbation have also been excluded from the plot. For all time-varying covariates except PEF, SYM, RELI, and AWAK, only the most recent measurement was included, per subject and exacerbation. The gray area represents the 95% confidence interval of the smooth, but should be interpreted with caution, because some subjects contribute more than one observation. AQLQ(S), standardized asthma quality of life questionnaire; AWAK, diary symptom awakenings; C_{trough}, astegolimab trough concentration; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; RELI, short-acting rescue medication use; sST2, soluble ST2; SYM, diary symptom score



Covariate	Mean/reference	Point estimate [90% CI]
BEOS	190 cells/uL	-18.6 % [-38.2, +5.17]
		+26.8 % [-5.04, +63.6]
BWST2	12 ng/mL	-13.9 % [-33.7, +10]
		+17.2 % [-8.46, +46.4]
BWPEF	290 L/min	+6.51 % [-16.6, +34]
		-4.41 % [-28, +22.6]
BWFENO	29 ppb	-3.32 % [-17.3, +11.4]
		+12.2 % [-22.7, +57.1]
BWPFEV1	59 %	+21.8 % [-6.52, +54]
		-15.8 % [-34.9, +6.93]
BACQ5	2.8	-36.8 % [-50.4, -22.6]
		+79.1 % [+36.5, +134]
BAQLQS	4.3	+58.2 % [+20.4, +104]
		-30.9 % [-45.4, -14.6]
Sex	female	+4.94 % [-25.7, +42]
Age	52 years	+13.6 % [-14.8, +49.1]
		-8.38 % [-29.1, +14.8]
Height	170 cm	+6.3 % [-18.9, +35.5]
		-3.66 % [-28.5, +26]
Weight	79 kg	-20.9 % [-39.8, -0.61]
		+27.3 % [+0.58, +60.9]
Region	Asia, C and E Europe or Latin America	+113 % [+51.4, +185]
Race	White	+20.9 % [-24.9, +83.1]
BMI	28 kg/m2	-29 % [-45.3, -8.87]
		+38 % [+8.54, +70.3]
EXAHIST	1.4 /year	-19.2 % [-25.7, -12.3]
		+143 % [+69.8, +233]
Ethnicity	Not Hispanic or Latino	+70.9 % [+6.88, +154]
IL1RL1	Positive	+5.43 % [-26.5, +45.1]
BWSYM	3.8	-49.6 % [-60.6, -37.2]
		+118 % [+66.9, +179]
BWRELI	0.64	-16.8 % [-39.5, +8.85]
		+12.4 % [-4.65, +32.6]
BWAWAK	0.54	+1.6 % [-19.2, +23.2]
		-0.02 % [-16.1, +19.5]

FIGURE 2 Baseline covariate full random effects modeling (FREM) results for the final model. Plot shows the estimated change in hazard for individuals with different covariate values. For continuous covariates, the 5th (red dot) and 95th (blue triangle) percentiles of the observed range of the covariate are compared to a reference value: the mean of the observed covariate values (dashed line, at 0% difference). Categorical covariates (green square) use the most abundant category as reference (dashed line). Along with each point estimate, the 90% confidence interval (CI) is included as error bars, to represent parameter uncertainty. The illustrated change in hazard represents the FREM translation of univariate effect for a single covariate effect (accounting for correlations and as if covariate values for all other covariates were not available). Non-White includes Black, African American, Asian, American Indian or Alaska native, multiple, and other. See Table 1 for definitions of abbreviations. BMI, body mass index

at $p<0.05$ but was included given the limited size of the dataset and the magnitude of the point estimate of reduction in hazard (28%).

A visit-effect in the hazard was significant (dOFV = −13.2), predicting 90% higher hazard just prior to and during visits and when overdue for a visit. The predicted

increase in hazard was similar both before and after including time-varying covariates, and was present also in subjects randomized to placebo (Figure S1). The cutoff-value 0.9 in Equation 3 was motivated by the graphical exploration, showing that exacerbations occurred more frequently at RATOUT > 0.9 (Figure S1).

In the SCM, the diary-based symptom score (dOFV = −83.7) and short-acting rescue medication use (dOFV = −33.5) were selected. Both coefficients were positive, yielding higher hazard when these variables increased (i.e., worsening of asthma). Finally, FEV1 was selected (dOFV = −14.9) with a negative coefficient, predicting reduced hazard following FEV1 improvement. PEF met forward inclusion criteria ($p = 0.0087$) but was eliminated in the backward step (i.e., $0.001 < p < 0.01$).

Because time-varying covariates captured majority of the drug-exposure effect, after the time-varying covariates were included, exposure was not statistically significant ($p > 0.05$, dOFV = −2.1) but was included anyway. This conservative measure made the model specific for astegolimab treatment, which should be considered when using this model to predict asthma exacerbations for other treatments. Exposure could not be determined as clinically irrelevant, given the effect size of 28% reduction in hazard. A step function described the data better than linear or log-linear exposure-response relationships. The Markovian element was significant (dOFV = −13.7) and improved VPCs for time-to-second and third exacerbations (Figures S2 and S3, respectively). The final model included a log-normally distributed IIV in the hazard. A Box-Cox transformation was not statistically significant ($p > 0.05$, dOFV = −3.47). Example NONMEM code for the final model (ExampleNONMEMCode) is provided as a supplementary material.

Sensitivity analyses

Including exposure prior to inclusion of time-varying covariates was statistically significant ($p < 0.01$, dOFV = −7.84, performed as a sensitivity analysis), which is consistent with the treatment effect of asthma exacerbation rate reduction in the Zenyatta study.[16] An SCM performed on placebo subjects only (sensitivity analysis) selected the same three time-varying covariates (at $p < 0.05$), as in the SCM described above (based on all subjects in Zenyatta). The time-varying covariate coefficients were comparable to those of the final model (Table S1).

Model evaluation

The final model described the observed data well according to a VPC for time-to-first exacerbation (Figure 3),

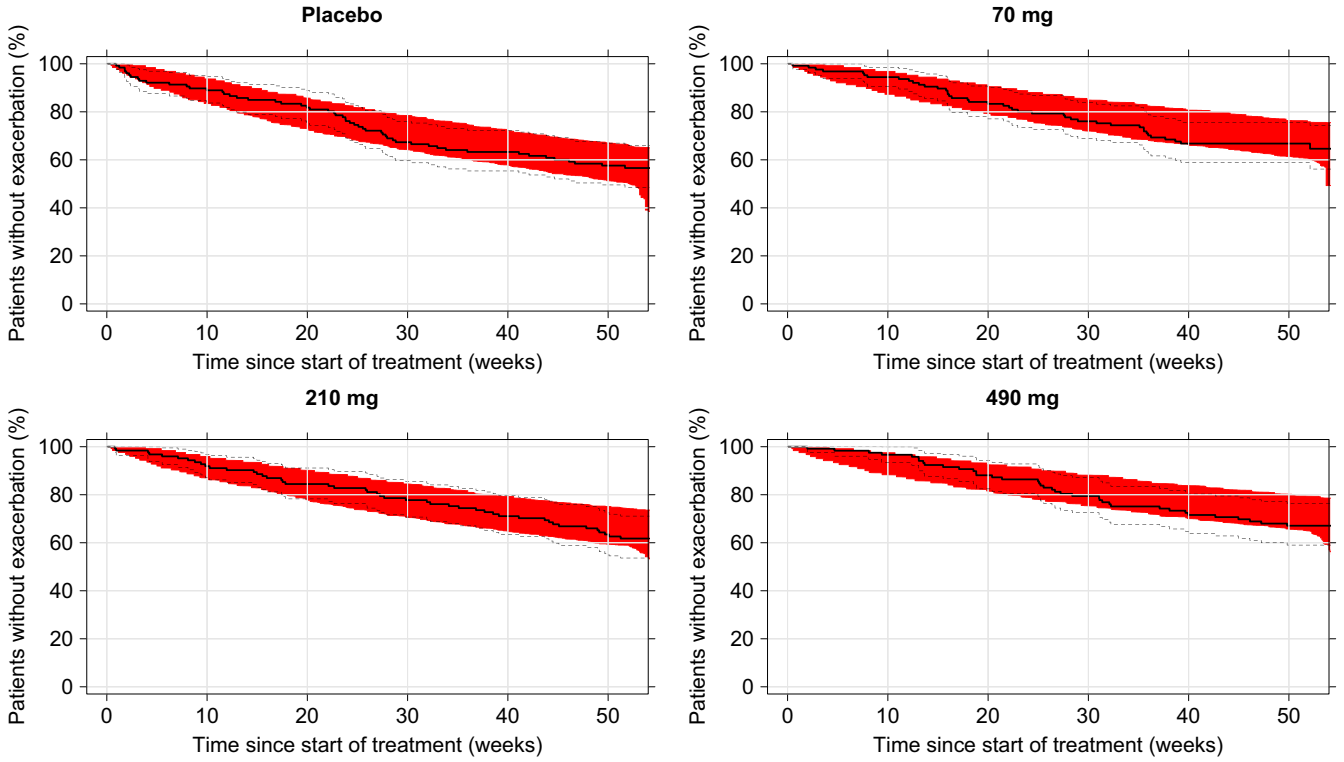


FIGURE 3 Final model Kaplan–Meier visual predictive check for time-to-first exacerbation, stratified on astegolimab treatment arm. The solid lines are the Kaplan–Meier estimated percentage of subjects without any exacerbation, the dashed lines represent the 95% confidence intervals of the Kaplan-Meier estimator. The red area is the 95% confidence interval based on the Kaplan-Meier estimates across each of 1000 simulated studies

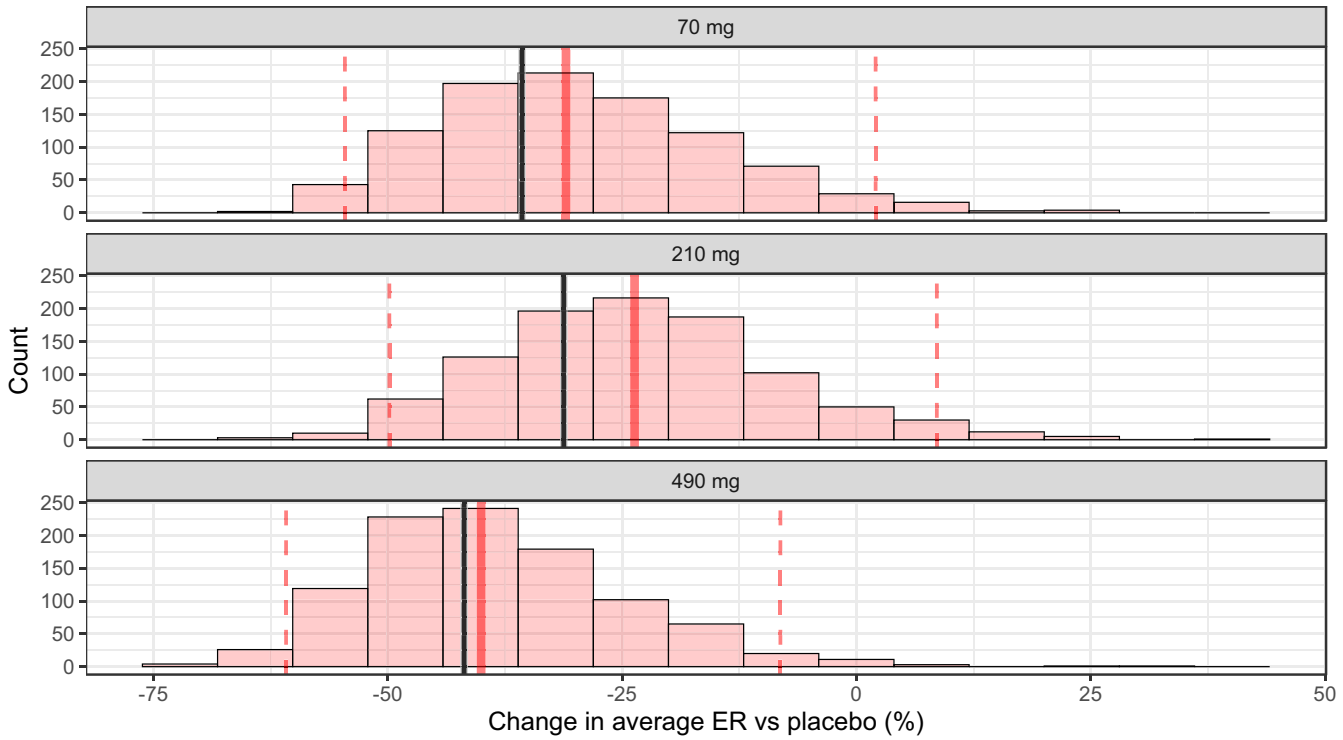


FIGURE 4 Final model posterior predictive check for the difference in mean-weighted exacerbation rate (ER) for active arms versus placebo, stratified on (active) astegolimab treatment arm. The black line marks the observed change in mean-weighted exacerbation rate versus placebo. The dashed, red lines show the 95% confidence interval of difference in mean-weighted exacerbation rates based on 1000 simulated studies, whereas the solid red line shows the 50th percentile (i.e., the median) difference in mean-weighted exacerbation rate based on the 1000 simulated studies. The distribution of difference in mean-weighted exacerbation rate for each of the 1000 simulated studies are shown as red bars

as well as the time-to-second and third exacerbations (Figures S2 and S3, respectively). A PPC showed that the difference in exacerbation rates for active treatment arms versus placebo were well predicted (Figure 4). Importantly, the model correctly predicted the ranking among the treatment arms (i.e., the model captured the observed trend of higher exacerbation rate for the 210-mg arm than for both the 70-mg and 490-mg arms).

The parameters were estimated with reasonable precision (Table 3), however, the exposure-response step effect parameter ($\theta_{\text{E-R,step}}$) had a quite large RSE of 59%, which is not surprising because it was not statistically significant after inclusion of time-varying covariates.

DISCUSSION

The observed exacerbation data was adequately captured by the final RTTE model. The identified time-varying covariates were diary-based symptom score, diary-based short acting rescue medication use, and FEV1. The most influential baseline covariates were diary-based symptom score and history of exacerbations. All estimated relationships between covariates and the hazard are considered plausible. The model predicted increased exacerbation hazard at high values of symptom score, rescue medication use, and history of exacerbations. The model predicted lower hazard with increasing FEV1 and C_{trough}.

This work demonstrated that a population RTTE approach can be used to characterize exacerbation hazard in patients with severe asthma where relevant baseline and time-varying covariates (i.e., predictors) of exacerbations were identified. In order to explore time-varying covariates and non-constant hazard, a parametric TTE or RTTE analysis, or a semiparametric nonproportional hazard analysis,[26] is required. In this analysis, an RTTE approach was selected in order to describe repeated events. The RTTE approach also simplified the baseline covariate analysis (conducted using FREM), because FREM requires IIV in the model, which is normally included in an RTTE model. FREM was considered a good approach in this application because many covariates were of potential interest of which some were correlated (e.g., body weight-body-mass index, and different inflammatory biomarkers). FREM allows estimation of covariate coefficients despite correlation among covariates, and without regard to lack of statistical significance (i.e., a prespecified covariate model). In addition, FREM handles missingness well. Because FREM does not easily

TABLE 3 Parameter estimates for structural model and time-varying covariates

Parameter	Definition	Unit	Value	RSE (%)[a]
OFV	Objective function value		30,465	
$h_{6\ months}$	Baseline hazard for a typical placebo subject at 6 months after start of treatment	$Year^{-1}$	0.472	19
$Weibull_{shape}$	Shape parameter to account for a time-varying baseline hazard		0.322	23
θ_{RO}	Coefficient for the effect of outpatient time ratio		0.641	20
$\theta_{\Delta RELI}$	Coefficient for the effect of the absolute diary short-acting rescue medication use change from baseline (summarized as a 4-day average)		1.54	18
$\theta_{\Delta SYM}$	Coefficient for the effect of the absolute diary symptom score change from baseline (summarized as a 4-day average)		0.357	16
θ_{RFEV1}	Coefficient for the effect of ratio of forced expiratory volume in 1 s versus baseline		−1.98	24
$t_{½Markov}$	Half-life for the recovery of the hazard after an exacerbation	Weeks	3.21	48
θ_{Exp}	Coefficient for the step function exposure-response based on trough concentration		−0.333	59
IIV_{Hazard}[b]	Log-normal interindividual variability in hazard	CV	1.30	11

The final model was described by the following:

$$h(t) = \begin{cases} h_{6\,mo} \cdot e^{Weibull_{shape} \cdot \log\left(\frac{t}{6\ months}\right)} \cdot e^{ROCOV(t)} \cdot e^{RESP(t)} \cdot e^{RESP_{exp}(t)} \cdot Markov(t), & \text{if } t_{exac} > 8\,days \\ 0, & \text{if } t_{exac} \le 8\,days \end{cases}$$

where

$$ROCOV(t) = \begin{cases} \theta_{RO} \cdot -0.1, & \text{if } RATOUT(t) \le 0.9 \\ \theta_{RO} \cdot (1-0.1), & \text{if } RATOUT(t) > 0.9 \end{cases}$$

$$RATOUT(t) = \begin{cases} \frac{TSLV(t)}{TUNV(t)+TSLV(t)}, & \text{if } TSLV(t) > 0.8\,days \\ 1, & \text{if } TSLV(t) \le 0.8\,days \end{cases}$$

$$RESP(t) = \theta_{\Delta SYM} \cdot (\Delta SYM + 0.73) + \theta_{\Delta RELI} \cdot (\Delta RELI + 0.01) + \theta_{RFEV1} \cdot (RFEV1 - 1.04)$$

$$RESP_{exp}(t) = \begin{cases} 0, & \text{if } C_{trough}(t) < LLOQ \\ \theta_{exp}, & \text{if } C_{trough}(t) \ge LLOQ \end{cases}$$

$$Markov(t) = 1 - e^{-\frac{\log(2)}{t_{1/2,Markov}} \cdot (t_{exac} - t_{lag})}$$

Abbreviations: C_{trough}, astegolimab trough concentration; CV, coefficient of variation; FREM, Full Random Effects Modeling; IIV, interindividual variability; LLOQ, lower limit of quantification; RSE, relative standard error, TSLV, time since last visit; TUNV, time until the next planned visit.

[a]The RSE for IIV parameters are reported on the approximate standard deviation scale (RSE of variance scale/2). The condition number was $6.18 \cdot 10^5$, due to correlated baseline covariates (coefficients for these not listed in this table).

[b]The η-shrinkage for IIV_{Hazard} was 27.3%. IIV includes total variability and includes unexplained variability and variability explained by baseline covariates. A feature of FREM is that it allows quantification of unexplained IIV and IIV explained by baseline covariates. The FREM components are not included in the parameter table.

handle time-varying covariates,[17] SCM was used for time-varying covariates. We applied SCM after FREM, which was preferred because when testing time-varying covariates, it is often desirable to have the corresponding baseline covariate in the model. With our approach, all covariates treated as time-varying had the corresponding baseline covariate included using FREM (prior to the SCM). This approach is considered successful, given the aim of the task and flexibility of allowing prediction into studies where not all baseline covariates are available.

Time-varying covariates were tested based on the observed change from baseline. This means that the current approach can be applied to another dataset, with the requirement that it includes information on the time-varying covariates. However, including covariates based on observed changes makes the selection sensitive to the design of the trial. Covariates with rich sampling (such as diary-based symptom score and collected daily) are expected to be more informative than covariates with sparse sampling (such as AQLQ[S]; Table 2). Thus, a dataset with different sampling/recording of time-varying covariates may result in a different selection of covariates, or a less optimal prediction by the current model.

The model was not assumed to be agnostic to treatment, because astegolimab exposure was included as a treatment effect. The treatment effect was present when C_{trough} greater than or equal to LLOQ, resulting in no treatment effect for placebo subjects and also in subjects randomized to active treatment if time since the last dose greater than or equal to 56 days. Of note, after introducing this treatment effect, the coefficients for the time-varying

covariates ($\theta_{\Delta SYM}$, $\theta_{\Delta RELI}$, and θ_{RFEV1}) did not change notably. This indicates that the model has a strong preference of allowing changes in individual time-varying covariates to drive the changes in hazard, rather than allowing the treatment effect to drive the changes. This, in turn, brings further confidence that the selected time-varying covariates can be valuable predictors of hazard for other drugs than astegolimab. An SCM for the placebo arm identified the same set of time-varying covariates, which also supports that the selected time-varying covariates may be regarded as relevant, regardless of astegolimab treatment.

Event duration was not included in this analysis, which could introduce bias of underpredicting the time between exacerbations in subjects who experience long-lasting exacerbations with worsening in time-varying covariates during the exacerbation. However, this was accounted for by including a Markov element for time since the most recent exacerbation. Because the model predicted the time between exacerbations well (Figures S2 and S3), this was a successful approach.

The model captures the observation that exacerbations are more frequent when the patient is due for the next visit, which in this study is closely linked to the next dose administration. However, this visit-effect was also not only present in subjects on active treatment, but also in subjects on placebo (Figure S1). Therefore, this visit-effect is likely not an artifact of inadequate effect duration, and rather reflects that these types of exacerbations are often not initiated until visiting the clinic (where the treating physician will recommend/prescribe systemic corticosteroids).

The selection of time-varying covariates used in this work will lead to selection of covariates that have the strongest correlation to exacerbations. Because the dataset included covariates measured on the day of an exacerbation, this may lead to selection of covariates whose changes drive occurrence of exacerbations as well as covariates whose changes are driven by the exacerbation. The former is the hallmark behavior of a predictive covariate and may be regarded as more useful than the latter. In the observed dataset, there were trends of changes in the selected time-varying covariates (diary-based symptom score, diary-based short-acting rescue medication use, and FEV1) 10–20 days prior to an exacerbation (Figure 1), supporting that these covariates are predictive of exacerbations, rather than the opposite. Changes in diary-based symptom score has been suggested as a potential predictor of exacerbations (although collected in another format),[27] in line with our analysis.

In 2017, Fuhlbrigge et al.[28] introduced CompEx, a novel composite outcome for evaluation of asthma therapies, and showed this composite end point can predict asthma exacerbations, at least at the group (treatment arm) level. They evaluated four diary worsening events (symptom score, short-acting rescue medication use, PEF, and awakening) and concluded that diary symptom score, short-acting rescue medication use, and PEF were predictive of asthma exacerbations. Interestingly, two of these components (diary-symptom score and short-acting rescue medication use) were also significant time-varying covariates using our approach. However, it should be noted that the definitions of these diary variables were similar but not identical between the Zenyatta study and studies in the CompEx publication. With regard to PEF, in our analysis, this was a less significant predictor than FEV1 (both reflecting lung function), after the two other daily diary variables had been included in the model. However, both PEF and FEV1 are indicators for lung function and are expected to be highly correlated. Our model is based on smaller patient material than Fuhlbrigge et al., but instead expands the analysis to individual level and accounting for covariates and time-varying hazard.

To our knowledge, there are no previously published parametric RTTE analyses for asthma exacerbations, or any other respiratory indication. A TTE model for time-to-first exacerbation exists for asthma.[29] Models for predicting exacerbations in chronic obstructive pulmonary disease exist[30,31] (these are not parametric TTE models). A TTE analysis has been published for time-to-first exacerbation in idiopathic pulmonary fibrosis.[32]

The model we present can be used to predict asthma exacerbations based on observed time-varying covariates from other patient studies (even for other drugs) where the relevant time-varying covariates have been collected, but the patient material and study duration is not necessarily sufficient for directly assessing outcomes in exacerbations. This information would be relevant during early stage asthma drug development and can likely streamline decision making regarding design for future studies within asthma drug development (e.g., dose selection and sample size determinations). Note that the possibility to predict well depends on availability of observed changes in individual time-varying covariates, or alternatively that a model is used to predict individual biomarkers. In addition to potentially using the presented model to predict exacerbations for other trials, this work resulted in better knowledge of predictors of asthma exacerbations. Better understanding of predictors for asthma exacerbations may favor more efficient trial designs in terms of selection and sampling of biomarkers, spirometry and diaries/questionnaires, patient selections, etc.

In this work, the asthma exacerbation data was well-described by the final population RTTE model. Baseline symptom score and history of asthma exacerbations were the most influential baseline covariates. Diary-based symptom score, diary-based short-acting rescue medication use, and FEV1 were identified as important

time-varying covariates for predicting asthma exacerbations. The presented model is specific for astegolimab because a treatment effect was included (although not statistically significant on top of the model with time-varying covariates), which should be considered when using this model to predict asthma exacerbations in studies of other treatment mechanisms. Further evaluation on additional studies will be needed to assess if the current model is applicable for such cases. This work demonstrated the utility of a population RTTE approach to characterize exacerbation hazard in patients with severe asthma.

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CONFLICT OF INTEREST

R.Z., M.D., S.V., D.C., T.S., D.F.C., W.P., J.J., N.B., and A.Q. are current or former Genentech employees and Roche shareholders. N.K. is a current employee of Chugai/Genentech. R.J.S. and J.R. are Pharmetheus employees. M.O.K. is an Uppsala University professor and contracted via Pharmetheus. J.R. and M.O.K. are Shareholders/Partners in Pharmetheus AB.

AUTHOR CONTRIBUTIONS

R.J.S., J.R., R.Z., and N.K. wrote the manuscript. R.Z., N.B., J.R., M.O.K., N.K., A.Q., D.C., T.S., D.F.C., M.D., J.J., and W.P. designed the research. R.J.S., J.R., R.Z., and N.K. performed the research. R.J.S., J.R., R.Z., N.K, S.V., A.Q., M.O.K., D.C., and J.J. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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