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ARTICLE

Neovascular Age-Related Macular Degeneration: A Visual Acuity Model of Natural Disease Progression and Ranibizumab Treatment Effect

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Intravitreal ranibizumab is a first-line therapy for neovascular age-related macular degeneration (nAMD), but there is a need to optimize patient outcomes while minimizing treatment burden. Here, we developed an indirect response, nonlinear, mixed effects model of disease progression and drug effect in anti-vascular endothelial growth factor (VEGF) treatment-naïve patients. A total of 1,524 treatment-naïve patients and 29,754 visual acuity observations from the ANCHOR, MARINA, PIER, and EXCITE clinical trials informed the model. The model accurately described natural nAMD disease progression and predicted mean visual acuity gains in the HARBOR study, notably with a 2.0 mg ranibizumab dose not used for model development. Furthermore, individualized treatment regimens were shown by simulation to be a viable alternative to the commonly used *pro re nata* or fixed monthly dosing regimen approaches. Therefore, this model could be a useful tool to predict the outcomes of different, more patient-tailored treatment regimens in nAMD.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Modeling can be used as a tool for interpolating and extrapolating existing knowledge to novel treatment regimens and doses. In nAMD, simulations of treatment regimens have been used to supplement clinical data for ranibizumab, resulting in an update to the label for individualized treatment.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study aimed to develop a model that could accurately describe the longitudinal change in visual acuity for natural disease progression in nAMD and enable simulations of the anti-VEGF treatment effect at different dose regimens.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ This study offers an externally evaluated model of natural nAMD disease progression and treatment effect of ranibizumab administered at therapeutic doses.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ The devised model could have utility in predicting the result of clinical studies in nAMD and could be used as a supplementary tool in drug development by identifying effective alternative doses and treatment regimens of benefit to patients.

Age-related macular degeneration (AMD) is a degenerative disease affecting the macular region of the retina, leading to a progressive loss of vision. The most aggressive form is neovascular AMD (nAMD; also known as wet AMD),[1] which is historically responsible for ~80–90% of all AMD vision loss cases.[1,2]

Overexpression of vascular endothelial growth factor (VEGF) is a consistent feature of nAMD and induces choroidal neovascularization (CNV), the formation of abnormal blood vessels that leak fluid into the subretinal space resulting in rapid vision loss.[1,3–6] Inhibition of VEGF causes neovessel regression and reduces vascular permeability, ultimately reducing the presence of pathological retinal fluid. Consequently, intraocular anti-VEGF therapy greatly improves visual acuity (VA) in patients with nAMD.[7,8]

Ranibizumab is a humanized anti-VEGF monoclonal antibody fragment (Fab) that inhibits the biological activity of multiple isoforms of VEGF-A.[9,10] It was first approved for the treatment of nAMD in the United States in 2006[11] and in the European Union in 2007.[12] The pivotal MARINA[7] and ANCHOR[8] phase III studies, in which patients received fixed monthly intravitreal injections, initially informed the ranibizumab dosing regimen. Subsequent clinical experience suggested that less than monthly dosing may be feasible

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and offer advantages in treatment schedules to patients and overburdened healthcare systems.[13,14] According to its European label, ranibizumab is licensed for administration via intravitreal injection at a starting dose of 0.5 mg once monthly until maximum VA is achieved and/or there are no signs of disease activity (typically 3 or more monthly injections; known as a "loading dose"). Thereafter, monitoring and treatment regimens are individualized and tailored by the physician to the patient's need and disease activity.[12]

Individualized treatment regimens with a fixed observation visit schedule with treatment given "as needed" are referred to as *pro re nata* (PRN) regimens,[13] whereas in "treat-and-extend" (T&E) regimens,[14] patients are treated at every visit, but the time between visits can be increased or decreased based on the physician's assessment of disease activity. In this study, we aim to predict patient treatment responses in which patients are injected at fixed monthly, bimonthly, or quarterly intervals assigned by observation of individual treatment need after three monthly loading injections. In reviewing the results, we expect to gain better understanding of individualized treatment regimens that optimize treatment by minimizing treatment burden without compromising efficacy.

Modeling techniques are particularly attractive for such assessments: once comprehensive evaluation demonstrates a model can reproduce actual observed data, simulations can allow reliable interpolation or limited extrapolation of untested scenarios to support the development of alternative anti-VEGF drugs or treatment regimens.

Previously, we developed a model for ranibizumab in patients with nAMD utilizing 1-year data from the ANCHOR,[7] MARINA,[8] PIER[15], and EXCITE[16] clinical studies. This model supported treatment recommendations for optimal dosing and a label update approved by the European Medicines Agency (EMA).[17] This study will further develop this model to include second-year data from these trials. This study also aims to estimate effects of covariates, such as age, baseline VA, or gender, on treatment efficacy and visual deterioration rate in nAMD. External data from the HARBOR clinical trial[18] will be used to evaluate the predictive performance of the model.

METHODS

Clinical studies

Data from four multicenter, randomized, double-blinded, phase III, ranibizumab clinical studies—ANCHOR,[7] MARINA,[8] PIER[15], and EXCITE[16]—were used to develop the model. All studies complied with the Declaration of Helsinki. The methodology of these trials has been extensively described elsewhere.[7,8,15,16]

Briefly, male and female patients 50 years of age or greater and with a study eye best-corrected visual acuity (BCVA) score from 25–70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters were included. All enrolled patients were treatment-naïve to anti-VEGF. The ANCHOR study compared the safety and efficacy of monthly ranibizumab (0.3 mg and 0.5 mg) to photodynamic therapy (PDT; verteporfin).[7] The MARINA study evaluated the efficacy of monthly dosing of ranibizumab 0.3 mg and 0.5 mg vs. sham,[8] whereas the PIER study determined the efficacy of ranibizumab 0.3 mg and 0.5 mg once-monthly for 3 months, then once-quarterly vs. sham.[15] The EXCITE study was an active-controlled, three-arm study of ranibizumab 0.3 mg or 0.5 mg once-monthly for 3 months and then once-quarterly vs. ranibizumab 0.3 mg once-monthly (see **Table 1**).[16]

The primary end point in all four studies was the mean change in BCVA score. The BCVA was assessed using standardized VA charts, expressed as the number of ETDRS letters ranging from 0–100. The BCVA was assessed at baseline, 1 week after the first injection, and then monthly in all studies except the PIER study, in which it was assessed quarterly at treatment visits after the first 3 months.

All available individual patient data from the EXCITE and MARINA studies were used for model building. The PDT treatment arm of the ANCHOR study was excluded from the dataset, as were second-year data from the PIER study, due to the nonrandomized reassignment of patients to different treatment arms. Thus, the ANCHOR and MARINA data span 2 years of treatment, whereas EXCITE and PIER data span 1 year of treatment.

Model development

Graphical analysis indicated that the drug effect can best be described using an indirect response pharmacokinetic (PK)/pharmacodynamic model.[19] An indirect response model was, therefore, used to capture the gradual decrease of VA due to disease progression under sham treatment and the effect of vitreous ranibizumab on VA. The PK data were not systematically collected, thus for all modeling we used results of a previous population PK analysis[20] that concluded the vitreous concentration of ranibizumab follows first-order elimination PKs, with a half-life of 9 days and a coefficient of variation (CV) on interindividual variability of about 22%. Due to the absence of vitreous PK data, intersubject variability of PK parameters was disregarded.

Mean BCVA score in the sham arm of the MARINA study gradually decreased over the 2-year study period (**Figure 1**). Visual worsening from natural disease progression can be described using an indirect response model by treating the BCVA score as not being at steady state value k_{in}/k_{out} at baseline. Thus, the VA score in a typical patient will decrease from baseline value to the stationary value k_{in}/k_{out} at rate k_{out} with no treatment. This description assumes delayed BCVA deterioration at the same rate constant k_{out} after discontinuation of treatment effect. Data from the EXCITE study support this hypothesis as the mean BCVA decreased in the intertreatment intervals in the q12w arms.

Because most observed data correspond to monthly BCVA assessments at trough drug concentrations, and there were no treatment interruptions of sufficient duration to remove the drug effect, some model parameters (e.g., half-maximal effective concentration (EC_{50})) needed prior knowledge for convergence of model fitting. We used a Bayesian approach and defined informative prior distributions around plausible values.

We tested effects of age, baseline BCVA score, and gender covariates on visual deterioration rate parameter k_{out} and maximum drug effect parameters. The covariate effect coefficients were given weakly informative priors centered

Table 1 Summary of study data used for model development (ANCHOR, EXCITE, MARINA, and PIER studies) and external evaluation (HARBOR)

	ANCHOR		EXCITE			MARINA			PIER			HARBOR	
Study duration	2 years		1 year			2 years			2 years			1 year	
Study design	Active-treatment controlled (PDT, verteporfin)		Active-treatment controlled			Sham-injection controlled			Sham-injection controlled			Monthly and as-needed (PRN)	
Inclusion criteria	Predominantly classic CNV		Classic, minimally classic or occult CNV			Minimally classic or occult CNV			CNV with or without classic CNV			All CNV lesion types	
Treatment regimen	q4w	q4w	q12w	q12w	q4w	q4w	q4w	sham	q12w	q12w	sham	q4w	q4w
Treatment dose, mg	0.3	0.5	0.3	0.5	0.3	0.3	0.5	–	0.3	0.5	–	0.5	2.0
No. of patients	137	139	120	118	115	238	239	236	59	61	62	275	274
Injections per patient	21.5	21.3	5.7	5.5	11.5	22	21.7	–	5.9	5.8	–	11.3	11.2
Observations per patient	23.9	24	13.3	12.9	13.5	24.6	24.5	22.3	8.3	8.2	8	Summary data	Summary data
Percent male	52	53	42	38	43	36	37	33	44	46	32	41	38
Age (SD), years	77.3 (7.3)	75.9 (8.5)	75.1 (7.5)	75.8 (7.0)	75 (8.3)	77.4 (7.6)	76.8 (7.6)	77.1 (6.6)	78.6 (6.2)	78.8 (7.9)	77.8 (7.1)	78.8 (8.4)	79.3 (8.3)
Baseline BCVA (SD), letters	47.1 (12.8)	47.1 (13.2)	55.8 (11.8)	57.7 (13.1)	56.5 (12.2)	53.1 (12.9)	53.7 (12.8)	53.9 (13.7)	55.8 (12.3)	53.7 (15.5)	55.1 (14.0)	54.2 (13.3)	53.5 (13.1)
BCVA change at month 12 (SD), letters	9.4 (14.5)	12.6 (14.1)	4 (14.9)	3 (13.7)	7.9 (11.5)	7.2 (12.2)	7.1 (15.3)	–10.9 (17.3)	–1.1 (14.8)	0.3 (13.5)	–15.1 (21.5)	10.1 (13.3)	9.2 (14.6)

BCVA, best corrected visual acuity; CNV, choroidal neovascularization; q4w/q12w, every 4/12 week administration; PDT, photodynamic therapy; PRN, pro re nata.

at zero and tested simultaneously.[21] In the final model, only those with posterior means significantly different from zero were retained (i.e., the posterior probability was >95% for a coefficient to be >0, or >95% to be <0).

Data from anti-VEGF and sham treatment arms were modeled simultaneously.

Model evaluation and simulations

The final model was evaluated using posterior visual predictive checks (**Figure 2**) and by simulating mean BCVA change from baseline of monthly treatment arms from HARBOR (both 0.5 mg [n = 274] and 2.0 mg [n = 275] ranibizumab doses), a study not used for model development.[18] The study arms were simulated 500 times. Individual patient data from the HARBOR study were not available. Population parameters were sampled from posterior distributions of model parameters, whereas covariates (age and baseline BCVA) were sampled from analyzed data, as mean BCVA and mean age were close to those in the HARBOR study. The predicted mean BCVA change from baseline (and 95% prediction interval for the mean) was then compared to the observed HARBOR study results (**Figure 3**). The dropout rate in the HARBOR study was about 6%, and small enough to be ignored.

To illustrate the impact of the patient's baseline BCVA and age on the visual acuity improvement, we simulated 1,000 studies of 1,000 patients each with covariates sampled from analyzed data and presented the change from baseline BCVA at month 12 in **Figure 4a,b**.

The model was used to predict change from baseline BCVA score over 12 months at individualized treatment regimens. All patients were administered three initial intravitreal injections at months 0, 1, and 2. If at month 3 the BCVA did not improve or decreased compared to the previous visit at month 2, a patient was assigned to monthly (q4w) treatment. Otherwise, the BCVA was observed at month 3 and again if BCVA did not improve or decreased compared to the previous visit at month 3, a patient was assigned bimonthly treatment (q8w), or quarterly (q12w) otherwise. This resulted in ~40% at patients assigned to q4w, 27% to q8w, and 33% to q12w dosing from a total of 300 patients in 1,000 simulated trials.

Data analysis

Model fitting was performed using Stan software version 2.15.1 (Stan Development Team, <www.mc-stan.org>). Ordinary differential equations were solved using a discrete approximation to reduce computational (see Stan model specification in **Supplementary File S1**).

RESULTS

Data summary

A total of 1,524 patients and 29,754 VA observations informed the model. The dataset from the four studies (MARINA, EXCITE, ANCHOR, and PIER) consisted of BCVA score observations at monthly (868 patients), quarterly (238 patients), and sham (298 patients) injections.

Mean baseline BCVA across studies was 54 ± 13 letters (range, 3–84 letters). Mean age of patients at baseline was 77 ± 7.5 years (range, 52–96 years), with about 40% of patients being male.

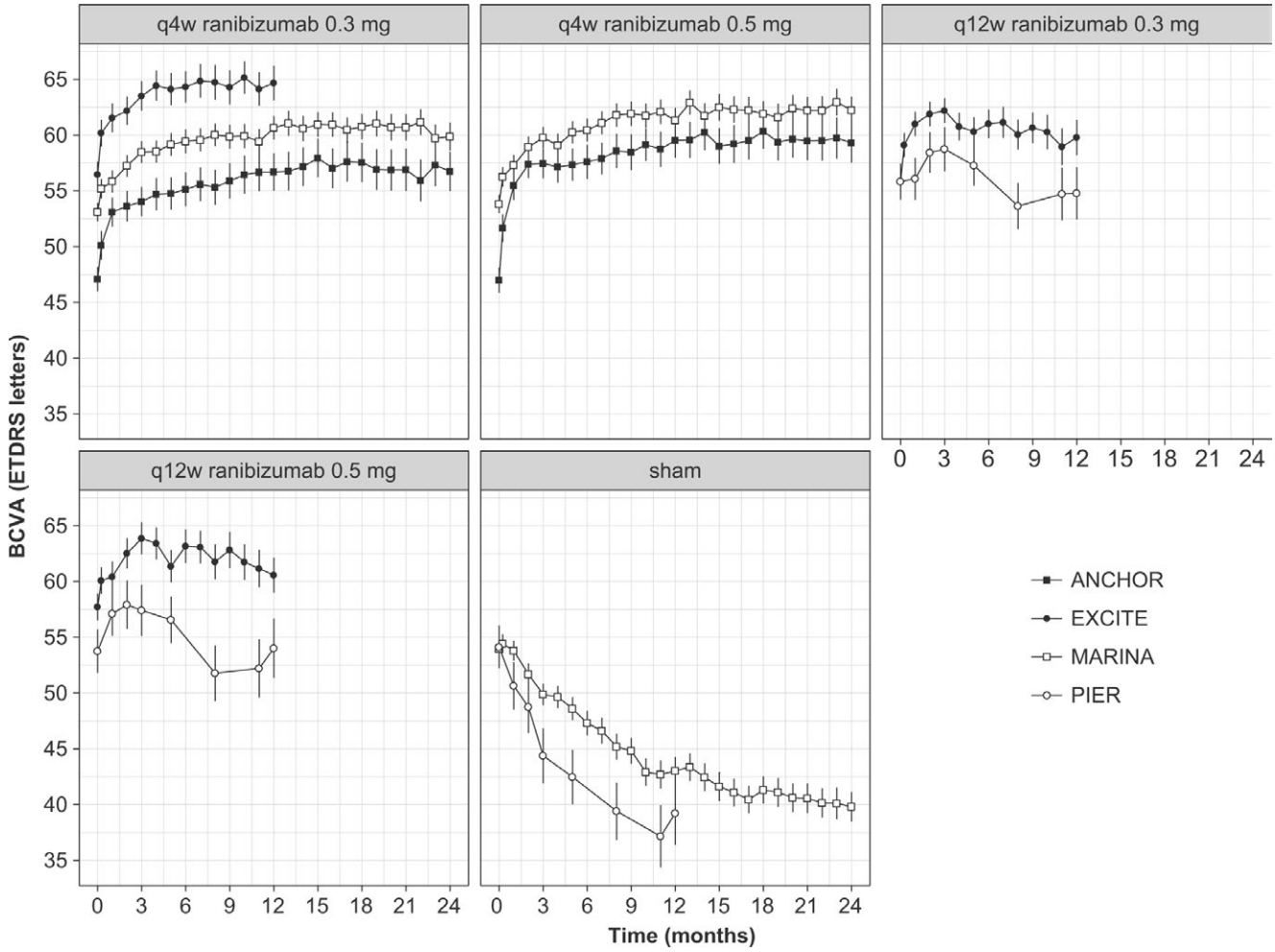

Figure 1 Mean best corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study (ETDRS) letters) from the ranibizumab treatment arms of the ANCHOR, EXCITE, MARINA, and PIER studies (q4w, once monthly dosing; q12w, once quarterly dosing; sham, untreated arms).

Inclusion criteria for the ANCHOR and MARINA studies differed by CNV type. As baseline BCVA score and CNV type are strongly correlated, baseline BCVA score rather than CNV type was tested as a covariate in the model.

Model development

Stimulation of k_{in} rather than suppression of k_{out} was selected to describe the drug effect as it led to better stability of model fit with no other significant differences.

The structural indirect response model of VA $g_i(t)$ for the ith patient is defined by:

$$\frac{dg_{i}(t)}{dt} = k_{in,i}\left(1 + E_{max_i}(t)\frac{C_i(t)}{EC_{50}+C(t)}\right) - k_{out,i}g_i(t)$$
$$g_i^0(t=0) = g_i^0 \quad (1)$$

where $C_i(t)$ is vitreous drug concentration following first-order elimination PKs with the same half-life of 9 days in all patients. It is estimated by setting the vitreous volume to 4 mL[22] for all patients, thus $C_i(t)$ is different between patients only due to differences in dosing. Parameters $k_{in,i}$ and $k_{out,i}$ are the BCVA score improvement and deterioration rate constants, respectively, for the ith patient, and EC_{50} is the concentration corresponding to half the maximum effect. Without treatment, the BCVA score decreases from baseline value g_i^0 to a steady state $g_i^{ss}=k_{in,i}/k_{out,i}$.

Anti-VEGF treatment leads to a rapid initial increase of VA, reaching a plateau after only a few injections, reflecting the strong initial VA response in treatment-naïve patients due to fluid leakage resolution where the room for improvement in subsequent injections decreases. To properly fit these data, we introduced time dependence into maximum effect (E_{max}). The E_{max} was set to start at a high initial value and decrease to a lower steady state value by the end of the 3-month loading dose period.

The time-dependent $E_{max_i}(t)$ was parametrized as follows:

$$E_{max_i}(t) = E_{max_i}^{ss} + \Delta E_{max_i}^{0} \cdot \exp\left(-k_{E_{max}} t\right) \quad (2)$$

Here, the drug effect for ith individual starts from $E_{max_i}^{ss} + \Delta E_{max_i}^{0}$ and decreases to steady state value $E_{max_i}^{ss}$ at the rate k_{Emax}. Due to sparse (monthly) BCVA sampling,

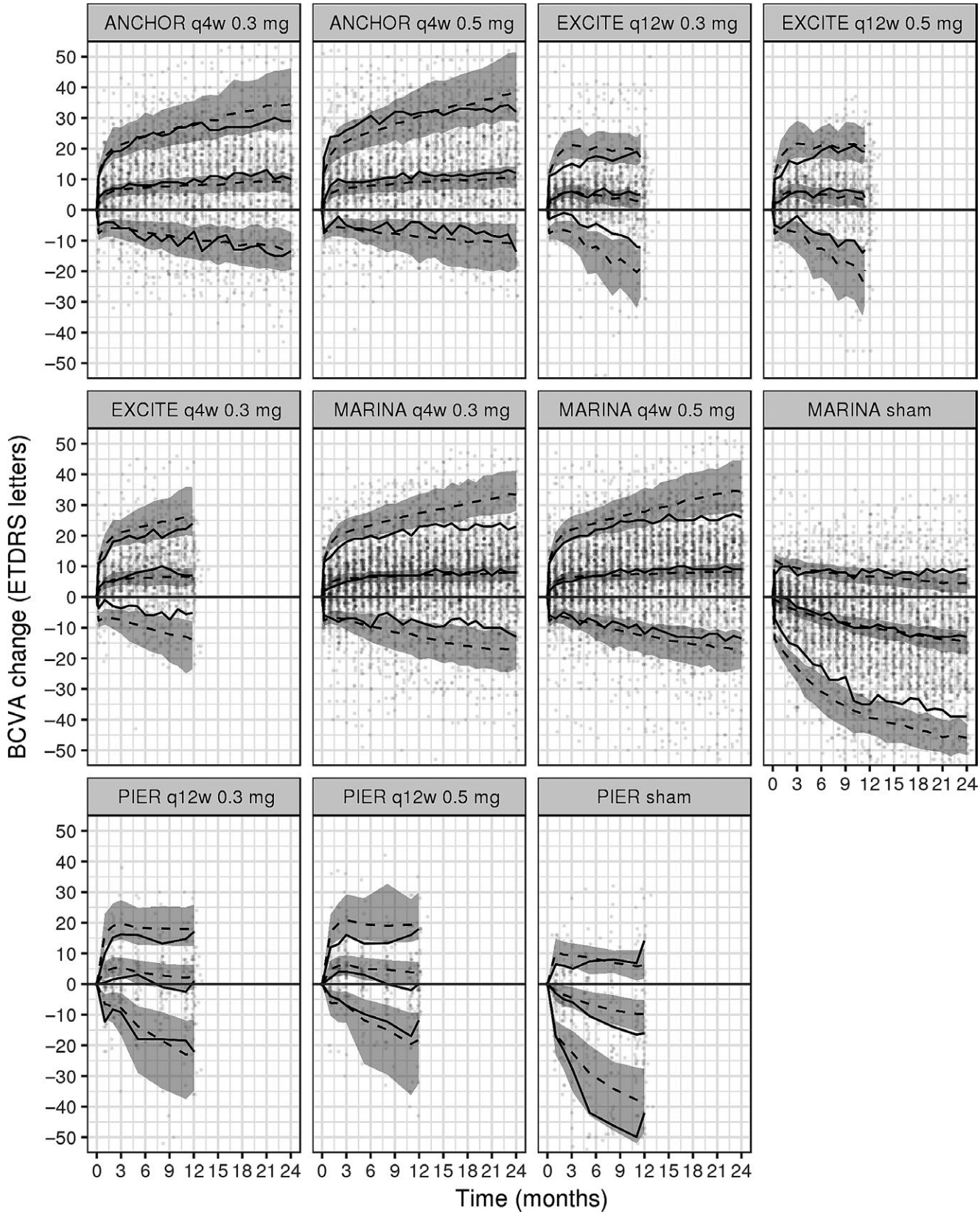

Figure 2 Visual predictive checks for ranibizumab treatment regimens. Charts show 10th, 50th, and 90th percentiles for the observed best corrected visual acuity (BCVA) change (Early Treatment Diabetic Retinopathy Study (ETDRS) letters) from baseline (solid lines) in treatment arms of the analyzed studies and the medians (dotted line) with 95% confidence intervals (shaded areas) of the same percentiles from model-simulated data.

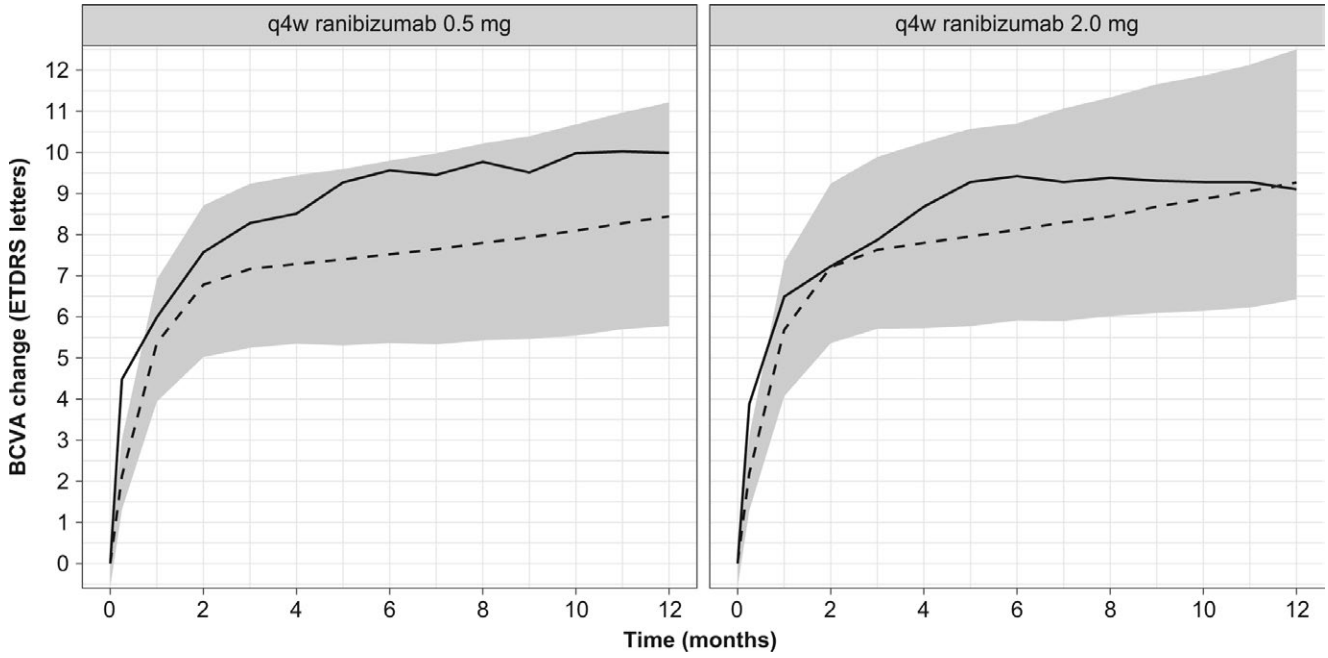

Figure 3 Comparison of the HARBOR study mean best corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study (ETDRS) letters; black line) and out of sample model predicted mean BCVA (ETDRS letters; dotted line) for ranibizumab treatment regimens. Shaded area is 95% credible interval for the predicted mean.

k_{Emax} parameter was not readily identifiable. Because high E_{maxi} values are necessary only for the onset of treatment, the value of k_{Emax} should correspond to a few weeks half-life. Sensitivity analysis showed the model was not sensitive to k_{Emax} corresponding to half-lives between 1 and 3 weeks. Thus, we set $k_{Emax} = \log(2)/14$ days^{-1}.

Not all individual random effects on model parameters were identifiable. Patients participated either in sham or drug treatment arms, therefore, individual random effects for untreated steady state BCVA score g_i^{ss} and $E_{max_i}^{ss}$, which defines treated steady state BCVA, would be confounded. We used a random effect on E_{max} parameters and modeled $g^{ss} = k_{in,i}/k_{out,i}$ without individual random effects. Most patients were treated every month, therefore, vitreous drug concentrations were maintained well above expected EC_{50} values, which impeded estimation of individual EC_{50} parameters, thus EC_{50} was also estimated without intersubject variability. The remaining model parameters (baseline BCVA g_i^0, VA deterioration rate constant $k_{out,i}$, drug effect parameters $\Delta E_{max_i}^{0}$ and $E_{max_i}^{ss}$) included individual random effects.

Because change from baseline VA at the study end was our end point of interest, unbiased estimates of initial or baseline BCVA values g_i^0 were crucial.[23] We modeled baseline VA g_i^0 as normally distributed around observed value BVA_i: $g_i^0 = BVA_i + \eta_{1,i}$. Effects of patient age, gender, and model-estimated baseline VA (g_i^0) on $\Delta E_{max_i}^{0}$, $E_{max_i}^{ss}$ and k_{out} parameters were tested. Individual random effects and covariate effects on model parameter $k_{out,i}, E_{max_i}^{ss}, \Delta E_{max_i}^{0}$ were in the following form:

$$\theta_{k,i} = \theta_k \cdot \left(\frac{AGE_i}{77}\right)^{\beta_{k,AGE}} \cdot \left(\frac{g_i^0}{55}\right)^{\beta_{k,BVA}} \cdot \beta_{k.sex}{}^{I(sex_i=male)} \cdot e^{\eta_{k,i}} \quad (3)$$

where I is an indicator function, 77 is mean age (years), and 55 is mean BCVA (ETDRS letters) at baseline. Random effects $\eta_{k,i}$ on four model parameters $\left(g^0, k_{out}, E_{max}^{ss}, \Delta E_{max}^{0}\right)$ are assumed to be normally distributed with a covariance Σ. Observed BCVA values $y_{i,j}$ of the ith patient at time $t_{i,j}$, were modeled as being normally distributed around predicted BCVA $g(t_{i,j})$ with residual variance σ^2: $p(y_{i,j}|\theta_i, \sigma^2) \sim N\left(g\left(t_{i,j}, \theta_i\right), \sigma^2\right)$, where θ_i denotes all individual model parameters. We allowed for different values of residual variance for treatment and sham arms.

Most patients were dosed monthly and full drug effect was maintained. Only quarterly treatment arms displayed decrease of the effect at intertreatment intervals. Thus, the data mainly informs that EC_{50} is less than the vitreous concentration 1 month after an injection (12.5 μg/mL) and comparable to or greater than the concentration 3 months after an injection (0.12 μg/mL) – two orders of magnitude range. Thus, to deal with identifiability, the log-normal prior for EC_{50} was centered at 2.5 μg/mL and covered range of concentrations from 1–7 μg/mL within the SD. Simulations of the fitted data were not sensitive to the choice of the EC_{50} prior, thus simulations with intertreatment intervals are reliable, but only up to 12 weeks that was present in the fitted data. Weakly informative prior distributions were assigned to all other model parameters.

Estimated parameters for the indirect response model (Eq. 1) are presented in **Table 2** and **Table S1**. According to the fitted model, natural disease progression of a typical patient with nAMD leads to a gradual decrease of VA to a steady state value $g^{ss} \approx 11$ ETDRS letters, an upper limit for definition of near-blindness by the International Council of Ophthalmology,[24] at the rate of about 20% per year for BCVA score above g^{ss}. Very high variation in individual variability in VA deterioration rates k_{out} was found (CV of 730%).

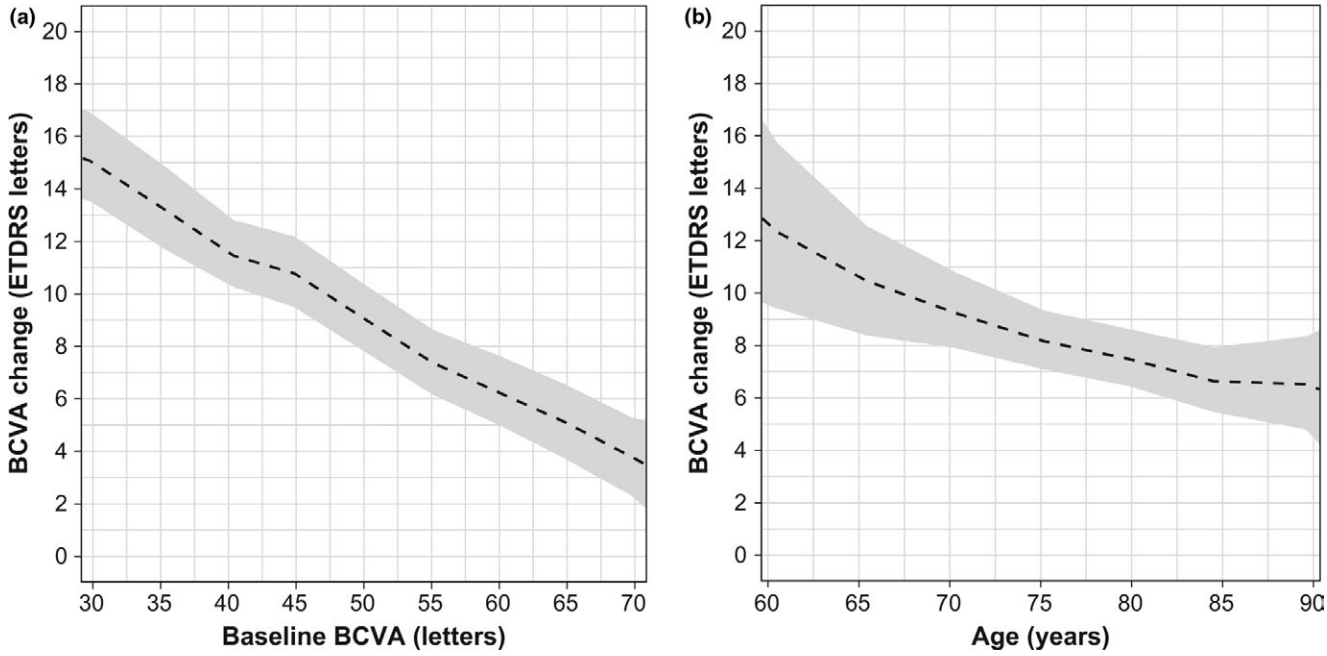

Figure 4 (a) Best corrected visual acuity (BCVA) score change from baseline after 12 months of 0.5 mg monthly ranibizumab treatment vs. patient's baseline BCVA score. **(b)** BCVA score change from baseline after 12 months of 0.5 mg monthly ranibizumab treatment vs. patient's age. ETDRS, Early Treatment Diabetic Retinopathy Study.

Table 2 Model parameter estimates (means of the posterior parameter samples)

Parameter	Description	Estimate	RSE, %
k_{elim}, 1/day	Rate constant for drug elimination from the vitreous	0.077 ($t_{1/2}$ = 9 days)	0, fixed
g^{ss}, letters	Equilibrium BCVA reached at natural progression	11	5
k_{out}, 1/year	BCVA deterioration rate constant at natural disease progression	0.19 ($t_{1/2}$ = 3.6 years)	9
E_{max}^{ss}	Drug effect on BCVA at mean age (77 years)	6.1	7
ΔE_{max}^{0}	Additional drug effect at the onset of treatment	41	12
k_{Emax}, 1/day	Rate of E_{max} change	0.046 ($t_{1/2}$ = 15 days)	0, fixed
EC_{50}, μg/mL	Drug concentration for half of the maximal effect	2.1	35
$\beta_{E_{max}^{ss},AGE}$	Age effect on drug on E_{max}^{ss}	–1.4	18
IIV g^0, letters	Interindividual variability	4.1	3
IIV k_{out} CV, %	Interindividual variability	730	3
IIV E_{max}^{ss} CV, %	Interindividual variability	110	7
IIV ΔE_{max}^{0} CV, %	Interindividual variability	1,100	4
σ_{sham}, letters	Residual error for BCVA of untreated patients	7	1
$\sigma_{treatment}$, letters	Residual error for BCVA of treated patients	5	0.5

BCVA, best corrected visual acuity; CV, coefficient of variation; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; $t_{1/2}$, half-life.

The EC_{50} estimate was 2 μg/ml (relative standard error 30%), corresponding to a vitreous drug concentration reached about 2.5 months after a single 0.5 mg injection (**Table 2**).

Among the tested covariate effects, only the effect of patient's age on steady state drug effect parameter E_{max}^{ss} was significant and included in the final model.

Model evaluation and simulations

Goodness-of-fit plots (see **Figures S1-S5**) did not reveal model misspecifications. Visual predictive checks show the model accurately describes the median decline of VA in untreated patients and improvement in a treated population, although the predicted interindividual variability of the BCVA score change was slightly larger in the model than in analyzed data (**Figure 2**).

Figure 4 shows the impact of baseline BCVA score and patient's age on BCVA change from baseline after 12-months treatment with monthly 0.5 mg ranibizumab. There was a nearly linear relationship between baseline BCVA and BCVA gain at study end (**Figure 4a**). For every 10 letters of lower baseline BCVA, there are 3 letter gains in BCVA improvement at the end of 12 months with monthly treatment.

Patient's age was a significant covariate on E_{max}^{ss}, with older patients exhibiting a smaller improvement in VA. However, the age effect is modest, with a 4 ETDRS letter reduction in VA improvement for 85 compared to 65 year-old patients (**Figure 4b**). For comparison, the SD of the BCVA change from baseline to month 12 due to interindividual variability is about 14 ETDRS letters.

Predictive performance of the model was evaluated by comparing model predicted mean BCVA to observed mean BCVA from monthly treatment arms of the HARBOR study. The predicted mean BCVA change from baseline profiles are in good agreement with HARBOR, with the 12-month end point of 8.5 and 9.2 ETDRS letters improvement in mean BCVA compared to observed 10 and 9 ETDRS letters for the 0.5 mg and 2.0 mg dose arms, respectively. The similarity between simulated responses for both doses suggests that, with monthly dosing, a 0.5 mg dose is sufficient to maintain the treatment effect at maximum levels (**Figure 3**).

Simulations showed that the individualized treatment schedule based on observation of individual treatment

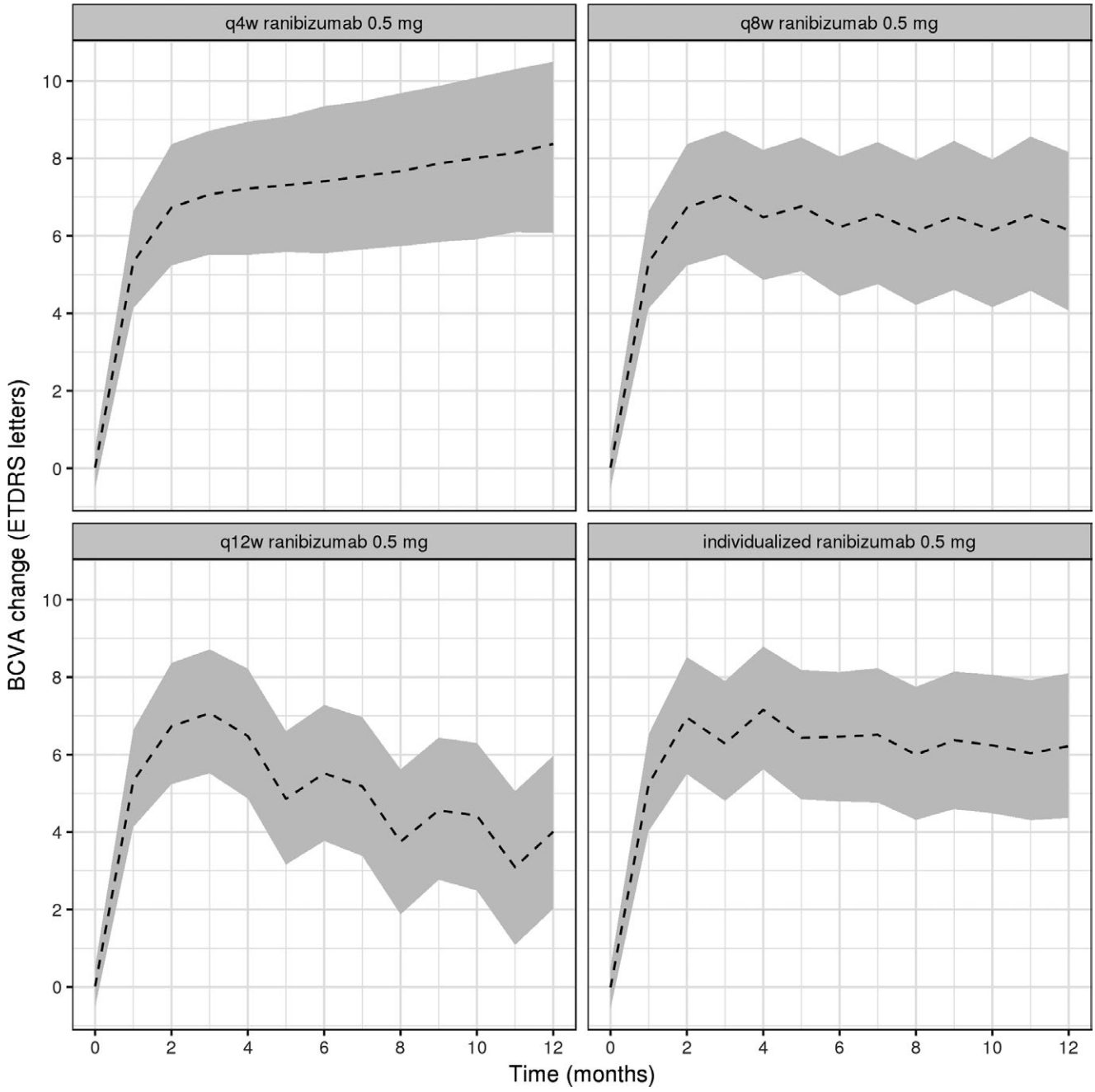

Figure 5 Simulation results comparing q4w, q8w, and q12w, 0.5 mg ranibizumab treatment to an individualized regimen. Mean predicted change from baseline best corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study (ETDRS) letters) presented as dotted line, shaded area is 95% credible interval for the predicted mean.

need could lead to a better clinical outcome compared with a q12w regimen, with an average improvement of 6 vs. 4 ETDRS letters (**Figure 5**).

DISCUSSION

This study successfully developed a model that accurately describes loss of VA during natural nAMD progression and the treatment effect of intravitreal ranibizumab administered to patients with nAMD at therapeutic doses. In contrast to previous modeling approaches,[17,25] this model describes natural disease progression, treatment effect, and rapid initial visual improvement in a single model using the largest number of analyzed studies.

The model predicted mean BCVA outcomes in the HARBOR study, including the 2.0 mg ranibizumab arm, a dose not used for model generation. Modeled BVCA gain for HARBOR was ~9 ETDRS letters for both 0.5 mg and 2.0 mg doses, agreeing with actual BCVA gains in the HARBOR study of 10.1 and 9.2 ETDRS letters for 0.5 and 2.0 mg doses, respectively.[18] The MARINA study[8] has the largest amount of observational data and demonstrated a mean ETDRS letter improvement of only seven letters at comparable values of the covariates. This may explain why the predicted mean letter responses for HARBOR in this study is slightly lower than the actual HARBOR values, but within a 95% credible interval.

The model accurately depicts median change from baseline in both anti-VEGF and sham treated patients under monthly and quarterly treatment regimens. High interpatient variability of BCVA score changes was well captured by the model through between-patient variability of VA deterioration rate constant and of the drug effect parameters.

Sham treatment data in patients with nAMD are no longer available as anti-VEGF treatment is now a standard of care, thus, the model provides a unique opportunity to demonstrate BCVA score behavior under natural disease progression. The model described a gradual decrease in BCVA to near blindness levels of 11 ETDRS letters in the absence of treatment. At ~3.5 years half-life for VA deterioration, this level would be reached beyond study duration; however, variability of the visual deterioration rate among patients was very high (700% CV), suggesting that patients require immediate treatment intervention upon nAMD diagnosis.

Since publication of the pivotal clinical studies used for developing the model, patients are now treated earlier in their course of the disease, which might influence the treatment effect on BCVA. However, by using a Bayesian framework for the model, straightforward updates are enabled using data from newer studies. Furthermore, the model could provide a foundation to be expanded to other anti-VEGF drugs, using prior knowledge of natural disease progression and the modeled treatment effect of ranibizumab.

Patient's age had a statistically significant, but modest covariate effect on E_{max}^{ss}. A smaller treatment effect in older patients was expected due to decreased VA, even in the absence of CNV. This result agrees with the recent AURA study, which demonstrated the negative effect of age at treatment initiation on anti-VEGF treatment outcomes.[26]

The EC_{50} value of 2 μg/mL indicates that at monthly dosing (with $C_{min} = 12.5\ \mu g/mL$) intravitreal ranibizumab concentration is consistently higher than EC_{50}, but the drug effect is suboptimal with quarterly treatment (with $C_{min} = 0.12\ \mu g/mL$). This can be readily observed in the EXCITE study data by oscillations in the q12w dosing arms (**Figure 1**), where the mean VA decreases during treatment intervals. No oscillations of mean BCVA are observed in q12w arms of the PIER study because BCVA was assessed only at treatment visits. A previously reported estimate of the analogous parameter IC_{50} from a different model examining an E_{max}-type effect of intravitreal ranibizumab concentration on BCVA was $6.5\ \mu g/mL$.[17] This broadly agrees with our EC_{50} value and is approximately equal to vitreous drug concentration 8 weeks after a single injection of 0.5 mg of ranibizumab.

Ranibizumab approval in nAMD was originally based on data for monthly dosing; however, other treatment regimens, such as PRN or T&E, with smaller burden on the patient and healthcare systems, can be used for effective disease control. Our model was developed to have utility in predicting patient outcomes using prespecified, individualized treatment regimes. A model based on VA alone has limited applicability to accurately predict response to regimens where re-treatment decisions are based on multiple clinical factors. However, simulations showed that the model can be applied to simulations of individualized treatment regimens where there is no need to for multiple retreatment decisions during treatment as in T&E or PRN regimens. Simulations using our model demonstrated that individualized monthly, bimonthly, or quarterly treatment schedule based on observed re-treatment need could elicit a better VA response compared with a q12w regimen, with a gain of 6 ETDRS letters. The mean number of injections during the first year of treatment was 8.7, whereas a year of treatment after initial loading would require 7.7 injections per visit. The mean BCVA improvement was worse than for monthly treatment (6 vs. 8.5 ETDRS letters) and similar to BCVA improvement at bimonthly treatment (**Figure 5**), however, such individualized treatment greatly reduces the overall treatment burden compared to q4w without unnecessary loss of vision in patients that need more frequent than q8w treatment.

These results compare favorably with PRN treatment data from the 1-year SUSTAIN study, where a mean BCVA gain of 3.8 letters and average 5.7 injections per patient were reported with a total of 12 visits.[27] The simulation results suggest that more proactive treatment regimes, such as T&E could be more beneficial than PRN, where treatment is administered only after disease activity is detected. Indeed, numerous studies have demonstrated the benefits of the T&E regimen compared with PRN,[28–32] resulting in its approval by the regulatory authorities. The recent 12-month TREND study showed that ranibizumab 0.5 mg administered according to T&E regimen resulted in 6.2 ETDRS letters gain in BCVA at mean number of 8.7 injections and visits.[29]

One limitation of the model is that it is based on data from studies of treatment-naïve patients,[7,8,15,16] thus, only treatment-naïve patient populations can be simulated with confidence using this model. Another limitation is that treatment intervals longer than 12 weeks cannot be simulated due to identifiability of a key model parameter EC_{50}.

In conclusion, VA modeling approaches have been successfully utilized in the past to supplement clinical data decision making and regulatory approvals.[17] It is envisaged that the model developed in this study may have similar future utility in testing and supporting the development and approval of novel anti-VEGF treatment regimens and doses for nAMD therapy.

Supporting Information

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website. (www.psp-journal.com)

Figure S1. Goodness-of-fit plots. Pairs plot of individual random effects.
Figure S2. Goodness-of-fit plots. Random effects vs. covariates.
Figure S3. Goodness-of-fit plots. Observations vs. population predictions.
Figure S4. Goodness-of-fit plots.. Residuals vs. time.
Figure S5. Goodness-of-fit plots.. Residuals vs. individual predictions.
Table S1. Correlations of modeled random effects
File S1. Stan model specification file

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Conflict of Interest. Sebastian Weber, Zufar Mulyukov, Etienne Pigeolet, Andreas Clemens, and Amy Racine are employees of Novartis Pharma AG and own stocks in the company. Thorsten Lehr has no conflict of interest to declare.

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