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Effect of Anti-VEGF Therapy on the Disease Progression of Neovascular Age-Related Macular Degeneration: A Systematic Review and Model-Based Meta-Analysis

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Abstract

Anti–vascular endothelial growth factor (VEGF) therapy is used to slow the disease progression of neovascular age-related macular degeneration. Due to the treatment burden of frequent intravitreal injections, anti-VEGFs are often used on treat and extend protocols rather than the labeled frequency. The current goal of anti-VEGF drug development is to minimize treatment burden by reducing the number of intravitreal injections. The purpose of this systemic review and model-based meta-analysis (MBMA) was to (1) perform modeling to describe the disease progression of neovascular age-related macular degeneration in the absence of treatment, as well as in the presence of abicipar, aflibercept, brolucizumab, or ranibizumab intervention; (2) and to simulate virtual head-to-head comparisons among the drugs with an extended dose schedule of once every 12 weeks (Q12). Data sources were PubMed, internal Allergan data, www.clinicaltrials.gov, and www.clinicaltrialsregister.eu. Eligibility assessment was performed by 2 independent review authors. Randomized, controlled trials that had at least 1 arm with an anti-VEGF (aflibercept, abicipar, bevacizumab, brolucizumab, pegaptanib, or ranibizumab), a control arm of placebo or anti-VEGF, a treatment duration of at least 4 months, reported best-corrected visual acuity data, and at least 20 patients were included. A total of 22 trials, consisting of 55 arms, from across 9500+ subjects and 500+ best-corrected visual acuity observations were used to develop the model. Consistent with reported data, results from the model showed that abicipar Q12 underperformed ranibizumab (every 4 weeks), aflibercept (every 4 weeks), and brolucizumab (every 8 weeks/Q12) labeled dosing schedules. However, when all drugs were virtually tested using the extended schedule, abicipar outperformed ranibizumab and aflibercept and produced a similar week 52 change from baseline as brolucizumab. Predicted week 52 changes from baseline were 5.92 $\pm$ 1.02, 3.04 $\pm$ 1.61, 6.61 $\pm$ 0.284, and 3.02 $\pm$ 2.35 best-corrected visual acuity letters for abicipar, aflibercept, brolucizumab, and ranibizumab, respectively, using the Q12 schedule. Results demonstrate the feasibility of Q12 dosing with clinically meaningful letter gains for abicipar and brolucizumab. The model developed under this MBMA has utility for exploring different regimens for existing or novel anti-VEGF agents.

Keywords

disease progression, model-based meta-analysis, modeling, neovascular age-related macular degeneration, pharmacodynamics, pharmacokinetics

Age-related macular degeneration (AMD) can cause irreversible visual impairment due to macular damage. Although choroidal neovascular or wet AMD (nAMD) is the less common type of AMD, it is the cause of more cases of severe vision loss.[1] nAMD occurs when pathological vessels start to grow from the choroid towards the retina. The abnormal growth and leakage of the vessels can cause exudation and hemorrhage, which can damage the retinal layers, leading to vision loss.[2,3]

Therapies that slow or inhibit abnormal vessel growth by targeting vascular endothelial growth factors (VEGFs), key mediators of angiogenesis, are known as anti-VEGFs. Many function by binding to VEGFs and inhibit VEGF activity by preventing interaction with their receptors.[4–6] The use of anti-VEGFs has led to significant improvement in visual outcomes for many patients with nAMD.[5] Three first-line anti-VEGFs for nAMD treatment are aflibercept, brolucizumab, and ranibizumab. Aflibercept (Eylea) is a recombinant protein that acts as a decoy receptor by binding to multiple isoforms of human VEGF-A, VEGF-B, and placental growth factor.[7,8] Its recommended and approved dosing interval is once every 4 weeks (Q4) for the first 3 months, followed by a dosing interval of once every 8 weeks

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(Q8). Some patients may continue to need Q4 dosing, while others may move to quarterly dosing (once every 12 weeks [Q12]) after a year of successful therapy.[9] Out of the anti-VEGF treatments, aflibercept has the highest reported mean change from baseline (CFB) in best correct visual acuity (9.24) at week 52 with Q4 dosing. Brolucizumab (Beovu) is a humanized antibody fragment that binds all isoforms of VEGF-A. After 3 months of Q4 dosing (once every 4 weeks and monthly is often used interchangeably, in this case monthly was specified), brolucizumab is approved to move to Q8 or Q12 dosing.[10] Ranibizumab (Lucentis) is a humanized IgG1 antibody fragment that binds all isoforms of VEGF-A.[11,12] It is recommended and approved for Q4 dosing. Although less effective, some move to Q12 dosing after 4 months of Q4 dosing.[13] Abicipar is an investigational anti-VEGF intended for the treatment for nAMD that also binds VEGF-A. It is a Designed Ankyrin Repeat Protein whose design combines high binding affinity, low molecular weight, and long ocular half-life to have Q12 dosing.[14–16] Due to the adverse event of intraocular inflammation, brolucizumab has limited use, and abicipar has not been approved by the US Food and Drug Administration as of the date of this publication.[17–20]

Anti-VEGFs are administered via intravitreal injection. Due to treatment burden, extending the dosing interval and reducing the number of times patients need to visit the clinic for treatment has become a goal for anti-VEGF therapy.[21] One of the largest unmet needs in nAMD treatment is less frequent dosing while maintaining the standard of care efficacy. Thus, there is a need to develop anti-VEGFs with Q12 or longer dosing. Brolucizumab is the only approved drug recommended for Q12 dosing,[10] while abicipar has shown significant efficacy on a fixed Q12 schedule.[22] Anti-VEGFs are often used on treat and extend protocols rather than the labeled frequency.[23] Therefore, the purpose of this investigation was to model how an investigational molecule (abicipar) that was designed for extended duration compares to treat and extend protocols of the most prevalent treatment options (aflibercept, brolucizumab, ranibizumab) currently on the market.

Although extended dosing has been explored in some clinical trials, no trials simultaneously conducted head-to-head comparisons of the investigational drug (such as abicipar), with first-line, commonly used anti-VEGFs. As abicipar is being developed for fixed Q12 dosing, there is an interest in benchmarking it against the standard of care anti-VEGFs as they are frequently used in clinical practice (ie, treat and extend). The purpose of this study was to conduct a model-based meta-analysis (MBMA) to describe the disease progression of nAMD in the absence of treatment and in the presence of abicipar, aflibercept, brolucizumab, or ranibizumab intervention, and to use the model to conduct virtual head-to-head comparisons among the 4 drugs, particularly with extended Q12 dosing.

Methods

This MBMA consisted of (1) a literature search for best-corrected visual acuity data for major anti-VEGF medications in patients with nAMD, (2) the development of a natural disease progression and pharmacokinetic (PK)/pharmacodynamic (PD) drug intervention model for best-corrected visual acuity, and (3) virtual head-to-head comparisons using simulations based on an extended Q12 dosing. The model does not need to be used to compare the letter gains of approved products based on their labeled schedules since those data are already published.

Clinical Outcomes Database

A systematic literature search was conducted on Medline via PubMed, internal Allergan data (for abicipar), the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), and the EU Clinical Trials Register (www.clinicaltrialsregister.eu). The statistical and clinical sections of the New Drug Approval web pages of regulatory authorities in the United States and Europe were reviewed for approved drugs (www.fda.gov, www.ema.europa.eu). Additionally, relevant studies were identified by manual search of the bibliographies of references retrieved from PubMed. For all literature sources, only English articles were screened. The original literature search took place on March 23, 2018, and the last updated search took place on July 10, 2019.

Inclusion criteria for the literature search were as follows: (1) randomized, controlled trials in patients with nAMD; (2) at least 1 arm with an anti-VEGF (aflibercept, abicipar, bevacizumab, brolucizumab, pegaptanib, or ranibizumab); (3) placebo or anti-VEGF as the control arm; (4) treatment duration of at least 4 months; (5) reported best-corrected visual acuity data; and (6) sample size of at least 20 patients. PubMed was searched using the following strategy: ((macular degeneration[tiab]) OR AMD[tiab]) and (randomized controlled trial[publication type]) AND (English[language]) and (aflibercept or ranibizumab or abicipar or bevacizumab or pegaptanib or brolucizumab or RTH258). For each drug listed in the inclusion criteria, the following search filter was applied on Clinicaltrials.gov and clinicaltrialsregister.eu: Interventional Studies (Clinical Trials) AND Age Related Macular Degeneration AND Studies with Results.

Initial screening, based on retrieved abstracts, as well as the eligibility assessment based on full-text publications, were performed by 2 independent review

authors. One scientist was responsible for the execution and documentation, and the other provided support as a therapeutic area expert. Discrepancies were resolved through discussion or consultation with a third independent reviewer. The database and the subsequent analysis comprised aggregate longitudinal data from relevant end points and aggregate baseline patient demographics (eg, baseline best-corrected visual acuity, age, and weight) for the trial arms meeting the specified inclusion criteria. No individual-level data were included. For the analysis, only monotherapy anti-VEGF arms and longitudinal best-corrected visual acuity data were included. Although the inclusion criteria specified that only trials with placebo or anti-VEGF control arms would be included, given the clinical importance of ANCHOR for being a landmark and well-cited trial (along with MARINA) that showed improvement in visual outcomes in patients with nAMD,[24,25] the study was included, despite the photodynamic therapy control arm.

While data from the phase 2 abicipar studies in patients with AMD (BAMBOO and CYPRESS) were included in the Clinical Outcomes Database, aggregate data from the phase 3 studies were not yet published at the time of analysis. Individual best-corrected visual acuity data for the abicipar and ranibizumab arms in CEDAR and SEQUOIA were summarized as the mean best-corrected visual acuity and mean CFB best-corrected visual acuity at each visit in each arm for inclusion in the analysis data set. Relevant patient demographics were also summarized.

Model Development

The disease progression model was based on the model previously developed by Mulyukov et al.[26] The formal development of the model can be found in the original reference. In brief, the model was a modification of a standard indirect-response PK/PD model[27] and expressed as:

$$\frac{dg(t)}{dt} = k_{in} \cdot \left[1 + \left[E_{max}^{ss} \cdot \left(1 + \Delta E_{max}^{0} \cdot e^{-k_{Emax} \cdot t}\right)\right] \cdot \frac{C(t)}{EC_{50} + C(t)}\right] - k_{out} \cdot g(t) \quad (1)$$

where $g(t)$ is best-corrected visual acuity as a function of time, k_{in} is the zero-order improvement rate of best-corrected visual acuity, k_{out} is the first-order deterioration rate of best-corrected visual acuity, ${E_{max}}^{ss}$ is the maximal drug effect on k_{in}, $\Delta {E_{max}}^{0}$ is the additional effect of E_{max} at the onset of treatment that declines with the rate constant k_{Emax}, and $C(t)$ is the drug concentration in the vitreous. The model assumed that, in the absence of drug intervention, best-corrected visual acuity will decrease from baseline to an estimated constant (g^{ss}) at steady state where $g^{ss} = k_{in}/k_{out}$. See Mulyukov et al[26] for additional details of the model.

The pharmacokinetics of all treatments were described by a 1-compartment model representing the vitreous having first-order elimination:

$$\frac{dA(t)}{dt} = -k_{el} \cdot A(t) \quad (2)$$

where $A(t)$ is the amount of drug in the vitreous compartment, and k_{el} is the elimination rate of the drug from the vitreous. The k_{el} for each drug was obtained from published estimates of the systemic or vitreal elimination half-life[10,28] or, for abicipar, from a separate population PK model (unpublished). The half-life values are listed in Table 1 (unpublished data, Allergan, an AbbVie Company).[29–33] The vitreous concentration $C(t)$ was obtained by assuming the vitreous had a well-established volume of 4 mL.[33] Nominal dosing based on the published study design was assumed for each trial arm. Trial arms with pro re nata or "treat and extend" dosing were not included in the analysis data set.

For model development, the disease progression parameters (g^{ss} and k_{out}) were first estimated in the absence of drug interventions based on summary sham data from the literature.[25,34–36] Once estimates for g^{ss} and k_{out} were obtained, the drug effect model was estimated with fixed disease progression parameters. Given the limited range of drug concentrations to inform the drug effect estimates for all treatments, initial efforts were limited to ranibizumab. Data from ranibizumab arms were included to estimate drug effect parameters for ranibizumab. Once ranibizumab parameters were obtained, the remaining treatments (abicipar, aflibercept, and brolucizumab) were added to the model. For drugs with sufficient data, drug-specific half-maximal effective concentration (EC_{50}) estimates were tested both as covariates on the ranibizumab EC_{50} and as estimates based on the ratio of in vitro estimates of half-maximal inhibitory concentration (IC_{50}), thus enabling the differentiation of potencies between drugs. An vitro IC_{50} estimate was not available for pegaptanib; hence, to simplify the drug effect model, pegaptanib data were excluded from the analysis.

Table 1. Model Parameter Estimates

Parameter	Description	Estimate	% Relative Standard Error
g^{ss}	Steady-state visual acuity	35.4 Letters	1.46[a]
HL_k_{out}	Half-life of the rate of disease progression (ln2/k_{out})	21.6 Weeks	22.4[a]
HL_Rani	Intravitreal half-life for ranibizumab	1.29 Weeks (Fixed)[29,30]	NA
HL_Bro	Intravitreal half-life for brolucizumab	0.629 Weeks (Fixed)[31]	NA
HL_Aflib	Intravitreal half-life for aflibercept	0.786 Weeks (Fixed)[30,32]	NA
HL_Abic	Intravitreal half-life for abicipar	0.649 Weeks (Fixed)	NA
$E_{max}{}^{ss}$	Maximal drug effect	0.842	3.24
$\Delta E_{max}{}^{0}$	Fold change over $E_{max}{}^{ss}$ at onset of treatment	5.87	15.8
HL_kE_{max}	Half-life of the rate of decline of ΔE_{max} (ln2/kE_{max})	0.494 Weeks	32.7
Ra_EC_{50}	Ranibizumab EC_{50}	14.7 nM	8.43
Af_EC_{50}	Aflibercept EC_{50}	1.12 nM	87.1
Ab_EC_{50}	Abicipar EC_{50}	0.0308 nM	6.04
Br_EC_{50}	Brolucizumab EC_{50}	0.0026 nM	6.11
$Base\_HL\_k_{out}$	Baseline covariate effect on HL_k_{out}	2.57	23.9
$Base\_E_{max}$	Baseline covariate effect on E_{max}	2.00	6.95
Between-arm variability HL_k_{out}	Between-arm variability on HL_k_{out}	99%	22.9
Between-arm variability E_{max}	Between-arm variability on E_{max}	9.35%	33.6
Between-arm variability ΔE_{max}	Between-arm variability on ΔE_{max}	118%	26.0
Sigma 1	Treatment residual error (standard error)	5.2 Letters	28.1
Sigma 2	Treatment late residual error (standard error)	4.84 Letters	15.1
Sigma 3	Sham residual error (standard error)	6.64 Letters	5.35

EC50, half maximal effective concentration; NA, not applicable.
[a] Parameters were estimated based on the disease progression model using sham data only. The bevacizumab EC_{50} was not estimated due to insufficient data.

Between-arm variability was included on the following parameters: $E^{SS}{}_{max}$, $\Delta E_{max}{}^{0}$, and HL_k_{out} (half-life associated with k_{out}). Between-arm variability was modeled as additive to logit-transformed parameters. Residual unknown variability was modeled as additive to the untransformed best-corrected visual acuity observed in the studies, with separate estimates for sham data, and for best-corrected visual acuity observations during the first year and after the first year of treatment. The residual error was weighted by the square root of the number of subjects assessed in each data point. Covariates were initially evaluated graphically against Bayesian post-hoc random-effect (eta) values. Covariates with notable covariate-eta trends were added to the model and retained if the covariate effect estimate's 95%CI did not include the null. Continuous covariates were centered on a typical value, eg, the median of the study population. Relationships between PK/PD parameters and covariates were tested in log-space with a linear model.

Adequacy of the model to describe the data was evaluated using standard goodness-of-fit (GOF) criteria, including (1) good agreement in plots of observations versus population and individual predictions, (2) plots of observations, population predictions, and individual predictions versus time by study, treatment, and dose regimen. The statistical model was assessed with the following diagnostic plots (results not shown): (1) histograms of η estimates and (2) pairwise plots of individual η estimates. The final NONMEM model was evaluated based on the following criteria: (1) a "minimization successful" statement by the NONMEM program and (2) parameter estimates judged to be meaningful and not close to a boundary.

All model development was completed using NONMEM version 7.4 (ICON Development Solutions, Ellicott City, Maryland) and Perl speaks NONMEM version 4.6. Data management, graphical evaluations, and simulations were performed in R version 3.4.0 or later (R Foundation for Statistical Computing, Vienna, Austria). The Cochrane Risk of Bias Tool for randomized controlled trials was used for the entire data set.

Results

A comprehensive literature search was performed as of July 10, 2019, using the predefined search criteria. Of 290 references screened, 71 references (46 uniquely identified randomized controlled trials were selected for inclusion into the entire database (Figure 1). Of the references excluded, the large majority were due to irrelevant study design (35.6%; 78/219) or treatment (20.5%; 45/219). The ANCHOR study was included in the analysis even though the control was photodynamic therapy, which did not meet the initial inclusion criteria. However, a sensitivity analysis excluding ANCHOR confirmed that the inclusion of the study had minimal impact on the resulting model (results not shown).

A total of 22 trials consisting of 55 arms and 9548 subjects were selected for analysis. Trial information is summarized in Table 2.[16,24,25,34–49] The anti-VEGFs

Table 2. Trials Included in the Analysis Data Set

Trial	No. of Arms	No. of Subjects	Length (Weeks)	Data Points[e]	Arms	Dose Schedules	Average Baseline Best-Corrected Visual Acuity	References
ANCHOR	2	280	52	28	Ranibizumab	0.3 mg Q4[a]	47	[24,37]
						0.5 mg Q4[a]	47.1	
					Photodynamic therapy	Day 0[b]	NA	
BAMBOO	3	25	20	21	Abicipar	2 mg Q4×3	58.5	Allergan, [38]
						1 mg Q4×3	54.3	
					Ranibizumab	0.5 mg Q4×5	55.8	
BRAMD	2	327	52	26	Ranibizumab	0.5 mg Q4[a]	60.0	[39]
					Bevacizumab	1.25 mg Q4[a]	60.0	
C-10-083	5	194	4.33	25	Brolucizumab	0.5 mg SD	63.6	[40]
						3 mg SD	57.9	
						4.5 mg SD	56.8	
						6 mg SD	54.9	
					Ranibizumab	0.5 mg SD	56.6	
C-12-006	2	89	12	8	Brolucizumab	6 mg Q8 weeks 8-32, week 44, and as needed	54.1	[41], clinicaltrials.gov
					Aflibercept	2 mg Q8 and as needed	55.6	
CANTREAT	1	258	52	2	Ranibizumab	0.5 mg Q4[a]	59.5	[42]
CATT	2	587	52	12	Ranibizumab	0.5 mg Q4	60.1	[43,44]
					Bevacizumab	1.25 mg Q4[a]	60.2	
CEDAR	3	931	52	42	Abicipar	2 mg Q12	56.4	Allergan
						2 mg Q8	56.5	
					Ranibizumab	0.5 mg Q4	56.4	
CYPRESS	3	25	20	21	Abicipar	1 mg Q4×3	55.2	Allergan, [38]
						2 mg Q4×3	59.0	
					Ranibizumab	0.5 mg Q4×5	57.6	
EOP1003	1	152	54	10	Sham	NA	51.3	[34]
EOP1004	1	144	54	10	Sham	NA	54.0	[34]
EXCITE	3	353	52	42	Ranibizumab	0.3 mg Q12[c]	55.8	[45]
						0.5 mg Q12[c]	57.7	
						0.3 mg Q4[a]	56.5	
HAGA	1	20	52	2	Aflibercept	2 mg Q8[d]	63.1	[46]
HARRIER	2	739	48	26	Brolucizumab	6 mg Q12	61.5	[47]
					Aflibercept	2 mg Q8	60.8	
HAWK	3	1078	48	39	Brolucizumab	3 mg Q12	61.0	[47]
						6 mg Q12	60.8	
					Aflibercept	2 mg Q8	60.0	
MARINA	3	716	104	54	Sham	NA	53.6	[25]
					Ranibizumab	0.3 mg Q4[a]	53.1	
						0.5 mg Q4[a]	53.7	
MORI	1	28	52	4	Aflibercept	2 mg Q8[d]	65.8	[48]
PIER	3	184	52	24	Sham	NA	55.1	[35,36]
					Ranibizumab	0.3 mg Q12[b]	55.8	
						0.5 mg Q12[b]	53.7	
REACH	3	64	20	21	Abicipar	1 mg Q4×3	58.4	[16]
						2 mg Q4×3	58.5	
					Ranibizumab	0.5 mg Q4×5	60.4	
SEQUOIA	3	942	52	42	Abicipar	2 mg Q12	56.4	Allergan
						2 mg Q8	57.2	
					Ranibizumab	0.5 mg Q4	57.0	
VIEW 1	4	1210	52	60	Ranibizumab	0.5 mg Q4	54.0	[49]
					Aflibercept	2 mg Q4[a]	55.2	
						0.5 mg Q4[a]	55.6	
						2 mg Q8[d]	55.7	
VIEW 2	4	1202	52	60	Ranibizumab	0.5 mg Q4[a]	53.8	[49]
					Aflibercept	2 mg Q4[a]	52.8	
						0.5 mg Q4[a]	51.6	
						2 mg Q8[d]	51.6	

NA, not applicable; Q4, every 4 weeks; Q8, every 8 weeks; Q12, every 12 weeks; SD, standard deviation.

"Allergan" refers to Allergan internal data.

[a] Administration was monthly.

[b] Administered on day 0, then if needed at month 3, 6, 9, or 12.

[c] Administration was once every 3 months.

[d] Administration was once every 2 months.

[e] Data points are the total number of best-corrected visual acuity observations for each trial.

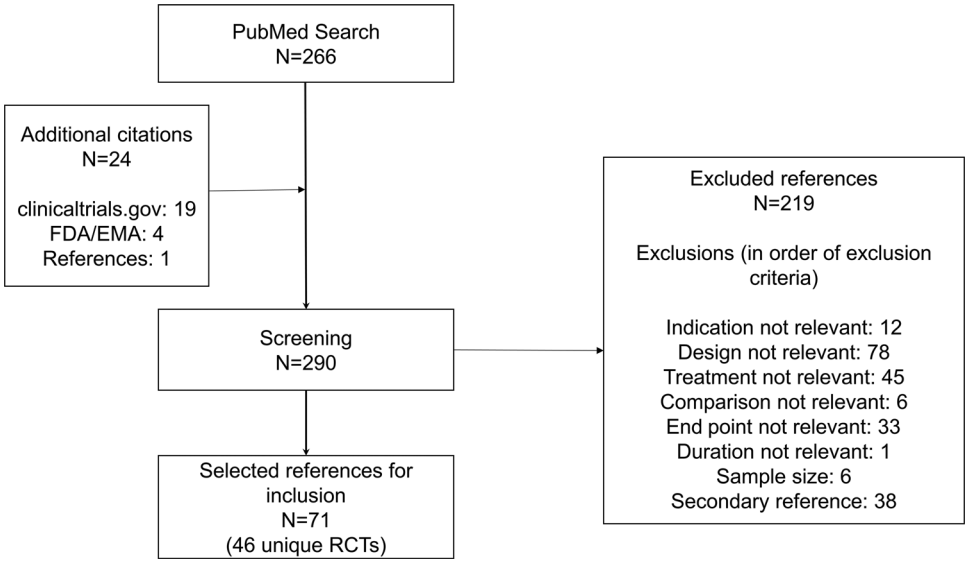


Figure 1. Literature search and study selection process. EMA, European Medicines Agency; FDA, US Food and Drug Administration; RCT, randomized controlled trial.

included in the analysis data set were abicipar, aflibercept, brolucizumab, bevacizumab, and ranibizumab. Table 1 lists the model parameters, their descriptions, estimates, and relative standard errors. Baseline best-corrected visual acuity was a statistically significant covariate influencing the k_{out} half-life and E_{max}. Figure 2 shows the model fit at the population and individual-arm levels, and Figure 3 shows the plots of observations vs individual and population predictions by drug. Overall, the nonlinear mixed-effects model adequately described the data. The plots of observed vs population estimates for bevacizumab and brolucizumab show some model misfit, as the model slightly overpredicts bevacizumab and brolucizumab data at the population level, particularly at best-corrected visual acuity >65. For bevacizumab, data were available only at 1.25 mg Q4 (monthly); hence, a bevacizumab-specific EC_{50} was not estimated, and the ranibizumab EC_{50} was assumed, likely contributing to the model misfit. For brolucizumab, the misfit is likely due to the lack of precise information regarding dosing frequencies in the HAWK and HARRIER studies.

Due to uncertainties in model parameters, as reflected in the high percent relative standard error of the between-arm variabilities of some parameters, simulations were conducted based on individual predictions instead of population predictions. For each arm from the original data set, the expected response was simulated using empirical Bayesian estimates, and results were summarized (mean and standard deviation) across all arms of each drug. Figure 4 shows the mean simulated week 52 outcomes compared to observed data for various regimens for each drug (including the labeled dosing frequency for each), demonstrating that the model was well calibrated against the data. Bevacizumab was excluded from the simulations due to the inability to estimate an EC_{50} given the limited data available in the database (2 arms).

Simulated week 52 CFB best-corrected visual acuity following Q12 dosing are shown in Figure 5. The model predicts a 5.92, 3.04, 6.61, and 3.02 letter gain based on loading doses at weeks 0, 4, and 12, followed by Q12 dosing for abicipar, aflibercept, brolucizumab, and ranibizumab, respectively, when baseline best-corrected visual acuities were kept the same as in the original trials. While these simulations do not reflect the labeled dosing frequency for aflibercept, brolucizumab, or ranibizumab, they are intended to reflect commonly used treat and extend protocols.

Discussion

Although extended dosing has been explored in some clinical trials, no trial has simultaneously conducted head-to-head comparisons of an investigational drug against more than one standard-of-care anti-VEGF. Brolucizumab (3 and 6 mg) was tested on a Q8/Q12 as-needed dosing against the 2-mg aflibercept Q8 dosing as the standard of care in HAWK and HARRIER.[47] In VIEW 1 and VIEW 2, 0.5 mg aflibercept on Q4 (monthly) dosing and 2-mg aflibercept on Q8 (once every 2 months) dosing were compared to 0.5 mg ranibizumab on Q4 (monthly) dosing. CEDAR and SEQUOIA tested 2 mg abicipar on fixed Q8 or fixed Q12 dosing against 0.5 mg ranibizumab on Q4 dosing.[38] In addition, a direct head-to-head comparison of fixed Q12 (or quarterly) dosing, which is the current goal of anti-VEGF therapy, across several standard-of-care

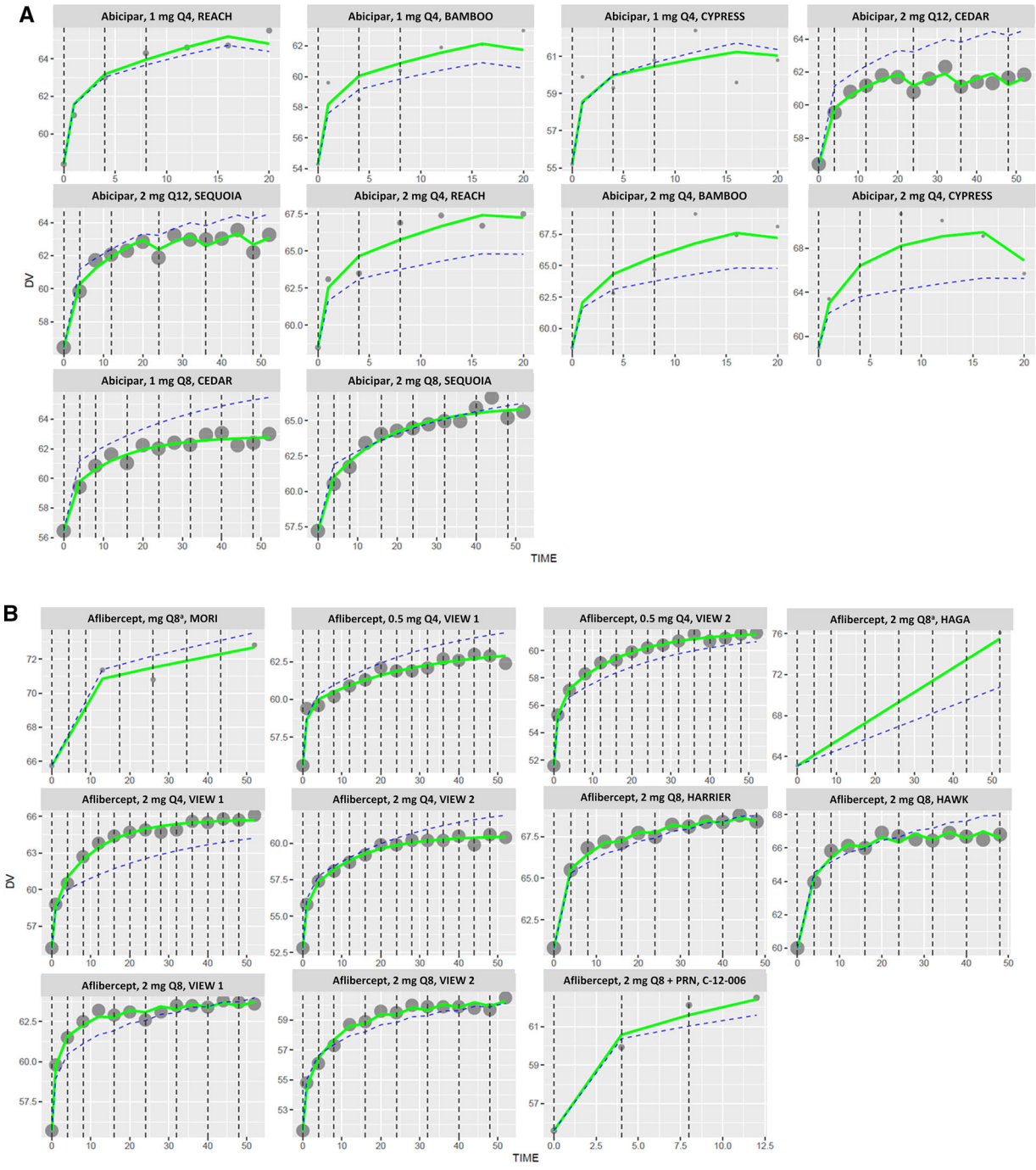


Figure 2. Individual fit by arm for (A) abicipar, (B) aflibercept, (C) ranibizumab, (D) brolucizumab, (E) bevacizumab, and (F) sham. The green lines represent trial-specific model predictions, and the blue dashed lines represent the average prediction across trials. The solid circles represent the observed data, and the size is proportional to the number of subjects. The vertical dashed lines indicate nominal treatment administration. DV, dependent variable; Q4, every 4 weeks; Q8, every 8 weeks; Q12, every 12 weeks; TIME, time from first dose, weeks.

anti-VEGFs has not been conducted. As it is not practical to conduct direct comparisons between all anti-VEGF treatments using multiple extended dosing schedules in a large trial, modeling and simulation is a useful tool to conduct such an investigation. In this work, we performed a MBMA using existing data from the literature, which included 22 trials consisting of 55 arms and 9548 subjects, to assess the feasibility of Q12 dosing for abicipar, aflibercept, brolucizumab, and ranibizumab. Our MBMA predictions showed good correspondence with published data (Figures 2, 3, and 4). For example, in CEDAR and SEQUOIA,

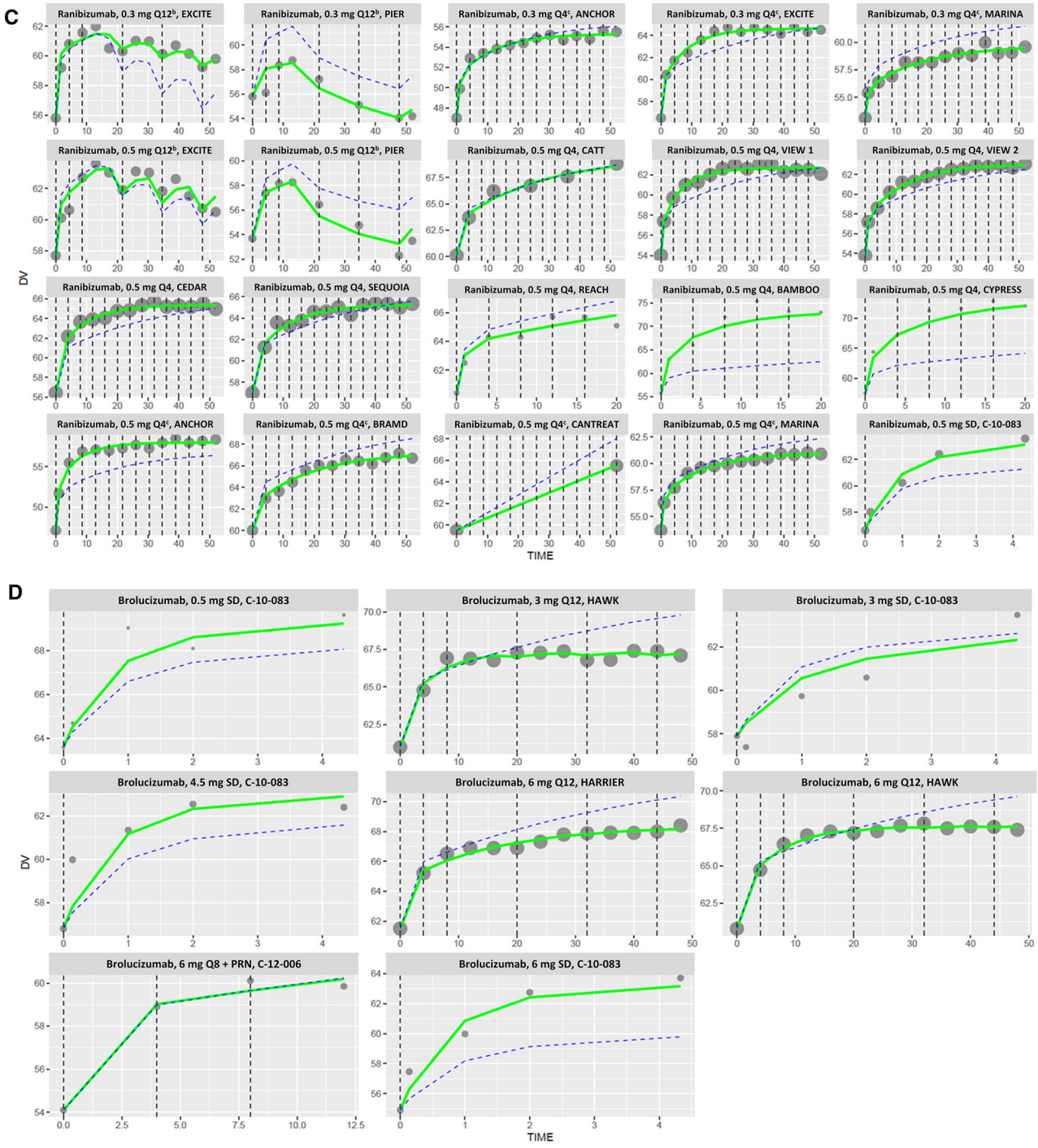
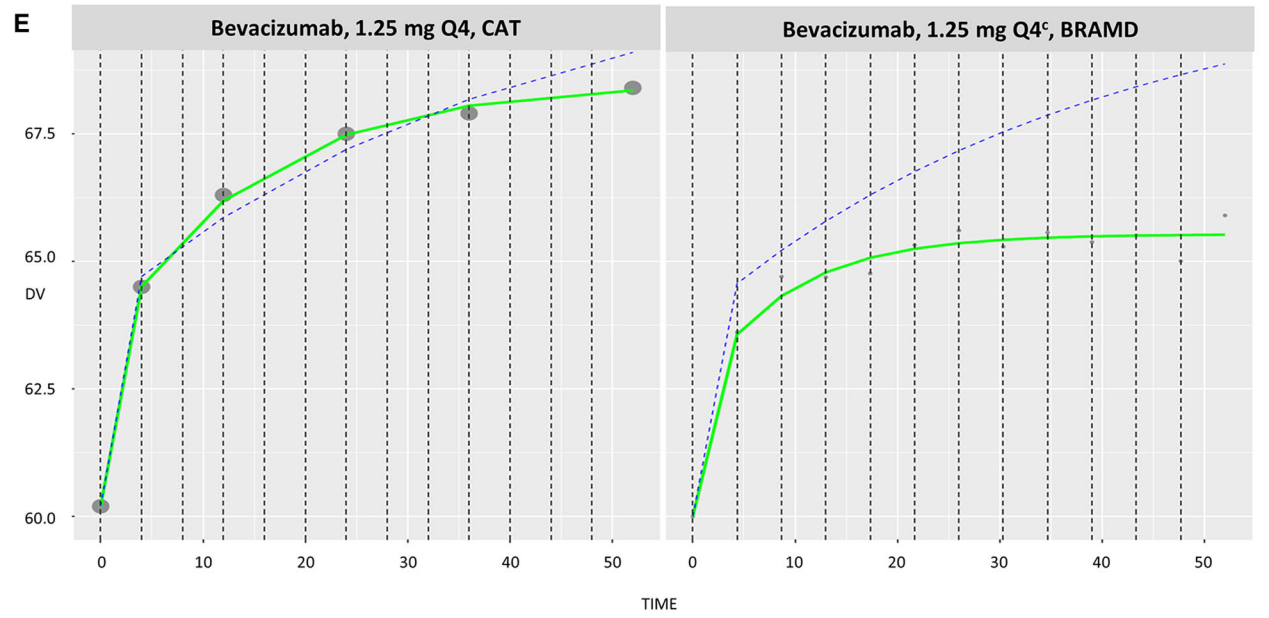
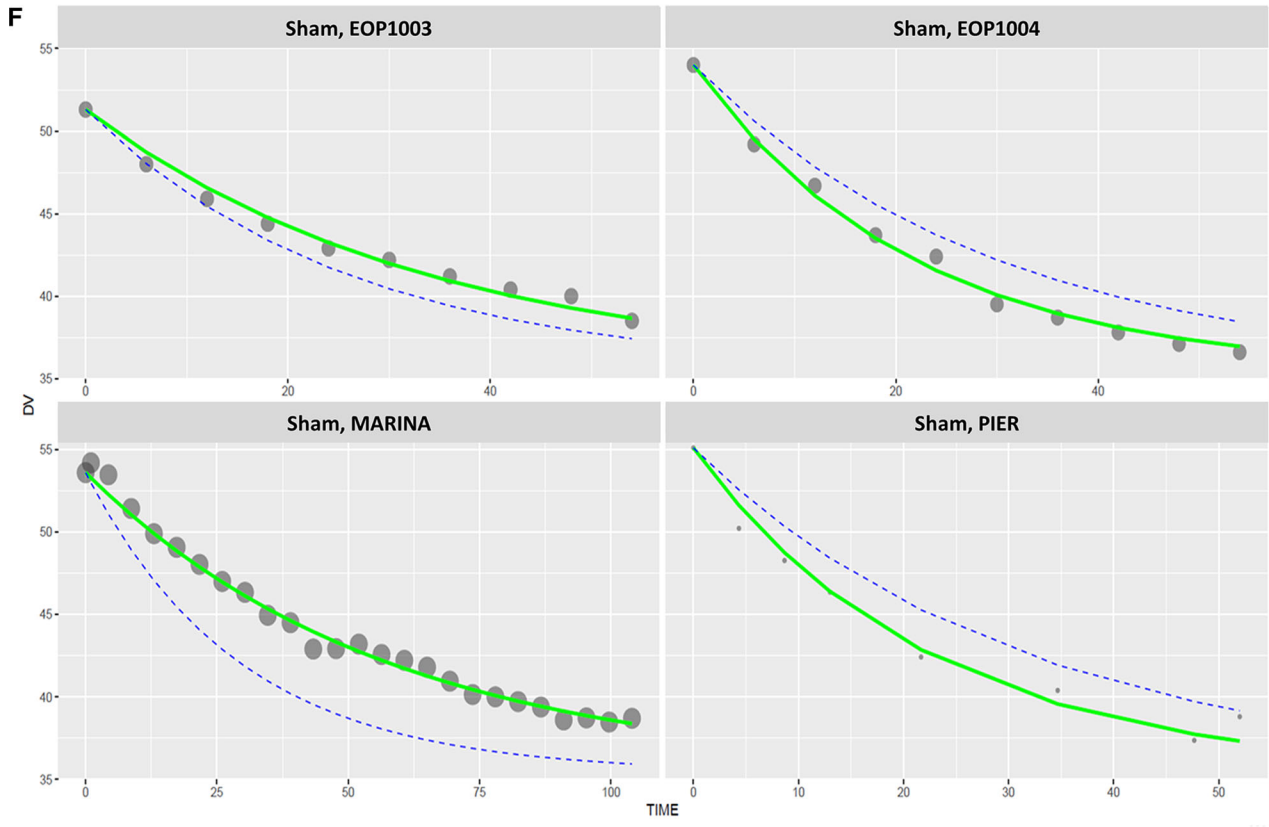


Figure 2. *Continued*

2 mg abicipar demonstrated a week 52 mean CFB of 6.4 letters on Q12 dosing, whereas the comparator arm, ranibizumab Q4, had an improvement of 8.4 letters.[38] In HAWK and HARRIER, brolucizumab demonstrated a week 48 mean CFB of 6.6 letters for the 6-mg dose on Q8 to Q12 as-needed dosing, with most patients (51.0%-55.6%) remaining on fixed Q12 dosing.[50] The MBMA predicted a 6.0 letter gain for abicipar on Q12 dosing and a 6.6 letter gain for brolucizumab on Q12 dosing, similar to the 6.4- and 6.6-letter gains reported in CEDAR/SEQUOIA and HAWK/HARRIER, respectively. In the EXCITE trial, 0.3 mg and 0.5 mg of ranibizumab on Q12 dosing resulted in 4.9 and 3.8 letters gained at month 12, respectively.[45] However, in the PIER trial, Q12 dosing of ranibizumab resulted in –1.6 and –0.2 letter gains





[a]Administration was once every 2 months. [b]Administration was once every 3 months. [c]Administration was monthly.

Figure 2. *Continued*

for the 0.3-mg and 0.5-mg dose groups.[36] Our analysis accounted for the available ranibizumab literature data from randomized controlled trials with placebo or an anti-VEGF as control. The model, built from a database including ranibizumab data from EXCITE, PIER, MARINA, VIEW, and others (Table 2), predicted only a 3-letter gain for ranibizumab on fixed Q12 dosing.

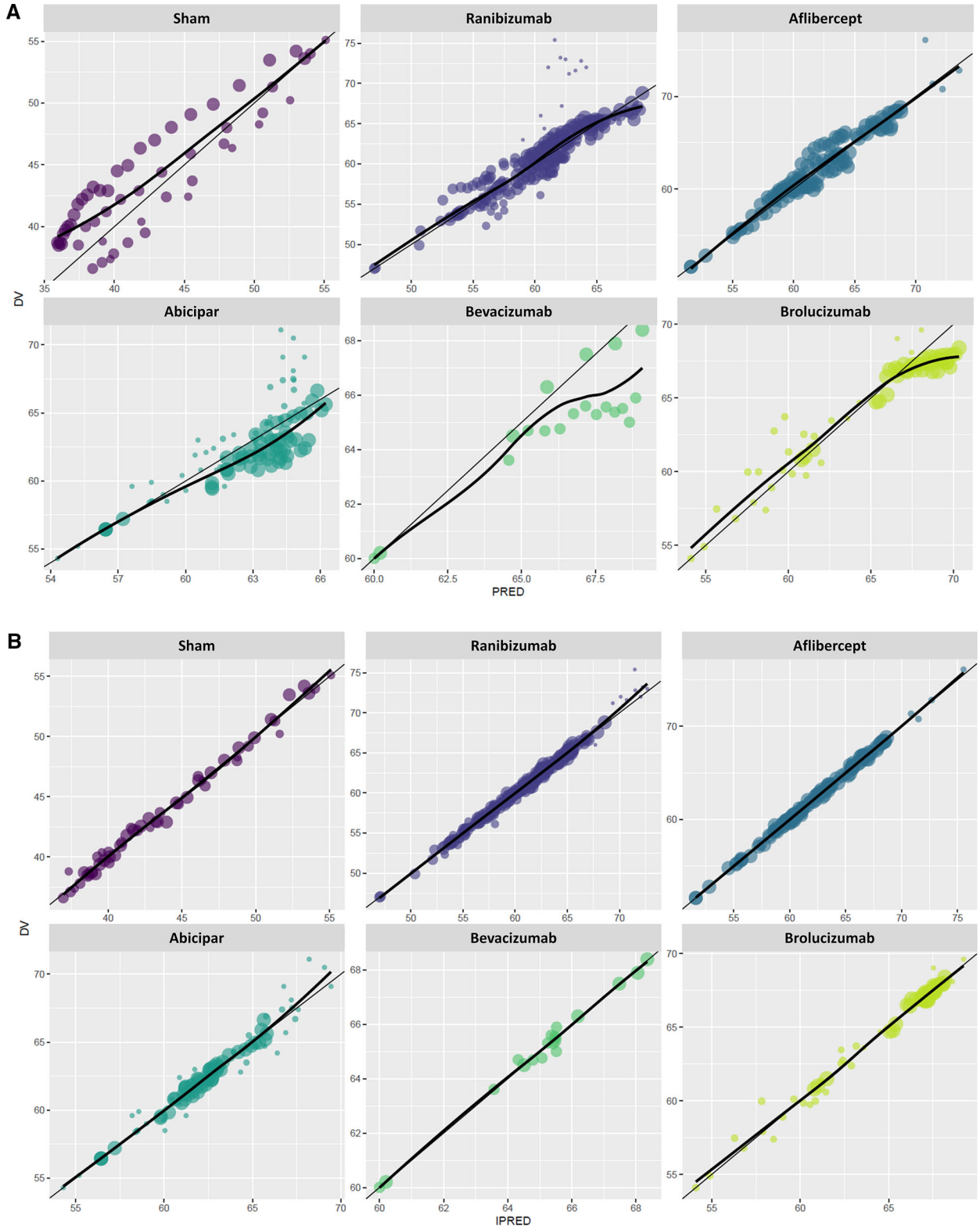


Figure 3. Diagnostic plots of observations vs (A) population and (B) individual predictions for the model-based meta-analysis model stratified by drug. Each symbol size is proportional to the number of subjects. The thick black line represents a loess smooth through the observed data. DV, dependent variable; PRED, population prediction; IPRED, individual prediction.

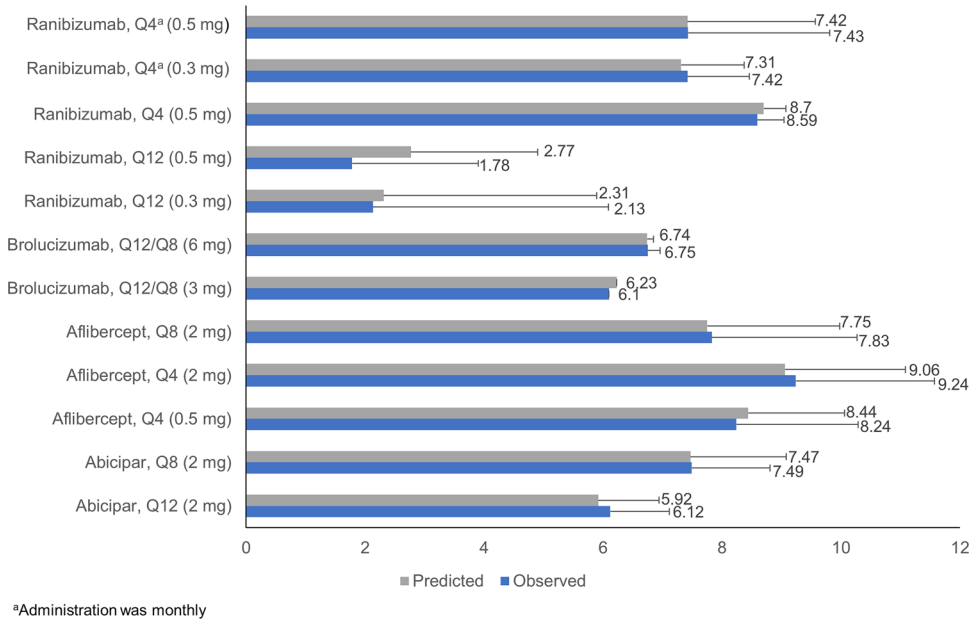


Figure 4. The predicted vs observed mean change from baseline best-corrected visual acuity (standard deviation) at week 48 or 52 based on the analysis data set of the model-based meta-analysis. Q4, every 4 weeks; Q8, every 8 weeks; Q12, every 12 weeks.

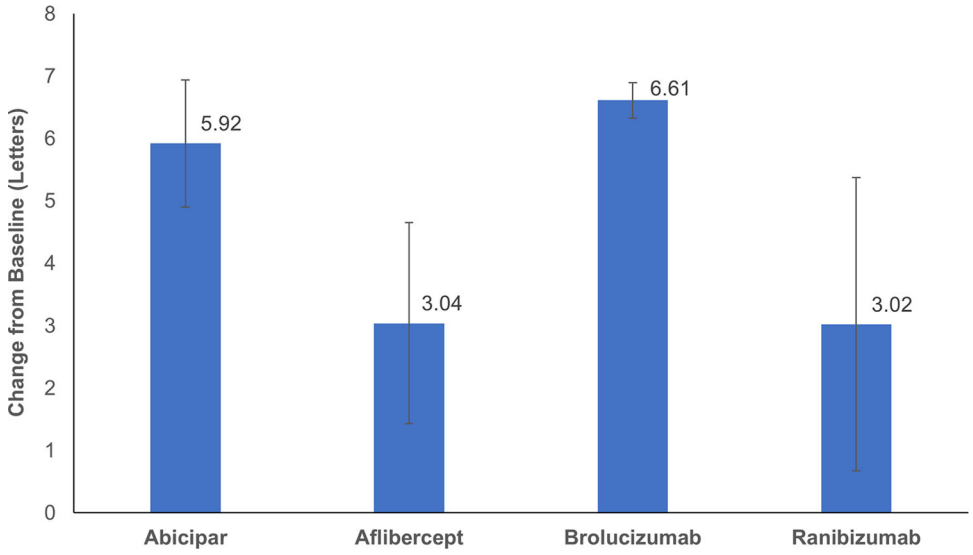


Figure 5. Virtual head-to-head comparisons in change from baseline in letters (standard deviation) between abicipar, aflibercept, brolucizumab, and ranibizumab at week 52 with loading doses at weeks 0, 4, and 12 followed by fixed Q12 dosing (ie, extended dosing for aflibercept and ranibizumab compared to their labeled frequency) using the baseline best-corrected visual acuity reported in the original trials. Q12, every 12 weeks.

Aflibercept and ranibizumab are not approved for use on a fixed Q12 dosing regimen but have been used with a treat and extend protocol to reduce treatment burden.[51,52] No data from a fixed Q12 dosing study were available for aflibercept. In a post hoc analysis of VIEW 1 and VIEW 2 studies, mean best-corrected visual acuity gains from baseline were 9.9 and 9.7 letters when patients were treated with aflibercept for a year on fixed Q4 or Q8 dosing, respectively, followed by ≥Q12 dosing for the second year.[50] In the same analysis, the mean best-corrected visual acuity gain was 8.7 letters when patients were treated with ranibizumab for a year on fixed Q4 dosing followed by a second year on ≥Q12 dosing. This analysis does not provide a fair performance assessment of either ranibizumab or aflibercept on fixed Q12 or longer dosing, as the results were from a subgroup of patients in the second year after those patients had received shorter dosing (Q4 or Q8) in the first year. More frequent treatment in the first year may have contributed to significant

disease modification that led to a more favorable response in the second year. In addition, the similarity in letter gains between the ranibizumab and aflibercept subgroups suggests that these ≥Q12 patients were more likely to be responsive to anti-VEGF therapies than the typical patient. Based on modeling the totality of the available data we collected, our simulations suggest that on fixed Q12 dosing without as-needed–based dose modification, the best-corrected visual acuity gain for aflibercept in the typical patient would be 3 letters.

Based on labeled dose schedules, the MBMA confirmed that aflibercept Q4 faired best in terms of letter gains (9.24 observed and 9.06 model-predicted) followed by ranibizumab Q4 (8.59 observed and 8.7 model-predicted) and brolucizumab Q12/Q8 (6.75 observed and 6.74 model-predicted) as shown in Figure 4. Consistent with reported data, abicipar Q12 showed fewer letters gained (6.12 observed vs 5.92 model-predicted) to the above marketed drugs based on their labeled schedules. However, when we used the model to virtually test all drugs on an extended schedule of Q12, aflibercept and ranibizumab performed the poorest, with letter gains of 3.04 and 3.02, respectively, whereas abicipar and brolucizumab have more meaningful letter gains of 5.92 and 6.61 letters, respectively. These results would argue against treat and extend for aflibercept and ranibizumab, as their efficacy declines significantly when the schedule is extended far beyond their labeled schedules. The results also demonstrate that newer agents such as abicipar and brolucizumab inherently have longer duration of activities compared to older agents, albeit they did not compare well based on labeled schedules for approved drugs.

Consistent with the reported clinical results, the model predicted clinically meaningful letter gains for abicipar and brolucizumab.[42] This suggests that it is feasible for abicipar and brolucizumab to have Q12 dosing while maintaining meaningful visual gains. As previously stated, less frequent nAMD treatment while maintaining efficacy is an unmet clinical need. Data from real-world studies demonstrate the importance of moving to a less frequent treatment schedule. Currently, patients often miss or delay anti-VEGF treatments, and some discontinue treatment. Undertreatment of nAMD greatly increases the risk of vision loss.[53–55] Poor compliance is often due to the need for continual treatment, which can be as often as once a month, and due to the invasive nature of anti-VEGF treatments. The cumbersome visits to the physician's office place a heavy burden on patients with nAMD and those who care for them.[56,57] Moving to Q12 dosing would reduce treatment burden and potentially reduce the number of undertreated patients.

The MBMA was developed to include published trial data for the 5 anti-VEGFs analyzed. In contrast to the model of Mulyukov et al,[26] which was based on individual data from 4 phase III ranibizumab trials, our MBMA was developed using summary data from a total of 22 phase I to III trials involving anti-VEGFs ranibizumab, aflibercept, brolucizumab, bevacizumab, and abicipar. The comprehensive data set across multiple drugs and trials provided more confidence in the estimation of the model parameters common across drugs, for example, the maximal drug effect, the fold change over the maximal effect at the onset of treatment, and the half-life of the decline of ΔE_{max}. In addition, the 22 trials investigated a wide range of different dose schedules and dose levels, in multiple-arm trials, providing informative data for model calibration and thus more confidence in the model predictions and comparisons across drugs that may not have been directly compared in a clinical trial.

The ability to accurately estimate random effects can be limited when using aggregate-level data. This is an inherent issue with MBMAs as has been addressed in an analysis by Ahn and French.[58] While the authors suggest inclusion of multiple levels of random effects (eg, study and treatment arm), implementation may not be straightforward. Though diagnostics indicate some bias at the population level, the empirical Bayes estimates from our model provided accurate predictions relative to observed data at the individual (arm) level and allowed us to confidently infer from the simulation results. The vast majority of meta-analyses are performed on aggregate-level data mainly because published studies rarely contain individual data. However, individual-data meta-analysis can be more reliable and can answer more detailed questions than aggregate-level data meta-analysis.[59] Generally, analyses of aggregate-level data do not provide information for individualized therapies.

There are some limitations of MBMA models that should be noted. Model analysis includes multiple different trials, and differences between the trials, such as inclusion and exclusion criteria, may influence the results. Although covariates are used to control for these differences, some covariates that impact the results may not have been included in the model due to limited data or limited influence on the data at the summary level. Additionally, in the analysis data set and literature, sham data were extremely limited relative to treatment data. This is likely reflected in the divergent estimates of disease progression parameters of our analysis (g^{ss}, 35.4 letters; k_{out} half-life, 21.6 weeks) compared to Mulyukov and colleagues'[26] (g^{ss}, 11 letters; k_{out} half-life, 187.2 weeks). Estimates from our MBMA were more consistent with estimates from a previous analysis of individual-level data from Lu et al. (g^{ss}, 27 letters; k_{out}, 26.8 weeks).[60] Since sham data collected over an extended period of time is needed to accurately predict the underlying disease progression, estimates

of the disease progression parameters in all analyses should be interpreted with caution. The inclusion of 5 monotherapy arms may limit the ability to distinguish between trial variability and between-arm variability. In our analysis, all variability was assessed as between-arm variability. Finally, the literature search was limited to English articles. Though this is a common inclusion criterion for MBMA, only 6 non-English articles were identified by the search but were not relevant to the final model.

Conclusions

Virtual head-to-head comparisons of abicipar, aflibercept, brolucizumab, and ranibizumab were conducted using a model-based meta-analytical approach. Consistent with reported data, results from the model showed that abicipar Q12 underperformed ranibizumab (Q4), aflibercept (Q4), and brolucizumab (Q8/Q12) labeled schedules. However, when all drugs were virtually tested using the model on an extended (Q12) schedule, abicipar outperformed ranibizumab and aflibercept and had a similar week 52 CFB in best-corrected visual acuity as brolucizumab. The analysis supports the feasibility for abicipar and brolucizumab to have fixed Q12 dosing with clinically meaningful letter gains (6 and 6.6 letters, respectively), whereas aflibercept and ranibizumab each resulted in only a 3-letter gain at the same dose schedule. The model has utility for exploring different regimens for existing anti-VEGF agents or providing benchmarks for a novel anti-VEGF agent.

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Conflicts of Interest

K.L. was an employee of AbbVie Inc. at the time of the study and during the early drafts of the manuscript. J.S. and M.A. are employees of and hold stock options for AbbVie Inc. M.G. was an employee of Certara at the time the analysis was conducted, is a current employee of qPharmetra, and is a stockholder of AbbVie. C.W. is an employee of Certara, USA. The study was supported by Allergan plc, Irvine, California (prior to its acquisition by AbbVie). Neither honoraria nor other form of compensation were provided for authorship. Writing and editorial assistance was provided to the authors by Stephanie Kuwahara, PhD, of AbbVie and Evidence Scientific Solutions Inc, Philadelphia, Pennsylvania.

Data-Sharing Statement

The data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data-Sharing Agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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