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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761235
Link to EDR	\\CDSESUB1\EVSPROD\BLA761235\0001
Submission Date	05/28/2021
Submission Type	BLA 351(a); Priority Review
Brand Name	VABYSMO
Generic Name	Faricimab (RO6867461)
Dosage Form and Regimen	6 mg/0.05 mL solution in a single-dose vial for injection; 6 mg (0.05 mL) administered Q4W for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to Q16W for nAMD, DME, and DR; some patients may be dosed as frequently as Q4W
Route of Administration	Intravitreal injection
Proposed Indication	Treatment of Neovascular (wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)
Applicant	Genentech, Inc.
Associated IND	IND 119225
OCP Review Team	Nisha Kwatra, Ph.D.; Yangbing Li, Ph.D.; Jiang Liu, Ph.D.; Ping Ji, Ph.D.
OCP Final Signatory	Suresh Doddapaneni, Ph.D., Director (Acting), Division of Immune and Inflammation Pharmacology, Office of Clinical Pharmacology

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1 EXECUTIVE SUMMARY

Genentech, Inc. (the Applicant) submitted an original BLA on May 28th, 2021, seeking marketing approval for faricimab (RO6867461) intravitreal injection for the proposed indication of neovascular (wet) age-related macular degeneration (nAMD), diabetic macular edema (DME), diabetic retinopathy (DR). Faricimab is humanized bispecific immunoglobulin G1 (IgG1) antibody that selectively binds to, and neutralizes, both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). The Fc domain of faricimab has been engineered to abolish binding to Fcγ receptors, located on immune effector cells, and to the antibody recycling neonatal Fc receptor (FcRn). The proposed drug product is supplied as a 6 mg/0.05 mL solution in a single-dose vial for injection. The proposed dosing regimen is 6 mg (0.05 mL) administered every 4 weeks (Q4W) for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to every 16 weeks (Q16W) for nAMD, DME, and DR; some patients may be dosed as frequently as Q4W.

The clinical pharmacology of faricimab was assessed in two Phase 1 studies (Study BP28936 in patients with nAMD and Study JP39844 in Japanese patients with nAMD and DME/DR), three Phase 2 studies (Studies CR39521 and BP29647 in patients with nAMD and Study BP30099 in patients with DME and DR), and four Phase 3 studies (Studies GR40306 and GR40844 in patients with nAMD and Studies GR40349 and GR40398 in patients with DME and DR). The to-be-marketed formulation was used in the Phase 3 studies.

The clinical pharmacology review is focused on the appropriateness of the proposed dosing regimen of 6 mg (0.05 mL) administered Q4W for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to Q16W for nAMD, DME, and DR.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of BLA 761235 and finds the application acceptable to support approval from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of effectiveness is based on four randomized controlled Phase 3 trials (Studies GR40306, GR40844, GR40349, and GR40398) in patients with nAMD or DME and DR. Exposure-response analysis provided supportive evidence of effectiveness.
General dosing instructions	6 mg (0.05 mL) administered every 4 weeks (Q4W) for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to every 16 weeks (Q16W) for nAMD, DME, and DR; some patients may be dosed as frequently as Q4W.
Dosing in patients (intrinsic and extrinsic factors)	No dose adjustment is recommended for patients based on intrinsic and extrinsic factors.

Labeling	The proposed labeling concepts are generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the Phase 3 studies.

1.2 Post Marketing Requirement

None.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody which selectively binds to, and neutralizes, both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). The Fc domain of faricimab has been engineered to abolish binding to Fcγ receptors, located on immune effector cells, and to the antibody recycling neonatal Fc receptor (FcRn). PK of faricimab was evaluated in nine clinical studies in patients with nAMD and DME/DR.

Pharmacokinetics
Maximum faricimab plasma concentrations (C_{max}) were estimated to occur approximately 2 days post-dose and were estimated to be 0.23 µg/mL and 0.22 µg/mL in nAMD and in DME/DR patients, respectively. Maximum free faricimab concentrations in plasma are predicted to be approximately 600 and 6000-fold lower than in aqueous and vitreous humor, respectively. Vc/F was 1.48 L, consistent with a limited distribution. No accumulation of faricimab was apparent in the vitreous or in plasma when administered as repeat doses.

Faricimab is expected to be catabolized in lysosomes to small peptides and amino acids, which may be excreted renally, in a similar manner to the elimination of endogenous IgG. The estimated mean apparent systemic half-life of faricimab is 7.5 days. Due to the flip flop kinetics, the faricimab plasma concentration-time profile declined in parallel with the aqueous humor and vitreous. The estimate of the plasma CL/F was 2.33 L/day, corresponding to a rapid $t_{1/2}$ of approximately 0.44 days.

Pharmacodynamics
A decrease from baseline of ocular free Ang-2 and free VEGF-A concentrations was observed from day 7 onwards throughout the treatment interval in the four Phase 3 studies.

Immunogenicity
In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The recommended dosing regimen is 6 mg (0.05 mL) administered every 4 weeks (Q4W) for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to every 16 weeks (Q16W) for nAMD, DME, and DR; some patients may be dosed as frequently as Q4W. This dosing regimen was evaluated in four randomized controlled clinical trials with patients with nAMD and DME/DR. In nAMD studies TENAYA and LUCERNE, faricimab at intervals up to Q16W demonstrated non-inferiority to aflibercept Q8W in change from baseline in BCVA averaged over Weeks 40, 44 and

48. The change from baseline in BCVA over time was comparable between the faricimab up to Q16W arm and the aflibercept Q8W arm in both TENAYA and LUCERNE, with 80% and 78% of patients in the faricimab dosing arms on a fixed ≥ Q12W dosing regimen (46% and 45% on Q16W, 34% and 33% on Q12W) in TENAYA and LUCERNE, respectively, at Week 48. In DME/DR studies YOSEMITE and RHINE, both faricimab Q8W and up to Q16W adjustable dosing (PTI) treatment regimens demonstrated non-inferiority in mean change from baseline in BCVA at Week 48/52/56 compared to aflibercept Q8W in patients with DME and DR. The non-inferiority of the faricimab PTI regimen compared with the aflibercept Q8W regimen on the primary endpoint in these analyses showed the durability of faricimab with more than 50% of patients in YOSEMITE and RHINE on a Q16W regimen at Week 52. Defer to clinical/statistical review for additional details on benefit/risk assessments.

2.2.2 Therapeutic Individualization

Therapeutic individualization is not applicable for faricimab because it is locally administered with minimum systemic exposure.

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The proposed labeling concepts are generally acceptable.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Faricimab (also known as RO6867461) is a humanized bispecific IgG1 antibody developed for intravitreal use which selectively binds to, and neutralizes, both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). The Fc domain of faricimab has been engineered to abolish binding to Fcγ receptors, located on immune effector cells, and to the antibody recycling neonatal Fc receptor (FcRn).

A summary of key clinical pharmacology-related discussions and correspondence with the Applicant are listed in Table 1 below.

A summary of key discussions and correspondence with the Applicant are listed in Table 1 below.

Table 1: Summary of Key Communication/Meetings with the Applicant

IND 119225, (03 April 2017)	▪ Type C face-to-face meeting for chemistry, manufacturing, & control (CMC) and nonclinical

IND 119225 (17 November 2017)	▪ Type C face-to-face meeting for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and diabetic retinopathy (DR) to discuss clinical development program
EOP 2 (24 April 2018)	▪ Type B (end-of-phase 2 [EOP2]) face-to-face meeting for DME and DR to discuss clinical and nonclinical development ▪ The Agency agreed that that additional clinical pharmacology studies in patients with impaired renal or hepatic function, drug-drug interaction studies, or a thorough QT (TQT) study are not needed to support a BLA submission. The Agency also agreed with the Sponsor's proposal to evaluate the impact of patients' baseline characteristics (age, renal function, liver function) or co-medications on systemic exposure to faricimab using a population pharmacokinetic approach with all the data from Phase 1, 2, and 3 studies. ▪ The Agency recommended that the Applicant collect additional blood samples during the Week 4 visit for the immunogenicity assessment. ▪ The Agency asked the Applicant to provide information on the observed differences (if any) in the immunogenicity rate between the treatment arm receiving 1.5 mg faricimab vs. the treatment arm receiving 6 mg faricimab.
EOP1/2 (30 August 2018)	▪ Type B (end-of-phase 2 [EOP2]) face-to-face meeting for nAMD to discuss clinical and nonclinical development
IND 119225 (15 January 2020)	▪ FDA Type C WRO for nAMD, DME, and DR to discuss the statistical analysis plan
IND 119225 (1 July 2020)	▪ Type C teleconference meeting for nAMD, DME, and DR to discuss data independent BLA content and format
IND 119225 (7 July 2020)	▪ Type C WRO meeting to discuss clinical actual use and human factors studies
Pre-BLA (29 March 2021)	▪ Type B (Pre-BLA) teleconference meeting (meeting cancelled) for nAMD, DME, and DR (meeting preliminary comments served as final minutes for the cancelled teleconference) ▪ The Agency asked the Applicant to provide summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results correlation between anti-drug antibody status and titers with PK/PD/efficacy/safety data.

Source: Reviewer's summary based on meeting minutes (DARRTS; IND 119225)

3.2 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and PK of faricimab were evaluated in nine clinical studies in patients with nAMD and DME/DR. However, the to-be-marketed formulation was used in the Phase 3 studies only. A summary of the Phase 3 studies in patients with nAMD are summarized in Table 2, and Phase 3 studies in DME/DR are summarized in Table 3.

Table 2: Summary of Phase 3 nAMD Studies Contributing to Pharmacokinetic, Pharmacodynamic, and Immunogenicity

Study Number (Name) [Region]	Study Design	Patient Population	Number of Patients Enrolled	Route and Dose Regimen(s)	Analytes Measured		
					Faricimab PK	PD	ADA
Pivotal Phase III Studies							
TENAYA (GR40306) [Global] **LUCERNE** (GR40844) [Global]	Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled, 112-Week Study	Treatment-naive patients with nAMD	**TENAYA** Faricimab:N=334 Aflibercept: N=337 **LUCERNE** Faricimab: N=331 Aflibercept: N=327	• Faricimab up to Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI to Week 108 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W to Week 108 Patients will return for a final visit at Week 112.	AH and plasma	Ang-2, AH and plasma VEGF-A, AH and plasma	Plasma

Table 3: Summary of Phase 3 DME and DR Studies Contributing to Pharmacokinetic, Pharmacodynamic, and Immunogenicity Data

Study Number (Name) [Region]	Study Design	Patient Population	Number of Patients Enrolled	Dose, Duration	Analytes Measured		
					Faricimab PK	PD	ADA
Pivotal Phase III Studies							
YOSEMITE (GR40349) [Global] **RHINE** (GR40398) [Global]	Phase III, Randomized, Double−Masked, Active Comparator-Controlled, Three Parallel Groups, 100−Week Study	Patients with DME, DR	**YOSEMITE** Faricimab Q8W: N=315 (N=238 treatment-naive) Faricimab PTI: N=313 (N=245 treatment-naive) Aflibercept: N=311 (N=242 treatment-naive) **RHINE** Faricimab Q8W: N=317 (N=254 treatment-naive) Faricimab PTI: N=319 (N=255 treatment-naive) Aflibercept: N=315 (N=248 treatment-naive)	• Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W to Week 20 followed by Q8W to Week 96 • Faricimab PTI [a]: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI to Week 96 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W to Week 16 followed by Q8W to Week 96	AH and plasma	Ang-2: AH and plasma VEGF-A: AH and plasma	Plasma

Table 4: Summary of clinical pharmacology and pharmacokinetics

Pharmacology	
Mechanism of Action	Faricimab (also known as RO6867461) is the first humanized bispecific immunoglobulin G1 (IgG1) antibody developed for intravitreal use which selectively binds to, and neutralizes, both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). The Fc domain of faricimab has been engineered to abolish binding to Fcγ receptors, located on immune effector cells, and to the antibody recycling neonatal Fc receptor (FcRn). The Applicant stated that the dual inhibition of Ang-2 and VEGF-A with faricimab is expected to reduce vascular permeability and inflammation, inhibit pathological angiogenesis, and restore vascular stability. These faricimab effects are expected to translate into improved durability and/or efficacy in nAMD, DME, and DR when compared to anti-VEGF monotherapy.
Active Moieties	Faricimab
QT Prolongation	No thorough QTc study has been performed with faricimab, as monoclonal antibodies are not known to cause QT prolongation, and faricimab plasma concentrations were low. Thus, the risk of QT prolongation with intravitreal administration of faricimab appears low.
General Information	
Bioanalysis	Faricimab concentrations in aqueous humor (AH) and plasma were measured using validated colorimetric enzyme-linked immunosorbent assays (ELISA). The concentration of free Ang-2 in AH was determined with a validated bead-based immunoassay on the Single Molecule Array (SIMOA) immunoassay platform. The concentration of total and free Ang-2 was determined in K3EDTA plasma using validated quantitative Elecsys electrochemiluminescence technology. The concentrations of free VEGF-A were determined in AH samples using a validated bead-based sandwich ELISA on the SIMOA platform. The concentration of free

	VEGF was determined in plasma samples using a validated ELISA method. Anti-drug antibodies (ADAs) were measured in plasma samples from all patients enrolled in all trials using a validated semi-quantitative ELISA.
Healthy vs. Patients	Systemic exposure of omidenepag was assessed in patients with nAMD and DME/DR only.
Drug exposure at steady state following the therapeutic dosing regimen	**nAMD:** Following 6 mg of intravitreal faricimab Q4W up to Week 12, followed by Q16W, Q12W, or Q8W (based on disease activity) up to Week 60, mean (SD) faricimab plasma concentrations 4 weeks after the most recent dose were 0.029 (0.0194) μg/mL (Week 4 visit), 0.034 (0.027) μg/mL (Week 16 visit), and 0.022 (0.018) μg/mL (Week 48 visit). Observed mean (SD) faricimab AH concentrations 4 weeks after the most recent dose were 23.0 (16.9) μg/mL (at the Week 16 visit) and 8.0 (8.7) μg/mL (Week 24 visit). The ratio of faricimab AH to plasma on Day 7 was approximately 450. **DME/DR:** Doses administered in DME/DR patients included 6 mg of intravitreal faricimab Q4W up to Week 20, followed by Q8W up to Week 92 or 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by personalized treatment interval (PTI) dosing. Observed mean faricimab 4 week-post-dose AH concentrations (μg/mL) were 12.2 (10.4) (Week 16 visit), 18.8 (16.1) (Week 20 visit), 8.1 (7.9) (Week 32 visit) for the Q8W regimen, and 15.7 (12.4) (Week 16 visit), 15.7 (12.9) (Week 20 visit), 16.0 (19.5) (Week 32 visit) for the PTI regimen. Observed mean (SD) faricimab 8 week-post-dose AH concentrations (μg/mL) was 2.12 (2.49) (Week 20 visit) for the PTI regimen. Observed mean faricimab 4 week-post-dose plasma concentrations (μg/mL) were 0.019 (0.016) (at the Week 4 visit) for the Q8W regimen and 0.018 (0.014) (Week 4 visit), 0.018 (0.014) (Week 52 visit) for the PTI regimen. Observed mean faricimab 8 week-post-dose plasma concentrations (μg/mL) were 0.003 (0.004) (Week 28 visit), 0.003 (0.004) (Week 52 visit) for the Q8W regimen and 0.003 (0.004) (Week 28 visit), 0.003 (0.004) (Week 52 visit) for the PTI regimen. The faricimab AH-to-plasma ratio on Day 7 was ~480−700.
Range of effective dose or exposure	In patients with nAMD, DME, and DR, higher faricimab vitreous exposure and longer vitreous $t_{1/2}$ was associated with longer Ang-2 and VEGF-A duration of suppression. Following intravitreal administration, no apparent suppression of free VEGF-A and Ang-2 was observed in plasma. A flat relationship was identified between BCVA and faricimab vitreous exposure in either nAMD or DME/DR populations and the 6 mg doses provide a broad range of efficacious concentrations. Patients with longer vitreous $t_{1/2}$ have a higher probability of needing less frequent dosing.
Maximally tolerated dose or exposure	Not identified
Dose Proportionality	Faricimab concentrations in plasma at Week 12 were approximately 3-fold higher following administration of faricimab 6 mg Q4W (mean 0.058 μg/mL) compared with 1.5 mg Q4W (0.019 μg/mL) suggesting a dose-proportional increase in exposure. Faricimab doses tested ranged from 0.5 mg to 6 mg (This study used Formulation F03 and not the to-be-marketed formulation). The popPK model was a 3-compartment linear catenary model, which described well the AH and plasma concentration-time data at all doses. This model also described the single and multiple dose AH and plasma data well.

Accumulation	No faricimab accumulation in the ocular or plasma compartments was observed, with steady state reached by the end of the 12 week Q4W initiation dosing period.
Variability (%)*	Aqueous humor C_{max}: 40 – 394% Plasma C_{max}: 44 – 144% Aqueous humor Ang-2: 36 - 134% Aqueous humor VEGF-A: 47 – 270%
Absorption	
Bioavailability	Not determined
Median T_{max} (h)	Median Tmax in Plasma for Steady State dosing of 6mg dose was around 0.33 days in Aqueous Humor and around 2 to 2.5 days in Plasma irrespective of disease (nAMD or DME) or dosing regimen (Q4W, Q8W, Q12W or Q16W)
Distribution	
Volume of Distribution	1.48 L
Plasma Protein Binding	NA
Substrate transporter systems [*in vitro*]	NA
Elimination	
Terminal Elimination half-life (SD)	Vitreous elimination half-life: 7.5 days Plasma half-life: 0.44 days
Effective Elimination half-life	NA
Excretion	
Primary excretion pathways (% dose) ±SD	proteolysis, without recycling, leading to rapid systemic elimination
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	NA
Inhibition/Induction of transporter systems	NA
Immunogenicity	In Phase 3 studies, ADA baseline prevalence was 1.8% in nAMD studies and 0.8% in DME/DR studies. Treatment-emergent ADA incidence was 10.4% in nAMD studies and 8.4% in DME/DR studies, this was consistent with incidence seen in Phase 2 studies.
Impact of Immunogenicity on PK, efficacy, and Safety	Population PK analyses showed that plasma ADA had an effect on vitreous elimination $t_{1/2}$. Patients with detectable ADAs had 30.4% higher ocular elimination rate. As a consequence, ADA positive patients had 23.4% lower ocular exposure at steady state compared with ADA negative patients. Presence of plasma ADA had no effect on the plasma exposure. Given that ADA incidence was low, the impact on ocular exposure was minor, and exposure-response analysis has shown a similar response across the range of vitreous exposure in Phase 3, providing support that that the changes in vitreous exposure in ADA-positive patients are unlikely to be associated with a change in efficacy.

	Furthermore, results showed that there was no apparent difference between ADA-positive and ADA-negative patients in change from baseline BCVA at Week 40, Week 44 and Week 48 in patients with nAMD or change from baseline BCVA at Week 48, Week 52 and Week 56 or proportion of patients with ≥2 steps improvement in Diabetic Retinopathy Severity Scale (DRSS) from baseline to Week 52 in patients with DME and DR. Based on all available data, no meaningful impact of ADA was observed on efficacy and on overall safety in patients with nAMD and DME/DR. Further details on immunogenicity and its impact on PK, efficacy, and safety are summarized in Section 4.3.
Pharmacodynamics	Following intravitreal administration of faricimab at a dose of 6 mg, a rapid and sustained suppression of free Ang-2 and VEGF-A in AH was observed. No apparent suppression of Ang-2 or VEGF-A was observed in plasma.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

PK and PD samples were collected in nine clinical studies in patients with nAMD and DME/DR. The Applicant further conducted population PK and exposure-response modeling for efficacy and safety to provide further support for the effectiveness of faricimab. In patients with nAMD, higher faricimab vitreous exposure and longer vitreous $t_{1/2}$ was associated with longer Ang-2 and VEGF-A duration of suppression (Figure 48). In patients with DME, Ang-2 and VEGF-A were strongly suppressed, and no appreciable differences were observed with high and low VH exposure following 6 mg Q8W dosing (Figure 50). Following intravitreal administration, no apparent suppression of free VEGF-A and Ang-2 was observed in plasma (see Appendix 4.2). A flat relationship was identified between BCVA and faricimab vitreous exposure in either nAMD or DME/DR populations and the 6 mg dose provide a broad range of efficacious concentrations (Figure 1). Patients with longer vitreous $t_{1/2}$ have a higher probability of needing less frequent dosing. In both nAMD and DME/DR populations, the percentage of patients with intraocular inflammation (IOI) was low, and higher vitreous faricimab concentrations were not associated with higher rate of IOI (Figure 54 and Figure 55).

These efficacy and safety data from the pivotal studies along with the exposure-response modeling results provide support for the effectiveness of faricimab in patients with nAMD, DME, and DR (refer to clinical/statistical review for the efficacy and safety results and Appendix 4.3 for exposure-response modeling results).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 6 mg (0.05 mL) administered Q4W for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to Q16W was appropriate for patients with nAMD, DME, and DR.

6 mg DoseSelection (nAMD, DME, DR): The 6 mg dose was selected based on the results of the Phase 2 studies where doses of 1.5 and 6 mg were tested in patients with nAMD (AVENUE) and in patients with DME and DR (BOULEVARD). In both populations, the 6 mg dose was as well tolerated as the lower dose (1.5 mg) and resulted in approximately 3 to 4 times higher faricimab concentrations in aqueous humor, with a safety profile consistent with monthly ranibizumab (Figure 7, Figure 11). Based on the dose-proportional ocular PK of faricimab and its mechanism of action (inhibition of ocular soluble Ang-2 and VEGF-A), intravitreal administration of a 6 mg dose is expected to maintain a given minimal pharmacologically active concentration for a longer period than a 1.5 mg dose. This formed the rationale for the selection of the 6 mg dose for the Phase 3 studies in patients with nAMD and DME/DR. The proposed does of 6 mg is further supported by Phase 3 exposure-PD data showing that higher faricimab vitreous exposure resulted in longer duration of aqueous Ang-2 and VEGF-A suppression. The combined evidence from the Phase 2 and Phase 3 studies in nAMD and DME indicated that the proposed 6 mg faricimab dose delivers comparable efficacy to approved anti-VEGF treatments (ranibizumab and aflibercept), but more importantly, has shown potential to be given at significantly less-frequent treatment intervals.

The benefit of faricimab was coupled with a favorable safety profile. Exposure-safety analysis from the Phase 3 demonstrated that higher vitreous faricimab concentrations were not associated with higher rate of IOI, supporting the 6 mg dose and dosing regimen (Figure 54 and Figure 55).

Dosing Frequency Selection (nAMD): Phase 2 studies assessed several dosing regimens of 6 mg faricimab, Q4W and Q8W for 36 weeks (AVENUE) and Q12W and Q16W for 52 weeks (STAIRWAY). The Phase 3 studies, TENAYA and LUCERNE, assessed 6 mg faricimab at Q16W, Q12W and Q8W dosing regimens after 4 monthly initiation doses. The dosing regimens tested shown comparable safety and efficacy versus ranibizumab Q4W in the Phase 2 and aflibercept Q8W in the Phase 3 studies. The combined evidence from Phase 2 and Phase 3 studies showed that a minimum of four Q4W faricimab initiation doses resulted in almost complete suppression of Ang-2 and VEGF-A which was maintained throughout the initiation phase (Figure 17, Figure 18, Figure 21, Figure 22). This was accompanied by a robust reduction in CST and gain in BCVA that could be maintained even with extension of the treatment interval in a significant proportion of patients. The primary analysis results from Phase 3 studies TENAYA/LUCERNE showed non-inferiority of the faricimab up to Q16W arm to the aflibercept Q8W arm, which supported the suitability of extended faricimab dosing regimens based on disease activity after four monthly initiation doses (see clinical/statistical review for more details).

The safety and efficacy of faricimab 6 mg Q4W was comparable to both the faricimab 6 mg Q8W regimen and the active comparator ranibizumab Q4W regimen tested in the Phase 2 AVENUE study. The steady state vitreous exposure of faricimab Q4W in AVENUE was comparable to the steady state exposure reached after the monthly initiation faricimab doses in the Phase 3 TENAYA

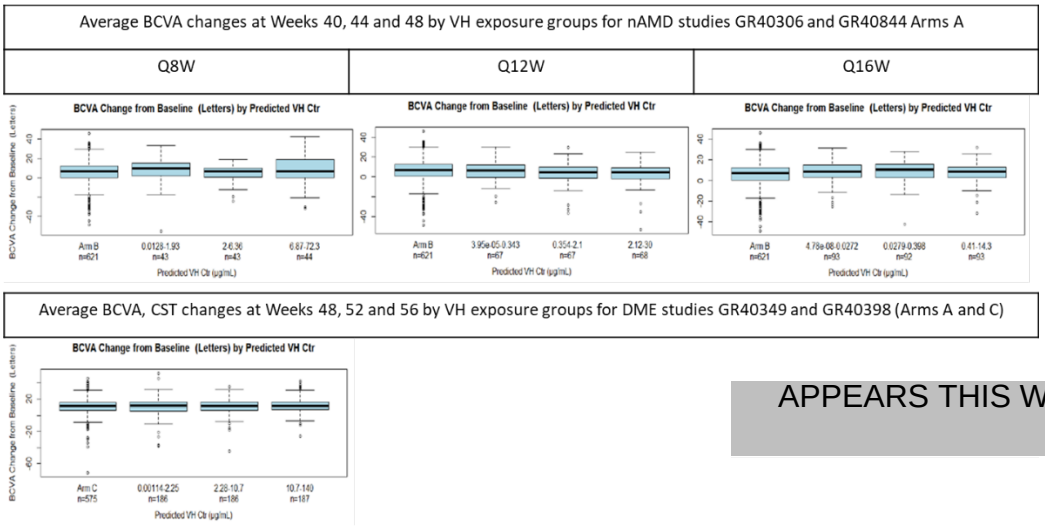
and LUCERNE studies. Population PK analysis showed that the maximum vitreous faricimab concentrations are similar for a Q4W and Q8W dosing regimen and no faricimab accumulation occurs in vitreous, aqueous or plasma. Exposure-safety analysis showed that higher vitreous faricimab concentrations was not associated with higher rate of IOI and the safety profile of faricimab was consistent between the Phase 2 and 3 studies (Figure 54 and Figure 55). Therefore, the AVENUE data and exposure-safety analysis supported a positive benefit-risk balance for nAMD patients who may need to be dosed as frequently as every 4 weeks.

Dosing Frequency Selection (DME and DR): The Phase 2 BOULEVARD study assessed the Q4W dosing regimen of 6 and 1.5 mg faricimab with an observational period following the 20-week treatment phase in order to assess the duration of effect up to week 36. Clinical evidence of durability of the 6 mg faricimab dose (based on disease re-activation during the off-treatment period) supported less frequent dosing requirements for a high proportion of patients. The Phase 3 studies, YOSEMITE and RHINE, assessed 6 mg faricimab on a fixed Q8W regimen and on an up to Q16W adjustable dosing (PTI) regimen. All of the faricimab regimens showed comparable safety and efficacy versus ranibizumab Q4W in the Phase 2 and aflibercept Q8W in the Phase 3 studies (see clinical/statistical review).
The combined evidence from Phase 2 and 3 have shown that a minimum of four Q4W faricimab initiation doses resulted in almost complete suppression of Ang-2 and VEGF-A, which was maintained throughout the initiation phase (Figure 25, Figure 26, Figure 29, Figure 30), robust reduction in CST, and gain in BCVA, with the potential to subsequently extend the treatment interval in a significant proportion of patients.

Results from Phase 3 studies YOSEMITE and RHINE showed non-inferiority of both faricimab treatment arms to aflibercept Q8W arm. At Week 52, 51.9%, 20.5%, 15.5% and 12.1% of patients in the DME and DR population in the PTI arm were on faricimab Q16W, Q12W, Q8W and Q4W dosing regimens, respectively. With over 70% of patients on ≥ Q12W dosing visual outcomes for patients treated with faricimab were comparable with those achieved with aflibercept dosed every 8 weeks (see clinical/statistical review for further details). These data supported a faricimab dosing interval of up to every 16 weeks.

Across indications (nAMD, DME, and DR), the probability of requiring a more frequent dosing regimen decreased with longer vitreous half-life, suggesting that faricimab vitreous clearance is one of the factors contributing to the dosing regimen needed for control of disease activity. Other factors such as baseline PEDT in nAMD, baseline CST, cataract surgery or previously treatment in DME may contribute to the selection of the dosing regimen. Shorter dosing interval of faricimab could increase the vitreous exposures. While for each dosing frequency in nAMD, DME, and DR, change in BCVA and other efficacy endpoints were similar across the ranges of faricimab exposure, suggesting that each dosing regimen provided exposure at the top of the concentration-response (Figure 1). Although incidence rate of IOI was low and did not increase with faricimab VH exposure, slightly higher incidence rate of IOI was observed in patients with more frequent dosing in nAMD studies. Overall, the proposed dosing regimen for faricimab is acceptable. While the necessity of shorter dosing interval for patients is inconclusive due to the relative flat E-R relationship for efficacy and safety.

Figure 1. BCVA changes by VH exposure groups for nAMD and DME studies.



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Source: PK and ER of Faricimab, Report # 1105763, Page 254-258, Figure 158-162, Page 283, Figure 187.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Overall, the treatment is response guided based on the assessment of disease activity after the first four monthly treatment. An alternate dosing regimen is not needed. The intended site of faricimab delivery and action is the eye; therefore, the extent of systemic exposure does not relate with its efficacy.

Based on the population PK analyses, the Applicant did not identify any covariate with a clinically meaningful impact on the plasma or ocular exposure of faricimab (See Appendix 4.3.1). Faricimab is eliminated through proteolytic catabolism; therefore, the potential effect of renal and hepatic impairment was assessed through population PK analysis only.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The drug product is a humanized bispecific immunoglobulin G1 (IgG1) antibody to be administered as an intravitreal injection; therefore, the issue of a food-drug or drug-drug interaction is not relevant. No formal drug-drug interaction studies have been performed. IOP-lowering drugs did not have any effect on faricimab ocular PK.

3.3.5 Was there PK bridging between to-be-marketed product and clinical trial product?

There was a change in drug manufacturing process and formulation during the clinical development program. Drug substance process version v0.1 was used in the Phase 1 studies, v0.2 in the Phase 2 studies, and v0.3 in the Phase 3 studies. In the Phase I Study BP28936, faricimab (60 mg/mL) was administered intravitreally using a 50 μL (0.5 mg, 1.5 mg and 3 mg) or 100 μL (6 mg) volume (Formulation F03). In the Phase 2 studies, faricimab was administered at a concentration of 120 mg/mL (Formulation F04). In the Phase 3 studies, faricimab was administered as a 50 μL intravitreal injection at a concentration of 120 mg/mL (to-be-marketed formulation; Formulation F06).

Faricimab systemic clearance was 18% slower with formulations F03/F04 (used in Phase 1/2 studies) compared with F06 (used in all Phase 3studies), and elimination from AH was 28% slower with F03/F04 compared with the F06 formulation. The formulation effect resulted in 23% lower overall plasma exposure in Phase 3 studies compared with Phase 1 and 2 studies. Results of the population PK covariate analysis did not show any Phase 3 formulation effect on vitreous exposure (Table 26).

There was a change in drug manufacturing process between the drug product used in Phase 3 studies (process version v0.3) and the commercial drug product (process version v1.0). Both the process v0.3 and v1.0 shared the same cell bank, manufacturing scale, drug substance formulation and manufacturing site. The process changes included minor changes to improve process robustness and the drug product manufacturing sites. An analytical comparability assessment was performed on v0.3-derived and v1.0-derived drug product batches to account for changes between the development drug product process and the drug product proposed commercial process (v1.0-derived). The analytical comparability assessment results support the comparability between the materials manufactured from these two processes (refer to CMC review for further details).

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods were developed for quantification of faricimab (PK assessments), Ang-2, and VEGF-A concentrations (both pharmacodynamic [PD] assessments) in aqueous humor (AH) and plasma, and ADAs in plasma. A summary of assays used in clinical studies in this program is provided in Table 5.

The concentration of free faricimab in AH in clinical studies was measured using a colorimetric quantitative ELISA method. For Phase 1 and Phase 2 clinical studies, this method was considered qualified (Method Qualification #1, 1062732). For Phase 3 studies, the same assay method was used and underwent a complete validation (Method Validation #2, 1106459); with the acceptance criteria for back-calculated concentrations of the calibration standards tightening from 30% for the Phase 1 and 2 studies to 20% for Phase 3 studies and testing of selectivity and target interference. The method validation is summarized in Table 6. The concentration of free faricimab in Phase 1, 2 and 3 clinical studies was determined in K3EDTA plasma using a validated colorimetric quantitative ELISA method. A summary of the method is provided in Table 7 below.

Table 5: Summary of Bioanalytical Methods for the Analysis of Pharmacokinetics, Pharmacodynamics, and Anti-Drug Antibodies in Clinical Studies

Clinical Study [Indication]	Free Faricimab Pharmacokinetics		Faricimab ADAs	Ang-2		Free VEGF	
	AH	Plasma	Plasma	AH	Plasma	AH	Plasma
Phase I							
BP28936 [nAMD]	1062732 [a]	1061938	1061515	1106421 [b] 1107911	free Ang-2: 1066773	X [c]	1065323
JP39844 [nAMD/DME, DR]	NA [d]	1061938	1061515	NA [d]	total Ang-2: 1106189 free Ang-2: 1106189	NA [d]	1065323
Phase II							
AVENUE [nAMD]	1062732 [a]	1061938	1061515	1106421 [b] 1107911	total Ang-2: 1106188, 1106189 free Ang-2: 1106188	1085875	
STAIRWAY [nAMD]	1062732 [a]	1061938	1061515	1106421 [b] 1107911	NA [e]	1085875	NA [e]
BOULEVARD [DME, DR]	1062732 [a]	1061938	1061515	1106421 [b] 1107911	total Ang-2: 1106188, 1106189 free Ang-2: 1106188, 1106189	1085875	1065323
Phase III							
TENAYA [nAMD]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
LUCERNE [nAMD]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
YOSEMITE [DME, DR]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710
RHINE [DME, DR]	1106459 [a]	1061938	1061515	1105680	total Ang-2: 1102300 free Ang-2: 1105351	1085875	1105710

ADA = anti-drug antibody; AH = aqueous humor Ang-2 = angiopoietin-2; DME = diabetic macular edema; DR = diabetic retinopathy; NA = not applicable; nAMD = neovascular age-related macular degeneration; PD =pharmacodynamics; PK = pharmacokinetics; VEGF = vascular endothelial growth factor; X = assay performed using other method (see footnotes).

[a]: The same method was used for all studies; however, for Phase I and II (1062732) this method was considered qualified. For Phase III this method underwent complete validation (1106459).

[b]: Analysis of free Ang-2 in AH (Section 1.4.3.1) and plasma (Section 1.4.3.2) required a pre-treatment step to deplete bound faricimab.

[c]: BP28936 used a commercially available assay (Section 1.4.3.3 and CSR BP28936, Report 1058993, page 2886

[d]: AH sample collection was optional, and no samples were collected in Study JP39844; therefore, PK and PD assessments in AH were not performed.

[e]: Not analyzed per protocol.

Table 6: Validation Summary of Bioanalytical Method Used to Measure Pharmacokinetics of Faricimab in Aqueous Humor

Quality Control Samples:	The observed mean concentrations of at least two-thirds of the run acceptance QC samples (with at least 50% at each of the three concentration levels) must be within ± 20.0% of their nominal concentrations and their precision is ≤ 20.0%. The inter-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the LLOQ and ULOQ), the inter-run precision should not deviate by more than 20.0% (25.0% at the LLOQ and ULOQ), and the total error should be less than or equal to 30.0% (≤ 40.0% at the ULOQ and LLOQ). The intra-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the LLOQ and ULOQ) and the intra-run precision should not deviate by more than 20.0% (25.0% at the LLOQ and ULOQ).	Table 7: Run Acceptance QC Samples Human Aqueous Humor Inter-assay precision results: ≤ 12.5% Inter-assay accuracy results: -10.8% to 1.50% Inter-assay total error results: ≤ 21.5% Intra-assay precision results: ≤ 20.4% Intra-assay accuracy results: -17.4% to 17.5% Intra-assay total error results: ≤ 29.5% Table 8: Precision and Accuracy (Human) Bovine Aqueous Humor Inter-assay precision results: ≤ 10.5% Inter-assay accuracy results: -20.2% to -4.00% Inter-assay total error results: ≤ 28.3% Intra-assay precision results: ≤ 16.4% Intra-assay accuracy results: -27.8% to 4.40% Intra-assay total error results: ≤ 31.3% Intra-assay accuracy did not meet the acceptance criteria within Run 4 and Run 6. However, these two runs are not representative to the rest of the precision and accuracy assessment, since intra-assay accuracy at the LLOQ QC level is acceptable within the other five runs. Table 9: Precision and Accuracy (Bovine)
Limits of Quantitation:	The lower limit of quantitation is defined as the lowest analyte concentration that can be quantitated with acceptable accuracy and precision (± 25.0%). The upper limit of quantitation is defined as the highest analyte concentration that can be quantitated with acceptable accuracy and precision (± 25.0%).	LLOQ = 7.81 ng/mL ULOQ = 500 ng/mL Previously established during (b) (4) qualification # 181046.
Minimum Dilution:	The minimum required dilution (MRD) was predetermined to be 1/100.	For this validation, a 1/100 dilution of human aqueous humor to a final concentration of 1% was employed. This dilution will be used for all QC samples and experimental specimens in future studies.
Matrix Blank:	Mean concentration must be < LLOQ.	There was no significant response observed in the buffer blank, human aqueous humor blank, or bovine aqueous humor blank. For all non-precision and accuracy runs, the buffer blank will be the only blank assessed. Table 3: Blank Results
Calibration Standards:	At least three-quarters of all calibrators (including the LLOQ, ULOQ, and 4 other concentration levels) should have mean back-calculated values that deviate no more than ± 20.0% (± 25.0% at the upper limit of quantitation (ULOQ) and lower limit of quantitation (LLOQ)) from the nominal value at all concentrations with precision ≤ 20.0% (≤ 25.0% at the ULOQ and LLOQ). No two consecutive calibration standard levels between the LLOQ and ULOQ may be masked.	Table 4: Calibration Curve Raw Signals Table 5: Calibration Curve Parameters Table 6: Calibration Curve Back-Calculated Concentrations A representative calibration curve is presented in Figure 1.
Matrix Effects and Selectivity:	The observed mean concentrations of at least two-thirds of the QC samples must be within ± 20.0% (± 25.0% at the LLOQ) of their nominal values with precision ≤ 20.0% (≤ 25.0% at the LLOQ). At least 80% of the individual lots tested must meet the criteria. The observed mean concentrations of the blank matrix must be < LLOQ in at least 80% of the lots tested. The observed mean concentrations of at least two-thirds of the preparation (spike) control samples must be within ± 20.0% (± 25.0% at the LLOQ) of their nominal values with precision ≤ 20.0% (≤ 25.0% at the LLOQ). The observed mean concentrations of the preparation control blank must be < LLOQ.	Matrix effects was evaluated in ten individual lots of human aqueous humor. Eight of the ten spiked individual lots met the acceptance criteria. All ten blank individual lots met the acceptance criteria. Table 10: Matrix Effects
Dilution Integrity and Prozone:	The observed concentrations of at least 80% of the within-range QC samples should not deviate by more than ± 20.0% of the nominal value. Samples diluted above the quantitative range should yield values ALQ.	Prozone was not observed up to a RO6867461 concentration of 100,000 ng/mL. Maximum validated dilution factor = 1/242,000 (1/24,200,000 overall dilution which includes MRD) Table 11: Dilution Integrity
Interference:	The observed concentrations of at least two-thirds of the QC samples must be within ± 25.0% of their nominal values with precision ≤ 20.0%. Concentrations of interference drugs tested: • 0.00, 0.100, 1.00, 5.00, 10.0, 50.0, 100, 500, and 1000 ng/mL recombinant human VEGF 165 • 0.00, 0.100, 1.00, 5.00, 10.0, 50.0, 100, 500, and 1000 ng/mL recombinant human angiopoietin-2 • 0.00, 0.100, 1.00, 10.0, 100, 1000, and 10,000 ng/mL Aflibercept	No interference was observed in the QC samples with up to 1000 ng/mL recombinant human VEGF 165. No interference was observed in the QC samples with up to 1000 ng/mL recombinant human angiopoietin-2. No interference was observed in the QC samples with up to 10,000 ng/mL Aflibercept (Eylea). Table 12: Interference (Recombinant Human VEGF 165) Table 13: Interference (Recombinant Human Angiopoietin-2) Table 14: Interference (Eylea)

Benchtop Stability:	The overall accuracy at each concentration level should not deviate by more than ± 20.0% from the nominal concentration and the overall precision at each concentration level should not deviate by more than 20.0%.	Human aqueous humor 2 hours at ambient temperature 4 hours on ice Table 15: Benchtop (Ambient) Stability (Human) Table 16: Benchtop (Ice) Stability (Human) Bovine aqueous humor 4 hours at ambient temperature Table 17: Benchtop (Ambient) Stability (Bovine)
Freeze/Thaw Stability:	The overall accuracy at each concentration level should not deviate by more than ± 20.0% from the nominal concentration and the overall precision at each concentration level should not deviate by more than 20.0%.	Human aqueous humor Freeze/thaw stability at -70°C was previously established for 3 cycles under (b) (4) qualification job # 181046).
Long Term Stability:	The overall accuracy at each concentration level should not deviate by more than ± 20.0% from the nominal concentration and the overall precision at each concentration level should not deviate by more than 20.0%.	Human aqueous humor Could not be established at -20°C past the previously qualified 7 day timepoint (b) (4) qualification job # 181046). Long term stability at -70°C was previously established for 748 days under (b) (4) job # 183082). Table 18: 101 Day Frozen (-20°C) Stability (Human) Bovine aqueous humor 101 days at -70°C Table 19: 101 Day Frozen (-70°C) Stability (Bovine)
Parallelism:	The precision of each dilution should be ≤ 20.0% and the precision of the mean results of the back-calculated values for the samples in the dilution series that fall within the assay range should be ≤ 30.0%. At least 5 of the 6 samples should meet the acceptance criteria.	Parallelism was not assessed during validation as per (b) (4) Validation Plan # 187421 but will be performed upon availability of incurred samples during sample analysis. The reportable result will be determined as per SOP BC15 and the data from this assessment may be included in an addendum to this validation report.

Table 7: Validation Summary of Bioanalytical Method Used to Measure Pharmacokinetics of Faricimab in Plasma

Validation Parameter	Validation Result
Validated calibration range	0.400 ng/mL to 50.0 ng/mL (concentration in plasma)
Validated quantifiable range	0.800 ng/mL to 50.0 ng/mL (concentration in plasma)
Lower limit of quantitation	0.800 ng/mL (concentration in plasma)
Upper limit of quantitation	50.0 ng/mL (concentration in plasma)
Assay precision	Intra-assay precision: 2.99% to 8.44% Inter-assay precision: 2.75% to 6.10%
Assay accuracy	Intra-assay accuracy: -7.47% to 6.50% Inter-assay accuracy: -4.20% to 3.00%
Selectivity	Assay signals in all 10 tested individual lots of normal human plasma were below the LLOQ
Selectivity in hemolyzed and lipemic matrix	Assay signals in normal EDTA human plasma supplemented with 0%, 2.5%, or 5% hemolysate were below the LLOQ. Assay signals in 2 individual lots of normal human plasma supplemented with intralipid IV were below the LLOQ.
Mean recovery of RO6867461 (2.00 ng/mL and 37.5 ng/mL) from 10 individual human EDTA plasma samples	All 10 tested individual lots of normal EDTA human plasma met the acceptance criteria
Dilution linearity	Maximum validated dilution factor: 1,600,000
Prozone	The absence of a hook effect was demonstrated
Interference	500 ng/mL and higher of VEGF 165 interfered with the quantification of RO6867461. Up to 1000 ng/mL of Angiopoietin-2 did not interfere with the quantification of RO6867461. 250 ng/mL and higher of mAb<Id>VEGF>>m-2.45.51-IgG interfered with the quantification of RO6867461. 50.0 ng/mL and higher of mAb<Id-mAb<Ang2>>M-2.6.81-IgG interfered with the quantification of RO6867461.
Bench top stability	at least 24 hours at room temperature
Freeze-thaw stability	at least 5 cycles at -70°C
Long term frozen stability	at least 7 days at -20°C and -70°C

Assessment of the immunogenic potential of a therapeutic monoclonal antibody (MAb) requires detection, specificity confirmation and titration of ADAs in appropriate assays. The ADA assay strategy used a three-tiered approach. Firstly, K3EDTA plasma samples taken from patients during clinical studies were screened. ADA positive screened samples were further analyzed by competitive binding with faricimab to confirm the positive response to be specific for faricimab. Samples which were confirmed ADA positive were then further diluted to obtain a value in titer units. Immunogenicity against faricimab in all clinical studies was determined in K3EDTA plasma using a validated ELISA method (1061515). A summary of the method is provided in Table 8.

In Phase 3 studies, the concentration of free Ang-2 in AH was determined with a validated bead-based immunoassay on the Single Molecule Array (SIMOA) immunoassay platform (1105680). A summary of the method is provided in Table 9.

For Phase 3, the concentration of total and free Ang-2 was determined in K3EDTA plasma using validated quantitative Elecsys Electrochemiluminescence (ECL) technology (1102300). The assay is based on the quantitative sandwich Ang-2 binding to monoclonal Ang-2-specific antibodies. summary of the method used in Phase III is provided in Table 10.

In Phase 2 and 3 studies, the concentrations of free VEGF-A were determined in AH samples using a validated bead-based sandwich ELISA on the SIMOA platform (1085875) (Table 11). The assay utilized paramagnetic-microspheres coated with a specific anti-VEGF-A capture antibody, incubated with biotinylated anti-VEGF-A detection antibody after a washing step.

In Phase 3 clinical studies, the assay was based on a SIMOA platform (1105710) (Table 12). The assay is based on capturing VEGF-A with a monoclonal anti-VEGF-A antibody and detection of VEGF-A with polyclonal antibodies against VEGF-A.

Table 8: Validation Summary of Bioanalytical Method Used to Measure Anti-Drug Antibodies to Faricimab

Validation Parameter	Validation Result
Minimum required dilution	predetermined to be 1:10
Positive controls	128 ng/mL (concentration in 100% human plasma (EDTA)) 1.37 ng/mL (concentration in 100% human plasma (EDTA))
Screening cut point	Multiplicative cut point factor of 2.00
Confirmatory assay cut point	37.2% (20.0 µg/mL of RO6867461)
Assay precision	Intra-assay precision: ≤ 9.86% Inter-assay precision: 3.05 – 6.82%
Estimated assay sensitivity	0.957 ng/mL (concentration in 100% human plasma (EDTA))
Selectivity	Assay signals in ten out of ten human plasma (EDTA) blank lots tested were below the plate specific cut point. Ten of the ten high and ten of the ten low positive control samples met the acceptance criteria.
Drug tolerance	At 3.13, 6.25, and 12.5 ng/mL of anti-RO6867461 antibodies, addition of 1.00 µg/mL and higher of RO6867461 resulted in negative signals, indicating interference. At 50.0 ng/mL of anti-RO6867461 antibodies, addition of 10.0 µg/mL and higher of RO6867461 resulted in a negative signal, indicating interference. At 200 ng/mL and 400 ng/mL of anti-RO6867461 antibodies, addition of 100 µg/mL of RO6867461 resulted in negative signals, indicating interference.
Drug tolerance factor	35.0
Prozone effect	No prozone effect detected for anti-drug antibody concentrations of up to 292,500 ng/mL of mAb<Id<Ang2>>M-2.6.81-IgG and 267,500 ng/mL of mAb<Id<VEGF>>M-2.45.51-IgG.
Stability	Positive control samples at 1.37 ng/mL and 128 ng/mL in 100% human plasma were stable at room temperature for at least twenty-four hours, stable for up to at least five freeze/thaw cycles, and stable at -20°C and -70°C for at least twelve days.

Table 9: Validation Summary of Bioanalytical Method Used to Measure Free Ang-2 in Aqueous Humor (Phase 3 Studies)

Analyte	Free Angiopoietin-2
Analytical Method at CRO	MD056 - Methodenbeschreibung Simoa- immunoassay, Rev. 02
Method	The applied analytical SIMOA method for quantification of Angiopoietin-2 in human aqueous humor requires the

	depletion (sample pre-treatment) of the endogenous ANG- 2 bound to Faricimab (RO6867461), because the applied assay is not a free ANG-2 assay with respect to Faricimab. This is done by incubation of the samples with paramagnetic beads coated with anti-idiotypic antibody to the anti-VEGF binding part of Faricimab prior to the analysis of the remaining free ANG-2. In the subsequent analysis only the remaining free ANG-2 portion in quantified using a SIMOA sandwich immunoassay. The assay is processed following SOP MD056A028.
Validation Period	Analytical runs: 17-Sep-2020 to 03-Oct-2020 (core validation)
Reference Standard	Recombinant Angiopoietin-2, (b) (4)
Critical Reagents	mAb<Ang2>M-2.36.68-IgG (Capture Antibody) Anti-human ANG-2 SIMOA Conjugated Beads mAb<Ang2>M-2.47.70-IgG-Bi (Detection Antibody) Angiopoietin-2 Protein (Calibrator) RO6867461 (Faricimab) Drug Aflibercept Drug mAb<Id<VEGF>>M-2.45.51 (Anti-Idiotypic Antibody to RO6867461) Anti-Idiotypic Antibody to RO6867461 coated Beads Individual or Pooled Human Serum or Plasma Human Aqueous Humor
Biological Matrix	Human Aqueous Humor
Analytical Run	Pass rate for validation runs: 8/14
Calibration Curve Model	4-PL, weighted by $1/Y^2$
Calibration Curve Range	4.04 pg/mL to 1750 pg/mL (concentration in 100 % human aqueous humor)
Sensitivity = Lower Limit of Quantitation (LLOQ)	4.04 pg/mL (concentration in 100 % human aqueous humor)
Upper Limit of Quantitation (ULOQ)	1750 ng/mL (concentration in 100 % human aqueous humor)
Minimal Required Dilution (MRD)	1:8.75
Sample Volume	20 µL are needed for one duplicate determination at MRD
Assay Precision	Intra-assay precision: 3.4 % to 8.3 % Inter-assay precision: 4.3 % to 9.3 %
Assay Accuracy	Intra-assay accuracy: -5.8 % to 14.9 % Inter-assay accuracy: -6.4 % to 12.2 %
Spike-in Recovery	Spike-in recovery with recombinant standard protein failed acceptance criteria
Interference with Faricimab and Aflibercept	Target engagement was observed with Faricimab starting at Faricimab concentrations between 0.22 and 2 µg/ml (1.51 and 13.7 nM). No interference with

	Aflibercept was detected for Aflibercept concentrations up to 540 µg/mL (4700 nM).
Parallelism	Maximum validated dilution factor: 2 (MRD is not included)
Prozone	No hook effect (tested until 65-fold ULOQ)
Bench Top Stability	at least 4 hours at RT
Freeze-Thaw Stability	at least 3 cycles DFZ
Long Term Stability	Will be amended once performed. Data from Roche Penzberg show a long term stability of ANG-2 in native pools of human aqueous humor of at least 17 month when stored at -80°C.
QC Storage and Handling Conditions	PQC (pretreatment quality control sample) sample was prepared 14-Aug-2020. Other QC samples were prepared 08-Sep-2020. All QC samples were aliquoted for single use and stored in DFZ. AH samples included in A&P runs were obtained from commercial sources, aliquoted and stored in DFZ.
Dilutional Linearity	Won`t be performed as the spike-in recovery experiment with recombinant ANG-2 failed.
Special Issues	Spike-in recovery failed, but as parallelism showed that analyte can be diluted up to 1:2 (without considering MRD), selectivity of endogenous ANG-2 is proven despite the failed spike-in recovery. Allowed final dilution factors (incl. MRD) for analysis of clinical samples are 8.75 to 17.5 based on parallelism experiments.

Table 10: Validation Summary of Bioanalytical Method Used to Measure Total and Free Ang-2 in Plasma

Validation parameter	Validation result	Validation criteria	Criteria met
Dilution buffer effect	Sample Dilution in 1x PBS compared to Universal Diluent: ACC: 103.5 % to 104.0 % CV: 2.5 % to 5.8 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Intra-assay precision and accuracy	ACC: 96.3 % to 111.1 % CV: 4.9 % to 5.7 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Inter-assay precision and accuracy	ACC: 85.2 % to 117.2 % CV: 1.6 % and 14.0 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Selectivity			
Hemolysis	ACC: 96.2 % to 97.8 % CV: 4.2 % to 6.2 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Lipemia	ACC: 102.3 % and 102.5 % CV: 2.5 % to 7.2 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Lot comparison of magnetic Sepharose beads	ACC: 96.3 % to 104.5 % CV: 1.3 % to 6.2 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Lot comparison of Mab<ID<VEGF>M-2.45.51-IgG-Bi Capture Antibody	ACC: 95.6 % to 98.1 % CV: 4.7 % to 5.4 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Stability of free ANG-2 in pre-treated samples:			
for 24 h at 4 °C	ACC: 103.1 % to 104.2 % CV: 0.8 % to 12.8 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
for 24 h at RT	ACC: 102.5 % to 109.2 % CV: 1.0 % to 3.3 %	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
Freeze-thaw stability	ACC: 98.6 % to 107.3 % CV: 1.5 % to 9.4 % for up to 5 Freeze/Thaw Cycles	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**
mid-term stability at ≤-65°C	ACC: 95.1 % to 107.5 % CV: 1.9 % to 13.0 % for up to two months	**ACC 70.0 % to 130.0 %** **CV ≤ 30.0 %**	**Yes**

Table 11: Validation Summary of Bioanalytical Method Used to Measure Free VEGF in Aqueous Humor (Phase 2 and 3 Studies)

Validation Parameter	Validation Result
Validated calibration range	0.122 pg/mL to 400 pg/mL (concentration in assay) 1.46 pg/mL to 4800 pg/mL (full matrix concentration[1])
Validated quantifiable range	0.122 pg/mL to 400 pg/mL (concentration in assay) 1.46 pg/mL to 4800 pg/mL (full matrix concentration[1])
Lower limit of quantitation	0.122 pg/mL (concentration in assay) 1.46 pg/mL (full matrix concentration[1])
Upper limit of quantitation	400 pg/mL (concentration in assay) 4800 pg/mL (full matrix concentration[1])
Lower limit of detection	0.091 pg/mL (concentration in assay) 1.092 pg/mL (full matrix concentration[1])
Assay precision	Intra-assay precision: 2.1 % to 15.8 % Inter-assay precision: 12.2 % to 23.8 %
Parallelism	Minimal required dilution = 12
Prozone	N/A
Bench top stability	at least 4 hours at room temperature
Freeze-thaw stability	Given for at least 4 cycles at -80°C at full matrix concentration levels of approx. 1.60 and 780 pg/mL, stability evaluation at -20°C ongoing
Long term frozen stability	Evaluated temperature and storage time: at -20 °C for 1 and 3 month at -80 °C for 1, 3, 6 and 12 month Evaluation ongoing, will be reported in an amendment to this report

Table 12: Validation Summary of Bioanalytical Method Used to Measure Free VEGF-A in Plasma (Phase 3)

Validation Parameter	Validation Result
Calibration Curve Range (Section 5.1, Table 3, Table 4)	3.66 pg/mL to 7500 pg/mL
Sensitivity = Lower Limit of Quantitation (LLOQ)	3.66 pg/mL (concentration in 100 % human CTAD plasma)
Upper Limit of Quantitation (ULOQ)	7500 pg/mL (concentration in 100 % human CTAD plasma)
Lower limit of Detection (LOD)	0.979 pg/mL (concentration in 100 % human CTAD plasma)
Minimal Required Dilution (MRD)	1:7.5
Sample Volume	20.0 µL are needed for one duplicate determination.
Assay precision (CV in %) (Section 5.2, Table 5)	Intra-assay precision: 1.0 % to 10.0 % Inter-assay precision: 5.0 % to 17.8 %
Assay accuracy (RE in %) (Section 5.2, Table 5)	Intra-assay accuracy: -5.7 % to 14.8 % Intra-assay accuracy: -1.3 % to 8.0 %
Total Error (TE in %)	Inter-run total error: 6.3 % to 25.8 %
Prozone (Section5.4, Table 10)	No hook effect (tested until 55-fold ULOQ)
Parallelism (Section 5.3, Table 8, Table 9)	Validated dilution factors for endogenous VEGF-A concentrations: 1:7.5 to 1:15.
Spike/Recovery (Section 5.5, Table 11)	Spike/Recovery has been demonstrated in DME samples. (Results of spike/recovery in AMD samples will be amended once performed).
Drug Interference/Target engagement (Section 5.6.1, Table 12)	Tested drugs: RO6867461 (Faricimab), Aflibercept Target engagement was observed for both drugs. The Simoa VEGF-A assay is an assay for detection of free VEGF-A in human CTAD plasma with respect to Faricimab and Aflibercept.
Receptor Interference (Section 5.6.2, Table 13)	Tested receptor: VEGFR1, VEGFR2 VEGFR1: Interference observed. VEGFR2: No interference observed.
Matrix Interference (Section 5.6.3, Table 14)	Tested matrix: Hemolyzed and lipemic CTAD plasma Interference effects were observed in 1 of 2 samples.
Bench Top Stability (Section 5.8.2, Table 16)	at least 4 hours at room temperature
Freeze-Thaw Stability (Section 5.8.3, Table 16)	at least 4 cycles at ≤ -60 °C
Long Term Stability (Section 5.8.4, Table 16)	at least 18 months at ≤ -60 °C (Results of 24 months stability assessment will be amended once performed) at least 3 months at ≤ -15 °C
Special issues	Deviations in Section 6.

Reviewer's comments:

- *Plasma and Aqueous Humor concentrations of Faricimab, Ang-2, and VEGF-A in pivotal studies were determined using a validated assays.*
- *For Faricimab in AH The lower limit of quantification (LLOQ) was 7.81 ng/mL and the upper limit of quantification (ULOQ) was 500 ng/mL defining the quantification range of the assay in 100% human AH. For plasma the LLOQ was 0.800 ng/mL and the ULOQ was 50.0 ng/mL defining the quantification range of the assay in 100% human K3EDTA plasma.*
- *Validation results indicated no matrix effects or selectivity issues in AH samples of healthy subjects. Validation results indicated also indicated no matrix effects or selectivity issues in K3EDTA plasma samples of patients with nAMD and DME/DR, hemolyzed or lipemic K3EDTA human plasma.*
- *Interference experiments with recombinant human Ang-2 revealed that up to 1000 ng/mL Ang-2 did not interfere with the quantification of faricimab. Recombinant VEGF 165 concentration tested up to 1000 ng/mL did not interfere with faricimab analysis in either AH or plasma.*
- *The human PK assay in AH and K3EDTA plasma uses the same assay format allowing comparison of PK results in both matrices.*
- *The method was precise and accurate, and the Method Validation is* ***adequate.***
- *For the validation of the ADA assay,* the confirmatory cut point (CCP) of 24.4% was used in all Phase 3 faricimab studies, whereas the CCP of 37.2% was used in Phase 1 and 2 studies.
- *The ADA detection method was found to be precise and sensitive, and the Method Validation is* ***adequate.*** *The method had a sensitivity of 0.957 ng/mL (original validation) and 1.04 ng/mL of positive control in 100% human plasma.*
- *Validation results For Ang-2 measurement in AH indicated no selectivity issues in AH samples of healthy subjects proven by parallelism tests with endogenous Ang-2. Lower Ang-2 concentrations were measured when faricimab was added to the sample starting at faricimab concentrations between 0.22−2 µg/mL (1.51−13.7 nM).*
- *Validation results indicated faricimab, up to a concentration of 60.5 µg/mL does not interfere with the quantification of Ang-2 in human K3EDTA plasma samples.*
- *In Study BP28936, this method for determining free VEGF-A levels in plasma was validated with a LLOQ of 31.3 pg/mL; however, it was observed that the free VEGF-A levels in clinical study samples were very low and that the LLOQ of the assay was often too high to quantify VEGF-A. Therefore, the initial calibration curve was extended by an additional 1:2 dilution step, which resulted in a concentration of 15.6 pg/mL for the new lowest calibrator and for the new LLOQ used in Studies JP39844, BOULEVARD, and AVENUE. The LLOQ of 15.6 pg/mL and the ULOQ of 1000 pg/mL defined the quantification range of the assay in 100% CTAD plasma in Studies JP39844, BOULEVARD, and AVENUE.*

Overall, bioanalytical method validation and analysis for Faricimab, Ang-2, VEGF-A in both AH and plasma as well as method validation and analysis of ADA samples in plasma are considered acceptable.

4.2 Clinical PK Assessment

4.2.1 Phase 1 Study # BP28936: Phase I multicenter, non-randomized, uncontrolled, open-label, SAD and MAD, parallel study in previously treated patients with CNV secondary to nAMD.

The study was conducted to assess the safety and ocular and plasma pharmacokinetics of faricimab after single and multiple intravitreal doses. The study was divided in two parts; Part A where single ascending doses (SAD) were administered, and Part B, multiple ascending doses (MAD), where three doses were administered at Q4W intervals to 6 patients/dose. Part B was initiated only once the maximum tolerated dose was identified in Part A. In Part A, 3 patients were enrolled at each dose level and the doses evaluated sequentially were 0.5 mg, 1.5 mg, 3 mg, and 6 mg (N=12). In Part B, 6 patients were enrolled at each dose level and the doses evaluated were 3 mg and 6 mg Q4W.

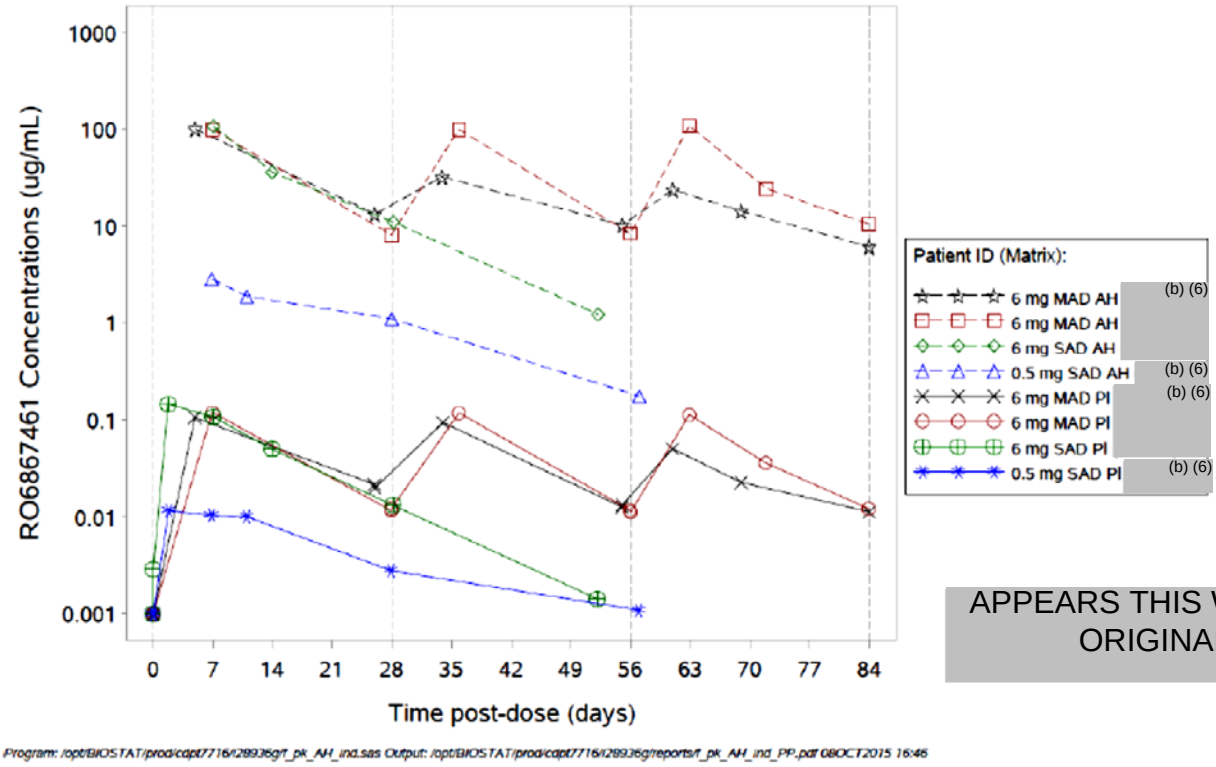
The plasma and aqueous humor free drug concentrations was measured for assessment of faricimab pharmacokinetics. Plasma and aqueous humor (optional) samples were collected for the measurement of VEGF-A and Ang-2 levels as PD biomarkers. Anti-drug antibodies (ADAs) were assessed prior to the start of dosing and up to six times over 12 weeks for the SAD part and up to seven times over 20 weeks for the MAD part. The following pharmacokinetic parameters of faricimab were evaluated: AUC, C_{max}, T_{max}, $t_{1/2.}$

PK/PD/Immunogenicity results

Pharmacokinetics in Aqueous Humor

The individual concentration time profiles for the patients that had evaluable AH and plasma data are presented in Figure 2, individual $t_{1/2}$ in plasma and AH are presented in Table 13. For each patient, the AH concentration time profile declined in parallel to the profile in plasma and is consistent with flip flop kinetics, where the slowest rate, i.e., the elimination from the vitreous, governs the overall elimination of faricimab from the body. AH concentrations were higher in the 3 patients treated with 6 mg, compared with the 1 patient treated with 0.5 mg. The individual $t_{1/2}$ in AH ranged from 6 to 13 days.

Figure 2: Individual Faricimab Plasma and Aqueous Humor Concentration vs. Time Profiles for Patients with Available Aqueous Humor Samples (Study BP28936)



APPEARS THIS WAY ON ORIGINAL

Program: /opt/BIOSTAT/prod/capt7716/r28936g/f_pk_AH_ind.sas Output: /opt/BIOSTAT/prod/capt7716/r28936g/reports/f_pk_AH_ind_PP.pdf 08OCT2015 16:46

AH=aqueous humor; MAD=multiple ascending dose; PI=plasma; SAD=single ascending dose

Source: CSR BP28936, Report 1058993, Figure 9

Table 13: Individual Faricimab Plasma and Aqueous Humor Apparent Terminal t1/2 for Patients with Available Aqueous Humor Samples (Study BP28936)

Patient ID, Part, Dose	$t_{1/2}$ (days) in Plasma	$t_{1/2}$ (days) in Aqueous Humor
(b) (6) SAD, 0.5 mg	15.4	13.4
, SAD, 6.0 mg	7.71	7.61
MAD, 6.0 mg	6.61	6.08
, MAD, 6.0 mg	9.29	8.38

MAD=multiple ascending dose; SAD=single ascending dose; $t_{1/2}$=apparent terminal $t_{1/2}$, 3rd interval used for MAD.

Seven patients consented to the collection of aqueous samples with five enrolled in the SAD part and two in the MAD part. Three patients were considered not evaluable due to loss of sample, patient withdrawal, or lack of evidence of drug administration.

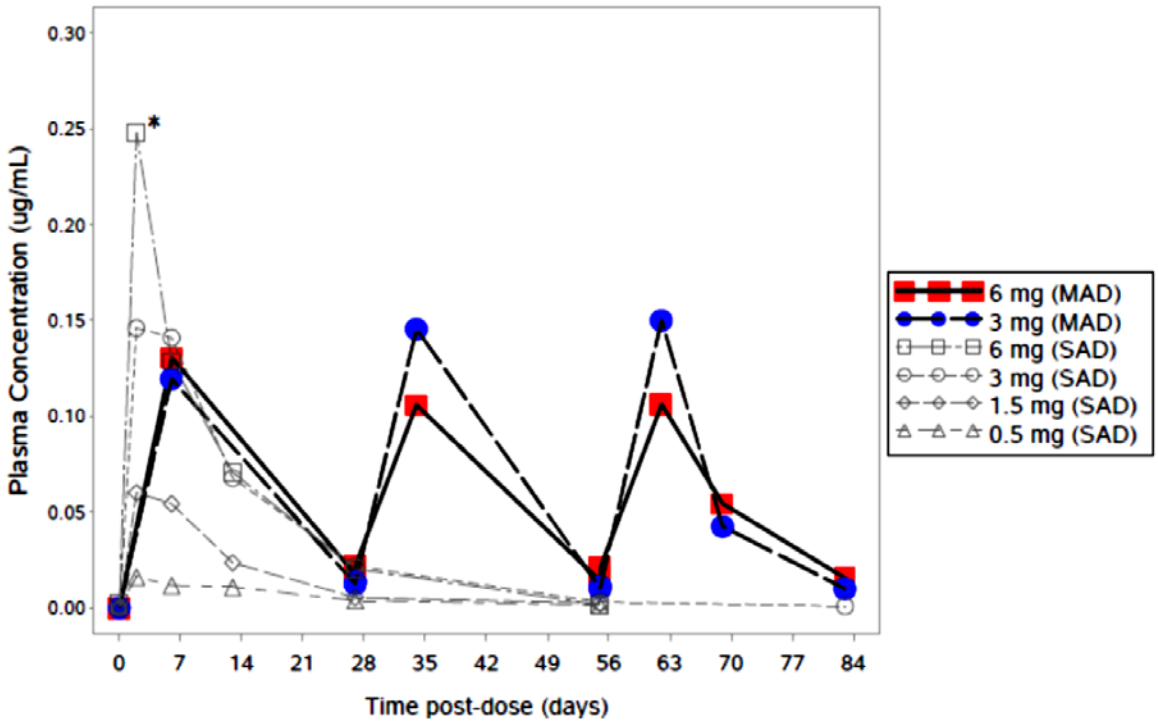
Source: CSR BP28936, Report 1058993, Table 8

Pharmacokinetics in Plasma

Figure 3 shows median plasma faricimab concentration versus time profiles after intravitreal administration of single doses of 0.5 mg to 6 mg faricimab for the SAD part, and multiple doses of 3 mg and 6 mg for the MAD part. PK parameters are reported in Table 14.

Plasma concentrations observed in the MAD part were in the range expected from the 3 mg and 6 mg faricimab dose groups of the SAD part. Based on single dose C_{max} and AUC, there was an approximate dose-proportional increase in faricimab plasma exposure up to 3 mg. There was no apparent increase in systemic exposure for the 6 mg dose group as compared to the 3 mg dose group. Based on C_{max}, plasma faricimab concentrations were >100-fold lower than those in AH. The estimated apparent plasma $t_{1/2}$ ranged from 5−15 days across SAD and MAD. The T_{max} was either Day 3 or Day 7 in the SAD part, independent of dose. Following the first and second administration in the MAD part, only a 1-week post-dose visit was scheduled, where T_{max} was achieved as expected at Week 1 post-dose. Following the third administration, T_{max} was reached at the Day 63 visit, i.e., 1 week following the last administration.

Figure 3: Median Faricimab Plasma Concentration vs. Time Profile for Patients in the Single Ascending Dose and Multiple Ascending Dose Parts (Study BP28936)



MAD = multiple ascending dose; SAD = single ascending dose.

Notes: For the SAD part, median values are shown only when a minimum of two values were available, except for the 6 mg group, where (*) indicates that only data from one patient (# (b) (6)) were available. For the MAD part, time truncated at Day 84 as later timepoints had ≤ 3 measurable concentrations.

Source: CSR BP28936, Report 1058993, Figure 6

Table 14: Summary of Main Plasma Pharmacokinetic Parameters of Faricimab (Study BP28936)

Dose/schedule	N	C_{max} (µg/mL)	AUC (µg • h/mL)	$t_{1/2}$ (days)
0.5 mg SAD	3	0.0162 [0.00746-0.0409]	8.79,10.5 [a]	7.29, 15.4 [a]
1.5 mg SAD	3	0.0600 [0.0316-0.0701]	17.9 [16.4-22.3]	6.02 [5.06-12.6]
3.0 mg SAD	3	0.160 [0.0725-0.171]	51.1 [42.7-65.0]	7.41 [6.16-11.8]
3.0 mg MAD	6	0.152 (34) [0.0725-0.210]	36.5 (23) [24.8-46.3]	5.91 (51) [3.14-10.6]
6.0 mg SAD	2	0.126[b], 0.248 [a]	54.2 [43.6-64.7]	7.24 [6.76-7.71]
6.0 mg MAD	6	0.116 (37) [0.0734-0.176]	35.2 (31) [23.5-50.4]	7.34 (14) [6.50-9.29]

AUC = area under the concentration–time curve; AUC_{inf} = area under the concentration–time curve from Time 0 to infinity; AUC_{tau} = area under the concentration–time curve during one dosing interval (Day 0 to Day 28; C_{max} = maximum concentration observed; MAD = multiple ascending dose; SAD = single ascending dose; $t_{1/2}$ = half-life.

Notes: AUC_{inf} calculated for SAD; AUC_{tau} (0 to Day 28) calculated for MAD.

Median [range] reported for SAD if N > 2, Mean (CV%) [range] of third interval.

[a] individual values for 2 patients.

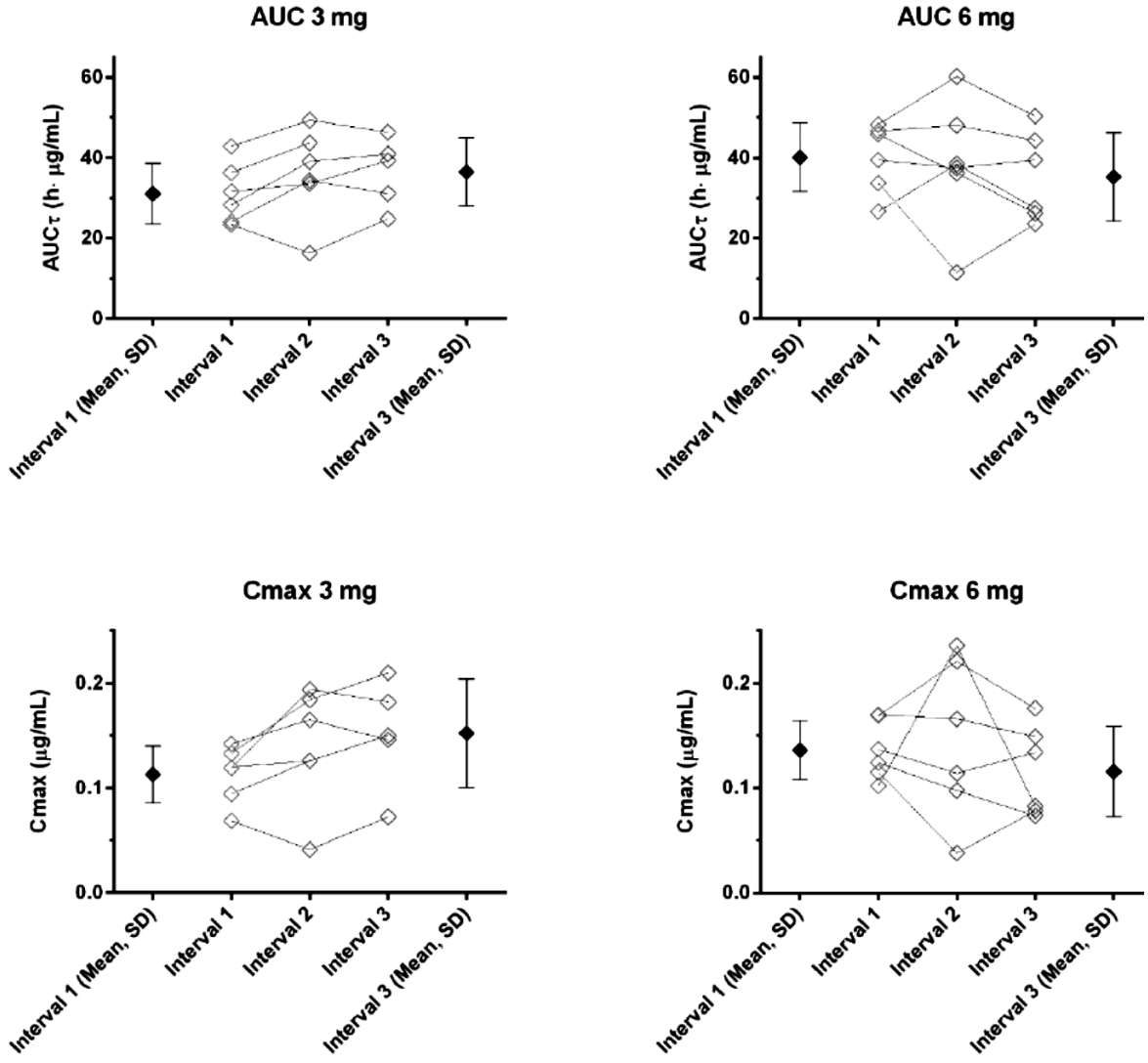
[b] Patient missed the Day 2 sample.

one patient in the SAD 6 mg was excluded because of undetectable plasma drug levels

Source: CSR BP28936, Report 1058993, Table 7

Figure 4 shows the AUCs and C_{max} following multiple administrations of 3 mg and 6 mg faricimab. There was no apparent faricimab accumulation in plasma following multiple faricimab administration, as assessed with AUC_{tau} and C_{max}. These findings were consistent with the predicted mean accumulation ratio of 1.17, based on the AUC_{inf}/AUC_{tau} ratio from the SAD.

Figure 4: Multiple Ascending Dose Part: Mean (SD) of AUCtau and Cmax from the First and Third Dosing Interval and Individual Values for the First, Second and Third Dosing Interval Following 3 and 6 mg Faricimab Administration (Study BP28936)



AUC = area under the concentration–time curve; AUC_{tau} = area under the concentration–time curve during one dosing interval (0 to Day 28); C_{max} = maximum concentration observed; MAD = multiple ascending dose; $t_{1/2}$ = half-life.

Source: CSR BP28936, Report 1058993, Figure 8

Pharmacodynamics in Aqueous Humor

AH PD data were available for 3 patients in the SAD part and 2 patients in the MAD part. Faricimab administration resulted in target engagement i.e., decrease in AH VEGF-A and Ang-2.

Pharmacodynamics in Plasma

There was an apparent minor increase from baseline in free and total Ang-2 concentrations in plasma, in particular at the Week 1 visit following intravitreal administration of faricimab in the SAD and MAD parts. Following multiple dose administration of 3 mg and 6 mg faricimab, there was no apparent pattern for change over time in concentrations of free VEGF-A in plasma.

Immunogenicity

No patients were ADA-positive at baseline and no patients were ADA-positive following faricimab administration.

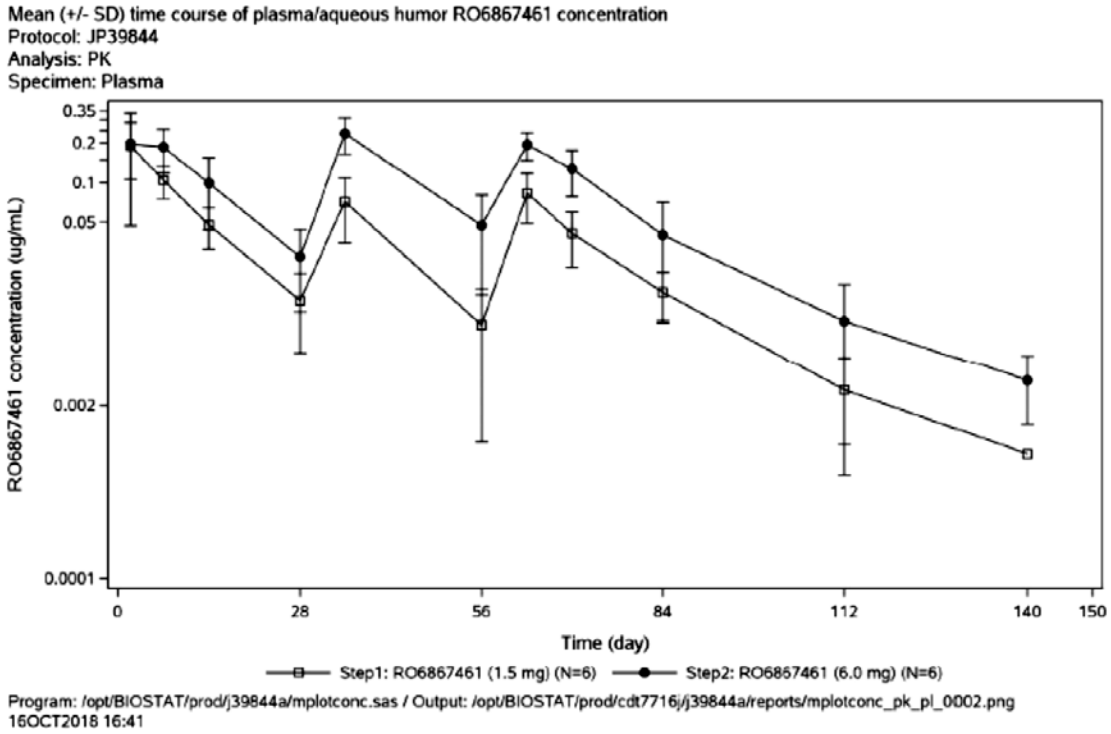
4.2.2 Phase 1 Study # JP39844: A Phase I Study of RO6867461 in Japanese Patients with Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema

Study JP39844 was a Phase I study conducted in Japanese patients with nAMD or DME/DR. This open-label study evaluated the safety, tolerability, PK and PD of multiple intravitreal doses of faricimab in patients with nAMD or DME/DR. Patients were previously treated with anti-VEGF therapy, with the last dose administered ≥ 4 weeks prior to the first faricimab administration. In Step 1, patients (N=6) received 1.5 mg intravitreal faricimab Q4W (for a total of up to three doses). Step 2 was initiated upon demonstration of safety in Step 1 and different patients (N=6) received 6 mg intravitreal faricimab every Q4W (for a total of up to three doses). Plasma samples were collected for measurement of faricimab as well as Ang-2 and VEGF-A, and ADA. AH sample collection was optional in Study JP39844, and no samples were collected; therefore, AH PK and PD assessments were not performed. ADAs were assessed prior to start of dosing and up to Day 141 after faricimab administration.

Figure 5 shows the mean faricimab plasma concentration-time profiles, and the PK parameters are summarized in Table 15.

Faricimab plasma exposure were 1.6 to 3-fold higher following administration of 6 mg faricimab compared with 1.5 mg based on AUC_{tau}. The mean plasma faricimab concentration peaked 2 days after administration with a monophasic elimination with a mean steady-state $t_{1/2}$ of approximately 10 days at both dose levels. Consistent with the observed $t_{1/2}$, the accumulation index was approximately 1, which is similar to the ratio in non-asian patients observed in Study BP28936.

Figure 5: Mean (SD) Time Course of Plasma Faricimab Concentration in Patients Receiving 1.5 mg or 6 mg of Faricimab Q4W (Study JP39844)



Source: CSR JP39844, Report 1106179, Figure 11.4.1-1

Table 15: Study JP39844: Mean (SD) Faricimab Pharmacokinetic Parameters (Study JP39844)

Dose	C_{max} (µg/mL)	T_{max} [a] (day)	AUC [b] (day•µg/mL)	$t_{1/2}$ (day)
Single Dose				
1.5 mg	n = 6 0.196 (0.138)	n = 6 0.90 [1.82–7.89]	n = 5 2.23 (0.883)	n = 5 6.40 (2.48)
6 mg	n = 6 0.225 (0.0745)	n = 6 1.97 [1.88–8.11]	n = 4 3.53 (0.944)	n = 4 8.03 (3.75)
Multiple Dose				
1.5 mg	n = 6 0.0830 (0.0341)	n = 6 6.87 [4.87–7.85]	n = 6 1.03 (0.341)	n = 3 9.92 (2.42)
6 mg	n = 6 0.195 (0.0462)	n = 6 7.05 [1.90–8.89]	n = 6 3.15 (0.936)	n = 4 9.96 (3.25)

AUC = area under the concentration–time curve; $AUC_{0-\infty}$ = area under the concentration–time curve from time 0 to infinity; AUC_{tau} = AUC from time 0 to the end of the dosing period; C_{max} = maximum concentration observed; $t_{1/2}$ = half-life; T_{max} = time to maximum concentration.

[a] T_{max} values given as median [min–max]

[b] $AUC_{0-\infty}$ for single dose, AUC_{tau} for multiple dose

Source: CSR JP39844, Report 1106179, Table 11.4.1-1

Pharmacodynamics in Plasma

At both dose levels, no consistent patterns were observed in plasma VEGF-A concentrations.

Immunogenicity

No subjects were ADA-positive at baseline and no subjects were ADA-positive following faricimab administration.

Studies in nAMD

4.2.3 Phase 2 Study # CR39521 (STAIRWAY): A multicenter, randomized, active comparator controlled, subject and outcome-assessor masked, parallel group (three treatment arms), 52-week study to investigate the efficacy, safety, and pharmacokinetics of faricimab administered at 12- and 16-week intervals in treatment-naive patients with nAMD.

This was a Phase 2 study that evaluated the efficacy, safety, and pharmacokinetics of faricimab at 12- and 16-week intervals in treatment-naive patients with nAMD. Eligible patients were randomized to one of three treatment arms:

- Faricimab Q12W: 6 mg faricimab Q4W by intravitreal injection up to Week 12 (four injections), followed by 6 mg faricimab Q12W up to Week 48 (injections at Weeks 24, 36, and 48; three injections) (N=29)
- Faricimab Q16W: 6 mg faricimab Q4W by intravitreal injection up to Week 12 (4 injections), followed by 6 mg faricimab Q16W up to Week 48 (injections at Weeks 28 and 44; two injections). A protocol-defined assessment of disease activity at Week 24 required patients with active disease to then receive a Q12W dosing interval of 6 mg faricimab for the remainder of the study, with injections commencing at Week 24 and repeated at Weeks 36 and 48 (N=31).
- Ranibizumab Q4W (comparator arm): 0.5 mg ranibizumab Q4W by intravitreal injection for 48 weeks (13 injections) (N=16)

ADAs were assessed at Weeks 16, 24, 28, 44 and up to Week 52.

Pharmacokinetics in Aqueous Humor

Faricimab PK in AH are summarized in Table 16. AH samples were collected for 14 faricimab-treated patients (N=11 for patients receiving 6 mg Q12W and N=3 for patients receiving 6 mg Q16W). Due to the low number of patients in the Q16W arm, the data should be interpreted with caution.

Faricimab concentrations in AH were higher when 6 mg was administered Q12W, compared with Q16W, at 4- 8-, and 12-weeks post-dose. However, for the 12-week post-dose data, 6/14 samples were BLQ, whereas for the 16-week post-dose data, all three available samples were BLQ.

Table 16: Summary of Faricimab Concentrations in Aqueous Humor (Study STAIRWAY)

Visit	Faricimab Q12W	Faricimab Q16W
4-Week Post-dose [a]		
N	8	3
Mean (SD), µg/mL	18.96 (14.91)	2.99 (1.14)
Median, µg/mL	14.35	2.87
8-Week Post-dose [b]		
N	11	3
Mean (SD), µg/mL	4.73 (4.52)	0.09 (0.13)
Median, µg/mL	4.24	0.024
12-Week Post-dose [c]		
N	11	3
Mean (SD), µg/mL	1.14 (1.24)	0.205 (0.0286)
Median, µg/mL	1.01	0.00391

BLQ=below limit of quantification; LLOQ=lower limit of quantification; Q12W=once every 12 weeks.

[a] Corresponding to Week 28 for the Q12W and Week 32 for the Q16W group

[b] Corresponding to Week 32 for the Q12W and Week 36 for the Q16W group

[c] Corresponding to Week 36 for the Q12W and Week 24 for the Q16W group

Values BLQ were imputed with LLOQ/2 (0.00781 µg/mL/2).

Source: t_pk_blq_ah_PK_AH

Pharmacokinetics in Plasma

Faricimab PK in plasma are summarized in Table 17. At Week 16 (i.e., 4 weeks following administration of the fourth Q4W faricimab dose), concentrations in plasma were similar in both groups with mean values of approximately 0.030 µg/mL. After Week 16, patients received faricimab either Q12W or Q16W. For the faricimab Q12W group, 4 weeks after administration of a previous dose, plasma concentrations were >580-fold lower than those in the AH.

Table 17: Summary of Faricimab Pharmacokinetics in Plasma (Study STAIRWAY)

Visit	Faricimab Q12W	Faricimab Q16W
4-Weeks Post fourth Monthly Dose (Week 16)		
N	34	18
Mean (SD), µg/mL	0.0322 (0.0176)	0.0306 (0.0211)
Median, µg/mL	0.0330	0.0301
8-Weeks Post-dose [a]		
N	30	15
Mean (SD), µg/mL	0.0045 (0.00450)	0.00363 (0.00387)
Median, µg/mL	0.00383	0.00203
12-Weeks Post-dose (Week 24)		
N	34	18
Mean (SD), µg/mL	0.00138 (0.00232)	0.00107 (0.00129)
Median, µg/mL	0.00040	0.00040

BLQ=below limit of quantification; LLOQ=lower limit of quantification; Q12W=once every 12 weeks; Q16W=once every 16 weeks.

[a] Corresponding to Week 44 for the Q12W and Week 52 for the Q16W group

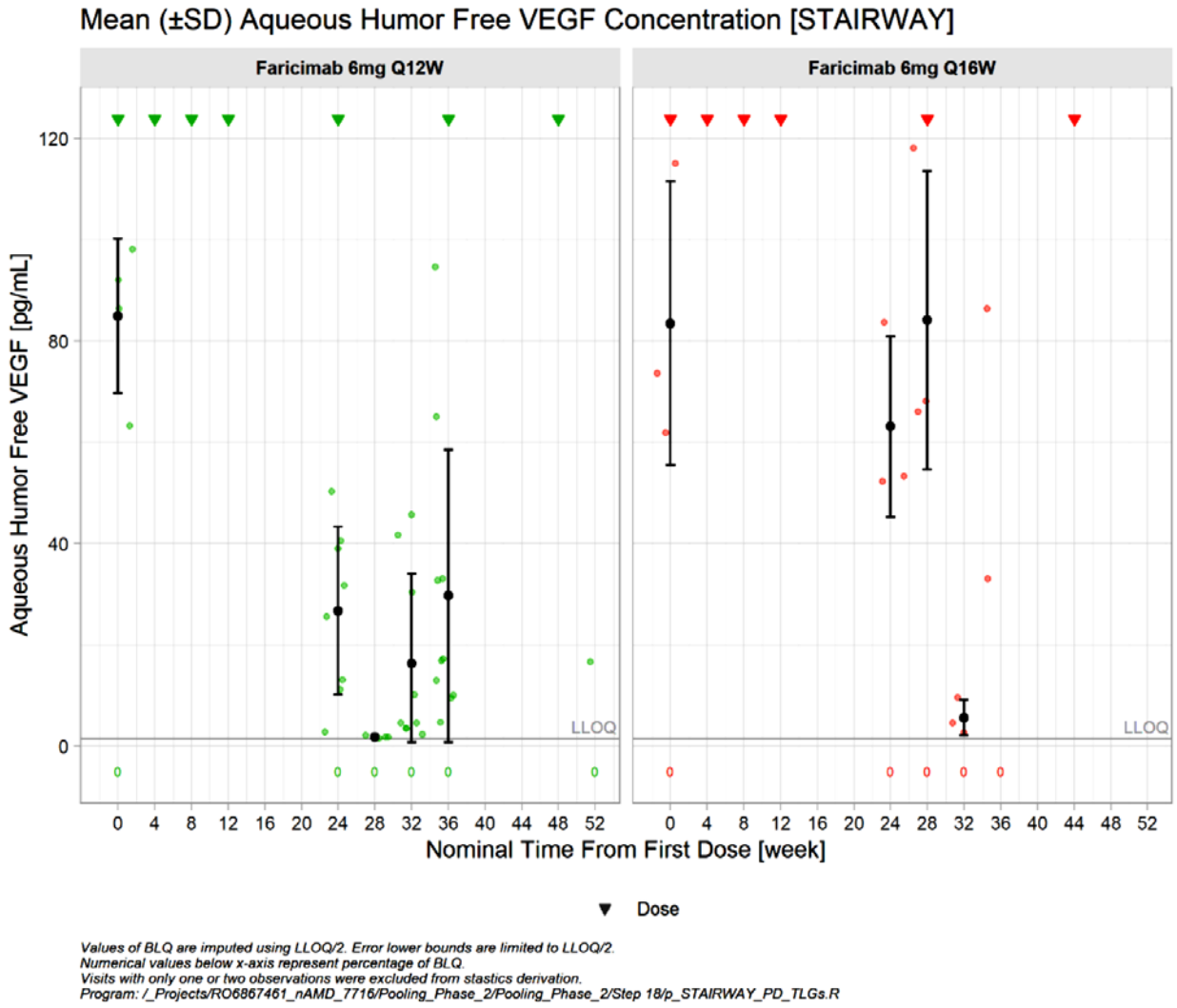
Values BLQ were imputed with LLOQ/2 (LLOQ=0.00781 µg/mL).

Source: t_pk_cb_blq_PK_PL

Pharmacodynamics in Aqueous Humor

AH samples were available for 11 patients in the 6 mg faricimab Q12W arm and 3 patients in the Q16W arm. Therefore, the data from Q16W should be interpreted with caution. The majority of free Ang-2 levels were BLQ at baseline in AH. Mean free VEGF-A concentration-time profiles in AH are shown in Figure 6. Prior to faricimab administration, free mean (SD) AH VEGF-A concentrations were 84.90 (15.25) pg/mL and 83.47 (27.94) pg/mL for the Q12W and Q16W regimen, respectively. Four weeks post-dose, VEGF-A was suppressed to a mean (SD) value of 1.753 (0.233) (Week 28) for Q12W and 5.587 (3.54) pg/mL (Week 32) for Q16W. In the Q12W treatment group, free VEGF-A concentrations in AH were lower than baseline with a mean (SD) of 16.23 (17.83) pg/mL 8 weeks post-dose (Week 32) and a mean (SD) of 29.64 (28.9) pg/mL 12 weeks post-dose (Week 36).

Figure 6: Mean Free VEGF-A Concentration−Time Profiles in Aqueous Humor (Study STAIRWAY)



Values of BLQ are imputed using LLOQ/2. Error lower bounds are limited to LLOQ/2.
Numerical values below x-axis represent percentage of BLQ.
Visits with only one or two observations were excluded from stastics derivation.
Program: /_Projects/RO6867461_nAMD_7716/Pooling_Phase_2/Pooling_Phase_2/Step 18/p_STAIRWAY_PD_TLGs.R

Immunogenicity

No patients were ADA positive prior to faricimab administration. Overall, 6/55 (10.9%) patients had positive antibody titers at any time during the study; 2 patients in the Q12W and 4 in the Q16W group; all 6 were classified as treatment-induced ADA. The onset of ADA response ranged from Week 16 to Week 34. There was no apparent effect of ADA on the systemic pharmacokinetics.

4.2.4 Phase 2 Study # BP29647 (AVENUE): A multicenter, multiple-dose and regimen, randomized, active comparator controlled, double-masked, five-parallel group, 36-week study in patients with nAMD.

This Phase 2 study evaluated the efficacy, safety, pharmacokinetics of faricimab compared to ranibizumab monotherapy in treatment-naïve and anti-VEGF incomplete-responder patients with CNV secondary to nAMD. A total of 273 patients were randomized into five treatment arms and were administered study treatment by intravitreal injection from Day 1 to Week 32 according to the following schedule:

- Ranibizumab 0.5 mg Q4W (N = 68): 0.5 mg ranibizumab Q4W for 32 weeks (nine injections)
- Faricimab 1.5 mg Q4W (N = 46): 1.5 mg faricimab Q4W for 32 weeks (nine injections)
- Faricimab 6 mg Q4W (N = 39): 6 mg faricimab Q4W for 32 weeks (nine injections)
- Faricimab 6 mg Q8W (N = 46): 6 mg faricimab Q4W up to Week 12 (four injections), followed by 6 mg faricimab Q8W (i.e., on Weeks 20 and 28; 2 injections)
- Ranibizumab 0.5 mg Q4W followed by faricimab 6 mg Q4W (N = 64): 0.5 mg ranibizumab Q4W up to Week 8 (three injections), followed by 6 mg faricimab Q4W (six injections)

The primary efficacy outcome measure in the treatment-naive population (for comparison of Arms A, B, C, and D) was the change in BCVA from baseline to Week 36 using the ETDRS-modified charts. The primary efficacy outcome measure in the anti-VEGF−incomplete-responder population was the change in BCVA from Week 12 baseline to Week 36.

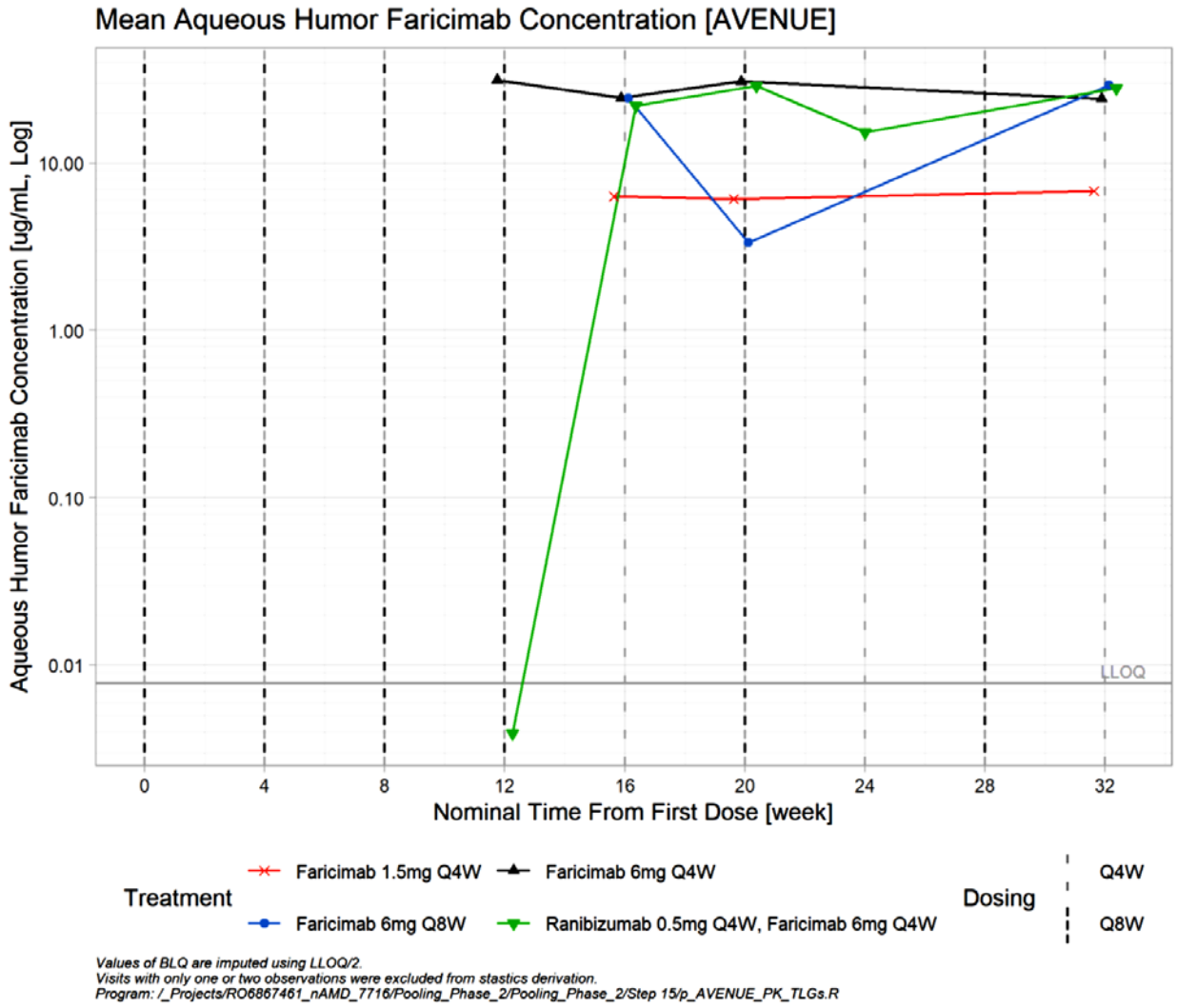
ADAs were assessed prior to the start of dosing and up to Week 36 after faricimab administration.

Pharmacokinetics in Aqueous Humor

AH samples were collected in 10 patients randomized to faricimab 1.5 mg Q4W, 9 patients randomized to faricimab 6 mg Q4W, and 9 patients randomized to faricimab 6 mg Q8W. Mean faricimab concentration-time profiles in AH are presented in Figure 7. Faricimab concentrations in AH were approximately 4-fold higher in the faricimab 6 mg Q4W arm compared with the faricimab 1.5 mg Q4W treatment arm at 4 weeks post-dose. At Week 16, mean (SD) AH faricimab concentrations were 6.33 (6.23) µg/mL and 24.5 (21.4) µg/mL in the faricimab 1.5 mg and 6 mg Q4W treatment arms, respectively. Week 20 values were similar to Week 16.

In patients administered faricimab Q4W until Week 12 followed by administration on Weeks 20 and 28, mean (SD) AH concentration at Week 16 (i.e. 4 weeks after previous dose) was 24.4 (21.4) µg/mL and declined to 3.36 (2.25) µg/mL at Week 20 (i.e. 8 weeks after previous dose).

Figure 7: Mean Faricimab Concentration−Time Profiles in Aqueous Humor (Study AVENUE)



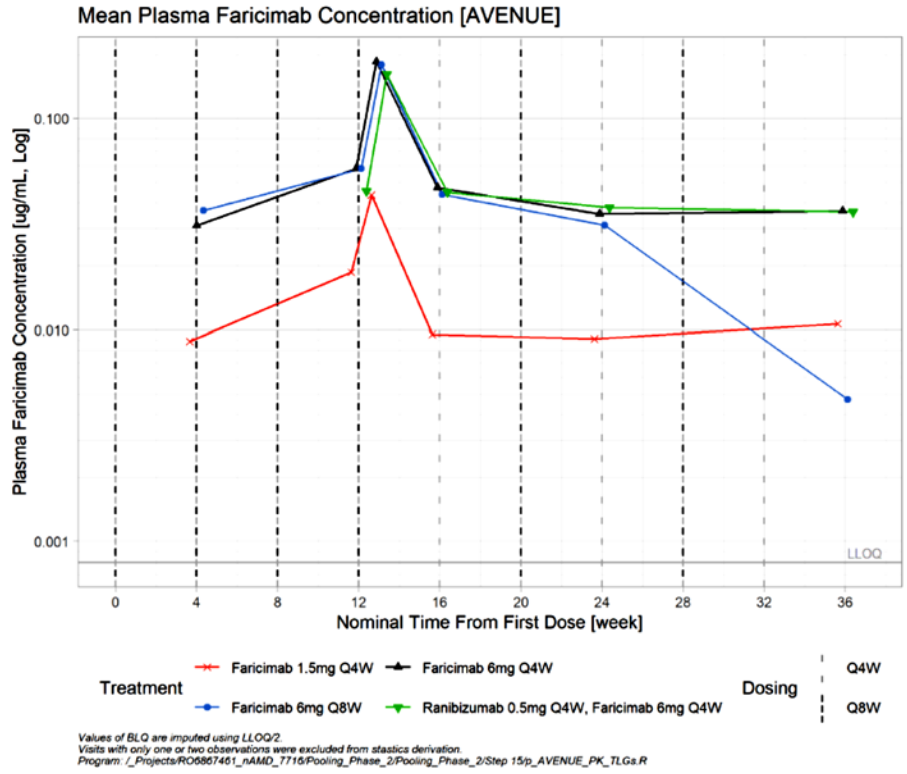
Pharmacokinetics in Plasma

Mean faricimab concentration-time profiles in plasma are presented in Figure 8. Faricimab concentrations in plasma at Week 12 were approximately 3-fold higher following administration of faricimab 6 mg Q4W (mean 0.058 µg/mL) compared with 1.5 mg Q4W (0.019 µg/mL) suggesting a dose-proportional increase in exposure. As expected, faricimab concentrations were similar for both 6 mg groups at Week 12, since they had received the same number of doses at that timepoint with mean of approximately 0.058 µg/mL. From Week 12, faricimab concentrations in plasma were subsequently lower in patients receiving the less frequent Q8W dosing compared with Q4W dosing.

The maximum mean (SD) concentrations were observed at Week 13 (i.e., 1 week following administration of the fourth dose) for the three faricimab dose regimens. These were 0.043 (0.032) µg/mL for the 1.5 mg faricimab Q4W arm, 0.184 (0.102) µg/mL for the 6 mg faricimab Q4W for

32 week arm, and 0.178 (0.120) µg/ml for faricimab 6 mg Q4W followed by Q8W. Eight weeks following administration of the last faricimab dose of 6 mg, mean (SD) plasma concentration was 0.0047 (0.0072) µg/mL. Based on the Week 12 concentrations, plasma concentrations were >400 times lower than those in AH.

Figure 8: Mean (SD) Faricimab Concentration-Time Profiles in Plasma (Study AVENUE)



BLQ=below limit of quantification; LLOQ=lower limit of quantification; Q4W=every 4 weeks; Q8W=every 8 weeks.
Source: t_pk_conc_AP

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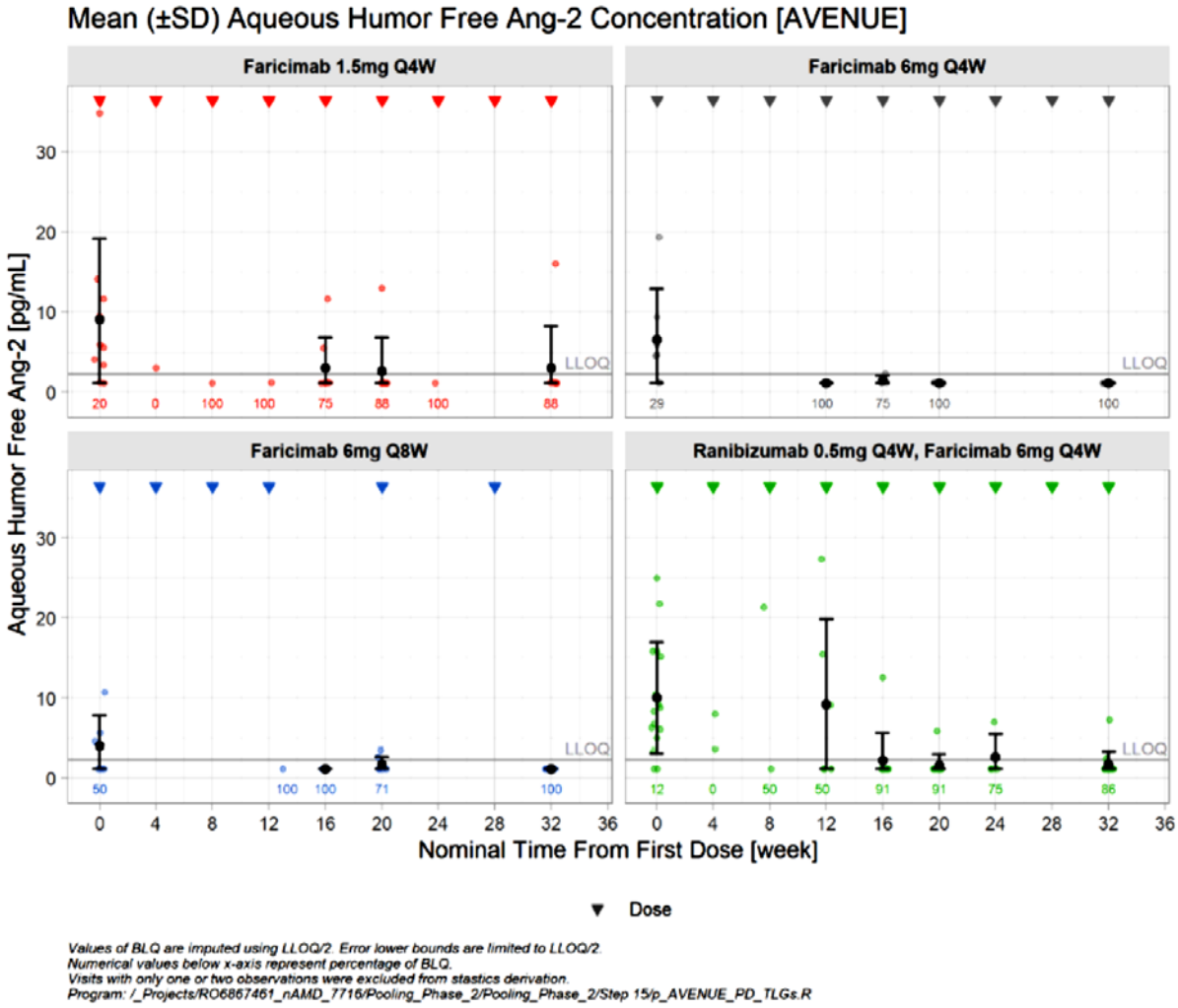
Pharmacodynamics in Aqueous Humor

Figure 9 summarizes mean free Ang-2 concentration-time profiles in AH. At baseline, depending on the dose group, 13%−50% free Ang-2 AH concentrations were BLQ, up to 100% of post-dose concentrations were BLQ. Mean baseline free Ang-2 AH concentrations ranged from 4.04 to 9.99 pg/mL across all four arms where faricimab was administered. At Week 32, free Ang-2 AH concentrations were BLQ or remained lower than at baseline with mean (SD) free AH Ang-2 of 2.98 (5.26) pg/mL and 1.12 (0) pg/mL for 1.5 mg faricimab Q4W and 6 mg faricimab Q4W, respectively, suggesting target suppression for at least 4 weeks, when faricimab was administered Q4W at doses of either 1.5 mg or 6 mg for a total of eight doses. In patients who had first received ranibizumab, concentrations of free Ang-2 in AH remained unchanged during treatment with ranibizumab and declined at Week 16, after switching to faricimab.

Figure 9: Mean Free Ang-2 Concentration−Time Profiles in Aqueous Humor (Study AVENUE)



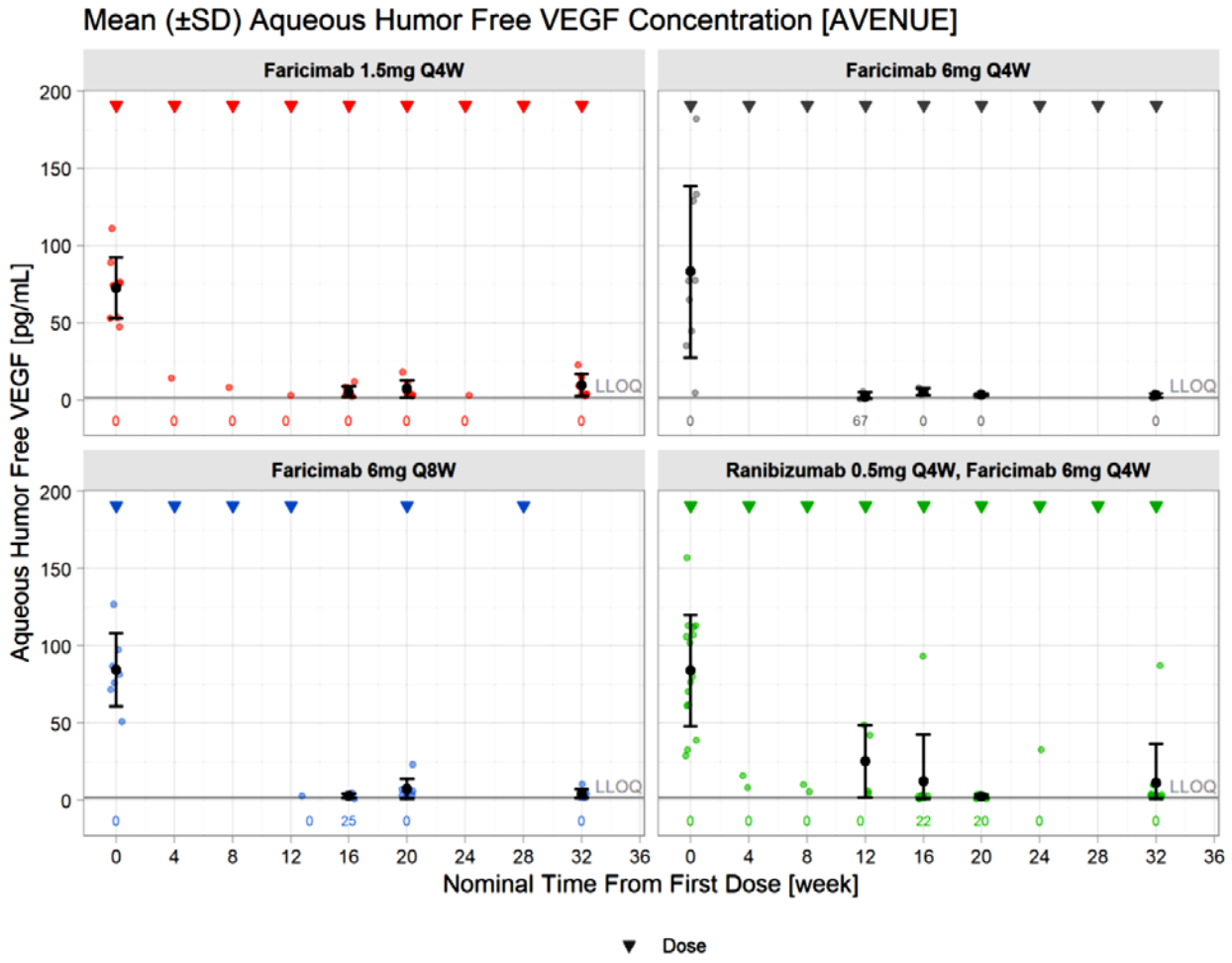
Ang-2 = angiopoietin-2 (protein); BLQ = below limit of quantification; LLOQ = lower limit of quantification; Q4W = every 4 weeks; Q8W = every 8 weeks.

Source: CSR AVENUE, Report 1083912, page 713

Figure 10 summarizes mean free VEGF-A concentration-time profiles in AH. Mean (SD) baseline VEGF-A concentrations in AH ranged from 72.5 (19.8) pg/mL to 86.9 (46.3) ng/mL across all four faricimab-treated groups. At Week 16 (i.e., 4 weeks after administration of the fourth monthly dose), free VEGF-A concentrations in AH were similar across all four groups with mean values ranging from 2.73−12.2 pg/mL. At Week 32, the mean (SD) VEGF-A concentration in AH was 2.89 (1.42) pg/mL for the 6 mg faricimab Q4W (i.e., 4 weeks post-dose), and 4.05 (2.99) pg/mL for the faricimab 6 mg Q4W followed by Q8W arm (i.e., 8 weeks after the previous 6 mg dose) suggesting similar VEGF-A suppression for the Q4W and the Q8W administration. In patients

who had first received ranibizumab, concentrations of VEGF-A in AH remained suppressed during the entire treatment period.

Figure 10: Mean Free VEGF-A Concentration−Time Profiles in Aqueous Humor (Study AVENUE)



Values of BLQ are imputed using LLOQ/2. Error lower bounds are limited to LLOQ/2.
Numerical values below x-axis represent percentage of BLQ.
Visits with only one or two observations were excluded from stastics derivation.
Program: /_Projects/RO6867461_nAMD_7716/Pooling_Phase_2/Pooling_Phase_2/Step 15/p_AVENUE_PD_TLGs.R

Pharmacodynamics in Plasma

There was no apparent change from baseline of mean free Ang-2 in plasma across all treatment arms except for slightly higher levels at 1 week post-dose (Week 13) across all groups. There was no apparent change from baseline in concentrations of free VEGF-A in plasma following 1.5 mg faricimab Q4W. At Week 13, a decrease in plasma free VEGF-A (based on the increased proportion of values BLQ) was seen in both treatment groups administered 6 mg faricimab Q4W; however, there was no consistent decrease in free VEGF-A at other time points and a high number of samples were BLQ.

Immunogenicity

At baseline (Day 1), 5/195 (2.6%) patients were ADA-positive. A total of 22/195 (11.3%) patients receiving faricimab had treatment-induced (i.e., negative at baseline and positive at any time after dosing) or treatment-boosted (i.e., positive at baseline and increased in titer any time after dosing) ADAs. A total of 3/46 patients in the faricimab 1.5 mg Q4W arm, 3/39 patients in the faricimab 6 mg Q4W arm, 9/46 patients in the faricimab 6 mg Q4W followed by 6 mg faricimab Q8W arm, and 7/64 patients in the 0.5 mg ranibizumab Q4W followed by 6 mg faricimab Q4W arm had treatment-induced or treatment-boosted ADAs. The onset of ADA response ranged from Week 4 to Week 36. There was no apparent effect of ADA on the systemic PK.

Studies in DME and DR

4.2.5 Phase 2 Study # BP30099 (BOULEVARD): A multicenter, multiple-dose, randomized, active comparator-controlled, double-masked, parallel-group study investigating the safety, tolerability, PK, and efficacy of faricimab in patients with DME and DR.

This study evaluated the efficacy, safety, and pharmacokinetics of faricimab compared with the active comparator in treatment-naive patients with DME/DR. A total of 229 patients (168 treatment-naive and 61 previously treated) were randomized to one of the following treatment arms:

- Ranibizumab 0.3 mg Q4W, N=90 (59 treatment-naive, 31 prior anti-VEGF treated)
- Faricimab 1.5 mg Q4W, N=55 (54 treatment-naive, 1 prior anti-VEGF treated)
- Faricimab 6 mg Q4W, N=84 (55 treatment-naive, 29 prior anti-VEGF treated)

Study treatment was administered on Day 1 followed by Q4W for a total of six intravitreal injections. The primary efficacy outcome was mean change in BCVA from baseline at Week 24.

At the end of the treatment phase (Week 20), patients went into an observational period where they were evaluated Q4W up to Week 36. Any patient who met both the pre-specified criteria (i.e., CST increased by ≥ 50 μm and BCVA decreased by ≥ 5 letters due to DME) received a single dose of 0.3 mg ranibizumab and exited the study. Otherwise, patients finished the study once they had completed the observational visit at Week 36.

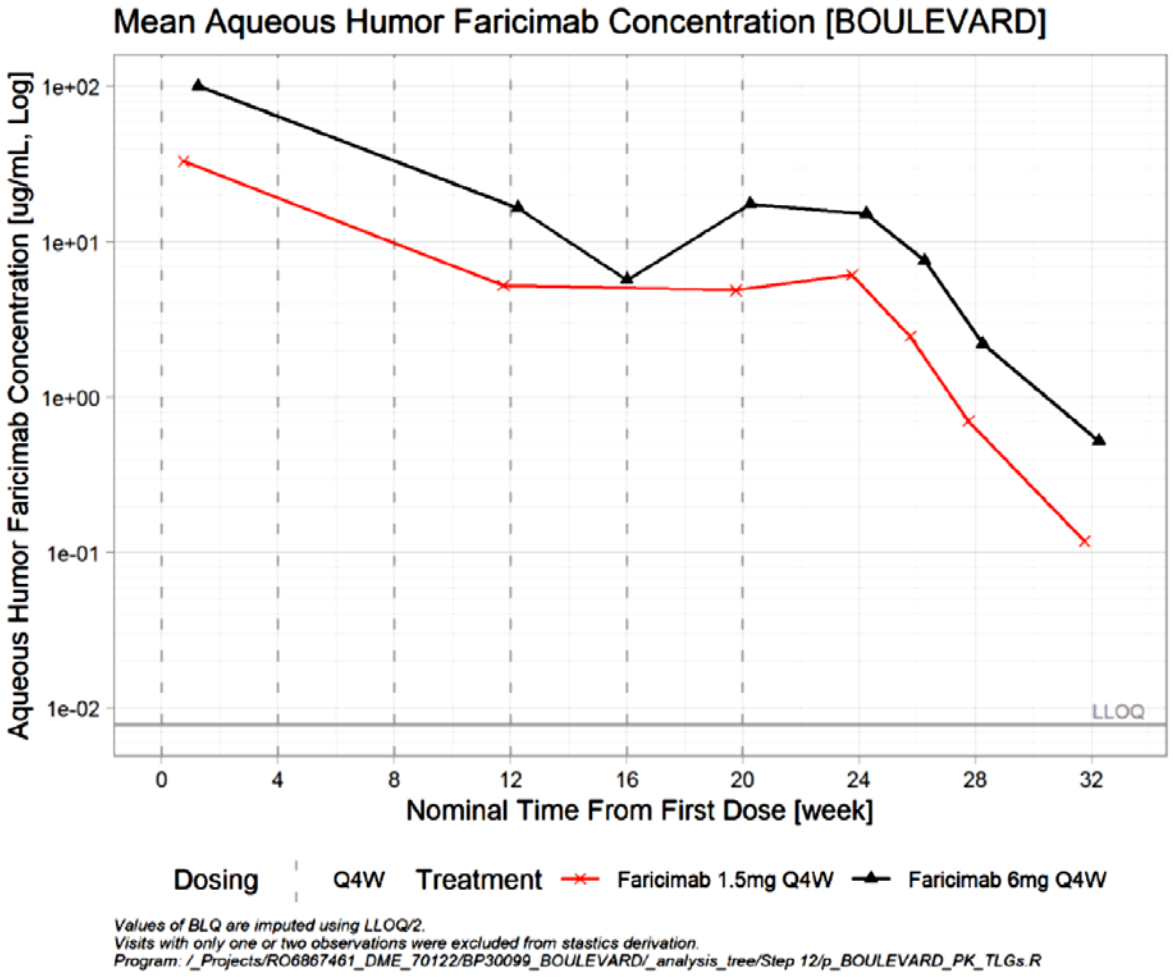
Plasma and AH samples were collected throughout the study for measurement of faricimab, Ang-2, VEGF-A, and ADA. ADAs were assessed at each visit up to Week 36. On days where treatment was administered, samples were taken prior to treatment administration.

Pharmacokinetics in Aqueous Humor

Mean faricimab concentration-time profiles in AH are presented in Figure 11. Samples of AH were collected for 46 faricimab-treated patients (N=16 for 1.5 mg arm and N=30 for 6 mg arm). One week after administration of the first dose, mean (SD) AH concentration was 33.1 (17.1) μg/mL and 101 (43.1) μg/mL for the 1.5 mg and 6 mg arm, respectively. At Week 12, mean AH

concentration was approximately 3-fold higher for the 6 mg arm compared with the 1.5 mg arm with mean (SD) of 5.26 (3.15) µg/mL for the 1.5 mg arm and 16.5 (16.7) µg/mL for the 6 mg arm. Faricimab concentrations in AH remained stable with Q4W dosing. Following administration of the last dose (Week 20), faricimab concentrations in AH declined in parallel at both dose levels. Eight weeks after administration of the last dose (i.e., Week 28), AH faricimab concentrations had declined with mean (SD) concentrations of 0.707 (0.796) µg/mL and 2.21 (2.80) µg/mL for the 1.5 mg and 6 mg arms, respectively. Twelve weeks after the last dose (i.e. Week 32) mean (SD) AH concentrations were 0.119 (0.135) µg/mL and 0.522 (0.970) µg/mL for the 1.5 mg and 6 mg arms, respectively.

Figure 11: Mean Faricimab Concentration−Time Profiles in Aqueous Humor (Study BOULEVARD)



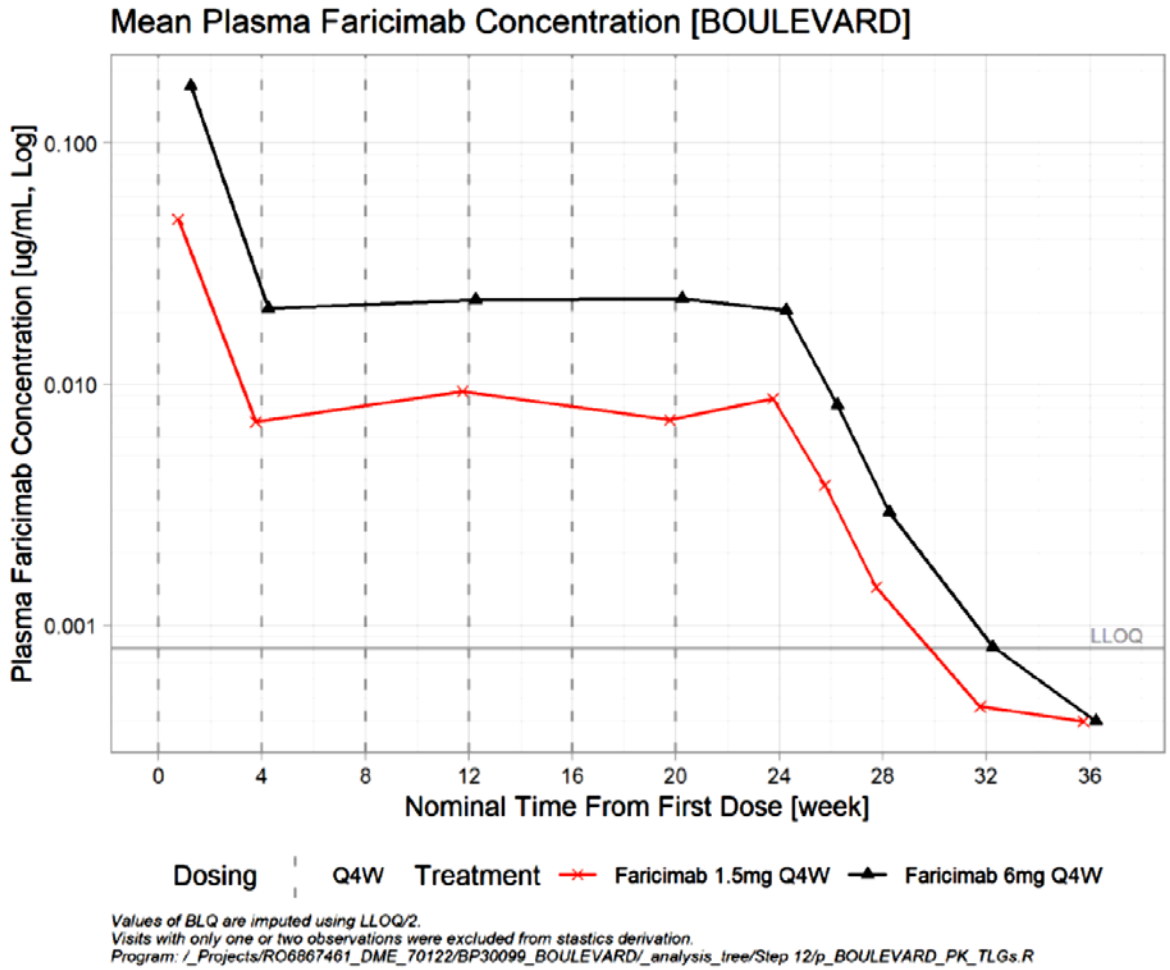
BLQ=below limit of quantification; LLOQ=lower limit of quantification; Q4W=every 4 weeks.
Source: CSR BOULEVARD, Report 1083913, t_pk_conc_ITT

Pharmacokinetics in Plasma

The mean faricimab plasma concentration−time profiles are presented in Figure 12. One week after administration of the first dose, mean (SD) faricimab concentration in plasma was 0.0484 (0.00225) µg/mL and 0.172 (0.0806) µg/mL for the 1.5 mg and 6 mg arms, respectively. Mean (SD) steady-state concentration at the end of the dosing interval (Ctrough) (4 weeks post-dose) was 0.0069 (0.00496) µg/mL and 0.0206 (0.01346) µg/mL for the 1.5 mg and 6 mg arms, respectively. Plasma concentrations remained stable with subsequent Q4W doses at both dose levels, similar to the aqueous profiles. Eight weeks after administration of the last dose (Week 28), faricimab reached mean (SD) plasma concentrations of 0.00144 (0.00242) µg/mL and 0.00294 (0.00307) µg/mL for the 1.5 mg and 6 mg arms, respectively. Twelve weeks after administration of the last dose (Week 32), faricimab concentrations declined further and reached mean (SD) plasma concentration of 0.000460 (0.000230) µg/mL and 0.000820 (0.000970) µg/mL for the 1.5 mg and 6 mg arms, respectively. Overall, plasma C_{trough} faricimab concentrations were approximately 2−4 times higher following administration of 6 mg, compared with 1.5 mg.

On Day 7, plasma concentrations were >580 times lower than those in AH.

Figure 12: Mean Faricimab Concentration−Time Profiles in Plasma (Study BOULEVARD)

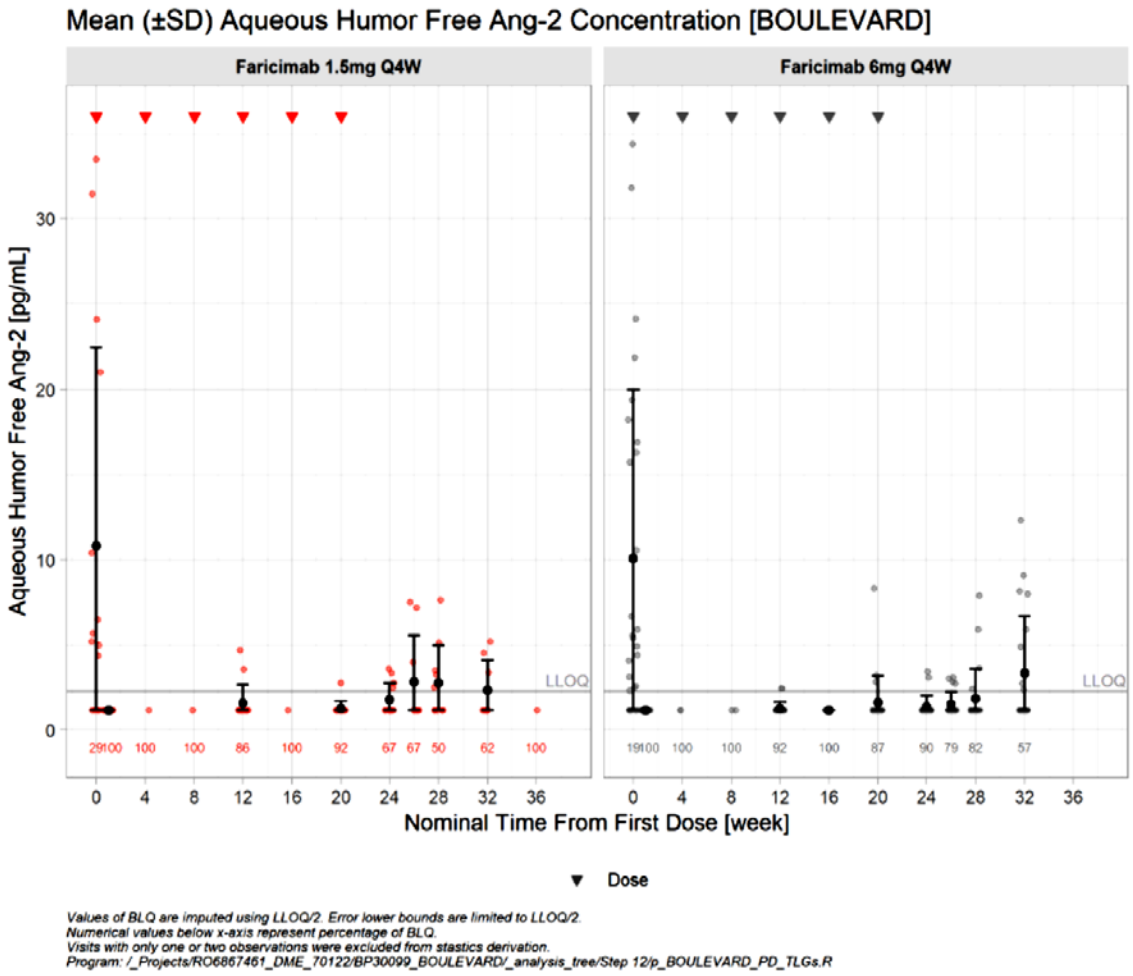


BLQ=below limit of quantification; LLOQ=lower limit of quantification; Q4W=every 4 weeks.
Source: CSR BOULEVARD, Report 1083913, t_pk_conc_ITT

Pharmacodynamics in Aqueous Humor

Mean free Ang-2 concentration−time profiles in AH are presented in Figure 13. A high percentage of free Ang-2 levels in AH were BLQ, including baseline values, which limits the interpretation of the Ang-2 data. Baseline mean (SD) AH free Ang-2 concentration was 10.8 (11.6) pg/mL and 10.1 (9.92) pg/mL for the 1.5 mg and 6 mg arms, respectively. One week after the first administration, mean Ang-2 concentrations in AH were BLQ at both dose levels. Free Ang-2 concentrations in AH remained suppressed during the treatment phase. Eight weeks after the last dose (Week 28), free Ang-2 remained lower than at baseline, with mean (SD) of 2.75 (2.2) pg/mL and 1.82 (1.77) pg/mL for the 1.5 mg and 6 mg arms, respectively. At 12 weeks after the last dose (Week 32) , free Ang-2 concentrations in AH remained lower than at baseline with mean (SD) of 2.33 (1.74) pg/mL and 3.33 (3.37) pg/mL for the 1.5 mg and 6 mg arms, respectively (Figure 13).

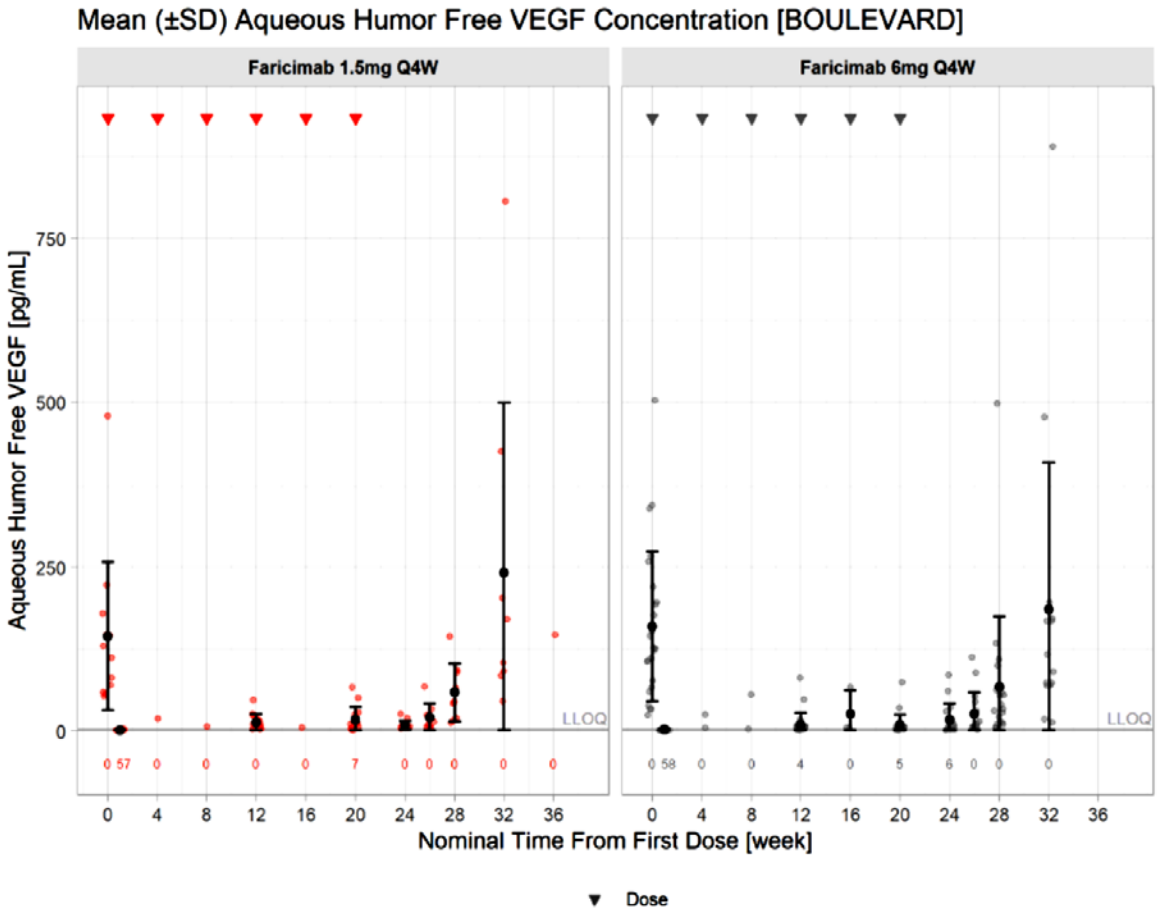
Figure 13: Mean Free Ang-2 Concentration−Time Profiles in Aqueous Humor (Study BOULEVARD)



Ang-2 = angiopoietin-2; BLQ = below limit of quantification; LLOQ = lower limit of quantification.
Source: CSR BOULEVARD, Report 1083913, t_avbanginf_ITT

Mean free VEGF-A concentration-time profiles in AH are presented in Figure 14. Baseline mean (SD) free VEGF-A concentration in AH was 145 (113) pg/mL and 160 (114) pg/mL for the 1.5 mg and 6 mg arms respectively. One week after administration of the first dose, free VEGF-A concentrations in AH decreased at both dose levels reaching mean (SD) of 1.29 (0.770) pg/mL and 1.54 (1.17) pg/mL for the 1.5 mg and 6 mg arms, respectively and remained suppressed during the treatment phase. Eight weeks after administration of the last dose (Week 28), free VEGF-A concentration in AH remained lower than at baseline with a mean (SD) of 58.6 (44.0) pg/mL and 67.3 (107.7) pg/mL for the 1.5 mg and 6 mg dose arms, respectively. Twelve weeks after administration of the last dose (Week 32), mean (SD) values for free VEGF-A concentrations in AH were 242 (258) pg/mL and 186 (225) pg/mL for the 1.5 mg and 6 mg arms, respectively.

Figure 14: Mean Free VEGF-A Concentration−Time Profiles in Aqueous Humor (Study BOULEVARD)



BLQ=below limit of quantification; LLOQ=lower limit of quantification; VEGF-A=vascular endothelial growth factor-A.

Source: CSR BOULEVARD, Report 1083913, t_avbanginf_ITT

Pharmacodynamics in Plasma

There was no apparent change from baseline of mean free Ang-2 in plasma across the treatment arms. There were slightly lower mean free VEGF-A levels in plasma at 1 week post-dose compared to baseline, as well as compared with later timepoints at trough across the treatment arms. However, a high number of samples (> 50%) were BLQ (15.6 pg/mL) of the assay which limits the interpretation of this data.

Immunogenicity

Baseline prevalence of ADA was 3/135 (2.2%) patients. Overall, 10/135 (7.4%) patients receiving faricimab had treatment-induced (negative at baseline and positive after dosing) or treatment-boosted (positive at baseline and increased titer after dosing) ADA; 3 patients were in the 1.5 mg arm and 7 patients in the 6 mg arm. The onset of ADA ranged from Week 1 to Week 36. There was no apparent effect of positive ADA on systemic PK.

Pharmacokinetic/Pharmacodynamic/Immunogenicity Results from Phase 3 Studies

nAMD

Phase 3 Study # GR40306 (TENAYA): A multicenter, randomized, active comparator−controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.

Patients were enrolled globally and randomized in a 1:1 ratio to one of two treatment arm:

- Faricimab up to Q16W: 6 mg of intravitreal faricimab Q4W up to Week 12 (4 injections). Patients randomized to Arm A received 6 mg of intravitreal faricimab every 4 weeks (Q4W) up to Week 12 (four injections). At Week 20, following a protocol-defined assessment of disease activity, patients in Arm A with active disease received faricimab at that visit and continued on a fixed-Q8W dosing regimen. At Week 24, following a second protocol-defined assessment of disease activity, patients in Arm A with active disease (excluding those with active disease at Week 20) received faricimab at that visit, and continued on a fixed-Q12W dosing regimen. Patients in Arm A who did not have active disease at Week 20 and Week 24 according to the protocol-defined criteria were treated with on a fixed-Q16W dosing regimen of faricimab. These fixed regimens of faricimab dosing continued until Week 60.

From Week 60 (when all patients in Arm A are scheduled to receive faricimab) onward, all patients in Arm A were treated according to a personalized treatment interval (PTI) dosing regimen up to Week 108.

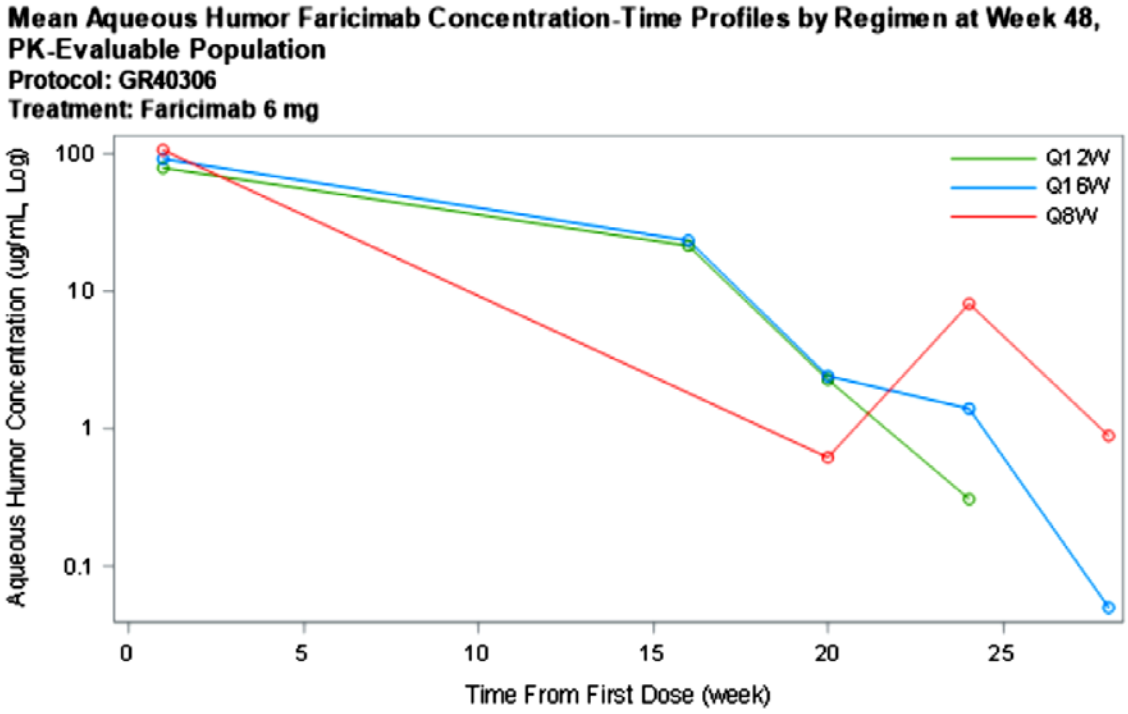
- Aflibercept Q8W: 2 mg of invitreal aflibercept Q4W up to Week 8 (3 injections), followed by 2 mg of invitreal aflibercept Q8W up to Week 108.

The primary objective of the study was to evaluate the efficacy of intravitreal injections of the 6 mg dose of faricimab on BCVA outcomes compared with aflibercept in patients with nAMD. A total of 334 treatment-naive patients with nAMD were randomized to the faricimab arm in TENAYA. AH PK and PD assessments were performed in 47 patients consenting to optional AH sampling, and plasma data was analyzed in 333 patients.

Pharmacokinetics in Aqueous Humor

The mean faricimab AH concentration time profile in TENAYA is displayed in Figure 15. High inter-patient variability (coefficient of variation [CV] 40%−394%) was observed in faricimab AH concentrations. The maximum observed concentration was 1 week post-dose (first timepoint following the first faricimab administration). Observed mean (SD) faricimab AH concentrations at Week 1 (one week after the first administration) were 92.5 (37.0) µg/mL. Observed mean (SD) faricimab AH concentrations 4 weeks after the most recent dose were 23.0 (16.9) µg/mL (at the Week 16 visit) and 8.0 (8.7) µg/mL (Week 24 visit). Observed mean (SD) faricimab AH concentrations 8 weeks after the most recent dose were 2.0 (2.3) µg/mL (Week 20 visit) and 0.87 (0.96) µg/mL (Week 28 visit). Observed mean (SD) faricimab AH concentrations 12 and 16 weeks after the most recent dose were 1.14 (4.49) µg/mL (Week 24 visit) and 0.05 (0.05) µg/mL (Week 28 visit). Faricimab was measurable throughout the study. At 12 and 16 weeks post-dose, approximately 13% and 26% of the samples were BLQ.

Figure 15: Mean Aqueous Humor Faricimab Concentration-Time Profiles by Treatment (Study TENAYA)



BLQ=below limit of quantification; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

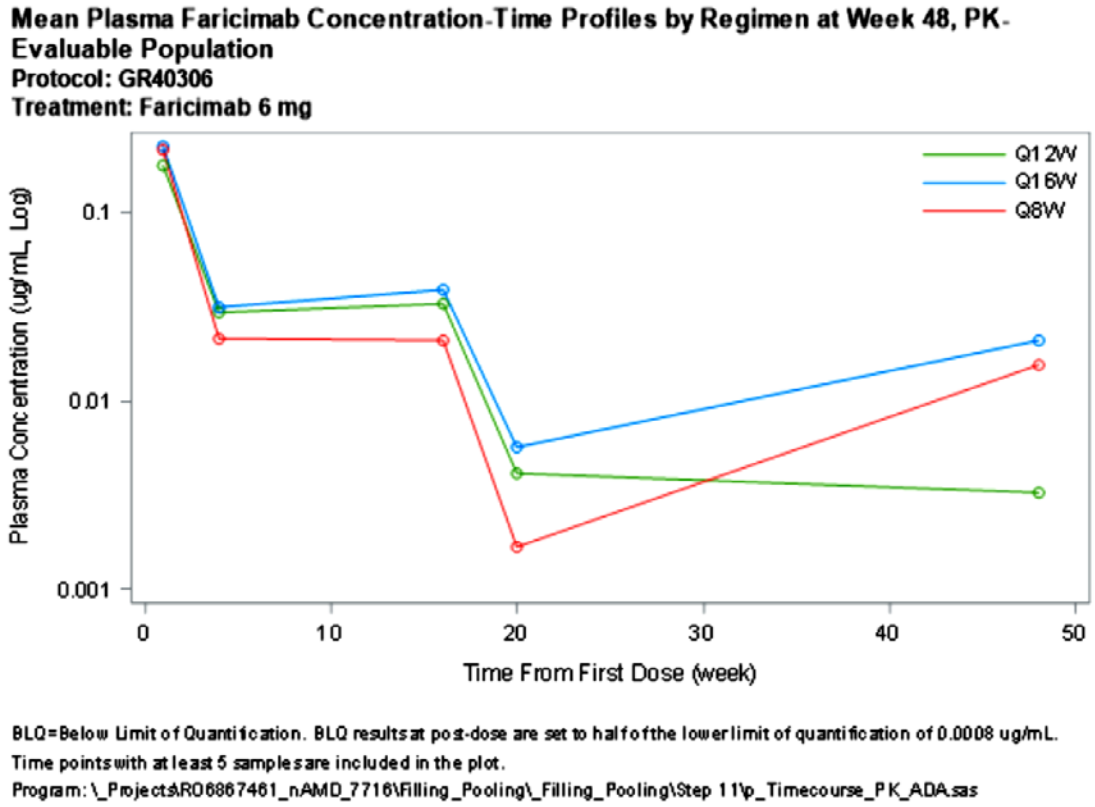
Source: CSR TENAYA, Rep1102954, Figure 11

Pharmacokinetics in Plasma

The mean plasma concentration-time profiles are shown in Figure 16. High inter-patient variability (CV 44%−144%) was observed in faricimab plasma concentrations. The maximum observed concentration was 1 week post-dose (first timepoint following the first faricimab administration). Observed mean (SD) faricimab plasma concentrations at Week 1 (1 week after the first administration) were 0.207 (0.091) µg/mL. Observed mean (SD) faricimab plasma concentrations 4 weeks after the most recent dose were 0.029 (0.0194) µg/mL (at the Week 4 visit), 0.034 (0.027) µg/mL (Week 16 visit), and 0.022 (0.018) µg/mL (Week 48 visit). Observed mean (SD) faricimab plasma concentrations 8 weeks after the most recent dose were 0.004 (0.006) µg/mL (Week 20 visit) and 0.003 (0.003) µg/mL (Week 48 visit). Faricimab was measurable up to 8 weeks post-dose, where approximately 30% of the samples were BLQ.

The ratio of faricimab AH to plasma on Day 7 was approximately 450.

Figure 16: Mean Plasma Faricimab Concentration-Time Profiles by Treatment Interval (Study TENAYA)



BLQ=below limit of quantification; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Source: CSR TENAYA, Report 1102954, Figure 12

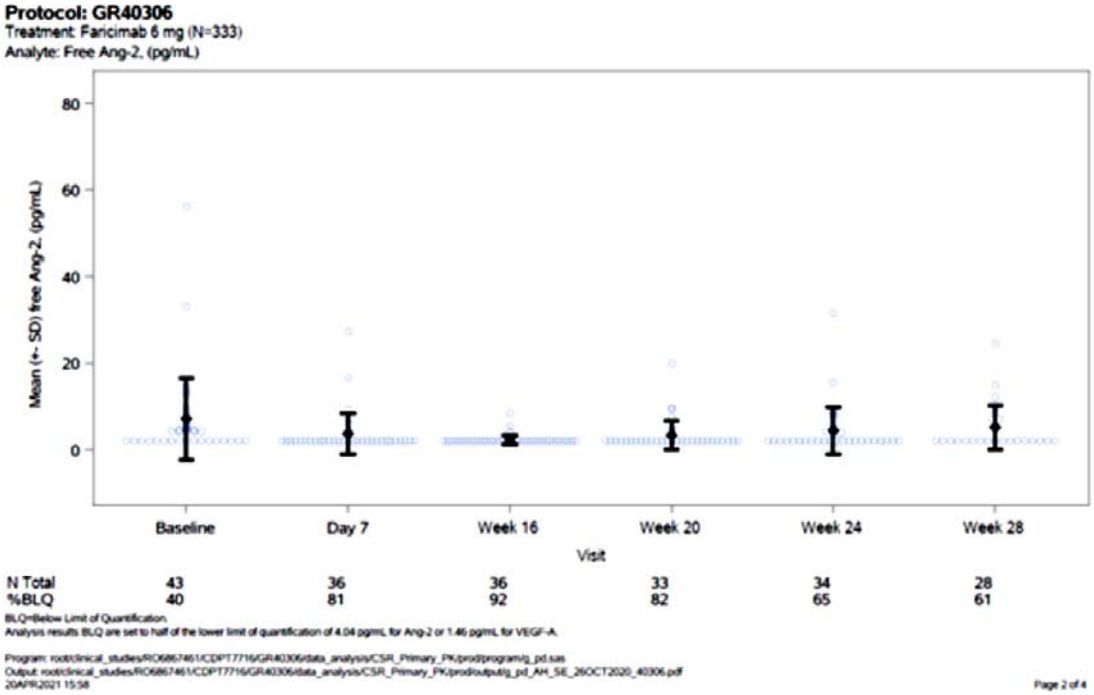
Pharmacodynamics in Aqueous Humor

High inter-patient variability was observed in AH Ang-2 (CV 36%−134%) and VEGF-A (CV 47%−270%) concentrations. Mean baseline Ang-2 concentrations were 7.2 (9.6) pg/mL. Forty percent of the samples were BLQ at baseline and increased to up to > 90% following faricimab administration up to Week 16. Rapid suppression of Ang-2 starting 7 days post-dose (mean Ang-2 concentration 3.7 pg/mL, 81% BLQ) was observed and maintained at least up to Week 20, after which patients were assigned to a regimen based on disease activity. The percentage of Ang-2 levels measured BLQ decreased as the time from most recent dose increased. However, at 16 weeks post-dose, a higher proportion of samples continued to have Ang-2 concentrations measured BLQ compared to at baseline.

Free Ang-2 concentrations in AH in TENAYA are shown in Figure 17. Mean (SD) baseline VEGF-A concentration was 47.9 (25.5) pg/mL. Rapid suppression of VEGF-A was shown starting 7 days post-dose (mean concentration 2.8 pg/mL) and remained suppressed at least up to Week 20 (mean < 13 pg/mL), after which patients were assigned to different dosing regimens (Q8W, Q12W, or Q16W) based on disease activity. VEGF-A levels increased as the sampling time from most recent

dose increased and were approaching baseline values 16 weeks post-dose. Free VEGF-A concentrations in AH in TENAYA are shown in Figure 18.

Figure 17: Aqueous Humor Free Ang-2 Concentrations for the Faricimab Treatment Arm (Study TENAYA)



Ang-2 = angiopoietin-2 (protein); BLQ = below limit of quantification.
Source: CSR TENAYA, Report1102954, Figure 14

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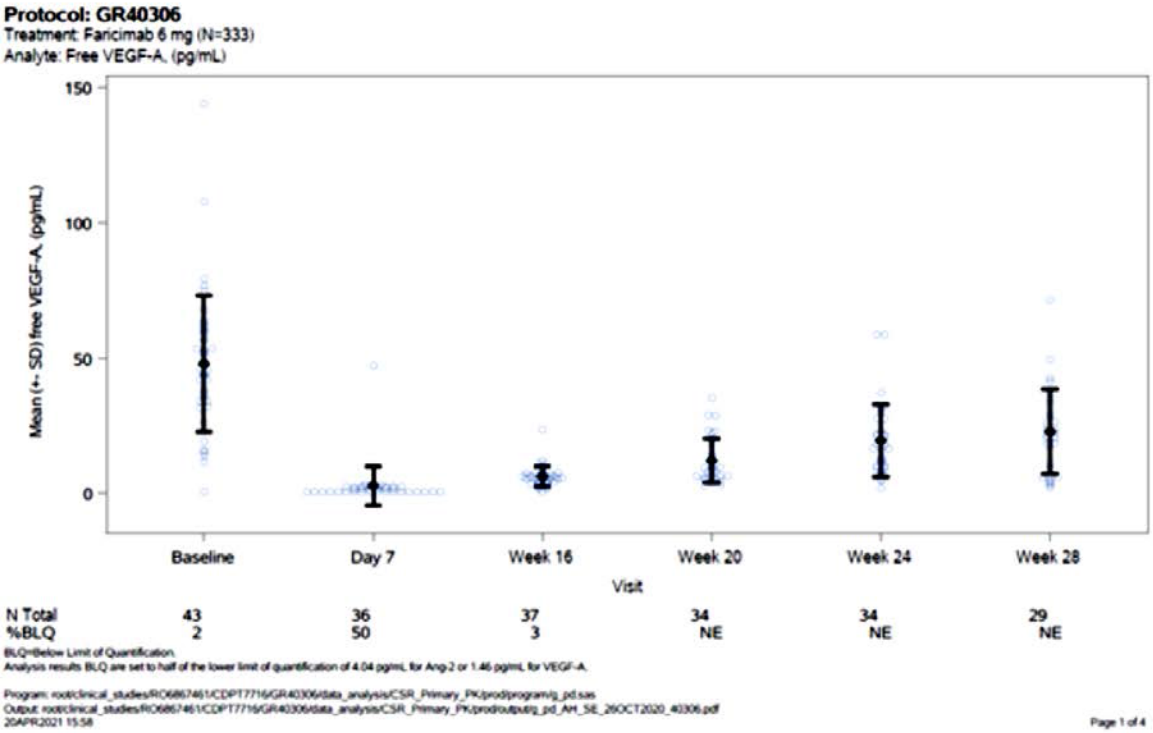
Figure 18: Aqueous Humor Free VEGF-A Concentrations for the Faricimab Treatment Arm (Study TENAYA)



BLQ=below limit of quantification; NE=not estimable; VEGF-A=vascular endothelial growth factor-A.

Source: CSR TENAYA, Report 1102954, Figure 13

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Pharmacodynamics in Plasma

No change in free VEGF-A or in free Ang-2 was observed post-dose as compared to baseline in any of the faricimab treatment arm.

Immunogenicity

The baseline prevalence of faricimab ADAs in the study was 3.0%. Overall, 29/328 (8.8%) patients receiving faricimab had treatment-emergent ADAs, 28/328 (8.5%) patients were treatment-induced and 1/328 (0.3%) patient was treatment-enhanced.

Phase 3 Study # GR40844 (LUCERNE): A multicenter, randomized, active comparator−controlled, double-masked, parallel-group, 112-week study to investigate the efficacy, safety, durability, and pharmacokinetics of faricimab administered at up to 16-week intervals to treatment-naive patients with nAMD.

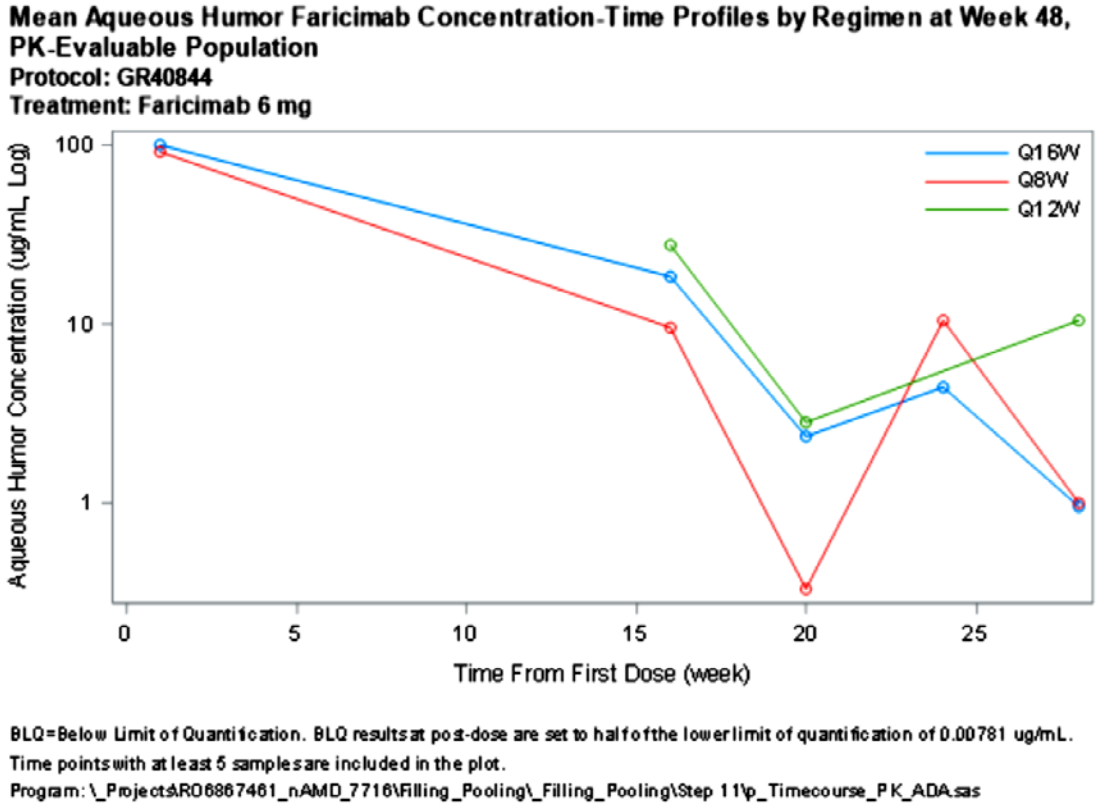
The study design for this study was identical to the study design of TENAYA (see above). A total of 331 treatment-naive patients with nAMD were randomized to the faricimab arm in LUCERNE.

AH PK and PD assessments were performed in 34 patients consenting to optional AH sampling, and plasma data was analyzed in 331 patients.

Pharmacokinetics in Aqueous Humor

High inter-patient variability (coefficient of variation [CV] 51%−245%) was observed in faricimab AH concentrations. The maximum observed concentration was 1 week post-dose (first timepoint following the first faricimab administration). Observed mean (SD) faricimab AH concentrations at Week 1 (one week after the first administration) were 101.2 (52.0) μg/mL. The time from most recent dose for the different dosing regimens was used for the following data description. Observed mean (SD) faricimab 4-week-post-dose AH concentrations were 19.3 (21.6) μg/mL (at the Week 16 visit) and 12.5 (8.0) μg/mL (Week 24 visit). Observed mean (SD) faricimab 8-week-post-dose AH concentrations were 1.8 (4.2) μg/mL (Week 20 visit) and 1.6 (1.4) μg/mL (Week 28 visit). Observed mean (SD) faricimab 12- and 16-weeks post-dose AH concentrations were 1.3 (3.1) μg/mL. (Week 24 visit) and 0.4 (0.8) μg/mL (Week 28 visit). Faricimab was measurable throughout the study. At 12- and 16-weeks post-dose, approximately 21% and 58% of the samples were BLQ. The mean faricimab AH concentration time profile is displayed in Figure 19.

Figure 19: Mean Aqueous Humor Faricimab Concentration-Time Profiles by treatment interval (Study LUCERNE)



BLQ=below limit of quantification; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

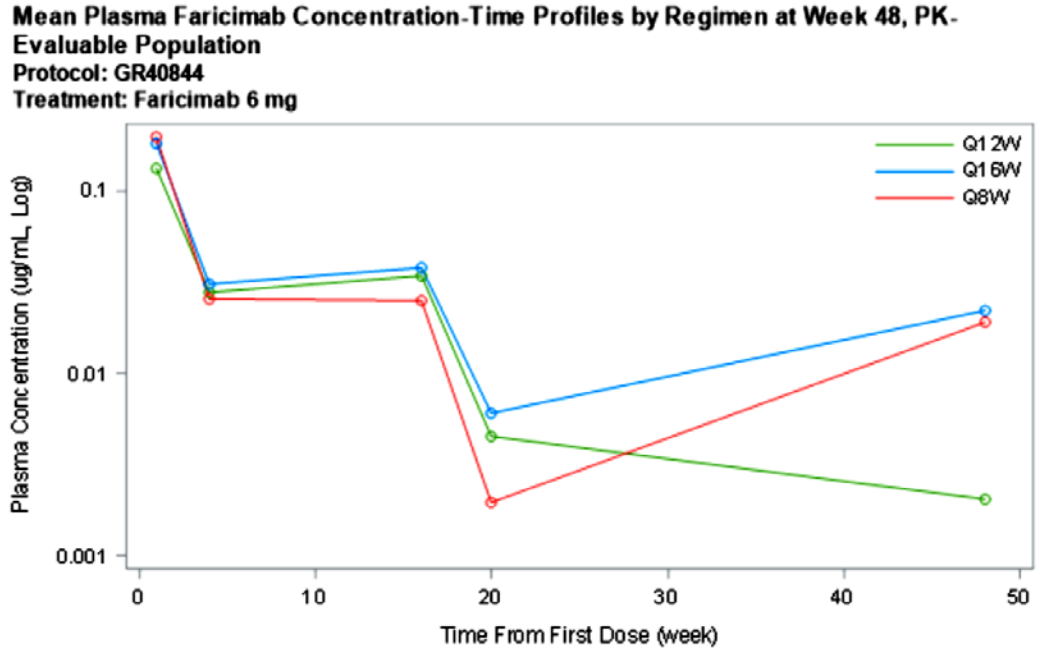
Source: CSR LUCERNE, Report 1102955, Figure 11

Pharmacokinetics in Plasma

The mean faricimab plasma concentration-time profiles are displayed in Figure 20. High inter-patient variability (CV 48%−154%) was observed in faricimab plasma concentrations. The maximum observed concentration was 1 week post-dose (first timepoint following the first faricimab administration). Observed mean (SD) faricimab plasma concentrations at Week 1 (1 week after the first administration) was 0.180 (0.087) µg/mL. The time from most recent dose for the different dose regimens was used for the following data description. Observed mean (SD) faricimab 4-week post-dose plasma concentrations were 0.029 (0.021) µg/mL (at the Week 4 visit), 0.033 (0.025) µg/mL (Week 16 visit), and 0.025 (0.019) µg/mL (Week 48 visit). Observed mean (SD) faricimab 8-week post-dose plasma concentrations were 0.005 (0.005) µg/mL (Week 20 visit) and 0.005 (0.006) µg/mL (Week 48 visit). Faricimab was measurable up to 8 weeks post-dose, where approximately 26% of the samples were BLQ.

The ratio of faricimab AH to plasma on Day 7 was approximately 560.

Figure 20: Mean Plasma Faricimab Concentration-Time Profiles by Dosing Regimen, Treatment Interval (Study LUCERNE)

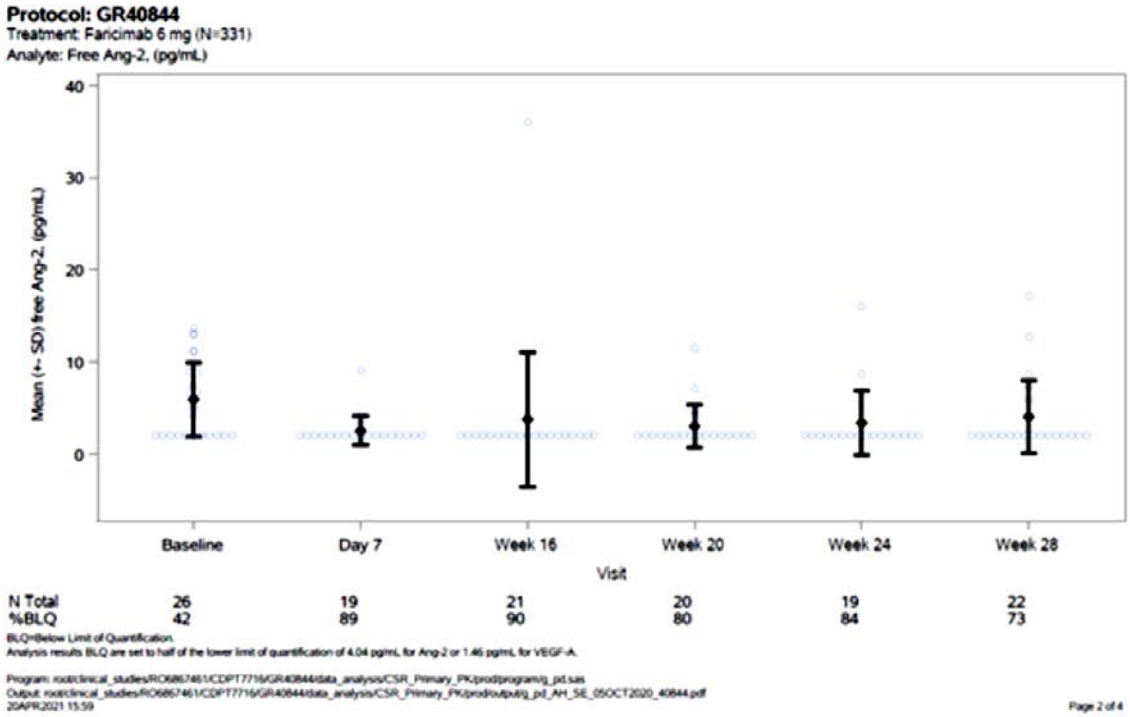


BLQ=below limit of quantification; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.
Source: CSR LUCERNE, Report 1102955, Figure 12

Pharmacodynamics in Aqueous Humor

High inter-patient variability was observed in AH Ang-2 (CV 35%−198%) and VEGF-A (CV 39%−103%) concentrations. Mean baseline Ang-2 concentrations were 5.9 (4.1) pg/mL. Approximately 40% of the samples were BLQ at baseline and increased up to 90% following faricimab administration up to Week 16. Rapid suppression of Ang-2 starting 7 days post-dose (mean Ang-2 concentration 2.5 pg/mL, 89% BLQ) was observed and maintained at least up to Week 20, after which patients were assigned to a regimen based on disease activity. The percentage of Ang-2 levels measured BLQ decreased as the time from last-dose increased. However, at 16 weeks after last dose, a higher proportion of samples continued to have Ang-2 concentrations measured BLQ compared to baseline. Free Ang-2 concentrations in AH in LUCERNE are shown in Figure 21. Due to the high percentage BLQ levels, time-dependent changes in Ang-2 could not be quantified.

Figure 21: Aqueous Humor Free Ang-2 Concentrations for the Faricimab Treatment Arm (Study LUCERNE)



Ang-2 = angiopoietin 2 (protein); BLQ = below limit of quantification.
Source: CSR LUCERNE, Report 1102955, Figure 13

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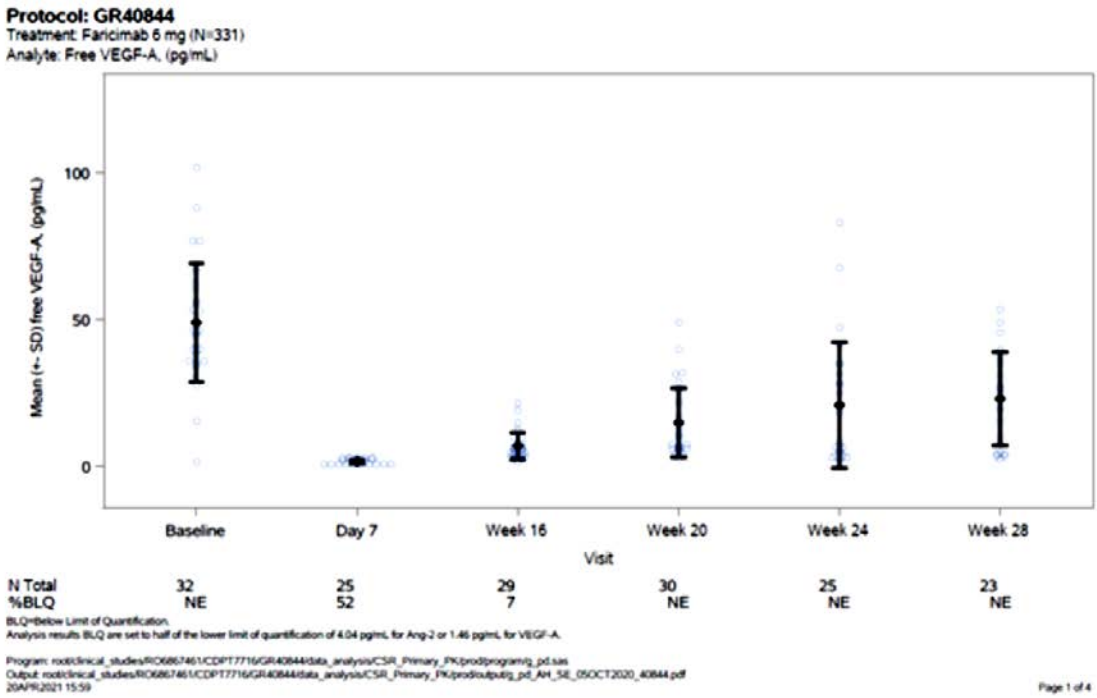
Mean (SD) baseline VEGF-A concentration was 49.0 (20.5) pg/mL. Rapid suppression of VEGF-A was shown starting 7 days post-dose (mean concentration 1.7 pg/mL) and maintained suppressed at least up to Week 20 (mean ≤ 15 pg/mL), after which patients were assigned to different dosing regimens (Q8W, Q12W, or Q16W) based on disease activity. VEGF-A levels increased as the sampling time from last-dose increased and were approaching baseline values 16 weeks after the last dose. Free VEGF-A concentrations in AH in LUCERNE are shown in Figure 22.

Figure 22: Aqueous Humor Free VEGF-A Concentrations for the Faricimab Treatment Arm (Study LUCERNE)



BLQ=below limit of quantification; VEGF-A=vascular endothelial growth factor-A.
Source: CSR LUCERNE, Report 1102955, Figure 14

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Pharmacodynamics in Plasma

No change in free VEGF-A or in free Ang-2 was observed post-dose as compared to baseline in any of the faricimab treatment arm.

Immunogenicity

The baseline prevalence of ADAs to faricimab in the study was 0.6%. Overall, 39/329 patients (11.9%) receiving faricimab had treatment-emergent ADAs, all of which were treatment induced.

DME/DR

Phase 3 Study # GR40349 (YOSEMITE): A multicenter, randomized, double-masked, active comparator-controlled, parallel-group studies evaluating the efficacy and safety of faricimab in patients with DME and DR.

This Phase 3 study evaluated the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab in patients with DME and DR.

Patients were randomized in a 1:1:1 ratio to one of three treatment arms:

- Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W to Week 20, followed by 6 mg faricimab injections Q8W to Week 92, followed by the final study visit at Week 100.
- Faricimab PTI: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI dosing of 6 mg faricimab intravitreal injections to Week 96, followed by the final study visit at Week 100.
- Aflibercept Q8W (comparator arm): 2 mg intravitreal aflibercept injections Q4W to Week 16, followed by 2 mg intravitreal aflibercept injections Q8W to Week 96, followed by the final study visit at Week 100.

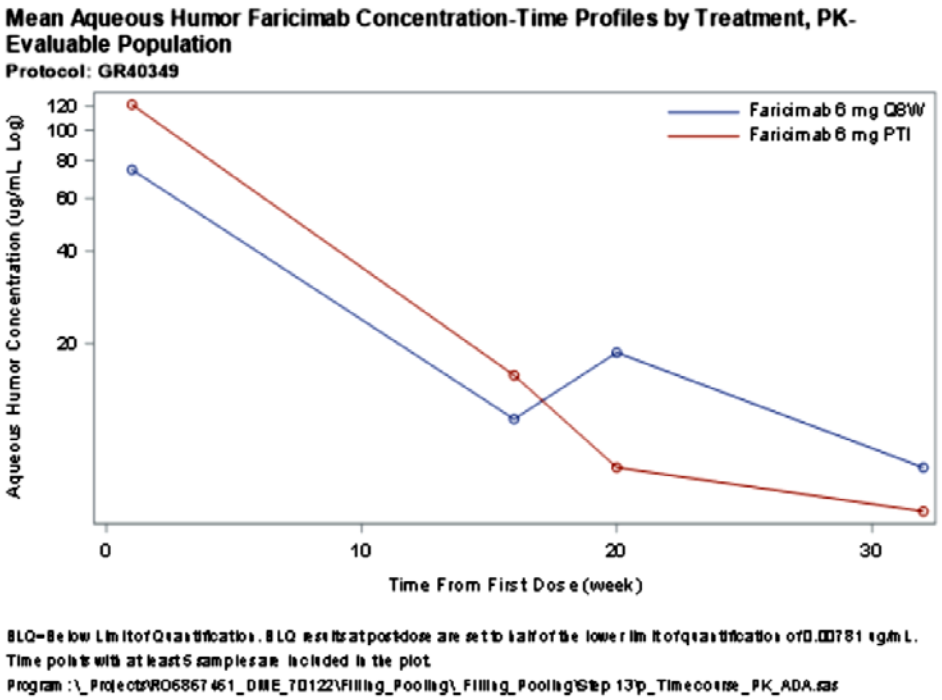
PK, PD and immunogenicity analyses were performed when all patients had either completed the first year of the study through Week 56 or had discontinued from the study prior to Week 56. A total of 315 patients with DME were randomized to the faricimab Q8W arm and 313 to the PTI arm in YOSEMITE. AH faricimab concentrations from 80 patients consenting to optional AH sampling were included in the PK data analysis, and AH concentrations from 85 patients consenting to optional AH sampling were included in the PD data analysis. Plasma data from 621 patients were included in the PK data analysis and from 623 patients in the PD data analysis.

Pharmacokinetics in Aqueous Humor

The mean faricimab aqueous concentration time profile in YOSEMITE is shown in Figure 23. Faricimab was measurable throughout the study in both treatment arms. High inter-patient variability (CV: 59−100% for the Q8W regimen) was observed in faricimab AH concentrations. The maximum observed concentration was observed at the first time point collected i.e. 1 week post-dose. Observed mean (SD) faricimab AH concentrations (μg/mL) at Week 1 (1 week after the first administration) were 74 (43.3) and 121.6 (71.4) for the Q8W and PTI regimen, respectively. Observed mean faricimab 4 week-post-dose AH concentrations (μg/mL) were 12.2 (10.4) (at the Week 16 visit), 18.8 (16.1) (Week 20 visit), 8.1 (7.9) (Week 32 visit) for the Q8W regimen, and 15.7 (12.4) (Week 16 visit), 15.7 (12.9) (Week 20 visit), 16.0 (19.5) (Week 32 visit) for the PTI regimen. Observed mean (SD) faricimab 8 week-post-dose AH concentrations (μg/mL) was 2.12 (2.49) (Week 20 visit) for the PTI regimen.

At 12 weeks post-dose, approximately 30% of the samples were BLQ.

Figure 23: Mean Aqueous Humor Faricimab Concentration-Time Profiles (Study YOSEMITE)



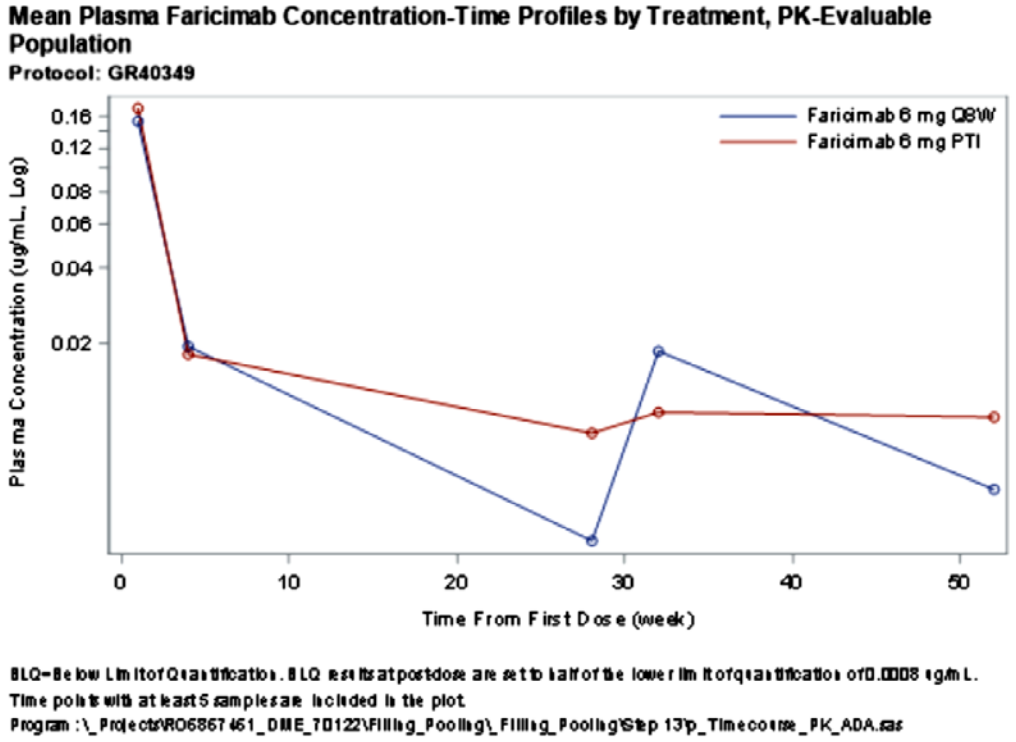
BLQ=below limit of quantification; PTI=personalized treatment interval; Q8W=every 8 weeks.
Source: CSR YOSEMITE, Report 1102956, Figure 30

Pharmacokinetics in Plasma

The mean plasma concentration-time profiles in YOSEMITE are shown in Figure 24. High inter-patient variability (CV 45 − 199 % in the Q8W regimen) was observed in faricimab plasma concentrations. The maximum observed concentration was 1 week post-dose (first time point collected after drug administration). Observed mean (SD) faricimab plasma concentrations (µg/mL) at Week 1 (1 week after the first administration) were 0.154 (0.070) and 0.173 (0.071) for the Q8W and PTI regimen respectively. Observed mean faricimab 4 week-post-dose plasma concentrations (µg/mL) were 0.019 (0.016) (at the Week 4 visit) for the Q8W regimen and 0.018 (0.014) (Week 4 visit), 0.018 (0.014) (Week 52 visit) for the PTI regimen. Observed mean faricimab 8 week-post-dose plasma concentrations (µg/mL) were 0.003 (0.004) (Week 28 visit), 0.003 (0.004) (Week 52 visit) for the Q8W regimen and 0.003 (0.004) (Week 28 visit), 0.003 (0.004) (Week 52 visit) for the PTI regimen. Faricimab was measurable up to 8 weeks post-dose, where approximately 30−50% of the samples were BLQ.

The faricimab AH-to-plasma ratio on Day 7 was ~480−700.

Figure 24: Mean (SD) Plasma Faricimab Concentration-Time Profiles (Study YOSEMITE)



BLQ=below limit of quantification; PTI=personalized treatment interval; Q8W=every 8 weeks.
Source: CSR YOSEMITE, Report 1102956, Figure 31

Pharmacodynamics in Aqueous Humor

High inter-patient variability was observed in AH Ang-2 (CV: 51−89% in the Q8W arm) and VEGF-A (CV 80− 222% in the Q8W arm) concentrations. Mean baseline Ang-2 concentrations were 12.6 (11.2) and 13.3 (12.8) pg/mL for the Q8W and PTI arm respectively. Approximately 20% of the AH samples were BLQ at baseline and following faricimab administration increased up to approximately 90%. Both faricimab arms showed rapid suppression of Ang-2 starting 7 days post-dose (mean 3 pg/mL) and mean concentrations remained below mean baseline throughout the study. Free Ang-2 concentrations in AH by treatment arm in YOSEMITE are shown in Figure 25.

Mean (SD) baseline VEGF-A concentrations were 148.6 (184.7) and 102.1 (72.7) pg/mL for the Q8W and PTI arm respectively. Both faricimab treatment arms showed rapid suppression of VEGF-A (mean concentration < 5 pg/mL) from day 7 onwards and thereafter sustained target suppression was observed in both arms. For the Q8W arm mean VEGF-A concentration was < 20 pg/mL up to the last visit and in the PTI arm mean VEGF-A concentration was highest at Week 32 (44.0 pg/mL) with a trend for increased VEGF-A concentrations as sampling time from

last dose increased. Free VEGF-A concentrations in AH by treatment arm in YOSEMITE are shown in Figure 26.

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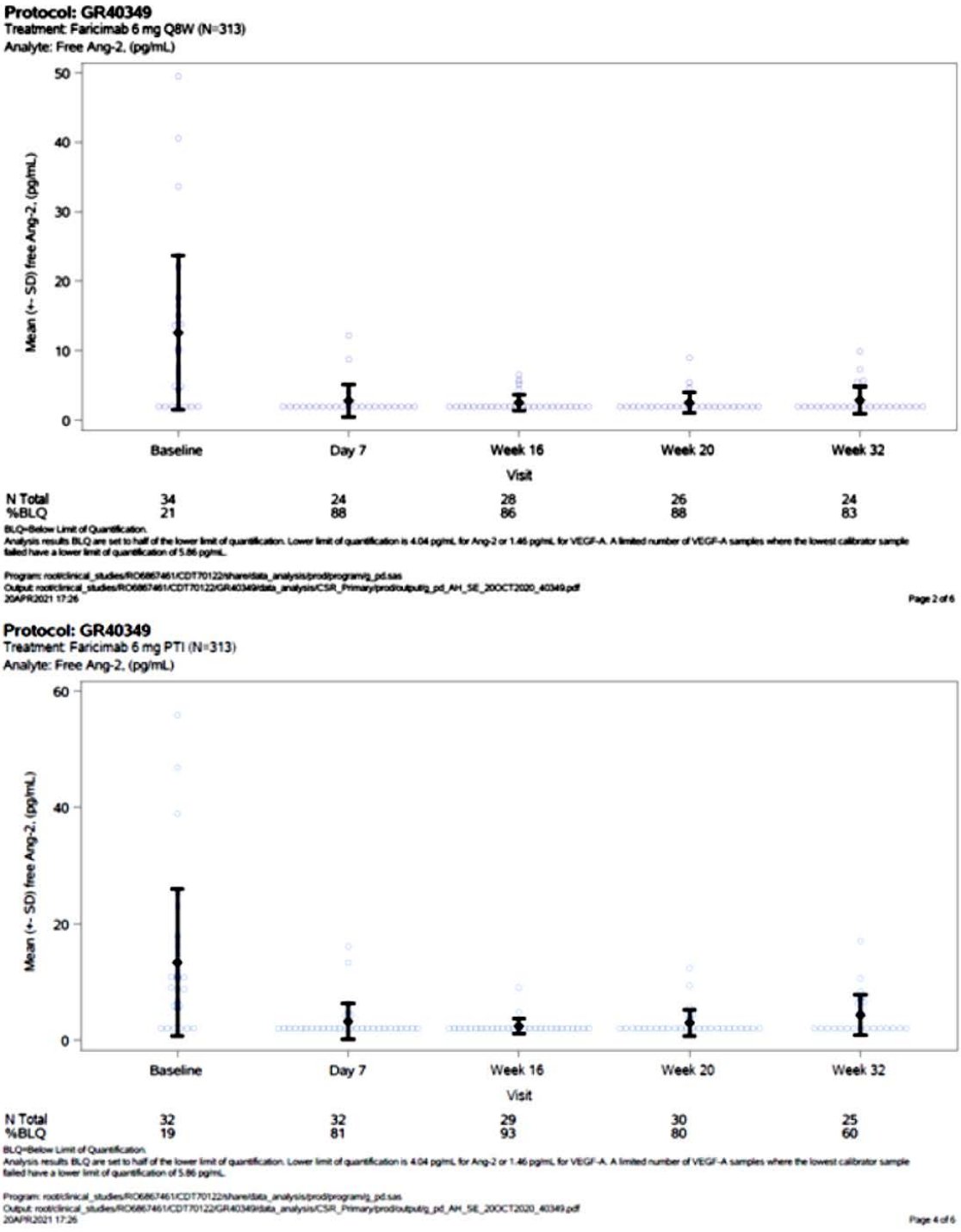
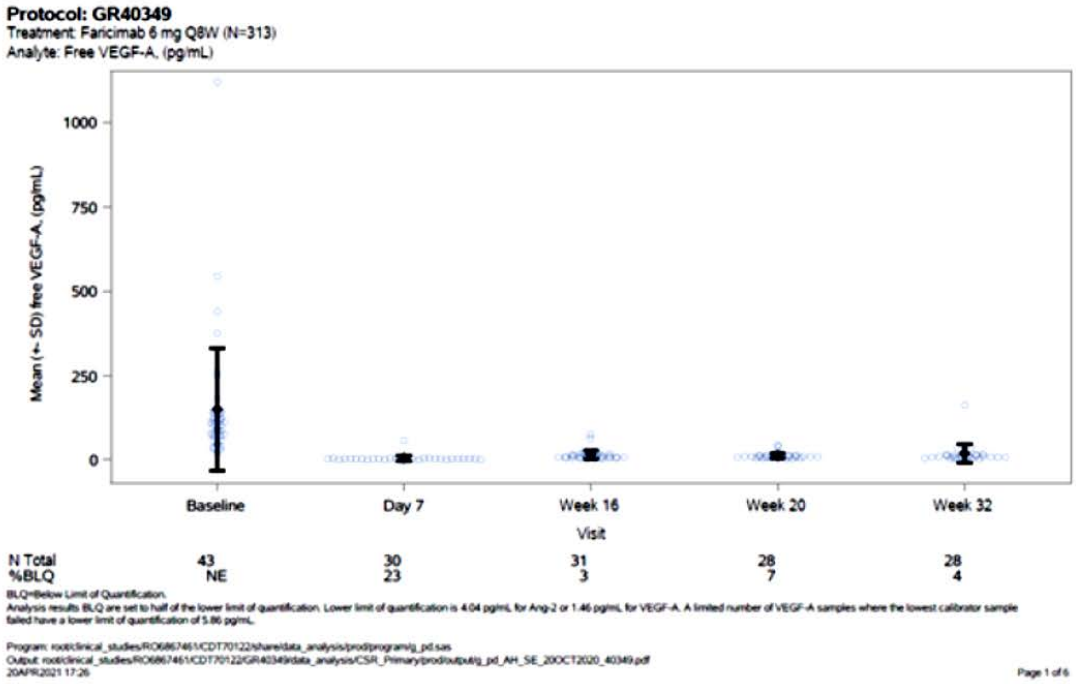
Figure 25: Aqueous Humor Free Ang-2 Concentrations by Treatment Arm (Study YOSEMITE)

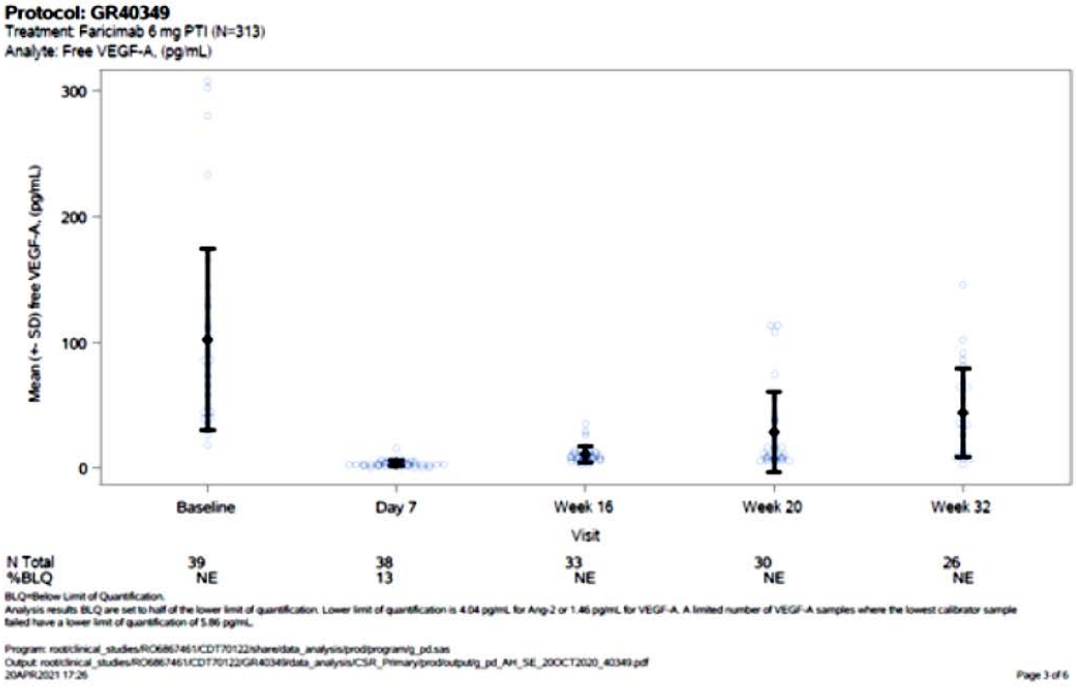


Ang-2=angiopoietin-2 (protein); BLQ=below limit of quantification; LLOQ=lower limit of quantification; PTI= personalized treatment interval; Q8W=every 8 weeks.

Source: CSR YOSEMITE, Report 1102956, Figure 33

Figure 26: Aqueous Humor Free VEGF-A Concentrations by Treatment Arm (Study YOSEMITE)





BLQ=below limit of quantification; LLOQ=lower limit of quantification; PTI= personalized treatment interval; Q8W=every 8 weeks; VEGF-A=vascular endothelial growth factor-A.

Source: CSR YOSEMITE, Report 1102956, Figure 32

Pharmacodynamics in Plasma

No change in free VEGF-A or in free Ang-2 was observed post-dose, as compared to baseline, in any of the faricimab treatment arms.

Immunogenicity

The baseline prevalence of ADAs to faricimab in the study was 1%. Overall, 62/619 (10.0%) patients receiving faricimab had treatment-emergent ADAs, of which 61 were treatment-induced (31 and 30 were in the faricimab Q8W and PTI arm, respectively) and 1 patient in the PTI arm was treatment-boosted.

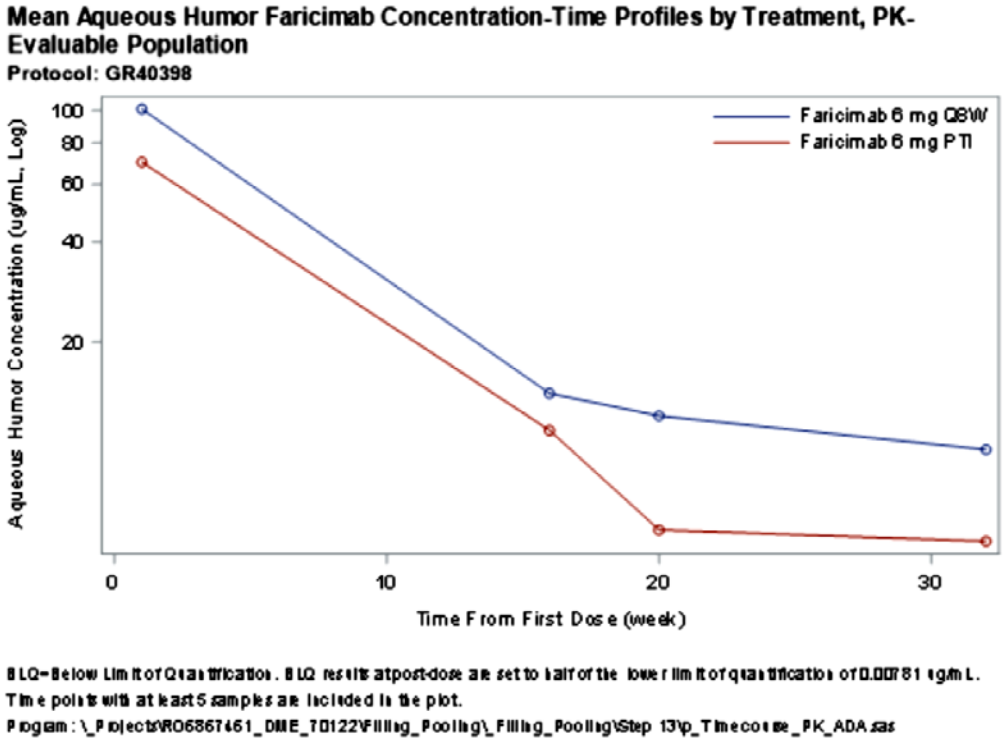
Phase 3 Study # GR40398 (RHINE): A multicenter, randomized, double-masked, active comparator-controlled, parallel-group studies evaluating the efficacy and safety of faricimab in patients with DME and DR.

The study design for this study was identical to the study design of YOSEMITE (see above). A total of 317 patients with DME/DR were randomized to the faricimab Q8W arm and 319 to the PTI arm. AH faricimab concentrations from 44 patients consenting to optional AH sampling were included in the PK data analysis, and AH concentrations from 46 patients consenting to optional AH sampling were included in the PD data analysis. Plasma data from 630 patients were included in the PK and PD data analyses.

Pharmacokinetics in Aqueous Humor

Mean faricimab AH concentration-time profiles in RHINE are shown in Figure 27. Faricimab was measurable throughout the study in both treatment arms. High inter-patient variability (CV: 69−105% for the Q8W regimen) was observed in faricimab AH concentrations. The maximum observed concentration was observed at the first time point collected i.e. 1 week post-dose. Observed mean (SD) faricimab AH concentrations (μg/mL) at Week 1 (1 week after the first administration) were 101.5 (70.3) and 69.8 (45.1) for the Q8W and PTI regimen, respectively. Observed mean faricimab 4 week-post-dose AH concentrations (μg/mL) were 14.8 (12.8) (at the Week 16 visit), 13.7 (12.7) (Week 20 visit), 9.4 (8.3) (Week 32 visit) for the Q8W regimen; and 11.5 (10.9) (Week 16 visit), 16.3 (15.9) (Week 20 visit), 11.2 (12.9) (Week 32 visit) for the PTI regimen. Observed mean (SD) faricimab 8 week-post-dose AH concentrations was 0.44 (0.56) (μg/mL) (Week 20) visit for the PTI regimen. At 12 weeks post-dose, approximately 40% of the samples were BLQ.

Figure 27: Mean Aqueous Humor Faricimab Concentration−Time Profiles (Study RHINE)



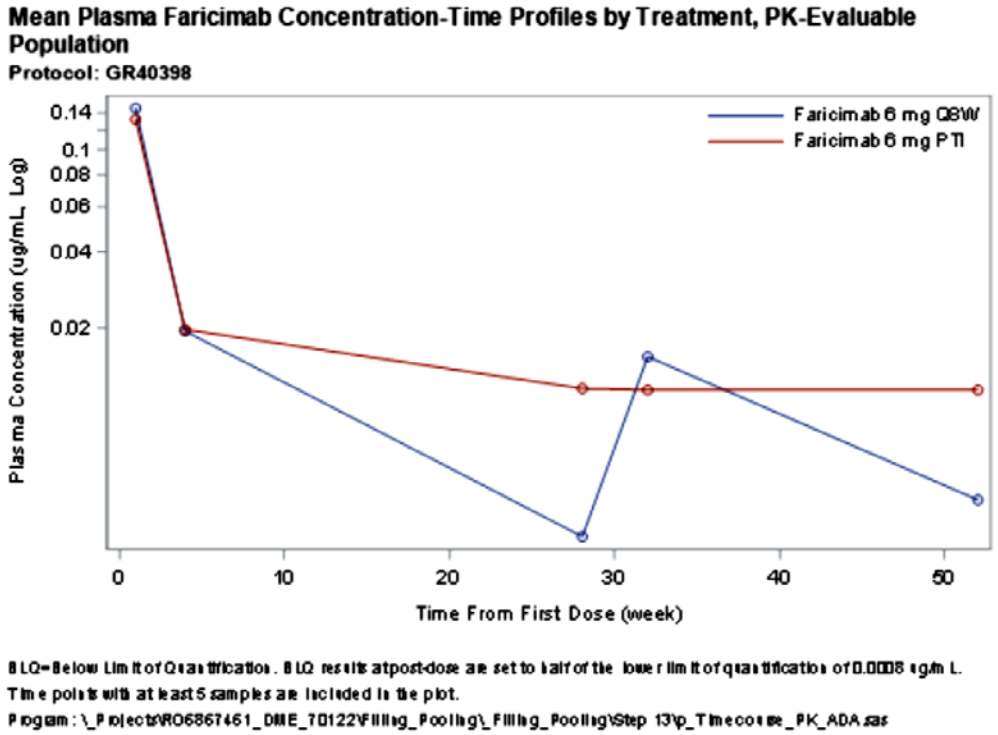
BLQ=below limit of quantification; PTI= personalized treatment interval; Q8W=every 8 weeks.
Source: CSR RHINE, Report 1102957, Figure 30

Pharmacokinetics in Plasma

Mean plasma concentration-time profiles in RHINE are shown in Figure 28. High inter-patient variability was observed in faricimab plasma concentrations. The maximum observed concentration was 1 week post-dose. Observed mean (SD) faricimab plasma concentrations (µg/mL) at Week 1 (1 week after the first administration) were 0.147 (0.077) and 0.131 (0.078) for the Q8W and PTI regimen respectively. Observed mean faricimab 4 week-post-dose plasma concentrations (µg/mL) were 0.019 (0.016) (a the Week 4 visit) for the Q8W regimen and 0.020 (0.015) (Week 4 visit), 0.019 (0.014) (Week 52 visit) for the PTI regimen. Observed mean faricimab 8 week-post-dose plasma concentrations (µg/mL) were 0.003 (0.004) (Week 28 visit), 0.002 (0.003) (Week 52 visit) for the Q8W regimen and 0.003 (0.004) (Week 28 visit), 0.002 (0.003) (Week 52 visit) for the PTI regimen. Faricimab was measurable up to 8 weeks post-dose, where approximately 40% of the samples were BLQ.

The faricimab AH-to-plasma ratio on Day 7 was ~530−700.

Figure 28: Mean Plasma Faricimab Concentration-Time Profiles (Study RHINE)

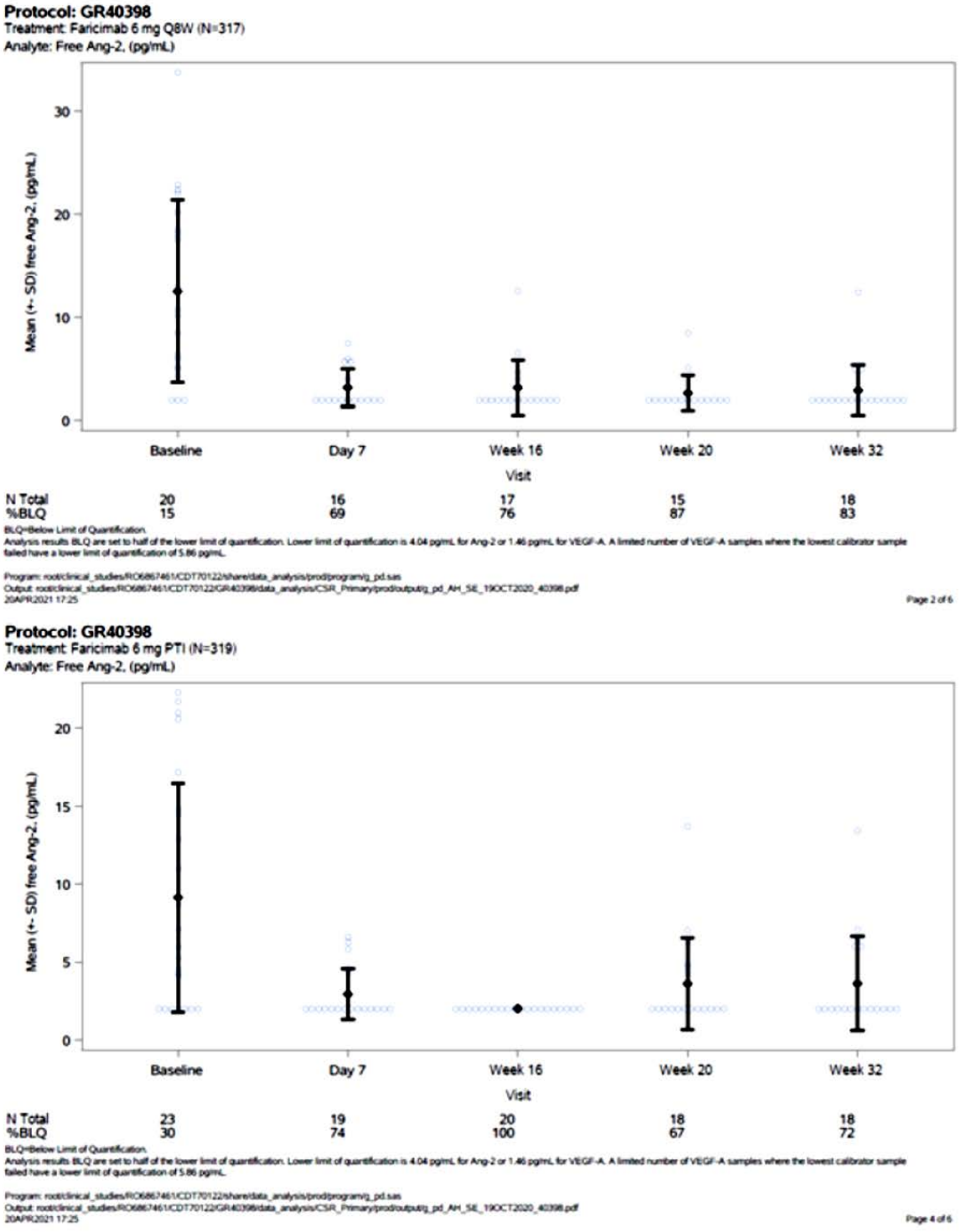


BLQ=below limit of quantification; PTI= personalized treatment interval; Q8W=every 8 weeks.
Source: CSR RHINE, Report 1102957, Figure 31

Pharmacodynamics in Aqueous Humor

High inter-patient variability was observed in AH Ang-2 (CV 60 − 87% in the Q8W arm) and VEGF-A (CV 66 − 197% in the Q8W arm) concentrations. Mean baseline Ang-2 concentrations were 12.5 (8.9) and 9.1 (7.4) -pg/mL for the Q8W and PTI arm respectively. Approximately 15-30% of the samples were BLQ at baseline and increased to up to 100% following faricimab administration. Both faricimab arms showed rapid suppression of Ang-2 starting 7 days post-dose (mean Ang-2 concentration 3 pg/mL) and mean concentrations remained below mean baseline throughout the study. Free Ang-2 concentrations in AH by treatment arm in RHINE are shown in Figure 29. Mean (SD) baseline VEGF-A concentrations were 175.6 (159.7) and 96.3 (60.9) pg/mL for the Q8W and PTI arm respectively. Both faricimab treatment arms showed rapid suppression of VEGF-A (mean VEGF-A concentration ≤ 7 pg/mL) from day 7 onwards and thereafter sustained target suppression was observed in both arms. For the Q8W arm mean VEGF-A concentration was ≤ 30 pg/mL up to the last visit. In the PTI arm mean VEGF-A concentration was highest at Week 20 (90.9 pg/mL, this value was driven by an outlier) and Week 32 (59 pg/mL) with a trend for increased VEGF-A concentrations as sampling time from last dose increased.
Free VEGF-A concentrations in AH by treatment arm in RHINE are shown in Figure 30.

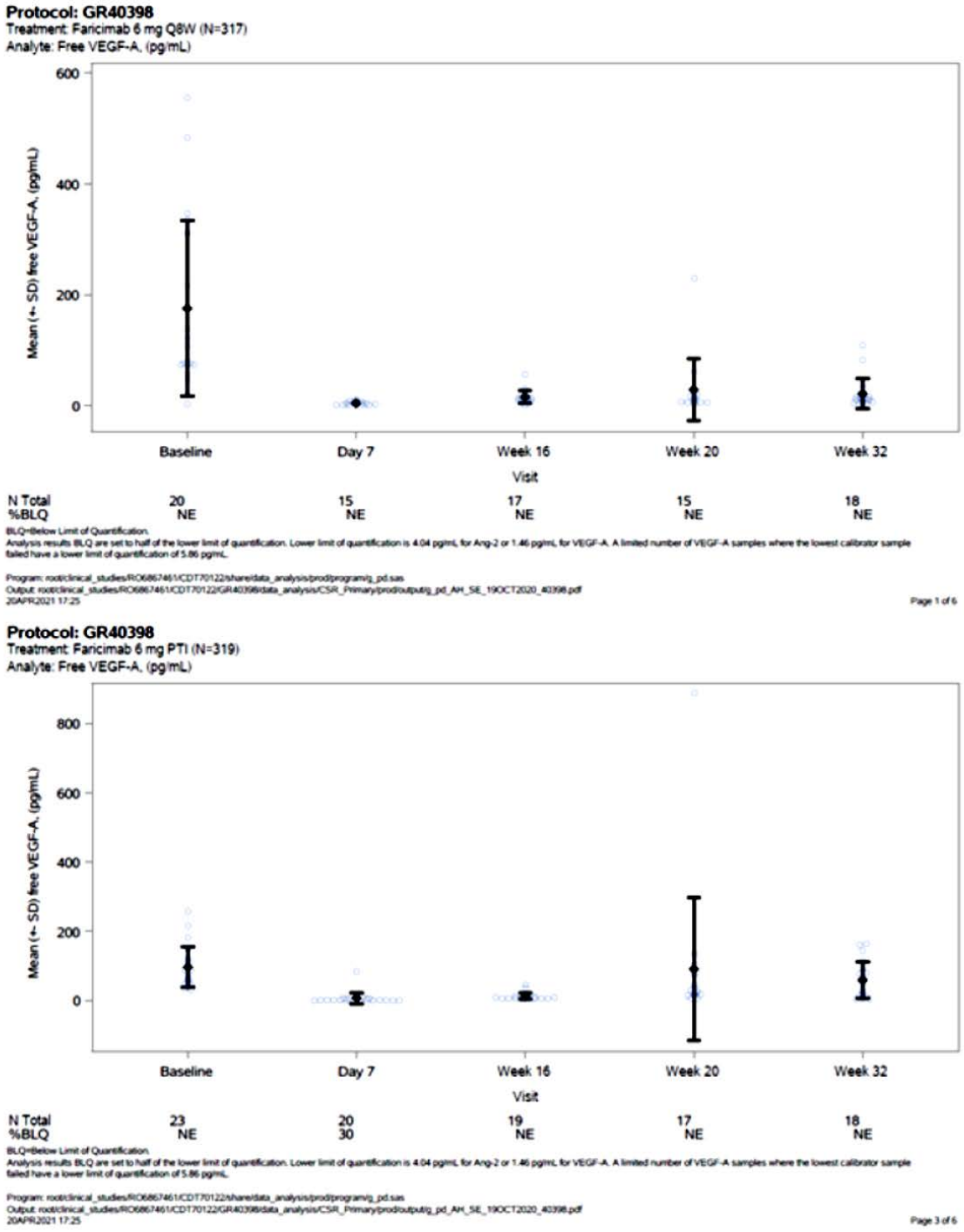
Figure 29: Aqueous Humor Free Ang-2 Concentrations by Treatment Arm (Study RHINE)



Ang-2 = angiopoietin-2 (protein); BLQ = below limit of quantification; PTI = personalized treatment interval; Q8W = every 8 weeks.

Source: CSR RHINE, Report 1102957, Figure 33

Figure 30: Aqueous Humor Free VEGF-A Concentrations by Treatment Arm (Study RHINE)



BLQ=below limit of quantification; PTI= personalized treatment interval; Q8W=every 8 weeks; VEGF-A=vascular endothelial growth factor-A.

Source: CSR RHINE, Report 1102957, Figure 32

Pharmacodynamics in Plasma

No change in free VEGF-A or in free Ang-2 was observed post-dose as compared to baseline, in any of the faricimab treatment arms.

Immunogenicity

The baseline prevalence of ADAs to faricimab in the study was 0.6%. Overall, 43/624 (6.9%) patients receiving faricimab had treatment-emergent ADAs, of which 43 were treatment-induced (20 and 23 were in the faricimab Q8W and PTI arm, respectively).

Impact of Immunogenicity on PK, Efficacy, and Safety

Population PK analyses showed that plasma ADA had an effect on vitreous elimination $t_{1/2}$. Patients with detectable ADAs had 30.4% higher ocular elimination rate. As a consequence, ADA positive patients had 23.4% lower ocular exposure at steady state compared with ADA negative patients. Presence of plasma ADA had no effect on the plasma exposure.
Given that ADA incidence was low, the impact on ocular exposure was minor, and exposure-response analysis has shown a similar response across the range of vitreous exposure in Phase 3, providing support that the changes in vitreous exposure in ADA-positive patients are unlikely to be associated with a change in efficacy.

Furthermore, results showed that there was no apparent difference between ADA-positive and ADA-negative patients in change from baseline BCVA at Week 40, Week 44 and Week 48 in patients with nAMD or change from baseline BCVA at Week 48, Week 52 and Week 56 or proportion of patients with ≥2 steps improvement in Diabetic Retinopathy Severity Scale (DRSS) from baseline to Week 52 in patients with DME and DR.

In pooled Phase 3 studies with regard to the ADA-positive subgroup the incidence of patients with SAEs was 10.7% in the faricimab arm in nAMD, and 28.1% in the faricimab Q8W arm and 26.8% in the faricimab PTI arm in DME/DR, with isolated individual events within MedDRA System Organ Classes (SOCs) and no pattern identified. Of the patients who were ADA positive and experienced ocular AEs, they were mainly non-serious, suspected not to be related to study treatment, did not result in a sustained drop in BCVA ≥ 30 letters or study withdrawal, and were not associated with severe IOI events. Incidence rate of IOI was low (≤2% in each of the disease indications. Approximately 90% of patients overall were ADA-negative; however, the incidence of IOIs was greater in ADA-positive patients. Of the 13 patients who experienced IOI events in the faricimab arms in the nAMD studies, ADA results were available for 12 patients. The incidence of IOIs in ADA-positive patients was 5/75 (6.7%), the incidence of IOIs in ADA-negative patients was 7/582 (1.2%). Patients with high ADA titers (>20000) were observed in both patients, with IOI and without IOI. Of the 17 patients who experienced IOI events through Week 56 in the faricimab arms in the DME/DR studies, the incidence of IOIs in ADA-positive patients was 11/113 (9.7%), the incidence of IOIs in ADA-negative patients was 6/1130 (0.5%) (Table 19). DME/DR patients with high ADA titers (>20000) were all in the group of patients that experienced IOI. Based on the low incidence of immunogenicity, the low incidence of IOI for which the majority of the events were of mild to moderate severity and had a reversible character, no meaningful impact of ADA was observed on overall safety.

Based on all available data, no meaningful impact of ADA was observed on efficacy and on overall safety in patients with nAMD and DME/DR. Further details on immunogenicity and its impact on PK, efficacy, and safety are summarized in Section 4.3.

4.3 Population Pharmacokinetics and Exposure-Response Analyses

Executive Summary:

Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) that selectively binds antivascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang-2). Under BLA 761235, the Applicant is seeking the Agency's approval of indication for the treatment of Neovascular (wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The recommend dose is 6 mg by intravitreal injection every 4 weeks for the first 4 doses, followed by 6 mg via intravitreal injection at intervals of up to every 16 weeks based on the assessment of disease activity after the first four monthly treatment.

In support of the proposed indication, the Applicant conducted population PK analysis with data from two Phase I studies (BP28936, JP39844), three Phase 2 studies (BP29647, CR39521, BP30099) and four Phase 3 studies (GR40306, GR40844, GR40349, GR40398) and exposure-response (E-R) analysis with the four Phase 3 studies.

The population PK and E-R analysis for faricimab by applicant are acceptable. Patients with higher VH clearance (short VH elimination half-life) and more severe disease burden in the studies tended to receive more frequent dosing of faricimab, which resulted in higher VH exposure. Overall, the recommended dosing regimen is acceptable based on the clinical experience. For all indications, the majority of patients (> 70%) had received less frequent dosing (dosing interval of 12 weeks or higher). There are some remained uncertainties for the necessity of shorter dosing interval for those patients given the relative flat E-R relationship for efficacy and increased IOI with more frequent dosing.

4.3.1 Population PK Analysis

Population PK Summary Table

General Information	
Objectives of PPK Analysis	• Develop and evaluate the population PK model to describe the pharmacokinetics of faricimab in vitreous humor (VH), aqueous humor (AH) and in plasma following intravitreal (IVT) administration.

		• Identify covariates that may impact the disposition of faricimab in patients with DME or nAMD and quantify their effects on faricimab plasma and AH PK. • Compute individual exposure measures for exposure-response analyses.
Study Included		• Phase I (BP28936, JP39844) • Phase II (BP29647, CR39521, BP30099) • Phase III (GR40306, GR40844, GR40349, GR40398) Table 18, Table 19, Table 20
Dose(s) Included		0.5 mg: 3 (0.13 %) 1.5 mg: 9 (0.4%) 3.0 mg: 110 (4.9%) 6.0 mg: 2124 (94.6%) Table 24
Population Included		• Subjects with nAMD: 880 (39.2%) • Subjects with DME: 1366 (60.8%)
Population Characteristics	General	• Age (years): Median: 68 (Range: 24 - 99), 20.7% subjects >75 years , 5.1% subjects >85 years • Weight (kg): Median: 80 (Range: 37.3 - 209) • BMI (kg/m^2): Median: 28.4 (Range: 16.5 – 85.7) • BSA (m^2): Median: 1.92 (Range: 1.21 – 3.14) • Male: 1167 (52 %) • Race: White 1843 (82.1%); Black or African American 107 (4.8%); Asian 201 (8.9%); other or unknown 95 (4.2%) • Formulation: Phase I-II 365 (16.3%), Phase III 1881 (83.7%) Table 23, Table 24
	Organ Impairment	• Hepatic Impairment: Normal: 2073 (92.3%) Mild: 121 (5.4%) Moderate: 5 (0.2%) Missing: 47 (2.1%) • Renal Impairment: Normal: 781 (34.8%) Mild: 857 (38.2%) Moderate: 532 (23.7%)

		Severe: 37 (1.6%) Failure: 2 (0.1%) Missing: 37 (1.6%) Table 24
	Pediatrics (if any)	No pediatric subjects were involved in the analysis
No. of Patients, PK Samples, and BLQ		• AH: 1095 observations from 284 patients, 68 BQL samples (6.2%) • Plasma: 8372 plasma observations from 2246 patients, 1579 BQL samples (18.9%) Table 22
Covariates Evaluated		Covariates evaluated in the population PK model were summarized in Table 21.
Final Model		**Summary**
Software and Version		The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, Version 7.5.0 The first-order conditional estimation method with LAPLACIAN and INTERACTION options was used.
Model Structure		3-compartment linear model, composed of the VH compartment, where the drug is injected, AH compartment, and the plasma compartment with clearance CL and volume V_C, VH volume was fixed to 0.0045 L. Inter-individual random effects (IIV) were included on all parameters except VH and AH volumes. The random effects on k_{VH} and k_{AH}, k_{AH} and CL were correlated. Different magnitudes of the proportional residual errors in Phase I, Phase II and Phase III trials were estimated.
Model Parameter Estimates		Table 25
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		Fixed effect parameters and IIV were estimated with good precision. The relative standard errors (RSE) for most parameters were below 13% except for the correlations between the random effects of k_{VH} and k_{AH} (29%), and k_{AH} and CL (21.1%)
BLQ for Parameter Accuracy		M3 method was used for BQL observations.
GOF, VPC		Goodness-of-fit plots for the final PK model are shown in Figure 31 and Figure 32. No apparent bias was observed in the overall model fit for the data except for the high deviations in CWRES and NPDE versus TAD at large TAD values (TAD > 50 days) due to the large fraction of BQL observations. The VPC, pcVPC, and NPDE on the final PK

	model are shown in Figure 33 - Figure 36. The model generally captured both the central tendency and the inter-individual variability of the faricimab pharmacokinetics in AH and plasma.
Significant Covariates and Clinical Relevance	The covariate effects of this model are summarized in Table 26. Ocular Disposition: Age was identified as a significant covariate for VH elimination rate constant (k_{VH}). And k_{VH} declined with age. The presence of plasma ADA (about 10% of the patients) led to shorter vitreous $t_{1/2}$ resulting in 23% decrease in vitreous exposure. Plasma Disposition: In plasma, both CL/F and Vc/F increased with body weight. Plasma clearance was 13.7% lower in female patients compared with male patients but no difference in vitreous exposure.

Table 18. Summary of Phase I studies contributing to pharmacokinetic, pharmacodynamic, and immunogenicity data

Study Number [Region]	Study Design	Patient Population	Number of Patients Enrolled	Dose, Duration	Analytes Measured		
					Faricimab PK	PD	ADA
Phase I Studies							
BP28936 [UK / US]	Phase I, Multiple Center, Single-and Multiple Ascending-Dose, Non-Randomized, Open-Label	Patients with nAMD	**Single Dose** 0.5 mg: N = 3 1.5 mg: N = 3 3.0 mg: N = 3 6.0 mg: N = 3 **Multiple Dose** 3.0 mg: N = 6 6.0 mg: N = 6	Part A: (Single Faricimab Doses): 0.5, 1.5, 3, or 6 mg intravitreal injection Part B: (Multiple Faricimab Doses): 3 or 6 mg intravitreal injections Q4W (3 doses)	AH and plasma	Ang-2: AH and plasma VEGF-A: AH and plasma	Plasma
JP39844 [Japan]	Phase I, Non-Randomized, Open-Label, Multiple Ascending Dose Study	Patients with DME and DR or nAMD	1.5 mg: N = 6 6.0 mg: N = 6	Faricimab intravitreal administration of either 1.5 mg or 6 mg dose Q4W (3 doses)	Plasma	Ang-2: plasma VEGF-A, plasma	Plasma

Source: 2.7.2 – Summary of Clinical Pharmacology Studies, Page 23, Table 1.

Table 19. Summary of nAMD studies contributing to pharmacokinetic, pharmacodynamic, and immunogenicity data

Study Number (Name) [Region]	Study Design	Patient Population	Number of Patients Enrolled	Route and Dose Regimen(s)	Analytes Measured		
					Faricimab PK	PD	ADA
Pivotal Phase III Studies							
TENAYA (GR40306) [Global] **LUCERNE** (GR40844) [Global]	Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled, 112-Week Study	Treatment-naive patients with nAMD	**TENAYA** Faricimab:N=334 Aflibercept: N=337 **LUCERNE** Faricimab: N=331 Aflibercept: N=327	• Faricimab up to Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI to Week 108 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W to Week 108 Patients will return for a final visit at Week 112.	AH and plasma	Ang-2, AH and plasma VEGF-A, AH and plasma	Plasma
Supportive Studies							
STAIRWAY (CR39521) [US]	Phase II, Multiple Regimen, Randomized, Active Comparator-Controlled, Subject and Assessor Masked, Three Parallel Groups, 52-Week Study	Patients with nAMD	Faricimab Q12W: N=29 Faricimab Q16W: N=31 Ranibizumab Q4W: N=16	• Faricimab Q12W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q12W up to Week 48 • Faricimab Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q16W up to Week 48. Patients assessed with active disease at Week 24 were switched to a Q12W regimen for the remainder of the study. • Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 48 weeks	AH and plasma	Ang-2, AH and plasma VEGF-A, AH and plasma	Plasma
AVENUE (BP29647) [US]	Phase II, Multiple Center, Multiple Dose and Regimen, Randomized, Active Comparator-Controlled, Double-Masked, Five Parallel Groups, 36-Week Study	Patients with nAMD	**Faricimab** 1.5 mg Faricimab Q4W: N=46 6 mg Faricimab Q4W: N=39 6 mg Faricimab Q8W: N=46 **Ranibizumab** 0.5 mg Ranibizumab Q4W: N=68 0.5 mg Ranibizumab Q4W±6 mg Faricimab Q4W: N=64	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q8W (i.e., on Weeks 20 and 28) • 0.5 mg Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 32 weeks 0.5 m Ranibizumab Q4W+6 mg Faricimab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W up to Week 8, followed by 6 mg faricimab intravitreal injections Q4W to Week 32	AH and plasma	Ang-2, AH and plasma VEGF-A, AH and plasma	Plasma

ADA= anti-drug antibodies; AH=aqueous humor; Ang-2=angiopoietin-2; nAMD=neovascular age-related macular degeneration; PD=pharmacodynamic; PK=pharmacokinetic; PTI=personalized treatment interval; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks; VEGF-A=vascular endothelial growth factor-A.

Source: 2.7.2 – Summary of Clinical Pharmacology Studies, Page 35-37, Table 5.

Table 20. Summary of Phase III and Phase II DME and DR studies contributing to pharmacokinetic, pharmacodynamic, and immunogenicity data.

Study Number (Name) [Region]	Study Design	Patient Population	Number of Patients Enrolled	Dose, Duration	Analytes Measured		
					Faricimab PK	PD	ADA
Pivotal Phase III Studies							
YOSEMITE (GR40349) [Global] **RHINE** (GR40398) [Global]	Phase III, Randomized, Double−Masked, Active Comparator-Controlled, Three Parallel Groups, 100−Week Study	Patients with DME, DR	**YOSEMITE** Faricimab Q8W: N=315 (N=238 treatment-naive) Faricimab PTI: N=313 (N=245 treatment-naive) Aflibercept: N=311 (N=242 treatment-naive) **RHINE** Faricimab Q8W: N=317 (N=254 treatment-naive) Faricimab PTI: N=319 (N=255 treatment-naive) Aflibercept: N=315 (N=248 treatment-naive)	• Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W to Week 20 followed by Q8W to Week 96 • Faricimab PTI [a]: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI to Week 96 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W to Week 16 followed by Q8W to Week 96	AH and plasma	Ang-2: AH and plasma VEGF-A: AH and plasma	Plasma
Supportive Study							
BOULEVARD (BP30099) [US]	Phase II, Multiple Center, Multiple Dose, Randomized, Active Comparator−Controlled, Double−Masked, Three Parallel Groups, 36−week Study	Patients with DME, DR	1.5 mg Faricimab Q4W: N=90 (59 treatment-naive; 31 prior anti-VEGF treated) 6 mg Faricimab Q4W: N=55 (54 treatment-naive; 1 prior anti-VEGF treated) 0.3 mg Ranibizumab Q4W: N=84 (55 treatment-naive; 29 prior anti-VEGF treated)	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 20 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 20 weeks • 0.3 mg Ranibizumab Q4W: 0.3 mg ranibizumab intravitreal injections Q4W for 20 weeks Followed by an observational period (up to 16 weeks); if eligible, patients received one injection of 0.3 mg ranibizumab then exited the study	AH and plasma	Ang-2: AH and plasma VEGF-A: AH and plasma	Plasma

ADA = anti-drug antibodies; AH = aqueous humor; Ang-2 = angiopoietin-2; DME = diabetic macular edema; DR = diabetic retinopathy, PD = pharmacodynamic; PK = pharmacokinetic; PTI = personalized treatment interval; Q4W = every 4 weeks; Q8W = every 8 weeks;; VEGF = vascular endothelial growth factor; VEGF-A = vascular endothelial growth factor-A.

Source: 2.7.2 – Summary of Clinical Pharmacology Studies, Page 66-67, Table 8.

Table 21. Covariates investigated in population PK analysis.

Covariate	Parameter	Rationale
Weight	CL and V_C	Body size influences model parameters for many of known drugs. Influence of weight was evaluated by inclusion into the model. Effects of BSA and BMI were evaluated by diagnostic plots.
Sex	CL and V_C	Evaluation of the sex effect is clinically important. Sex may influence clearance and/or volume. Its influence was evaluated by inclusion into the model.
Age	k_{VH} and k_{AH}	Evaluation of the age effect is clinically important. Its influence was evaluated by inclusion into the model.
Race	k_{VH}, k_{AH}, CL, and V_C	Evaluation of the race effect is clinically important. Its influence was evaluated graphically.
Formulation	k_{VH}	Formulation may impact the extent of drug absorption. It is important to determine whether faricimab exposure is affected by formulation. Its influence was evaluated by inclusion into the model.
Anti-drug antibodies (ADA) subgroup	CL, k_{VH}, k_{AH}	ADAs can reduce exposure. Their influence was evaluated by inclusion into the model.
Normalized creatinine clearance, Renal impairment	CL	Markers of renal function were investigated only by diagnostic plots, as the high molecular weight of faricimab precludes its elimination through renal excretion.
ALT, AST, total bilirubin, total protein. Hepatic Impairment	CL	Markers of hepatic function and hepatic impairment were investigated only by diagnostic plots as they are not expected to influence faricimab PK.
Disease: DME versus nAMD	k_{VH}, k_{AH}, CL	The effect of the disease was evaluated by inclusion in the model.
nAMD: type of CNV, Pigment epithelium detachment thickness, cystoid spaces, lesion thickness, IOP, cataract surgery	k_{VH} and k_{AH}	Effects of the disease characteristics for sub-populations with sufficient representation were evaluated by diagnostic plots.
DME : NPDR/PDR, laser history, history of prior steroids, Naive/not Naive, IOP, cataract surgery, PRP	k_{VH} and k_{AH}	Effects of the disease characteristics for sub-populations with sufficient representation was evaluated by diagnostic plots.

Source: PK and ER of Faricimab, Report # 1105763, Page 66, Table 2.

Table 22. Summary of number of subjects and observations, by study

Compartment	Study	Number of subjects	Total number of observations	Number (%) of quantifiable samples	Number (%) of BQL samples
AH	**Total**	**284**	**1095**	**1027 (93.8%)**	**68 (6.2%)**
	BP28936	4	24	24 (100%)	0 (0%)
	BP29647	23	67	67 (100%)	0 (0%)
	BP30099	50	272	253 (93%)	19 (7%)
	CR39521	14	56	47 (83.9%)	9 (16.1%)
	GR40306	45	160	148 (92.5%)	12 (7.5%)
	GR40349	73	242	233 (96.3%)	9 (3.7%)
	GR40398	42	135	130 (96.3%)	5 (3.7%)
	GR40844	33	139	125 (89.9%)	14 (10.1%)
Plasma	**Total**	**2246**	**8372**	**6793 (81.1%)**	**1579 (18.9%)**
	BP28936	23	198	165 (83.3%)	33 (16.7%)
	BP29647	135	766	726 (94.8%)	40 (5.2%)
	BP30099	137	874	691 (79.1%)	183 (20.9%)
	CR39521	58	261	174 (66.7%)	87 (33.3%)
	JP39844	12	132	117 (88.6%)	15 (11.4%)
	GR40306	330	1214	1034 (85.2%)	180 (14.8%)
	GR40349	615	1886	1425 (75.6%)	461 (24.4%)
	GR40398	606	1814	1408 (77.6%)	406 (22.4%)
	GR40844	330	1227	1053 (85.8%)	174 (14.2%)

Source: PK and ER of Faricimab, Report # 1105763, Page 67, Table 3.

Table 23. Summary of continuous covariates at baseline, overall, by study phase, and by disease.

Covariate	Median (Range)				
	All	Phase I-II	Phase III	DME	nAMD
N	2246	365	1881	1366	880
WT	80 [37.3-209]	78.5 [42.1-147]	80 [37.3-209]	83.9 [40.5-209]	73.5 [37.3-172]
BMI	28.4 [16.5-85.7]	27.9 [16.7-57.2]	28.5 [16.5-85.7]	29.4 [17.3-85.7]	27 [16.5-58.1]
BSA	1.92 [1.21-3.14]	1.9 [1.29-2.66]	1.93 [1.21-3.14]	1.98 [1.28-3.14]	1.83 [1.21-2.87]
AGE	68 [24-99]	72 [34-96]	67 [24-99]	63 [24-91]	77 [50-99]
CREAT	80 [35-1410]	80.4 [35.4-1410]	80 [35-579]	84 [35-826]	79 [35-1410]
CRCL	77.5 [2-381]	67.6 [2-262]	79.9 [17.3-381]	87.3 [10.3-381]	65.5 [2-189]
NCRCL	70.1 [2.4-221]	63 [2.4-204]	72.1 [15.1-221]	77.1 [8.1-221]	63.1 [2.4-133]
LOWLUM	33 [0-78]	27 [0-63]	33 [0-78]	-	33 [0-78]
AST	19 [6-175]	19 [8-169]	19 [6-175]	18 [6-86]	20 [8-175]
ALT	18 [5-215]	17 [5-144]	18 [5-215]	18 [5-215]	16 [5-144]
TBILI	7 [1.5-51]	6.84 [1.71-32.5]	7 [1.5-51]	6 [1.5-35]	7 [1.5-51]
HBA1C	7.4 [3.6-11.9]	6.1 [3.6-11.9]	7.5 [5-11.6]	7.5 [4.8-11.9]	5.7 [3.6-7.6]
LEAK	5.46 [0-46.6]	5.92 [0-26.2]	5.29 [0.01-46.6]	0 [0-20.3]	5.52 [0.01-46.6]
SFTM	75.2 [0-529]	47.8 [0-529]	95.5 [10-489]	0 [0-529]	96 [0-489]
BCVA	64 [8-86]	61 [8-85]	64 [24-86]	64 [15-86]	62 [8-83]
CST	410 [124-1170]	400 [132-1000]	412 [124-1170]	457 [234-1170]	336 [124-1010]
PEDT	180 [0-1030]	154 [0-858]	191 [45-1030]	-	180 [0-1030]
LESTHIC	580 [323-1120]	580 [323-1120]	-	-	580 [323-1120]
DRSS	43 [10-90]	47 [20-90]	43 [10-90]	43 [10-90]	-
MAEDTO	30.9 [3.4-75.7]	30.9 [3.4-75.7]	-	30.9 [3.4-75.7]	-
Free AH VEGF-A	74 [1.46-1120]	88.8 [4.47-503]	65.8 [1.46-1120]	102 [3.69-1120]	53.3 [1.46-182]
Free AH Ang-2	5.9 [1.12-56.3]	4.57 [1.12-34.8]	6.65 [4.04-56.3]	8.62 [1.12-55.9]	4.39 [1.12-56.3]
Free Plasma VEGF-A	20.6 [0-423]	0 [0-177]	21.5 [3.66-423]	21.3 [0-391]	19.4 [0-423]
Free Plasma Ang-2	1.5 [0-20.8]	1.89 [0-10.4]	1.47 [0.3-20.8]	1.54 [0-20.8]	1.47 [0-13.6]
Plasma Ang-2	1.68 [0.124-21.4]	1.72 [0.124-13.5]	1.67 [0.3-21.4]	1.7 [0.124-21.4]	1.65 [0.128-14.2]

Source: PK and ER of Faricimab, Report # 1105763, Page 68-69, Table 4.

Table 24. Summary of categorical covariates at baseline, overall, by study phase, and by disease: number (percent) of subjects

Covariate		All	Phase I-II	Phase III	DME	nAMD
Name	Level					
LDOS: Dose (mg)	0.5	3 (0.1%)	3 (0.8%)	-	-	3 (0.3%)
	1.5	110 (4.9%)	110 (30.1%)	-	59 (4.3%)	51 (5.8%)
	3	9 (0.4%)	9 (2.5%)	-	-	9 (1%)
	6	2124 (94.6%)	243 (66.6%)	1881 (100%)	1307 (95.7%)	817 (92.8%)
Disease (DIS)	DME	1366 (60.8%)	145 (39.7%)	1221 (64.9%)	1366 (100%)	-
	nAMD	880 (39.2%)	220 (60.3%)	660 (35.1%)	-	880 (100%)
NAIVE	Naive, nAMD	880 (39.2%)	220 (60.3%)	660 (35.1%)	-	880 (100%)
	Not naive, DME	309 (13.8%)	38 (10.4%)	271 (14.4%)	309 (22.6%)	-
	Naive, DME	1057 (47.1%)	107 (29.3%)	950 (50.5%)	1057 (77.4%)	-
ADA	No	2028 (90.3%)	332 (91%)	1696 (90.2%)	1245 (91.1%)	783 (89%)
	Yes	218 (9.7%)	33 (9%)	185 (9.8%)	121 (8.9%)	97 (11%)
Sex (SEXF)	Male	1167 (52%)	154 (42.2%)	1013 (53.9%)	820 (60%)	347 (39.4%)
	Female	1079 (48%)	211 (57.8%)	868 (46.1%)	546 (40%)	533 (60.6%)
Race (RACE)	White	1843 (82.1%)	315 (86.3%)	1528 (81.2%)	1057 (77.4%)	786 (89.3%)
	Black	107 (4.8%)	25 (6.8%)	82 (4.4%)	104 (7.6%)	3 (0.3%)
	Asian	201 (8.9%)	14 (3.8%)	187 (9.9%)	132 (9.7%)	69 (7.8%)
	Am.Ind. or AlaskVH	16 (0.7%)	3 (0.8%)	13 (0.7%)	13 (1%)	3 (0.3%)
	Hawaiian or Pacific	4 (0.2%)	-	4 (0.2%)	4 (0.3%)	-
	Unknown	75 (3.3%)	8 (2.2%)	67 (3.6%)	56 (4.1%)	19 (2.2%)
REGION	N. America	1201 (53.5%)	344 (94.2%)	857 (45.6%)	680 (49.8%)	521 (59.2%)
	Europe	630 (28%)	9 (2.5%)	621 (33%)	417 (30.5%)	213 (24.2%)
	Japan	78 (3.5%)	12 (3.3%)	66 (3.5%)	48 (3.5%)	30 (3.4%)
	Asia	150 (6.7%)	-	150 (8%)	90 (6.6%)	60 (6.8%)
	S. America	149 (6.6%)	-	149 (7.9%)	113 (8.3%)	36 (4.1%)
	Oceania	38 (1.7%)	-	38 (2%)	18 (1.3%)	20 (2.3%)
Formulation	Ph. 1-2	365 (16.3%)	365 (100%)	-	145 (10.6%)	220 (25%)
	Ph. 3	1881 (83.7%)	-	1881 (100%)	1221 (89.4%)	660 (75%)
Renal Impairment (RENIMP)	Miss.	37 (1.6%)	9 (2.5%)	28 (1.5%)	25 (1.8%)	12 (1.4%)
	Normal	781 (34.8%)	90 (24.7%)	691 (36.7%)	614 (44.9%)	167 (19%)
	Mild	857 (38.2%)	150 (41.1%)	707 (37.6%)	479 (35.1%)	378 (43%)
	Moderate	532 (23.7%)	104 (28.5%)	428 (22.8%)	234 (17.1%)	298 (33.9%)
	Severe	37 (1.6%)	10 (2.7%)	27 (1.4%)	13 (1%)	24 (2.7%)
	Failure	2 (0.1%)	2 (0.5%)	-	1 (0.1%)	1 (0.1%)
Hepatic Impairment (HEPIMP)	Miss.	47 (2.1%)	10 (2.7%)	37 (2%)	27 (2%)	20 (2.3%)
	Normal	2073 (92.3%)	331 (90.7%)	1742 (92.6%)	1266 (92.7%)	807 (91.7%)
	Mild	121 (5.4%)	23 (6.3%)	98 (5.2%)	70 (5.1%)	51 (5.8%)
	Severe	5 (0.2%)	1 (0.3%)	4 (0.2%)	3 (0.2%)	2 (0.2%)
FET	No	1073 (47.8%)	239 (65.5%)	834 (44.3%)	451 (33%)	622 (70.7%)
	Yes	1173 (52.2%)	126 (34.5%)	1047 (55.7%)	915 (67%)	258 (29.3%)
Type of CNV	Miss.	1380 (61.4%)	148 (40.5%)	1232 (65.5%)	1366 (100%)	14 (1.6%)
	Occult	455 (20.3%)	109 (29.9%)	346 (18.4%)	-	455 (51.7%)
	Classic & Occult, Minimally Classic	142 (6.3%)	81 (22.2%)	61 (3.2%)	-	142 (16.1%)
	Classic or Predominantly Classic	230 (10.2%)	27 (7.4%)	203 (10.8%)	-	230 (26.1%)
	RAP	28 (1.2%)	-	28 (1.5%)	-	28 (3.2%)
	PCV	11 (0.5%)	-	11 (0.6%)	-	11 (1.2%)
SF	Miss.	942 (41.9%)	272 (74.5%)	670 (35.6%)	147 (10.8%)	795 (90.3%)
	No	783 (34.9%)	18 (4.9%)	765 (40.7%)	770 (56.4%)	13 (1.5%)
	Yes	521 (23.2%)	75 (20.5%)	446 (23.7%)	449 (32.9%)	72 (8.2%)
CYSSPA	Miss.	1403 (62.5%)	173 (47.4%)	1230 (65.4%)	1366 (100%)	37 (4.2%)
	No	354 (15.8%)	60 (16.4%)	294 (15.6%)	-	354 (40.2%)
	Yes	489 (21.8%)	132 (36.2%)	357 (19%)	-	489 (55.6%)
PDR/ NPDR	Miss.	885 (39.4%)	220 (60.3%)	665 (35.4%)	5 (0.4%)	880 (100%)
	not PDR orNPDR	53 (2.4%)	4 (1.1%)	49 (2.6%)	53 (3.9%)	-
	PDR	105 (4.7%)	9 (2.5%)	96 (5.1%)	105 (7.7%)	-
	NPDR	1203 (53.6%)	132 (36.2%)	1071 (56.9%)	1203 (88.1%)	-
STEROID	Miss.	228 (10.2%)	228 (62.5%)	-	8 (0.6%)	220 (25%)
	No	1922 (85.6%)	133 (36.4%)	1789 (95.1%)	1264 (92.5%)	658 (74.8%)
	Yes	96 (4.3%)	4 (1.1%)	92 (4.9%)	94 (6.9%)	2 (0.2%)
LASER	No	2242 (99.8%)	365 (100%)	1877 (99.8%)	1362 (99.7%)	880 (100%)
	Yes	4 (0.2%)	-	4 (0.2%)	4 (0.3%)	-
CATARACT	No	1010 (45%)	155 (42.5%)	855 (45.5%)	764 (55.9%)	246 (28%)
	Yes	1236 (55%)	210 (57.5%)	1026 (54.5%)	602 (44.1%)	634 (72%)
PRP	Miss.	12 (0.5%)	12 (3.3%)	-	8 (0.6%)	4 (0.5%)
	No	2059 (91.7%)	353 (96.7%)	1706 (90.7%)	1183 (86.6%)	876 (99.5%)
	Yes	175 (7.8%)	-	175 (9.3%)	175 (12.8%)	-
IOP	Miss.	12 (0.5%)	12 (3.3%)	-	8 (0.6%)	4 (0.5%)
	No	2185 (97.3%)	346 (94.8%)	1839 (97.8%)	1322 (96.8%)	863 (98.1%)
	Yes, study eye	44 (2%)	2 (0.5%)	42 (2.2%)	31 (2.3%)	13 (1.5%)
	Yes, unknown eye	5 (0.2%)	5 (1.4%)	-	5 (0.4%)	-
REG Dosing regimen at Week 52 (DME) or Week 48 (nAMD)	Miss.	1042 (46.4%)	365 (100%)	677 (36%)	790 (57.8%)	252 (28.6%)
	Q4W	71 (3.2%)	-	71 (3.8%)	71 (5.2%)	-
	Q8W	221 (9.8%)	-	221 (11.7%)	89 (6.5%)	132 (15%)
	Q12W	330 (14.7%)	-	330 (17.5%)	120 (8.8%)	210 (23.9%)
	Q16W	582 (25.9%)	-	582 (30.9%)	296 (21.7%)	286 (32.5%)

Source: PK and ER of Faricimab, Report # 1105763, Page 74-76, Table 8.

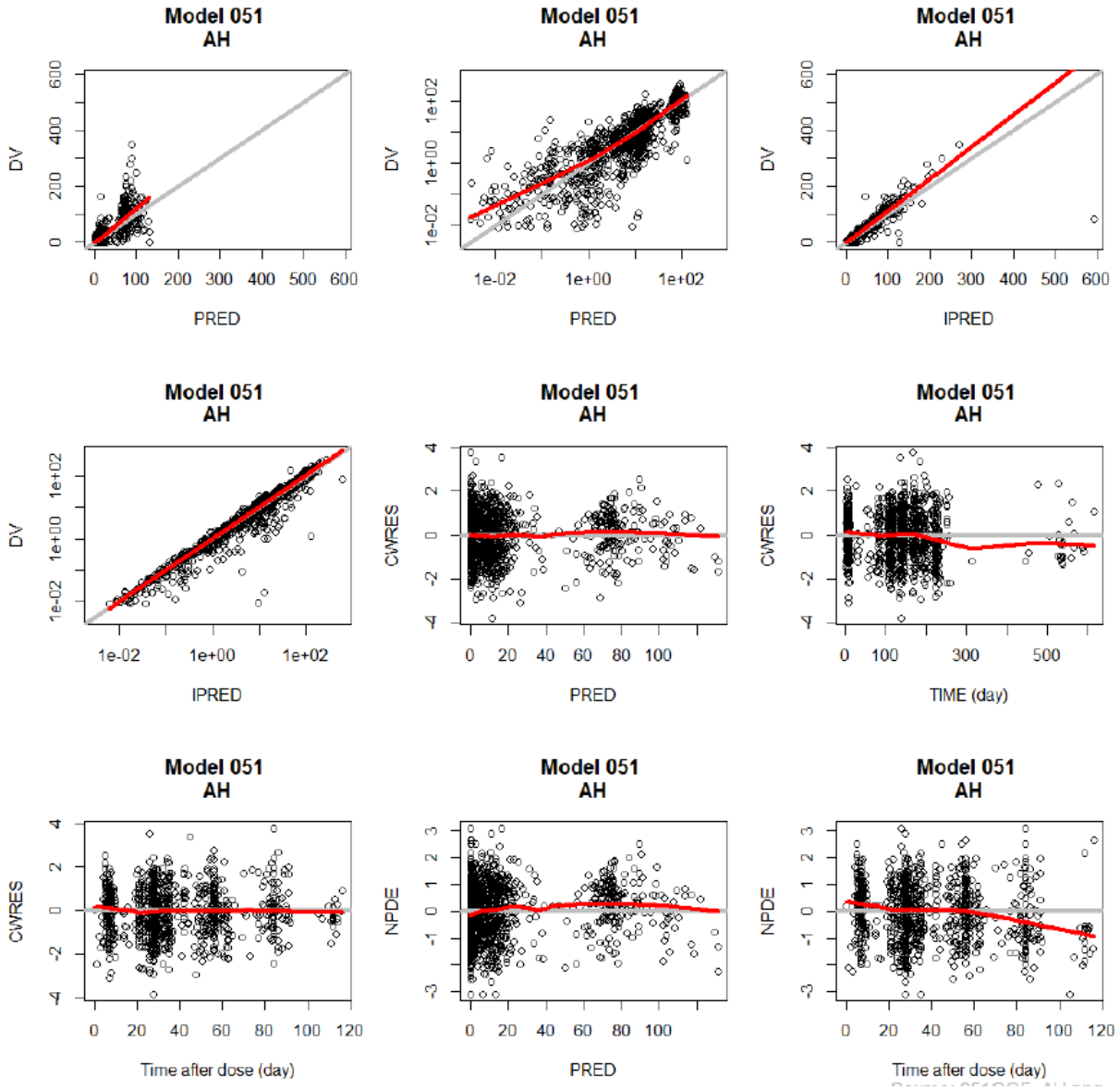
Table 25. Parameter estimates of the final faricimab population PK model

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
V_A (mL)	θ_1	0.253	12.4	0.191 ; 0.315		
V_C (L)	θ_2	1.48	4.47	1.35 ; 1.61		
k_{VH} (1/day)	θ_3	0.0929	0.674	0.0917 ; 0.0941		
k_{AH} (1/day)	θ_4	15.6	12.9	11.6 ; 19.5		
CL (L/day)	θ_5	2.33	1.29	2.27 ; 2.39		
SD_{prop}	θ_6	0.414	1.44	0.402 ; 0.426		
SD_{PhaseI}	θ_7	0.614	5.28	0.55 ; 0.677		
$SD_{PhaseII}$	θ_8	0.788	2.61	0.748 ; 0.828		
$V_{C,WT}$	θ_9	1.00	10.6	0.795 ; 1.21		
CL_{WT}	θ_{10}	0.773	4.88	0.699 ; 0.847		
CL_{female}	θ_{11}	0.863	1.56	0.836 ; 0.889		
$CL_{formulation1}$	θ_{12}	0.816	1.71	0.788 ; 0.843		
$k_{VH,age}$	θ_{13}	-0.533	6.46	-0.6 ; -0.465		
$k_{VH,ADA}$	θ_{14}	1.30	1.5	1.27 ; 1.34		
$k_{AH,formulation1}$	θ_{15}	0.719	6.48	0.628 ; 0.81		
ω^2_{VC}	$\Omega(1,1)$	1.34	5.4	1.2 ; 1.48	CV=115.6%	60.5%
ω^2_{kVH}	$\Omega(2,2)$	0.087	2.33	0.083 ; 0.091	CV=29.5%	5.0%
R ω_{kVH} ω_{kAH}	$\Omega(2,3)$	0.0251	29	0.0108 ; 0.0394	R=0.174	
ω^2_{kAH}	$\Omega(3,3)$	0.24	9.11	0.197 ; 0.282	CV=48.9%	60.0%
R ω_{kAH} ω_{CL}	$\Omega(3,4)$	0.0311	21.1	0.0182 ; 0.0439	R=0.349	
ω^2_{CL}	$\Omega(4,4)$	0.0331	7.75	0.028 ; 0.0381	CV=18.2%	52.9%
ω^2_{ε}	$\Omega(5,5)$	0.086	7.03	0.0741 ; 0.0978	CV=29.3%	42.3%
σ^2_{AH}	$\Sigma(1,1)$	1	Fixed			10.6%
σ^2_{plasma}	$\Sigma(2,2)$	1	Fixed			17.5%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100·abs(SE/PE); 95% CI: 95% confidence interval; SD: Standard Deviation; CV: coefficient of variation, CV = 100*SD %.

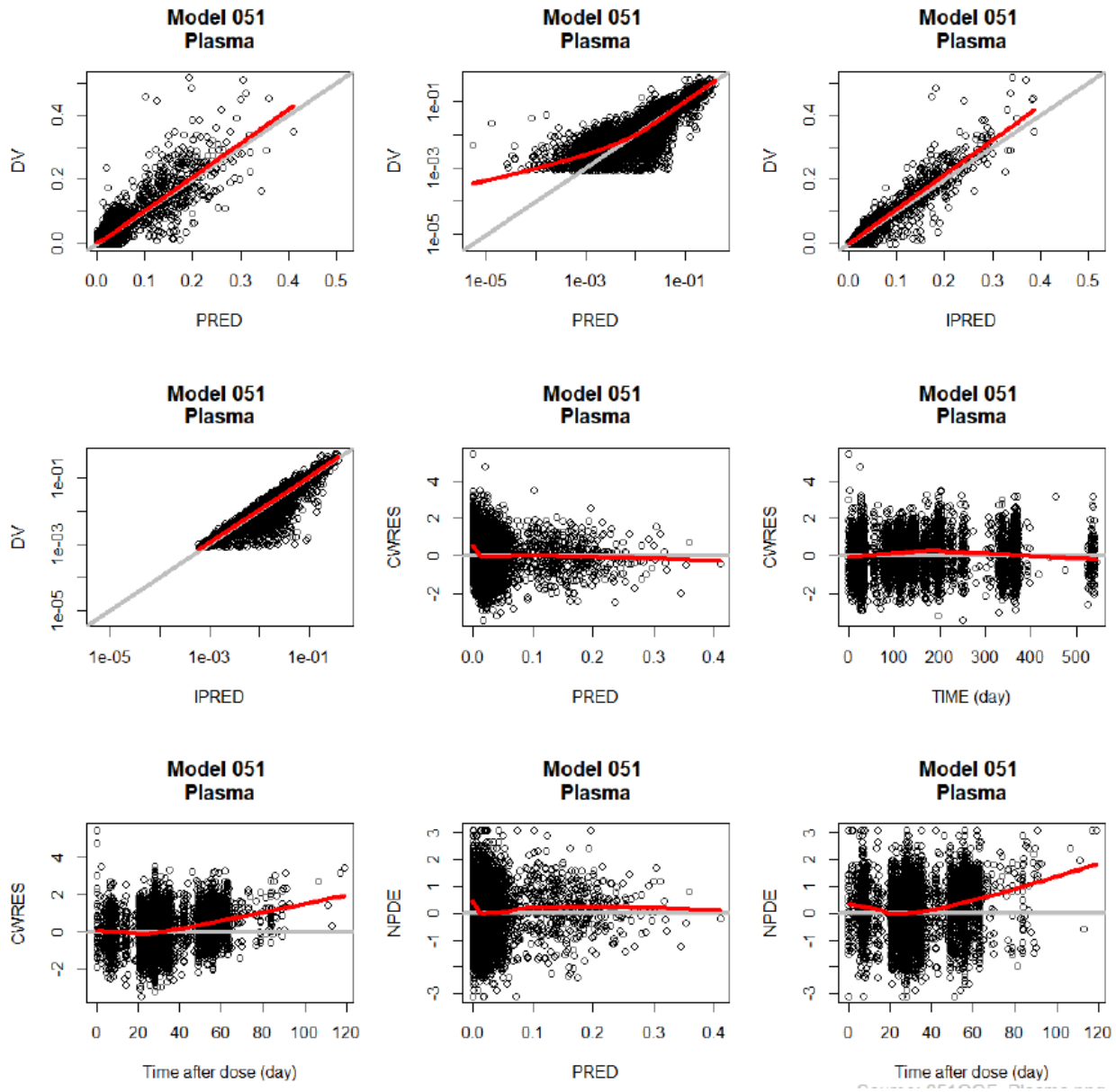
Source: PK and ER of Faricimab, Report # 1105763, Page 84, Table 14.

Figure 31. Goodness of fit plots for final model: AH



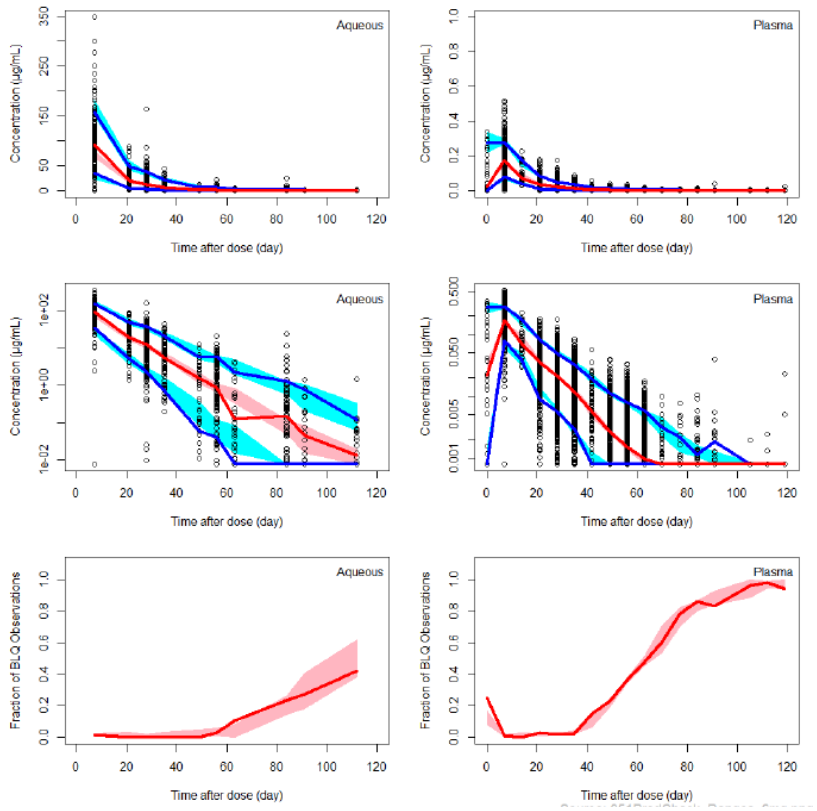
Source: PK and ER of Faricimab, Report # 1105763, Page 141, Figure 45.

Figure 32. Goodness of fit plots for final model: plasma



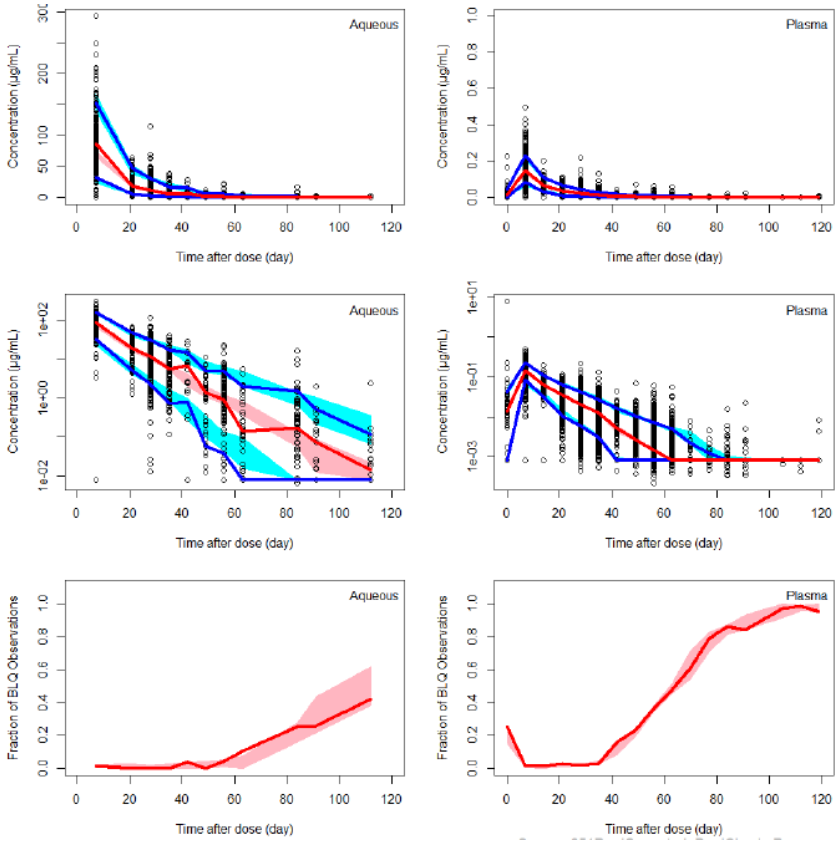
Source: PK and ER of Faricimab, Report # 1105763, Page 142, Figure 46.

Figure 33. VPC for final model following 6 mg Dose.



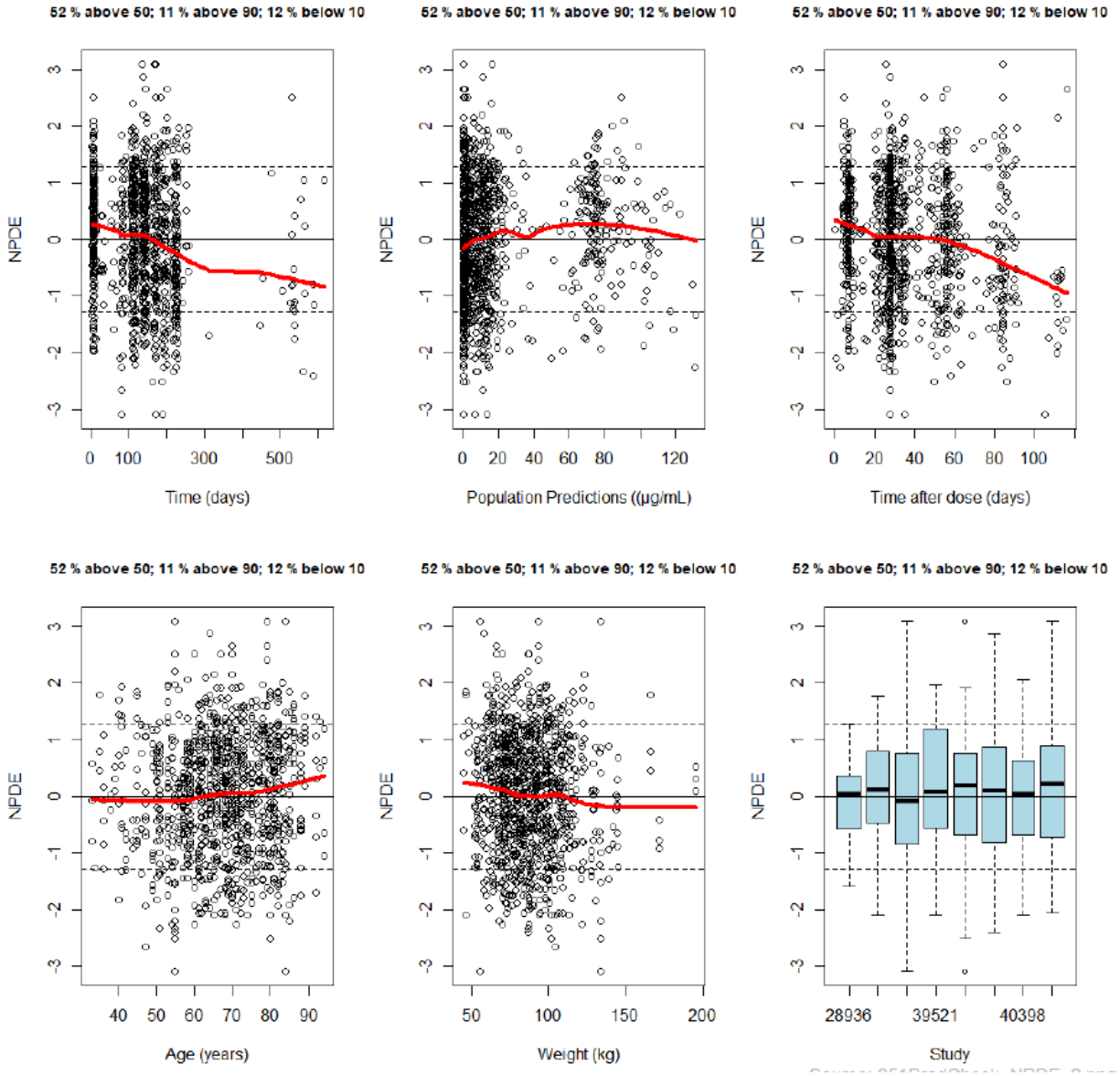
Source: PK and ER of Faricimab, Report # 1105763, Page 189, Figure 93.

Figure 34. pcVPC for final model (All Data)



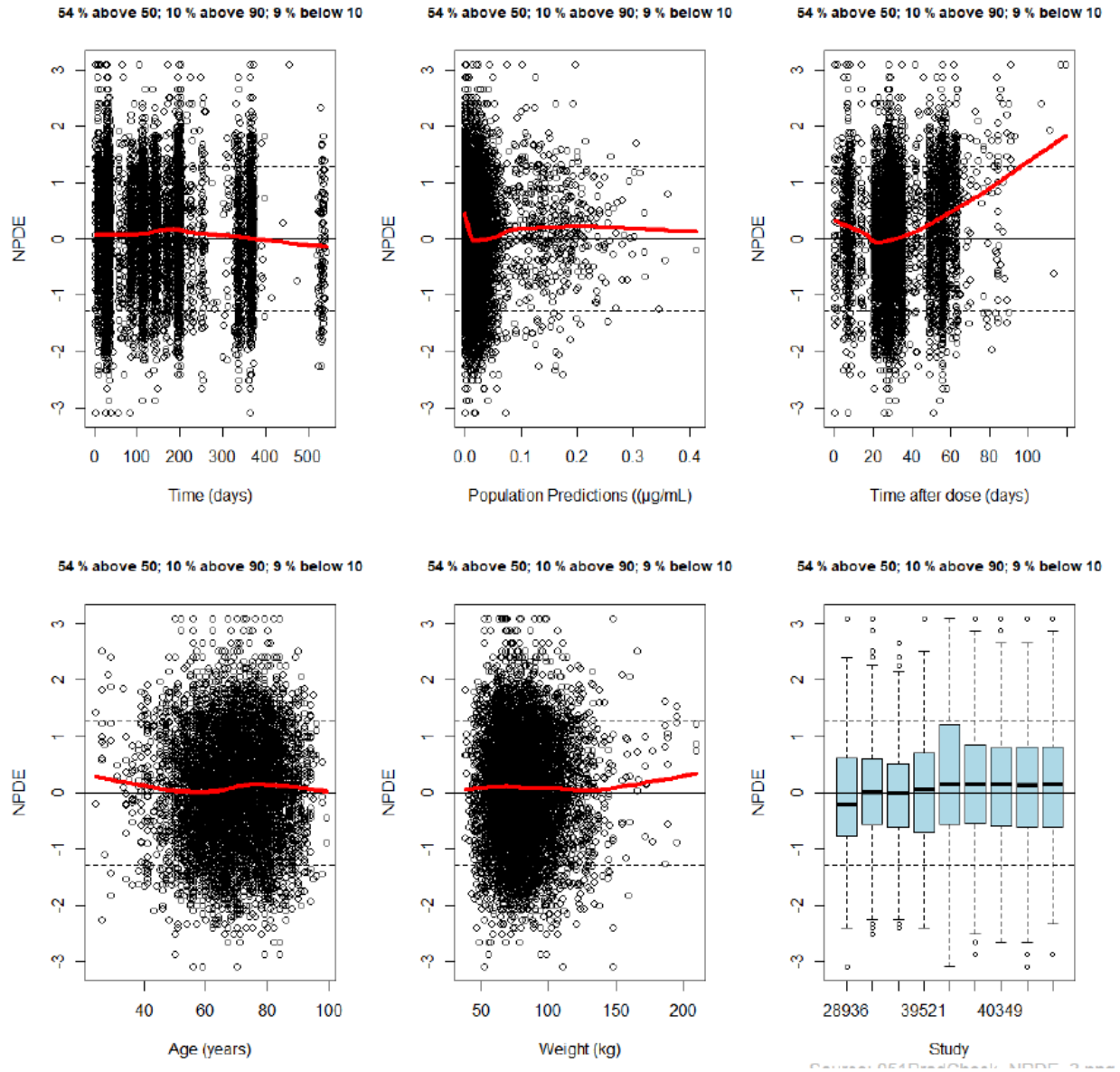
Source: PK and ER of Faricimab, Report # 1105763, Page 190, Figure 94.

Figure 35. NPDE plots for final model: AH



Source: PK and ER of Faricimab, Report # 1105763, Page 191, Figure 95.

Figure 36. NPDE Plots for final model: plasma



Source: PK and ER of Faricimab, Report # 1105763, Page 192, Figure 96.

Table 26.Covariate effects of faricimab as estimated by final population PK model

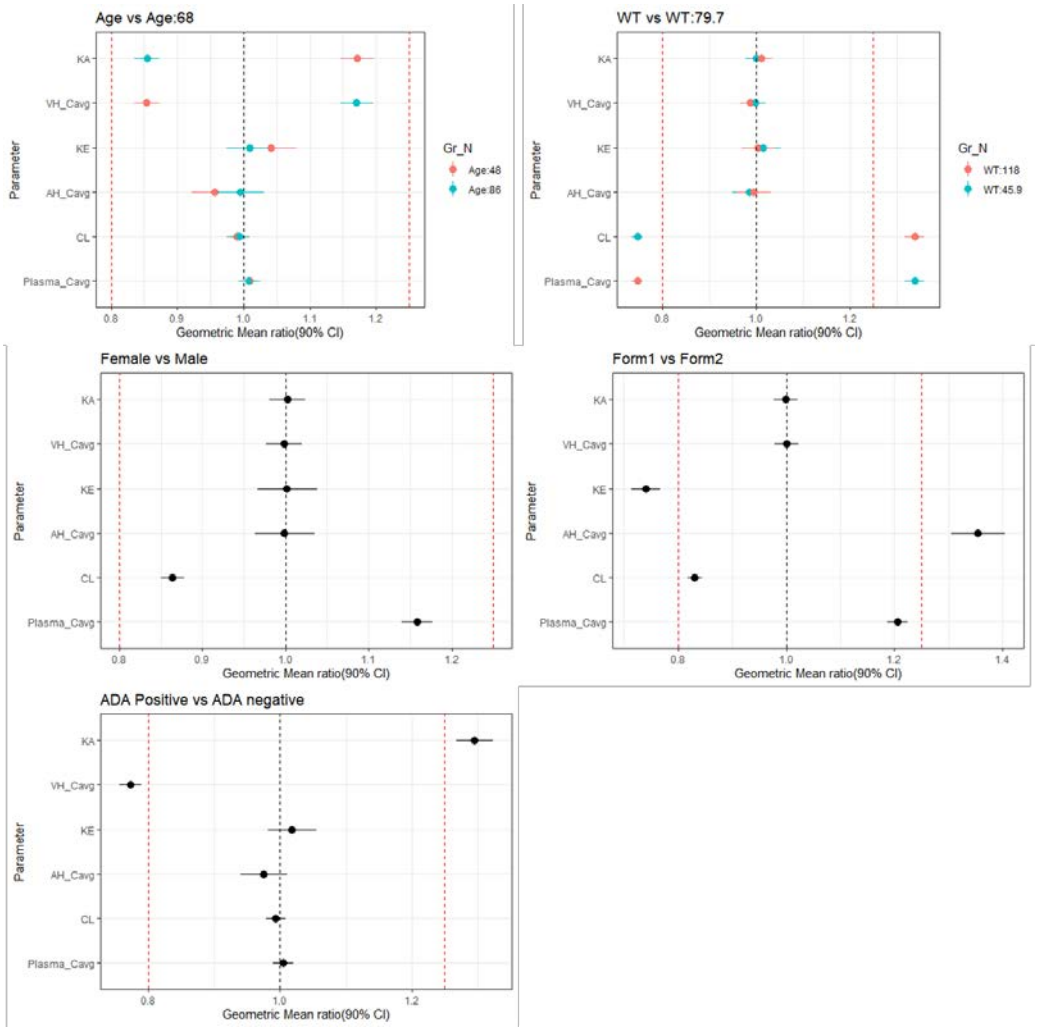
Parameter	Covariate	Reference	Value	Effect [95%CI]
Central Volume (V_C)	Weight (kg)	80	51	-36.4 [-42.1;-30.1]
			129	61.5 [46.2;78.4]
Clearance (CL)	Weight	80	51	-29.4 [-31.7;-27]
			129	44.7 [39.7;49.9]
	SEXF	Male	Female	-13.7 [-16.4;-11.1]
	Formulation	Phase III	Phase I-II	-18.4 [-21.2;-15.7]
VH elimination rate constant (k_{VH})	Age (years)	65	44	23.1 [19.9;26.4]
			89	-15.4 [-17.1;-13.6]
	ADA	no ADA	ADA	30.4 [26.6;34.3]
AH elimination rate constant (k_{AH})	Formulation	Phase III	Phase I-II	-28.1 [-37.2;-19]
Plasma AUC	Weight	80	51	41.6 [37;46.4]
			129	-30.9 [-33.3;-28.4]
	SEXF	Male	Female	15.9 [12.5;19.6]
	Formulation	Phase III	Phase I-II	22.6 [18.6;26.9]
VH AUC	Age (years)	65	44	-18.8 [-20.9;-16.6]
			89	18.1 [15.7;20.7]
	ADA	no ADA	ADA	-23.3 [-25.5;-21]
AH AUC	Formulation	Phase III	Phase I-II	39.1 [23.5;59.4]

Source: PK and ER of Faricimab, Report # 1105763, Page 85, Table 15.

The FDA's Comments:

The population PK model developed by the applicant was verified by the reviewer. The model appears to be reasonable in general given the good agreement between observations and predictions for faricimab concentration in AH and plasma. The covariates effects were shown in Figure 37. Age was identified as a significant covariate on k_{VH}. Old patients tend to have lower VH elimination rate and higher VH exposure. ADAs, detected in about 10% of the patients, also affect the VH elimination rate. Patients with ADAs were predicted to have higher k_{VH} and lower faricimab exposure in VH. The age and ADA effect on efficacy or safety (IOI) may be limited due to the relatively flat E-R relationship with VH elimination rate. Renal impairment, race and gender were not identified as significant covariate for VH elimination rate. Empirical bayes estimation of k_{VH} and CL/F in subjects with mild to severe renal impairment were similar. So, dosage modification is not required for these population (e.g. elderly, gender, race).

Figure 37. Covariate Effects on faricimab exposures and clearance.



Source: Reviewer's analysis

4.3.2 Exposure-Response Analysis for Efficacy

ER Efficacy Summary Table

General Information	
Goal of ER analysis	• Evaluate the relationships between faricimab VH exposure and the following efficacy endpoints: - Best-corrected visual acuity (BCVA); - Central subfield thickness (CST). • Evaluate the relationships between faricimab exposure in VH and the following pharmacodynamic (PD) endpoints: - AH free VEGF-A;

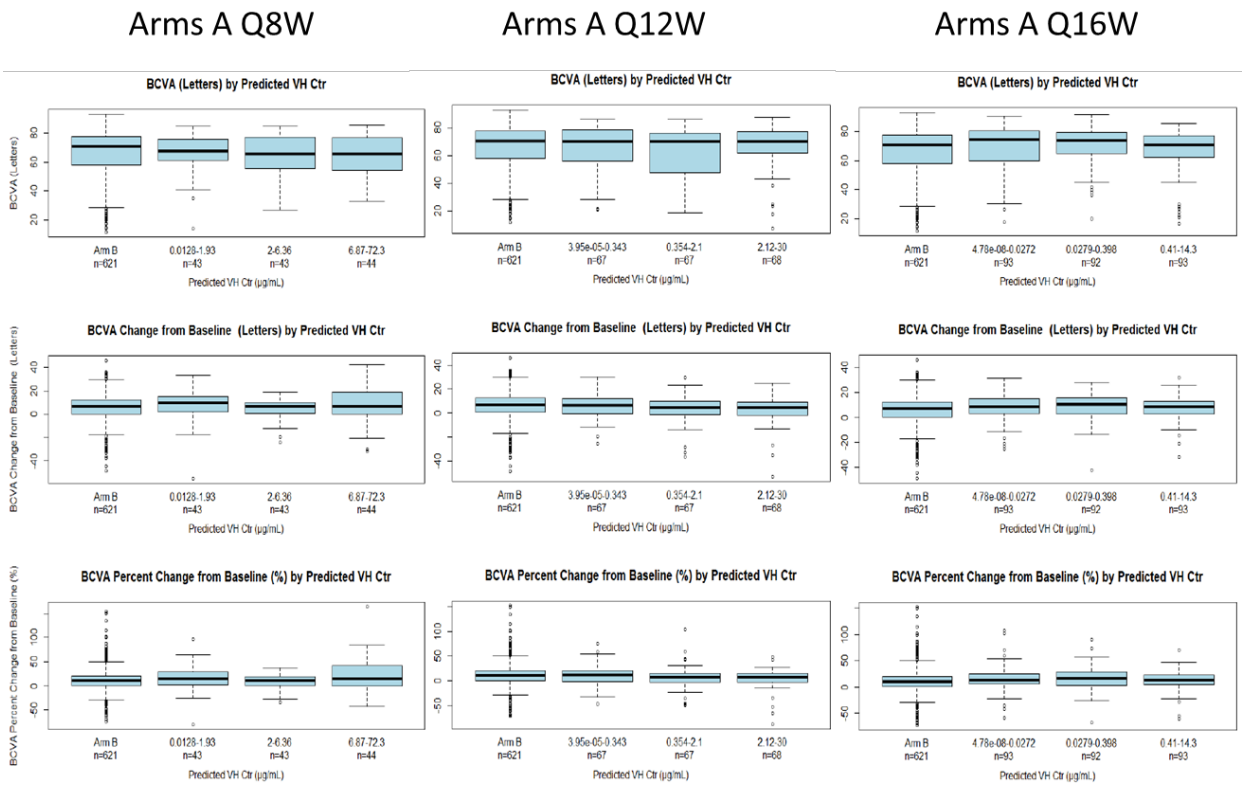
		- AH free Ang-2.
Study Included		• Phase III for nAMD: GR40306 and GR40844, Arm A • Phase III for DME: GR40349 and GR40398, Arm A and B
Endpoint		nAMD: • Primary endpoint: Average change from baseline in Best-Corrected Visual Acuity (BCVA) at week 48 • Other endpoints: average BCVA at Weeks 40, 44 and 48 (BCVAend) average change from baseline of BCVA at Weeks 40 and 44 (dBCVAend) % average change from baseline of BCVA at Weeks 40, 44 and 48 (pdBCVAend) average CST at Weeks 40, 44 and 48 (CSTend) average change from baseline of CST at Weeks 40, 44 and 48 (dCSTend) % average change from baseline of CST at Weeks 40, 44 and 48 (pdCSTend) DME: • Primary endpoint: Average change from baseline in Best-Corrected Visual Acuity (BCVA) at 1 year • Other endpoints: average BCVA at Weeks 48, 52 and 56 (BCVAend); average change from baseline of BCVA at Weeks 48 and 56 (dBCVAend); % average change from baseline of BCVA at Weeks 48, 52 and 56 (pdBCVAend); average CST at Weeks 48, 52 and 56 (CSTend); average change from baseline of CST at Weeks 48, 52 and 56 (dCSTend); % average change from baseline of CST at Weeks 48, 52 and 56 (pdCSTend).
Population Characteristics	General	Age (years): Median: 67 (Range: 24 – 98) Weight (kg): Median: 80 (Range: 37.3 - 209)

		Male: 982 (54.6 %) Race: White 1456 (81%); Black or African American 82 (4.6%); Asian 179 (10%); other or unknown 83 (4.5%) Disease: 1221 (66%) subjects with DME, 577 (34%) subjects with nAMD
	Pediatrics (if any)	No pediatrics were involved in the analysis.
Dose(s) Included		6.0 mg
Exposure Metrics Explored (range)		nAMD: VH $t_{1/2}$ (day): 3.22 – 17.1 $C_{trough,SS,VH}$ (µg/mL): 0.0128 – 72.3 DME: VH $t_{1/2}$ (day): 3.22 – 17.1 $C_{trough,SS,VH}$ (µg/mL): 0.0128 – 72.3
Final Model Parameters		**Summary**
Model Structure		Analysis of continuous endpoints: • Individual values of BCVA, dBCVA, pdBCVA, CST, dCST, and pdCST plotted versus time by the exposure categories. • Box plots of dBCVAend, pdBCVAend, dCSTend, and pdCSTend were plotted by the exposure category. • Individual values of dBCVAend, pdBCVAend, dCSTend and pdCSTend plotted versus exposure. • Linear regression models were implemented to assess the relationships of dBCVAend and dCSTend with exposure. Analysis of binary endpoints: • Logistic regression to assess the relationships between the probability of shorter dosing interval and VH elimination half-life. The dosing interval was determined by the disease activity assessment after first 4-month treatment. In nAMD trials Arm A, disease activity was evaluated at Weeks 20 and 24. Dosing interval for patients with active disease were reduced to Q8W or Q12W until week 60. In DME trials Arm B, disease activity was evaluated at or after Week 20 visit. The dosing interval for patients were extended, reduced, or maintained at Q8W based on assessments made at

	dosing visits by the IxRS (interactive voice or web-based response system) algorithm.
Visualization of E-R relationships	**The box plots of BCVAend, dBCVAend, pdBCVAend, CSTend, dCSTend, and pdCSTend by VH elimination half-life categories or by exposure categories were shown in** Figure 38 and Figure 39 for subjects with nAMD and Figure 40 for subjects with DME. No clear differences between the different half-life categories or exposure categories for any of the dosing groups were observed. Linear regression analysis also suggests flat relationships between these endpoints and faricimab exposures. Based on population PK simulation, steady-state exposure parameters in Phase III studies following 6 mg doses are summarized by disease type and dosing group in Table 27 and Table 28. $C_{max,VH}$ are similar while $C_{trough,VH}$ and $C_{avg,VH}$ were lower with longer dosing intervals. The relationship between faricimab vitreous elimination rate constant and drug administration frequency for nAMD and DME/DR patients in Phase III were shown in Figure 41 and Figure 44. Overall, the figures indicate a trend, despite the overlap between the different dosing regimens, for patients who were treated less frequently to have lower vitreous elimination rate constant, and therefore longer vitreous $t_{1/2}$. In nAMD trials, probability of Q8W dosing, probability of Q8W or Q12W dosing were studied by logistic regression analysis. Both were declined with the increase of VH elimination half-life (Figure 41). The probability of Q8W dosing was lower for patients with longer VH elimination half-life and for ADA-positive patients, and it was higher for patients with higher baseline PEDT in the final model. (Figure 42, Figure 43 and Table 29) In DME administered PTI (personalized treatment interval)-guided dosing (Arm B), probability of dropout, probability of Q4W regimen at Week 52, probability of Q4W or Q8W regimen at Week 52, probability of Q4W, Q8W or Q12W regimen at Week 52 were studied by logistic regression analysis. Probability of dropout was independent of exposure parameters, while others were declined with the increase of VH elimination half-life (Figure 44). Patients with shorter VH elimination half-life, high baseline CST, patients with cataract surgery or previously treated patients were more likely to require more frequent dosing (Table 30 and Figure 45 - Figure 47)

	The relationship of free VEGF-A and Ang-2 in nAMD and DME studies were shown in Figure 48 - Figure 50. In nAMD studies, patients with higher faricimab VH exposure had longer VEGF-A and Ang-2 suppression. In DME studies, no appreciable differences between patients with high and low VH exposure following 6 mg Q8W dosing were noticeable.

Figure 38. Average BCVA and BCVA changes at Weeks 40, 44 and 48 by VH exposure groups for nAMD studies GR40306 and GR40844



Source: PK and ER of Faricimab, Report # 1105763, Page 254-259, Figure 158, 160, 162.

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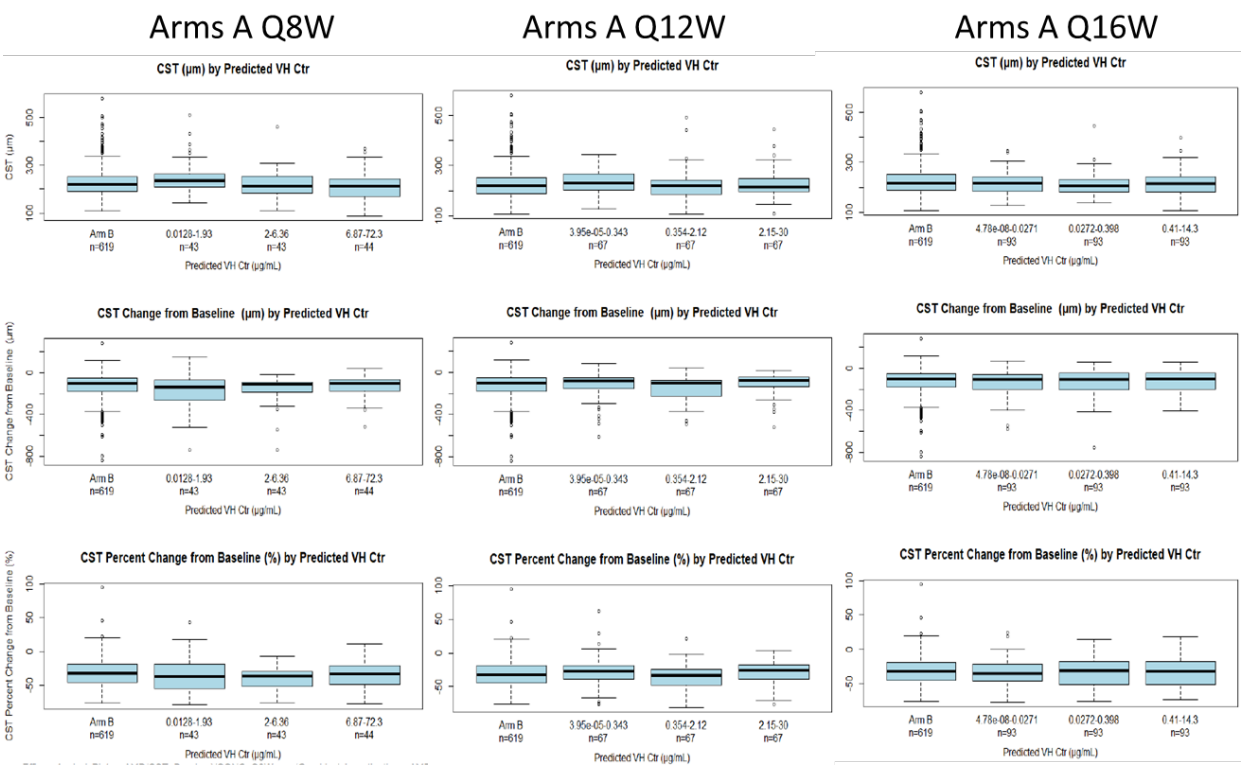
Figure 39. Average CST and CST changes at Weeks 40, 44 and 48 by VH exposure groups for nAMD studies GR40306 and GR40844



Source: PK and ER of Faricimab, Report # 1105763, Page 254-259, Figure 159, 161, 163.

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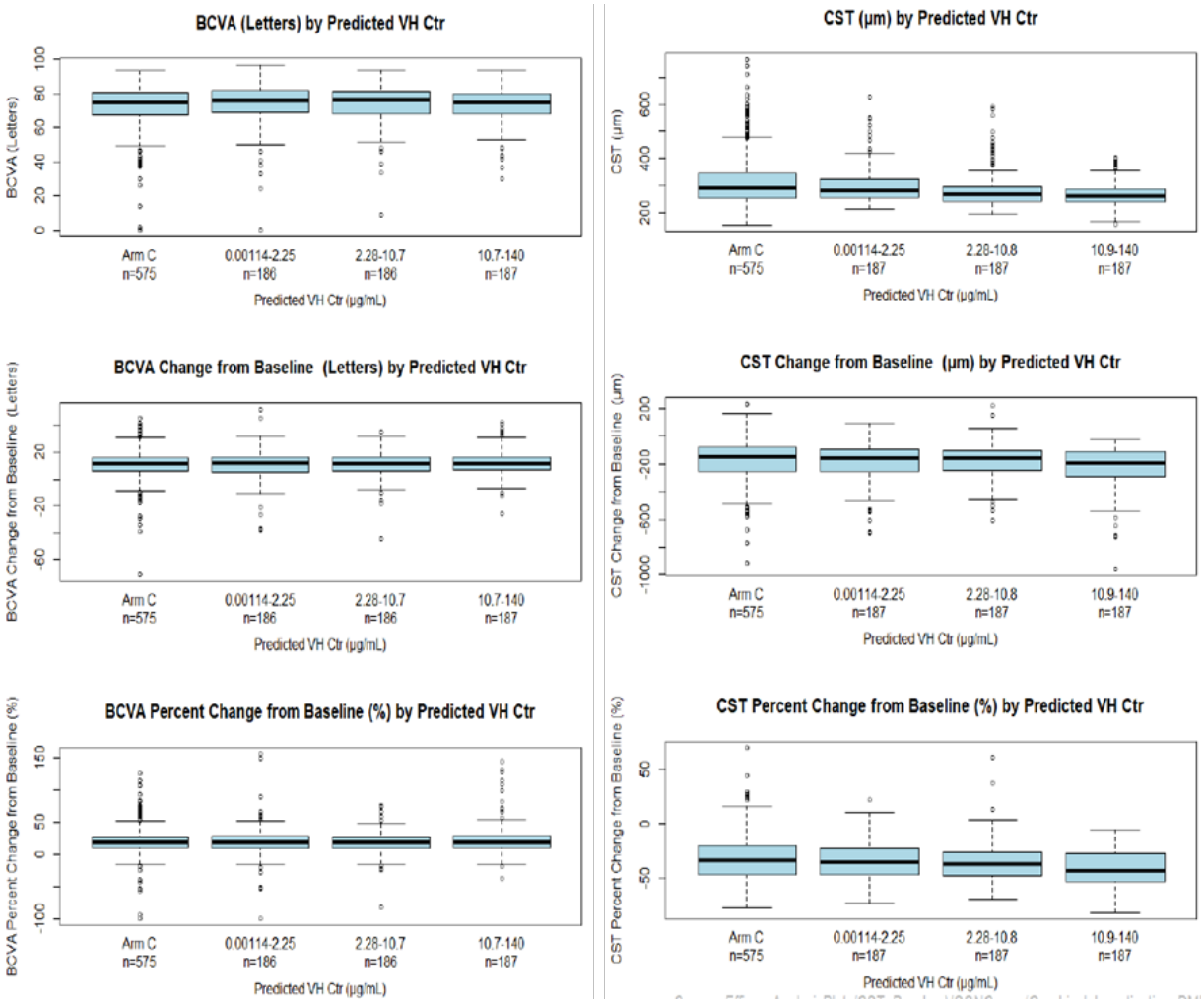
Figure 40. Average BCVA, BCVA changes, CST and CST changes at Weeks 48, 52 and 56 by VH exposure groups for DME studies GR40349 and GR40398 (Arms A and C)



Source: PK and ER of Faricimab, Report # 1105763, Page 283-284, Figure 187-188.

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Table 27. Summary of individual estimates of faricimab steady-state exposures following 6 mg dosing, by final dosing regimen (patients from Phase III studies): median (95% prediction interval)

Group	Compartment	N	Cavg (ug/mL)	C_{max} (µg/mL)	$C_{trough,ss}$ (µg/mL)
DME Arm B Q4W	VH	71	417 (245 – 710)	1390 (1340-1580)	58.4 (5.97-244)
	AH		52 (35 – 65)	163 (124-252)	7.2 (1.09-21.8)
	Plasma		0.093 (0.067 -0.135)	0.25 (0.15-0.395)	0.0139 (0.00248-0.0448)
DME Arm B Q8W	VH	89	232 (146 – 395)	1340 (1330-1380)	4.4 (0.143-47.4)
	AH		26.6 (21.4 – 36.2)	152 (101-250)	0.448 (0.0242-4.01)
	Plasma		0.044 (0.029 – 0.071)	0.217 (0.109-0.328)	0.00101 ($3.37 \cdot 10^{-5}$-0.00736)
DME Arm B Q12W	VH	120	160 (105 – 259)	1330 (1330-1340)	0.311 (0.00408-7.9)
	AH		18 (15 – 28)	147 (97.7-238)	0.0369 (0.000642-0.591)
	Plasma		0.032 (0.02 – 0.046)	0.216 (0.129-0.348)	$7.06 \cdot 10^{-5}$ ($1.37 \cdot 10^{-6}$-0.00126)
DME Arm B Q16W	VH	296	126 (70 – 215)	1330 (1330-1340)	0.0348 ($6.74 \cdot 10^{-6}$-2.76)
	AH		13.8 (10.4 – 19.4)	142 (90.2-231)	0.00364 ($1.09 \cdot 10^{-6}$-0.227)
	Plasma		0.023 (0.016 – 0.037)	0.209 (0.109-0.381)	$6.91 \cdot 10^{-5}$ ($3.01 \cdot 10^{-9}$-0.000497)
nAMD Arm A Q8W	VH	132	233 (141 – 368)	1340 (1330-1370)	3.45 (0.105-36.5)
	AH		26.3 (20.4 – 34.3)	151 (96.3-226)	0.408 (0.0179-3.03)
	Plasma		0.054 (0.036 – 0.078)	0.242 (0.153-0.403)	0.00102 ($3.85 \cdot 10^{-5}$-0.00675)
nAMD Arm A Q12W	VH	210	181 (106 – 305)	1330 (1330-1350)	0.863 (0.00478-17)
	AH		18.5 (14.4 – 23.1)	133 (89.2-206)	0.0884 (0.000763-1.17)
	Plasma		0.036 (0.024 – 0.053)	0.219 (0.131-0.364)	0.000184($1.95 \cdot 10^{-6}$-0.00258)
nAMD Arm A Q16W	VH	286	144 (74.7 – 238)	1330 (1330-1340)	0.129 ($2.45 \cdot 10^{-5}$-5.02)
	AH		14 (10.2 -25)	127 (80.9-248)	0.0134 ($3.57 \cdot 10^{-6}$-0.392)
	Plasma		0.028 (0.018 – 0.042)	0.209 (0.113-0.438)	$2.59 \cdot 10^{-5}$ ($1.09 \cdot 10^{-8}$-0.000926)

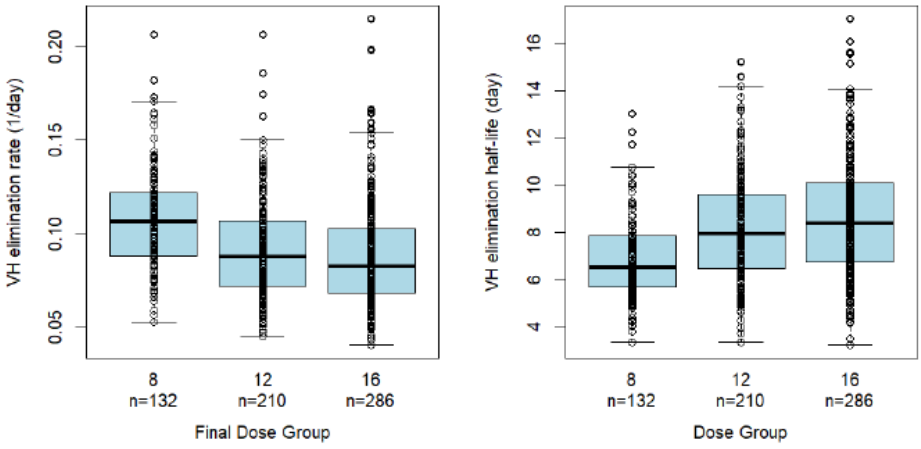
Source: Based on PK and ER of Faricimab, Report # 1105763, Page 91, Table 21.

Table 28. Summary of predicted faricimab steady-state exposures following 6 mg dosing for different dosing regimens: median (95% prediction interval)

Group	Comp.	Cavg (ug/mL)	C_{max} (µg/mL)	$C_{trough,ss}$ (µg/mL)
DME Q4W	VH	475 (267 - 843)	1420 (1340-1680)	86 (9.31-347)
	AH	54 (40 - 76)	157 (116-245)	9.87 (1.46-28.7)
	Plasma	0.09 (0.06 - 0.14)	0.227 (0.136-0.399)	0.0182 (0.00314-0.0509)
DME Q8W	VH	238 (134 - 421)	1340 (1330-1390)	4.87 (0.063-59.1)
	AH	27 (20 - 38)	149 (97.1-239)	0.569 (0.0092-4.8)
	Plasma	0.05 (0.03 – 0.07)	0.212 (0.116-0.385)	0.00104 ($2.01 \cdot 10^{-5}$-0.00823)
DME Q12W	VH	158 (89 – 281)	1330 (1330-1340)	0.291 (0.000429-11.7)
	AH	18 (13 – 25)	148 (93.8-239)	0.0339 ($6.1 \cdot 10^{-5}$-0.954)
	Plasma	0.03 (0.02 – 0.05)	0.21 (0.113-0.384)	6.2·10-5 ($1.35 \cdot 10^{-7}$-0.00162)
DME Q16W	VH	119 (67 – 211)	1330 (1330-1340)	0.0175 ($2.92 \cdot 10^{-6}$-2.39)
	AH	14 (10 – 19)	148 (92.9-239)	0.002 ($4.33 \cdot 10^{-7}$-0.2)
	Plasma	0.02 (0.015 – 0.036)	0.21 (0.113-0.384)	$3.71 \cdot 10^{-5}$($9.03 \cdot 10^{-10}$-0.000342)
nAMD Q4W	VH	536 (290 – 939)	1450 (1350-1760)	121 (13.9-428)
	AH	55 (41 – 79)	148 (109-236)	12.5 (2.39-32.8)
	Plasma	0.11 (0.07 – 0.16)	0.245 (0.149-0.414)	0.026 (0.00627-0.0642)
nAMD Q8W	VH	268 (145 – 470)	1340 (1330-1420)	9.23 (0.139-83.4)
	AH	27.5 (20.5 -39.8)	136 (89.7-219)	0.949 (0.0234-6.25)
	Plasma	0.055 (0.036 – 0.08)	0.223 (0.125-0.407)	0.0021 ($7.46 \cdot 10^{-5}$-0.0122)
nAMD Q12W	VH	179 (97 – 313)	1330 (1330-1350)	0.757 (0.00141-19.3)
	AH	18 (14 – 27)	136 (86.8-217)	0.0804 (0.000233-1.33)
	Plasma	0.037 (0.02 -0.05)	0.221 (0.122-0.406)	0.000174($7.09 \cdot 10^{-7}$-0.00268)
nAMD Q16W	VH	134 (73 -235)	1330 (1330-1340)	0.0625 ($1.42 \cdot 10^{-5}$-4.61)
	AH	14 (10.3 – 19.9)	136 (86-217)	0.00651 ($2.36 \cdot 10^{-6}$-0.317)
	Plasma	0.028 (0.018 - 0.04)	0.221 (0.122-0.406)	$1.4 \cdot 10^{-5}$ ($7.18 \cdot 10^{-9}$-0.000626)

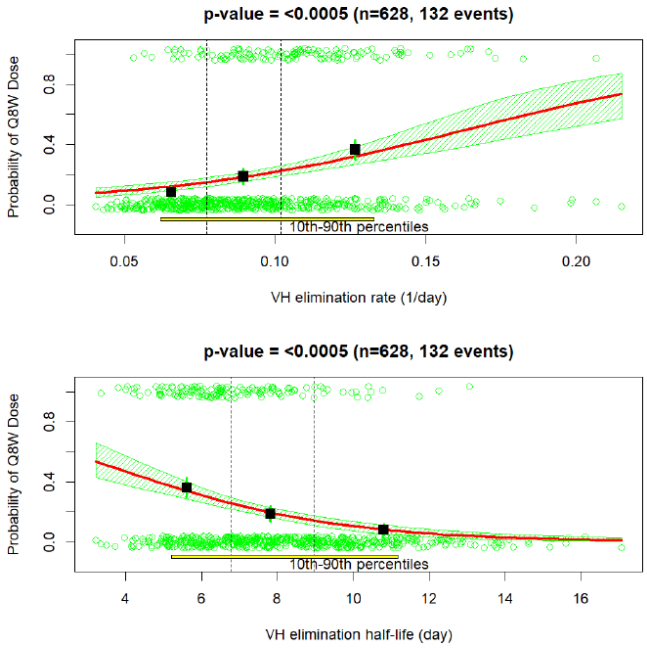
Source: Based on PK and ER of Faricimab, Report # 1105763, Page 94, Table 24.

Figure 41. Distributions of k_{VH} by dose group for nAMD Studies GR40306 and GR40844 (Arms A)



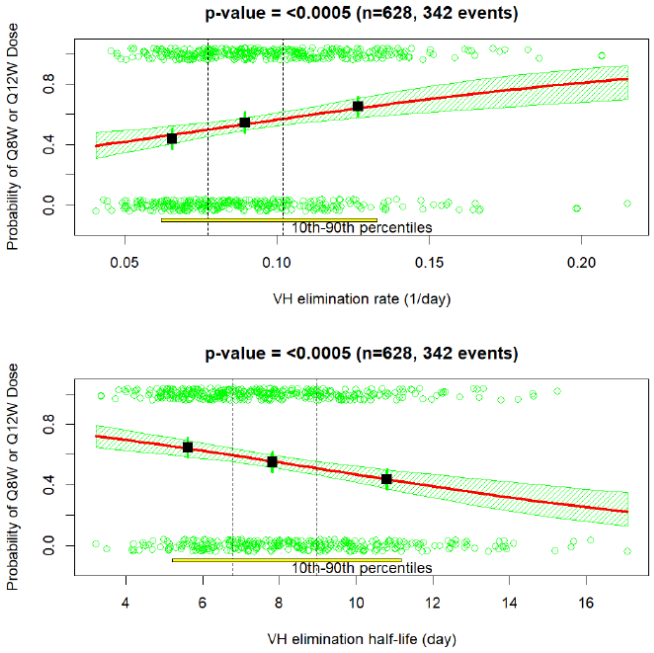
Source: PK and ER of Faricimab, Report # 1105763, Page 268, Figure 172.

Figure 42. Logistic regression for probability of requiring a Q8W dosing for nAMD studies GR40306 and GR40844 (Arms A).



Source: PK and ER of Faricimab, Report # 1105763, Page 269, Figure 173.

Figure 43. Logistic regression for probability of requiring a Q8W or Q12W dosing for nAMD studies GR40306 and GR40844 (Arms A)



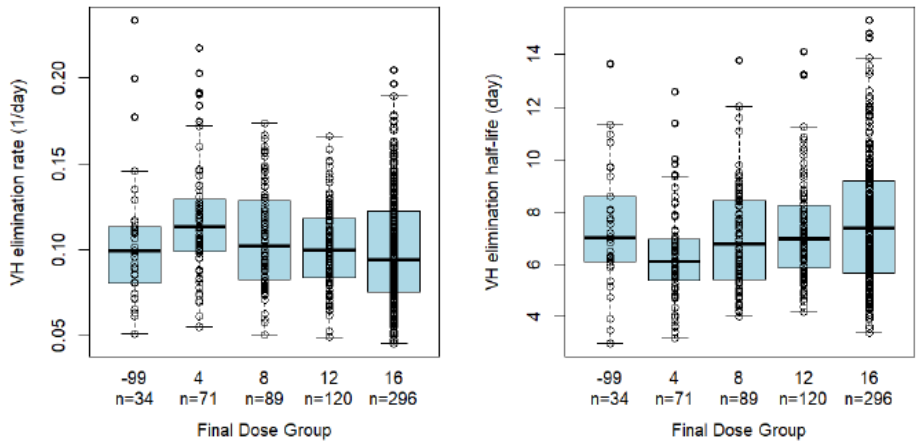
Source: PK and ER of Faricimab, Report # 1105763, Page 270, Figure 174.

Table 29. Logistic regression final model of Q8W dosing regimen (Arms A of Phase III nAMD studies)

Parameter	Coefficient	SE	RSE	95% CI	p-value	Group
Intercept	1.234	0.4613	37.39	0.3295;2.138	0.007	Q8W
VH half-life	-0.4365	0.06166	14.13	-0.5573;-0.3156	<0.0005	
PEDT	0.00305	0.00053	17.38	0.002011;0.004089	<0.0005	
ADA = Yes	-1.008	0.3514	34.86	-1.697;-0.3194	0.004	

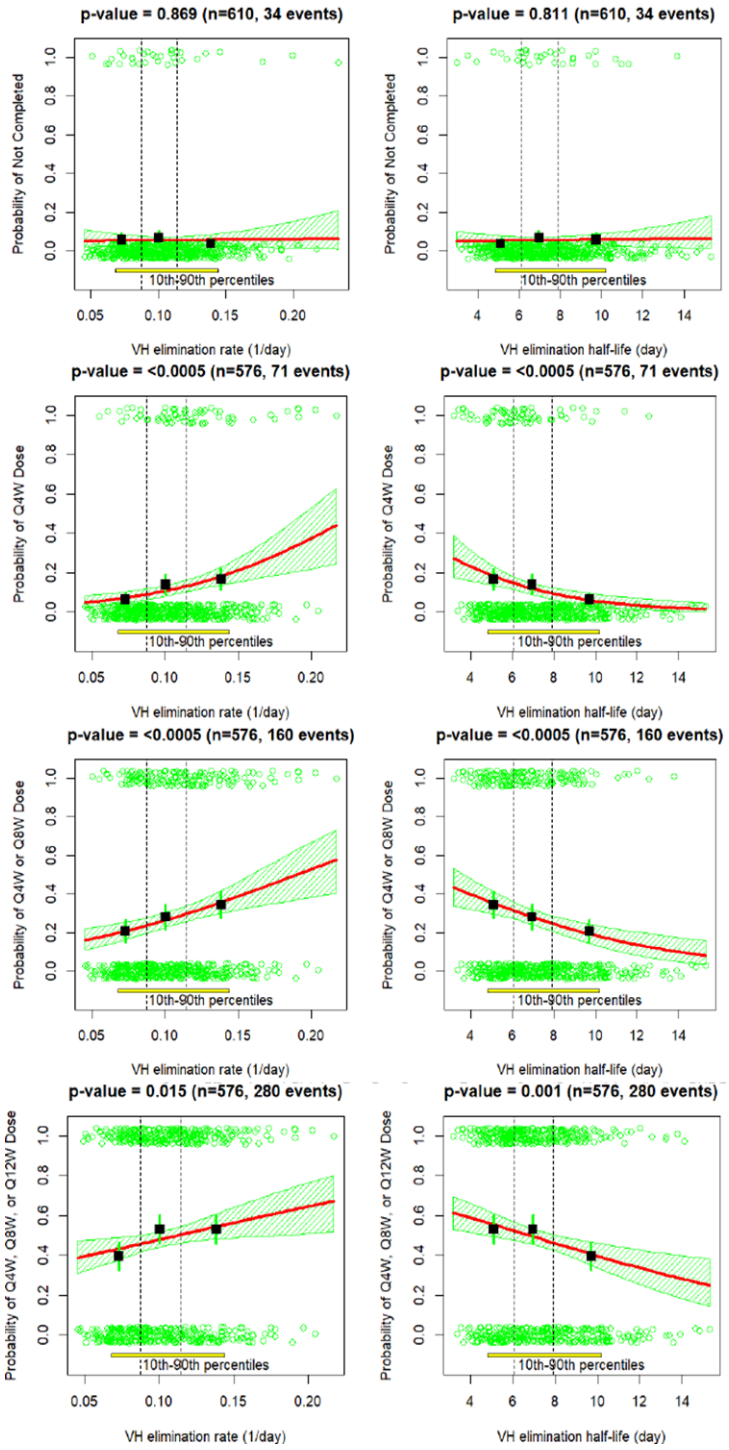
Source: PK and ER of Faricimab, Report # 1105763, Page 97, Table 30.

Figure 44. Distributions of k_{VH} by dose group at Week 52 for DME Studies GR40349 and GR40398 (Arms B).



Source: PK and ER of Faricimab, Report # 1105763, Page 319, Figure 223.

Figure 45. Logistic regression for probability of dropout, Q4W regimen, Q4W or Q8W regimen, Q4W, Q8W or Q12W regimen at Week 52 for DME studies GR40349 and GR40398 (Arms B)



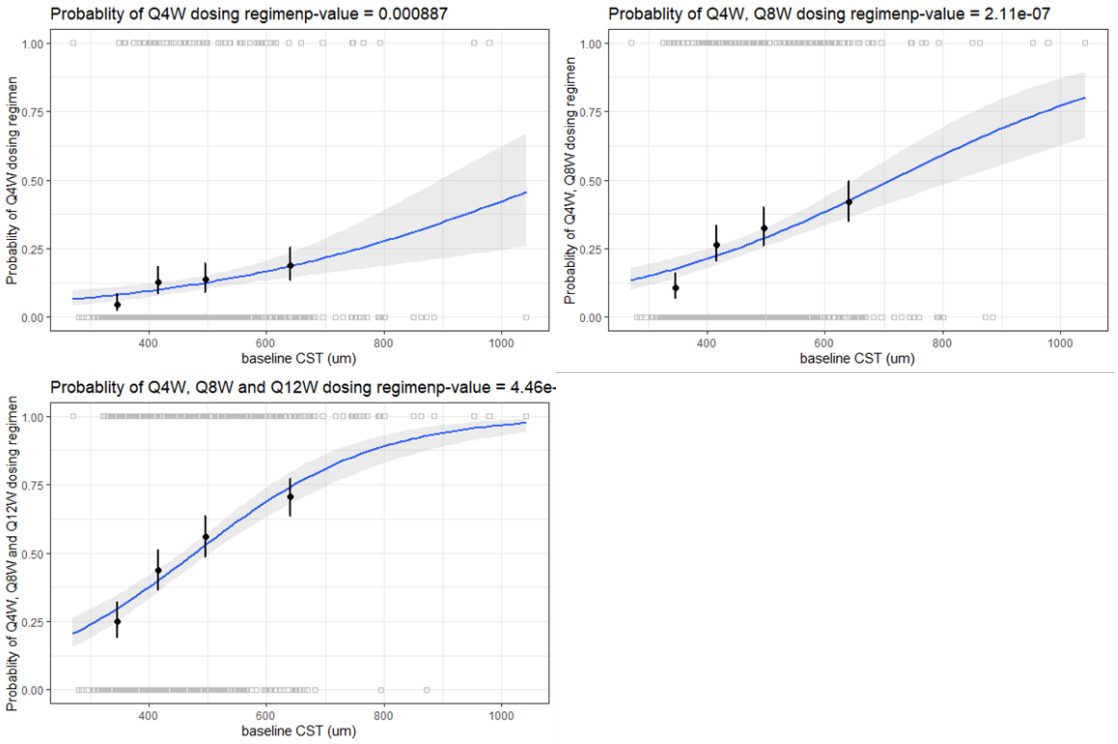
Source: PK and ER of Faricimab, Report # 1105763, Page 320-323, Figure 224-227.

Table 30. Logistic regression final models for dosing regimen at Week 52 (Arms B of Phase III DME Studies)

Parameter	Coefficient	SE	RSE	95% CI	p-value	Endpoint
Intercept	-1.919	0.6759	35.22	-3.244;-0.5942	0.005	Q4W at W52
VH half-life	-0.2795	0.07552	27.02	-0.4275;-0.1315	<0.0005	
CST	0.003753	0.000946	25.2	0.001899;0.005606	<0.0005	
Intercept	-1.51	0.5421	35.89	-2.573;-0.4478	0.005	Q4W, Q8W at W52
VH half-life	-0.1777	0.05093	28.67	-0.2775;-0.07783	<0.0005	
CST	0.004783	0.000802	16.78	0.00321;0.006355	<0.0005	
NAIVE	-0.6854	0.2255	32.9	-1.127;-0.2434	0.002	
Intercept	-2.553	0.5194	20.34	-3.571;-1.535	<0.0005	Q4W, Q8W, or Q12W at W52
VH half-life	-0.1368	0.04337	31.7	-0.2218;-0.0518	0.002	
CST	0.006959	0.000892	12.82	0.005211;0.008707	<0.0005	
CATARACT	0.5062	0.1839	36.33	0.1457;0.8667	0.006	

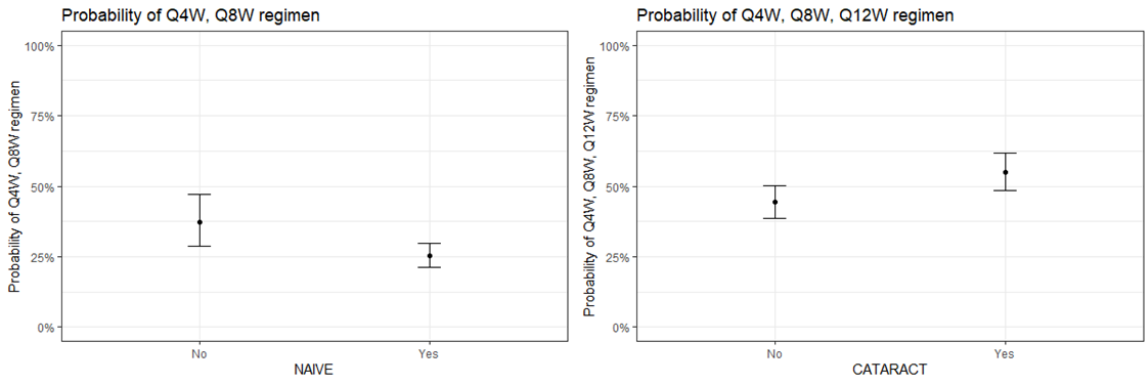
Source: PK and ER of Faricimab, Report # 1105763, Page 98, Table 33.

Figure 46. Logistic regression for probability of Q4W regimen, Q4W or Q8W regimen, Q4W, Q8W or Q12W regimen at Week 52 with baseline CST for DME studies GR40349 and GR40398 (Arms B)



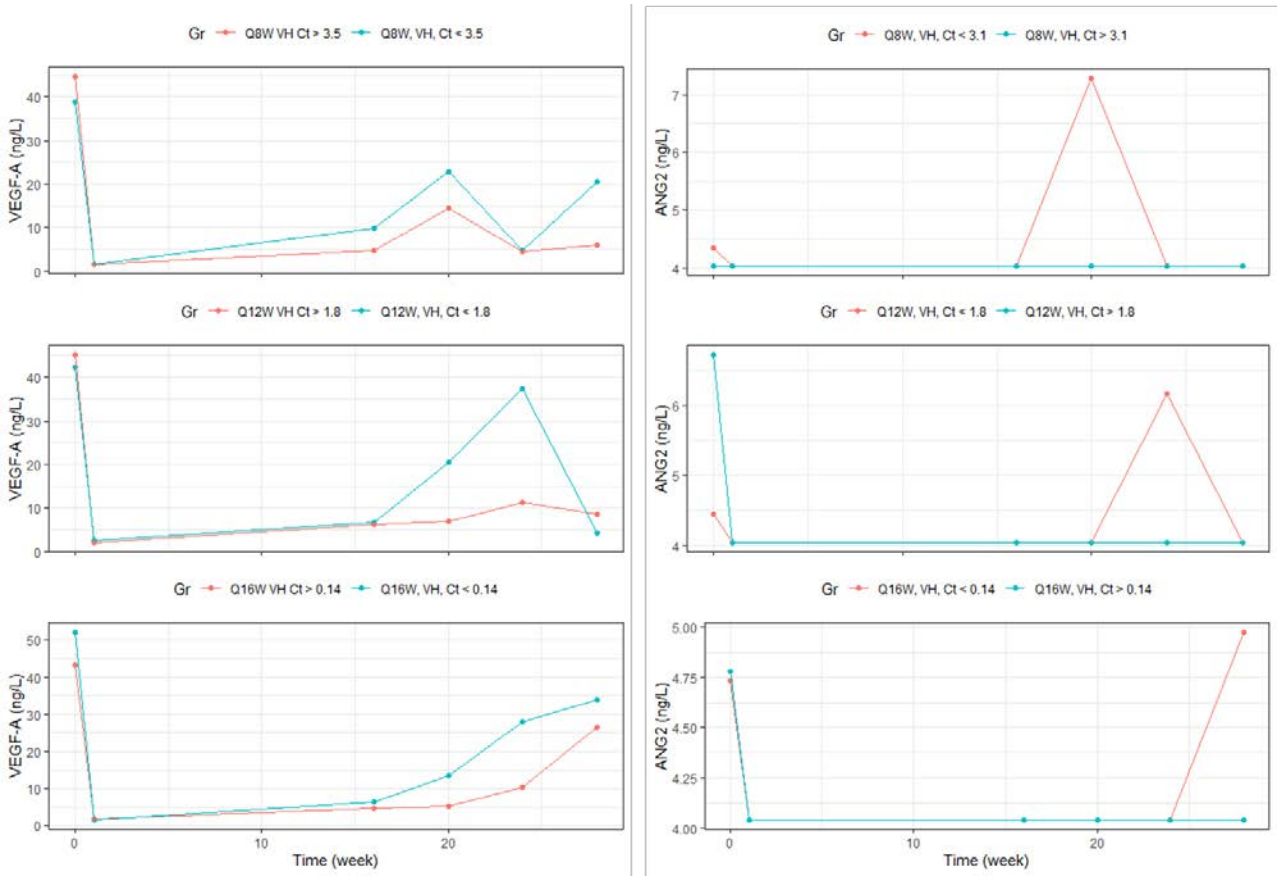
Source: Reviewer's analysis

Figure 47. Probability of Q4W or Q8W regimen, Q4W week 52 vs previous treatment, Q8W or Q12W regimen at Week 52 vs cataract surgery for DME studies GR40349 and GR40398 (Arms B)



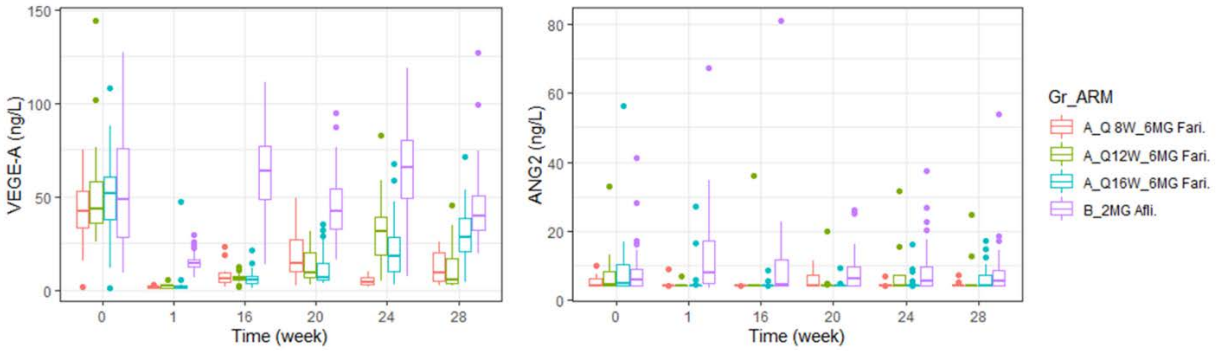
Source: Reviewer's analysis

Figure 48. Medians of Free VEGF-A and Ang-2 AH Concentrations versus Time by dosing regimen for nAMD Studies GR40306 and GR40844 (Arms A)



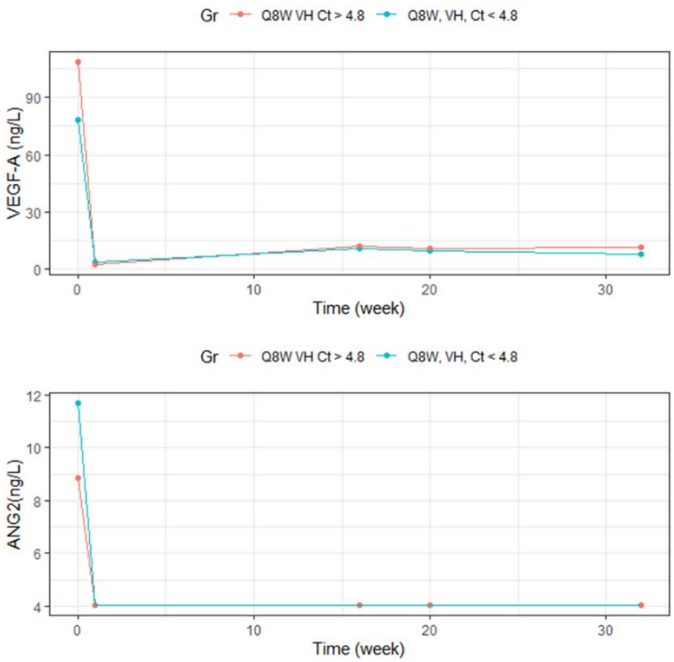
Source: Reviewer's analysis

Figure 49. Comparison of Free VEGF-A and Ang-2 AH Concentrations versus Time in dosing regimen for nAMD Studies GR40306 and GR40844 (Arms A)



Source: Reviewer's analysis

Figure 50. Medians of Free VEGF-A AH Concentrations versus Time by dosing regimen for DME Studies GR40349 and GR40398 (Arms A)



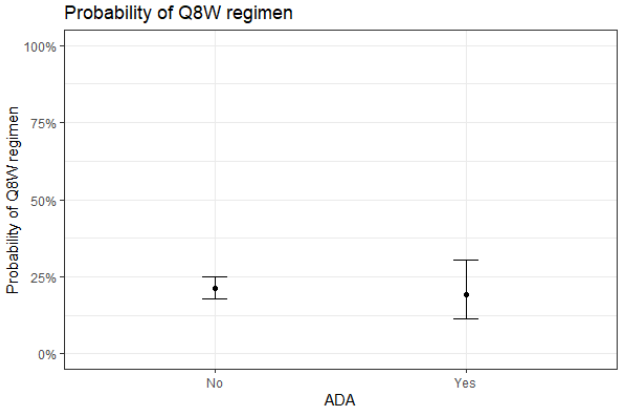
Source: Reviewer's analysis

The FDA's Comments:

The results of E-R analysis for efficacy were verified by reviewer. No apparent differences were observed in patients with different VH exposure within dosing frequency regimen and between patients from all dosing regimens with different VH half-lives in subjects with nAMD or DME after response-guided treatment. E-R analyses based on all subjects could be confounded by the response-guided treatment. While the flat E-R analysis within each dosing interval is more informative to support the flat relationship.

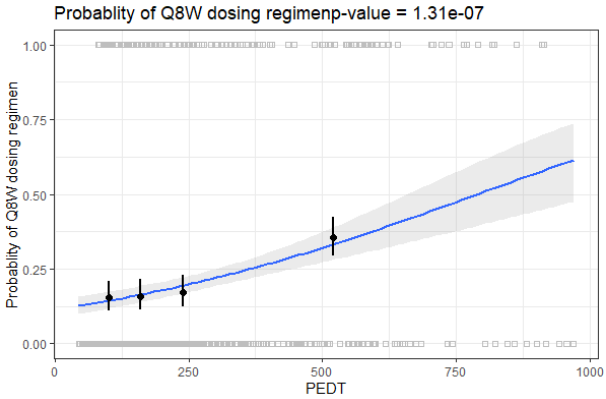
In nAMD trials, logistic regression showed that the probability of Q8W dosing was higher for patients with higher VH elimination rate (shorter VH elimination half-life), but age was not identified as significant predicter in logistic regression for the probability of Q8W dosing (Table 12 and Figure 17). Although ADA was identified as significant covariate for the probability of Q8W dosing regimen, the difference in two ADA groups were not apparent (Figure 51). While patients with high values of PEDT and shorter VH elimination half-life might need more frequent dosing of faricimab (Figure 52).

Figure 51. Probability of Q8W dosing regimen in ADA positive and negative patients with nAMD Studies GR40306 and GR40844 (Arms A).



Source: reviewer's analysis

Figure 52. Logistic regression for probability of requiring a Q8W Dosing with PEDT for nAMD studies GR40306 and GR40844 (Arms A)



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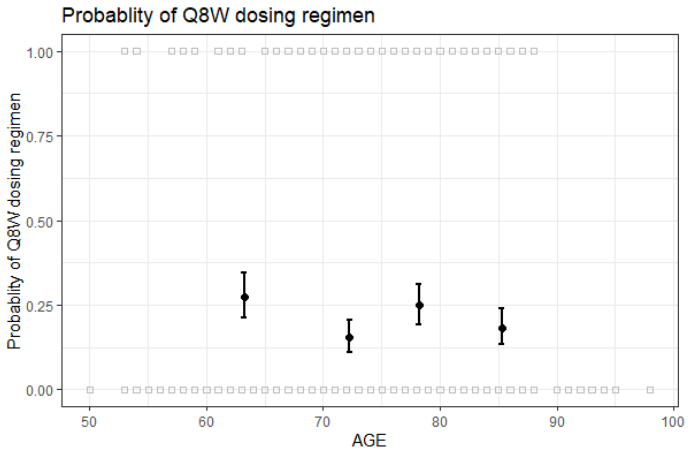
Source: reviewer's analysis

Figure 53. Logistic regression for probability of requiring a Q8W dosing with age for nAMD studies GR40306 and GR40844 (Arms A)



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Source: reviewer's analysis

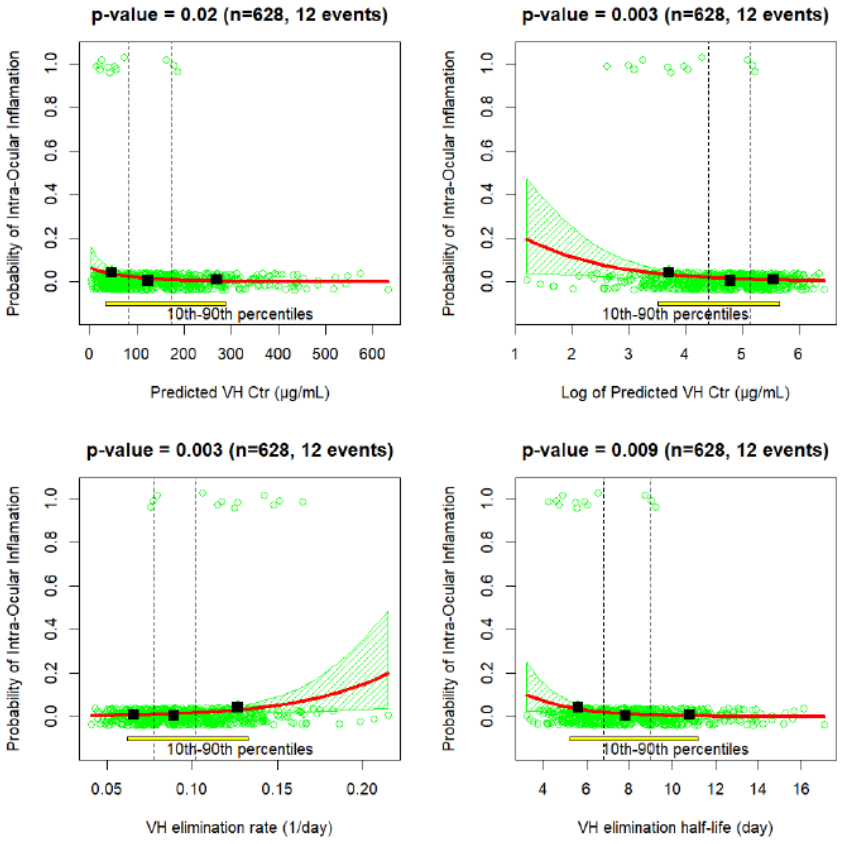
4.3.3 Exposure-Response Analysis for Safety

ER Safety Summary Table

General Information		
Goal of ER analysis		Evaluate relationships between faricimab VH exposure and occurrence and probability of the intra-ocular inflammation (IOI)
Study Included		Phase III for nAMD: GR40306 and GR40844 Phase III for DME: GR40349 and GR40398
Population Included		nAMD: 628 subjects DME: 1221 subjects
Endpoint		intra-ocular inflammation (IOI)
Population Characteristics	General	Patients' population: 1849 Age (years): Median: 67 (Range: 24 – 98) Weight (kg): Median: 80 (Range: 37.3 - 209) Male: 1002 (54.2 %) Race: White 1501 (81%); Black or African American 82 (4.4%); Asian 183 (9.9%); other or unknown 83 (4.5%) Disease: 1221 (66%) subjects with DME, 628 (34%) subjects with nAMD
	Organ impairment	• Hepatic Impairment (NCI): Normal: 1712 (92.3%)

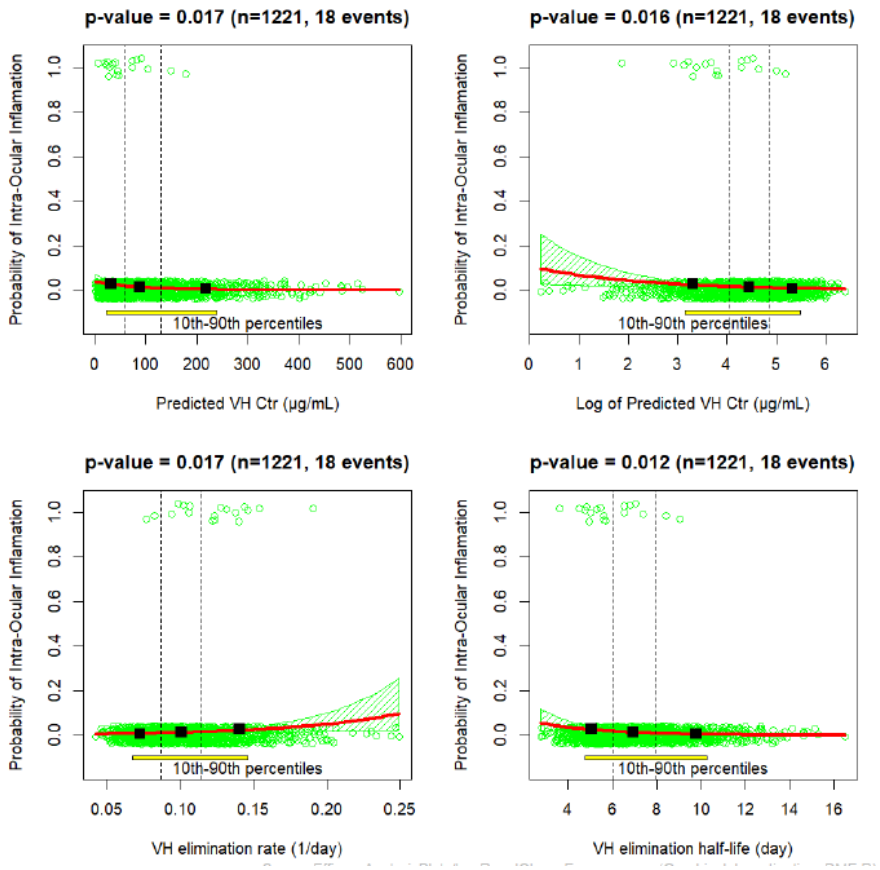
		Mild: 97 (5.2%) Moderate: 4 (0.2%) Missing: 36 (1.9%) • Renal Impairment (CRCL): Normal: 686 (37%) Mild: 698 (38%) Moderate: 415 (22%) Severe: 23 (1.2%) Missing: 27 (1.5%)
	Pediatrics (if any)	No pediatric subjects were involved in the analysis.
	Geriatrics (if any)	616, 33% subj >=65 yr 351, 19% subj >=75 yr 58, 3.1% subj >=85 yr
Dose(s) Included		6.0 mg
Exposure Metrics Explored (range)		nAMD: $C_{trough,ss,VH}$: 3.32 – 632 µg/mL DME: $C_{trough,ss,VH}$: 1.27 - 597 µg/mL
Final Model Parameters		**Summary**
Model Structure		Logistic regression models were implemented to assess the correlation between the probability of occurrence of IOI and exposure predictors ($C_{trough,ss}$, log($C_{trough,ss}$), k_{VH}, and $t_{1/2,kVH}$).
Visualization of E-R relationships		Figure 54 and Figure 55
Overall Clinical Relevance for ER		The incidence of IOI did not increase with faricimab exposure.

Figure 54. Logistic regression for probability of IOI in patients receiving faricimab in nAMD studies GR40306 and GR40844.



Source: PK and ER of Faricimab, Report # 1105763, Page 202, Figure 106.

Figure 55. Logistic regression for probability of IOI in patients receiving faricimab in DME studies GR40349 and GR40398 (Arms A and B)



Source: PK and ER of Faricimab, Report # 1105763, Page 203, Figure 107.

Source: Reviewer's analysis.

<u>The FDA's Comments:</u>
The E-R analysis for IOI with faricimab VH exposures were verified by the reviewer. Figure 54 showed that incidence rate might decrease with the VH elimination half-life, which is correlated with dosing frequency. The incidence rate of IOI is higher in subjects with shorter dosing interval (Table 31). The incidence of IOI was low in both indication and it did not increase with faricimab exposure in VH. Flat E-R relationship was identified with IOI and faricimab $C_{trough,ss,VH}$, $C_{max,ss,VH}$ *and AUC with pooled data with subjects with nAMD or DME.*

Table 31. IOI stratified by dosing regimen in subjects with nAMD.

Dosing Regimen	# of Patients	Incidence of IOI	Incidence Rate
Q16W	286	3	1%

Q12W	210	4	1.9%
Q8W	132	5	3.8%

Source: Reviewer's analysis

4.3.4 Overall benefit-risk evaluation based on E-R analyses:

E-R analysis for efficacy showed that there were no apparent differences between patients with different faricimab VH exposure within each dosing frequency regimen for subjects with nAMD or DME. In nAMD studies, patients with higher VH elimination rate (short VH elimination half-life) and higher values of PEDT were more likely to require more frequent dosing of faricimab. In DME studies Arm B, patients with shorter VH elimination half-life were more likely to require more frequent dosing, as were patients with higher baseline CST, cataract surgery or previously treatment. In E-R analysis for safety, no positive relationship was identified between IOI and faricimab VH exposure and the incidence rate of IOI was low. It was noticed that patients received more frequent dosing had high incidence rate of IOI in nAMD studies.

Overall, the proposed dosing for faricimab is acceptable. For all indications, the majority of patients (> 70%) had received less frequent dosing (dosing interval of 12 weeks or higher). There are some remained uncertainties for the necessity of shorter dosing interval for a small group of patients based on assessment of disease active after first four monthly treatment, given the relative flat E-R relationship for efficacy and increased IOI with more frequent dosing.

4.4 Clinical Immunogenicity Assessment

The overall incidence of treatment-emergent ADAs was low (ranging from 0−11%), based on Phase I and II, and remained low (8−10%), based on Phase III study results (Table 32).

In the Phase I and Phase II studies of faricimab in patients with nAMD and DME/DR ≤11% of post-dose evaluable patients demonstrated treatment-induced or treatment-boosted ADA responses. In the pooled Phase III studies, 68/663 (10.4%) patients with nAMD and 105/1255 (8.4%) patients with DME/DR showed treatment-induced or treatment-boosted ADA responses, which were persistent in 75−85% of the patients. Persistence was defined as an ADA positive result was detected at the last post-baseline sampling timepoint, or at 2 or more timepoints during treatment where the first and last ADA positive samples are separated by a period of 16 weeks, irrespective of any negative samples in between. The median time to onset of ADA response was 20 to 28 weeks.

Table 32: Overall Summary of Immunogenicity Results by Study

Study	Indication	Baseline-ADA Evaluable Patients n	Baseline ADA Prevalence n (%)	Post-baseline ADA Evaluable Patients n	Treatment-Induced or Boosted ADAs n (%)
Phase I					
BP28936	nAMD	24	0 (0.0%)	24	0 (0.0%)
JP39844	nAMD/DME, DR	12	0 (0.0%)	12	0 (0.0%)
Phase II					
AVENUE	nAMD	195	5 (2.6%)	195	22 (11.3%)
STAIRWAY	nAMD	55	0 (0.0%)	55	6 (10.9%)
BOULEVARD	DME, DR	135	3 (2.2%)	135	10 (7.4%)
Phase III					
TENAYA	nAMD	322	10 (3.1%)	328	29 (8.8%)
LUCERNE	nAMD	318	2 (0.6%)	329	39 (11.9%)
YOSEMITE	DME, DR	603	6 (1.0%)	619	62 (10.0%)
RHINE	DME, DR	604	4 (0.6%)	624	43 (6.9%)
Pooled	nAMD	640	12 (1.8%)	657	68 (10.4%)
Pooled	DME, DR	1207	10 (0.8%)	1243	105 (8.4%)

ADA = anti-drug antibodies; DME = diabetic macular edema; DR = diabetic retinopathy; nAMD = neovascular age-related macular degeneration.

Source: CSR JP38944, Report 1106179, Section 12.5.4; CSR BP28936, Report 1058993, Section 6.10.4, CSR BP30099; Report 1083913, Section 8.12.4; CSR BP26947, Report 1083912, Section 8.12.4; CSR CR39521, Report 1085977, Section 8 CSR GR40349, Report 1102956, Table 36; CSR GR40398, Report 1102957, Table 36; CSR GR40306, Report 1102954, Table 36; CSR GR40844, Report 1102955, Table 36; t_ada_base_IG_nAMD_HLS; t_ada_base_IG_DME_HLS

Impact of ADA on Pharmacokinetics

Population PK covariate analyses showed that plasma ADA had an effect on vitreous elimination $t_{1/2}$. Patients with detected ADAs had 30.4% higher ocular elimination rate. As a consequence, ADA positive patients had 23.4% lower ocular exposure at steady state compared with ADA negative patients. Presence of plasma ADA had no effect on the plasma exposure. ADA incidence was low, the impact on ocular exposure was minor, and exposure-response analysis showed a similar response across the range of vitreous exposure in Phase III, suggesting that the changes in vitreous exposure in ADA-positive patients are unlikely to be associated with a change in efficacy. Based on all available data to date, no meaningful impact of ADA was observed on efficacy.

Impact of ADA on PD

There was no apparent meaningful difference between ADA-positive and ADA-negative patients in change from baseline CST at Week 40, Week 44 and Week 48 in patients with nAMD. It should be noted that there were few (approximately 10%) ADA-positive patients in the Phase III studies.

Impact of ADA on Efficacy

There was no apparent difference between ADA-positive and ADA-negative patients in change from baseline BCVA at Week 40, Week 44 and Week 48 in patients with nAMD (Table 33) or change from baseline BCVA at Week 48, Week 52 and Week 56 or proportion of patients with ≥2 steps improvement in Diabetic Retinopathy Severity Scale (DRSS) from baseline to Week 52 in patients with DME and DR (Table 34). It should be noted there were few (approximately 10%) ADA-positive patients in the Phase III studies.

Table 33: Changes in BCVA in the Study Eye in ADA-Negative and ADA-Positive Patients (Patients with nAMD)

	Pooled TENAYA and LUCERNE Faricimab 6 mg
Change in BCVA in the Study Eye (letters)	
ADA negative	**N=589**
N	505
Mean (SD) change to Week 40	6.4 (12.0)
95% CI	5.4–7.5
N	499
Mean (SD) change to Week 44	6.5 (12.0)
95% CI	5.4–7.5
N	492
Mean (SD) change to Week 48	6.1 (12.2)
95% CI	5.0–7.2
ADA positive	**N=75**
N	69
Mean (SD) change to Week 40	7.3 (13.2)
95% CI	4.2–10.5
N	67
Mean (SD) change to Week 44	6.4 (13.0)
95% CI	3.2–9.5
N	67
Mean (SD) change to Week 48	5.9 (14.6)
95% CI	2.4–9.5

ADA=anti-drug antibody; BCVA=best corrected visual acuity; nAMD=neovascular age-related macular degeneration

Source: t_ef_cb_SBCVA_PREST_ADAN_IT_nAMD_HLS, t_ef_cb_SBCVA_PREST_ADAP_IT_nAMD_HLS

Table 34: Changes in BCVA and DRSS in the Study Eye in ADA-Negative and ADA-Positive Patients (Patients with DME and DR)

	Pooled YOSEMITE and RHINE Patients	
	Faricimab 6 mg	**Faricimab PTI**
BCVA in the Study Eye		
ADA negative	**N=562**	**N=568**
n	457	490
Mean (SD) change to Week 48	11.3 (9.6)	11.3 (9.8)
95% CI	10.5–12.2	10.4–12.1
n	459	477
Mean (SD) change to Week 52	11.0 (10.1)	11.4 (9.7)
95% CI	10.1–11.9	10.6–12.3
n	444	469
Mean (SD) change to Week 56	11.7 (10.5)	11.7 (9.6)
95% CI	10.7–12.7	10.8–12.6
ADA positive	**N=57**	**N=56**
n	42	53
Mean (SD) change to Week 48	11.3 (11.1)	10.0 (12.2)
95% CI	7.9–14.8	6.7–13.4
n	44	50
Mean (SD) change to Week 52	10.0 (13.7)	9.0 (11.3)
95% CI	5.8–14.2	4.8–11.2
n	39	45
Mean (SD) change to Week 56	12.5 (12.2)	9.6 (12.0)
95% CI	8.6–16.5	6.0–13.2
≥2 Steps DRSS Improvement from Baseline		
ADA negative	**N=562**	**N=568**
n	425	447
Proportion of patients at Week 52	45.2%	42.7%
95% CI for proportion	40.4%, 49.9%	38.1%, 47.3%
ADA positive	**N=57**	**N=56**
n	38	42
Proportion of patients at Week 52	39.5%	42.9%
95% CI for proportion	23.9%, 55.0%	27.9%, 57.8%

Impact of ADA on Safety/Risks

In pooled Phase III studies with regard to the ADA-positive subgroup the incidence of patients with SAEs was 10.7% in the faricimab arm in nAMD, and 28.1% in the faricimab Q8W arm and 26.8% in the faricimab PTI arm in DME/DR, with isolated individual events within MedDRA System Organ Classes (SOCs) and no pattern identified. Of the patients who were ADA positive and experienced ocular AEs, they were mainly non-serious, suspected not to be related to study treatment, did not result in a sustained dropn BCVA ≥ 30 letters or study withdrawal, and were not associated with severe IOI events. Incidence rate of IOI was low (≤2% in each of the disease indications. Approximately 90% of patients overall were ADA-negative; however, the incidence of IOIs was greater in ADA-positive patients. Of the 13 patients who experienced IOI events in the faricimab arms in the nAMD studies ADA results were available for 12 patients. The incidence of IOIs in ADA-positive patients was 5/75 (6.7%), the incidence of IOIs in ADA-negative patients was 7/582 (1.2%) (Table 35). Patients with high ADA titers (>20000) were observed in both patients, with IOI and without IOI.

Of the 17 patients who experienced IOI events through Week 56 in the faricimab arms in the DME/DR studies, ADA results were available for all 17 patients. The incidence of IOIs in ADA-positive patients was 11/113 (9.7%), the incidence of IOIs in ADA-negative patients was 6/1130 (0.5%) (Table 36). DME/DR patients with high ADA titers (>20000) were all in the group of patients that experienced IOI.

Based on all available data to date, no meaningful impact of ADA was observed on efficacy and on overall safety. Although a higher incidence of IOI was observed in ADA-positive compared with ADA-negative patients, this observation is not currently considered to be clinically relevant. Based on the low incidence of immunogenicity, the low incidence of IOI for which the majority of the events were of mild to moderate severity and had a reversible character. The potential risk of immunogenicity in the context of IOI will continue to be monitored through signal detection in all ongoing Phase 3 faricimab studies.

Table 35: Adverse Events of IOI by ADA Status (Pooled nAMD population)

Ocular AE of IOI	Pooled ADA positive N=75	Pooled ADA negative N=582
Total patients with at least one AE	5 (6.7%)	7 (1.2%)
Iritis	2 (5.7%)	1 (0.2%)
Uveitis	1 (2.9%)	1 (0.2%)
Iridocyclitis	1 (2.5%)	2 (0.3%)
Vitritis	1 (2.5%)	2 (0.3%)
Chorioretinitis	0 (0.0%)	1 (0.2%)

ADA=anti-drug antibody; AE=adverse event; IOI=intraocular inflammation; nAMD=neovascular age-related macular degeneration

Source: CSR TENAYA, Report 1102954, t_ae_pt_SOCUL_IOI_W48_ADAN_SE_26OCT2020_40306 and t_ae_pt_SOCUL_IOI_W48_ADAP_SE_26OCT2020_40306; CSR LUCERNE, Report 1102955, t_ae_pt_SOCUL_IOI_W48_ADAN_SE_05OCT2020_40844 and t_ae_pt_SOCUL_IOI_W48_ADAP_SE_05OCT2020_40844

Table 36: Adverse Events of IOI by ADA Status (Pooled DME population)

Ocular AE of IOI	Pooled ADA positive N=113	Pooled ADA negative N=1130
Total patients with at least one AE	11 (9.7%)	6 (0.5%)
Uveitis	4 (3.5%)	2 (0.2%)
Iridocyclitis	3 (2.7%)	1 (0.1%)
Iritis	3 (2.7%)	2 (0.2%)
Vitritis	3 (2.7%)	1 (0.1%)
Anterior Chamber inflammation	1 (0.9%)	0 (0.0%)
Chorioretinitis	1 (0.9%)	0 (0.0%)
Keratic precipitates	1 (0.9%)	0 (0.0%)
Keratouveitis	1 (0.9%)	0 (0.0%)

ADA=anti-drug antibody; AE=adverse event; DME=diabetic macular edema; IOI=intraocular inflammation

Source CSR YOSEMITE, Report 1102956, t_ae_pt_SOCUL_IOI_ADAN_W56_SE_20OCT2020_40349 and t_ae_pt_SOCUL_IOI_ADAP_W56_SE_20OCT2020_40349; CSR RHINE, Report 1102957, t_ae_pt_SOCUL_IOI_ADAN_W56_SE_19OCT2020_40398 and t_ae_pt_SOCUL_IOI_ADAP_W56_SE_19OCT2020_40398.

Based on all available data, no meaningful impact of ADA was observed on efficacy, PD and on overall safety. Although a higher incidence of IOI was observed in ADA-positive (nAMD: 5/75

[6.7%] patients; DME/DR: 11/113 [9.7%]) compared with ADA-negative (nAMD: 7/582 [1.2%]; DME/DR: 6/1130 [0.5%]) patients, this observation is not clinically relevant based on the low incidence of immunogenicity, the low incidence of IOI for which the majority of the events were of mild to moderate severity and had a reversible character.

Reviewer's comments:

Pharmacokinetics and Pharmacodynamics of faricimab was assessed in nine clinical studies (two Phase 1, three Phase 2, and four Phase 3 studies).

Following SAD and MAD dosing administered intravitreally to patients with nAMD in Phase 1 study (BP28936), faricimab apparent $t_{1/2}$ in AH ranged from 6−13 days, which is similar to the range of mean apparent $t_{1/2}$ in plasma (6−15 days) and consistent with flip-flop kinetics. Plasma faricimab exposure increased approximately dose-proportionally up to 3 mg faricimab. No plasma accumulation was observed following Q4W administration, consistent with faricimab apparent $t_{1/2}$, with steady state reached by the end of the 12-week Q4W initiation dose period. Faricimab concentrations in plasma were >100-fold lower than those in AH. The reviewer confirmed the PK parameters reported by the Applicant by performing NCA analysis using plasma concentration data from the Phase 1 study and observed similar values.

Based on the Phase 2 and 3 studies, both 1.5 mg and 6 mg doses administered Q4W and Q8W resulted in suppression of free Ang-2 and VEGF-A in AH. Following intravitreal administration of faricimab at a dose of 6 mg, a rapid and sustained suppression of free Ang-2 and VEGF-A in AH was observed. Faricimab rapid plasma clearance resulted in systemic plasma exposure approximately 6000-fold lower than in the vitreous. High inter-patient variability was observed in faricimab, free VEGF-A and free Ang-2 AH and plasma concentrations. Rapid suppression of VEGF-A and Ang-2 in AH was seen starting 7 days post-dose and remained suppressed at least up to Week 20, after which patients were assigned to different dosing regimens based on disease activity. No change in plasma free VEGF-A or free Ang-2 was observed post-dose.

Population PK analyses showed that the covariates affecting faricimab vitreous disposition were age and the presence of faricimab ADAs in plasma. Covariates affecting plasma disposition were body weight, sex, and formulation. However, the effects of these covariates not considered clinically meaningful. In patients with nAMD, DME, and DR, higher faricimab vitreous exposure and longer vitreous $t_{1/2}$ was associated with longer Ang-2 and VEGF-A duration of suppression. A flat relationship was identified between BCVA and faricimab vitreous exposure in either nAMD or DME/DR populations and the 6 mg doses provide a broad range of efficacious concentrations. Patients with longer vitreous $t_{1/2}$ have a higher probability of needing less frequent dosing. In both nAMD and DME/DR populations, the percentage of patients with intraocular inflammation (IOI) was low, and higher vitreous faricimab concentrations were not associated with higher rate of IOI.

The Applicant proposed a dose of 6 mg (0.05 mL) administered Q4W for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to Q16W for nAMD, DME, and DR. The 6 mg dose was selected based on Phase 2 results where 6 mg was well tolerated and resulted in approximately 3 to 4 times higher faricimab concentrations in aqueous humor compared to 1.5 mg, with a safety profile consistent with monthly ranibizumab. Intravitreal administration of a 6 mg dose is expected

to maintain a given minimal pharmacologically active concentration for a longer period than 1.5 mg dose which was supported by Phase 2 and 3 exposure-PD data showing that higher faricimab vitreous exposure resulted in longer duration of aqueous Ang-2 and VEGF-A suppression. The combined evidence from Phase 2 and 3 studies showed that a minimum of four Q4W faricimab initiation doses resulted in almost complete suppression of Ang-2 and VEGF-A which was maintained throughout the initiation phase. This was accompanied by a robust reduction in CST and gain in BCVA that could be maintained even with extension of the treatment interval in a significant proportion of patients. The primary analysis results from Phase 3 studies TENAYA/LUCERNE showed non-inferiority of the faricimab up to Q16W arm to the aflibercept Q8W arm, which supports the suitability of extended faricimab dosing regimens based on disease activity after four monthly initiation doses. The safety and efficacy of faricimab 6 mg Q4W was comparable to both the faricimab 6 mg Q8W regimen and the active comparator ranibizumab Q4W regimen tested in the Phase 2 AVENUE study. Population PK analysis showed that the maximum vitreous faricimab concentrations were similar for a Q4W and Q8W dosing regimen and no faricimab accumulation occurs in vitreous, aqueous or plasma. Therefore, the AVENUE data and exposure-safety analysis supports a positive benefit-risk balance for nAMD patients who may need to be dosed as frequently as every 4 weeks.

Based on the efficacy and safety results from the Phase 3 studies and the supportive evidence from the exposure-response analyses, the proposed dosing regimen of 6 mg (0.05 mL) administered Q4W for the first 4 doses, followed by 6 mg (0.05 mL) at intervals of up to Q16W for nAMD, DME, and DR patients appears reasonable.

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/s/

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