Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. List of PANORAMA Study Investigators

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eMethods 2. Patient Inclusion/Exclusion Criteria, Randomization and Masking, Methods to Assess Efficacy and Safety Outcomes, Protocol Amendments, Sample Size Calculation, and Statistical Analyses

Patient Inclusion/Exclusion Criteria

Please refer to the provided study protocol for inclusion and exclusion criteria in full. Briefly, adult subjects (age ≥18 years) with type 1 or 2 diabetes mellitus who had moderately severe to severe nonproliferative diabetic retinopathy (NPDR; Diabetic Retinopathy Severity Scale [DRSS] level 47 or 53 confirmed by the central reading center) in an eye in which panretinal photocoagulation (PRP) could be safely deferred for ≥6 months were eligible for enrollment. best corrected visual acuity (BCVA) of ≥69 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (approximately 20/40 or better) was required in the study eye. Subjects were excluded if they had macular edema (ME) within 1000 µm of the foveal center, retinal neovascularization, anterior segment neovascularization (ASNV), vitreous hemorrhage, or tractional retinal detachment. Subjects were also excluded if they had prior treatment with focal, grid, or PRP, intraocular steroids, or anti-vascular endothelial growth factor (VEGF) agents. Only one eye per patient was enrolled in the study.

Randomization and Masking

Patients were randomized according to a central randomization scheme with treatment assignments provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

The study was conducted in double-masked fashion, and masking was maintained to the end of the study (week 100). Study patients and masked study site personnel remained masked to all randomization assignments throughout the study. To preserve the masking, sham injections were performed for the 2q8 and 2q16 groups at treatment visits in which patients did not receive an active injection through week 96; sham injections were performed at all treatment visits for the sham group from baseline to week 96. A masked physician was responsible for all study procedures and assessments except for study drug administration, which was performed by a separate unmasked physician. Every effort was made to ensure that all study site personnel other than those designated as unmasked remained masked to treatment assignment. The central reading center responsible for the assessment of the DRSS for the primary endpoint was masked to treatment assignment throughout the study. In addition, the Sponsor/ Contract research organization (CRO) team members who were in regular contact with study sites remained masked to all patient randomization assignments.

Methods to Assess Efficacy and Safety Outcomes

Diabetic retinopathy (DR) severity was evaluated using feature-based grading of visible pathologic characteristics on fundus photographs taken at baseline and weeks 8, 12, 24, 40, 52, and all visits from week 56 through 100 designating an eye to one of 12 distinct categories on the ETDRS DRSS.[1] BCVA and central subfield thickness (CST; termed central retinal thickness [CRT] in the clinical study protocol) were assessed using the ETDRS protocol[2] and spectral domain optical coherence tomography (SD-OCT) at every visit, respectively. Masked readers at an independent reading center graded all images (Fundus Photograph Reading Center, Madison, Wisconsin).

Vision-threatening complication (VTC) events were determined either by the reading center if a DRSS score of ≥ level 61 was assigned, or by the investigator on fundus photography, fluorescein angiography, and/or clinical exam. Center-involved diabetic macular edema (CI-DME) was diagnosed by the investigator using clinical exam and/or SD-OCT. If identified by the investigator, VTC and CI-DME events could be recorded at any visit, scheduled or unscheduled.

Safety outcomes included the proportion of subjects who developed ocular adverse events (AEs), nonocular AEs, and Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic events.

Efficacy and safety variables were assessed using the full analysis set and safety analysis set, respectively, which were identical and included all randomized eyes that received any study treatment.

Protocol Amendments

Amendments 1 and 2: Following discussions with the Food and Drug Administration (FDA) (and well before the study began), the primary outcome measure of the study was amended to be the proportion of patients who improved by ≥2 steps from baseline in the DRSS score at week 24 in the combined 2q8 and 2q16 groups, and at week 52 for each group separately. Secondary endpoints were modified slightly; a few were separated into 2 endpoints. The 2q8 group regimen was updated to transition to a flexible dosing regimen based on the investigator's assessment of DRSS score beginning at week 56. Significance levels for testing of the secondary efficacy endpoints were also revised per FDA feedback. Hemoglobin A1c (HbA1c) assessment at week 24 and fundus photography (FP) at week 8 were added per Pharmaceuticals and Medical Devices Agency (PMDA) feedback.

Amendment 3: An exclusion criterion was updated to exclude women who were breastfeeding from participation in the study.

Amendment 4 (Japan only): Eligibility criteria were revised to exclude periocular steroid in the study eye within 120 days of day 1 and patients with fluorescein allergy precluding ability to perform fluorescein angiography, per request from the PMDA.

Amendment 5: The timepoint for evaluation of the secondary endpoints (parameters associated with the prevention of VTCs secondary to DR, and CI-DME) was changed from week 100 to week 52, with additional exploratory analysis of the secondary endpoints at week 100. This change was made because at week 24, when these measures were assessed from a safety perspective, there was a marked separation between the Intravitreal Aflibercept Injection (IAI) and sham groups, suggesting that IAI had a profound impact on these outcomes in diabetic retinopathy patients. Due to these results, the study sponsor felt it was important to make these data available to the DR community through approved labelling as soon as possible.

Sample Size Calculation

Based on data from the VISTA and VIVID trials[3,4] of IAI for treatment of DME, it was anticipated that approximately 41% versus 17% of eyes in the IAI and sham treatment groups would achieve a ≥2-step improvement from baseline in DRSS score, respectively. It was calculated that 120 eyes per treatment group were needed to detect a difference between IAI and sham treatment with 90% power at a 2-sided significance level of 1.67%, assuming a 15% dropout rate.

Statistical Analyses

Proportions were analyzed using the Cochran-Mantel-Haenszel test stratified by baseline DRSS score. Continuous variables were analyzed using analysis of covariance with baseline measurements as covariates and treatment and baseline DRSS score stratification as fixed factors. Missing or non-gradable post-baseline values were imputed using the last observation carried forward method. Data for eyes receiving rescue treatment was censored from the time of rescue. Cumulative incidence of events and event rates was estimated using the Kaplan–Meier method. Hazard ratios were calculated using a Cox model including factors of treatment group and baseline DRSS score stratification variable. The primary efficacy endpoints were tested at the significance level of 1.67% ($P<0.0167$). The significance threshold for the secondary endpoints was dependent on the outcomes of the primary endpoints. All analyses were performed using Statistical Analysis System software (SAS; Cary, North Carolina).

eTable 1. Treatment Experience Through Week 100

Treatment	Mean number of injections from baseline to week 52	Mean number of injections from week 52 to week 100	Mean total injections through week 100
IAI 2q16 (N=135)	5.5 (of 6 expected)	2.6 (of 3 expected)	7.8 (of 9 expected)
IAI 2q8/PRN (N=134)	8.6 (of 9 expected)	1.8 (of 0 to max. 6)	10.3 (of 9 to max. 15)

Not including IAI rescue injections. Patients entering the 2nd year: 2q16 n=121, 2q8 n=122 (41 patients in the 2q8 group did not receive any injections in year 2).

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; IAI, intravitreal aflibercept injection; max., maximum; PRN, pro re nata.

eTable 2. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Weeks 24, 52, and 100 Using LOCF Method

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]
Week 24			
IAI 2q16 (N=135)	83/135 (61.5)	55.4 (46.3, 64.5)	<.001
IAI 2q8/PRN (N=134)	74/134 (55.2)	49.2 (39.9, 58.6)	<.001
IAI 2mg combined (N=269)	157/269 (58.4)	52.3 (45.2, 59.5)	<.001
Sham (N=133)	8/133 (6.0)		
Week 52			
IAI 2q16 (N=135)	88/135 (65.2)	50.1 (40.1, 60.1)	<.001
IAI 2q8/PRN (N=134)	107/134 (79.9)	64.8 (55.8, 73.9)	<.001
Sham (N=133)	20/133 (15.0)		
Week 100			
IAI 2q16 (N=135)	84/135 (62.2)	49.4 (39.4, 59.4)	<.001
IAI 2q8/PRN (N=134)	67/134 (50.0)	37.2 (27.1, 47.4)	<.001
Sham (N=133)	17/133 (12.8)		

[a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; LOCF; last observation carried forward; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 3. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Week 52 Using aLOCF Method

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]
IAI 2q16 (N=135)	89/135 (65.9)	41.8 (31.0, 52.6)	<.001
IAI 2q8/PRN (N=134)	107/134 (79.9)	55.8 (45.9, 65.7)	<.001
Sham (N=133)	32/133 (21.4)		

LOCF method was used to impute missing or non-gradable post-baseline data regardless of whether rescue treatment was given. Baseline was carried forward if all post-baseline observations were missing or non-gradeable. [a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; aLOCF; ancillary last observation carried forward; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 4. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Week 100 Using aLOCF Method

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]
IAI 2q16 (N=135)	87/135 (64.4)	36.6 (25.5, 47.7)	<.001
IAI 2q8/PRN (N=134)	67/134 (50.0)	22.2 (10.9, 33.5)	<.001
Sham (N=133)	37/133 (27.8)		

LOCF method was used to impute missing or non-gradable post-baseline data regardless of whether rescue treatment was given. Baseline was carried forward if all post-baseline observations were missing or non-gradeable. [a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; aLOCF; ancillary last observation carried forward; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 5. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Week 52 Using aOC Method

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]
IAI 2q16 (N=135)	72/108 (66.7)	40.7 (28.4, 53.0)	<.001
IAI 2q8/PRN (N=134)	96/116 (82.8)	56.4 (45.5, 67.4)	<.001
Sham (N=133)	27/106 (25.5)		

All observed values were used for analysis regardless of whether rescue treatment was given. [a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; aOC; ancillary observed case; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 6. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Week 100 Using aOC Method

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]
IAI 2q16 (N=135)	66/101 (65.3)	38.0 (24.8, 51.2)	<.001
IAI 2q8/PRN (N=134)	48/100 (48.0)	19.8 (6.2, 33.4)	0.0050
Sham (N=133)	24/88 (27.3)		

All observed values were used for analysis regardless of whether rescue treatment was given. [a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; aOC; ancillary observed case; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 7. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Week 52 Using Multiple Imputation

Treatment	n/N, (%)[a]	Difference, %	Adjusted difference, % (95% CI)[b]	P-value[c]
IAI 2q16 (N=135)	89/135 (66.3)	46.3	46.3 (36.0, 56.6)	<.001
IAI 2q8/PRN (N=134)	110/134 (81.9)	62.0	62.0 (52.8, 71.2)	<.001
Sham (N=133)	27/133 (19.9)			

[a]Calculated from the average of 100 imputed data; [b]Calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable for each imputed data, then results averaged; [c]Calculated from Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable for each imputed data, then P-value calculated after Wilson Hilferty transformation.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 8. Proportion of Patients With a 2-Step or Greater Improvement in DRSS Score From Baseline to Week 100 Using Multiple Imputation

Treatment	n/N, (%)[a]	Difference, %	Adjusted difference, % (95% CI)[b]	P-value[c]
IAI 2q16 (N=135)	83/135 (61.8)	44.4	44.4 (34.0, 54.8)	<.001
IAI 2q8/PRN (N=134)	63/134 (47.2)	29.9	29.9 (19.3, 40.4)	<.001
Sham (N=133)	23/133 (17.4)			

[a]Calculated from the average of 100 imputed data; [b]Calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable for each imputed data, then results averaged; [c]Calculated from Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable for each imputed data, then p-value calculated after Wilson Hilferty transformation.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; CI, confidence interval; DRSS, diabetic retinopathy severity scale; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 9. Proportion of Patients Who Developed Any Vision-Threatening Complication (PDR/ASNV) Through Week 52 and Week 100

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]	Reduction from Sham, %
Week 52				
IAI 2q16 (N=135)	5/135 (3.7)	–16.6 (–24.2, –9.1)	<.001	81.8
IAI 2q8/PRN (N=134)	4/134 (3.0)	–17.3 (–24.7, –9.9)	<.001	85.3
Sham (N=133)	27/133 (20.3)			
Week 100				
IAI 2q16 (N=135)	11/135 (8.1)	–19.0 (–27.8, –10.1)	<.001	69.9
IAI 2q8/PRN (N=134)	8/134 (6.0)	–21.1 (–29.6, –12.5)	<.001	77.9
Sham (N=133)	36/133 (27.1)			

[a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; ASNV, anterior segment neovascularization; CI, confidence interval; IAI, intravitreal aflibercept injection; PDR, proliferative diabetic retinopathy; PRN, pro re nata.

eTable 10. Proportion of Patients Who Developed CI-DME Through Week 52 and Week 100

Treatment	n/N, (%)	Adjusted difference, % (95% CI)[a]	P-value[b]	Reduction from Sham, %
Week 52				
IAI 2q16 (N=135)	9/135 (6.7)	–18.9 (–27.5, –10.4)	<.001	73.9
IAI 2q8/PRN (N=134)	11/134 (8.2)	–17.3 (–26.2, –8.5)	<.001	67.9
Sham (N=133)	34/133 (25.6)			
Week 100				
IAI 2q16 (N=135)	14/135 (10.4)	–22.8 (–32.2, –13.3)	<.001	68.7
IAI 2q8/PRN (N=134)	18/134 (13.4)	–19.6 (–29.6, –9.7)	<.001	59.4
Sham (N=133)	44/133 (33.1)			

[a]Difference in CI is calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS variable; [b]P-value is calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS variable.

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; CI, confidence interval; CI-DME, center-involved diabetic macular edema; IAI, intravitreal aflibercept injection; PRN, pro re nata.

eTable 11. Proportion of Patients With Panretinal Photocoagulation or Vitrectomy Through Week 100

Treatment	n/N, (%)	P-value
IAI 2q16 (N=135)	2/135 (1.5)	<.002
IAI 2q8/PRN (N=134)	2/134 (1.5)	<.002
Sham (N=133)	14/133 (10.5)	

2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; IAI, intravitreal aflibercept injection; PRN, pro re nata.

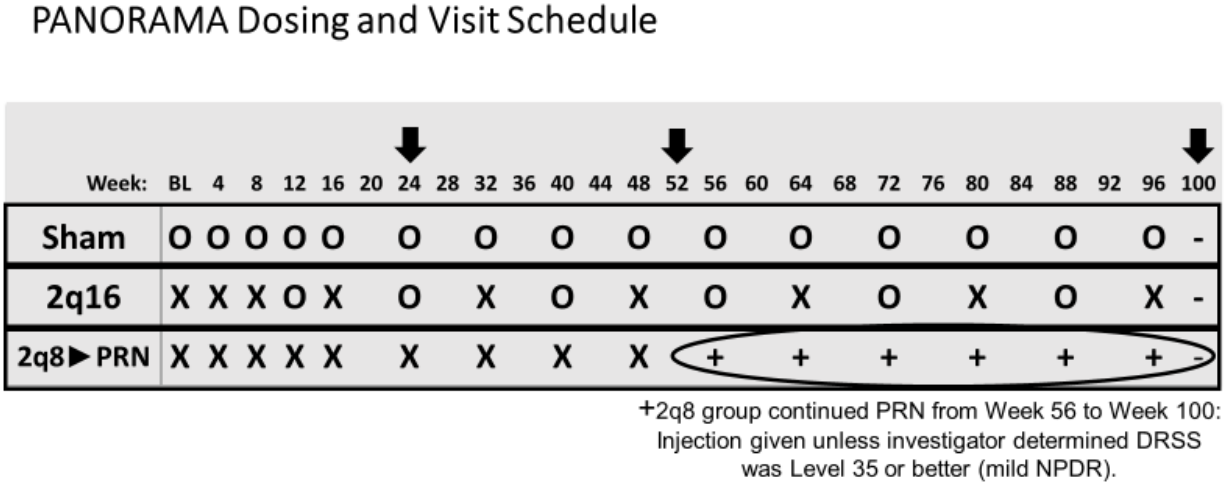
eTable 12. Nonocular SAEs Occurring in 1% of Patients or More in Any Treatment Group from Baseline Through Week 100

	Sham (N=133)	IAI 2q16 (N=135)	IAI 2q8/PRN (N=134)	All IAI (N=269)
Subjects with ≥1 nonocular SAE, N (%)	35 (26.3)	37 (27.4)	42 (31.3)	79 (29.4)
Abscess (limb)	0	0	2 (1.5)	2 (0.7)
Cellulitis	1 (0.8)	2 (1.5)	5 (3.7)	7 (2.6)
Pneumonia	2 (1.5)	3 (2.2)	3 (2.2)	6 (2.2)
Sepsis	1 (0.8)	0	3 (2.2)	3 (1.1)
Osteomyelitis	4 (3.0)	1 (0.7)	0	1 (0.4)
Acute kidney injury	2 (1.5)	1 (0.7)	3 (2.2)	4 (1.5)
Myocardial infarction	1 (0.8)	2 (1.5)	1 (0.7)	3 (1.1)
Acute myocardial infarction	2 (1.5)	2 (1.5)	0	2 (0.7)
Coronary artery disease	1 (0.8)	5 (3.7)	4 (3.0)	9 (3.3)
Coronary artery stenosis	0	2 (1.5)	0	2 (0.7)
Cardiac failure congestive	1 (0.8)	2 (1.5)	3 (2.2)	5 (1.9)
Left ventricular failure	2 (1.5)	0	0	0
Anemia	0	2 (1.5)	0	2 (0.7)
Diabetic ketoacidosis	0	2 (1.5)	0	2 (0.7)
Cerebrovascular accident	0	3 (2.2)	1 (0.7)	4 (1.5)
Ischemic stroke	3 (2.3)	0	0	0

Dehydration	1 (0.8)	0	3 (2.2)	3 (1.1)
Hypoglycemia	0	2 (1.5)	0	2 (0.7)
Diabetic foot	0	1 (0.7)	2 (1.5)	3 (1.1)
Diabetic foot infection	0	3 (2.2)	0	3 (1.1)
Acute respiratory failure	1 (0.8)	0	2 (1.5)	2 (0.7)
Pleural effusion	2 (1.5)	1 (0.7)	1 (0.7)	2 (0.7)
Pulmonary hypertension	2 (1.5)	0	0	0

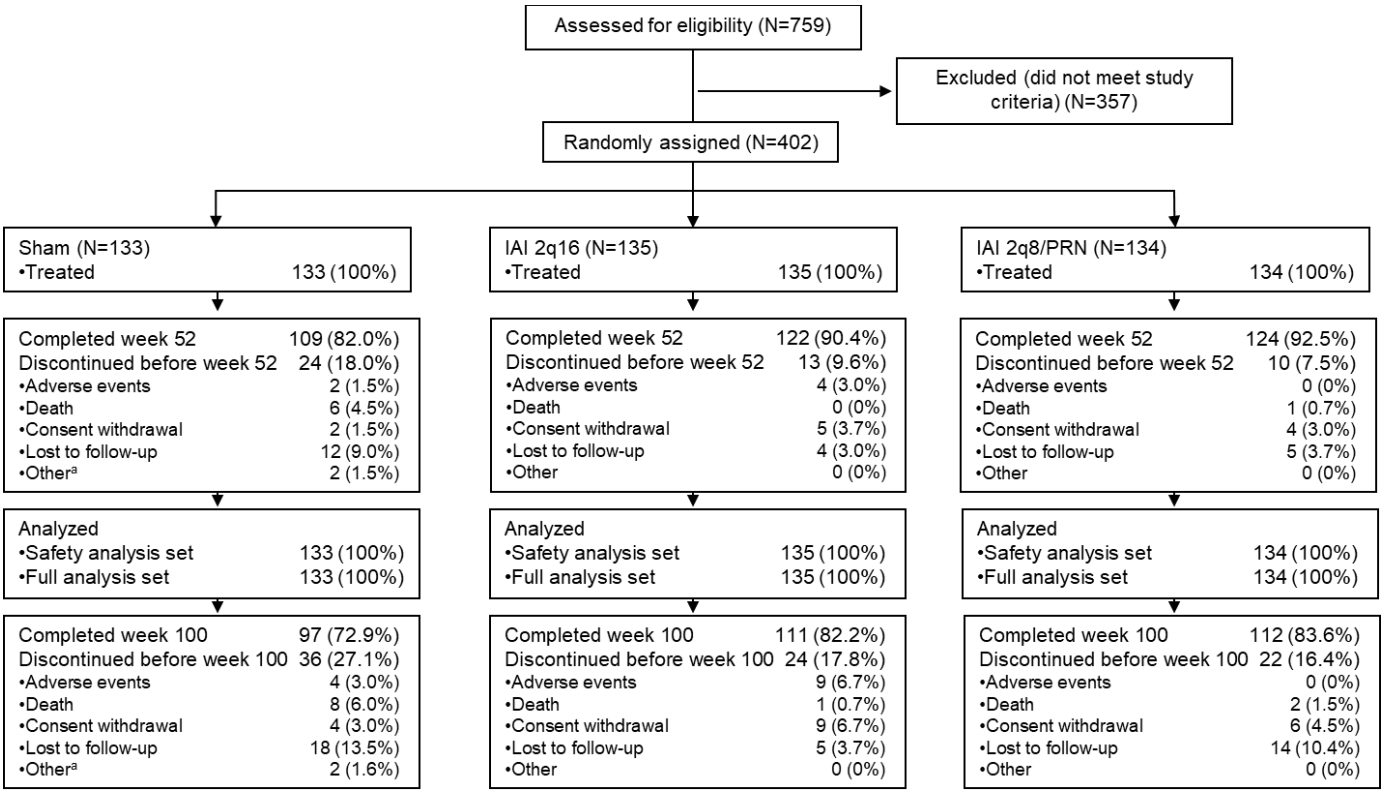
IAI, intravitreal aflibercept injection; IAI 2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; IAI 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; PRN, pro re nata; SAE, serious adverse event.

eFigure 1. Visit and Dosing Schedule of the Phase 3 Double-Masked PANORAMA Randomized Clinical Trial



2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; ASNV, anterior segment neovascularization; BL, baseline; CI-DME, center-involved diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; IAI, intravitreal aflibercept injection; NPDR, nonproliferative diabetic retinopathy, PDR, proliferative diabetic retinopathy; PRN, pro re nata.

eFigure 2. Patient Disposition



[a]One (0.8%) patient discontinued due to protocol deviation, and 1 (0.8%) patient discontinued due to pregnancy.

IAI, intravitreal aflibercept injection; IAI 2q8, 2 mg IAI every 8 weeks after 5 initial monthly doses; IAI 2q16, 2 mg IAI every 16 weeks after 3 initial monthly doses and 1 8-week interval; PRN, pro re nata.

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