Baseline Disease Characteristics of Patients Who Maintained 12- and 16-Week Aflibercept 8 mg Dosing Versus Patients with Shortened Treatment Intervals Through Week 48 in the Phase 2/3 PHOTON Trial

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Disclosures

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DME

- David M. Brown serves as a scientific advisor for Regeneron/Bayer and Genentech/Roche and as a member of the Regeneron Combination Products Steering Committee
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) and co-funded by Bayer AG (Leverkusen, Germany). The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of this presentation
- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
- Writing support was provided by Stephanie Agbu, PhD, and Disha Patel, PhD, of Regeneron Pharmaceuticals, Inc.

PHOTON Study Design

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DME

Multi-center, randomized, double-masked study in patients with DME[a]
Randomized 1 (2q8) : 2 (8q12) : 1 (8q16)
Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections

2q8
Aflibercept 2 mg every 8 weeks after 5 initial monthly injections
n=167

8q12
8 mg every 12 weeks after 3 initial monthly injections
n=328

8q16
8 mg every 16 weeks after 3 initial monthly injections
n=163

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)

Key secondary endpoint:
Proportion of patients with ≥2-step improvement in DRSS at Week 48

↓

End of study at Week 96

[a]Treatment-naïve and previously treated.
BCVA, best-corrected visual acuity; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Score.

Key Eligibility Criteria

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DME

Inclusion Criteria

- Adults (≥18 years of age) with type 1 or type 2 diabetes
- DME with central involvement with CRT ≥300 µm (or ≥320 µm on Spectralis) in the study eye as determined by the reading center
- BCVA of 78-24 letters (Snellen equivalent 20/32-20/320) with decreased vision due to DME

Exclusion Criteria

- Active PDR in the study eye
- PRP or laser photocoagulation in the study eye within 12 weeks of screening visit
- IVT anti-VEGF treatment in the study eye within 12 weeks of screening visit
- Intraocular or periocular steroids in the study eye within 16 weeks of the screening visit

CRT, central retinal thickness; IVT, intravitreal; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

Dosing Schedule and DRM Criteria in Year 1

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DME
Primary Endpoint

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections

Stippled boxes = initial treatment phase; X=active injection; o=sham injections.
DRM, dose regimen modification; Wk, week.

Dosing Schedule and DRM Criteria in Year 1

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DME

Primary Endpoint

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections

DRM Criteria for Shortening Dosing Interval[a]

- >10-letter loss in BCVA due to persistent or worsening DME

AND

- >50-micron increase in CRT

[a]All assessments compared to Week 12

Stippled boxes = initial treatment phase; X=active injection; o=sham injections.
DRM, dose regimen modification; Wk, week.

Dosing Schedule and DRM Criteria in Year 1

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Primary Endpoint

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections

DRM Criteria for Shortening Dosing Interval[a]

- >10-letter loss in BCVA due to persistent or worsening DME

AND

- >50-micron increase in CRT

[a]All assessments compared to Week 12

DRM in Year 1

Intervals can only be **shortened**

Multiple opportunities to shorten interval

Minimum interval for all patients was **Q8**

- **Week 16 and 20:** Patients on 8q12 and 8q16 meeting DRM criteria shortened to Q8
- **Week 24:** Patients on 8q16 meeting DRM criteria shortened to Q12
- **Week 32 and 44 for 8q12 and Week 36[b] and 40 for 8q16:** Treatment interval shortened by 4 weeks for patients meeting DRM criteria

Stippled boxes = initial treatment phase; X=active injection; o=sham injections. Note: Figure does not reflect all dosing options once a patient is shortened.
[b]At Week 36, patients on 8q16 who were previously shortened to Q12 could have been shortened to Q8.
DRM, dose regimen modification; Wk, week.

PHOTON: 48-Week BCVA
Primary Endpoint Met in Both 8 mg Groups

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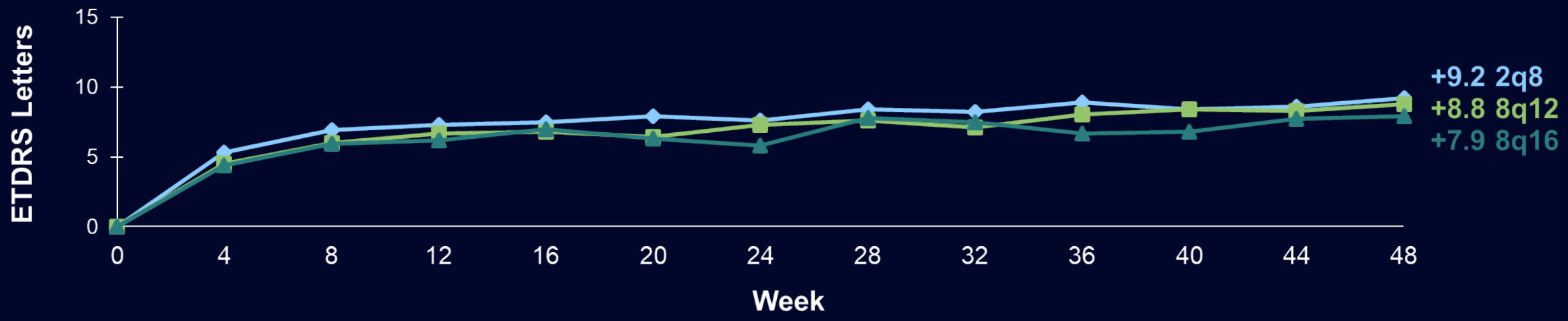
DME

BCVA Change From Baseline[a]

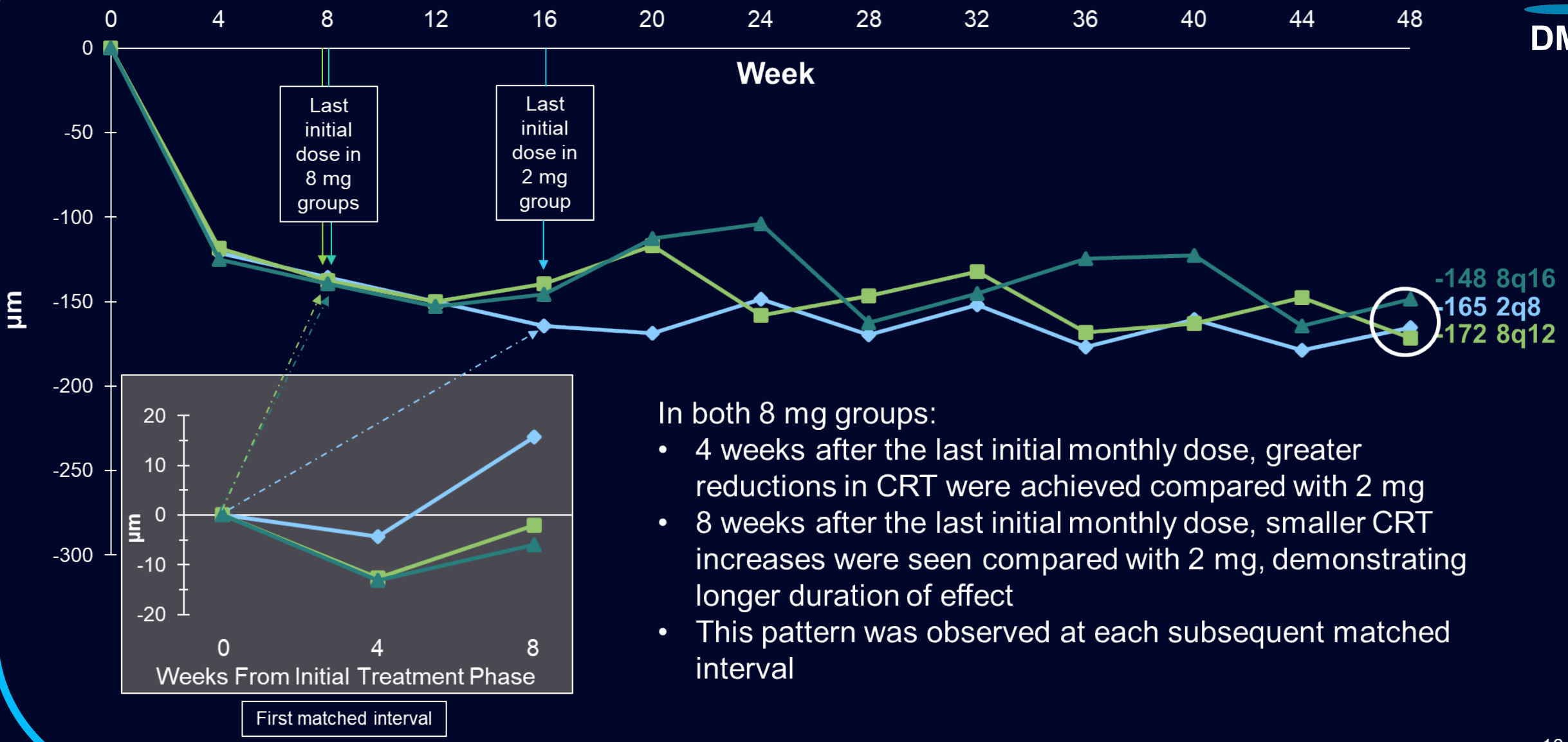


	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs. 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	8.7			
8q12	8.1	-0.57	-2.26, 1.13	p < 0.0001
8q16	7.2	-1.44	-3.27, 0.39	p = 0.0031

[a]Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
BL, baseline; Diff, difference; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

Mean Change in Central Retinal Thickness

Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections



In both 8 mg groups:

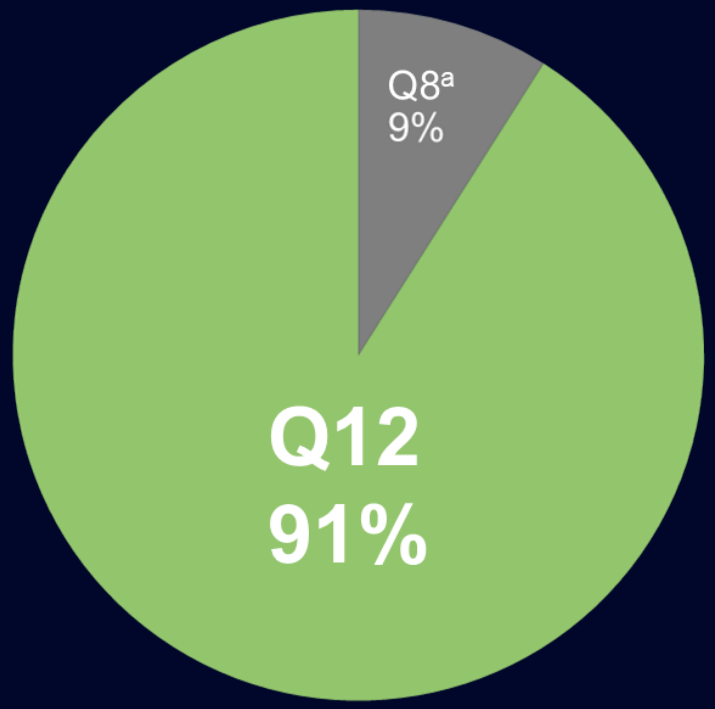
- 4 weeks after the last initial monthly dose, greater reductions in CRT were achieved compared with 2 mg
- 8 weeks after the last initial monthly dose, smaller CRT increases were seen compared with 2 mg, demonstrating longer duration of effect
- This pattern was observed at each subsequent matched interval

Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

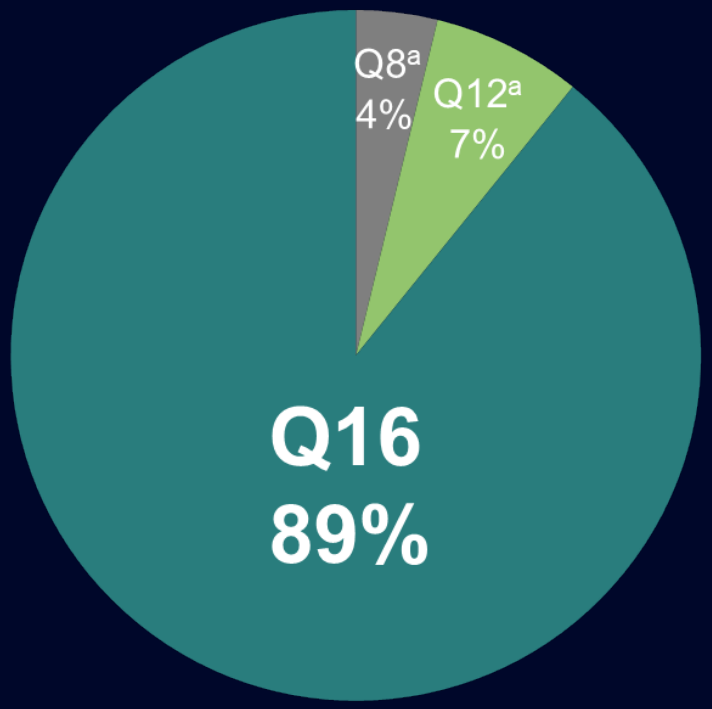
Proportion of 8 mg Patients Maintaining Q12- and Q16-Week Intervals Through Week 48

DME

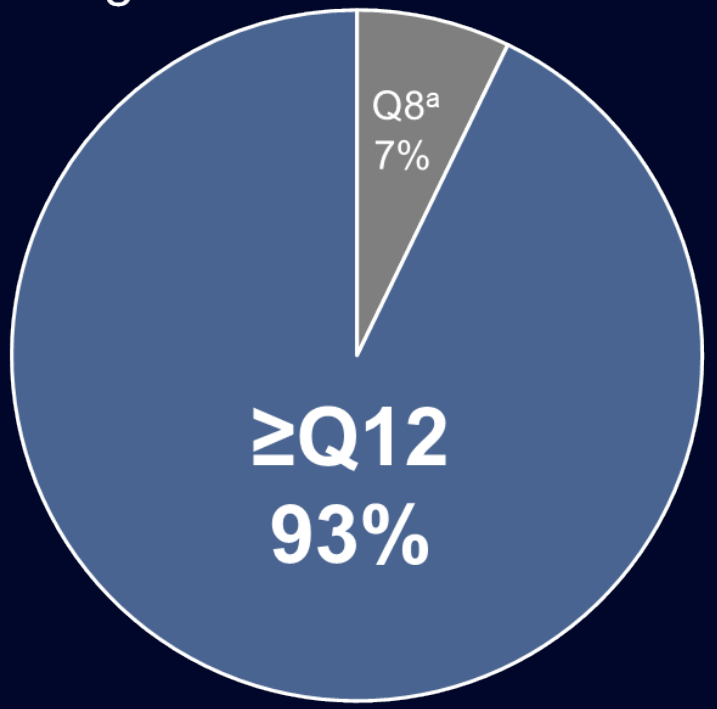
93% of 8 mg patients maintained dosing intervals ≥12 weeks



8q12 (n=300)[b]



8q16 (n=156)[b]



All 8 mg (n=456)[b]

[a]Patients shortened based on DRM assessments at some point through Week 48.
[b]Patients completing Week 48.

Large Majority of 8 mg Patients Maintained Randomized Intervals Through Week 48

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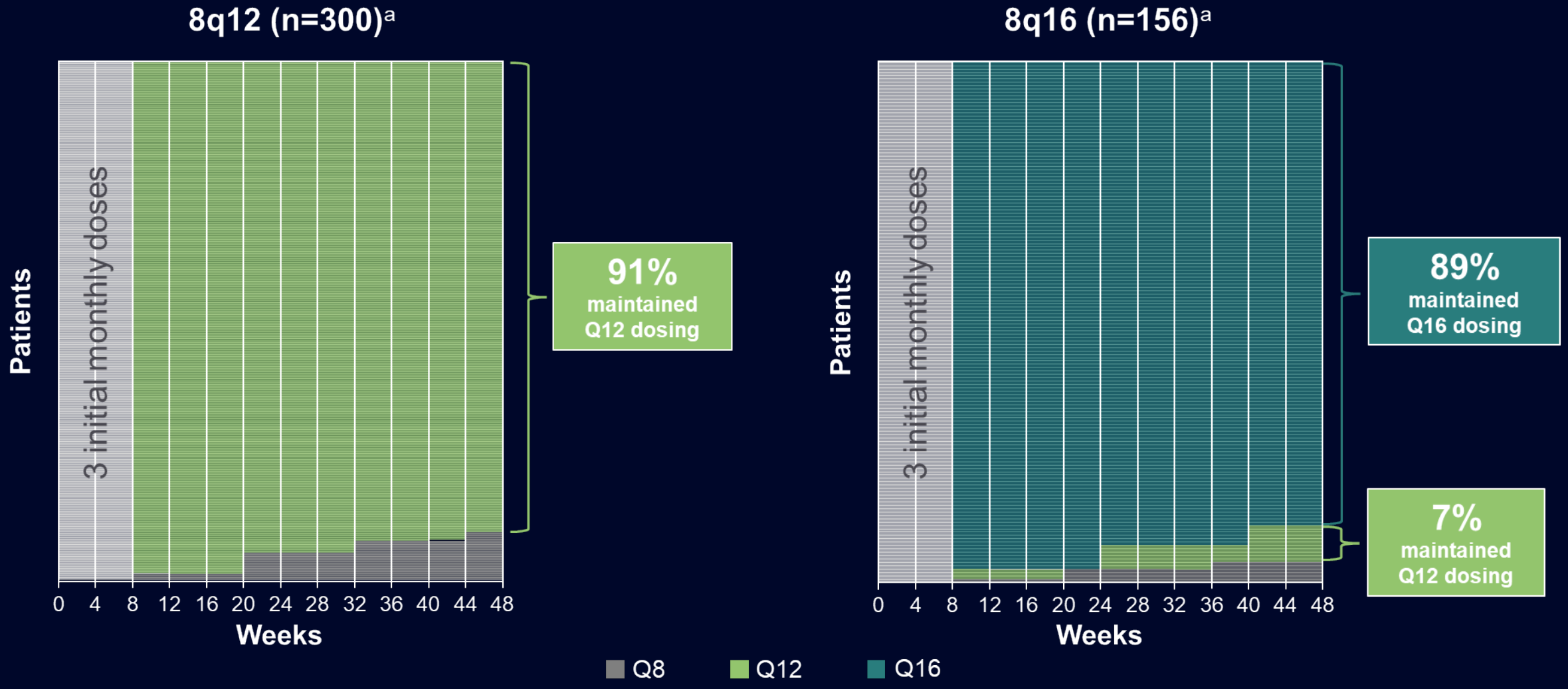
DME



aPatients completing Week 48.

PHOTON: 48-Week Safety Results

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DME

- Safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg
- No cases of endophthalmitis or occlusive retinal vasculitis were reported
- No clinically relevant change was observed in IOP with aflibercept 8 mg throughout the study
- Incidence of APTC events, hypertension events, and death was similar between aflibercept 8 mg and 2 mg

APTC, Anti-Platelet Trialists' Collaboration; IOP, intraocular pressure.

Objectives and Methods

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DME

Objectives:

- To describe baseline characteristics of patients with maintained vs shortened dosing intervals
- To identify baseline characteristics associated with shortened dosing intervals
- To evaluate visual and anatomic outcomes at Week 48 in patients with maintained vs shortened dosing intervals

Methods:

- To identify associations between baseline characteristics and shortened dosing intervals:
  - Univariable Cox regression analysis (adjusted for randomization strata) assessed baseline factors (diabetes type, hemoglobin A1c, duration of diabetes, BMI, BCVA, CRT, DRSS, prior DME treatment) associated with the incidence of dosing interval shortening
  - Identified baseline characteristics were subsequently assessed in a multivariable analysis with stepwise regression
  - A ROC analysis was performed to identify the optimal cutoff point for predicting shortened dosing intervals
  - Data for aflibercept 8 mg groups were pooled for the univariable, multivariable, and ROC analyses
- BCVA and CRT were evaluated at baseline and Week 48 using observed values

P-values were considered nominal. No correction was made for multiplicity.
ROC, receiver operating characteristics.

Baseline Demographics by Dosing Interval

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DME

	8q12 (n=300)[a]		8q16 (n=156)[a]	
	Maintained	Shortened	Maintained	Shortened
n (%)	273 (91.0)	27 (9.0)	139 (89.1)	17 (10.9)
Age (years)	62.2 (10.9)	59.1 (13.9)	62.0 (9.6)	60.1 (9.9)
Sex (%)				
Female	36.3	25.9	41.0	29.4
Male	63.7	74.1	59.0	70.6
Race (%)[b]				
White	69.6	70.4	77.0	88.2
Black or African American	10.3	14.8	6.5	0
Asian	15.8	14.8	14.4	11.8
Other[c]	2.9	0	0.7	0
Not reported	1.5	0	1.4	0

Data are mean (SD) unless otherwise indicated.
[a]Patients from the FAS who completed Week 48.
[b]The sum of proportions may not equal 100% due to rounding.
[c]Other includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and Multiple.

Baseline Demographics by Dosing Interval

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DME

	8q12 (n=300)[a]		8q16 (n=156)[a]	
	Maintained	Shortened	Maintained	Shortened
n (%)	273 (91.0)	27 (9.0)	139 (89.1)	17 (10.9)
Ethnicity (%)[b]				
Hispanic or Latino	16.1	3.7	23.0	5.9
Not Hispanic or Latino	81.3	96.3	75.5	88.2
Not reported	2.6	0	1.4	5.9
Type 2 diabetes (%)	94.5	92.6	95.0	94.1
Duration of diabetes (years)	15.5 (10.1)	11.1 (9.7)	15.6 (10.5)	15.8 (11.0)
NEI VFQ-25 total score	77.1 (17.3)	76.1 (16.4)	78.7 (15.5)	72.4 (16.8)
BMI (kg/m^2)	30.3 (6.1)	29.3 (6.6)	31.1 (6.3)	30.5 (4.8)
Hemoglobin A1c (%)	8.0 (1.5)	7.8 (1.4)	7.9 (1.5)	7.8 (1.9)

Data are mean (SD) unless otherwise indicated.
[a]Patients from the FAS who completed Week 48.
[b]The sum of proportions may not equal 100% due to rounding or missing values.
BMI, body mass index; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25.

Baseline Demographics by Dosing Interval

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DME

	8q12 (n=300)[a]		8q16 (n=156)[a]	
	Maintained	Shortened	Maintained	Shortened
n (%)	273 (91.0)	27 (9.0)	139 (89.1)	17 (10.9)
Ethnicity (%)[b]				
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BMI (kg/m^2)	30.3 (6.1)	29.3 (6.6)	31.1 (6.3)	30.5 (4.8)
Hemoglobin A1c (%)	8.0 (1.5)	7.8 (1.4)	7.9 (1.5)	7.8 (1.9)
Hemoglobin A1c category (%)[b]				
≤8%	57.5	70.4	63.3	70.6
>8%	41.8	29.6	35.3	29.4

Data are mean (SD) unless otherwise indicated.
[a]Patients from the FAS who completed Week 48.
[b]The sum of proportions may not equal 100% due to rounding or missing values.
BMI, body mass index; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25.

Baseline Ocular Characteristics by Dosing Interval

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DME

	8q12 (n=300)[a]		8q16 (n=156)[a]	
	Maintained	Shortened	Maintained	Shortened
n (%)	273 (91.0)	27 (9.0)	139 (89.1)	17 (10.9)
BCVA (ETDRS letters)	63.9 (10.1)	59.4 (10.0)	62.7 (11.2)	53.7 (12.8)
CRT (μm)	444.9 (129.8)	511.4 (117.5)	447.1 (112.5)	534.8 (134.3)
Baseline DRSS score (%)				
Level 43 or better	61.2	51.9	66.9	58.8
Level 47 or worse	33.7	40.7	26.6	41.2
Ungradable	5.1	7.4	6.5	0
Prior DME treatment, n (%)	42.5	55.6	44.6	47.1

Compared with patients who maintained their randomized dosing intervals, those whose dosing intervals were shortened had on average **lower** BCVA and **greater** CRT at baseline

Data are mean (SD) unless otherwise indicated.
[a]Patients from the FAS who completed Week 48.

Univariable Analysis: Baseline Characteristics Associated With the Incidence of Dosing Interval Shortening

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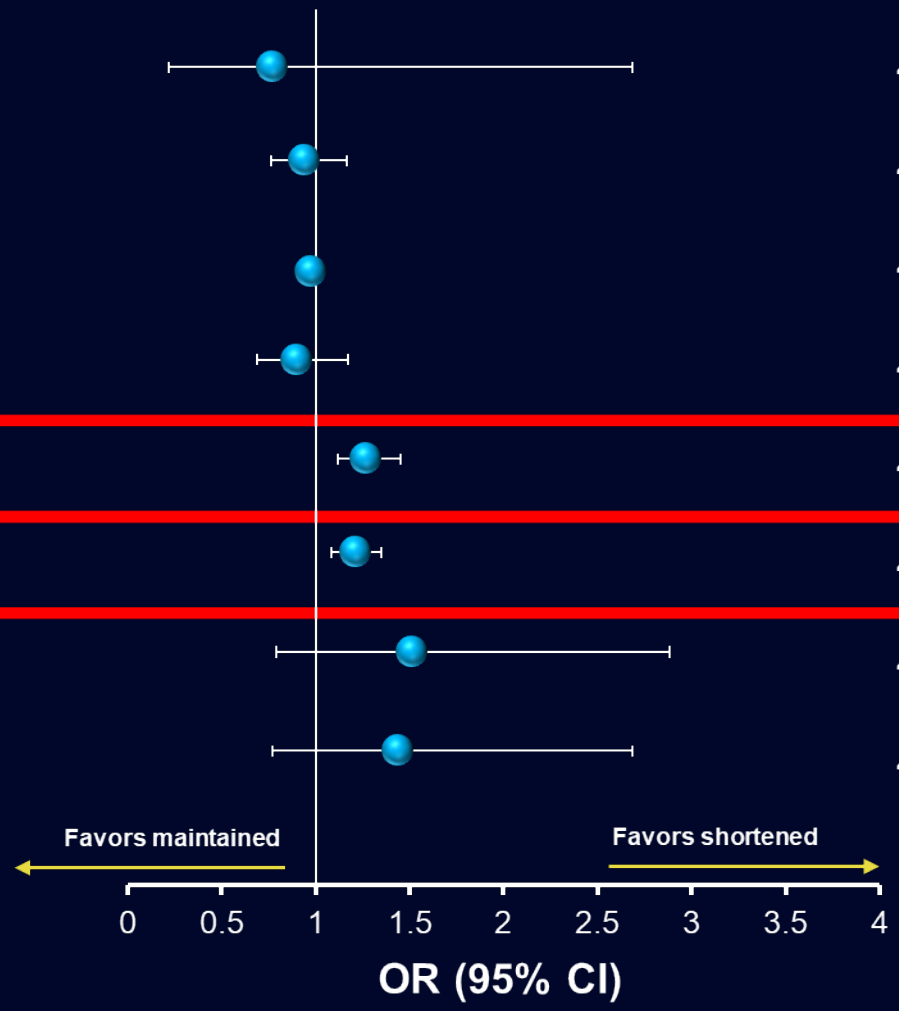
DME



	N	n	OR (95% CI)	*P*-value
Diabetes type (Type 2 vs. Type 1)	456	431	0.77 (0.22, 2.69)	0.6827
Hemoglobin A1c (per 1% increase)	452	–	0.94 (0.76, 1.17)	0.5871
Duration of diabetes (per 1-year increase)	454	–	0.97 (0.94, 1.01)	0.1048
BMI (per 5-kg/m^2 increase)	455	–	0.90 (0.69, 1.17)	0.4273
BCVA (per 5-letter decrease)	456	–	1.27 (1.12, 1.45)	0.0003
CRT (per 50-µm increase)	455	–	1.21 (1.09, 1.35)	0.0005
DRSS (≥47-<90 vs ≤43)	431	147	1.51 (0.79, 2.89)	0.2101
Prior DME treatment (Yes vs No)	456	201	1.44 (0.77, 2.68)	0.2513

OR, odds ratio.
N, number of patients evaluated for the specified baseline characteristic; n, number of patients in the first specified category.

Multivariable Analysis: Baseline Characteristics Associated With the Incidence of Dosing Interval Shortening

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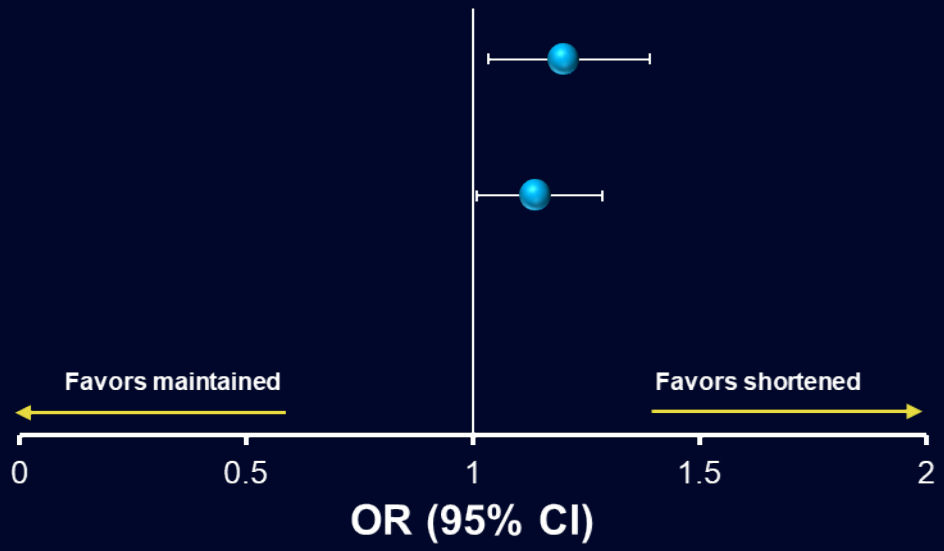
DME

	OR (95% CI)	*P*-value
BCVA (per 5-letter decrease)	1.20 (1.03, 1.40)	0.0165
CRT (per 50-micron increase)	1.14 (1.01, 1.29)	0.0345



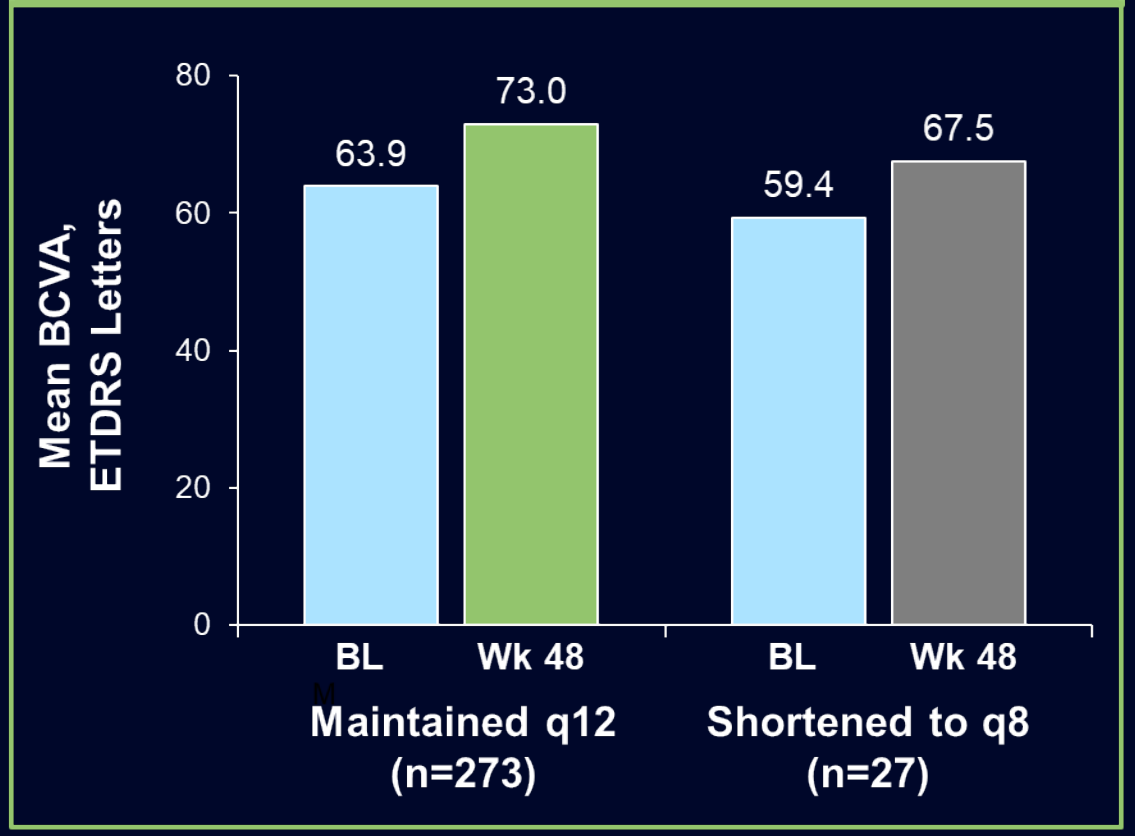
A subsequent ROC analysis of pooled data for aflibercept 8 mg demonstrated that patients with BCVA ≤58 letters or CRT ≥474 µm at baseline were more likely to have shortened dosing intervals through Week 48 in this trial

ROC, receiver operating characteristics.

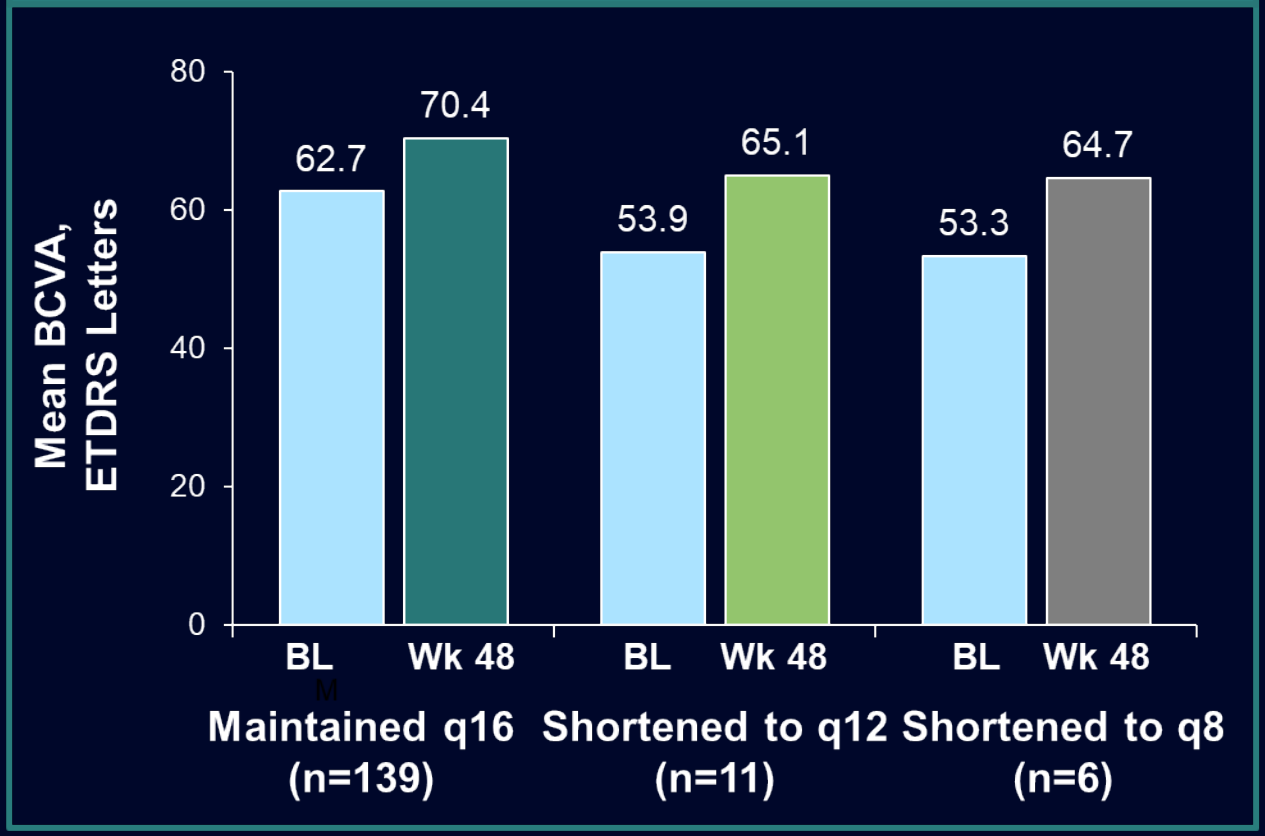
Absolute BCVA at Baseline and Week 48 by Dosing Interval

DME

8q12 (n=300)[a]



8q16 (n=156)[a]



[a]Patients from the FAS who completed Week 48.
FAS, observed values (censoring data post-ICE).

Absolute CRT at Baseline and Week 48 by Dosing Interval

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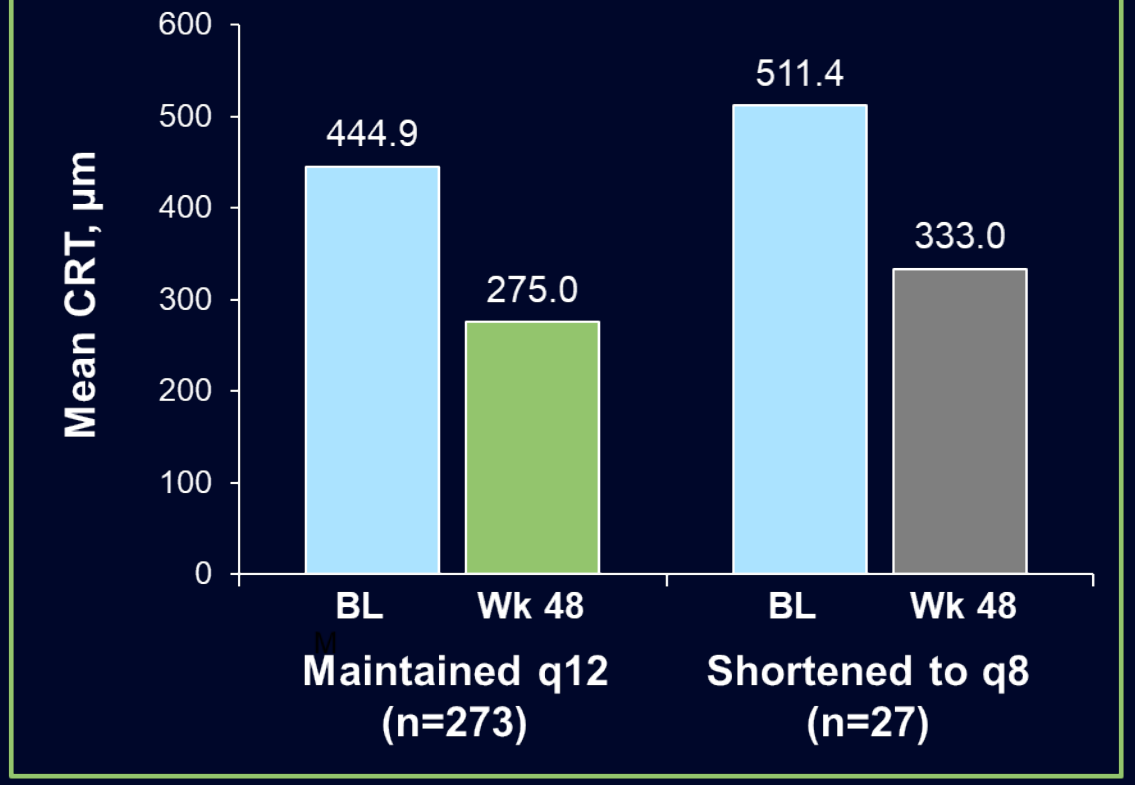
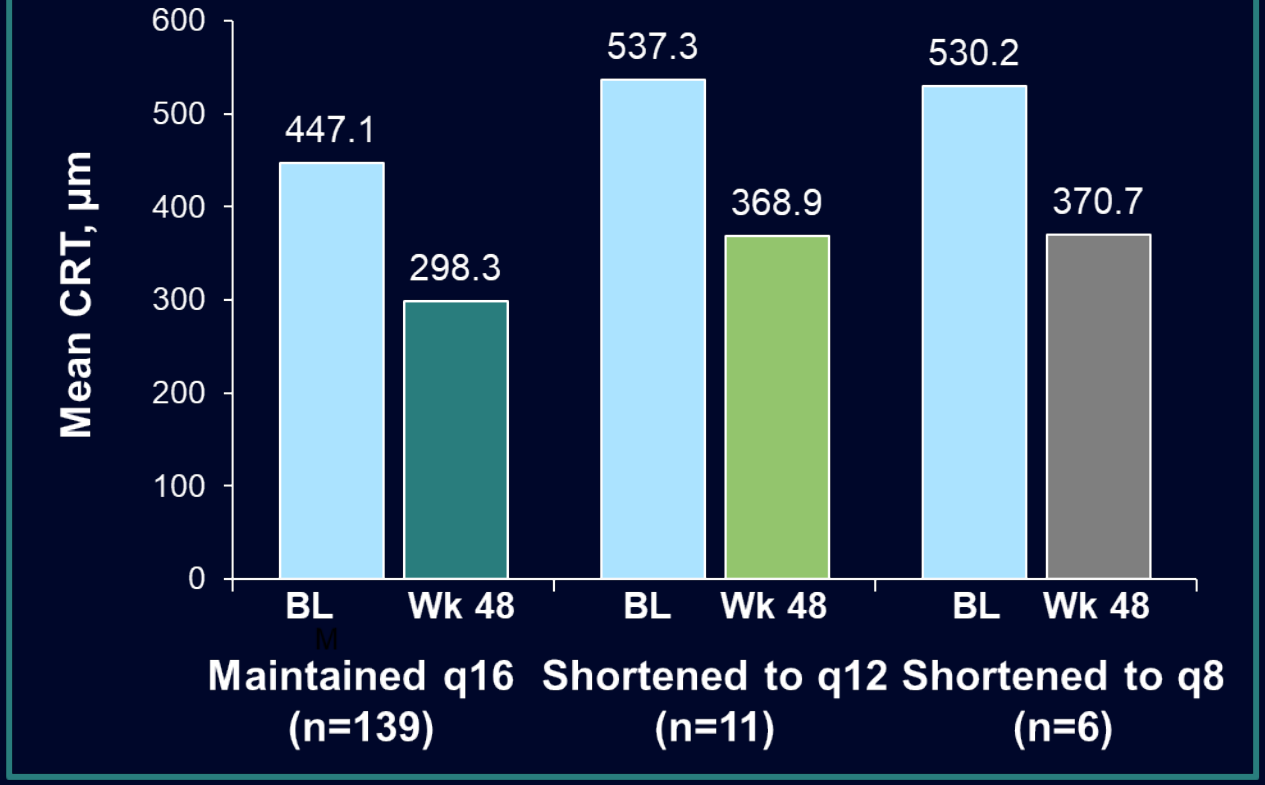
DME

8q12 (n=300)[a]



8q16 (n=156)[a]



[a]Patients from the FAS who completed Week 48.
FAS, observed values (censoring data post-ICE).

Conclusions

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DME

- Aflibercept 8q12 and 8q16 demonstrated non-inferior BCVA gains compared to aflibercept 2q8 at Week 48, with a large majority of patients maintaining their randomized 12- or 16-week dosing intervals
  - Dosing intervals were shortened in approximately 10% of patients
- Lower BCVA and greater CRT at baseline were associated with shortened dosing intervals in patients receiving aflibercept 8 mg in this trial
- Aflibercept 8 mg-treated patients with shortened dosing intervals had meaningful BCVA gains and CRT improvements at Week 48, although absolute BCVA and CRT values at Week 48 were not equivalent to those of patients with maintained dosing intervals