Tolerability and Safety of Intravitreal Aflibercept 8 mg in the Phase 3 PULSAR Trial of Patients with Neovascular Age-Related Macular Degeneration

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Disclosures

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PULSAR Study Design

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Multicenter, randomized, double-masked study in patients with treatment-naïve nAMD
Randomized at baseline 1 (2q8) : 1 (8q12) : 1 (8q16)

2q8
Aflibercept 2 mg every 8 weeks after 3 initial monthly injections
n=336

8q12
Aflibercept 8 mg every 12 weeks after 3 initial monthly injections
n=335

8q16
Aflibercept 8 mg every 16 weeks after 3 initial monthly injections
n=338

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

Key secondary endpoint at Week 16:
Proportion of patients without IRF and SRF in the center subfield

End of study at Week 96
with optional, 1-year extension through Week 156

2q8, aflibercept 2 mg every 8 weeks; **8q12**, aflibercept 8 mg every 12 weeks; **8q16**, aflibercept 8 mg every 16 weeks; **BCVA**, best-corrected visual acuity; **IRF**, intraretinal fluid; **nAMD**, neovascular age-related macular degeneration; **SRF**, subretinal fluid.

PULSAR: Dosing Schedule and Regimen Modification in Year 1

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	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	o	X	o	X	o	X	o	X
8q12	X	X	X		o	X	o	o	X	o	o	X	o
8q16	X	X	X		o	o	X	o	o	o	X	o	o

DRM Criteria for Shortening Dosing Interval

- >5-letter loss in BCVA compared with Week 12, due to persistent or worsening nAMD

AND

- >25 µm increase in CST compared with Week 12, or new-onset foveal neovascularization, or foveal hemorrhage

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 40 for 8q16:** Treatment interval shortened by 4 weeks for patients meeting DRM criteria

Stippled boxes = initial treatment phase; X = active injection; o = sham injection. Note: Table does not reflect all dosing options once a patient's dosing interval is shortened.
CST, central subfield thickness; **DRM**, dose regimen modification; **Q8**, every 8 weeks; **Q12,** every 12 weeks; **Wk**, week.

Patient Disposition at Week 48

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	2q8	8q12	8q16	Total
Randomized, n	337	336	338	1011
Treated	99.7%	99.7%	100%	99.8%
Completing Week 48	92.3%	94.6%	92.9%	93.3%
Discontinued before Week 48	7.4%	5.1%	7.1%	6.5%
Reasons for discontinuation				
Withdrawal by patient	1.8%	1.5%	3.8%	2.4%
Adverse events	1.5%	0.6%	1.2%	1.1%
Death	1.5%	0.9%	0.3%	0.9%
COVID-19 related	0.6%	0.6%	0.6%	0.6%
Physician decision	0.3%	0.6%	0.6%	0.5%
Other[a]	1.8%	0.9%	0.6%	1.1%

[a]Includes "lost to follow-up", "lack of efficacy", and "protocol deviation". Categories were combined to maintain masking of individual patients.

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

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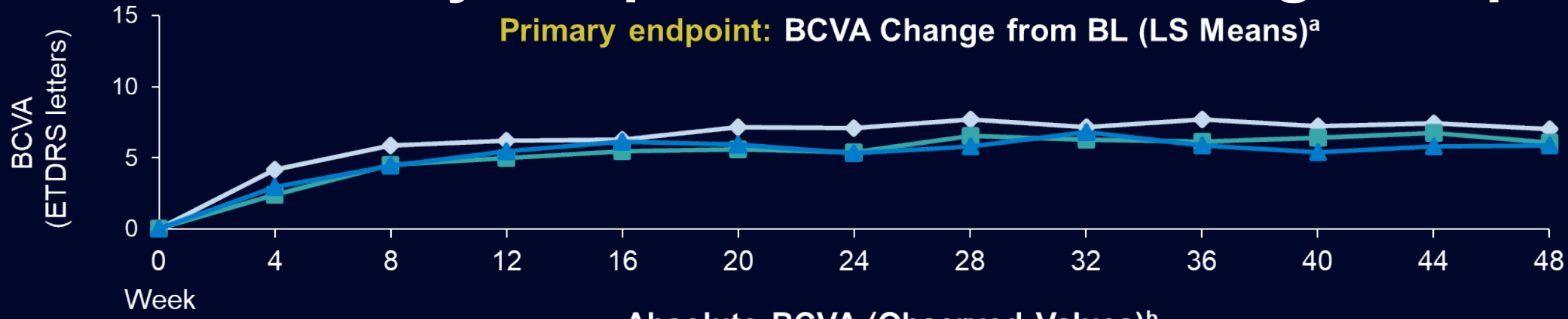
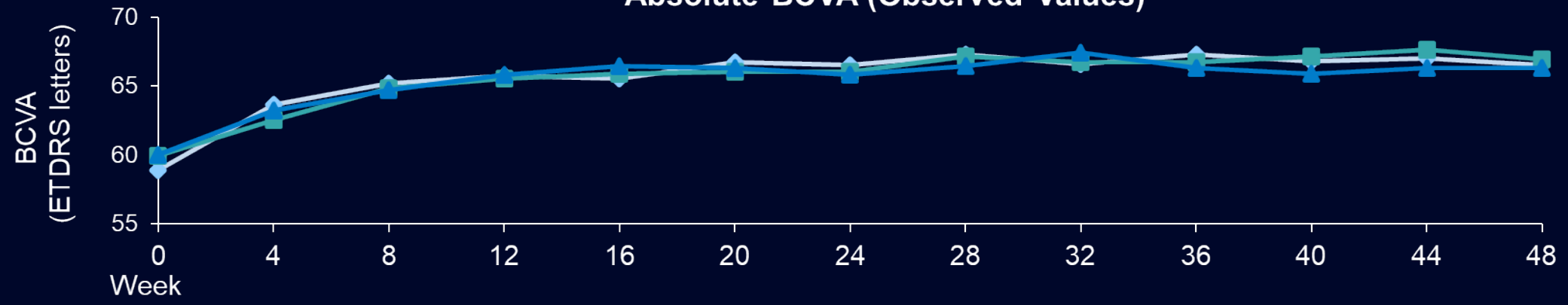
Primary endpoint: BCVA Change from BL (LS Means)[a]



Absolute BCVA (Observed Values)[b]



	LS mean change from BL at Week 48 (MMRM)	Difference in LS means vs. 2q8	Two-sided 95% CI	One-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

[a]LS mean values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). LS means were generated using MMRM, with baseline BCVA measurement as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16), visit, and stratification variables (geographic region [Japan vs. Rest of World] and BL BCVA [<60 vs. ≥60]) as fixed factors, and interaction terms for BL and visit and for treatment and visit. [b]Observed values (censoring data post-ICEs); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). **BL**, baseline; **ICE**, intercurrent event; **LS**, least squares; **MMRM**, mixed model for repeated measures.

Ocular AEs in the Study Eye Through Week 48

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	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Any ocular TEAE, n (%)	130 (38.7)	129 (38.5)	127 (37.6)	256 (38.0)
Any ocular TEAE ≥3% in any group[a], n (%)				
Cataract	10 (3.0)	12 (3.6)	12 (3.6)	24 (3.6)
Intraocular pressure increased	7 (2.1)	11 (3.3)	9 (2.7)	20 (3.0)
Retinal hemorrhage	14 (4.2)	11 (3.3)	10 (3.0)	21 (3.1)
Subretinal fluid	11 (3.3)	10 (3.0)	5 (1.5)	15 (2.2)
Visual acuity reduced	20 (6.0)	12 (3.6)	18 (5.3)	30 (4.5)
Vitreous floaters	11 (3.3)	4 (1.2)	12 (3.6)	16 (2.4)
Any serious ocular TEAE, n (%)	2 (0.6)	6 (1.8)	5 (1.5)	11 (1.6)
Angle closure glaucoma[b]	1 (0.3)	0	1 (0.3)	1 (0.1)
Retinal detachment[b]	0	3 (0.9)	1 (0.3)	4 (0.6)
Retinal hemorrhage[c]	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)
Cataract[c]	1 case[d]			
Choroidal detachment[b]	1 case[d]			
IOP[c]	2 cases[d]			
Skin laceration[c]	1 case[d]			
Vitreous hemorrhage[c]	1 case[d]			
Any ocular TEAE leading to discontinuation[e], n (%)	1 (0.3)	3 (0.9)	3 (0.9)	6 (0.9)

No cases of ischemic optic neuropathy were reported through Week 48

[a]One case of cataract, 5 cases of increased IOP, two cases of retinal hemorrhage, one case of subretinal fluid, 5 cases of reduced VA, and 3 cases of vitreous floaters were considered related to study drug treatment. [b]One case considered related to treatment. [c]All cases considered unrelated to treatment. [d]Data presented in this way to avoid unintentional patient unmasking. [e]To avoid unintentional patient unmasking, the following are reasons for discontinuation: Reduced VA, nAMD, choroidal detachment, subretinal fluid (all n=1), and retinal detachment and retinal hemorrhage (both n=2). **AE**, adverse event; **IOP**, intraocular pressure; **SAE**, serious adverse event; **SAF**, safety analysis set; **TEAE**, treatment-emergent adverse event.

Intraocular Pressure and Intraocular Inflammation Through Week 48

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	2q8	8q12	8q16	All 8 mg
N (SAF)	**336**	**335**	**338**	**673**
Patients with IOP ≥35 mmHg pre- or post-injection at any visit, n (%)	1 (0.3)	3 (0.9)	1 (0.3)	4 (0.6)

	2q8	8q12	8q16	All 8 mg
N (SAF)	**336**	**335**	**338**	**673**
Patients with ≥1 IOI AE[a], n (%)	2 (0.6)	4 (1.2)	1 (0.3)	5 (0.7)

- Pre-injection **IOP values** were similar to baseline values at all timepoints through Week 48
- **Reported IOI terms**:[b] chorioretinitis (n=1), iridocyclitis (n=2), iritis (n=1), vitreal cells (n=2), and vitritis (n=1)
  - No cases of endophthalmitis or occlusive retinal vasculitis

SAF. [a]Treatment-emergent events. [b]All were mild in intensity, except vitritis, which was moderate in intensity. **IOI**, intraocular inflammation.

Non-Ocular AEs Through Week 48

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	2q8	8q12	8q16	All 8 mg
N (SAF)	**336**	**335**	**338**	**673**
Any non-ocular TEAE, n (%)	178 (53.0)	175 (52.2)	182 (53.8)	357 (53.0)
Any non-ocular TEAE ≥3% in any group[a], n (%)				
COVID-19	11 (3.3)	10 (3.0)	21 (6.2)	31 (4.6)
Hypertension	8 (2.4)	14 (4.2)	13 (3.8)	27 (4.0)
UTI	9 (2.7)	7 (2.1)	10 (3.0)	17 (2.5)
Nasopharyngitis	15 (4.5)	12 (3.6)	14 (4.1)	26 (3.9)
Back pain	15 (4.5)	12 (3.6)	13 (3.8)	25 (3.7)
Any serious non-ocular TEAE[b], n (%)	46 (13.7)	34 (10.1)	32 (9.5)	66 (9.8)
Any serious non-ocular TEAE ≥1% in any group, n (%)				
UTI[c]	4 (1.2)	1 (0.3)	0	1 (0.1)
Any adjudicated TE APTC events[d], n (%)	5 (1.5)	1 (0.3)	1 (0.3)	2 (0.3)
Any TEAE of hypertension[e], n (%)	12 (3.6)	16 (4.8)	16 (4.7)	32 (4.8)
All AEs resulting in death[f], n (%)	5 (1.5)	3 (0.9)	1 (0.3)	4 (0.6)
Any non-ocular TEAE leading to discontinuation, n (%)	4 (1.2)	2 (0.6)	2 (0.6)	4 (0.6)

SAF. [a]Of the TEAEs listed below, 1 case of hypertension was considered related to study drug treatment. [b]Four serious TEAEs were considered related to study drug treatment: Myocardial infarction (n=1), cerebrovascular accident (n=2) and pulmonary embolism (n=1). [c]Considered unrelated to treatment. [d]APTC events: To avoid unintentional patient unmasking, overall there were 2 cases of myocardial infarction and cerebrovascular accident, and 1 case each of cardiac arrest, acute coronary syndrome, and cerebral infarction. [e]Reported events pertaining to hypertension include: Vascular disorders (hypertension, diastolic hypertension, systolic hypertension, and white coat hypertension) and investigations (BP increased, BP systolic increased, BP diastolic increased). [f]Causes of death were reported as metastatic neoplasm, non-small cell lung cancer, death, COVID-19 pnemonia, pneumonia aspiration, cardiac arrest, abdominal strangulated hernia, skull fracture, and cerebral infarction (all n=1). [g]To avoid unintentional patient unmasking, the reasons for discontinuation were neoplasm (n=5), and cerebrovascular accident, pain, and respiratory tract infection (all n=1). **APTC,** Anti-Platelet Trialists' Collaboration**; BP,** blood pressure**; TE**, treatment emergent; **UTI,** urinary tract infection.

Conclusions

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- The safety profile for aflibercept 8 mg was similar to that of aflibercept 2 mg[1,2]
- There were no new safety signals for aflibercept 8 mg or aflibercept 2 mg and no cases of retinal vasculitis, occlusive retinitis, or endophthalmitis
- Rates of APTC events and IOI were comparable with those reported with aflibercept 2 mg[3]

1. Heier et al. Ophthalmology 2012;119(12):2537-48; **2**. Schmidt-Erfurth et al. Ophthalmology 2014;121(1):193-201. Heier et al. Ophthalmology 2012;119(12):2537-48.
3. Bayer. Eylea (aflibercept) Prescribing Information (2011). Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf