Tolerability and safety of intravitreal aflibercept 8 mg in the Phase 3 PULSAR trial of patients with neovascular age-related macular degeneration

Jean-François Korobelnik,[1] Ursula Maria Schmidt-Ott,[2] Andrea Schulze,[2] Xin Zhang,[3] Sergio Leal[3] on behalf of the PULSAR study investigators

[1]CHU Bordeaux, Service d'Ophtalmologie, France; Univ. Bordeaux, INSERM, Bordeaux and Population Health Research Center, team LEHA, UMR 1219, F-33000 Bordeaux, France; [2]Bayer AG, Berlin, Germany; [3]Bayer Consumer Care AG, Basel, Switzerland

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PURPOSE

Intravitreal aflibercept 2 mg was approved for use in adults with neovascular age-related macular degeneration (nAMD) following the VIEW1 and VIEW2 studies[1,2]. Initial indications from CANDELA suggest a potential additional benefit of 8 mg over 2 mg aflibercept[3]. PULSAR was designed to study different aflibercept dosing regimens with the new 8 mg formulation over a longer follow-up period. This poster focuses on the tolerability and safety reported in PULSAR.

METHOD

PULSAR is an ongoing, double-masked, 96-week, Phase 3 trial. Patients aged ≥50 years with treatment-naïve nAMD were randomly assigned 1:1:1 to 8q12, 8q16 or 2q8, each after three initial monthly injections. From Week 16, dosing intervals for aflibercept 8 mg were shortened if patients met prespecified dose regimen modification criteria denoting disease activity (**Figure 1**).

Safety was monitored, and assessments included treatment-emergent (TE) adverse events (AEs) and serious adverse events (SAEs) through Week 48. The investigator also assessed the relationship between the study intervention and each occurrence of an AE or SAE, using clinical judgment to determine the relationship.

RESULTS

The primary endpoint was met with aflibercept 8q12 vs 2q8 and 8q16 vs 2q8 (non-inferiority margin at 4 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. **Figure 2** shows the mean absolute and arithmetic mean change from baseline to Week 48.

Table 1 and **2** show ocular and non-ocular AEs occurring through Week 48, respectively. Of 1,009 patients (mean age 74.5 years, female 54.5%) treated (2q8: n=336; 8q12: n=335; 8q16: n=338), 11 (1.1%) discontinued due to AEs. A similar proportion of patients reported ocular TEAE in the study eye across the treatment groups (**Table 1**). In all the treatment groups, the majority of ocular and non-ocular TEAEs were overall mild in intensity. The proportion of patients with pre- or post-dose of increased intraocular pressure (IOP) ≥35 mmHg was similar in all groups (**Table 1**). There was also no indication of sustained IOP based on mean change from baseline in pre-dose values through 48 weeks (data not shown).

RESULTS

FIGURE 1:
PULSAR: Dosing schedule and regimen modification in Year 1

	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 due to persistent or worsening nAMD

AND

>25-µm increase in CRT or new onset foveal neovascularization or foveal hemorrhage

*All assessments compared to Week 12

Stippled boxes = initial treatment phase;
X = active injection; o = sham injections.

Note: Table does not reflect all dosing options once a patient's treatment interval is shortened.

DRM in Year 1

- Intervals can only be shortened
- Multiple opportunities to shorten interval
- Minimum interval for all patients was q8

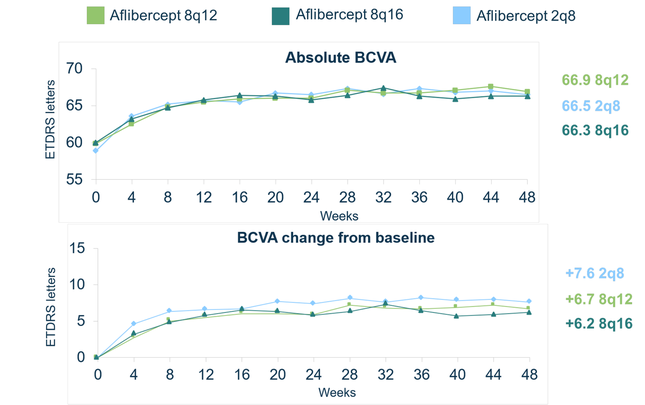
Week 16 and 20: Patients on 8q12 and 8q16 meeting DRM criteria shortened to q8

Week 24: Patients on 8q16 meeting DRM criteria shortened to q12

Week 32 and 44 for 8q12 and Week 36[a] and 40 for 8q16: Treatment interval shortened by 4 weeks for patients meeting DRM criteria

[a]At Week 36, patients on 8q16 who were previously shortened to q12 could have been shortened to q8.
BCVA, best corrected visual acuity; CRT, central retinal thickness; DRM, dose regimen modification; Wk, week.

FIGURE 2:
BCVA outcomes: Mean absolute and mean change from baseline at Week 48



Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline). BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. FAS, full analysis set; ICE, intercurrent events.

TABLE 1:
Ocular TEAEs in Study Eye Through Week 48

n (%)	2q8 n=336	8q12 n=335	8q16 n=338	All 8 mg n=673
Any ocular TEAE	130 (38.7)	129 (38.5)	127 (37.6)	256 (38.0)
Any ocular TEAE ≥3% in any group[a]				
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	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]			
Vitreous hemorrhage[c]	1 case[d]			
Skin laceration[c]	1 case[d]			
IOP[c]	2 cases[d]			
Any IOI TEAE[e]	2 (0.6)	4 (1.2)	1 (0.3)	5 (0.7)
Any pre- or post-dose IOP ≥35 mmHg	1 (0.3)	3 (0.9)	1 (0.3)	4 (0.6)
Any ocular TEAE leading to discontinuation[f]	1 (0.3)	3 (0.9)	3 (0.9)	6 (0.9)

SAS. [a]1 case of cataract, 5 cases of increased IOP, 2 cases of retinal hemorrhage, 1 case of subretinal fluid, 5 cases of reduced VA, and 3 cases of vitreous floaters were considered related to study drug treatment. [b]1 case considered related to treatment. [c]All cases considered unrelated to treatment. [d]Data presented in this way to avoid unintentional patient unmasking. [e]Reports included iridocyclitis (n=2), vitreal cells (n=2), chorioretinitis, iritis, vitritis (n=1 each); all were mild in intensity except vitritis which was moderate in intensity. There were no cases of endophthalmitis or (occlusive) retinal vasculitis. [f]To avoid unintentional patient unmasking, the reasons for discontinuation were reduced VA, nAMD, choroidal detachment, subretinal fluid (all n=1), and retinal detachment and retinal haemorrhage (both n=2). AE, adverse event; IOP, intraocular pressure; SAS, safety analysis set; TE, treatment-emergent; VA, visual acuity.

TABLE 2:
Non-ocular AEs in the Study Eye through Week 48

n (%)	2q8 n=336	8q12 n=335	8q16 n=338	All 8 mg n=673
Any non-ocular TEAE	178 (53.0)	175 (52.2)	182 (53.8)	357 (53.0)
Any non-ocular TEAE ≥3% in any group[a]				
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]	46 (13.7)	34 (10.1)	32 (9.5)	66 (9.8)
Any serious non-ocular TEAE ≥1% in any group				
UTI[c]	4 (1.2)	1 (0.3)	0	1 (0.1)
Any adjudicated TE APTC events[d]	5 (1.5)	1 (0.3)	1 (0.3)	2 (0.3)
Any TEAE of hypertension[e]	12 (3.6)	16 (4.8)	16 (4.7)	32 (4.8)
All AEs resulting in death[f]	5 (1.5)	3 (0.9)	1 (0.3)	4 (0.6)
Any non-ocular TEAE leading to discontinuation[g]	4 (1.2)	2 (0.6)	2 (0.6)	4 (0.6)

SAS. [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), stroke (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, pneumonia aspiration, cardiac arrest, abdominal strangulated hernia, skull fracture and cerebral infection (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; AE, adverse event; BP, blood pressure; TE, treatment-emergent; SAS, safety analysis set; UTI, urinary tract infection.

CONCLUSIONS

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 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[4].

References

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2. Schmidt-Erfurth et al. *Ophthalmology* 2014;121(1):193-201
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The oral presentation **"Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration: 48-week results from the Phase 3 PULSAR trial"** will be presented by Prof Martin Spitzer in the AMD antiVEGF session on April 23, 2023, at 12:15–12:30 pm.

Disclosures

J-FK: Consultant for Allergan-AbbVie, Apellis, Bayer, Janssen, NanoRetina, Roche, Thea, and Carl Zeiss Meditec; Data and Safety Monitoring Board (DSMB) member for Alexion, and Novo Nordisk; **USO** and **AS**: Employees of Bayer AG; **XZ** and **SL**: Employees of Bayer Consumer Care AG.

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