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ORIGINAL RESEARCH

Intraocular Pressure Outcomes with Intravitreal Aflibercept 8 mg: A 96-Week Pooled Analysis from PULSAR and PHOTON

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ABSTRACT

Introduction: This abstract aimed to explore the potential effect of a higher injection volume with aflibercept 8 mg (70 µl) versus 2 mg (50 µl) on intraocular pressure (IOP).

Methods: In PULSAR (NCT04423718), patients with neovascular age-related macular degeneration (nAMD) were randomised 1:1:1 to receive aflibercept 2 mg every 8 weeks (2q8) or aflibercept 8 mg every 12 (8q12) or 16 weeks (8q16), after three initial monthly doses. In PHOTON (NCT04429503), patients with diabetic macular oedema (DME) were randomised 1:2:1 to receive 2q8 after five monthly doses or 8q12 or 8q16 after three initial monthly doses. Increased IOP or glaucoma-related treatment-emergent adverse events (TEAEs) and pre- and post-injection IOP measurements were pooled through week 96 and summarised descriptively.

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Results: The safety analysis set included 1667 patients (8 mg: $n=1164$; 2 mg: $n=503$). Baseline mean (SD) IOP was 15.0 (3.2) mmHg and 15.1 (3.0) mmHg in patients receiving aflibercept 8 mg and 2 mg, respectively. Rates of TEAEs related to glaucoma (including TEAE of IOP increases) were low and similar across treatment groups (8 mg: 9/1000 injections; 2 mg: 6/1000 injections). Rates of paracentesis were low (8 mg: 1/1000 injections; 2 mg: 0). Mean pre-injection IOP values measured at each visit were similar, with no sustained increase over time across treatment groups.
Conclusions: Comparable IOP outcomes and no long-term IOP or glaucoma-related effects were observed with aflibercept 8 mg versus aflibercept 2 mg through week 96.
Trial Registration: PULSAR (NCT04423718) and PHOTON (NCT04429503) trials.

Keywords: Aflibercept; Diabetic macular oedema; Intraocular pressure; Glaucoma; Neovascular age-related macular degeneration; Treatment-emergent adverse events

Key Summary Points

Why carry out this study?

Transient post-injection increase in intraocular pressure (IOP) is common after intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents.

A low incidence of IOP increase post-injection has been observed with aflibercept 2 mg.

What was learned from the study?

Comparable IOP outcomes and no long-term IOP or glaucoma-related effects were observed with aflibercept 8 mg and aflibercept 2 mg through week 96 of this pooled analysis of the PULSAR and PHOTON trials.

Despite a 70 µl injection volume, no indication of sustained IOP increase or trend towards increased IOP over time were observed through week 96 with aflibercept 8 mg versus 2 mg (50 µl).

INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF) treatment is standard of care for the management of neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DME) with a well characterised safety profile from clinical trials and real-world use [1–7]. Newer formulations of drugs with anti-VEGF activity, such as aflibercept 8 mg, may offer the opportunity for visual and anatomic benefits with extended dosing intervals, thus reducing the treatment burden for many patients compared with other anti-VEGF agents [8–10].

Published studies generally agree that transient post-injection IOP spikes are common after intravitreal injections of anti-VEGF agents [4, 5, 8, 11–22]. Potential post-injection IOP rise can be divided into three categories: early/acute (a transient rise in IOP), intermediate (a rise lasting hours), and late (a chronic elevation over months) [19]. Most cases of IOP increase are transient and resolve without intervention [23]. However, there is a lack of consensus on the sequelae of repeated intravitreal injections on IOP and glaucoma-related outcomes over an extended period of time [19].

Increased IOP after intravitreal injections has been associated with a range of factors, including needle gauge, speed of injection, drug properties, and number of injections over time [23–26]. Injection volume may also be a factor, and some publications have recommended an upper limit of 100 µl for maximum intravitreal

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injection volume [23, 27, 28]. Aflibercept 2 mg is delivered in an injection volume of 50 µl, whereas aflibercept 8 mg, which delivers a four-fold higher molar dose compared with aflibercept 2 mg, is administered in a 70-µl injection volume [29, 30].

Aflibercept 8 mg has demonstrated comparable efficacy and safety versus aflibercept 2 mg at week 48 in the phase 3 nAMD PULSAR trial and the phase 2/3 DME PHOTON trial [10, 31], with sustained efficacy and overall safety at week 96 and with extended dosing intervals [32, 33]. The incidence of IOP increase with aflibercept 2 mg is low, with adverse events of increased IOP reported in 3.5–10.8% of patients in the VIEW trials in nAMD and VISTA/VIVID trials in DME [16, 17]. Similarly, PULSAR and PHOTON trials showed that no clinically relevant changes in IOP were reported with aflibercept 8 mg through 48 weeks of treatment [10, 31]. Given the delivery of aflibercept 8 mg in a higher injection volume compared with aflibercept 2 mg, the potential effect of a higher injection volume on IOP needed to be further characterised. This analysis evaluated IOP and glaucoma-related events with aflibercept 8 mg through 96 weeks by pooling data across the PULSAR and PHOTON clinical trials.

METHODS

Study Design

The study designs and methodologies for the PULSAR (NCT04423718) and PHOTON (NCT04429503) trials have been reported previously [10, 31]. Briefly, PULSAR and PHOTON were randomised, double-masked, non-inferiority, 96-week pivotal trials conducted in adults with nAMD and DME, respectively. Patients in both trials were randomly assigned to aflibercept 8 mg every 12 weeks (8q12) or aflibercept 8 mg every 16 weeks (8q16) after three initial monthly doses, or aflibercept 2 mg every 8 weeks, after three (PULSAR) or five (PHOTON) initial monthly doses. The treatment interval for the aflibercept 8-mg treatment groups could be shortened (years 1 and 2) or extended (year 2) based on prespecified criteria related to disease activity. The primary endpoint in the PULSAR and PHOTON trials was change in best-corrected visual acuity (BCVA) from baseline at week 48. Aflibercept 8 mg or 2 mg was administered per routine practice from a sterile, single-use vial using a 30-gauge needle. The PHOTON and PULSAR studies were conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki, and applicable local laws and regulations. Study protocols and amendments were approved by the relevant institutional review boards and independent ethics committees before study initiation [10, 31]. As this post hoc analysis was based on existing databases from the PHOTON and PULSAR studies, no additional informed consent was required.

IOP-Related Eligibility Criteria

The inclusion and exclusion criteria of PULSAR and PHOTON have previously been reported in full [10, 31]. In PULSAR, patients were ineligible for study inclusion if they had uncontrolled glaucoma in the study eye, defined as IOP > 25 mmHg despite treatment with anti-glaucoma medication. In PHOTON, patients were ineligible for study inclusion if they had IOP ≥ 25 mmHg in the study eye. Patients were also excluded from PULSAR or PHOTON if they had a history of, or likely future need for, glaucoma filtration surgery in the study eye.

IOP Assessment Procedures

In PULSAR and PHOTON, IOP was measured at all study visits. In both studies, bilateral IOP was measured pre-injection, and approximately 30–60 min (PULSAR) or approximately 30 min (PHOTON) post-injection in the study eye only. The exact timing was at the discretion of an unmasked investigator in both studies. IOP was measured with Goldmann applanation tonometry or Tono-pen™ in both PULSAR and PHOTON, or could also be measured using

iCare rebound tonometry in PULSAR. The same method of measurement was used for each patient throughout both trials. If symptoms or signs of IOP increase were noted after the injection, IOP was measured, assessed and managed at the investigator's discretion. Increased IOP was reported as an adverse event at the discretion of the investigator. The post-injection IOP that was collected was the last measurement recorded before the patient was permitted to leave the study site.

Assessment of Glaucoma-Related History and Events

At baseline, glaucoma-related history including previous IOP-lowering procedures and IOP-lowering medication use were assessed. IOP-lowering medication use and IOP-lowering procedures performed during the trials were recorded.

Preferred Terms for Glaucoma-Related History

The grouping for medical history of 'glaucoma-related history' in the study eye included the following preferred terms: 'glaucoma', 'borderline glaucoma', 'open angle glaucoma', 'ocular hypertension', 'angle closure glaucoma', 'glaucomatous optic neuropathy', 'optic nerve cupping', 'trabeculoplasty', 'intraocular pressure increased', 'glaucoma surgery' and 'uveitic glaucoma'.

Assessment of IOP-Lowering Medication Use

The grouping of IOP-lowering medications included the following fourth-level Anatomical Therapeutic Chemical (ATC) codes: 'sensory organs; beta blocking agents', 'sensory organs; prostaglandin analogues', 'sensory organs; carbonic anhydrase inhibitors', 'sensory organs; other antiglaucoma preparations'.

Preferred Terms for Glaucoma-Related TEAEs

The grouping for 'glaucoma-related' TEAEs in the study eye included the following preferred terms: 'glaucoma', 'borderline glaucoma', 'open angle glaucoma', 'ocular hypertension', 'angle closure glaucoma', 'glaucomatous optic neuropathy', 'optic nerve cupping', 'trabeculoplasty' and 'intraocular pressure increased'. Eyes were counted only once within each preferred term and grouping level.

Assessment of IOP-Lowering Procedures

The rates of paracentesis/anterior chamber puncture and other procedures for IOP reduction were determined for each treatment group.

Analysis

Data for the study eye in the safety analysis set, which included all patients who received study treatment, were pooled through week 96 for PULSAR and PHOTON. Glaucoma-related history including previous IOP-lowering procedures and IOP-lowering medication use were assessed, and during the study pre- and post-injection IOP measurements across visits, as well as glaucoma-related TEAEs and procedures were evaluated. Data were summarised descriptively and results are exploratory. The least squares mean difference between pre- and post-injection IOP at active injection visits for aflibercept 8 mg and aflibercept 2 mg was estimated with an analysis of variance (ANOVA).

In accordance with the study protocols, adverse events reported by study investigators were coded using the same version of Medical Dictionary for Regulatory Activities (MedDRA version 25.0) for both trials [10, 31]. No definitions, requirements or thresholds were defined for reporting IOP increase, and reporting of glaucoma-related TEAEs was based on the discretion of the investigator.

RESULTS

Patients

In this analysis of 1667 patients in the safety analysis set, the pooled aflibercept 8 mg (8q12 and 8q16 combined) group comprised 1164 patients, and the aflibercept 2 mg group comprised 503 patients (Table S1).

The baseline demographics and disease characteristics of the patients from the pooled PULSAR and PHOTON trials are summarised in Table 1. Proportions of patients with glaucoma-related medical history in the study eye and/or use of IOP-lowering medications in the study eye at baseline were comparable between the treatment groups (reported in 93 [8.0%] patients in the aflibercept 8 mg group and 41 [8.2%] patients in the aflibercept 2 mg group).

Rates of TEAEs Related to Glaucoma

Rates of TEAEs related to glaucoma (including TEAEs of IOP increase) in the study eye were comparable across treatment groups through week 96; overall, these events were reported in 53 (4.6%) and 22 (4.4%) patients in the aflibercept 8 mg and 2 mg groups, respectively (Table 2). In both treatment groups, higher rates of glaucoma-related TEAEs were reported for patients with glaucoma-related history and/or IOP-lowering agent use at baseline, compared with those without. In these patients, glaucoma-related TEAEs were reported in nine (9.7%) patients treated with aflibercept 8 mg and three (7.3%) patients treated with aflibercept 2 mg. Among patients with no glaucoma-related medical history or IOP-lowering agent use at baseline, glaucoma-related TEAEs were reported in 44 (4.1%) patients treated with aflibercept 8 mg and 19 (4.1%) patients treated with aflibercept 2 mg.

Treatment Exposure and Rates of Glaucoma-Related TEAEs per Injection

The total number of injections through week 96 for the pooled aflibercept 8 mg and 2 mg groups was 9762 and 6159, respectively. The rates of glaucoma-related TEAEs were low in both treatment groups (aflibercept 8 mg: 9 per 1000 injections; aflibercept 2 mg: 6 per 1000 injections) (Table 3).

Pre- and Post-Injection IOP

The mean (SD) pre-injection IOP at week 96 for the aflibercept 8 mg and 2 mg groups was 14.8 (3.2) and 14.7 (3.2) mmHg, respectively. Mean pre-injection IOP values were similar in both treatment groups by visit; neither a sustained increase in IOP nor a trend towards increased IOP over time was observed (Fig. 1). Pre-injection IOP of ≥ 35 mmHg was observed once each in two (0.2%) patients in the aflibercept 8 mg group and one (0.2%) patient in the aflibercept 2 mg group. These events were considered non-serious, not related to study drug, and recovered/resolved following treatment with brimonidine, brimonidine tartrate and/or timolol. For the patient in the aflibercept 2 mg group, study-drug treatment was interrupted in response to this event. None of the three patients required a paracentesis.

The mean (SD) post-injection IOP across visits through week 96 was 18.4 (4.0) mmHg and 17.6 (4.0) mmHg in the aflibercept 8 mg and 2 mg groups, respectively. Post-injection IOP of ≥ 35 mmHg was observed in four (0.3%) patients in the aflibercept 8 mg group and three (0.6%) patients in the aflibercept 2 mg group. One event was considered serious in the aflibercept 8 mg group and required a paracentesis. One event in the aflibercept 8 mg group was considered study-drug related. Three events in the aflibercept 8 mg group and one event in the aflibercept 2 mg group were considered injection-procedure related. All events recovered/resolved, some following concomitant treatment with acetazolamide, apraclonidine hydrochloride, brimonidine, dorzolamide hydrochloride, and/or timolol. Study-drug treatment was not interrupted in response to any of these events.

No clinically relevant differences in mean change in IOP were observed from pre- to post-injection across visits between treatment groups. The mean (SD) change from pre- to post-injection IOP at visits when drug was administered

Table 1 Baseline characteristics and glaucoma-related medical history in the study eye for patients in the PULSAR and PHOTON trials (pooled data)

	Aflibercept 2 mg (*n* = 503)	**Aflibercept 8 mg (*n* = 1164)**
Age, mean (SD)	70.5 (10.5)	69.3 (11.2)
Sex, *n* (%)		
Male	240 (47.7)	620 (53.3)
Female	263 (52.3)	544 (46.7)
Race, *n* (%)		
White	361 (71.8)	875 (75.2)
Asian[a]	113 (22.5)	222 (19.1)
Black or African American	20 (4.0)	46 (4.0)
Other	9 (1.8)	21 (1.8)
Ethnicity, *n* (%)		
Not Hispanic or Latino	455 (90.5)	1040 (89.3)
Hispanic or Latino	43 (8.5)	104 (8.9)
Not reported	5 (1.0)	20 (1.7)
IOP, mean (SD), mmHg	15.1 (3.0)	15.0 (3.2)
Number of patients with ≥ 1 glaucoma-related medical history term and/or IOP-lowering medication, n (%)	41 (8.2)	93 (8.0)
Glaucoma-related medical history, *n* (%)[b]	41 (8.2)	88 (7.6)
Angle-closure glaucoma	0	2 (0.2)
Borderline glaucoma	4 (0.8)	7 (0.6)
Glaucoma	19 (3.8)	36 (3.1)
Glaucomatous optic neuropathy	1 (0.2)	0
IOP increased	0	5 (0.4)
Ocular hypertension	6 (1.2)	7 (0.6)
Open-angle glaucoma	12 (2.4)	32 (2.7)
Optic nerve cupping	1 (0.2)	0
Trabeculoplasty	2 (0.4)	2 (0.2)
Other glaucoma surgery	0	0
Uveitic glaucoma	0	0
IOP-lowering medication at baseline, *n* (%)[c]	22 (4.4)	61 (5.2)
Beta-blocking agents	7 (1.4)	36 (3.1)

Table 1 continued

	Aflibercept 2 mg ($n = 503$)	Aflibercept 8 mg ($n = 1164$)
Carbonic anhydrase inhibitors	3 (0.6)	11 (0.9)
Prostaglandin analogues	15 (3.0)	28 (2.4)
Other anti-glaucoma preparations	1 (0.2)	3 (0.3)

Safety analysis set. Data are in the study eye. Aflibercept 8 mg includes patients receiving 8q12 and 8q16

8q12 aflibercept 8 mg every 12 weeks; *8q16* aflibercept 8 mg every 16 weeks, *ATC* Anatomical Therapeutic Chemical, *IOP* intraocular pressure, *SD* standard deviation

[a]Patients self-identified as Asian (Asian Indian, Chinese, Japanese, Korean, Thai or other)

[b]Patients are only counted once within each preferred term

[c]Medications started but not ended before the start of the study intervention are included in this table. An individual patient can be counted in more than one drug category at baseline if the patient is on multiple IOP-lowering medications. The grouping of IOP-lowering medications considers the following fourth level ATC codes: 'sensory organs; beta-blocking agents', 'sensory organs; prostaglandin analogues', 'sensory organs; carbonic anhydrase inhibitors', 'sensory organs; other antiglaucoma preparations'

was 3.7 (4.1) and 2.9 (3.9) in the aflibercept 8 mg and 2 mg groups, respectively. The difference in least squares mean (95% CI) change in IOP from pre- to post-injection was 0.83 (0.67, 0.99) mmHg between the aflibercept 8 mg and 2 mg groups.

New IOP-Lowering Medications Through Week 96

The proportion of patients receiving a new IOP-lowering medication at least once through week 96 was balanced between treatment groups (Table 4). New IOP-lowering medications were initiated in 58 (5.0%) and 22 (4.4%) of patients in the aflibercept 8 mg and 2 mg groups, respectively. The most frequently initiated medications were beta-blocking agents, prostaglandin analogues, and carbonic anhydrase inhibitors for both treatment groups. All IOP-lowering medications were delivered via topical administration and none were delivered systemically.

IOP-Lowering Procedures Through Week 96

Management of an acute elevation in post-injection IOP by paracentesis was performed in 5/1164 (0.4%) patients in the aflibercept 8 mg group (at a rate of 0.92 per 1000 intravitreal injections) versus 0/503 patients in the aflibercept 2 mg group. Two patients required a single paracentesis procedure each through week 96, two patients required two procedures and one patient required three procedures (Table S2). All patients who underwent a paracentesis procedure continued with aflibercept 8 mg treatment.

DISCUSSION

This pooled analysis of PULSAR and PHOTON, two pivotal trials in patients with nAMD and DME, respectively, treated with aflibercept 8 mg (70 µl) and 2 mg (50 µl), demonstrated comparably low rates of glaucoma-related TEAEs over 96 weeks in the aflibercept 8 mg and 2 mg treatment groups. No clinically relevant differences in pre-injection IOP or in mean change in IOP from pre- to post-injection through week 96 were observed between the aflibercept 8 mg and 2 mg doses, providing reassurance that repeated intravitreal administration of aflibercept 8 mg at the dosing intervals studied did not adversely affect IOP over time. In both treatment groups, patients with a glaucoma-related medical

Table 2 Patients with glaucoma-related TEAEs in the study eye in the overall population and by presence or absence of glaucoma-related medical history in the PULSAR and PHOTON trials (pooled data)

	Overall population		Patients with glaucoma-related medical history and/or receiving IOP-lowering medication at baseline[b]		Patients without glaucoma-related medical history and not receiving an IOP-lowering medication at baseline[b]	
	Aflibercept		Aflibercept		Aflibercept	
	2 mg (*n* = 503)	8 mg (*n* = 1164)	2 mg (*n* = 41)	8 mg (*n* = 93)	2 mg (*n* = 462)	8 mg (*n* = 1071)
Glaucoma-related TEAEs, *n* (%)[a]	22 (4.4)	53 (4.6)	3 (7.3)	9 (9.7)	19 (4.1)	44 (4.1)
Angle-closure glaucoma	1 (0.2)	2 (0.2)	0	1 (1.1)	1 (0.2)	1 (< 0.1)
Borderline glaucoma	0	2 (0.2)	0	0	0	2 (0.2)
Glaucoma	1 (0.2)	6 (0.5)	1 (2.4)	1 (1.1)	0	5 (0.5)
IOP increased	17 (3.4)	34 (2.9)	1 (2.4)	5 (5.4)	16 (3.5)	29 (2.7)
Ocular hypertension	3 (0.6)	12 (1.0)	1 (2.4)	2 (2.2)	2 (0.4)	10 (0.9)
Open-angle glaucoma	1 (0.2)	1 (< 0.1)	0	0	1 (0.2)	1 (< 0.1)

Safety analysis set. Aflibercept 8 mg includes patients receiving 8q12 and 8q16

8q12 aflibercept 8 mg every 12 weeks, *8q16* aflibercept 8 mg every 16 weeks, *ATC* Anatomical Therapeutic Chemical, *IOP* intraocular pressure, *TEAE* treatment-emergent adverse event

[a]The grouping of IOP-lowering medications includes the following fourth level ATC codes: 'sensory organs; beta-blocking agents', 'sensory organs; prostaglandin analogues', 'sensory organs; carbonic anhydrase inhibitors', 'sensory organs; other antiglaucoma preparations'

[b]Patients were only counted once within each safety topic and preferred term

history and/or IOP-lowering medication use at baseline had higher rates of glaucoma-related events than those without. The proportions of patients receiving new IOP-lowering medication at least once through week 96 were comparable between the aflibercept 8 mg versus 2 mg treatment groups. Small numerical differences in the use of specific baseline IOP-lowering medication classes were observed between treatment groups, but no corresponding differences in longitudinal IOP outcomes were identified. Across both trials, rates of paracentesis procedures were low in the aflibercept 8 mg group, occurring at a rate of 0.92 per 1000 intravitreal injections.

Transient post-injection IOP increase is a commonly reported TEAE in studies of intravitreal therapies in neovascular retinal disease, although criteria for meeting a TEAE of IOP increase was not defined in most cases [23]. Rates of IOP increase following intravitreal injections of 50 µl have been reported for up to 14.8% of patients with nAMD and up to 17.6% of patients with DME [5, 8, 11–15, 20, 34, 35], whereas rates of IOP increases have been reported for up to 19.0% of patients with nAMD who were treated with intravitreal injection volumes between 50 and 100 µl [18, 36–38].

This post hoc analysis evaluated the potential impact of the increased volume of the aflibercept 8 mg formulation on IOP. In patients with nAMD or DME, pre-dose IOP values in the study eye were considered broadly physiologically normal (as is in line with the trial inclusion and exclusion criteria) and similar through week 96 across treatment groups with no trend towards increased IOP over time. Regarding acute or intermediate post-injection IOP increases, this analysis showed that the proportion of study eyes with and without glaucoma-related history receiving a new IOP-lowering medication at least once was low across both treatment groups, and few eyes required a paracentesis procedure. In addition, rates of glaucoma-related TEAEs were low and there was very little difference in mean change in IOP from pre- to post-injection across visits between aflibercept 2 mg and 8 mg. Furthermore, the baseline history of angle-closure glaucoma was low across treatment groups, and angle-closure glaucoma-related TEAEs were low and balanced through week 96. Of note, recent real-world evidence from a prospective observational study of aflibercept in patients with nAMD or diabetic macular oedema has also indicated comparable IOP dynamics between intravitreal administration of aflibercept 8 mg and 2 mg, with rapid (≤ 30 min) normalisation of pressure spikes [39]. As further consideration, the additional 20 µL injection volume administered with aflibercept 8 mg versus aflibercept 2 mg represents only approximately 0.5% of the typical adult vitreous cavity volume (approximately 4 mL [40]) which, together with rapid post-injection physiological equilibration, may help explain the absence of clinically meaningful differences in IOP outcomes between aflibercept 8 mg and 2 mg observed approximately 30–60 min after injection.

As previously reported, overall safety findings for aflibercept 8 mg demonstrated that treatment was well tolerated with a comparable safety profile to aflibercept 2 mg through week 48 and week 96 [10, 31], and with a sustained clinical benefit through week 96 [32, 33]. In the PULSAR trial, patients with treatment-naive nAMD receiving aflibercept 8 mg at extended dosing intervals (12 and 16 weeks) showed visual and anatomic improvements through week 96 comparable to those of patients treated with aflibercept 2 mg every 8 weeks, with fewer injections on average, and with a consistent safety profile [32]. Similar findings were reported in the PHOTON trial of patients with DME where aflibercept 8 mg administered every 12 or 16 weeks achieved visual and anatomic improvements that were comparable to aflibercept 2 mg administered every 8 weeks through 96 weeks with up to six fewer injections [33]. Taken together, these findings highlight the potential of aflibercept 8 mg to decrease treatment burden by facilitating improved patient adherence with less frequent dosing. Regulatory approval of aflibercept 8 mg for the treatment of nAMD and DME has been obtained in the USA, the European Union, and Japan, among other countries, with dosing intervals up to every 6 months in the European Union [29].

One strength of this analysis is that the long duration of follow-up allowed evaluation of glaucoma-related TEAEs over 96 weeks in a large population of patients. While considered

Table 3 Rates of glaucoma-related TEAEs in the study eye per 1000 injections from the PULSAR and PHOTON trials (pooled data)

	Aflibercept 2 mg (*n* = 503)	**Aflibercept 8 mg (*n* = 1164)**
Active injections, *n*	6159	9762
Glaucoma-related TEAEs per 1000 injections, *n*	6	9
Angle-closure glaucoma	0	0
Borderline glaucoma	0	0
Glaucoma	0	1
IOP increased	5	6
Ocular hypertension	1	2
Open-angle glaucoma	0	0

Safety analysis set. Aflibercept 8 mg includes patients receiving 8q12 and 8q16. Values have been rounded to the nearest whole number

8q12 aflibercept 8 mg every 12 weeks, *8q16* aflibercept 8 mg every 16 weeks, *IOP* intraocular pressure, *TEAE* treatment-emergent adverse event

as standard in such trials, limitations include the timing of post-injection IOP measurement, which was approximately 30–60 min (PULSAR) or 30 min (PHOTON) after dosing, which may have missed transient increases in IOP occurring immediately after injection. Further, the reported IOP was the last measurement recorded before the patient was permitted to leave the study site. Consequently, the present analysis was designed to characterise clinically relevant post-injection IOP outcomes at protocol-specified assessment time points rather than immediate short-term fluctuation dynamics. In addition, the findings here are based on data collected in the rigorous randomised clinical trial setting; the value of real-world evidence for informing the management of patients with nAMD and DME in clinical practice is well-recognised, and as the use of aflibercept 8 mg becomes established in practice, it is expected that there will be a body of such evidence to draw upon.

It is acknowledged that comparing post-injection IOP outcomes across trials can be difficult owing to differences in the timing of measurements, techniques used, and variability of patient populations. Management of elevated IOP including the use of paracentesis and administration of IOP-lowering agents also varies among clinicians. In addition, this analysis was not powered to evaluate race- or sex-related differences in IOP outcomes, and included patients with either nAMD or DME, with baseline ocular characteristics and glaucoma-related medical history that may differ from other patient populations. Documentation of increased IOP was at investigator discretion,

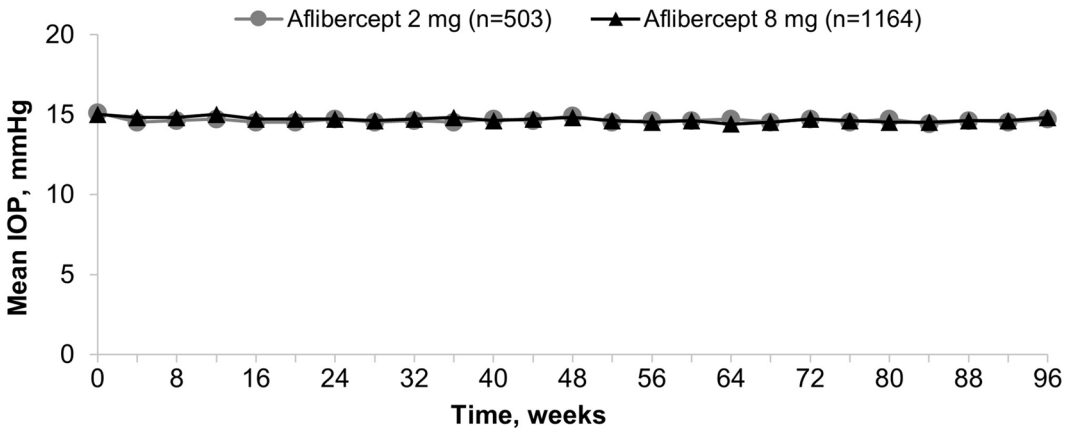

Fig. 1 Mean pre-injection IOP by visit through week 96 of the PULSAR and PHOTON trials (pooled data). Safety analysis set. Aflibercept 8 mg includes patients receiving 8q12 and 8q16. *8q12* aflibercept 8 mg every 12 weeks, *8q16* aflibercept 8 mg every 16 weeks, *IOP* intraocular pressure

Table 4 Proportions of patients initiated on new IOP-lowering medications at least once within the 96-week treatment period in the PULSAR and PHOTON trials (pooled data)

	Aflibercept 2 mg (*n* = 503)	**Aflibercept 8 mg (*n* = 1164)**
Any new IOP-lowering medication, *n* (%)	22 (4.4)	58 (5.0)
Beta-blocking agents	18 (3.6)	45 (3.9)
Carbonic anhydrase inhibitors	6 (1.2)	10 (0.9)
Prostaglandin analogues	5 (1.0)	18 (1.5)
Other anti-glaucoma preparations	0	1 (< 0.1)

Safety analysis set. Aflibercept 8 mg pooled includes patients receiving 8q12 and 8q16. The same drug may be counted in more than one category for an individual patient. The grouping of IOP-lowering prior medications considers the following fourth level ATC codes: 'sensory organs; beta-blocking agents', 'sensory organs; prostaglandin analogues', 'sensory organs; carbonic anhydrase inhibitors', 'sensory organs; other antiglaucoma preparations'

8q12 aflibercept 8 mg every 12 weeks, *8q16* aflibercept 8 mg every 16 weeks, *ATC* Anatomical Therapeutic Chemical, *IOP* intraocular pressure

without defined thresholds for reporting. Future studies evaluating post-injection IOP dynamics together with additional ocular anatomical characteristics, including axial length and anterior chamber configuration, may help further clarify factors associated with IOP elevations following intravitreal aflibercept administration.

Taken together with the overall efficacy and safety findings from the PULSAR and PHOTON trials, these results demonstrate that the extended treatment intervals offered with aflibercept 8 mg were achieved with safety and efficacy consistent with that of aflibercept 2 mg, with a low incidence of reported glaucoma-related TEAEs. Additional results for patients who participated in the extension phases through 156 weeks of the PULSAR and PHOTON trials further demonstrate the efficacy and safety of aflibercept 8 mg [41, 42]. The safety of aflibercept 8 mg will continue to be monitored with ongoing pharmacovigilance activities and is under evaluation in the real-world SPECTRUM (NCT06075147) observational study. In SPECTRUM, an international study in patients with nAMD or DME from North America, Europe, the Middle East and Asia Pacific, patients are followed for up to 2 years to assess visual, anatomic and safety outcomes.

CONCLUSIONS

The rates of glaucoma-related TEAEs were comparable across the aflibercept 8 mg and aflibercept 2 mg treatment groups in this pooled analysis of the PULSAR and PHOTON trials. There was no indication of sustained IOP increase or trend towards increased IOP over time through week 96 in either treatment group. Despite a 70 µl injection volume, no long-term IOP adverse effects were seen through week 96 with aflibercept 8 mg versus 2 mg (50 µl).

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Data Availability. Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA, 'principles for responsible clinical trial data sharing'. This pertains to scope, time point and process of data access. As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the 'study sponsors' section of the portal. Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Declarations

Conflicts of Interest. Anat Loewenstein has served as a consultant for 4DMT, AbbVie, Adverum, Astellas, Aviceda, Bayer, Beyeonics, Boeringer Ingelheim, EyePoint Pharma, NotalVision, Ocular Therapeutix, Oculis, Ocuphire Pharma, Opthea, Roche and Voiant. Ursula Schmidt-Ott was an employee of Bayer AG at the time of the analysis and is currently an employee of Regeneron Pharmaceuticals, Inc. Diana V. Do has served as a consultant for Boehringer Ingelheim, Genentech, Kodiak Sciences, Kriya and Regeneron Pharmaceuticals, Inc.; has received research funding from Boehringer Ingelheim, Genentech, Kriya and

Regeneron Pharmaceuticals, Inc.; and has stock options from Kodiak Sciences. Paolo Lanzetta has served as a consultant for 4DMT, AbbVie, Adverum, Aerie, Apellis, Bausch & Lomb, Bayer, Biogen, Boehringer Ingelheim, Celltrion, Genentech, EyeBio, EyePoint Pharma, I-Care, Novartis, Ocular Therapeutix, Outlook Therapeutics and Roche. Sergio Leal is an employee, investor and patent holder with Bayer Consumer Care AG. Karen W. Chu was an employee of Regeneron Pharmaceuticals, Inc. at the time of the analysis. Mark R. Barakat reports participation in a speakers' bureau, as consultant or in research for AbbVie Inc., Adverum Biotech, Alcon, Alimera, Alkeus, Allegro, Allergan, ANI Pharmaceuticals, Annexon Biosciences, Apellis, Arctic Vision, Astellas, Bausch & Lomb, Beacon, Biocryst, Biogen, Boehringer Ingelheim, CalciMedica, Celltrion, Cencora, Clearside Biomedical, Coherus Biosciences, EyeBio, EyePoint Pharma, Gemini Therapeutics, Genentech, Gyroscope Therapeutics, Harrow, Janssen, Kanghong/Vanotech, Kodiak Sciences, Novartis, Neurotech, Ocular Therapeutix, Oculis, Opthea, Outlook Therapeutics, Oxular, Oxurion, Palatin Technologies, Perceive Bio, Perfuse, Regeneron Pharmaceuticals, Inc., RegenxBio, ReNeuron, RetinAI, RevOpsis Therapeutics, Ribomic, Roche, Sanofi, Stealth Biotherapeutics, Surrozen and Unity Biotechnology; holds stock in NeuBase and Oxurion; and has stock options with RevOpsis Therapeutics. Ghassan Ghorayeb has nothing to disclose. Michael W. Stewart has served as a consultant for Alkahest, Bayer, Biogen, Revena, Regeneron Pharmaceuticals, Inc. and Bayer; receives funding from Allergan, Kanghong and Regeneron Pharmaceuticals, Inc. Michael W. Stewart is an Editorial Board member of *Ophthalmology and Therapy*. Michael W. Stewart was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Martin S. Spitzer has served as a consultant for 1stQ, AbbVie, Alcon, Apellis, Atheneum, Astellas, Bayer, Biogen, DORC, Neurogene, Nordic Pharma, Novartis, Roche, SHS, Stada and TelemedC; and receives funding from Boehringer Ingelheim, Fielmann Group AG and TRN. Xin Zhang and Lynne Brunck were employees of Bayer Consumer Care AG at the time of the analysis. Peter Morgan-Warren is an employee of Bayer Consumer Care AG. Alyson J. Berliner, April McCullough, Ajla Dupljak, Maggie Hymowitz and Anna Portnoy are employees of Regeneron Pharmaceuticals, Inc. Claudia Tueckmantel and Dianela Avila are employees of Bayer AG. Richard Gale has served as a consultant for AbbVie, Advanz, Apellis, Astellas, Bayer, Biogen, Boehringer Ingelheim, Novartis, Ocular Therapeutic, Outlook Therapeutics and Roche; and receives grant funding from Bayer, Heidelberg Engineering and Roche.

Ethical Approval. The PHOTON and PULSAR studies were conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki and applicable local laws and regulations. Study protocols and amendments were approved by the relevant institutional review boards and independent ethics committees before study initiation [10, 31]. As this post hoc analysis was based on existing databases from the PHOTON and PULSAR studies, no additional informed consent was required.

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