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VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study

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ABSTRACT

Aim To evaluate intravitreal VEGF Trap-Eye (VTE) in patients with macular oedema secondary to central retinal vein occlusion (CRVO).

Methods In this double-masked study, 177 patients were randomised (3:2 ratio) to intravitreal injections of VTE 2 mg or sham procedure every 4 weeks for 24 weeks. Best-corrected visual acuity was evaluated using the Early Treatment Diabetic Retinopathy Study chart. Central retinal thickness (CRT) was measured with optical coherence tomography.

Results From baseline until week 24, more patients receiving VTE (60.2%) gained ≥15 letters compared with those receiving sham injections (22.1%) (p<0.0001). VTE patients gained a mean of 18.0 letters compared with 3.3 letters with sham injections (p<0.0001). Mean CRT decreased by 448.6 and 169.3 μm in the VTE and sham groups (p<0.0001). The most frequent ocular adverse events in the VTE arm were typically associated with the injection procedure or the underlying disease, and included eye pain (11.5%), increased intraocular pressure (9.6%) and conjunctival haemorrhage (8.7%).

Conclusions VTE 2 mg every 4 weeks was efficacious in CRVO with an acceptable safety profile. Vision gains with VTE were significantly higher than with observation/panretinal photocoagulation if needed. Based on these data, VTE may provide a new treatment option for CRVO.

INTRODUCTION

Macular oedema is the most common cause of vision loss for patients with central retinal vein occlusion (CRVO).[1] Patients suffering from CRVO, particularly from non-perfused CRVO,[2] have the worst prognosis of all RVO patients.[3]

A wide variety of strategies have been used for the treatment of macular oedema secondary to CRVO including surgical procedures,[4–6] laser photocoagulation,[7] steroid implants,[8] intravitreal steroid injections[9] and, more recently, antivascular endothelial growth factor (anti-VEGF) agents.[10–14] Although effective in reducing macular oedema secondary to CRVO, macular grid laser photocoagulation did not appear to improve vision compared with observation.[2] Treatment with steroids resulted in vision gains, but was associated with higher rates of intraocular pressure (IOP) elevation, cataract formation and steroid-induced secondary glaucoma.[8 9 15] In contrast, intravitreal injections of anti-VEGF agents reduced macular oedema and improved vision with a better safety profile compared with intravitreal steroids.[10–14] Based on a survey from the American Society of Retinal Specialists, over 70% of the retinal specialists (n=619) use intravitreal anti-VEGF agents to treat macular oedema secondary to CRVO.[16]

VEGF Trap-Eye (VTE, aflibercept injection; Regeneron Pharmaceuticals, Inc. Tarrytown, New York, USA, and Bayer HealthCare Pharmaceuticals, Berlin, Germany) is a fusion protein comprising key domains from human VEGF receptors 1 and 2 with human IgG Fc that blocks all VEGF-A isoforms and placental growth factor.[17 18] Previous studies with VTE have demonstrated improvements in visual function for patients with neovascular age-related macular degeneration[19 20] and diabetic macular oedema.[21] GALILEO is one of two similar trials (with the COPERNICUS study)[22] designed to evaluate the efficacy and safety of intravitreal VTE in patients with macular oedema secondary to CRVO.

METHODS

GALILEO is a phase III, randomised, double-masked, multi-centre clinical study conducted across 63 centres in Europe (Austria 3; France 5; Germany 21; Hungary 5; Italy 7; Latvia 2) and the Asian/Pacific region (Australia 6; Japan 6; Singapore 2; South Korea 6). The total study duration is 76 weeks, with 68 weeks of treatment (figure 1). Herein the results from primary analyses at week 24 are reported, while the study continues in a masked fashion up to week 76 with an additional analysis planned at week 52 (registered as NCT01012973 on clinicaltrials.gov). The appropriate institutional review boards/ethic committees approved the protocol and all participants provided written informed consent.

Since at the time when the GALILEO and COPERNICUS studies were started there was no approved treatment for CRVO, health authorities requested that the duration of the sham treatment in GALILEO be extended to a full year (the sister study, COPERNICUS, conducted outside the EU maintained a sham arm for only the first 6 months). Considering this rather long duration of sham treatment, the visual acuity and other ocular findings were observed carefully by a team of masked medical reviewers. If, at any time, this review team had the impression that a patient might not benefit from further study participation or might be more adequately treated outside the

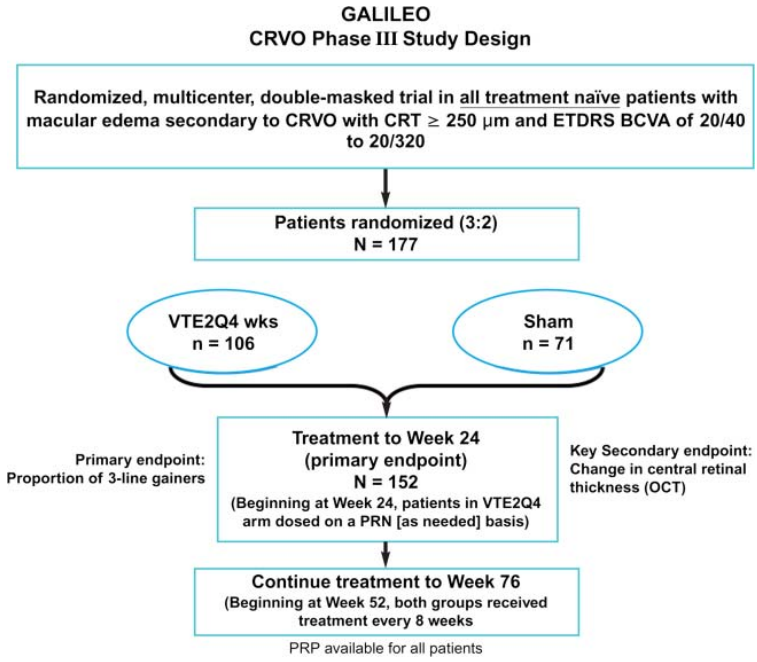

Figure 1 GALILEO study design. The two study arms consisted of VEGF Trap-Eye 2 mg every 4 weeks or sham intravitreal injections every 4 weeks. BCVA, best-corrected visual acuity; CRT, central retinal thickness; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; PRP, panretinal photocoagulation; VTE2Q4, VEGF Trap-Eye 2q4. This figure is only reproduced in colour in the online version.

study, the investigator was queried and asked to provide a reassessment of the patient.

Participants

Treatment-naive patients, age ≥18 years, were included if they had centre-involved macular oedema secondary to CRVO for a maximum of 9 months, with a central retinal thickness (CRT) ≥250 µm on optical coherence tomography (OCT) and an Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 73 to 24 letters (20/40 to 20/320) in the study eye. Patients were excluded if they were pregnant or had uncontrolled glaucoma (IOP≥25 mm Hg), filtration surgery, bilateral manifestation of RVO, iris neovascularisation, or previous treatment with anti-VEGF agents, pan-retinal or macular laser photocoagulation, or intraocular corticosteroids.

Treatments

Patients were randomised in a 3:2 ratio to receive either intravitreal injections of VTE 2 mg (VTE2Q4) or sham procedure every 4 weeks for 24 weeks. Sham procedure was performed by pressing an empty syringe with no needle to the conjunctival surface. Randomisation was stratified by region (Europe vs Asia/Pacific) and baseline BCVA (≤20/200 vs >20/200). Pan-retinal photocoagulation was allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus.

Endpoints

The primary endpoint was the proportion of patients who gained ≥15 letters in BCVA at week 24 compared with baseline. The secondary endpoints were: (a) the change from baseline to week 24 in BCVA and CRT, (b) the proportion of patients progressing to neovascularisation of anterior segment, optic disc or elsewhere in the fundus by week 24 and (c) the changes in vision-related and overall health-related quality of life (QoL) as assessed by the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) and European Quality of Life-5 Dimensions (EQ-5D) Health Questionnaire, respectively. Selected subscales of NEI VFQ-25 were assessed as tertiary efficacy variables.

Methodology

Visual function was assessed using the ETDRS charts.[23] Retinal characteristics were evaluated using OCT (Stratus OCT, Carl Zeiss Meditec, Jena, Germany). Baseline retinal perfusion status was determined by fluorescein angiography using the central vein occlusion study (CVOS) classification.[2] Patients were considered non-perfused if they had ≥10 disc areas of capillary non-perfusion. Vision-related and overall health-related QoL was assessed using the NEI-VFQ-25 and EQ-5D Health Questionnaires, respectively.

Statistics

A total of 150 patients (90 VTE/60 Sham) were considered necessary to detect a between-group difference of 25% in proportion of patients gaining ≥15 letters with a power of 90% using a two-sided Fisher's exact test. For the efficacy analyses, the full analysis set included all randomised patients who received any study treatment and had baseline and at least one postbaseline BCVA assessment. The safety analysis set included all patients who received any study treatment. For the primary endpoint analysis, the between-group difference was evaluated by a two-sided Cochran-Mantel-Haenszel (CMH) test at a 5% level stratified for regions and baseline visual acuity. In this analysis, patients who discontinued prior to week 24 were considered as non-responders. Several sensitivity analyses for the primary endpoint were performed by imputing the missing values with the last observation carried forward (LOCF) approach, using observed cases, or excluding patients who discontinued study prior to week 24 and received fewer than five injections.

Secondary endpoint analyses were performed sequentially according to the order in which the variables were defined to preserve an α of 0.05. Proportions were analysed with the CMH test. BCVA as a continuous variable was analysed by analysis of variance main effects model with treatment group,

region and baseline BCVA as fixed factors. A descriptive, post hoc analysis using a double-sided Fisher test was conducted to evaluate the between-group differences in the proportion of patients losing ≥1 and ≥10 letters.

RESULTS

Patient disposition, demographics and disease characteristics

A total of 240 patients were screened, 177 patients were randomised and 172 patients were included in the safety analysis set (table 1). One patient did not have any postbaseline BCVA assessment. Therefore, the full analysis set comprised 171 patients (table 1). Overall, 86.4% of VTE2Q4 patients and 79.4% of sham patients had a perfused retinal occlusion (table 2).

Visual outcomes

Significantly more VTE2Q4-treated patients gained ≥15 letters by week 24 than those receiving sham injections (60.2% vs 22.1%, p<0.0001) with a CMH-adjusted difference of 38.3% (table 3, figure 2). Similar results for the CMH-adjusted difference (95% CI) was obtained after imputing the missing values with the LOCF approach (41.1% (27.4% to 54.9%)), using the observed cases (38.7% (23.5% to 53.8%)), or excluding patients who discontinued study prior to week 24 and received fewer than five injections (39.2% (25.4% to 53.0%)).

Patients receiving VTE2Q4 had a significantly greater mean change in BCVA than the sham-treated patients at week 24 (18.0 vs 3.3 letters, respectively; p<0.0001; figure 3) resulting in an adjusted between-group difference of 14.7 letters (table 3). The VTE2Q4 arm also showed higher proportions of patients with vision gains of ≥0, ≥10 and ≥30 letters at week 24 (figure 4). In all, 11 (10.7%) patients in the VTE2Q4 group experienced a loss of one or more letters during the course of the 24 weeks compared with 27 (39.7%) patients in the sham arm (p<0.0001). A total of 8 patients (7.8%) in the VTE2Q4 group lost 10 or more ETDRS letters during the 24 weeks compared with 17 (25.0%) for the sham group (p=0.0033).

Larger numerical differences between VTE2Q4 and sham were seen in the subgroup of patients with disease duration <2 months compared with the difference noted in the study population as a whole (disease duration <2 months: unadjusted difference of 50.9% ((20.0% sham; 70.9% VTE2Q4)). Within the VTE2Q4 group, the proportion of patients who gained at least 15 letters at week 24 was higher (70.9%) for patients beginning treatment within 2 months of diagnosis compared with 50.0% of VTE2Q4 patients starting treatment ≥2 months after diagnosis.

Table 1 Patient disposition (all randomised patients) and overview of analysis sets

n (%)	VEGF Trap-Eye 2Q4 n=106	Sham n=71	Total n=177
Patients screened	–	–	240
Patients randomised	106 (100)	71 (100)	177 (100)
Patients treated	104 (98.1)	68 (95.8)	172 (97.2)
Patients (FAS)	103 (97.2)	68 (95.8)	171 (96.6)
Completed 24 weeks	96 (90.6)	56 (78.9)	152 (85.9)
Discontinued study before week 24	10 (9.4)	15 (21.1)	25 (14.1)
Adverse event	0	4 (5.6)	4 (2.3)
Protocol violation	5 (4.7)	2 (2.8)	7 (4.0)
Withdrawal of consent	3 (2.8)	3 (4.2)	6 (3.4)
Lack of efficacy	0	5 (7.0)	5 (2.8)
Lost to follow-up	1 (0.9)	0	1 (0.6)
Other	1 (0.9)	1 (1.4)	2 (1.1)
Discontinued treatment before week 24*	11 (10.4)	18 (25.4)	29 (16.4)
Adverse event	2 (1.9)	8 (11.3)	10 (5.6)
Protocol violation	5 (4.7)	2 (2.8)	7 (4.0)
Withdrawal of consent	3 (2.8)	3 (4.2)	6 (3.4)
Lack of efficacy	0	4 (5.6)	4 (2.3)
Lost to follow-up	1 (0.9)	0	1 (0.6)
Other	0	1 (1.4)	1 (0.6)
Safety analysis set	104 (98.1)	68 (95.8)	172 (97.2)
FAS	103 (97.2)	68 (95.8)	171 (96.6)
Per protocol set	87 (82.1)	51 (71.8)	138 (78.0)

Percentages are based on all randomised patients.
*In the sham group, patients discontinued receiving the sham procedure.
FAS, full analysis set.

Table 2 Baseline demographics and disease characteristics (study eye)

FAS*	VEGF Trap-Eye 2Q4 n=103	Sham n=68	Total n=171
Mean age, years (SD)	59.9 (12.4)	63.8 (13.3)	61.5 (12.9)
Geographic region			
Europe	73 (70.9)	48 (70.6)	121 (70.8)
Asia/Pacific	30 (29.1)	20 (29.4)	50 (29.2)
Gender			
Female	45 (43.7%)	31 (45.6%)	76 (44.4%)
Male	58 (56.3%)	37 (54.4%)	95 (55.6%)
Race			
White	74 (71.8%)	49 (72.1%)	123 (71.9%)
Asian	26 (25.2%)	15 (22.1%)	41 (24.0%)
Not reported	3 (2.9%)	4 (5.9%)	7 (4.1%)
Renal impairment			
Normal	61 (59.2)	37 (54.4)	98 (57.3)
Mild	36 (35.0)	17 (25.0)	53 (31.0)
Moderate	5 (4.9)	9 (13.2)	14 (8.2)
Severe	0	2 (2.9)	2 (1.2)
Missing	1 (1.0)	3 (4.4)	4 (2.3)
Hepatic impairment			
Yes	3 (2.9)	2 (2.9)	5 (2.9)
No	100 (97.1)	66 (97.1)	166 (97.1)
Retinal perfusion status			
Perfused	89 (86.4)	54 (79.4)	143 (83.6)
Non-perfused	7 (6.8)	7 (10.3)	14 (8.2)
Indeterminable	7 (6.8)	7 (10.3)	14 (8.2)
Time since CRVO diagnosis			
<2 months	55 (53.4)	35 (51.5)	90 (52.6)
≥2 months	46 (44.7)	33 (48.5)	79 (46.2)
Missing	2 (1.9)	0	2 (1.2)
Mean time since CRVO diagnosis in days (SD)	78.0 (89.6)	87.6 (79.1)	81.8 (85.4)
Mean ETDRS BCVA letter score (SD)	53.6 (15.8)	50.9 (15.4)	52.2 (15.7)
ETDRS BCVA >20/200	86 (83.5%)	56 (82.4%)	142 (83.0%)
Mean CRT μm (SD)	683.2 (234.5)	638.7 (224.7)	665.5 (231.0)
Mean IOP (mm Hg) (SD)	15.1 (2.8)	14.4 (2.7)	14.9 (2.7)

*n (%) unless otherwise noted
BCVA, best-corrected visual acuity; CRT, central retinal thickness; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; IOP, intraocular pressure.

Table 3 Primary and secondary endpoints

	VEGF Trap-Eye 2Q4	Sham
FAS	n=103	n=68
Primary endpoint		
No (%) of patients who gained at least 15 letters in BCVA at week 24	62 (60.2)	15 (22.1)
Difference,* %	38.1	–
CMH adjusted difference*,† % (95% CI)	38.3 (24.4 to 52.1)	–
p Value‡	<0.0001	–
Secondary endpoint	p Value	Adjusted difference between treatment groups (95% CI)
1. Change in BCVA letter score from baseline to week 24§,**	<0.0001 (favours VTE2Q4)	14.7 (10.8 to 18.7)
2. Change in CRT from baseline to week 24¶,**	<0.0001 (favours VTE2Q4)	−239.42 (−286.31 to −192.53)
3. Percentage of patients progressing to any neovascularisation by week 24‡,**	0.5947	−1.5 (−7.4 to 4.4)
4. Change in total NEI VFQ-25 score from baseline to week 24¶,**	0.0013§	4.2 (1.7 to 6.8)
5. Change in EQ-5D score from baseline to week 24¶,**	0.0627§	0.044 (−0.002 to 0.090)

*Difference is VTE2Q4 minus sham.
†Estimate and CI are calculated using CMH weights adjusted for region (Europe vs Asia/Pacific) and baseline BCVA category (>20/200 vs ≤20/200).
‡p Value is calculated using two-sided CMH test adjusted by region and baseline BCVA category. This applied for the primary endpoint and the third secondary endpoint (percentage of patients progressing to any neovascularisation by week 24).
§ANOVA with treatment group, geographic region and baseline BCVA category as fixed factors.
¶Analysis of covariance (ANCOVA) with treatment group, geographic region and baseline BCVA category as fixed factors and the respective baseline variable as a covariate.
**The hierarchical testing of the secondary endpoints had to be stopped after the testing of the proportion of patients progressing to any neovascularisation; the p values provided in this table for the subsequent steps (test #4 and test #5) were for descriptive purposes only.
ANOVA, analysis of variance; BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; CRT, central retinal thickness; FAS, full analysis set; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; VTE2Q4, VEGF Trap-Eye 2 mg every 4 weeks.

Anatomical outcomes

The difference between the treatment groups in mean changes in CRT at week 24 was 279.3 μm (figure 5) (difference between least squares mean changes 239.4; p<0.0001, table 3). Neovascularisation was developed in three VTE2Q4 patients (2.9%) (two anterior segment neovascularisation and one neovascularization elsewhere (NVE)) and three sham patients (4.4%) (one anterior segment neovascularisation and two NVE) (p=0.5947, table 3). Only one case of iris neovascularisation in the VTE2Q4 group required treatment with pan-retinal laser photocoagulation. The other cases reported to be neovascularisation in the VTE2Q4 group did not require therapy. All of the three sham patients with neovascularisation received pan-retinal laser photocoagulation. No further rescue laser treatment was applied until week 24.

QoL outcomes

The mean change from baseline to week 24 in total NEI-VFQ scores was 7.5 for the VTE2Q4 group and 3.5 for the sham group. The between-group difference in both the total NEI-VFQ score and the near-activities subscore was significant at week 24 (p=0.0013 and p=0.0003, respectively, table 3). A trend was observed between groups in favour of VTE2Q4 for the distance-activities subscore, dependency subscore and overall mean EQ-5D score at week 24 (p=0.0689, p=0.2552, p=0.0627, respectively).

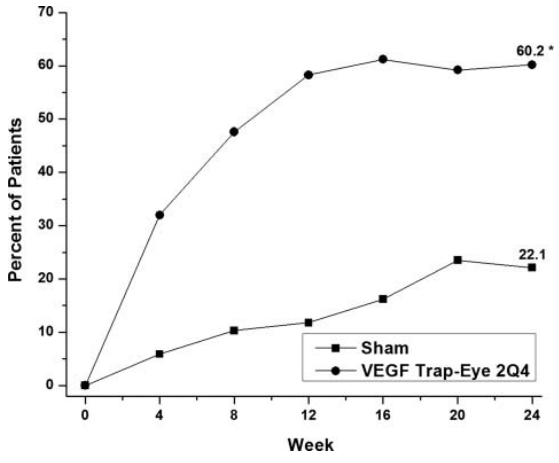

Figure 2 Percentage of patients who gained ≥15 letters over the course of 24 weeks. Full analysis set; patients who discontinued prior to respective visit evaluated as non-responders. VEGF Trap-Eye 2Q4, n=103; sham, n=68. Difference between groups at week 24=38.1%. *p<0.0001 VEGF Trap-Eye versus sham was calculated using two-sided Cochran-Mantel-Haenszel test adjusted by region and baseline best-corrected visual acuity category.

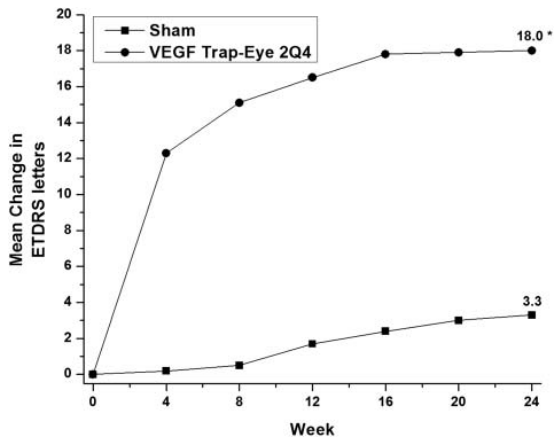

Figure 3 Mean change in visual acuity (Early Treatment Diabetic Retinopathy Study (ETDRS) letters). Full analysis set; LOCF. VEGF Trap-Eye 2Q4, n=103; sham, n=68. Difference between groups at week 24=14.7 letters. *p<0.0001 VEGF Trap-Eye versus sham based on treatment difference of the least squares mean changes derived from analysis of variance.

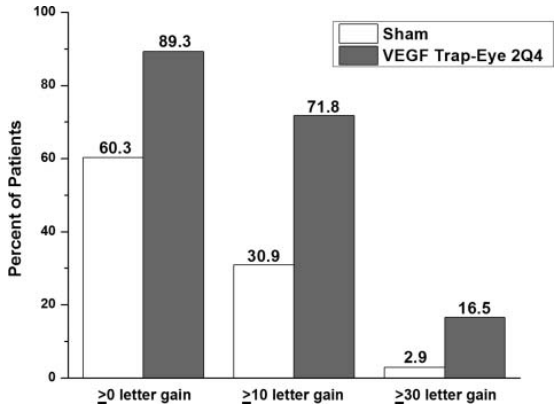

Figure 4 Proportion of patients who gained vision at week 24 compared with baseline. Full analysis set; patients who discontinued prior to week 24 evaluated as non-responders. VEGF Trap-Eye 2Q4, n=103; sham, n=68.

Safety

The most common treatment-emergent adverse events (AEs) for the VTE2Q4 patients were eye pain, increased IOP and conjunctival haemorrhage (table 4). A slight imbalance was seen in IOP-increased AEs between VTE2Q4 (10 (9.6%)) and sham (4 (5.9%)). Of note, 5 (4.8%) of these IOP-related AEs were procedure-related in the VTE2Q4 group, while only 1 (1.5%) in the sham group was related to procedure. Three incidents (2.9%) of increased IOP in the VTE2Q4 group were judged to be drug-related compared with 1 (1.5%) for the sham group. The IOP-increased events for reasons other than the injection procedure were well balanced across the arms (table 5). The proportions of patients experiencing predefined elevations in IOP (ie, ≥10 mm Hg change from baseline, >21 mm Hg or ≥35 mm Hg) were low and similar between treatment groups at all time points.

There were no incidences of endophthalmitis or cases of rhegmatogenous detachment in either treatment group. There was one incidence of uveitis in the VTE2Q4 arm that was considered to be mild and resolved without change of therapy. There were none in the sham group. Two patients in the VTE2Q4 group and four patients in the sham group had ocular SAEs (table 6). There were no arterial thromboembolic events or deaths reported in either treatment group during the 24-week study period.

Table 4 Treatment-emergent adverse events. Those events with an incidence ≥3% in either study group are shown

Safety analysis set	VEGF Trap-Eye 2Q4 n=104 n (%)	Sham n=68 n (%)
Eye disorders (study eye)		
Eye pain	12 (11.5)	3 (4.4)
Conjunctival haemorrhage	9 (8.7)	3 (4.4)
Retinal exudates	7 (6.7)	5 (7.4)
Foreign body sensation	6 (5.8)	5 (7.4)
Retinal vascular disorder	6 (5.8)	6 (8.8)
Ocular hyperaemia	5 (4.8)	4 (5.9)
Vitreous floaters	5 (4.8)	0 (0.0)
Macular oedema	4 (3.8)	11 (16.2)
Macular ischaemia	4 (3.8)	3 (4.4)
Optic disc vascular disorder	4 (3.8)	3 (4.4)
Eye irritation	3 (2.9)	7 (10.3)
Lacrimation increased	3 (2.9)	4 (5.9)
Papilloedema	2 (1.9)	3 (4.4)
Retinal ischaemia	1 (1.0)	3 (4.4)
Visual acuity reduced	0 (0.0)	7 (10.3)
Investigations		
IOP increased*	10 (9.6)	4 (5.9)
General disorder and administrative site conditions		
Injection site pain	5 (4.8)	2 (2.9)
Non-ocular events		
Nasopharyngitis	8 (7.7)	6 (8.8)
Headache	7 (6.7)	4 (5.9)
Hypertension	4 (3.8)	3 (4.4)
Back pain	3 (2.9)	3 (4.4)
Arthralgia	1 (1.0)	5 (7.4)
Fall	0 (0.0)	3 (4.4)

*The adverse event could occur prior to the injection or shortly after the injection, when the IOP was checked after the procedure. The postinjection IOP check had to occur approximately 30 min after the injection. In total 13 patients (therefore six in the VTE2Q4 arm) had at least a single IOP measurement of >21 mm Hg preinjection. One patient in each of the arms had neovascularisation of the chamber angle as the underlying cause and were treated. Two patients in the VTE2Q4 arm had a history of glaucoma and were treated accordingly. One patient in the sham arm had newly diagnosed ocular hypertension or glaucoma and treatment was initiated. All other cases (three in the VTE2Q4 and five in the sham arm) had IOPs >21 mm Hg at not more than two visits and had no therapy documented, with one exception (IOP of 24 mm Hg) who received an acute short-term treatment.
IOP, intraocular pressure; VTE2Q4, VEGF Trap-Eye 2 mg every 4 weeks.

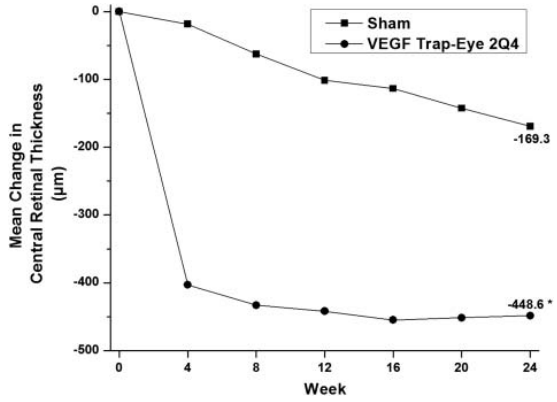

Figure 5 Mean change in central retinal thickness. Full analysis set; LOCF. VEGF Trap-Eye 2Q4, n=103; sham, n=67. Difference between groups at week 24=279.3 µm. *p<0.0001 VEGF Trap-Eye versus sham is based on treatment difference of the least-squares mean changes derived from analysis of covariance (ANCOVA).

DISCUSSION

VTE 2 mg every 4 weeks resulted in significantly better visual acuity outcomes than sham. Clinically relevant improvements in visual acuity in the VTE2Q4 group could be seen as early as the first post-treatment assessment (week 4) and reached a stable level, on average, around week 16. The better visual acuity outcome was accompanied by more favourable vision-related QoL measures in the VTE2Q4 group than in the sham group.

Several studies have investigated the efficacy of other anti-VEGF agents for the treatment of macular oedema secondary to CRVO. The CRUISE study reported that patients receiving monthly injections of 0.5 mg ranibizumab (n=130) experienced a mean change from baseline BCVA of 14.9 letters

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