NEW ZEALAND DATA SHEET

1. PRODUCT NAME

EYDENZELT aflibercept (rch) 40 mg/mL solution for intravitreal injection

EYDENZELT (Aflibercept) (rch) is a biosimilar medicine to EYLEA (Aflibercept).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of EYDENZELT solution contains 40 mg aflibercept.

Each vial and pre-filled syringe provides a usable amount to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

The prescribing physician should be involved in any decision regarding interchangeability (unless the product is known to be non-interchangeable). Additional information is available on the following website (www.medsafe.govt.nz/profs/RIss/Biosimilars.asp).

The comparability of EYDENZELT with EYLEA has been demonstrated with regards to physicochemical characteristics and efficacy and safety outcomes [see section 5.1 Pharmacodynamic properties, 5.2 Pharmacokinetic Properties and 4.8 Undesirable effects].

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Solution for intravitreal injection.

EYDENZELT is a clear to slightly opalescent, colourless to very pale brownish yellow, preservative-free, iso-osmotic solution.

The drug product is supplied as either a single-use pre-filled syringe or as a single-use vial.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EYDENZELT(aflibercept) is indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (wet AMD)
- visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)
- visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)
- diabetic macular oedema (DME)
- visual impairment due to myopic choroidal neovascularisation (myopic CNV)

4.2 DOSE AND METHOD OF ADMINISTRATION

EYDENZELT is for intravitreal injection only.

It must only be administered by a qualified ophthalmologist experienced in administering intravitreal injections.

Dose

The recommended dose for EYDENZELT is 2 mg aflibercept, equivalent to an injection volume of 50 µL. The interval between doses injected into the same eye should not be shorter than one month.

Advice on treatment initiation and maintenance of therapy specific to each patient population is described in the section below. Once optimal visual acuity is achieved and/or there are no signs of disease activity, treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If disease activity persists or recurs, the treatment interval may be shortened accordingly. Monitoring should be done at injection visits. The monitoring and treatment schedule should be determined by the treating ophthalmologist based on the individual patient's response. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, EYDENZELT should be discontinued.

Treatment of neovascular (wet) age-related macular degeneration (wet AMD)

EYDENZELT treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months.

Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, by increasing injection intervals in 2- or 4-weekly increments while maintaining stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened to a minimum of four weeks based on anatomical and/or visual outcomes.

Generally, once optimal visual acuity is achieved and/or there are no signs of disease activity, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Treatment intervals greater than four months (16 weeks) between injections have not been studied (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)

EYDENZELT treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)

EYDENZELT treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes.

Treatment of diabetic macular oedema (DME)

EYDENZELT treatment is initiated with one injection per month for five consecutive months.

Following the initiation period and based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may then be maintained at an injection every two months or further individualised, such as with a treat-and-extend dosing regimen, by increasing injection intervals in 2- or 4-weekly increments while maintaining stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. Treatment intervals shorter than 4 weeks or longer than 4 months have not been studied (see Section 5.1 PHARMCODYNAMIC PROPERTIES, Clinical trials).

Treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV)

EYDENZELT treatment is initiated with one injection of 2 mg aflibercept (equivalent to 50 µL).

Additional doses should be administered only if visual and/or anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease.

Patients with hepatic and/or renal impairment

No specific studies in patients with hepatic and/or renal impairment were conducted with aflibercept. Available data do not suggest a need for a dose adjustment with aflibercept in these patients (see Section 5.2 PHARMACOKINETIC PROPERTIES). Pharmacokinetic analysis of patients with wet AMD in the VIEW 2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.

Similar results were seen in patients with CRVO in the GALILEO study, with DME in the VIVID^{DME} study and with myopic CNV in the MYRROR study.

Use in elderly

No special considerations are needed. There is limited experience in patients older than 75 years with DMO (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Paediatric population

The safety and efficacy of EYDENZELT have not been studied in children or adolescents.

Method of administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified ophthalmologist experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide, have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each pre-filled syringe or vial should only be used for the treatment of a single eye.

The recommended dose is 2 mg aflibercept (equivalent to 50 µL solution for injection). The pre-filled syringe and the glass vial contain more than this recommended dose. Therefore**, the excess volume must be expelled before injecting** (see section 6.6 'Instruction for use/ handling'). Injecting the entire volume of the glass vial or the pre-filled syringe could result in overdose.

To expel the air bubbles along with excess drug in the pre-filled syringe, slowly depress the plunger to **align the base of the plunger dome (not the tip of the dome) with the black dosing line of the syringe**, this will ensure delivery equivalent to 50 µL i.e. 2 mg aflibercept (see section 6.6 'Instructions for use/ handling', section 4.9 'Overdose').

After injection any unused product must be discarded.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to aflibercept or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS)

- Ocular or periocular infection
- Active severe intraocular inflammation

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Endophthalmitis

Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis (see Section 4.8 UNDESIRABLE EFFECTS). Proper aseptic injection technique must always be used when administering aflibercept. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately.

Increase in intraocular pressure

Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including with aflibercept (see Section 4.8 UNDESIRABLE EFFECTS). Special precaution is needed in patients with poorly controlled glaucoma. In all cases both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity. Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Arterial thromboembolic events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors (see Section 4.8 UNDESIRABLE EFFECTS). ATEs include vascular death (e.g., due to stroke or myocardial infarction), non-fatal strokes and non-fatal myocardial infarction.

The risk of stroke may be greater in patients with known risk factors including a history of stroke or transient ischaemic attack (TIA). Patients should be carefully evaluated by their doctor to assess whether the benefits of treatment outweigh the potential risks.

Other

The safety and efficacy of aflibercept therapy administered to both eyes concurrently have not been systematically studied (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). As with other intravitreal injections, if bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events.

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating anti-VEGF therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired.

In the event of either a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity; or a subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥50% of the total lesion area, the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment.

The dose should be withheld in the event of performed or planned intraocular surgery within the previous or next 28 days.

In patients presenting with clinical signs of irreversible ischaemic visual function loss, the treatment is not recommended.

Populations with limited data

- Diabetic macular oedema due to type 1 diabetes
- Diabetic patients with HbA1c > 12%
- Proliferative diabetic retinopathy
- Active systemic infections
- Concurrent eye conditions (e.g., retinal detachment, macular hole)
- Uncontrolled hypertension
- In myopic CNV there is no experience with EYDENZELT in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

Use in the elderly

No special considerations are needed. There is limited experience in patients older than 75 years with DMO (see CLINICAL TRIALS).

Paediatric use

The safety and efficacy of aflibercept have not been studied in children or adolescents.

Effects on laboratory tests

No relevant effects on laboratory tests are known.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal drug interaction studies have been performed with aflibercept.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category D[1]

There are no data on the use of aflibercept in pregnant women. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration. Aflibercept should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Aflibercept produced malformations and other fetal abnormalities in pregnant rabbits with intravenous administration (at 3 to 60 mg/kg once every 3 days during the period of organogenesis) and with subcutaneous administration (0.1 to 1 mg/kg on gestational days 1, 7, and 13). A No Observed Effect Level (NOEL) for adverse effects on embryo-fetal development was not established. At the lowest dose tested (0.1 mg/kg), the systemic exposures based on C_{max} and cumulative AUC for

[1] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

free aflibercept were approximately 13-and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

Breastfeeding

It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. Aflibercept is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to abstain from aflibercept therapy.

Fertility

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg every one to two weeks. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility (considered consequential to male fertility) were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4900-fold and 1500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients may experience temporary visual disturbances after an intravitreal injection with aflibercept and the associated eye examinations (see section 4.8 UNDESIRABLE EFFECTS). Patients should not drive or use machinery until visual function has recovered sufficiently.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

A total of 3102 patients treated with aflibercept constituted the safety population in eight Phase III studies. Amongst those, 2501 patients were treated with the recommended dose of 2 mg.

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 2400 intravitreal injections with aflibercept and included endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous detachment and intraocular pressure increased (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The most frequently observed adverse reactions (in at least 5% of patients treated with aflibercept) were conjunctival haemorrhage (25.0%), visual acuity reduced (11.1%), eye pain (10.2%), cataract (7.6%), intraocular pressure increased (7.5%), vitreous detachment (7.4%), and vitreous floaters (6.9%).

In wet AMD, these adverse reactions occurred with a similar incidence in the ranibizumab treatment group.

Tabulated list of adverse reactions

The safety data described in Table 1 below include all adverse reactions (serious and non-serious) from eight Phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product over the 96 weeks study duration for wet AMD, over 100 weeks for CRVO, over 100 weeks for DMO, over 52 weeks for BRVO and over 48 weeks for myopic CNV.

The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to < 1/1,000 patients). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 1: All treatment-emergent adverse drug reactions reported in patients in Phase III studies

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Immune system disorders			Hypersensitivity***	
Eye disorders	Visual acuity reduced, Conjunctival haemorrhage, Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia Ocular hyperaemia	Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Anterior chamber flare, Corneal oedema	Blindness, Cataract traumatic, Vitritis, Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
** Culture positive and culture negative endophthalmitis
*** including allergic reactions

Post-marketing experience

In addition, the following adverse reactions have also been reported during the post-marketing period of aflibercept, for which a frequency could not be estimated.

Immune system disorders: hypersensitivity (including rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions).

Description of selected adverse reactions

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and aflibercept.

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause). The incidence of

adjudicated APTC ATEs in the VIEW 1 and VIEW 2 wet AMD studies during the 96 weeks study period was 3.3% (60 out of 1824) in the combined group of patients treated with aflibercept (2.4% in the aflibercept 2Q4 arm and 3.6% in the aflibercept 2Q8 arm), compared to 3.2% (19 out of 595) in patients treated with ranibizumab.

The incidence of adjudicated APTC ATEs in the CRVO studies (GALILEO and COPERNICUS) during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of aflibercept compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment.

The incidence of adjudicated APTC ATEs in the DME studies (VIVID^{DME} and VISTA^{DME}) during the 100 weeks study duration was 6.4% (37 out of 578) in the combined group of patients treated with aflibercept compared with 4.2% (12 out of 287) in the control group.

The incidence of APTC ATEs in the BRVO study (VIBRANT) during the 52 week study duration was 0% (0 out of 91) in patients treated with aflibercept compared with 2.2% (2 out of 92) in the control group.

The incidence of APTC ATEs in the myopic CNV study (MYRROR) during the 48 week study duration was 1.1% (1 out of 91) in the group of patients treated with aflibercept compared to 0% (0 out of 31) in the group of patients in the control group.

As with all therapeutic proteins, there is a potential for immunogenicity with aflibercept.

Comparability of EYDENZELT with EYLEA Adverse Effects

Safety

There were no notable differences in the incidence or nature of adverse events between the EYDENZELT and EYLEA treatment groups in Study CT-P42 3.1, and the safety profile of each treatment group was in line with the known safety profile of EYLEA. As a result, the analysis of adverse events obtained in the clinical study with EYDENZELT illustrated that the benefit-risk profile of EYDENZELT is similar to that of EYLEA.

During the main study period of Study CT-P42 3.1, 109 [62.6%] patients in the CT-P42 group and 117 [67.2%] patients in the Eylea group experienced treatment-emergent adverse events (TEAEs). Among them, 109 ocular TEAEs in the study eye were reported in 31 (17.8%) patients in the CT-P42 group and 38 (21.8%) patients in the Eylea group. A total of 102 ocular TEAEs in the fellow eye were reported in 37 (21.3%) patients in the CT-P42 group and 45 (25.9%) patients in the Eylea group. 392 non-ocular TEAEs were reported in 86 (49.4%) patients in the CT-P42 group and 93 (53.4%) patients in the Eylea group. The majority of TEAEs were Grade 1 or Grade 2 in intensity.

The majority of TEAEs were considered as unrelated to the study drug. TEAEs considered as related to the study drug were reported in 14 (4.0%) patients in total (8 [4.6%] patients in the CT-P42 group and 6 [3.4%] patients in the Eylea group).

Six (6) grade 3 adverse reactions in Table 2 were reported during Study CT-P42 3.1 EYDENZELT and EYLEA treatment groups but was ruled out from 'treatment-emergent adverse drug reactions reported in patients in Phase III studies' in Table 1. In all cases, causality assessment of the events in question was confounded by risk factors reported in medical history. And the number of incidents was limited to singular cases with no identifiable trends.

Table 2: Non-relative Adverse drug reactions reported in Phase III studies.

System Organ Class Preferred Term	**EYDENZELT** **(N=174)**	**EYLEA** **(N=174)**
Eye disorders		
Epiretinal membrane – Grade 3	1 (0.6%)	0

System Organ Class Preferred Term	EYDENZELT (N=174)	EYLEA (N=174)
Macular ischaemia – Grade 3	1 (0.6%)	0
Vascular disorders		
Hypertension – Grade 3	0	1 (0.6%)
Cardiac disorders		
Myocardial infarction – Grade 3	1 (0.6%)	0
Nervous system disorders		
Ischaemic stroke – Grade 3	0	1 (0.6%)
Investigations		
Blood pressure increased – Grade 3	0	1 (0.6%)

Adverse events of special interest

Arterial thromboembolic events

In each treatment group, 8 (4.6%) patients experienced at least 1 ATE with non-ocular events in Main Study Period. All the TEAEs classified as ATE were non-ocular TEAEs and considered to be unrelated to the study drug except 1 case (myocardial infarction, grade 3) in the EYDENZELT group and 1 case (ischaemic stroke, grade 3) in the Eylea group. The most frequently reported TEAE classified as ATE was carotid artery stenosis (1 [0.6%] and 2 [1.1%] patients in the EYDENZELT and Eylea groups, respectively).

Table 3: TEAE Classified as Arterial Thromboembolic Events by Relationship and Intensity in EYDENZELT Phase III study

System Organ Class Preferred Term	EYDENZELT (N=174)	EYLEA (N=174)
Cardiac disorders	**4 (2.3%)**	**1 (0.6%)**
Cardiac arrest – Grade 5	1 (0.6%)	0
Coronary artery disease – Grade 2	1 (0.6%)	0
Coronary artery disease – Grade 3	0	1 (0.6%)
Myocardial infarction – Grade 3	1 (0.6%)	0
Myocardial infarction – Grade 2	1 (0.6%)	0
General disorders and administration site conditions	**0**	**2 (1.1%)**
Death – Grade 5	0	2 (1.1%)
Infections and infestations	**1 (0.6%)**	**0**
Pneumonia – Grade 5	1 (0.6%)	0
Investigations	**0**	**1 (0.6%)**
Blood creatine phosphokinase increased – Grade 1	0	1 (0.6%)
Nervous system disorders	**1 (0.6%)**	**3 (1.7%)**
Carotid artery stenosis – Grade 3	1 (0.6%)	2 (1.1%)
Cerebral infarction – Grade 3	0	1 (0.6%)

System Organ Class Preferred Term	EYDENZELT (N=174)	EYLEA (N=174)
Ischaemic stroke – Grade 3	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	**1 (0.6%)**	**0**
Dyspnoea – Grade 5	1 (0.6%)	0
Vascular disorders	**1 (0.6%)**	**1 (0.6%)**
Peripheral arterial occlusive disease – Grade 3	1 (0.6%)	0
Peripheral artery occlusion – Grade 3	0	1 (0.6%)

Note: The total number of TEAEs counted included events classified as ATEs for all patients in the Safety Set for Main Study Period. At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted.

Intravitreal Injection Procedure events

Overall, the proportion of patients who experienced at least 1 TEAE related to IVT injection procedure was similar between the treatment groups (7 [4.0%] and 16 [9.2%] patients in the EYDENZELT and Eylea groups, respectively). Most of the patients with at least 1 TEAE related to IVT injection procedure had ocular TEAE in the study eye (7 [4.0%] and 15 [8.6%] patients, respectively).

Table 4: Ocular TEAE in the Study Eye Related to Intravitreal Injection Procedure by Relationship and Intensity in EYDENZELT Phase III study

System Organ Class Preferred Term	EYDENZELT (N=174)	EYLEA (N=174)
Eye disorders	**6 (3.4%)**	**11 (6.3%)**
Conjunctival haemorrhage – Grade 2	1 (0.6%)	0
Conjunctival haemorrhage – Grade 1	0	4 (2.3%)
Corneal erosion – Grade 1	1 (0.6%)	0
Eye irritation – Grade 1	1 (0.6%)	0
Eye pain – Grade 1	0	3 (1.7%)
Eyelid irritation – Grade 1	1 (0.6%)	2 (1.1%)
Foreign body sensation in eyes – Grade 1	1 (0.6%)	1 (0.6%)
Ocular hypertension – Grade 1	0	1 (0.6%)
Vitreous detachment – Grade 1	0	1 (0.6%)
Vitreous floaters – Grade 1	1 (0.6%)	0
Investigations	**1 (0.6%)**	**4 (2.3%)**
Intraocular pressure increased – Grade 1	1 (0.6%)	1 (0.6%)
Intraocular pressure increased – Grade 2	0	2 (1.1%)
Intraocular pressure increased – Grade 1	1 (0.6%)	1 (0.6%)

Note: The total number of TEAEs counted included events related to IVT injection procedure for all patients in the Safety Set for Main Study Period. At each level of summarization, patients were counted once if they reported 1 or more events. Only the most severe event was counted.

Immunogenicity

Immunogenicity was evaluated in Study CT-P42 3.1 using an MSD-ECL method. Only samples confirmed positive for anti-drug antibodies (ADAs) were subsequently analysed for neutralizing antibodies (NAbs).

The incidences of post-dose ADA and NAb in DME patients were similar between EYDENZELT and EYLEA treatment groups with ADA of 1.7% for EYDENZELT vs. 2.3% for EYLEA and NAb of 1.1% for both treatment groups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/}

4.9 OVERDOSE

In clinical trials doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased intraocular pressure. Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated (see section 6.6 'Instructions for use/ handling).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents

ATC code: S01LA05

Mechanism of action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergise with VEGF-A in these processes, and is also known to promote leukocyte infiltration and vascular inflammation. A variety of ocular diseases is associated with pathologic neovascularisation and vascular leakage, and/or can result in thickening and oedema of the retina, which is thought to contribute to vision loss.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (K_D) for aflibercept binding to human VEGF-A_{165} is 0.5 pM and to human VEGF-A_{121} is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

Pharmacodynamic properties

Neovascular (wet) age-related macular degeneration (wet AMD)
Wet AMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

In patients treated with aflibercept (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In pivotal phase III clinical studies, VIEW 1 and VIEW 2, there were mean decreases in retinal thickness on time domain optical coherence tomography (OCT) at week 52: -130 and 129 microns for the aflibercept 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 1; -149 and -139 microns for the aflibercept 2 mg every two months, and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 2.

The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

The supportive study, ALTAIR, enrolled Japanese patients with treatment naive wet AMD, using 3 initial monthly aflibercept 2 mg injections, followed by one injection after 2 months, and then continued with a treat-and-extend regimen with variable treatment intervals (2-week or 4-week adjustments) up to a maximum 16 week interval according to pre-specified criteria. At week 52, there were mean decreases in central retinal thickness (CRT) on spectral domain OCT of -134.4 and -126.1 microns for the 2-week adjustment group and the 4-week adjustment group, respectively. The proportion of patients without fluid on OCT at week 52 was 68.3% and 69.1% in the 2- and 4-week adjustment groups, respectively.

The reduction in retinal thickness was generally maintained in both treatment arms in the second year of the ALTAIR study.

Macular oedema following central retinal vein occlusion (CRVO)
In CRVO, retinal ischaemia occurs and signals the release of VEGF which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with aflibercept (one injection every month for six months), there was consistent, rapid and robust response in morphology (CRT as assessed by OCT). Improvements in mean CRT were maintained through week 24.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy endpoint in both the COPERNICUS and GALILEO studies. In both studies, the mean change in CRT from baseline to week 24 statistically significantly favoured aflibercept.

Table 5: Pharmacodynamic parameter at week 24, week 52 and week 76/100 (Full Analysis Set with Last Observation Carried Forward (LOCF)) in COPERNICUS and GALILEO studies

COPERNICUS						
Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**100 Weeks**	
	Control (N = 73)	**Aflibercept 2 mg Q4 (N = 114)**	**Control[c)] (N = 73)**	**Aflibercept 2 mg (N = 114)**	**Control[c,d)] (N = 73)**	**Aflibercept[d)] 2 mg (N = 114)**
Mean change in retinal thickness from baseline	-145	-457	-382	-413	-343	-390
Difference in LS mean[a,b,c)] (95% CI) p-value		-312 (-389, -234) p < 0.0001		-28 (-121, 64) p = 0.5460		-45 (-142, 53) p = 0.3661
GALILEO						
Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**100 Weeks**	
	Control (N = 68)	**Aflibercept 2 mg Q4 (N = 103)**	**Control (N = 68)**	**Aflibercept 2 mg (N = 103)**	**Control[e)] (N = 68)**	**Aflibercept[e)] 2 mg (N = 103)**
Mean change in retinal	-169	-449	-219	-424	-306	-389

thickness from baseline						
Difference in LS mean[a,b,c)] (95% CI) p-value		-239 (-286, -193) p < 0.0001		-167 (-217, -118) p < 0.0001		-44 (-99, 10) p = 0.1122

a) Difference is aflibercept 2 mg Q4 minus control
b) LS: Least square mean difference and confidence interval (CI) based on an ANCOVA model with baseline value as covariate and factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)
c) In COPERNICUS study, control group patients could receive aflibercept on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks
d) In COPERNICUS study, both control group and Aflibercept 2 mg patients received aflibercept 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary
e) In GALILEO study, both control group and aflibercept 2 mg patients received Aflibercept 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks

Macular oedema following branch retinal vein occlusion (BRVO)

In BRVO, retinal ischaemia occurs and signals the release of VEGF, which in turn destabilises the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal oedema, stimulation of endothelial cell growth and neovascularisation.

In patients treated with aflibercept (one injection every month for six months) in the VIBRANT study, there was consistent, rapid and robust response in retinal morphology (CRT as assessed by OCT). There was a statistically significant improvement in the aflibercept 2 mg group in comparison to the active control group treated with laser photocoagulation at week 24 (-280 microns vs. -128 microns). At week 24, the dosing interval was extended to every 2 months, and anatomic outcomes were maintained.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. This decrease from baseline was maintained to week 52, favouring aflibercept .

Table 6: Pharmacodynamic parameter at week 24 and at week 52 (Full Analysis Set with LOCF) in VIBRANT study

VIBRANT				
Efficacy Outcomes	**24 Weeks**		**52 Weeks**	
	Aflibercept 2 mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**Aflibercept 2 mg Q8 (N = 91)[b)]**	**Active Control[c)] (N = 90)**
Mean change in retinal thickness from baseline	-280	-128	-284	-249
Difference in LS mean (95% CI)[a)] p-value	-149 (-180, -117) p < 0.0001		-30 (-55, -4) p = 0.0218	

a) Aflibercept administered as 2 mg every 4 weeks through week 24. Laser treatment administered on day 1.
b) Last observation carried forward (LOCF) method was used to impute missing data.
c) Difference was aflibercept group minus laser group. Point estimate, 95% confidence interval (CI), and p-value were based on an analysis of covariance (ANCOVA) model with baseline measurement as covariate and treatment group, region, and baseline Best Corrected Visual Acuity (BCVA ≤ 20/200 and BCVA > 20/200) as fixed factors.
d) Starting from week 24, the treatment interval in the aflibercept treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.

e) Beginning at week 24, subjects in the Laser Group could receive rescue treatment with aflibercept, if they met at least one pre-specified eligibility criterion. A total of 67 subjects (74%) in this group received aflibercept rescue treatment. The fixed regimen for aflibercept rescue was aflibercept 2 mg every 4 weeks for three injections, followed by injections every 8 weeks.

Diabetic macular oedema (DMO)

Diabetic macular oedema is characterised by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

In patients treated with aflibercept, rapid and robust response in morphology (CRT) as assessed by OCT was seen soon after treatment initiation. The mean change in CRT from baseline to week 52 was statistically significant favouring aflibercept and was maintained through week 100.

Table 7: Pharmacodynamic parameter at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} and VISTA^{DME}

VIVID^{DME}						
Efficacy Outcomes	**52 Weeks**			**100 Weeks**		
	Aflibercept 2 mg Q8[a)] (N = 135)	**Aflibercept 2 mg Q4[c)] (N = 136)**	**Active Control (laser) (N = 132)**	**Aflibercept 2 mg Q8[a)] (N = 135)**	**Aflibercept 2 mg Q4[c] (N = 136)**	**Active Control (laser) (N = 132)**
Mean change in CRT score from Baseline (SD)	-192.4 (149.89)	-195.0 (146.59)	-66.2 (138.99)	-195.8 (141.75)	-211.8 (150.87)	-85.7 (145.84)
Difference in LS mean[a,b)] (97.5% CI) p-value	-142.8 (-179.3, -106.3) p < 0.0001	-157.0 (-190.9, -123.1) p < 0.0001		-126.8 (-164.6, -89.0) p < 0.0001	-154.4 (-189.1, -119.7) p < 0.0001	
VISTA^{DME}						
Efficacy Outcomes	**52 Weeks**			**100 Weeks**		
	Aflibercept 2 mg Q8[a)] (N = 151)	**Aflibercept 2 mg Q4[c)] (N = 154)**	**Active Control (laser) (N = 154)**	**Aflibercept 2 mg Q8[a)] (N = 151)**	**Aflibercept 2 mg Q4[c] (N = 154)**	**Active Control (laser) (N = 154)**
Mean change in CRT score from Baseline (SD)	-183.1 (153.50)	-185.9 (150.68)	-73.3 (176.72)	-191.1 (160.66)	-191.4 (180.01)	-83.9 (179.29)
Difference in LS mean[a,b)] (97.5% CI) p-value	-113.47 (-144.19, -82.75) p < 0.0001	-110.78 (-141.34, -80.22) p < 0.0001		-110.99 (-142.94, -79.04) p < 0.0001	-104.89 (-139.58, -70.21) p < 0.0001	

a) LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}. Aflibercept 2 mg Q8: From week 16 onwards, the treatment interval in aflibercept treatment group was extended for all subjects from 4 weeks to 8 weeks.

b) Difference is aflibercept group minus active control (laser) group.

c) Aflibercept administered 2 mg every 4 weeks.

The VIOLET study compared three different dosing regimens of aflibercept 2 mg for treatment of DME. Following 5 consecutive monthly doses and treatment at fixed 8 week intervals for at least 1 year, patients continued treatment with aflibercept 2mg according to one of the dosing regimens:

- treat-and-extend (2T&E) where treatment intervals were maintained at a minimum of 8 weeks and gradually extended based on clinical and anatomical outcomes
- pro re nata (2PRN) where patients were observed every 4 weeks and injected when needed based on clinical and anatomical outcomes, and
- dosed every 8 weeks (2Q8) for the second and third year of treatment.

At week 52 of the study, i.e., after at least two years of treatment, the mean changes in CRT from baseline were -2.1, 2.2 and -18.8 microns for 2T&E, 2PRN, and 2Q8 respectively. At week 100, i.e., after at least three years of treatment, the mean changes in CRT from baseline were 2.3, -13.9 and -15.5 microns, respectively (see section 'Clinical trials').

Myopic choroidal neovascularisation (myopic CNV)
Myopic CNV is a frequent cause of vision loss in adults with pathologic myopia. Eyes with pathologic myopia are elongated, often excessively, and have, in addition, pathologic tissue alterations such as retinal pigment epithelial thinning and defects, lacquer cracks and Bruch's membrane ruptures, choroidal neovascularisation, subretinal haemorrhage and choroidal atrophy. As a consequence of ruptures of Bruch's membrane, myopic CNV develops as a wound healing mechanism and at the same time represents the most vision-threatening event in pathologic myopia.

In patients treated with aflibercept (one injection given at the start of therapy, additional injection given in case of disease persistence or recurrence) retinal thickness assessed by OCT decreased soon after treatment initiation and the mean CNV lesion size was reduced. The mean change in CRT from baseline to week 24 was statistically significant favouring aflibercept.

Table 8: Pharmacodynamic parameter at week 24 and week 48 in MYRROR study (Full Analysis Set with LOCF[a])

MYRROR				
Efficacy Outcomes	**24 Weeks**		**24 Weeks**	
	aflibercept 2 mg[b] (N = 90)	**Sham (N = 31)**	**aflibercept 2 mg[c] (N = 90)**	**Sham / aflibercept 2 mg[d] (N = 31)**
Mean change in central retinal thickness from baseline	-79	-4	-83	-57
Difference in LS mean[e,f,g,h] (97.5% CI) p-value	-78 (-109, -47) p < 0.0001			-29 (-60, 2) P = 0.0650

a) LOCF: Last Observation Carried Forward
b) Aflibercept 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.
c) Aflibercept 2 mg administered from week 24 through week 44 potentially every 4 weeks in case of disease persistence or recurrence
d) Mandatory injection of aflibercept 2 mg at week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through week 44.
e) Difference is aflibercept 2 mg minus sham at week 24; difference is aflibercept 2 mg minus sham/aflibercept 2 mg at week 48.
f) LS mean: Least square means derived from ANCOVA model
g) CI: Confidence Interval
h) LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant.

Comparability of EYDENZELT with EYLEA

In vitro studies
EYDENZELT batches demonstrated comparable properties with respect to the biological activity when compared to EYLEA based on VEGF-A and -B binding, cell-based human vascular endothelial growth factor (VEGF) blockade, inhibition of human VEGF-A induced proliferation of human umbilical vein endothelial cells (HUVECs), galectin-1 binding affinity, Fc receptors binding (SPR).

Clinical trials

Neovascular (wet) age-related macular degeneration (wet AMD)

The safety and efficacy of aflibercept were assessed in two pivotal phase III randomised, multicentre, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW 1 and VIEW 2). In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

1. Aflibercept administered at 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8)
2. Aflibercept administered at 2 mg every 4 weeks (aflibercept 2Q4)
3. Aflibercept administered at 0.5 mg every 4 weeks (aflibercept 0.5Q4)
4. Ranibizumab administered at 0.5 mg every 4 weeks (Ranibizumab 0.5Q4)

Patient ages ranged from 49 to 99 years with a mean of 76 years. Approximately 89% (1616/1817) of the patients randomised to treatment with aflibercept were 65 years of age or older and approximately 63% (1139/1817) were 75 years of age or older.

In the follow-up exploratory phase of the studies (i.e. from week 52 onwards to week 96), patients continued to receive the dosage strength to which they were initially randomised but on a modified dosing schedule. Injections were given as frequently as every 4 weeks, but no less frequently than every 12 weeks based upon pre-specified retreatment criteria guided by assessment of visual and/or anatomic outcomes. After the first year of the studies, 90% of patients originally treated with aflibercept 2Q8 received 6 doses or less and 72% received 4 doses or less among the patients completing the follow-up exploratory phase of the studies.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. The studies were intended to test for non-inferiority against ranibizumab 0.5 mg given every 4 weeks.

In the VIEW 1 study, at week 52, 95.1% of patients in the aflibercept 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. Aflibercept treatment was shown to be non-inferior to the ranibizumab 0.5Q4 group.

In the VIEW 2 study, at week 52, 95.6% of patients in the afibercept 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. Aflibercept treatment was shown to be non-inferior to the ranibizumab 0.5Q4 group.

The VIEW 1 and VIEW 2 studies included four secondary efficacy endpoints: mean change in Best Corrected Visual Acuity (BCVA), proportion of patients who gained ≥15 letters, change in the total National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score, and change in CNV area.

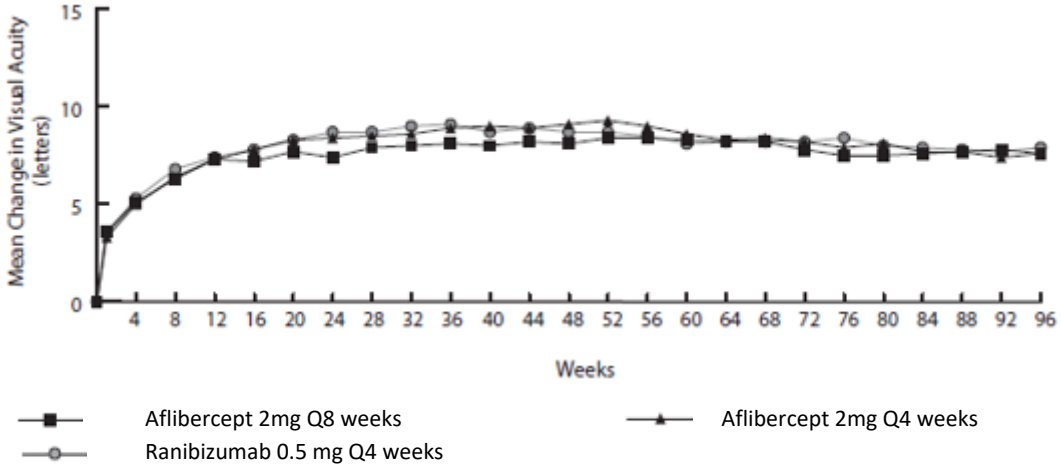
Detailed results from the combined analysis of both studies (primary* and secondary# endpoints) are shown in Table 9 and Figure 1 below.

Table 9: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW 1 and VIEW 2 studies[b)]

Efficacy Outcomes	Aflibercept 2 mg Q4 (N = 613)		Aflibercept 2 mg Q8[e)] (N = 607)		Ranibizumab 0.5 mg Q4 (N = 595)	
	Week 52	Week 96[h)]	Week 52	Week 96[h)]	Week 52	Week 96[h)]
Mean number of injections from baseline	12.3	16.0	7.6	11.2	12.3	16.5
Mean number of injections during week 52 to week 96	N/A	4.1	N/A	4.2	N/A	4.7
Proportion of patients with maintained visual acuity (<15 letters of BCVAa) loss) (Per Protocol Set)*	95.35%[b)]	92.17%	95.33%[b)]	92.42%	94.42%[b)]	91.60%
Difference[c)] (95% CI)[d)]	0.9% (-1.7, 3.5)[f)]	0.6% (-2.5, 3.6)[f)]	0.9% (-1.7, 3.5)[f)]	0.8% (-2.3, 3.8)[f)]	N/A	N/A
Mean change in BCVA as measured by ETDRSa) letter score from baseline#	9.26	7.60	8.40	7.62	8.74	7.89
Difference in LS[a)] mean (ETDRS letters)[c)] (95% CI)[d)]	0.60 (-0.94, 2.14)	-0.20 (-1.93, 1.53)	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)	N/A	N/A
Proportion of patients who gained at least 15 letters of vision from baseline#	33.44%	31.16%	30.97%	33.44%	32.44%	31.60%
Difference[c)] (95% CI)[d)]	1.0% (-4.3, 6.3)	-0.4% (-5.6, 4.8)	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)	N/A	N/A
Mean change in total score as measured by NEI VFQ-25 from baseline#	5.60	5.03	5.00	5.31	5.56	5.24
Difference in LS[a)] mean (NEI VFQ-25 score)[c)] (95% CI)[d)]	-0.75 (-2.20, 0.71)	-0.99 (-2.56, 0.58)	-1.26 (-2.72, 0.20)	-0.61 (-2.19, 0.97)	N/A	N/A
Mean change in CNV area as measured by FA[a)] from baseline #	-5.30	-5.09	-4.28	-4.26	-4.21	-4.27
Difference in LS[a)] mean (CNV area)[g)] (95% CI)[d)]	-0.74 (-1.27, -0.21)	-0.45 (-1.01, 0.10)	0.08 (-0.46, 0.61)	0.11 (-4.4, 0.67)	N/A	N/A

a) BCVA: Best Corrected Visual Acuity ETDRS: Early Treatment Diabetic Retinopathy Study
LS mean: least squares mean
FA: Fluorescein angiography
b) Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at week 52 which is Per Protocol Set (PPS)
c) The difference is the value of the aflibercept group minus the value of the ranibizumab group. A positive value favours aflibercept.
d) Confidence Interval (CI) calculated by normal approximation
e) After treatment initiation with three monthly doses
f) A confidence interval lying entirely above -10% indicates a non-inferiority of aflibercept to ranibizumab
g) The difference is the value of the aflibercept group minus the value of the ranibizumab group
h) Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria
* Primary endpoint
\# Secondary endpoint – see statistical comment below

Figure 1: Mean change in visual acuity from baseline to week 96*; combined data from the VIEW1 and VIEW2 studies



* From Baseline to Week 52, aflibercept was dosed every 8 weeks following 3 initial monthly doses (aflibercept 2 mg Q8 weeks) or every 4 weeks (aflibercept 2 mg Q4 weeks). From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks (Ranibizumab 0.5 mg Q4 weeks). Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

While there were small differences between aflibercept and ranibizumab, no clinically relevant differences were seen between the treatment groups across all four secondary efficacy endpoints, based on the confidence intervals for the differences between aflibercept and ranibizumab. All statistical tests on secondary efficacy endpoints were considered to be exploratory in the combined analysis of both studies. All secondary endpoint analyses supported the comparability of the efficacy of all 3 aflibercept treatment schedules and ranibizumab.

In combined data analysis of the VIEW 1 and VIEW 2 studies aflibercept demonstrated clinically meaningful changes from baseline in NEI VFQ-25 scores and subscales (near activities, distance activities, and vision-specific dependency). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in BCVA.

After the first year of the studies, efficacy was generally maintained through the last assessment at week 96. Over the 96 weeks period, patients in the aflibercept 2Q8 group received an average of 11.2 doses and patients in the ranibizumab group received an average of 16.5 doses.

Exploratory analyses of efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

The supportive study, ALTAIR, is a 96 week Phase IV multicentre, randomised, open-label study in 247 Japanese patients with treatment naive wet AMD, designed to assess the efficacy and safety of aflibercept following two different adjustment intervals (2-weeks and 4-weeks) of a treat-and-extend dosing regimen.

All patients received 3 monthly doses of aflibercept 2 mg, followed by one injection after a further 2 month interval. At week 16, patients were randomised 1:1 into two treatment groups: 1) aflibercept treat-and-extend with 2-week adjustments and 2) aflibercept treat-and-extend with 4-week adjustments. Extension or shortening of the treatment interval was decided based on visual and/or anatomic criteria defined by protocol with a maximum treatment interval of 16 weeks for both groups.

The primary efficacy endpoint was mean change in BCVA from baseline to week 52. The secondary efficacy endpoints were the proportion of patients who did not lose ≥15 letters and the proportion of patients who gained at least 15 letters of BCVA from baseline to week 52.

At week 52, patients in the treat-and-extend arm with 2-week adjustments gained a mean of 9.0 letters from baseline as compared to 8.4 letters for those in the 4-week adjustment group [LS mean difference in letters (95% CI): -0.4 (-3.8,3.0), ANCOVA]. The proportion of patients who did not lose ≥15 letters in the two treatment arms was similar (96.7% in the 2-week and 95.9% in the 4-week adjustment groups). The proportion of patients who gained ≥ 15 letters at week 52 was 32.5% in the 2-week adjustment group and 30.9% in the 4-week adjustment group. The proportion of patients who extended their treatment interval to 12 weeks and beyond was 42.3% in the 2-week adjustment group and 49.6 % in the 4-week adjustment group. Furthermore, in the 4-week adjustment group 40.7% of patients were extended to 16 week intervals. Ocular and systemic safety profiles were similar to the safety observed in the pivotal studies VIEW1 and VIEW2. There are no data directly comparing aflibercept administered in a treat-and extend dosing regimen with aflibercept administered every 8 weeks following 3 initial monthly doses during the first 12 months of treatment of wet AMD.

In the second year of the study, efficacy was generally maintained up to and including the last assessment at week 96, with a mean gain from baseline of 7.6 letters for the 2-week adjustment group and 6.1 letters for the 4-week adjustment group. The proportion of patients who extended their treatment interval to 12 weeks or beyond was 56.9% in the 2-week adjustment group and 60.2 % in the 4-week adjustment group. At the last visit prior to week 96, 64.9% and 61.2% of patients in the 2-week and 4-week adjustment groups, respectively, had their next injection scheduled at an interval of 12 weeks or beyond.

Between week 16 and 96, 43.1% (n = 53) and 54.5% (n = 67) of the patients (2-week and 4-week adjustment groups respectively) were extended to a treatment interval of 16 weeks at least once. Of these patients, 96.2% (n = 51 of 53) patients in the 2-week adjustment group and 77.6% (n = 52 of 67) patients in the 4-week adjustment group maintained a 16-week treatment interval until the end of study. During the 96 week study period, 41.5% (n = 51) and 46.3% (n = 57) of patients in the 2-week and 4-week adjustment groups respectively had a final treatment interval of 16 weeks.

During the second year of treatment patients in both the 2-week and 4-week adjustment groups received an average of 3.6 and 3.7 injections. Over the 2-year treatment period patients received an average of 10.4 injections.

The safety and efficacy of aflibercept were assessed in two randomised, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with aflibercept) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg aflibercept administered every 4 weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control) until week 52. Starting from this time point, all patients were offered treatment if they met pre-specified criteria.

Patient ages ranged from 22 to 89 years with a mean of 64 years. Approximately 52% (112/217) of the patients randomised to treatment with aflibercept were 65 years of age or older and approximately 18% (38/217) were 75 years of age or older.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. The studies were designed to evaluate superiority against the control group (receiving sham injections).

Change in visual acuity at week 24 compared to baseline was an important secondary endpoint in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favour of aflibercept in both studies, for the proportion of patients who gained at least 15 letters in BCVA and for mean change in visual acuity, at week 24 compared to baseline. In both pivotal studies, the maximal improvement in visual acuity was achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52. A difference was maintained through week 76/100.

Three other secondary endpoints were included in the studies: change in CRT, as assessed by OCT, at week 24 compared to baseline (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic effects); proportion of patients progressing to neovascularisation (anterior segment neovascularisation, neovascularisation of the optic disk, or neovascularisation of the retina elsewhere) at week 24; and change in the NEI VFQ-25 total score at week 24 compared to baseline.

Detailed results from the analysis of both studies (primary* and secondary# endpoints) are shown in Table 5 (see Section see Section 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic effects), Table 10 and Figure 2 below.

Table 10: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[c)]) in COPERNICUS and GALILEO studies

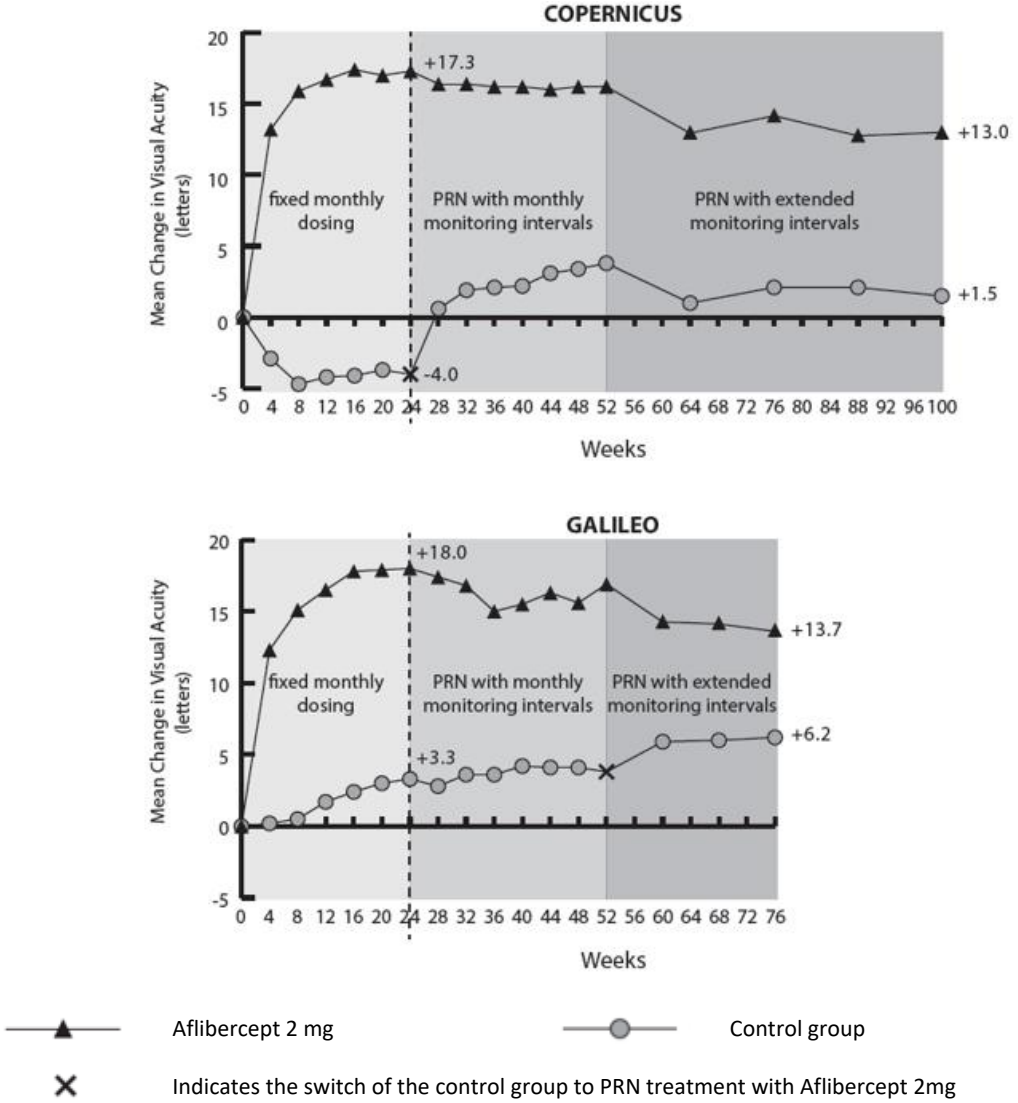
COPERNICUS						
Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**100 Weeks**	
	Control (N = 73)	**Aflibercept 2 mg Q4 (N = 114)**	**Control [e)] (N = 73)**	**Aflibercept 2 mg (N = 114)**	**Control [e,f)] (N = 73)**	**Aflibercept[f)] 2 mg (N = 114)**
Proportion of patients who gained at least 15 letters in BCVA [c)] from baseline*	12%	56%	30%	55%	23.3%	49.1%
Weighted difference [a,b,e)] (95% CI) p-value		44.8% (33.0, 56.6) p < 0.0001		25.9% (11.8, 40.1) p = 0.0006		26.7% (13.1, 40.3) p = 0.0003
Mean change in BCVA as measured by ETDRS[c)] letter score from baseline (SD)#	-4.0 (18.0)	17.3 (12.8)	3.8 (17.1)	16.2 (17.4)	1.5 (17.7)	13.0 (17.7)
Difference in LS mean[a,c,d,e)] (95% CI) p-value		21.7 (17.4, 26.0) p < 0.0001		12.7 (7.7, 17.7) p < 0.0001		11.8 (6.7, 17.0) p < 0.0001
Proportion of patients who developed any neovascularisation#	6.8%	0%	6.8%	0%	11.0%	5.3%

CHM adjusted difference [a,c,d,e)] (95% CI) p-value		-6.8 (-12.4, -1.2) p = 0.0059		-6.8 (-12.4, -1.2) p = 0.0059		-5.4 (-13.7, 2.8) p = 0.1810
LS mean change in total score as measured by NEI VFQ-25[c)] from baseline[#§]	2.5	8.8	6.9	9.3	3.6	6.3
Difference in LS mean [a,c,d,e)] (95% CI) p-value		6.3 (2.6, 9.9) p = 0.0009		2.4 (-1.4, 6.2) p = 0.2164		2.7 (-2.0, 7.3) p = 0.2628
GALILEO						
Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Control (N = 68)	**Aflibercept 2 mg Q4 (N = 103)**	**Control (N = 68)**	**Aflibercept 2 mg (N = 103)**	**Control [g)] (N = 68)**	**Aflibercept[g)] 2 mg (N = 103)**
Proportion of patients who gained at least 15 letters in BCVA[c)] from baseline*	22%	60%	32%	60%	29.4%	57.3%
Weighted difference[a,b,e)] (95% CI) p-value		38.3% (24.4, 52.1) p < 0.0001		27.9% (13.0, 42.7) p = 0.0004		28.0% (13.3, 42.6) p = 0.0004
Mean change in BCVA as measured by ETDRS[c)] letter score from baseline (SD)[#]	3.3 (14.1)	18.0 (12.2)	3.8 (18.1)	16.9 (14.8)	6.2 (17.7)	13.7 (17.8)
Difference in LS mean [a,c,d,e)] (95% CI) p-value		14.7 (10.8, 18.7) p < 0.0001		13.2 (8.2, 18.2) p < 0.0001		7.6 (2.1, 13.1) p = 0.0070
Proportion of patients who developed any neovascularisation[#]	4.4%	2.9%	8.8%	5.8%	8.8%	7.8
CHM adjusted difference [a,c,d,e)] (95% CI) p-value		-1.5 (-7.4, 4.4) p = 0.5947		-2.5 (-10.8, 5.8) p = 0.5185		-0.6 (-9.3, 8.1) p = 0.8887
LS mean change in total score as measured by NEI VFQ-25[c)] from baseline[#§]	0.3	4.5	1.7	5.3	1.1	4.0
Difference in LS mean [a,c,d,e)] (95% CI) p-value		4.2 (1.7, 6.8) p = 0.0013		3.6 (1.1, 6.0) p = 0.0049		2.9 (0.1, 5.7) p = 0.0445

a) Difference is aflibercept 2 mg Q4 weeks minus control
b) Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

c) BCVA: Best Corrected Visual Acuity ETDRS: Early Treatment Diabetic Retinopathy Study LOCF: Last Observation Carried Forward NEI VFQ-25: National Eye Institute Visual Function Questionnaire LS: Least Square means derived from ANCOVA SD: Standard Deviation
d) LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)
e) In COPERNICUS study, control group patients could receive aflibercept on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks
f) In COPERNICUS study, both control group and aflibercept 2 mg patients received aflibercept 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary
g) In GALILEO study, both control group and aflibercept 2 mg patients received 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks
* Primary endpoint
\# Secondary endpoint
§ In GALILEO, n=65 in the control group and n=96 in the aflibercept group at week 24; n=67 in the control group and n=98 in the aflibercept group at week 52

Figure 2: Mean change from baseline to week 52 and week 76/100 in visual acuity# by treatment group for the COPERNICUS and GALILEO studies (Full Analysis Set)



Exploratory analyses of efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

Macular oedema secondary to branch retinal vein occlusion (BRVO)

The safety and efficacy of aflibercept were assessed in a randomised, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO, which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with aflibercept) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg aflibercept administered every 4 weeks, with a total of 6 injections, or laser photocoagulation administered at baseline (laser control group). Patients in the laser control group could receive additional laser photocoagulation (called "rescue laser treatment") beginning at week 12, if at least one pre-specified rescue treatment criterion was met. The minimum interval between laser photocoagulation treatments was 12 weeks. After week 24, patients in the aflibercept group received 2 mg every 8 weeks through week 48, and patients in the control group could receive treatment with aflibercept 2 mg, if at least one pre-specified rescue criterion was met. Aflibercept rescue treatment consisted of a fixed regimen with 2 mg aflibercept administered every 4 weeks for 3 injections, followed by intravitreal injections every 8 weeks through week 48.

Patient ages ranged from 42 to 94 years with a mean of 65 years. Approximately 58% (53/91) of the patients randomised to treatment with aflibercept were 65 years of age or older, and approximately 23% (21/91) were 75 years of age or older.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at Week 24 compared to baseline. At Week 24, the aflibercept group was superior to laser control for the primary endpoint.

Change in visual acuity at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. The difference between treatment groups was statistically significant in favour of aflibercept. The course of visual improvement was rapid and maximal improvement was achieved at week 12, with subsequent stabilisation of the effect on visual acuity and central retinal thickness until week 24 and subsequent maintenance of the effect until week 52.

In the laser group 67 patients (74%) received rescue treatment with aflibercept beginning at week 24. In this treatment group, visual acuity improved by about 5 letters from week 24 to 52.

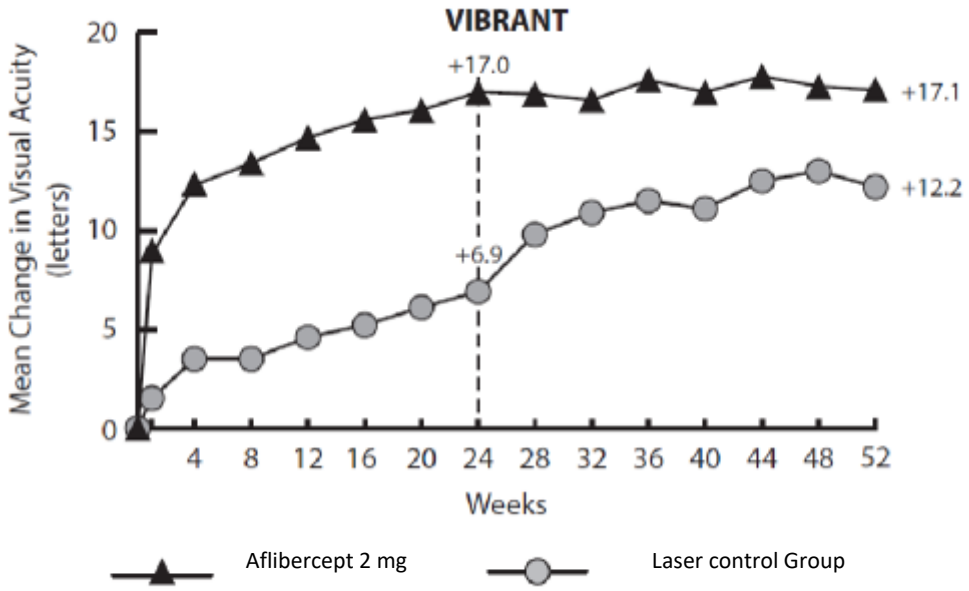
Detailed results from the analysis of the VIBRANT study are shown in Table 11 and Figure 3 below.

Table 11: Efficacy outcomes at week 24, and week 52 (Full Analysis Set LOCF) in the VIBRANT study

VIBRANT				
Efficacy Outcomes	**Aflibercept 2 mg Q4 (N = 91)**	**Active Control (laser) (N = 90)**	**Aflibercept 2 mg Q8 (N = 91)[d)]**	**Active Control[e)] (N = 90)**
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	52.7%	26.7%	57.1%	41.1%
Weighted Difference [a,b)] (%) (95% CI) p-value	26.6% (13.0, 40.1) p = 0.0003		16.2% (2.0, 30.5) p = 0.0296	
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	17.0 (11.9)	6.9 (12.9)	17.1 (13.1)	12.2 (11.9)
Difference in LS mean [a,c)] (95% CI) p-value	10.5 (7.1, 14.0) p < 0.0001		5.2 (1.7, 8.7) p = 0.0035	

a) Difference is aflibercept 2 mg Q4 weeks minus Laser Control
b) Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)
c) LS mean difference and 95% CI based on an ANCOVA model with treatment group, baseline BCVA category (> 20/200 and ≤ 20/200) and region (North America vs. Japan) as fixed effects, and baseline BCVA as covariate.
d) Starting from week 24, the treatment interval in the aflibercept treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.
e) Beginning at week 24, subjects in the Laser Group could receive rescue treatment with aflibercept if they met at least one pre-specified eligibility criterion. A total of 67 subjects (74%) in this group received aflibercept rescue treatment. The fixed regimen for aflibercept rescue was aflibercept 2 mg every 4 weeks for three injections, followed by injections every 8 weeks.

Figure 3: Mean change in BCVA as measured by ETDRS letter score from baseline to week 52 in VIBRANT study (Full Analysis Set, LOCF)



The proportion of retinal perfused patients in the aflibercept group at baseline was 60.4% (n = 55). At week 24, this proportion increased to 80.2% (n = 65) and was sustained at week 52 (77.9%, n = 67). The proportion of perfused patients that started on grid laser photocoagulation was 68.9% (n = 62) at baseline. Perfusion at the week 24 primary endpoint in the laser group was 67.1% (n = 55). Patients in the laser group were eligible for rescue treatment with aflibercept beginning at week 24 according to pre-specified criteria. At week 52, 78.0% (n = 64) were perfused at this time.

The beneficial effect of aflibercept treatment on visual function was similar in the baseline groups with perfused and non-perfused patients.

Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

Diabetic macular oedema (DME)

The safety and efficacy of aflibercept were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with DME. A total of 862 randomised and treated patients were evaluable for efficacy. Of those, 576 were randomised to the aflibercept groups in two studies (VIVID^{DME} and VISTA^{DME}). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens:

1. Aflibercept administered at 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8);
2. Aflibercept administered at 2 mg every 4 weeks (aflibercept 2Q4); and
3. Macular laser photocoagulation (active control).

Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept.

Patient ages ranged from 23 to 87 years with a mean of 63 years. Approximately 47% (268/576) of the patients randomised to treatment with aflibercept were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older. Efficacy and safety outcomes were consistent with the outcomes of the overall population.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was statistically significantly superior to the laser control group. This benefit was maintained through week 100.

Detailed results from the analysis of the VIVID^{DME} and VISTA^{DME} studies are shown in Table 12 and Figure 4 below.

Table 12: Efficacy outcomes at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} and VISTA^{DME} studies

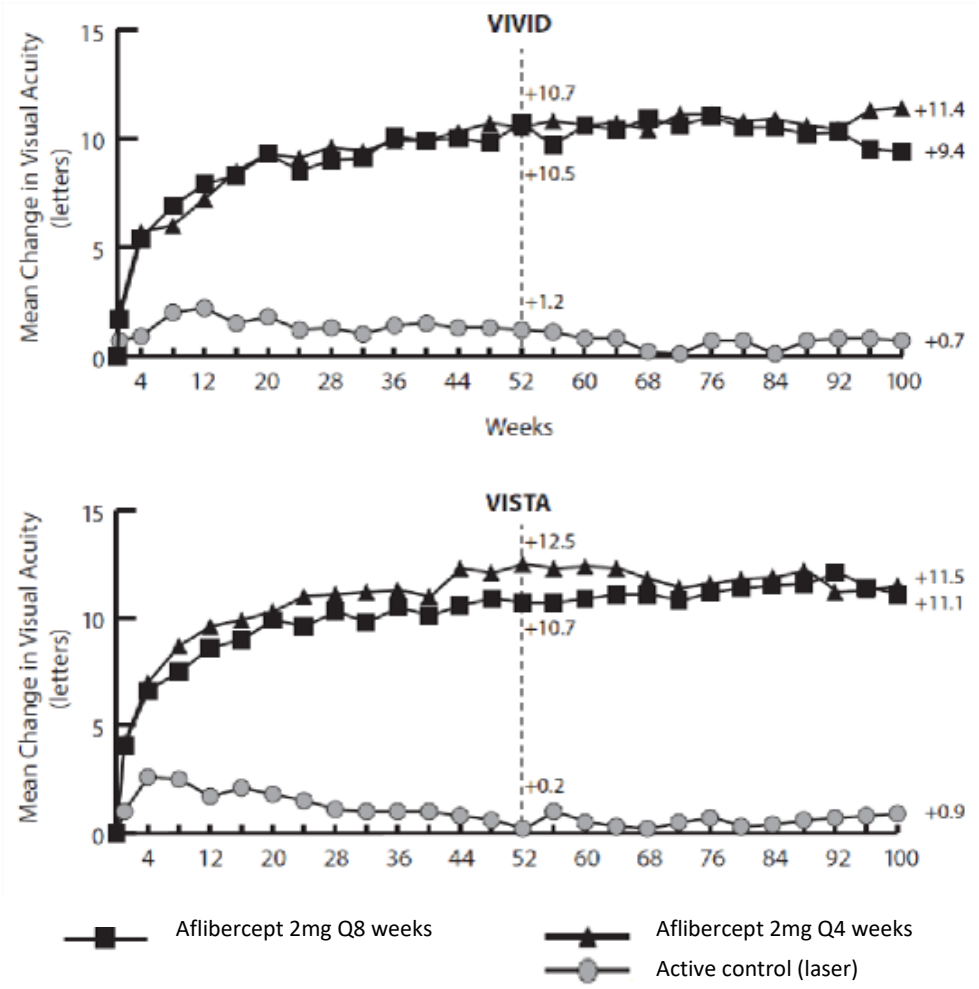
VIVID^{DME}						
Efficacy Outcomes	**52 Weeks**			**100 Weeks**		
	Aflibercept 2 mg Q8[a)] (N = 135)	**Aflibercept 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**Aflibercept 2 mg Q8[a)] (N =135)**	**Aflibercept 2 mg Q4 (N =136)**	**Active Control (laser) (N =132)**
Mean change in BCVA as measured by ETDRS[e)] letter score from Baseline (SD)	10.7 (9.32)	10.5 (9.55)	1.2 (10.65)	9.4 (10.53)	11.4 (11.21)	0.7 (11.77)
Difference in LS mean [b,c,e)] (97.5% CI) p-value	9.1 (6.3, 11.8) p < 0.0001	9.3 (6.5, 12.0) p < 0.0001		8.2 (5.2, 11.3) p < 0.0001	10.7 (7.6, 13.8) p < 0.0001	
Proportion of patients who gained at least 10 letters in BCVA[e)] from Baseline	53.3%	54.4%	25.8%	49.6%	58.1%	25.0%
Adjusted Difference [c,d,e)] (97.5% CI) p-value	27.5 (14.6, 40.5) p < 0.0001	28.7 (15.8, 41.6) p < 0.0001		24.6 (11.9, 37.3) p < 0.0001	33.1 (20.3, 45.9) p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[e)] from Baseline	33.3%	32.4%	9.1%	31.1%	38.2%	12.1%
Adjusted Difference[c,d,e)] (97.5% CI) p-value	24.2% (13.5, 34.9) p < 0.0001	23.3% (12.6, 33.9) p < 0.0001		19.0% (8.0, 29.9) p = 0.0001	26.1% (14.8, 37.5) p < 0.0001	

Proportion of patients with an improvement of >= 2 steps on the ETDRS DRSS[e,f]) from Baseline	27.7%	33.3%	7.5%	32.6%	29.3%	8.2%
Adjusted Difference[c,d)] (97.5% CI) p-value	19.3 (6.6, 32.1) p = 0.0006	25.8 (12.2, 39.4) p < 0.0001		24.4 (11.3, 37.4) p < 0.0001	20.9 (7.7, 34.2) p = 0.0004	
See Table 7 for Mean Change in CRT from Baseline						
Mean change in NEI VFQ-25 [e)] near activities subscale from Baseline	5.29 (19.058)	5.73 (18.932)	3.54 (16.768)	6.97 (19.280)	8.17 (20.193)	4.8 (15.433)
Difference in LS mean [b,c,e)] (97.5% CI) p-value	-1.21 (-5.79, 3.37) p = 0.5537	2.41 (-2.01, 6.82) p = 0.2208		-0.74 (-5.25, 3.78) p = 0.7144	3.64 (-0.70, 7.98) p = 0.0596	
Mean change in NEI VFQ-25[e]) distance activities subscale from Baseline	5.32 (18.475)	0.94 (16.487)	2.26 (15.923)	4.94 (20.253)	4.62 (17.618)	2.2 (16.684)
Difference in LS Mean [b,c,e)] (97.5% CI) p-value	-0.37 (-4.79, 4.05) p = 0.8498	-1.19 (-5.29, 2.91) p = 0.5138		-1.30 (-6.00, 3.39) p = 0.5325	2.57 (-1.73, 6.86) p = 0.1792	
VISTA[DME]						
Efficacy Outcomes	**52 Weeks**			**100 Weeks**		
	Aflibercept 2 mg Q8[a)] (N = 151)	**Aflibercept 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**Aflibercept 2 mg Q8[a)] (N =151)**	**Aflibercept 2 mg Q4 (N =154)**	**Active Control (laser) (N =154)**
Mean change in BCVA as measured by ETDRS[e] letter score from Baseline (SD)	10.7 (8.21)	12.5 (9.54)	0.2 (12.53)	11.1 (10.70)	11.5 (13.75)	0.9 (13.94)
Difference in LS mean[b,c,e)] (97.5% CI) p-value	10.45 (7.73, 13.17) p < 0.0001	12.19 (9.35, 15.04) p < 0.0001		10.14 (6.96, 13.32) p < 0.0001	10.64 (7.09, 14.18) p < 0.0001	
Proportion of patients who gained at least 10 letters in BCVA[e)] from Baseline	58.3%	64.9%	19.5%	59.6%	63.6%	27.9%
Adjusted Difference[c,d,e)] (97.5% CI) p-value	38.8 (27.2, 50.3) p < 0.0001	45.9 (34.7, 57.0) p < 0.0001		31.6 (19.5, 43.7) p < 0.0001	36.2 (24.3, 48.1) p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[e)] from Baseline	31.1%	41.6%	7.8%	33.1%	38.3%	13.0%

Adjusted Difference[c,d,e)] (97.5% CI) p-value	23.3% (13.5, 33.1) p < 0.0001	34.2% (24.1, 44.4) p < 0.0001		20.1% (9.6, 30.6) p < 0.0001	25.8% (15.1, 36.6) p < 0.0001	
Proportion of patients with an improvement of >= 2 steps on the ETDRS DRSS [e,f)] from Baseline	29.1%	33.8%	14.3%	37.1%	37.0%	15.6%
Adjusted Difference [c,d)] (97.5% CI) p-value	14.9 (4.4, 25.4) p = 0.0017	19.7 (9.0, 30.4) p < 0.0001		21.5 (10.4, 32.5) p = 0.0001	21.7 (10.8, 32.6) p < 0.0001	
See Table 7 for Mean Change in CRT from Baseline						
Mean change in NEI VFQ-25[e)] near activities subscale from Baseline	9.4 (18.50)	9.0 (20.60)	5.4 (20.44)	12.8 (21.36)	10.9 (23.12)	8.1 (22.10)
Difference in LS mean [b,c,e)] (97.5% CI) p-value	4.36 (-0.21, 8.93) p = 0.0323	5.19 (0.33, 10.04) p = 0.0168		5.05 (0.12, 9.98) p = 0.0218	4.59 (-0.73, 9.90) p = 0.0529	
Mean change in NEI VFQ-25[e)] distance activities subscale from Baseline	7.3 (19.32)	8.6 (20.99)	6.7 (19.85)	8.5 (20.35)	10.9 (22.05)	6.1 (20.42)
Difference in LS mean [b,c,e)] (97.5% CI) p-value	1.65 (-2.83, 6.13) p = 0.4067	2.86 (-1.82, 7.54) p = 0.1702		3.57 (-0.96, 8.11) p = 0.0772	5.80 (0.97, 10.64) p = 0.0072	

a) After treatment initiation with 5 monthly injections
b) LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as a factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}.
c) Difference is aflibercept group minus active control (laser) group
d) Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID^{DME} and medical history of MI or CVA for VISTA^{DME}
e) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA
DRSS: Diabetic Retinopathy Severity Scale
CI: Confidence interval
NEI VFQ-25: National Eye Institute Visual Function Questionnaire
f) VIVID^{DME}: based on the patients with gradable images at baseline and post-baseline [week 52: n=83 (aflibercept 2 mg Q8), n=81 (aflibercept 2 mg Q4), n=80 (laser); week 100: n=86 (aflibercept 2 mg Q8), n=82 (aflibercept 2 mg Q4), n=85 (laser)]

Figure 4: Mean change in BCVA as measured ETDRS letter score from baseline to Week 100 in VIVID[DME] and VISTA[DME] studies



At week 52, 33.3% and 33.8% of 2Q4 patients, 27.7% and 29.1% of 2Q8 patients, and 7.5% and 14.3% of laser control patients in the VIVID[DME] and VISTA [DME] studies, respectively experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in the diabetic retinopathy severity scale (DRSS). This improvement was maintained through week 100 (see Table 12).

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study and in the combined analysis were generally consistent with the results in the overall populations.

In the VIVID [DME] and VISTA [DME] studies, 36 (8.9%) and 197 (42.9%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naive prior to study participation.

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye. In the VISTA [DME] study, 217 (70.7%) of aflibercept patients received bilateral aflibercept injections until week 100; in the VIVID [DME] study, 97 (35.8%) of aflibercept patients received a different anti-VEGF treatment in their fellow eye until week 100.

An independent comparative trial (DRCR.net Protocol T) utilised a flexible dosing regimen based on strict OCT and vision re-treatment criteria. In the aflibercept treatment group (n = 224) at week 52,

this treatment regimen resulted in patients receiving a mean of 9.2 injections and mean gain of 13.3 letters, which was similar to the aflibercept 2Q8 group in VIVID ^{DME} and VISTA ^{DME}. (Mean number of injections: 8.7 and 8.4. Mean vision acquity improvement 10.7 letters). 42% of patients gained at least 15 letters in vision from baseline which also comparable to VIVID ^{DME} and VISTA ^{DME} E (33.3% and 31.1% respectively). Safety outcomes demonstrated that overall incidence of ocular and non-ocular adverse events (including ATEs) were comparable across all treatment groups in each of the studies and between the studies.

A propensity score matching methodology (PSM) analysis compared the flexible aflibercept treatment group in Protocol T with the combined 2Q8 treatment groups in VIVID and VISTA.

This PSM identified, subsets of 179 matched patients from pooled VIVID ^{DME} and VISTA ^{DME} (utilising a fixed aflibercept dosing regimen) and Protocol T (utilising a flexible dosing regimen based on strict OCT and vision re-treatment criteria).

The PSM analysis showed that mean change in BCVA from baseline at week 52 was 10.9 letters in the 2 mg aflibercept 2Q8 fixed dosing regimen (VIVID ^{DME} and VISTA ^{DME}) and 13.7 letters in the 2 mg aflibercept flexible dosing regimen (Protocol T).

VIOLET was a 100-week multicentre, randomised, open-label, active controlled study in 463 patients with DME. Patients were randomised in a 1:1:1 ratio to three regimens of aflibercept 2 mg for treatment of DME after at least one year of treatment at fixed intervals, where treatment was initiated with 5 consecutive monthly doses followed by dosing every 2 months. The study evaluated non-inferiority of

- Aflibercept 2 mg dosed according to a treat-and-extend regimen (2T&E) where treatment intervals were maintained at a minimum of 8 weeks and gradually extended based on clinical and anatomical outcomes. The increments and decrements for the treatment intervals were at the investigator's discretion; increments of 2 weeks were recommended in the study, and
- Aflibercept 2 mg dosed as needed (2PRN) where patients were observed every 4 weeks and injected when needed based on clinical and anatomical outcomes,

compared to aflibercept 2 mg dosed every 8 weeks (2Q8).

The primary efficacy endpoint (change in BCVA from baseline to week 52) was 0.5 ± 6.7 letters in the 2T&E group and 1.7 ± 6.8 letters in the 2PRN group compared to 0.4 ± 6.7 letters in the 2Q8 group, achieving statistical non-inferiority (NI) ($p<0.0001$ for both comparisons; NI margin 4 letters). The changes in BCVA from baseline to week 100 were consistent with the week 52 results: -0.1 ± 9.1 letters in the 2T&E group and 1.8 ± 9.0 letters in the 2PRN group compared to 0.1 ± 7.2 letters in the 2Q8 group. The mean number of injections over 100 weeks were 10.0, 11.5 and 12.3 for 2T&E, 2PRN and 2Q8, respectively.

Ocular and systemic safety profiles in all 3 treatment groups were similar to those observed in the pivotal studies VIVID and VISTA.

Myopic choroidal neovascularisation (myopic CNV)

The safety and efficacy of aflibercept were assessed in a randomised, multi-centre, double-masked, sham-controlled study (MYRROR) in patients with myopic CNV. A total of 121 patients were treated and evaluable for efficacy (90 with aflibercept). Patients were randomly assigned in a 3:1 ratio to either 2 mg aflibercept administered once at study start (with additional injections given in the case of disease persistence or reoccurrence) or sham injections. In total 6 injections was possible until the week 24 primary endpoint assessment in the study.

After the first 6 months, patients initially randomised to sham were eligible to receive the first dose of aflibercept at week 24. Following this, patients in this former sham arm and also patients in the

arm initially randomised to active treatment continued to be eligible for additional injections in case of disease persistence or recurrence.

Patient ages ranged from 27 to 83 years with a mean of 58 years. Approximately 36% (33/91) of the patients randomised to treatment with aflibercept were 65 years of age or older, and approximately 10% (9/91) were 75 years of age or older.

The primary efficacy endpoint was the change in visual acuity at week 24 compared to baseline. The confirmatory secondary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.

The difference between treatment groups was statistically significant in favour of aflibercept for the primary and confirmatory secondary efficacy endpoints at week 24. Differences for both endpoints were maintained through week 48.

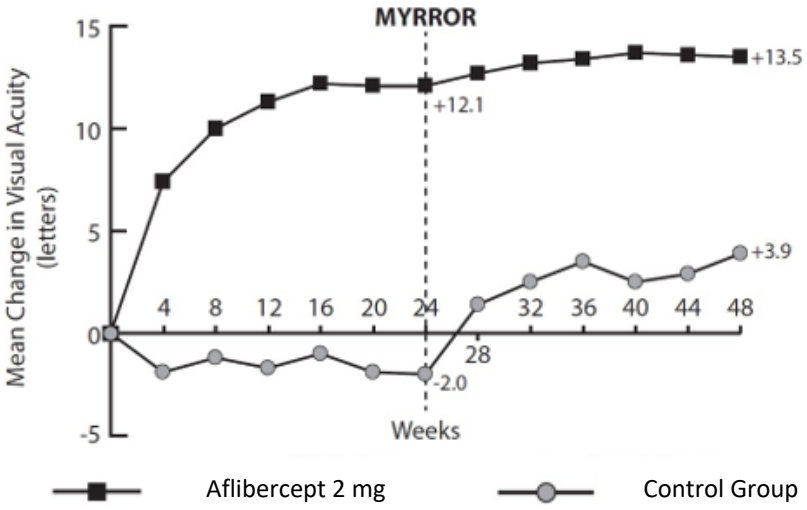
Detailed results from the analyses are shown in Table 13 and Figure 5 below.

Table 13: Efficacy outcomes at week 24 (primary analysis) and in week 48 in MYRROR study (Full Analysis Set with LOCF[a])

MYRROR				
Efficacy Outcomes	**24 Weeks**		**48 Weeks**	
	Aflibercept 2 mg[b] (N = 90)	**Sham (N = 31)**	**Aflibercept 2 mg[c] (N = 90)**	**Sham / Aflibercept 2 mg[d] (N = 31)**
Mean change in BCVA letter score as measured by ETDRS from baseline (SD)[e]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean [f,g,h,i] (95% CI) p-value	14.1 (10.8, 17.4) p < 0.0001		9.5 (5.4, 13.7) p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[e] from baseline	38.9%	9.7%	50.0%	29.0%
Weighted difference [f,h,j] (95% CI) p-value	29.2% (14.4, 44.0) p = 0.0001		21.0% (1.9, 40.1) p = 0.0308	

a) LOCF: Last Observation Carried Forward
b) Aflibercept 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.
c) Aflibercept 2 mg administered from week 24 through week 44 potentially every 4 weeks in case of disease persistence or recurrence
d) Mandatory injection of aflibercept 2 mg at week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through week 44.
e) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
SD: Standard Deviation
f) Difference is aflibercept 2 mg minus sham at Week 24 and aflibercept 2 mg minus sham/ aflibercept 2 mg at week 48.
g) LS mean: Least square means derived from ANCOVA model
h) CI: Confidence Interval
i) LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant.
j) Difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for country (country designations)

Figure 5: Mean change from baseline to week 48 in visual acuity by treatment group for the MYRROR study (Full Analysis Set, LOCF)



Treatment effects in all evaluable subgroups were in general, consistent with the results in the overall populations.

Comparability of EYDENZELT with EYLEA

The clinical comparability between EYDENZELT and EYLEA was demonstrated in randomised controlled double masked parallel group Phase 3 study in patients with Diabetic Macula Oedema (DME).

The result of a primary endpoint, the mean change from baseline in BCVA at Week 8 between the EYDENZELT and EYLEA treatment groups, is presented in Table 14 below. The estimate of treatment difference in LS means change from baseline in BCVA between EYDENZELT and EYLEA at Week 8 was 0.58 letters and the 95% CI was [-0.73, 1.88], which was entirely within the predefined equivalence margin of ± 3 letters.

Table 14: Analysis of Mean Change from Baseline in BCVA at Week 8 in Study CT-P42 3.1 (Full Analysis Set)

Timepoint	Treatment	n	LS Mean (SE)	Estimate of Treatment Difference in LS Means (EYDENZELT – EYLEA) [a)]	
				Mean	[95% CI]
Week 8	EYDENZELT (N=173)	169	9.43 (0.798)	0.58	[-0.73, 1.88]
	EYLEA (N=175)	172	8.85 (0.775)		

ANCOVA = analysis of covariance; BCVA = best corrected visual acuity; CI = confidence interval; LS mean = least squares mean; N = total number of patients; n = total number of patients with BCVA score at Week 8; SE = standard error

[a)] An ANCOVA was performed with change from baseline in BCVA at Week 8 as the dependent variable, treatment as a factor, and baseline BCVA and country as covariates.

5.2 PHARMACOKINETIC PROPERTIES

Aflibercept is administered directly into the vitreous to exert local effects in the eye.

Absorption / Distribution

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominantly observed in the systemic circulation as an inactive, stable complex with VEGF; however only free aflibercept is able to bind endogenous VEGF.

In a pharmacokinetic sub-study with frequent sampling in patients with wet AMD, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 µg/mL (range 0 to 0.054) within 1 to 3 days after 2 mg intravitreal injection, and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

These pharmacokinetic results were consistent in pharmacokinetic sub-studies in patients with CRVO, BRVO, DME or myopic CNV, with mean C_{max} of free aflibercept in plasma in the range of 0.03 to 0.05 µg/mL and individual values not exceeding 0.14 µg/mL. Thereafter, plasma concentrations of free aflibercept declined to values below or close to the lower limit of quantitation generally within one week; undetectable concentrations were reached before the next administration after 4 weeks in all patients.

Table 15: Tabulated summary of free aflibercept in plasma by indication

Indication	Mean Cmax of free Aflibercept (µg/mL)
Wet AMD	0.02 (0 – 0.054)
DME	0.03 (0 – 0.076)
CRVO	0.05 (0 – 0.081)
Myopic CNV	0.03*

* Based on a single subject

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF. Therefore, systemic pharmacodynamic effects are unlikely.

Biotransformation

As aflibercept is a protein-based therapeutic, no metabolism studies have been conducted.

Elimination

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted on the mutagenic or clastogenic potential of aflibercept. As a large protein molecule, aflibercept is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No studies have been conducted on the carcinogenic potential of aflibercept.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polysorbate 20

Histidine

Histidine hydrochloride monohydrate

Sodium chloride

Trehalose

Water for injections

6.2 INCOMPATIBILITIES

EYDENZELT must not be mixed with other medicinal products.

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

Keep the vial in its carton in order to protect from light.

Once removed from the refrigerator the product must be discarded if not used. It must not be returned to the refrigerator.

Keep the pre-filled syringe in its blister pack and carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

EYDENZELT is supplied in a single-use vial or pre-filled syringe.

Vial

Each carton includes a type I glass vial containing approximately 0.1 mL of extractable volume, with an elastomeric rubber stopper, and an 18 G x 38.1 mm 5 micron sterile filter needle for single-use only.

The intravitreal injection should be performed with a 30G x 12.7 mm injection needle and 1 mL Luer lock syringe (not included). Ensure a 30G x 12.7 mm injection needle and 1 mL Luer lock syringe are available.

Pre-filled syringe

Each carton includes a sealed blister pack with a sterile pre-filled Luer lock syringe, containing approximately 0.9 mL of extractable volume, sealed with an elastomeric plunger stopper and an elastomeric tip cap that is part of a closure system with Luer lock adaptor. The syringe has a pre-attached plunger rod and a finger flange.

The intravitreal injection should be performed with a 30-gauge x 12.7 mm sterile injection needle (not included). Ensure a 30-gauge x 12.7 mm injection needle is available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Instructions for use / handling

The pre-filled syringe and vial are for single use in one eye only. Extraction of multiple doses from a single vial or pre-filled syringe may increase the risk of contamination and subsequent infection.

Do not use if the package or its components are expired, damaged, or have been tampered with.

The pre-filled syringe contains more than the recommended dose of 2 mg EYDENZELT (equivalent to 50 microlitres).

Prior to administration visually inspect the solution for injection. Do not use the vial or pre-filled syringe if particulates, cloudiness, or discolouration are visible. Do not use if any part of the pre-filled syringe is damaged or loose, or if the syringe cap is detached from the Luer-lock.

Prior to usage, the EYDENZELT unopened vial or pre-filled syringe blister pack may be stored at room temperature (25°C) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.

Caution: Storage condition for EYDENZELT is at 2°C to 8°C and keep the vial or pre-filled syringe blister pack in its carton in order to protect from light.

Once removed from the refrigerator the product must be discarded if not used. It must not be returned to the refrigerator.

For the intravitreal injection a 30 G x 12.7 mm injection needle should be used.

Note for the Filter Needle provided with the vial pack:

Filter (Fill) Needle, **not** for skin injection.

Do **not** autoclave the Filter (Fill) Needle.

The filter needle is non-pyrogenic. Do **not** use it if individual packaging is damaged.

Discard the use Filter (Fill) Needle in approved sharps collector.

Caution: Re-use of the filter needle may lead to infection or other illness/ injury.

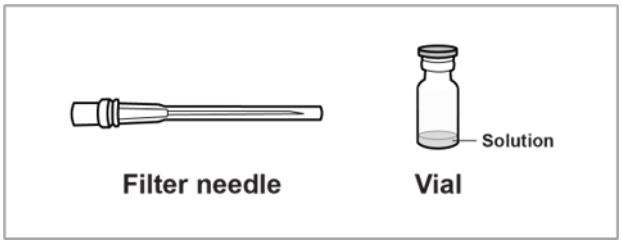
For intravitreal injection vial

The EYDENZELT vial kit includes the following single use materials:

- 18G x 38.1 mm, 5 micron sterile filter needle
- Vial

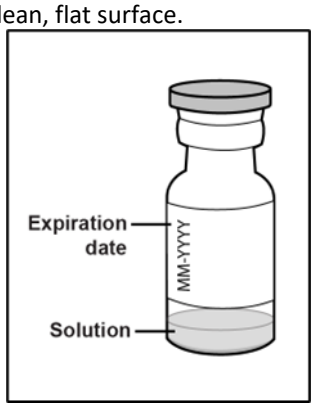
Supplies <u>not</u> included in the kit:

- 30G x 12.7 mm injection needle
- 1 mL Luer lock Syringe

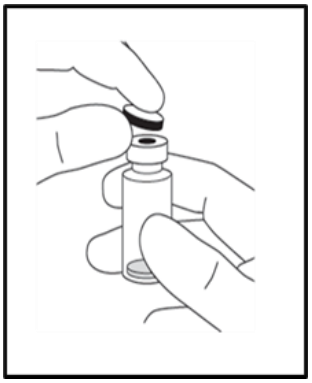


1. **Gather your supplies.**
   Using aseptic technique, gather your supplies and place them on a clean, flat surface.
2. **Inspect EYDENZELT**
   Look at the vial and make sure you have the correct medicine (EYDENZELT) and dosage.

   Check the expiration date on the label to make sure it has not passed.
   - **Do not** use EYDENZELT if particulates, cloudiness, or discoloration are visible.
   - **Do not** use if the expiration date has passed.



3. Remove the protective plastic cap from the vial



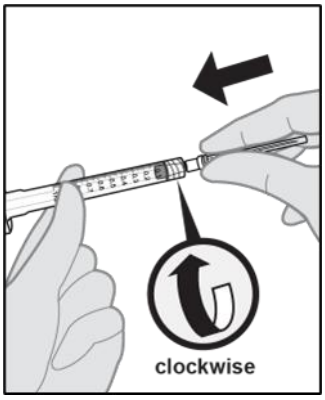
4. Disinfect the outer part of the rubber stopper of the vial with an alcohol wipe



5. Attach the filter needle to the syringe

Remove the 18G × 38.1 mm, 5-micron filter needle, supplied in the carton, and a 1 mL Luer lock syringe, not included in the carton, from their packaging.

Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip.



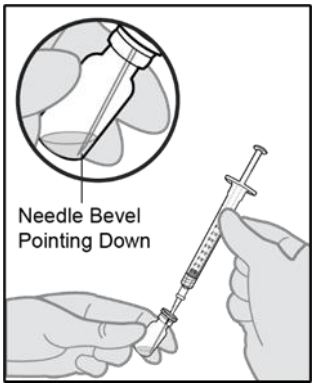
6. Insert the filter needle into the vial

Using aseptic technique, push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial, and the tip touches the bottom or bottom edge of the vial.

Tilt the vial during withdrawal, keeping the bevel of the filter needle submerged in the liquid to deter the introduction of air.

Withdraw all of the EYDENZELT vial contents into the syringe.

Note: Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.



7. Remove the filter needle.

Remove the filter needle from the syringe.

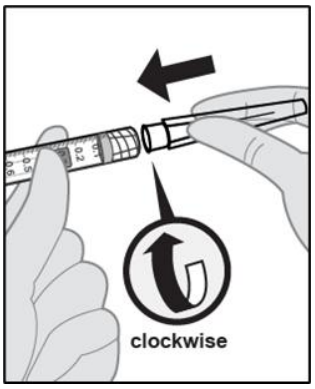
Properly dispose of the filter needle.

- **Do not** use the filter needle for intravitreal injection.
- **Do not** recap the filter needle to prevent pre-injection needle sticks.

8. Attach the injection needle to the syringe.

Remove the 30G × 12.7 mm injection needle, not included in the carton, from its packaging.

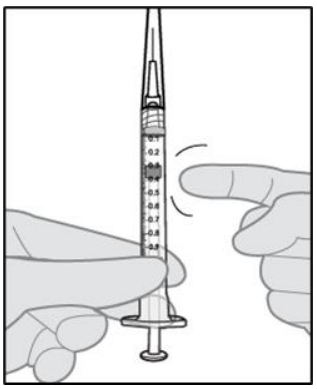
Using aseptic technique, attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip.



9. Check for air bubbles.

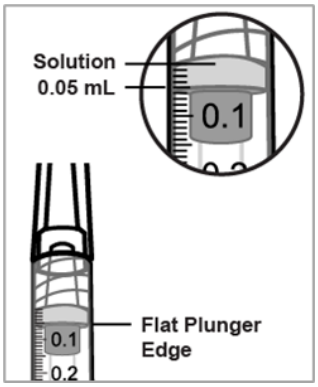
Holding the syringe with the injection needle pointing up, check for air bubbles in the syringe.

If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

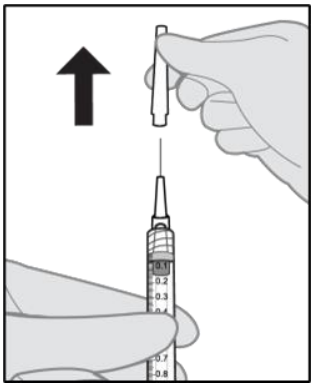


10. Remove air bubbles and confirm correct dose.

To remove all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe.



11. When ready to administer EYDENZELT, remove the plastic needle cap from the needle.



12 When ready, complete the intravitreal injection.

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYDENZELT is administered to the other eye.

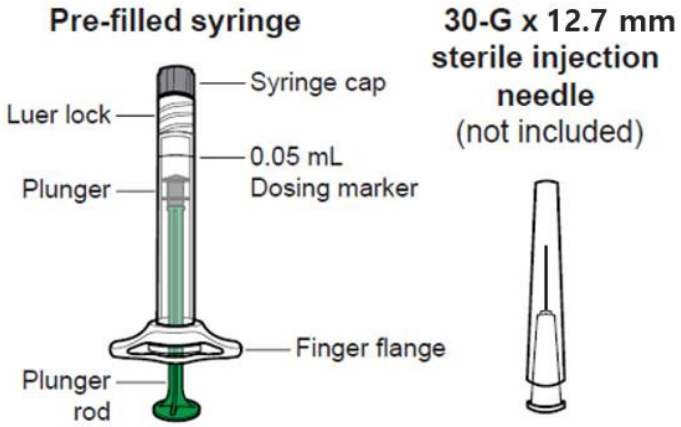
13 The vial is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection.

14 After the injection, monitor the patient.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.
Following intravitreal injection, patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

For intravitreal injection pre-filled syringe



The EYDENZELT PFS includes the following single use materials:

- sterile pre-filled Luer lock syringe sealed

Supplies <u>not</u> included:

- 30G x 12.7 mm injection needle

with an elastomeric plunger stopper and an elastomeric tip cap

1. **Gather your supplies.**
Using aseptic technique, gather your supplies and place them on a clean, flat surface.

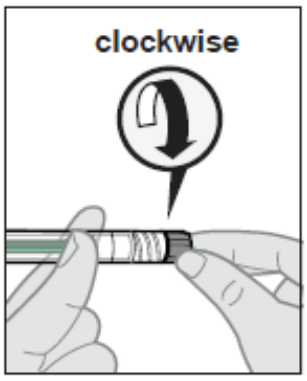
2. **Open the carton.**
When ready to administer EYDENZELT, open the carton and remove the sterilized blister pack. Carefully peel open the sterilized blister pack ensuring the sterility of its contents.
   - **Do not** remove the pre-filled syringe from the sterilized blister pack until you are ready to assemble it with the injection needle.
   - **Do not** use the pre-filled syringe if the expiration date has passed.
   - **Do not** open the sterile pre-filled syringe blister outside the clean administration room

3. **Remove the pre-filled syringe.**
Using aseptic technique, remove the pre-filled syringe from the sterilized blister pack.

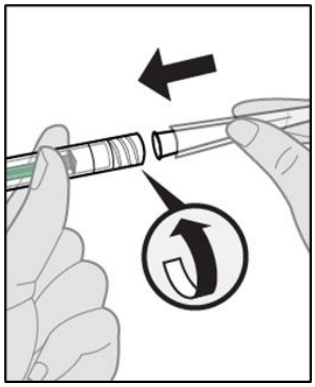
4. **Inspect the pre-filled syringe and drug product.**
4a. Look at the pre-filled syringe and make sure it is not damaged and the syringe cap is attached to the Luer lock.
   - Do not use if any part of the pre-filled syringe is damaged or if the syringe cap is detached from the Luer lock.

4b. Look at the medicine and confirm that it is clear to slightly opalescent, colourless to very pale brownish-yellow, and free of particles.
   - Do not use if particulates, cloudiness, or discoloration are visible.

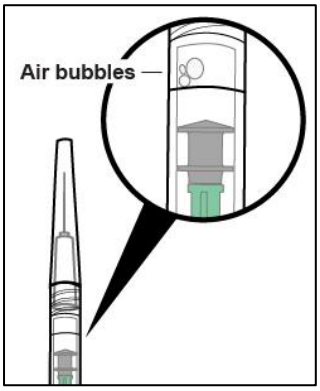
5. **Twist off the syringe cap.**
Twist off the syringe cap by holding the pre-filled syringe in one hand and the syringe cap with the thumb and forefinger of the other hand.
   - Do not snap off the syringe cap.
   - To avoid compromising the sterility of the drug product, do not pull back on the plunger rod.

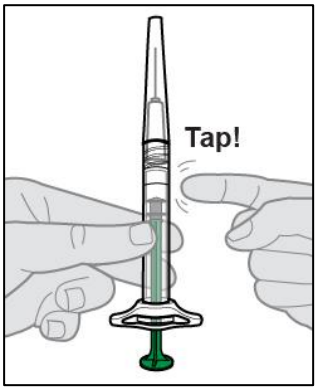


6. **Attach the needle to the pre-filled syringe.**
Using aseptic technique, firmly twist the 30-gauge × 12.7 mm injection needle onto the Luer-lock syringe tip.



7. **Check for air bubbles.**
Hold the pre-filled syringe with the needle pointing up and check the pre-filled syringe for bubbles. If there are bubbles, gently tap the pre-filled syringe with your finger until the bubbles rise to the top.

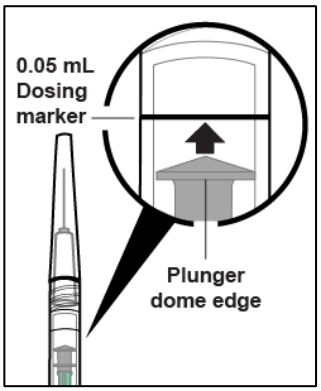


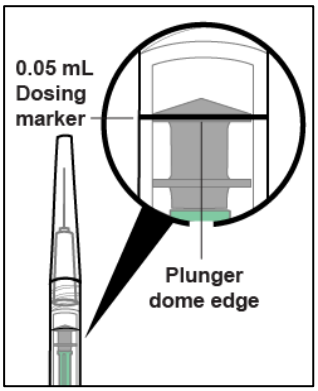


8. **Remove air bubbles and set the dose.**

To remove all bubbles and expel excess drug, SLOWLY depress the plunger rod to align the plunger dome edge with the dosing marker shown on the barrel of the pre-filled syringe (equivalent to 0.05 mL i.e. 2 mg EYDENZELT).

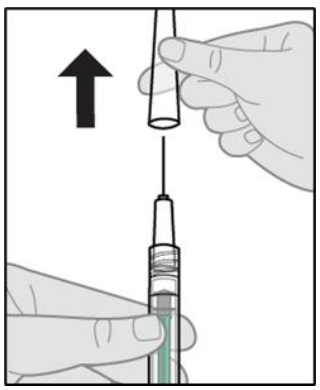
Note: This accurate positioning of the plunger is very important because incorrect plunger positioning can lead to delivering more or less than the labelled dose.





9. **Remove the needle shield.**

When ready to administer EYDENZELT, remove the plastic needle shield from the needle.



10. **When ready, complete the intravitreal injection.**
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Each sterile, pre-filled syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new sterile, pre-filled syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before Eydenzelt is administered to the other eye.

Inject by pressing the plunger rod carefully and with constant pressure. Do not apply additional pressure once the plunger rod has reached the bottom of the syringe. A small residual volume may remain in the syringe after a full dose has been injected. This is normal.

Do not administer any residual solution observed in the syringe.

11. **Inject while pressing the plunger rod carefully and with constant pressure.**

- Do not apply additional pressure once the plunger has reached the bottom of the syringe.
- Do not administer any residual solution observed in the syringe.

12. **The pre-filled syringe is for single use only.**
Extraction of multiple doses from a pre-filled syringe may increase the risk of contamination and subsequent infection. Any unused medical product or waste material should be disposed of in accordance with local requirements.

13. **After the injection, monitor the patient.**
Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

7. MEDICINE SCHEDULE

PRESCRIPTION ONLY MEDICINE

8. SPONSOR

Celltrion Healthcare New Zealand Limited

Celltrion Healthcare New Zealand Limited
Level 1, 46 Stanley Street
Parnell
Auckland 1010, New Zealand

Phone: 0800 838 899

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
23 October 2026

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	New document.