NOTICE OF FILING

Details of Filing

Document Lodged:	Statement of Claim - Form 17 - Rule 8.06(1)(a)
Court of Filing	FEDERAL COURT OF AUSTRALIA (FCA)
Date of Lodgment:	18/06/2025 5:45:31 PM AEST
Date Accepted for Filing:	19/06/2025 8:54:04 AM AEST
File Number:	VID715/2025
File Title:	REGENERON PHARMACEUTICALS, INC. & ORS v SANDOZ PTY LTD (ACN 075 449 553)
Registry:	VICTORIA REGISTRY - FEDERAL COURT OF AUSTRALIA

Registrar

Important Information

This Notice has been inserted as the first page of the document which has been accepted for electronic filing. It is now taken to be part of that document for the purposes of the proceeding in the Court and contains important information for all parties to that proceeding. It must be included in the document served on each of those parties.

The date of the filing of the document is determined pursuant to the Court's Rules.

Form 17
Rule 8.05(1)(a)

Amended Statement of Claim

No. VID 715 of 2025

Federal Court of Australia

District Registry: Victoria

Division: General

Regeneron Pharmaceuticals, Inc. and others

Applicants

Sandoz Pty Ltd (ACN 075 449 553)

Respondent

A. THE PARTIES

1. The First Applicant (**Regeneron**) has been at all material times:

   (a) a company incorporated under the laws of the United States of America; and

   (b) able to sue in its corporate name.

2. The Second Applicant (**Bayer Australia**) has been at all material times:

   (a) a company incorporated under the *Corporations Act 2001* (Cth); and

   (b) able to sue in its corporate name.

3. The Third Applicant (**Bayer Consumer Care**) has been at all material times:

   (a) a company incorporated under the laws of the Swiss Confederation; and

   (b) able to sue in its corporate name.

Filed on behalf of (name & role of party) The Applicants
Prepared by (name of person/lawyer) Aaron Yates, Lawyer; Grant Fisher, Lawyer
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Corrs Chambers Westgarth, 567 Collins Street, Melbourne, VIC, 3000

4. The Respondent (**Sandoz**) is and has been at all material times:

   (a) a company incorporated under the *Corporations Act 2001* (Cth); and

   (b) able to be sued in its corporate name.

B. THE 599 PATENT

5. Regeneron is and was at all material times registered under the *Patents Act 1990* (Cth) (**Act**) as the patentee of Australian Patent No. 2012205599 titled "Use of a VEGF antagonist to treat angiogenic eye disorders" (the **599 Patent**).

5A. Bayer Consumer Care is, and has been since 10 June 2025, the exclusive licensee of the 599 Patent in Australia.

Particulars

(i) Exclusive Licence Deed dated 10 June 2025.

6. The 599 Patent:

   (a) was filed in Australia on 11 January 2012;

   (b) was granted on 2 February 2017; and

   (c) has an expiry date of 11 January 2032 (the **Expiry Date**).

7. The 599 Patent is, and has at all material times been, valid, subsisting and in full force and effect.

C. THE EYLEA AFLIBERCEPT PRODUCTS

8. With Regeneron's authorisation prior to 10 June 2025, and with Bayer Consumer Care's authorisation from on and after 10 June 2025, Bayer Australia offers to supply, supplies, distributes and sells in Australia, pharmaceutical products comprising the active pharmaceutical ingredient aflibercept under the trade name EYLEA® for the intravitreal administration of 2mg (in the form of a vial or pre-filled syringe) of aflibercept (the **2mg Eylea Aflibercept Products**) and 8mg (in the form of a vial) of aflibercept (the **8mg Eylea Aflibercept Products**) (together, the **Eylea Aflibercept Products**).

9. Bayer Australia purchases the Eylea Aflibercept Products from Bayer Consumer Care in Basel, Switzerland, for exclusive distribution, supply and sale in Australia.

10. The Eylea Aflibercept Products are relevantly indicated for the treatment of neovascular (wet) age-related macular degeneration (**wet AMD**) and diabetic macular oedema (**DME**) and are supplied with reference to the Australian Product Information included in **Annexure A**.

Particulars

(ii) The Eylea Aflibercept Products are registered on the Australian Register of Therapeutic Goods (**ARTG**) in the name of the Second Applicant as follows:

ARTG ID	Product name
180859	EYLEA aflibercept (rch) 40 mg/mL solution for intravitreal injection vial with needle
180860	EYLEA aflibercept (rch) 40 mg/mL solution for intravitreal injection pre-filled syringe
405862	EYLEA aflibercept 114.3 mg/mL solution for intravitreal injection vial with needle

(iii) The above information (including the Product Information at **Annexure A**) is publicly available on the ARTG website at https://www.tga.gov.au/resources/artg.

11. The Eylea Aflibercept Products are included on the Schedule of Pharmaceutical Benefits under the Pharmaceutical Benefits Scheme maintained by the Australian Government under the *National Health Act 1953* (Cth) (**PBS**) in the name of Bayer Australia.

Particulars

(i) The Eylea Aflibercept Products are supplied on the PBS in relation to the treatment of wet AMD under the following PBS codes:

(a) 12152N (aflibercept 2 mg/0.05 mL injection)

(b) 13146X (aflibercept 2 mg/0.05 mL injection)

(c) 13167B (aflibercept 2 mg/0.05 mL injection)

(d) 2168D (aflibercept 2 mg/0.05 mL injection)

(e) 14594D (aflibercept 8 mg/0.07 mL injection)

(f) 14626T (aflibercept 8 mg/0.07 mL injection)

(ii) The Eylea Aflibercept Products are supplied on the PBS in relation to the treatment of DME under the following PBS codes:

(a) 10505X (aflibercept 2 mg/0.05 mL injection)

(b) 12153P (aflibercept 2 mg/0.05 mL injection)

(c) 13150D (aflibercept 2 mg/0.05 mL injection)

(d) 13164W (aflibercept 2 mg/0.05 mL injection)

(e) 14627W (aflibercept 8 mg/0.07 mL injection)

(f) 14635G (aflibercept 8 mg/0.07 mL injection)

(iii) The above information is publicly available on the PBS website at https://www.pbs.gov.au/medicine/item/10505X-11991D-12131L-12132M-12141B-12152N-12153P-13138L-13139M-13141P-13146X-13150D-13151E-13164W-13167B-14594D-14626T-14627W-14635G-2168D.

D. SANDOZ'S CONDUCT

12. On 27 May 2025, Sandoz obtained registration on the ARTG for pharmaceutical products in the form of a vial or a pre-filled syringe comprising aflibercept and having the trade names "Afqlir" and "Enzeevu" (each a **Sandoz Aflibercept Product** and together the **Sandoz Aflibercept Products**) as biosimilar medicines to the 2mg Eylea Aflibercept Products.

Particulars

(i) The Sandoz Aflibercept Products with the trade name "Afqlir" are registered on the ARTG in the name of Sandoz as follows:

ARTG ID	Product name
445959	AFQLIR aflibercept 40 mg/mL solution for intravitreal injection pre-filled syringe
445960	AFQLIR aflibercept 40 mg/mL solution for intravitreal injection vial with needle

(ii) The Sandoz Aflibercept Products with the trade name "Enzeevu" are registered on the ARTG in the name of Sandoz as follows:

ARTG ID	Product name
445957	ENZEEVU aflibercept 40 mg/mL solution for intravitreal injection pre-filled syringe
445958	ENZEEVU aflibercept 40 mg/mL solution for intravitreal injection vial with needle

(iii) The above information is publicly available on the ARTG website at https://www.tga.gov.au/resources/artg.

13. At a date presently unknown to the Applicants, but prior to 2 April 2025, Sandoz applied to list Sandoz Aflibercept Products on the PBS.

14. Sandoz has threatened to and intends to:

(a) import;

(b) offer to sell, supply or otherwise dispose of;

(c) sell, supply or otherwise dispose of;

(d) keep for the purpose of selling, supplying or otherwise disposing of; and

(e) authorise others to use,

the Sandoz Aflibercept Product having the trade name "Afqlir" in Australia from September 2025 during the term of the 599 Patent and the Sandoz Aflibercept Product having the trade name "Enzeevu" in Australia from 1 January 2026 during the term of the 599 Patent.

Particulars to paragraphs 13 and 14

(i) Letter from MinterEllison to Griffith Hack dated 30 April 2025 (**30 April Letter**).

(ii) Letter from Corrs Chambers Westgarth to MinterEllison dated 7 May 2025.

(iii) Letter from MinterEllison to Corrs Chambers Westgarth and Davies Collison Cave Law dated 12 May 2025 (**12 May Letter**).

(iv) Letter from MinterEllison to Corrs Chambers Westgarth and Davies Collison Cave Law dated 3 June 2025 (**3 June Letter**).

(v) In respect of the Sandoz Aflibercept Product having the trade name "Enzeevu", the threat to and intention to do each of the matters alleged may also be inferred from the facts alleged in paragraph 13 above.

Copies of the letters mentioned above can be inspected by appointment at the Applicants' solicitors' offices.

15. Neither Regeneron, before 10 June 2024, nor Bayer Consumer Care, from on and after 10 June 2025, has ~~not~~ authorised Sandoz to engage in the conduct alleged in paragraph 14 above.

E. THREATENED INFRINGEMENT OF THE 599 PATENT

Sandoz VEGF Antagonist

16. Each Sandoz Aflibercept Product is a solution for intravitreal injection comprising a VEGF antagonist wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising:

    (a) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2 in paragraph [0069] of the 599 Patent (**SEQ ID NO:2**);

    (b) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and

    (c) a multimerization component comprising amino acids 232 to 457 of SEQ ID NO:2,

    (the **Sandoz VEGF Antagonist**)

Particulars

(i) Pages 41 to 42 of the Australian Product Information for AFQLIR annexed to the 12 May Letter and reproduced at **Annexure B** (**AFQLIR Product Information**).

(ii) Pages 41 to 43 Australian Product Information for ENZEEVU annexed to the 12 May 2025 Letter and reproduced at **Annexure C** (**ENZEEVU Product Information**).

17. None of the Sandoz Aflibercept Products is a staple commercial product within the meaning of s 117(2)(b) of the Act.

The Wet AMD Use

18. The Sandoz Aflibercept Products are indicated in adults for the treatment of wet AMD.

19. Wet AMD is an angiogenic eye disorder and is a form of age-related macular degeneration.

20. Sandoz has notified, or threatens to notify, medical practitioners and consumers that Sandoz Aflibercept Products can be used in a method for the treatment of wet AMD in a patient, said method comprising sequentially administering to the patient:

    (a) a single initial dose of the Sandoz VEGF Antagonist;

    (b) followed by two secondary doses of the Sandoz VEGF Antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose;

    (c) followed by one or more tertiary doses of the Sandoz VEGF Antagonist, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose; and

    (d) wherein all doses of the Sandoz VEGF antagonist comprise 2 mg of the Sandoz VEGF Antagonist,

    (the **Wet AMD Use**).

Particulars

(i) Page 2 of the AFQLIR Product Information at **Annexure B**, which states that for the treatment of wet AMD, "*AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg injection per month for three consecutive months, followed by one injection every two months*."

(ii) Page 2 of the ENZEEVU Product Information at **Annexure C**, which states that for the treatment of wet AMD, "*ENZEEVU 2 mg treatment is initiated with one ENZEEVU 2 mg injection per month for three consecutive months, followed by one injection every two months.*"

21. By reason of the matters alleged in the preceding paragraph, the Wet AMD Use of Sandoz Aflibercept Products would infringe each of claims 1, 3, 4, 5 and 12, of the 599 Patent.

22. By reason of the matters alleged in paragraphs 12 to 20, Sandoz has reason to believe that Sandoz Aflibercept Products will be put to the Wet AMD Use.

Particulars

(i) The particulars to paragraphs 14, 16 and 20 are referred to and repeated.

23. The Wet AMD Use of Sandoz Aflibercept Products by a person would infringe each of claims 1, 3, 4, 5 and 12 of the 599 Patent.

The DME Use

24. The Sandoz Aflibercept Products are indicated in adults for the treatment of DME.

25. DME is an angiogenic eye disorder.

26. Sandoz has notified, or threatens to notify, medical practitioners and consumers that the Sandoz Aflibercept Products can be put to a use in a method for the treatment of DME in a patient, said method comprising sequentially administering to the patient:

(a) a single initial dose of the Sandoz VEGF Antagonist;

(b) followed by one or more secondary doses of the Sandoz VEGF Antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose;

(c) followed by one or more tertiary doses of the Sandoz VEGF Antagonist, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose; and

(d) wherein all doses of the Sandoz VEGF Antagonist comprise 2 mg of the Sandoz VEGF Antagonist,

(the **DME Use**).

Particulars

(i) Page 3 of the AFQLIR Product Information at **Annexure B**, which states that for the treatment of DME, "*AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg 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…".

(ii) Page 3 of the ENZEEVU Product Information at **Annexure C**, which states that for the treatment of DME, "*ENZEEVU 2 mg treatment is initiated with one ENZEEVU 2 mg injection per month for five consecutive months.*
Following the initiation period and based on the ophthalmologist's judgement of visual and/or anatomic outcomes, the treatment interval may then be maintained at an injection every two months…".

27. By reason of the matters alleged in the preceding paragraph, the DME Use of Sandoz Aflibercept Products would infringe each of claims 1, 4 and 12 of the 599 Patent.

28. By reason of the matters alleged in paragraphs 12 to 17 and 24 to 26 above, Sandoz has reason to believe that Sandoz Aflibercept Products will be put to the DME Use.

Particulars

(i) The particulars to paragraphs 14, 16 and 26 are referred to and repeated.

29. The DME Use of Sandoz Aflibercept Products by a person would infringe each of claims 1, 4 and 12, of the 599 Patent.

Threatened Infringement by Sandoz

30. By reason of the matters alleged in paragraphs 12 to 29 above, Sandoz has:

(a) threatened to infringe each of claims 1, 3, 4, 5 and 12 (**Asserted Claims**) pursuant to sections 117(1) and (2)(b) of the Act;

(b) further and in the alternative, threatened to authorise a person to infringe each of the Asserted Claims; and

(c) further and in the alternative, threatened to procure or induce the infringement of each of the Asserted Claims.

31. Further and in the alternative:

(a) the AFQLIR Product Information and the ENZEEVU Product Information (together, the **Sandoz Product Information**) are instructions or inducements for the use of the Sandoz Aflibercept Products;

(b) the Sandoz Product Information are published by or with the authority of Sandoz;

(c) the Wet AMD Use of Sandoz Aflibercept Products constitutes use of those products in accordance with the Sandoz Product Information; and

(d) the DME Use of Sandoz Aflibercept Products constitutes use of those products in accordance with the Sandoz Product Information.

Particulars

(i) The particulars to paragraphs 14, 16, 20 and 26 are referred to and repeated.

32. By reason of the matters alleged in paragraphs 12 to 29 and 31 above, Sandoz has:

(a) threatened to infringe each of the Asserted Claims pursuant to sections 117(1) and (2)(c) of the Act;

(b) further and in the alternative, threatened to authorise a person to infringe each of the Asserted Claims; and

(c) further and in the alternative, threatened to procure or induce the infringement of each of the Asserted Claims.

F. THREATENED CONTRAVENTION OF THE AUSTRALIAN CONSUMER LAW BY SUPPLY OF THE SANDOZ AFLIBERCEPT PRODUCTS

33. By engaging in the conduct pleaded in paragraphs 14, 20, 26, and 31 above, and in the absence of any warning to the contrary, Sandoz will make each of the following representations (the **Representations**):

(a) Sandoz is entitled to, or has all necessary authority to, recommend or permit the use of the Sandoz Aflibercept Products for the Wet AMD Use and the DME Use.

(b) Third parties have all necessary authority to use Sandoz Aflibercept Products for the Wet AMD Use and/or the DME Use.

Particulars

(i) 30 April Letter.

(ii) 12 May Letter.

(iii) 3 June Letter.

Copies of the letters mentioned above can be inspected by appointment at the Applicants' solicitors' offices.

34. The conduct alleged in paragraph 33 above is conduct in trade or commerce in Australia.

35. The Representations are false, in that the Wet AMD Use and / or the DME Use of the Sandoz Aflibercept Products by a third party in Australia will infringe one or more of the Asserted Claims of the 599 Patent unless authorised before 10 June 2025 by Regeneron, and from on and after 10 June 2025 by Bayer Consumer Care, ~~Regeneron~~ and neither Regeneron nor Bayer Consumer Care has provided ~~no~~ any such authority.

Particulars

(i) The matters alleged in paragraphs 16 to 32 are referred to and repeated.

36. By reason of the matters alleged in paragraphs 33 to 35 above, Sandoz has engaged in conduct which is misleading or deceptive or which is likely to mislead or deceive in contravention of section 18 of the *Australian Consumer Law* (**ACL**) as contained in Schedule 2 to the *Competition and Consumer Act 2010* (Cth).

G. LOSS AND DAMAGE

37. Sandoz threatens and intends to and will, if not restrained by this Honourable Court, infringe the 599 Patent in the manner threatened.

38. If not restrained, Sandoz will make profits.

Particulars

(i) Regeneron and Bayer Consumer Care ~~is~~ are unable to provide, at this time, a quantification of the precise

profits of Sandoz and reserves their ~~its~~ right to claim at trial any and all relief to which ~~it is~~ they are entitled.

39. If Sandoz is not restrained, Regeneron and Bayer Consumer Care will suffer substantial loss and damage.

40. The Applicants, by reason of Sandoz's threatened contravention of the ACL alleged in paragraphs 33 to 36 above, will suffer substantial loss and damage.

Particulars to paragraphs 38 and 39

(i) Loss of profits from the sale of the Eylea Aflibercept Products in Australia.

(ii) Reduction in the price at which the Eylea Aflibercept Products can be sold in Australia, including by operation of Part VII, Division 3A, Subdivision B and Part VII, Division 3B of the *National Health Act 1953* (Cth).

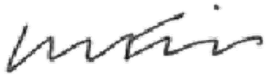
(iii) Reduction in the price at which the Eylea Aflibercept Products can be made available under the PBS.

(iv) Loss of profits from the sale of the Eylea Aflibercept Products by Bayer Consumer Care to Bayer Australia.

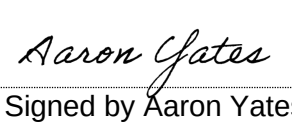
(v) The Applicants expressly reserve their right to seek additional damages under section 122(1A) of the Act if Sandoz seeks to supply or exploit Sandoz Aflibercept Products, despite these proceedings, and the correspondence between the parties, and the Applicants will rely on that fact at trial, together with any other relevant matters.

AND THE APPLICANTS CLAIM THE RELIEF SPECIFIED IN THE ACCOMPANYING ORIGINATING APPLICATION

Date: ~~4~~ 18 June 2025



Signed by Grant Fisher
Lawyer for the First Applicant



Signed by Aaron Yates
Lawyer for the Second and Third Applicant

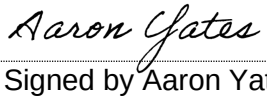
This pleading was prepared by Davies Collison Cave Law Pty Ltd and Corrs Chambers Westgarth and settled by Neil Murray SC, Kate Beattie SC and Clare Cunliffe of counsel.

Certificate of lawyer

We, Grant Fisher and Aaron Yates, certify to the Court that, in relation to the statement of claim filed on behalf of the Applicants, the factual and legal material available to us at present provides a proper basis for each allegation in the pleading.

Date: ~~4~~ 18 June 2025

Signed by Grant Fisher
Lawyer for the First Applicant



Signed by Aaron Yates
Lawyer for the Second and Third Applicant

Annexure A

AUSTRALIAN PRODUCT INFORMATION

EYLEA® aflibercept (rch) solution for intravitreal injection

1. NAME OF THE MEDICINE

Aflibercept (rch)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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

EYLEA 40 mg/mL (vial for 2 mg dosing): Each 1 mL of EYLEA solution contains 40 mg aflibercept. Each vial has a volume of 100 µL solution containing 4 mg aflibercept. This amount is sufficient to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

EYLEA 40 mg/mL (pre-filled syringe for 2 mg dosing): Each 1 mL of EYLEA solution contains 40 mg aflibercept. Each pre-filled syringe has a volume of 90 µL solution containing 3.6 mg aflibercept. This amount is sufficient to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

EYLEA 114.3 mg/mL (vial for 8 mg dosing): Each 1 mL of EYLEA solution contains 114.3 mg aflibercept. Each vial has a volume of 0.263 mL (263 µL) solution containing 30.1 mg aflibercept. This amount is sufficient to deliver a single dose of 70 µL solution for intravitreal injection containing 8 mg aflibercept.

EYLEA 114.3 mg/mL (pre-filled syringe with OcuClick dosing system for 8 mg dosing): Each 1 mL of EYLEA solution contains 114.3 mg/mL aflibercept. Each pre-filled syringe has a volume of 0.184 mL (184 µL) solution containing 21 mg aflibercept. This amount is sufficient to deliver a single dose of 70 µL solution for intravitreal injection containing 8 mg aflibercept.

3. PHARMACEUTICAL FORM

Solution for intravitreal injection.

EYLEA 40 mg/mL (for 2 mg dosing) is a sterile, clear, colourless to pale yellow, preservative-free, iso-osmotic aqueous solution.

EYLEA 114.3 mg/mL (for 8 mg dosing) is a sterile, clear to slightly opalescent, colourless to pale yellow, preservative-free, iso-osmotic aqueous solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EYLEA 2 mg (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).

EYLEA 8 mg (aflibercept) is indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (wet AMD)
- diabetic macular oedema (DME)

4.2 DOSE AND METHOD OF ADMINISTRATION

EYLEA is for intravitreal injection only.

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

Dosage for EYLEA 2 mg (for all approved indications)

The recommended dose for EYLEA 40 mg/mL 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, EYLEA 2 mg should be discontinued.

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

EYLEA 2 mg treatment is initiated with one EYLEA 2 mg injection per month for three consecutive months, followed by one injection every two months.

Based on the ophthalmologist'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)***

EYLEA 2 mg treatment is initiated with one EYLEA 2 mg 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)***

  EYLEA 2 mg treatment is initiated with one EYLEA 2 mg 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)***

  EYLEA 2 mg treatment is initiated with one EYLEA 2 mg injection per month for five consecutive months.

  Following the initiation period and based on the ophthalmologist'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 PHARMACODYNAMIC PROPERTIES, Clinical trials).

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

  EYLEA 2 mg treatment is initiated with one EYLEA 2 mg injection (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.

Dosage for EYLEA 8 mg (for wet AMD and DME indications only)

The recommended dose for EYLEA 114.3 mg/mL is 8 mg aflibercept, equivalent to an injection volume of 70 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. 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, EYLEA 8 mg should be discontinued.

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

EYLEA 8 mg treatment is initiated with one EYLEA 8 mg injection per month for three consecutive months, followed by one injection of EYLEA 8 mg every 8 to 16 weeks based on the ophthalmologist's judgment of visual and/or anatomic outcomes. Treatment with intervals of one month for more than three consecutive months has not been studied (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

- ***Treatment of diabetic macular oedema (DME)***

EYLEA 8 mg treatment is initiated with one EYLEA 8 mg injection per month for three consecutive months, followed by one injection of EYLEA 8 mg every 8 to 16 weeks based on the ophthalmologist's judgment of visual and/or anatomic outcomes. Treatment with intervals of one month for more than three consecutive months has not been studied (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

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 vial, pre-filled syringe or pre-filled syringe with OcuClick dosing system should only be used for the treatment of a single eye. The pre-filled syringe or the glass vial contains more than the recommended dose. Therefore, the **excess volume must be expelled before injecting** (see section 'Instruction for use/handling'). Injecting the entire volume of the glass vial or the pre-filled syringe could result in overdose (see section 4.9 'Overdose').

- EYLEA 40 mg/mL (vial for 2 mg dosing): To administer 2 mg aflibercept (equivalent to 50 µL solution for injection), eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 mL (equivalent to 50 µL) on the syringe before injecting.

- EYLEA 40 mg/mL (pre-filled syringe for 2 mg dosing): To administer 2 mg aflibercept (equivalent to 50 µL solution for injection), eliminate all bubbles and expel excess drug in the pre-filled syringe by slowly depressing the plunger to **align the base of the plunger dome (not the tip of the dome) with the dosing line on the syringe**. This will ensure a delivery equivalent to 50 µL i.e. 2 mg aflibercept.

- EYLEA 114.3 mg/mL (vial for 8 mg dosing): To administer 8 mg aflibercept (equivalent to 70 µL solution for injection), eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.07 mL (equivalent to 70 µL) on the syringe before injecting.

- EYLEA 114.3 mg/mL (pre-filled syringe with OcuClick dosing system for 8 mg dosing): To administer 8 mg aflibercept (equivalent to 70 µL solution for injection), eliminate all bubbles and expel excess drug by slowly depressing the plunger rod until it stops. i.e. when the guide on the plunger rod reaches the finger grip. Set the dose to administer 0.07 mL (equivalent to 70 µL). See the detailed description for the preparing the injecting the solution in the section *'Instructions for use / handling'* below.

After injection any unused product or waste material must be discarded.

- ***Instructions for use / handling***

The vial and the pre-filled syringe are for single use in one eye only. Extraction of multiple doses from a single vial, pre-filled syringe or pre-filled syringe with OcuClick dosing system 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.

Check the label on the vial, pre-filled syringe, or pre-filled syringe with OcuClick dosing system to make sure you have the correct EYLEA strength.

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 EYLEA 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.

For the intravitreal injection a 30 G x ½ inch injection needle should be used.

Note for the Filter Needle provided with the vial pack:

Filter (Fill) Needle, is **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.

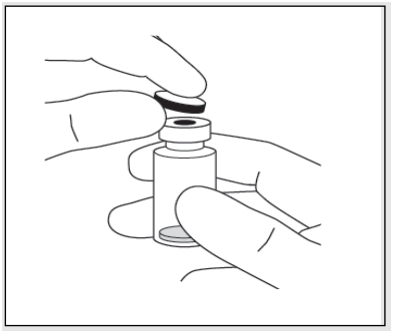
Discard the used Filter (Fill) Needle in approved sharps collector.

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

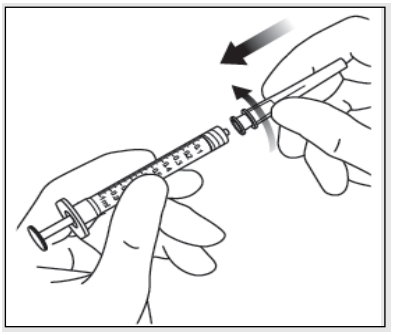
Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

EYLEA 40 mg/mL Vial (for 2 mg dosing)

1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.

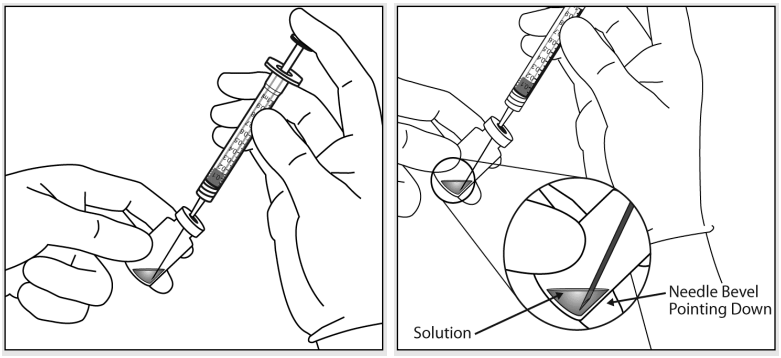


2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1 mL sterile, Luer-lock syringe.



3. Push the filter needle into the centre 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.

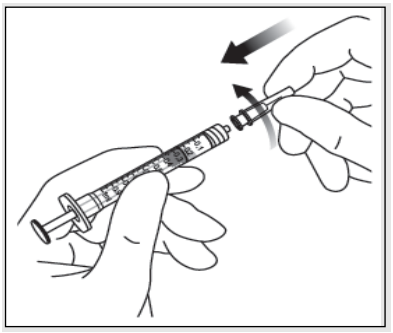
4. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.



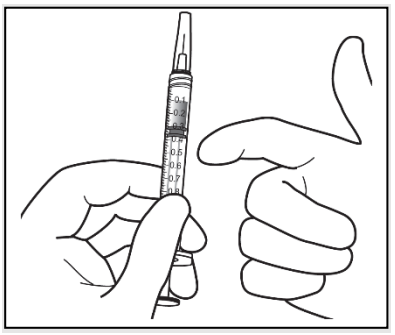
5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

6. Remove the filter needle and properly dispose of it. Note: Filter needle is not to be used for intravitreal injection.

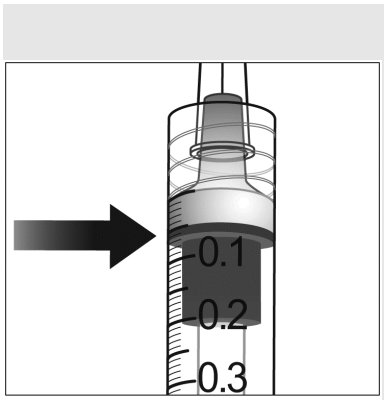
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle to the Luer-lock syringe tip.

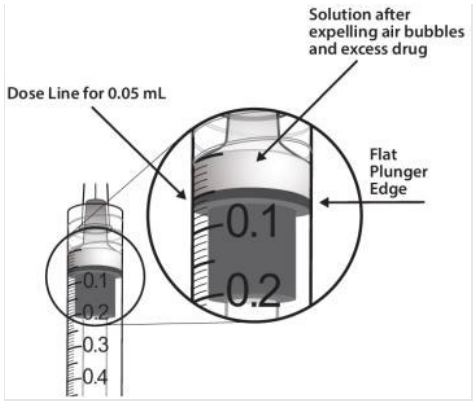


8. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



9. Eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 mL (equivalent to 50 µL) on the syringe.





10. After injection any unused product must be discarded.

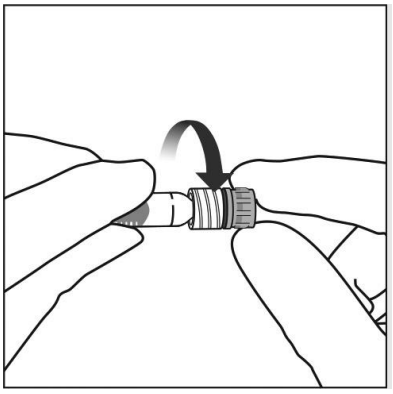
Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

EYLEA 40 mg/mL Pre-filled syringe (for 2 mg dosing)

1. When ready to administer EYLEA, open the carton and remove the sterilised blister pack. Carefully peel open the blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

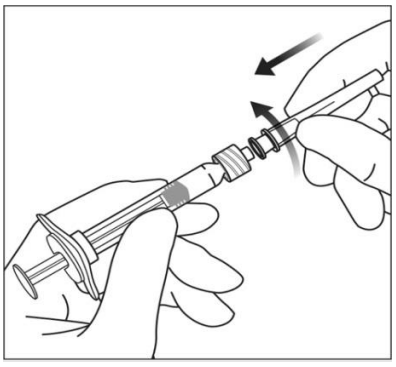
2. Using aseptic technique, remove the syringe from the sterilised blister pack.

3. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and forefinger. Please note: Twist off (do not snap off) the syringe cap.



4. To avoid compromising the sterility of the product, do not pull back on the plunger.

5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

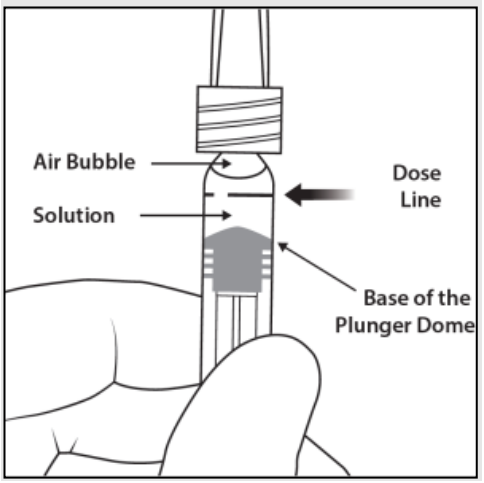


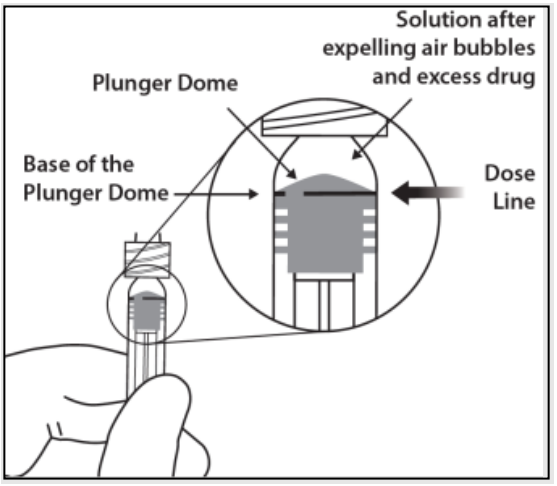
6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

7. The excess volume must be discarded prior to administration. To eliminate all bubbles and to expel excess drug, slowly depress the plunger **to align the base of the plunger dome (not the tip of the dome) with the dosing line on the syringe** (equivalent to 50 µL i.e. 2 mg aflibercept).

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





8. Inject by pressing the plunger 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.**

9. The pre-filled syringe is for single use only. After injection any unused product must be discarded.

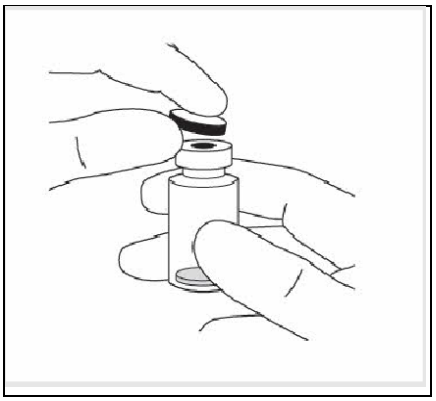
Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

EYLEA 114.3 mg/mL Vial (for 8 mg dosing)

1. Prior to administration visually inspect the solution for injection.

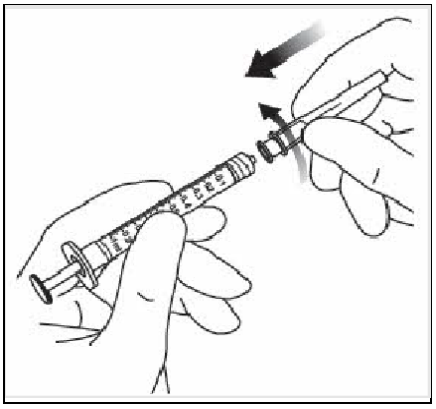
Do not use the vial if particulates, cloudiness, or discoloration are visible.

2. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.



3. Use aseptic technique to carry out steps 3-10.

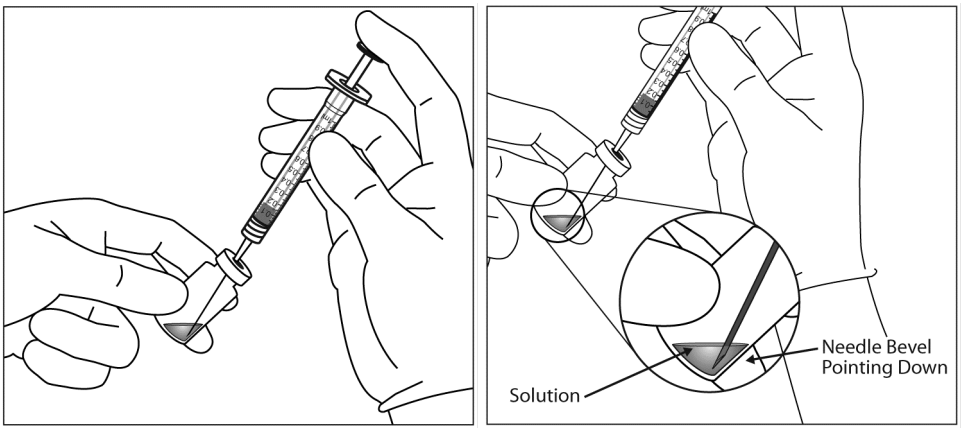
Attach the 18 G, 5-micron filter needle supplied in the carton to a 1-mL sterile, Luer-lock syringe.



Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

4. Push the filter needle into the centre 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.

5. Withdraw all of the EYLEA 8 mg vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.



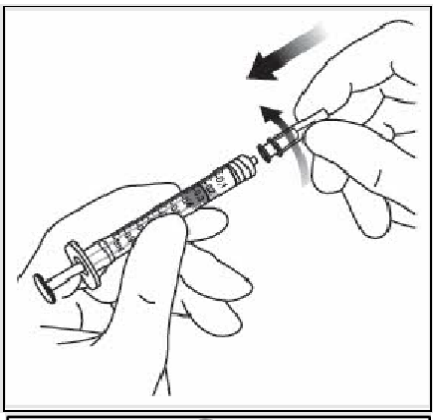
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle. After injection any unused product must be discarded.

7. Remove the filter needle and properly dispose of it.

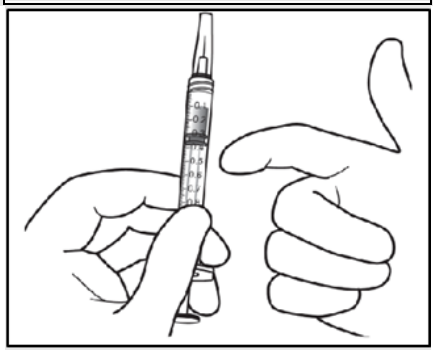
Note: Filter needle is **not** to be used for intravitreal injection.

8. Firmly twist the 30 G x ½ inch injection needle onto the Luer-lock syringe tip.

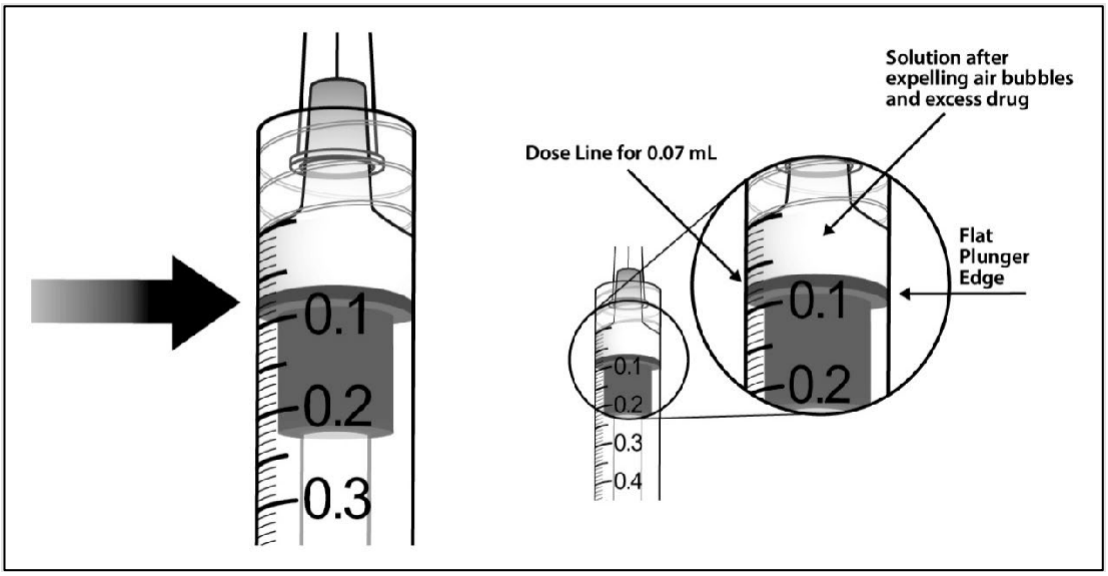
Use of a smaller size needle (higher gauge) than the recommended 30G x 1/2 inch injection needle may result in increased injection forces.



9. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



10. To eliminate all bubbles and to expel excess drug, slowly depress the plunger so that the flat plunger edge aligns with the line that marks **0.07 mL** on the syringe.

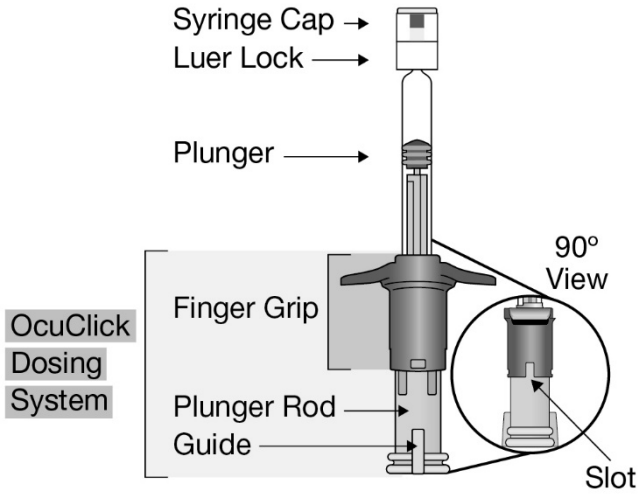


11. After injection any unused product must be discarded.

Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

EYLEA 114.3 mg/mL Pre-filled syringe with OcuClick dosing system (for 8 mg dosing)

PRE-FILLED SYRINGE WITH INTEGRATED OcuClick DOSING SYSTEM DESCRIPTION:



1. PREPARE

When ready to administer EYLEA 8 mg, open the carton and remove the blister pack. Carefully peel open the blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready to attach the injection needle.

Use aseptic technique to carry out steps 2-9.

2. REMOVE SYRINGE

Remove the syringe from the sterilised blister pack.

3. INSPECT SYRINGE AND SOLUTION FOR INJECTION

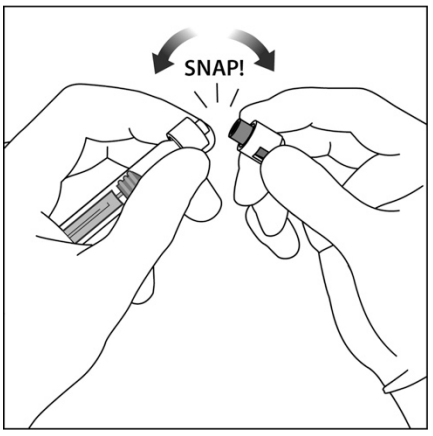
Do not use the pre-filled syringe if particulates, cloudiness, or discoloration are visible.

Do not use if any part of the pre-filled syringe with OcuClick system is damaged or loose, or if the syringe cap is detached from the Luer-lock.

4. SNAP OFF SYRINGE CAP

Snap off (do not twist off) the syringe cap by holding the syringe in one hand and the syringe cap with the thumb and forefinger of the other hand.

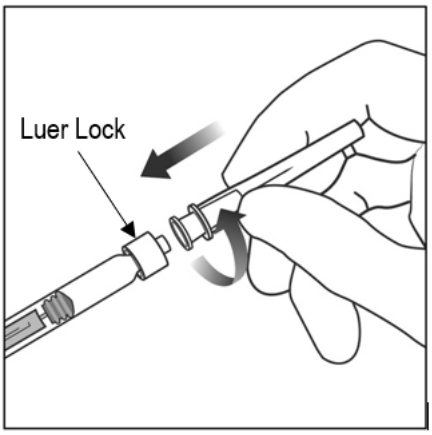
Note: Do not pull back on the plunger rod.



Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

5. ATTACH NEEDLE

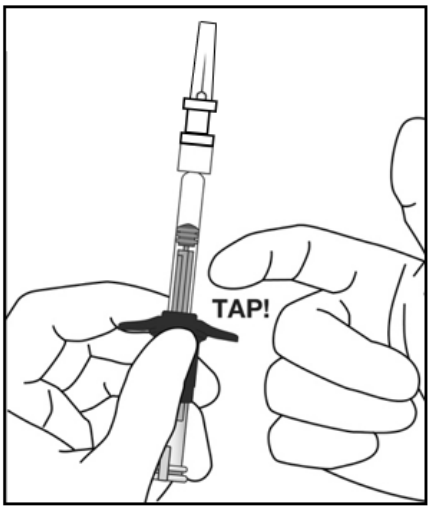
Firmly twist the 30 G x ½ inch injection needle onto the Luer-lock syringe tip



Use of a smaller size needle (higher gauge) than the recommended 30G x 1/2 inch injection needle may result in increased injection forces.

6. DISLODGE AIR BUBBLES

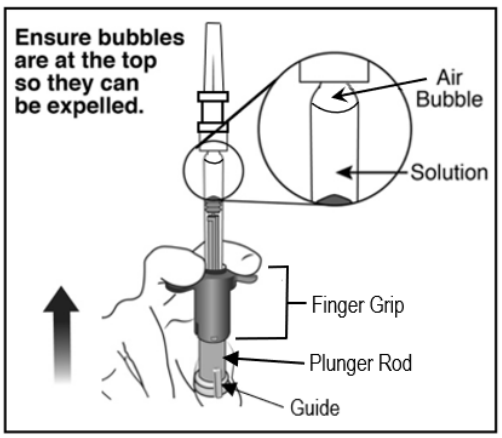
Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top



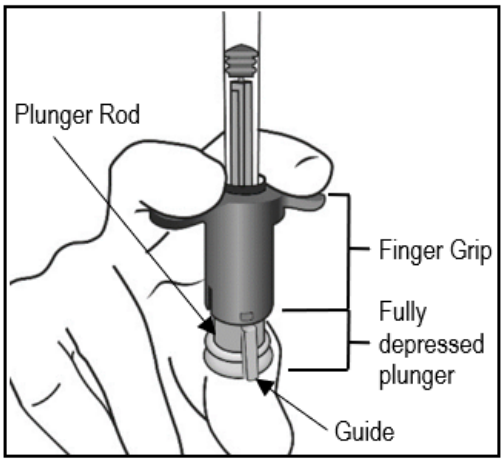
7. EXPEL AIR AND EXCESS VOLUME TO PRIME

The syringe does not have a dose line because it is designed to set the dose mechanically as shown in the steps below.

Priming and setting the dose must be done using the following steps. To eliminate all bubbles and to **expel excess drug, slowly depress the plunger** rod until it stops,



i.e. when the guide on the plunger rod reaches the finger grip.

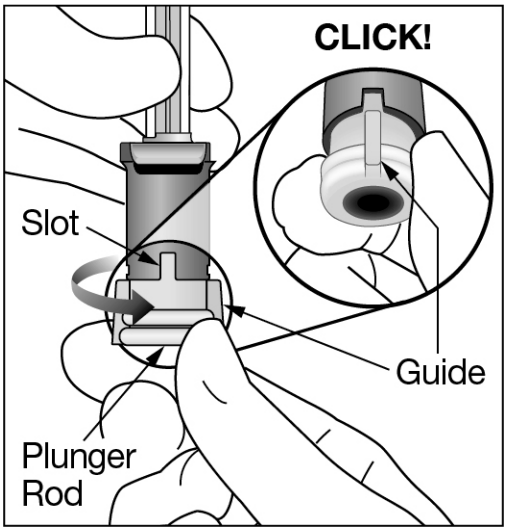


Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

8. SET TO DOSE

Turn the end of the plunger rod 90 degrees clockwise or counterclockwise until the guide of the plunger rod aligns with the slot. You may hear a “click”.

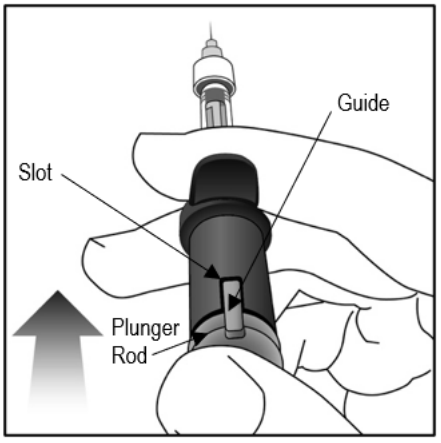
Note: Now the device is ready to dose. **Do not push the plunger rod before insertion into the eye.**



9. ADMINISTER THE INJECTION

Insert the needle into the ocular injection site.

Inject the solution by pushing in the plunger rod until it stops, i.e. until the guide is completely within the slot. Do not apply additional pressure once the guide is within the slot. It is normal to see a small amount of residual solution left in the syringe.



10.

The pre-filled syringe is for single dose administration and single use only.

After injection discard the used syringe into a sharps container.

Dosage adjustment in:

- ***Patients with hepatic and/or renal impairment***

No specific studies in patients with hepatic and/or renal impairment were conducted with EYLEA. Available data do not suggest a need for a dose adjustment with EYLEA in these patients (see Section 5.2 PHARMACOKINETIC PROPERTIES – Special populations).

For EYLEA 2 mg, 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***

Available data do not suggest a need for a dose adjustment with EYLEA in these patients (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

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, Retinal vasculitis and/or retinal occlusive vasculitis

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

Retinal detachment

Intravitreal injections, including those with EYLEA, have been associated with retinal detachment (see section ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Increase in intraocular pressure

Transient increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including with EYLEA (see Section 4.8 ADVERSE EFFECTS (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 ADVERSE EFFECTS (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.

Bilateral treatment

The safety and efficacy of bilateral treatment with EYLEA have not been systematically studied (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). 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.

Retinal pigment epithelial tear

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.

Withholding treatment

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

There is only limited experience with EYLEA treatment in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy or Type 1 diabetes. EYLEA has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with EYLEA in patients with uncontrolled hypertension. In myopic CNV there is no experience with EYLEA in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

This lack of information should be considered by the ophthalmologist when treating such patients.

Use in the elderly

Available data do not suggest a need for a dose adjustment with EYLEA in these patients (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). There is limited experience in patients with DME aged 75 years and older.

Paediatric use

The safety and efficacy of EYLEA have not been established in children or adolescents.

Effects on laboratory tests

No relevant effects on laboratory tests are known.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORM OF INTERACTION

No formal drug interaction studies have been performed with EYLEA.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

- the systemic exposures were approximately ~600 and ~180 higher, respectively, than the population PK estimated exposure in humans after an intravitreal dose of 8 mg. All changes were reversible.

Use in pregnancy

Category D[1]

There are limited data on the use of aflibercept in pregnant women.

EYLEA 2 mg: Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

EYLEA 8 mg: Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection of aflibercept.

EYLEA should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. The treating ophthalmologist in consultation with the treating

[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.

obstetrician need to consider the individual benefit-risk balance for each patient. This includes a consideration of timing of treatment, delaying treatment and other potential treatment options.

Population PK modelling estimated that EYLEA 8 mg given every 12 or 16 weeks was associated with 9 times the systemic exposure ($AUC_{0\text{-}28days}$) of free aflibercept when compared to EYLEA 2 mg given every 8 weeks.

Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration.

Aflibercept produced malformations and other fetal abnormalities in pregnant rabbits with intravenous (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 embryofetal development was not established.

At the lowest dose tested (0.1 mg/kg), the systemic exposures based on C_{max} and cumulative AUC for 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. At the lowest dose tested (0.1 mg/kg), the systemic exposures based on cumulative AUC for free aflibercept were below the corresponding values observed in humans after an intravitreal dose of 8 mg.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

<u>EYLEA 2 mg</u>

A total of 3102 patients treated with EYLEA 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 EYLEA 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 EYLEA) 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.

EYLEA 8 mg

A total of 1,217 patients treated with EYLEA 8 mg (n = 726 nAMD, n = 491 DME) and 556 patients treated with Eylea 2 mg constituted the safety population in three Phase II/III studies (CANDELA, PULSAR, PHOTON).

Serious adverse reactions were cataract (4.0%), retinal haemorrhage (2.6%), intraocular pressure increased (2.4%), vitreous haemorrhage (1.0%), cataract subcapsular (0.5%), retinal detachment (0.4%), and retinal tear (0.3%)

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,900 intravitreal injections with EYLEA 8 mg and included intraocular pressure increased, and retinal tear (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The most frequently observed adverse reactions in at least 2% of patients treated with EYLEA 8 mg were cataract (4.0%), vitreous floaters (3.5%), visual acuity reduced (3.2%), conjunctival haemorrhage (3.1%), vitreous detachment (2.9%), and intraocular pressure increased (2.4%).

Tabulated list of adverse reactions

EYLEA 2 mg

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 DME, 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 with EYLEA 2 mg

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,	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,	Blindness, Cataract traumatic, Vitritis, Hypopyon

		Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia Ocular hyperaemia	Corneal oedema	

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

EYLEA 8 mg

The safety data described below in Table 2 include all adverse reactions (serious and non- serious) with a reasonable possibility of causality to the injection procedure or medicinal product reported from EYLEA 8 mg phase II/III studies up to 60 weeks for the indications wet AMD and DME.

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 2: Treatment-emergent adverse drug reactions reported in patients with nAMD or DME in Phase II/III studies with EYLEA 8 mg

Primary System Organ Class Preferred term MedDRA version 25.0	2 mg N=556 (100%)	8Q12** N=716 (100%)	8Q16*** N=501 (100%)	All 8 mg N=1217 (100%)	Frequency category (ADR table 8 mg Eylea) Based on all 8 mg incidences
Eye disorders					
Cataract	2.9%	3.5%	4.8%	4.0%	common
Conjunctival haemorrhage	2.5%	3.5%	2.6%	3.1%	common
Eye pain	1.3%	2.1%	1.2%	1.7%	common
Visual acuity reduced	4.7%	2.4%	4.4%	3.2%	common
Vitreous detachment	1.8%	2.9%	2.8%	2.9%	common
Vitreous floaters	3.1%	3.2%	4.0%	3.5%	common
Vitreous haemorrhage	0.5%	1.0%	1.0%	1.0%	common
Intraocular pressure increased	2.7%	2.5%	2.2%	2.4%	common

Cataract cortical	0.4%	0.4%	0.2%	0.3%	uncommon
Cataract nuclear	0.7%	0.3%	0.4%	0.3%	uncommon
Cataract subcapsular	0.7%	0.7%	0.2%	0.5%	uncommon
Conjunctival hyperaemia	0.2%	0.4%	0	0.2%	uncommon
Corneal erosion	0	0.4%	0.8%	0.6%	uncommon
Detachment of retinal pigment epithelium	0.5%	0.1%	0.2%	0.2%	uncommon
Foreign body sensation in eyes	0	0.3%	0.2%	0.2%	uncommon
Iridocyclitis	0.4%	0	0.4%	0.2%	uncommon
Iritis	0	0.4%	0	0.2%	uncommon
Lacrimation increased	0	0.3%	0.2%	0.2%	uncommon
Punctate keratitis	1.4%	1.0%	2.0%	1.4%	common
Retinal detachment	0.2%	0.4%	0.4%	0.4%	uncommon
Retinal pigment epithelial tear	0.7%	0.8%	0.6%	0.7%	uncommon
Retinal tear	0	0.3%	0.4%	0.3%	uncommon
Vision blurred	1.1%	0.6%	0.4%	0.5%	uncommon
Vitritis	0	0.3%	0	0.2%	uncommon
Injection site haemorrhage	0	0	0.4%	0.2%	uncommon
Injection site pain	0.5%	0.4%	0.6%	0.5%	uncommon
Corneal abrasion	1.1%	1.1%	0.6%	0.9%	uncommon

Corneal oedema	0.2%	0	0.2%	0.08%	rare
Eyelid oedema	0	0	0.2%	0.08%	rare
Uveitis	0	0.1%	0	0.08%	rare
Injection site irritation	0	0.1%	0	0.08%	rare
Immune system disorders					
Hypersensitivity*	0.4%	1.0%	0.8%	0.9%	uncommon

*Reports of hypersensitivity included rash, pruritus, urticaria.
** Patients treated with EYLEA 8 mg administered every 12 weeks (8Q12), after 3 initial injections at 4-week intervals
*** Patients treated with EYLEA 8 mg administered every 16 weeks (8Q16), after 3 initial injections at 4-week intervals

Post-marketing experience

In addition, the following adverse reactions have also been reported during the post-marketing period of EYLEA 2 mg, for which a frequency could not be estimated.

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

The following adverse reactions have also been reported during the post-marketing period of EYLEA 8 mg, for which a frequency could not be estimated.

Eye disorders:	retinal vasculitis and retinal occlusive vasculitis, scleritis

Description of selected adverse reactions

The following adverse reactions of EYLEA 2 mg strength are also considered expected with EYLEA 8 mg but have not been reported in the studies with EYLEA 8 mg:

Anterior chamber flare, corneal epithelium defect, lenticular opacities, ocular hyperaemia, endophthalmitis, hypopyon, cataract traumatic, severe anaphylactic/anaphylactoid reactions.

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).

EYLEA 2 mg

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 EYLEA.

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 EYLEA (2.4% in the EYLEA 2Q4 arm and 3.6% in the EYLEA 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 EYLEA 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 EYLEA 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 EYLEA 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 EYLEA 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 EYLEA.

EYLEA 8 mg

The pooled incidence of APTC ATEs in the phase II/III nAMD studies CANDELA (through Week 44) and PULSAR (through Week 60) studies was 2.1% (8 out of 389) in the 2Q8 arm, 0.3% (1 out of 388) in 8Q12 arm, 0.6% (2 out of 338) in 8Q16 arm, all 0.4% (3 out of 726) in the pooled 8 mg arms (combined 8Q12 and 8Q16 arms).

The incidence of APTC ATEs in the DME study PHOTON (through Week 60) was 3.6% (6 out of 167) in the 2Q8 arm, 4.0% (13 out of 328) in the 8Q12 arm, 5.5% (9 out of 163) in the 8Q16 arm, and 4.5% (22 out of 491) in the pooled 8 mg arms (combined 8Q12 and 8Q16 arms).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating ophthalmologist, adequate treatment should be initiated (see section ‘Instructions for use/ handling’).

For information on the management of overdose, contact the Poison Information Centre

on 131126 (Australia).

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 effects***

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 EYLEA 2 mg (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 EYLEA 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively, in VIEW 1; -149 and -139 microns for the EYLEA 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 EYLEA 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.

In the PULSAR study with EYLEA 8 mg, at week 48, central retinal thickness (CRT) was reduced in patients treated with 8Q12, 8Q16 and 2Q8, and total lesion area was reduced in patients treated with 8Q12 and 8Q16 and showed minimal increase in patients treated with 2Q8.

Table 3: Pharmacodynamic parameter (Full Analysis Set) in PULSAR study

Efficacy Outcomes	Week	EYLEA 8mg 8Q12 (N = 335)	EYLEA 8mg 8Q16 (N = 338)	EYLEA 2mg 2Q8 (N = 336)
Change in CRT from baseline [microns]				
Arithmetic mean (SD), observed	48	-141.9 (120.1)	-147.1 (131.2)	-126.3 (124.3)
LS mean (SE) [A]		-147.37 (4.01)	-146.76 (3.76)	-136.25 (4.24)
Difference in LS means (95% CI) [A, B]		-11.12 (-21.06, -1.18)	-10.51 (-20.12, -0.90)	
Arithmetic mean (SD), observed	60	-149.7 (121.0)	-153.4 (134.1)	-143.0 (120.9)
LS mean (SE) [A]		-153.67 (3.53)	-150.69 (3.55)	-154.83 (3.07)
Difference in LS means (95% CI) [A, B]		1.16 (-6.75, 9.07)	4.14 (-3.87, 12.14)	
Change in total lesion area from baseline [mm^2]				
Arithmetic mean (SD), observed	48	-0.4 (2.9)	-0.2 (3.1)	0.1 (3.6)
LS mean (SE) [A]		-0.46 (0.19)	-0.35 (0.20)	0.09 (0.22)
Difference in LS means (95% CI) [A, B]		-0.55 (-1.04, -0.06)	-0.44 (-0.94, 0.06)	
Arithmetic mean (SD), observed	60	-0.5 (2.8)	-0.4 (3.2)	-0.3 (3.2)
LS mean (SE) [A]		-0.48 (0.20)	-0.54 (0.21)	-0.24 (0.20)
Difference in LS means (95% CI) [A, B]		-0.24 (-0.72, 0.24)	-0.29 (-0.79, 0.20)	

[A)] LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomization (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[B)] Absolute difference is EYLEA 8mg 8Q12 or 8Q16 groups minus EYLEA 2mg 2Q8 group, respectively.

CI: Confidence Interval; CRT: Central Retinal Thickness; LS: Least Squares; SD: Standard deviation; SE: Standard Error

Diabetic macular oedema (DME)

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 EYLEA 2 mg, 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 EYLEA and was maintained through week 100.

Table 4: 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**		
	EYLEA 2 mg Q8[a)] (N = 135)	**EYLEA 2 mg Q4[c)] (N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8[a)] (N = 135)**	**EYLEA 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**		
	EYLEA 2 mg Q8[a)] (N = 151)	**EYLEA 2 mg Q4[c)] (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8[a)] (N = 151)**	**EYLEA 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}.
EYLEA 2 mg Q8: From week 16 onwards, the treatment interval in EYLEA treatment group was extended for all subjects from 4 weeks to 8 weeks.
b) Difference is EYLEA group minus active control (laser) group
c) EYLEA administered 2 mg every 4 weeks.

The VIOLET study compared three different dosing regimens of EYLEA 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 EYLEA 2 mg 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').

In the PHOTON study with EYLEA 8 mg, at week 48, central retinal thickness (CRT) was reduced in patients treated with 8Q12, 8Q16 and 2Q8.

Table 5: Pharmacodynamic parameter (Full Analysis Set) in PHOTON study

Efficacy Outcomes	Week	EYLEA 8mg 8Q12 (N = 328)	EYLEA 8mg 8Q16 (N = 163)	EYLEA 2mg 2Q8 (N = 167)
Change in CRT from baseline [microns]				
Arithmetic mean (SD), observed	48	-171.65 (141.52)	-148.30 (133.20)	-165.31 (140.22)
LS mean (SE)[A]		-176.77 (5.73)	-148.84 (9.45)	-164.85 (8.79)
Difference in LS mean change [A, B] (95% CI)		-11.92 (-30.30, 6.47)	16.01 (-7.53, 39.54)	
Arithmetic mean (SD), observed	60	-176.24 (144.71)	-167.18 (127.18)	-191.31 (142.00)
LS mean (SE)		-181.95 (6.09)	-166.26 (8.56)	-194.16 (7.15)
Difference in LS mean change [A, B] (95% CI)		12.21 (-3.74, 28.16)	27.90 (8.06, 47.74)	
Change in leakage area from baseline [mm^2]				
Arithmetic mean (SD), observed	48	-13.9 (13.91)	-9.4 (11.50)	-9.2 (12.11)
	60	-13.9 (13.54)	-12.0 (13.26)	-14.4 (12.89)

[A)] LS mean and CI based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomization (geographical region, categorical baseline CRT, prior DME treatment) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[B)] Absolute difference is EYLEA 8mg 8Q12 or 8Q16 groups minus EYLEA 2mg 2Q8 group, respectively.

CI: Confidence Interval; CRT: Central Retinal Thickness; LOCF: Last Observation Carried Forward; LS: Least Squares; SD: Standard Deviation; SE: Standard Error.

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 EYLEA (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 EYLEA.

Table 6: 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)	**EYLEA 2 mg Q4 (N = 114)**	**Control[c]) (N = 73)**	**EYLEA 2 mg (N = 114)**	**Control[c, d)] (N = 73)**	**EYLEA[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)		-312 (-389, -234) p < 0.0001		-28 (-121, 64) p = 0.5460		-45 (-142, 53) p = 0.3661
p-value						
GALILEO						
Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**100 Weeks**	
	Control (N = 68)	**EYLEA 2 mg Q4 (N = 103)**	**Control (N = 68)**	**EYLEA 2 mg (N = 103)**	**Control[e]) (N = 68)**	**EYLEA[e)] 2 mg (N = 103)**
Mean change in retinal thickness from baseline	-169	-449	-219	-424	-306	-389
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 EYLEA 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 EYLEA 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 EYLEA 2 mg patients received EYLEA 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 EYLEA 2 mg patients received EYLEA 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 EYLEA 2 mg (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 EYLEA 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 EYLEA.

Table 7: Pharmacodynamic parameter at week 24 and at week 52 (Full Analysis Set with LOCF) in VIBRANT study

VIBRANT				
Efficacy Outcomes	**24 Weeks**		**52 Weeks**	
	EYLEA 2 mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**EYLEA 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)]	-149 (-180, -117)		-30 (-55, -4)	
p-value	p < 0.0001		p = 0.0218	

a) EYLEA 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 EYLEA 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 EYLEA 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 EYLEA, if they met at least one pre-specified eligibility criterion. A total of 67 subjects (74%) in this group received EYLEA rescue treatment. The fixed regimen for EYLEA rescue was EYLEA 2 mg every 4 weeks for three injections, followed by injections every 8 weeks.

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 EYLEA (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 EYLEA.

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

MYRROR				
Efficacy Outcomes	**24 Weeks**		**48 Weeks**	
	EYLEA 2 mg[b)] (N = 90)	**Sham (N = 31)**	**EYLEA 2 mg[c)] (N = 90)**	**Sham / EYLEA 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) EYLEA 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.
c) EYLEA 2 mg administered from week 24 through week 44 potentially every 4 weeks in case of disease persistence or recurrence
d) Mandatory injection of EYLEA 2 mg at week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through week 44.
e) Difference is EYLEA 2 mg minus sham at week 24; difference is EYLEA 2 mg minus sham/EYLEA 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.

Clinical trials

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

EYLEA 2 mg

The safety and efficacy of EYLEA were assessed in two pivotal phase III randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of
2412 patients were treated and evaluable for efficacy (1817 with EYLEA) 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. EYLEA administered at 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8)

2. EYLEA administered at 2 mg every 4 weeks (EYLEA 2Q4)

3. EYLEA administered at 0.5 mg every 4 weeks (EYLEA 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 EYLEA 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 EYLEA 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 EYLEA 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. EYLEA 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 EYLEA 2Q8 treatment group maintained vision compared to 94.4% of patients in the ranibizumab 0.5Q4 group. EYLEA 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)]

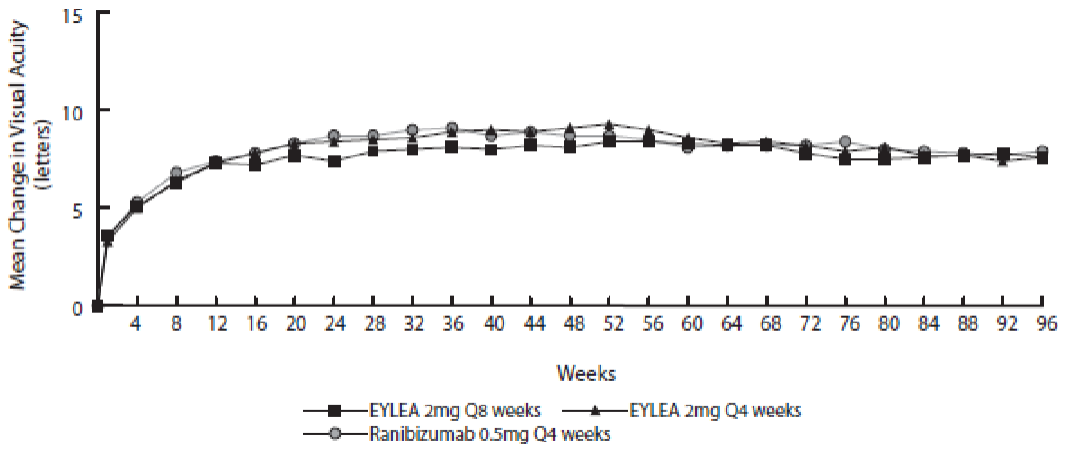
Efficacy Outcomes	EYLEA 2 mg Q4 (N = 613)		EYLEA 2 mg Q8[e)] (N = 607)		Ranibizumab 0.5 mg Q4 (N = 595)	
	Week 52	Week 96[h)]	Week 52	Week 96[h)]	Week 52	Week 96[h)]
Mean number of injections from baseline	12.3	16.0	7.6	11.2	12.3	16.5
Mean number of injections during week 52 to week 96	N/A	4.1	N/A	4.2	N/A	4.7
Proportion of patients with maintained visual acuity (<15 letters of BCVA[a)] 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 ETDRS[a)] 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 EYLEA group minus the value of the ranibizumab group. A positive value favours EYLEA.
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 EYLEA to ranibizumab
g) The difference is the value of the EYLEA 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, EYLEA was dosed every 8 weeks following 3 initial monthly doses (EYLEA 2 mg Q8 weeks) or every 4 weeks (EYLEA 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 EYLEA 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 EYLEA 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 EYLEA treatment schedules and ranibizumab.

In combined data analysis of the VIEW 1 and VIEW 2 studies EYLEA 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 EYLEA 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 EYLEA following two different adjustment intervals (2-weeks and 4-weeks) of a treat-and-extend dosing regimen.

All patients received 3 monthly doses of EYLEA 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) EYLEA treat-and-extend with 2-week adjustments and 2) EYLEA 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 EYLEA administered in a treat-and extend dosing regimen with EYLEA 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 maximum 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 the 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.

<u>EYLEA 8 mg</u>

The safety and efficacy of EYLEA 8 mg were assessed in a randomised, multi-centre, double- masked, active-controlled study (PULSAR) in patients with treatment naïve nAMD. The patients were assigned in a 1:1:1 ratio to 1 of 3 parallel treatment groups:

1. EYLEA 8 mg administered at 8 mg every 12 weeks (8Q12), after 3 initial injections at 4-week intervals,

2. EYLEA 8 mg administered at 8 mg every 16 weeks (8Q16), after 3 initial injections at 4-week intervals,

3. EYLEA 2 mg administered at 2 mg every 8 weeks (2Q8), after 3 initial injections at 4- week intervals.

Patients in the 8Q12 and 8Q16 groups could move to a more frequent dosing regimen based on visual and anatomic outcomes. Per study protocol the interval of the 8Q12- and 8Q16- groups was to be shortened if both of the following criteria were met:

1. >5 letters loss in BCVA from week 12, and

2. >25 microns increase in CRT from week 12 or new foveal haemorrhage or new foveal neovascularisation.

The minimum interval between injections was 8 weeks in all groups.

Patients with bilateral disease were eligible to receive EYLEA 2 mg treatment or another anti-VEGF medicinal product in their fellow eye.

The study population was aged from 50 to 96 years with a mean of 74.5 years. There were approximately 90% (604/673) and 51% (343/673) patients randomised to the 8Q12 and 8Q16 groups aged 65 years of age or older and 75 years of age or older respectively. The mean best corrected visual acuity (BCVA) at baseline (measured by the Early Treatment Diabetic Retinopathy Study [ETDRS] letter score) was 59.9, 60.0 and 58.9 in the 8Q12, 8Q16 and 2Q8 groups, respectively.

Patients in the 8Q12, 8Q16 and 2Q8 groups received a median (mean) of 6.0 (6.1), 5.0 (5.2) and 7.0 (6.9) injections, respectively, through week 48.

Patients in the 8Q12, 8Q16- and 2Q8-groups who completed week 60 received a median (mean) of 7.0 (7.1), 6.0 (6.2) and 9.0 (8.8) injections, respectively.

The primary efficacy endpoint was the mean change from baseline in BCVA at week 48.

Treatment with 8Q12 and 8Q16 was shown to be non-inferior to treatment with 2Q8 in terms of the primary efficacy endpoint ‘mean change in BCVA at week 48’ and the key secondary efficacy endpoint ‘mean change in BCVA at week 60’.

For the key secondary efficacy endpoint ‘proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield at week 16’, treatment with EYLEA 8 mg (pooled 8Q12 and 8Q16 groups) was shown to be superior to treatment with EYLEA 2 mg (2Q8).

Table 10: Efficacy outcomes from the PULSAR study

Efficacy Outcomes	**Week**	**EYLEA 8mg 8Q12 (N = 335)**	**EYLEA 8mg 8Q16 (N = 338)**	**EYLEA 2mg 2Q8 (N = 336)**
Change in BCVA from baseline as measured by ETDRS letter score [D]				
Arithmetic mean (SD), observed	48	6.7 (12.6)	6.2 (11.7)	7.6 (12.2)
LS mean (SE) [A]		6.06 (0.77)	5.89 (0.72)	7.03 (0.74)
Difference in LS means [A, B] (95% CI)		-0.97 (-2.87, 0.92)	-1.14 (-2.97, 0.69)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A, B]		0.0009	0.0011	
Arithmetic mean (SD), observed	60	6.6 (13.6)	6.6 (11.7)	7.8 (12.6)
LS mean (SE) [A]		6.37 (0.74)	6.31 (0.66)	7.23 (0.68)
Difference in LS means [A, B] (95% CI)		-0.86 (-2.57, 0.84)	-0.92 (-2.51, 0.66)	
Patients with no IRF and no SRF in the central subfield [D]				
Proportion (LOCF)	16	63.3%		51.6%

Adjusted difference in proportion [B, C] (95% CI)		11.7% (5.3%, 18.2%)		
p-value (one-sided superiority test) [B, C]		0.0002		
Proportion (LOCF)	48	71.1%	66.8%	59.4%
Adjusted difference in proportion [B, C] (95% CI)		11.7% (4.5%, 18.9%)	7.5% (0.1%, 14.8%)	
Proportion (LOCF)	60	74.6%	72.2%	74.6%
Adjusted difference in proportion [B, C] (95% CI)		0.0% (-6.6%, 6.7%)	-2.2% (-8.9%, 4.4%)	
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [D]				
Proportion (LOCF)	48	56.9%	54.3%	57.9%
Adjusted difference in proportion [B, C] (95% CI)		-0.2% (-6.6%, 6.2%)	-2.2% (-8.4%, 4.0%)	
Proportion (LOCF)	60	56.3%	54.6%	58.2%
Adjusted difference in proportion [B, C] (95% CI)		-1.1% (-7.5%, 5.3%)	-2.3% (-8.7%, 4.1%)	
Patients who gained at least 15 letters in BCVA from baseline [D]				
Proportion (LOCF)	48	20.7%	21.7%	22.1%
Adjusted difference in proportion [B, C] (95% CI)		-1.7% (-7.8%, 4.3%)	-0.9% (-7.0%, 5.1%)	
Patients maintained with Q16 treatment interval [E]				
Proportion	48	n/a	76.6%	n/a
	60	n/a	74.1%	n/a
Patients maintained with ≥Q12 treatment interval [E]				
Proportion	48	79.4%	87.2%	n/a
	60	77.8%	85.4%	n/a
Patients maintained with ≥Q12 treatment interval [E]				
Proportion (pooled 8Q12 and 8Q16 groups)	48	83.3%		n/a
	60	81.6%		n/a

[A)] LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomization (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[B)] Absolute difference is EYLEA 8mg 8Q12 or 8Q16 groups minus EYLEA 2mg 2Q8 group, respectively.

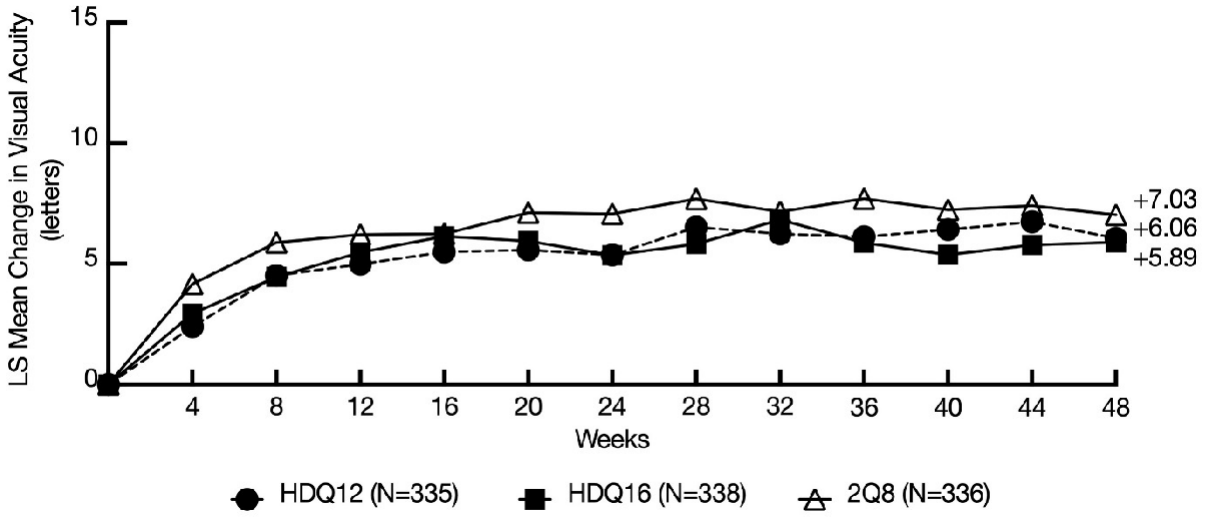
[C)] Mantel-Haenszel weighted treatment difference with stratification variables used for randomization (geographical region, categorical baseline BCVA) and CI calculated using normal approximation

[D)] Full Analysis Set

[E)] Safety Analysis Set; patients considered as completer for the respective timepoint

CI: Confidence Interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LOCF: Last Observation Carried Forward; LS: Least Squares; MMRM: Mixed Model for Repeated Measurements; SD: Standard Deviation; SE: Standard Error

Figure 2: LS mean change in BCVA as measured by ETDRS letter score from baseline through week 48 (Full Analysis Set) in PULSAR study



No clinically meaningful differences were found between the 8Q12-, 8Q16- and 2Q8-groups in changes of NEI VFQ-25 total score at week 48 from baseline.

Efficacy for the primary endpoint results in evaluable subgroups for age, gender, geographic region, ethnicity, race, baseline BCVA and lesion type were consistent with the results in the overall population.

- ***Diabetic macular oedema (DME)***

EYLEA 2 mg

The safety and efficacy of EYLEA 2 mg 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 EYLEA 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. EYLEA administered at 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8);
2. EYLEA administered at 2 mg every 4 weeks (EYLEA 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 EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

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 EYLEA 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 EYLEA 2Q8 and EYLEA 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 11 and Figure 3 below.

Table 11: 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**		
	EYLEA 2 mg Q8[a)] (N = 135)	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8[a)] (N =135)**	**EYLEA 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 4 for Mean Change in CRT from Baseline						

Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

VIVID[DME]						
Efficacy Outcomes	**52 Weeks**			**100 Weeks**		
	EYLEA 2 mg Q8[a)] (N = 135)	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8[a)] (N =135)**	**EYLEA 2 mg Q4 (N =136)**	**Active Control (laser) (N =132)**
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**		
	EYLEA 2 mg Q8[a)] (N = 151)	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8[a)] (N =151)**	**EYLEA 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	

Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

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	

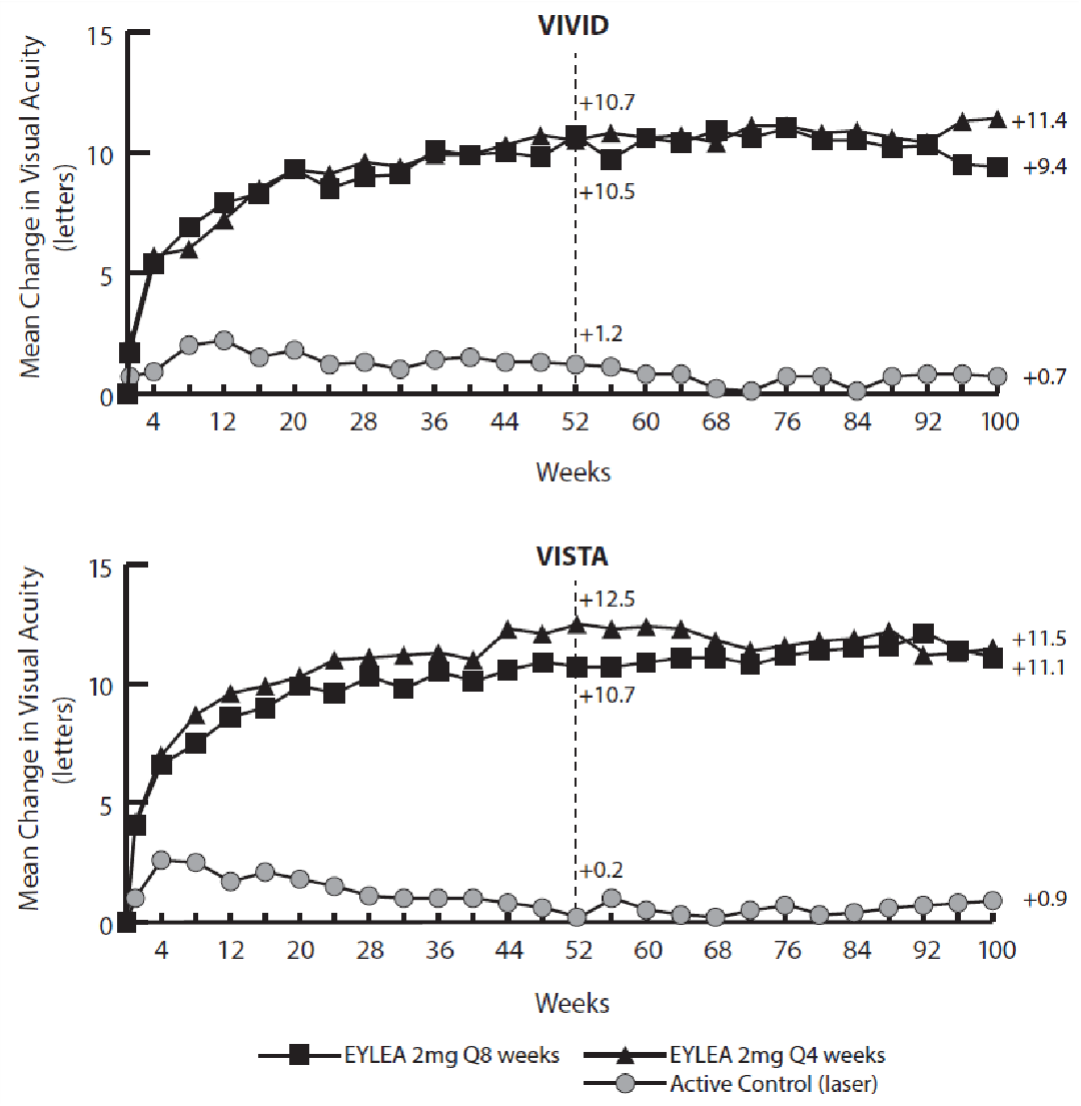
VISTA[DME]						
Efficacy Outcomes	**52 Weeks**			**100 Weeks**		
	EYLEA 2 mg Q8[a)] (N = 151)	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8[a)] (N =151)**	**EYLEA 2 mg Q4 (N =154)**	**Active Control (laser) (N =154)**
Proportion of patients with an improvement of >= 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 4 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 EYLEA 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 (EYLEA 2 mg Q8), n=81 (EYLEA 2 mg Q4), n=80 (laser); week 100: n=86 (EYLEA 2 mg Q8), n=82 (EYLEA 2 mg Q4), n=85 (laser)]

Figure 3: 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 11).

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 EYLEA patients received bilateral EYLEA injections until week 100; in the VIVID^{DME} study, 97 (35.8%) of EYLEA 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 EYLEA 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} (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 EYLEA 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

- EYLEA 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
- EYLEA 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 EYLEA 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.

<u>EYLEA 8 mg</u>

The safety and efficacy of EYLEA 8 mg were assessed in a randomised, multi-centre, double- masked, active-controlled study (PHOTON) in patients with DME. The patients

were assigned in a 2:1:1 ratio to 1 of 3 parallel treatment groups:

1. EYLEA 8 mg administered at 8 mg every 12 weeks (8Q12), after 3 initial injections at 4-week intervals,

2. EYLEA 8 mg administered at 8 mg every 16 weeks (8Q16), after 3 initial injections at 4-week intervals,

3. EYLEA 2 mg administered at 2 mg every 8 weeks (2Q8), after 5 initial injections at 4-week intervals.

Patients in the 8Q12 and 8Q16 groups could move to a more frequent dosing regimen based on visual and anatomic outcomes. Per study protocol the interval of the 8Q12- and 8Q16-groups was to be shortened if both of the following criteria were met:

1. >10 letter loss in BCVA from week 12 in association with persistent or worsening DME, and

2. >50 microns increase in CRT from week 12.

The minimum interval between injections was 8 weeks in all groups.

Patients with bilateral disease were eligible to receive EYLEA 2 mg treatment in their fellow eye.

The study population was aged from 24 to 90 years with a mean of 62.3 years. [i] There were approximately 44% (214/491) and 10% (50/491) patients randomised to the 8Q12 and 8Q16 groups aged 65 years of age or older and 75 years of age or older respectively.

The study population included treatment-naïve patients (56.4%) and patients previously treated for DME (43.6%).

Patients in the 8Q12, 8Q16 and 2Q8 groups received a median (mean) of 6.0 (6.0), 5.0 (5.0) and 8.0 (7.9) injections, respectively, through week 48.

The mean best corrected visual acuity (BCVA) at baseline (measured by the Early Treatment Diabetic Retinopathy Study [ETDRS] letter score) was 63.6, 61.4 and 61.5 in the 8Q12-, 8Q16- and 2Q8-groups, respectively.

The primary efficacy endpoint was the mean change from baseline in BCVA at week 48.

Treatment with EYLEA 8 mg (both 8Q12 and 8Q16 groups) was shown to be non-inferior to treatment with EYLEA 2 mg (2Q8), in terms of the primary efficacy endpoint ‘mean change in BCVA at week 48’.

For the key secondary efficacy endpoint ‘proportion of participants with ≥ 2-step improvement in DRSS score at Week 48, EYLEA 8Q12 was non-inferior to EYLEA 2Q8. Non-inferiority of EYLEA 8Q16 to EYLEA 2Q8 was not shown. See Table 12.

Table 12: Efficacy outcomes from the PHOTON study

Efficacy Outcomes	Week	EYLEA 8mg 8Q12 (N = 328)	EYLEA 8mg 8Q16 (N = 163)	EYLEA 2mg 2Q8 (N = 167)
Change in BCVA from baseline as measured by ETDRS letter score [D]				
Arithmetic mean (SD), observed	48	8.77 (8.95)	7.86 (8.38)	9.21 (8.99)
LS mean (SE) [A]		8.10 (0.61)	7.23 (0.71)	8.67 (0.73)
Difference in LS means [A, B] (95% CI)		-0.57 (-2.26, 1.13)	-1.44 (-3.27, 0.39)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A, B]		<0.0001	0.0031	
Arithmetic mean (SD), observed	60	9.05 (9.27)	7.96 (9.14)	9.62 (9.58)
LS mean (SE) [A]		8.52 (0.63)	7.64 (0.75)	9.40 (0.77)
Difference in LS means [A, B] (95% CI)		-0.88 (-2.67, 0.91)	-1.76 (-3.71, 0.19)	
p-value (one-sided non-inferiority test at a margin of 4 letters) [A, B]		0.0003	0.0122	
Patients achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) [D]				
Proportion (LOCF)	48	65.3%	62.6%	63.0%
Adjusted difference in proportions [B, C] (95% CI)		2.45% (-6.47%, 11.36%)	-0.67% (-11.16%, 9.82%)	
Proportion (LOCF)	60	64.7%	62.0%	60.6%
Adjusted difference in proportions [B, C] (95% CI)		4.34% (-4.72%, 13.40%)	1.63% (-8.91%, 12.17%)	
Patients who gained at least 15 letters in BCVA from baseline [D]				
Proportion (LOCF)	48	18.7%	16.6%	23.0%
Adjusted difference in proportions [B, C] (95% CI)		-4.64% (-12.30%, 3.02%)	-7.14% (-15.45%, 1.17%)	
Proportion (LOCF)	60	21.5%	16.0%	26.1%
Adjusted difference in proportions [B, C] (95% CI)		-5.01% (-13.04%, 3.02%)	-10.78% (-19.27%, -2.29%)	
Patients maintained with Q16 treatment interval [E]				
Proportion	48	n/a	89.1%	n/a
	60	n/a	85.5%	n/a
Patients maintained with ≥Q12 treatment interval [E]				
Proportion	48	91.0%	96.2%	n/a
	60	90.3%	93.4%	n/a
Patients maintained with ≥Q12 treatment interval [E]				
Proportion (pooled 8Q12 and 8Q16 groups)	48	92.8%		n/a
	60	91.4%		n/a

[A)] LS mean, CI and p-value based on an MMRM with baseline best corrected visual acuity (BCVA) measurement as covariate, treatment group as factor, visit and stratification variables used for randomization (geographical region, categorical baseline BCVA) as fixed factors as well as terms for the interaction between baseline BCVA and visit and for the interaction between treatment and visit.

[B)] Absolute difference is EYLEA 8mg 8Q12 or 8Q16 groups minus EYLEA 2mg 2Q8 group, respectively.

[C)] Mantel-Haenszel weighted treatment difference with stratification variables used for randomization (geographical region, categorical baseline BCVA) and CI calculated using normal approximation

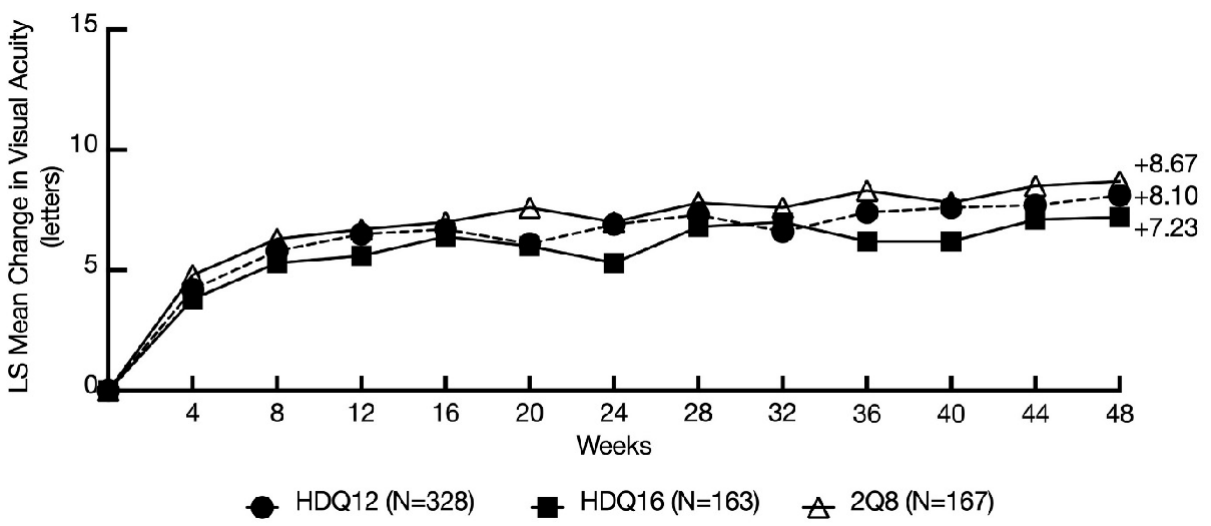
Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

[D)] Full Analysis Set

[E)] Safety Analysis Set; patients considered as completer for the respective timepoint

CI: Confidence Interval; LOCF: Last Observation Carried Forward; LS: Least Squares; SD: Standard Deviation; SE: Standard Error

Figure 4: LS mean change in BCVA as measured by ETDRS letter score from baseline to week 48 (Full Analysis Set) in PHOTON study



No clinically meaningful differences were found between the 8Q12-, 8Q16- and 2Q8-groups in changes of NEI VFQ-25 total score at week 48 from baseline.

Efficacy for the primary endpoint results in evaluable subgroups for age, gender, geographic region, ethnicity, race, baseline BCVA and baseline CRT and prior DME treatment were consistent with the results in the overall population.

For the pre-specified exploratory endpoint 'proportion of patients maintaining treatment intervals through Week 48', there were 92.8% of patients in the pooled 8Q12- and 8Q16-groups maintained on their original randomised dosing intervals of ≥12 weeks and 89.1% of patients in the8Q16 group maintained on dosing intervals of 16 weeks, while maintaining visual and anatomic outcomes.

- ***Macular oedema secondary to central retinal vein occlusion (CRVO)***

<u>EYLEA 2 mg</u>

The safety and efficacy of EYLEA 2 mg 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 EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA 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 EYLEA 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 EYLEA 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 2 (see Section see Section 5.1 PHARMACODYNAMIC PROPERTIES, Pharmacodynamic effects), Table 13 and Figure 5 below.

Table 13: 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)	**EYLEA 2 mg Q4 (N = 114)**	**Control[e] (N = 73)**	**EYLEA 2 mg (N = 114)**	**Control[e,f] (N = 73)**	**EYLEA[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]		21.7		12.7		11.8

(95% CI) p-value		(17.4, 26.0) p < 0.0001		(7.7, 17.7) p < 0.0001		(6.7, 17.0) p < 0.0001
Proportion of patients who developed any neovascularisation#	6.8%	0%	6.8%	0%	11.0%	5.3%

COPERNICUS

Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**100 Weeks**	
	Control (N = 73)	**EYLEA 2 mg Q4 (N = 114)**	**Control[e] (N = 73)**	**EYLEA 2 mg (N = 114)**	**Control[e,f] (N = 73)**	**EYLEA[f] 2 mg (N = 114)**
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

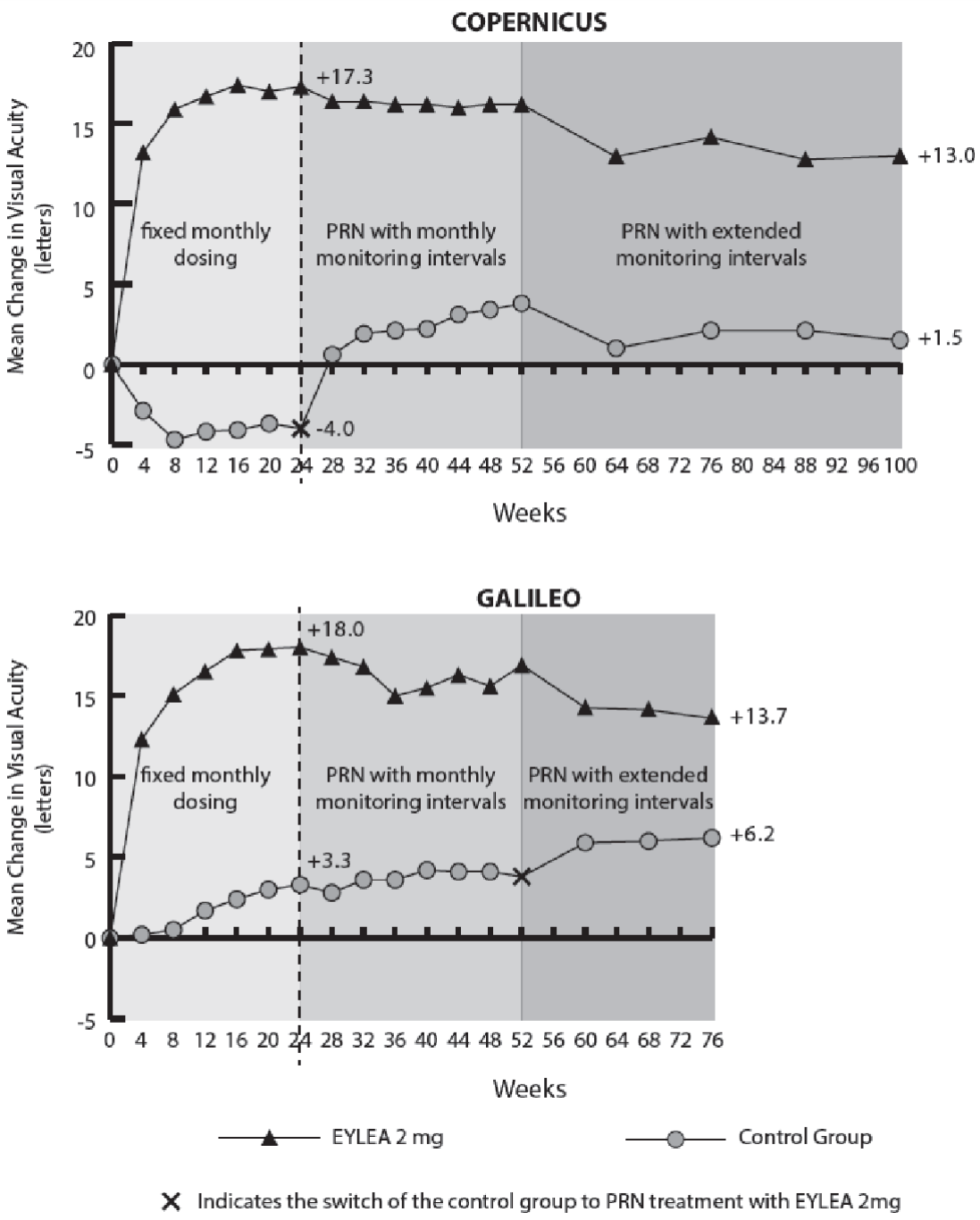
Efficacy Outcomes	**24 Weeks**		**52 Weeks**		**76 Weeks**	
	Control (N = 68)	**EYLEA 2 mg Q4 (N = 103)**	**Control (N = 68)**	**EYLEA 2 mg (N = 103)**	**Control[g] (N = 68)**	**EYLEA[g] 2 mg (N = 103)**
Proportion of patients who gained at least 15 letters in BCVA[c] from baseline*	22%	60%	32%	60%	29.4%	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%

Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

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 EYLEA 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 EYLEA 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 EYLEA 2 mg patients received EYLEA 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 EYLEA 2 mg patients received EYLEA 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 EYLEA group at week 24; n=67 in the control group and n=98 in the EYLEA group at week 52

Figure 5: 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)***

EYLEA 2 mg

The safety and efficacy of EYLEA 2 mg 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 EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA 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 EYLEA group received 2 mg every 8 weeks through week 48, and patients in the control group could receive treatment with EYLEA 2 mg, if at least one pre-specified rescue criterion was met. EYLEA rescue treatment consisted of a fixed regimen with 2 mg EYLEA 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 EYLEA 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 EYLEA 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 EYLEA. 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 EYLEA 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 14 and Figure 6 below.

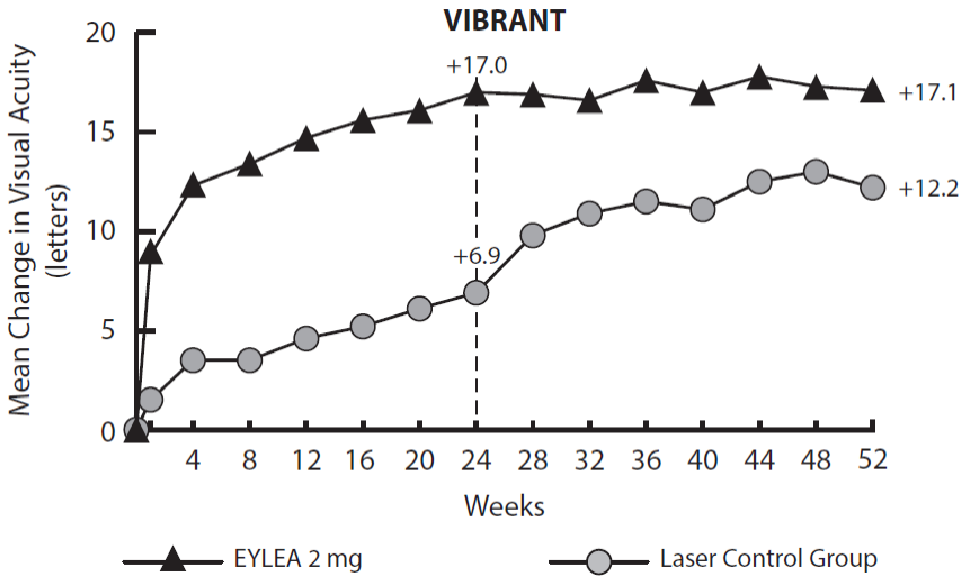
Table 14: Efficacy outcomes at week 24, and week 52 (Full Analysis Set LOCF) in the VIBRANT study

VIBRANT				
Efficacy Outcomes	**EYLEA 2 mg Q4 (N = 91)**	**Active Control (laser) (N = 90)**	**EYLEA 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 EYLEA 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 EYLEA 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 EYLEA if they met at least one pre-specified eligibility criterion. A total of 67 subjects (74%) in this group received EYLEA rescue treatment. The fixed regimen for EYLEA rescue was EYLEA 2 mg every 4 weeks for three injections, followed by injections every 8 weeks.

Figure 6: 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 EYLEA 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 EYLEA 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 EYLEA 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.

- ***Myopic choroidal neovascularisation (myopic CNV)***

<u>EYLEA 2 mg</u>

The safety and efficacy of EYLEA 2 mg 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 EYLEA). Patients were randomly

assigned in a 3:1 ratio to either 2 mg EYLEA 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 EYLEA 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 EYLEA 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 EYLEA 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 15 and Figure 7 below.

Table 15: Efficacy outcomes at week 24 (primary analysis) and in week 48 in MYRROR study (Full Analysis Set with LOCF[a])

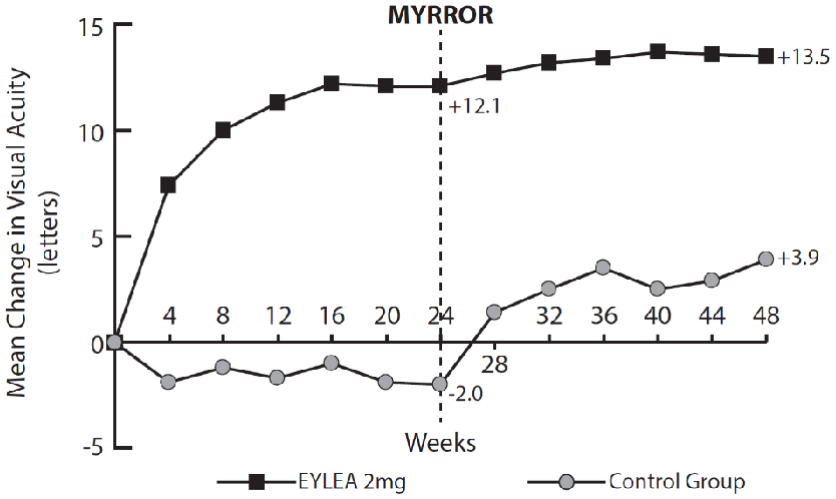
MYRROR				
Efficacy Outcomes	**24 Weeks**		**48 Weeks**	
	EYLEA 2 mg[b] (N = 90)	**Sham (N = 31)**	**EYLEA 2 mg[c] (N = 90)**	**Sham / EYLEA 2 mg[d] (N = 31)**
Mean change in BCVA letter score as measured by ETDRS from baseline (SD)[e]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean[f,g,h,i] (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) EYLEA 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.
c) EYLEA 2 mg administered from week 24 through week 44 potentially every 4 weeks in case of disease persistence or recurrence
d) Mandatory injection of EYLEA 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 EYLEA 2 mg minus sham at Week 24 and EYLEA 2 mg minus sham/EYLEA 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 7: 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption/distribution

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

EYLEA 2 mg

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 16: Tabulated summary of free aflibercept in plasma by indication

Indication	**Mean C_{max} 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*

Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

* 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.

EYLEA 8 mg

As no relevant differences in pharmacokinetics between the nAMD and DME populations were observed based on a population pharmacokinetic analysis of the data, population pharmacokinetic estimated parameters are presented for the two populations combined. Following unilateral intravitreal administration of 8 mg aflibercept, the mean (SD) C_{max} of free aflibercept in plasma was 0.30 (0.27) mg/L, and the median time to maximal plasma concentration in plasma was 2.89 days. The accumulation of free aflibercept in plasma following three initial monthly intravitreal doses was minimal (mean accumulation ratio 1.2); subsequently, no further accumulation was observed.

Metabolism

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

Excretion

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. The median time to reach non-quantifiable concentrations of free aflibercept in plasma for 8 mg administered intravitreally was 3.5 weeks.

Patients with renal/hepatic impairment

No special studies in patients with renal impairment or hepatic impairment have been conducted with EYLEA.

Population pharmacokinetic analysis revealed that systemic exposures to aflibercept in patients with mild to severe renal impairment were similar to those with normal renal function. Mild hepatic impairment had no influence on systemic exposures to aflibercept compared to patients with normal hepatic function.

See also ‘Dosage adjustment in patients with hepatic and/or renal impairment‘ section 4.2.

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

EYLEA 40 mg/mL (EYLEA 2 mg)
Polysorbate 20
Monobasic sodium phosphate monohydrate
Dibasic sodium phosphate heptahydrate
Sodium chloride
Sucrose
Water for injections

EYLEA 114.3 mg/mL (EYLEA 8 mg)
Polysorbate 20
Arginine hydrochloride
Histidine
Histidine hydrochloride monohydrate
Sucrose
Water for injections

6.2 INCOMPATIBILITIES

EYLEA must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

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

filled syringe in its blister pack and carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

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

Not all presentations are being distributed in Australia.

- ***EYLEA 40 mg/mL (EYLEA 2 mg) vial***

Each carton includes a type I glass vial containing approximately 100 µL of extractable volume, with an elastomeric rubber stopper, and an 18 G filter needle.

- ***EYLEA 40 mg/mL (EYLEA 2 mg) pre-filled syringe***

Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe, containing approximately 90 µL 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 plate.

- ***EYLEA 114.3 mg/mL (EYLEA 8 mg) vial***

EYLEA 8 mg is supplied in a single-use vial. Each carton includes a type I glass vial containing approximately 100 µL of extractable volume, with an elastomeric rubber stopper, and an 18 G filter needle.

- ***EYLEA 114.3 mg/mL (EYLEA 8 mg) pre-filled syringe with OcuClick dosing system***

Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe containing 184 µL fill volume, sealed with an elastomeric plunger stopper and an elastomeric tip cap. The pre-filled syringe comes with a customised integrated OcuClick dosing system consisting of finger flange and plunger rod.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

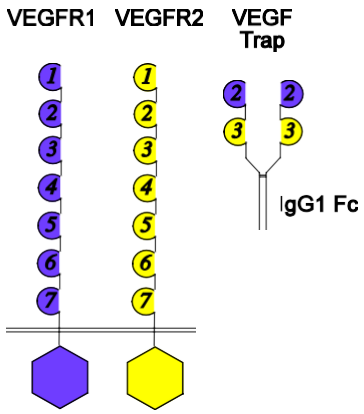
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

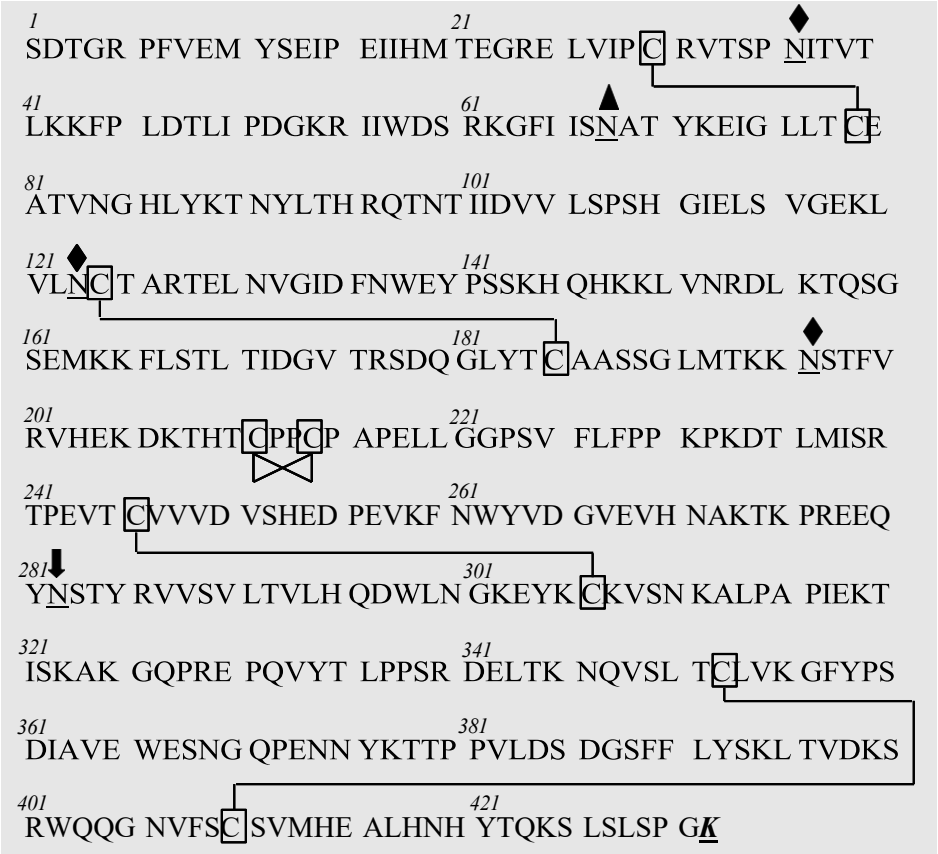
The secondary and tertiary structures of aflibercept as well as the amino acid structure are shown in Figure 8 and Figure 9.

Figure 8: Aflibercept secondary and tertiary structures



Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

Figure 9: Aflibercept amino acid structure



Chemical names:	Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer
Molecular weight:	97 kDa (protein molecular weight) 115 kDa (total molecular weight)

CAS number

862111-32-8

7. MEDICINE SCHEDULE

PRESCRIPTION ONLY MEDICINE (S4)

8. SPONSOR

Bayer Australia Ltd

ABN 22 000 138 714

875 Pacific Highway

Pymble NSW 2073

www.bayer.com.au

9. DATE OF FIRST APPROVAL

7 March 2012

10. DATE OF REVISION OF THE TEXT

25 March 2025

Summary table of changes

Section changed	Summary of new information
4.2	Update of dose line description

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Note: Eylea 114.3 mg/mL is also referred to as Eylea 8 mg;
Eylea 40 mg/mL is also referred to as Eylea 2 mg in this document.

Annexure B

AUSTRALIAN PRODUCT INFORMATION
AFQLIR® AFLIBERCEPT SOLUTION FOR INTRAVITREAL INJECTION (2 MG)

1. NAME OF THE MEDICINE

AFQLIR (aflibercept) 2 mg is a biosimilar medicine to EYLEA® (aflibercept) 2 mg. The comparability of AFQLIR (aflibercept) with EYLEA® (aflibercept) has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes (see sections; 5.1 Pharmacodynamic Properties, Clinical trials and 4.8 Adverse Effects (Undesirable Effects)).The evidence for comparability supports the use of AFQLIR for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see Section 6.1 List of excipients.

AFQLIR 40 mg/mL (vial for 2 mg dosing): Each 1 mL of AFQLIR solution contains 40 mg aflibercept. Each vial contains approximately 240 µL of solution. This amount is sufficient to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

AFQLIR 40 mg/mL (pre-filled syringe for 2 mg dosing): Each 1 mL of AFQLIR solution contains 40 mg aflibercept. Each pre-filled syringe contains approximately 165 µL of solution. This amount is sufficient to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

2 mg is the only dose of AFQLIR available. There is **NO** 8 mg AFQLIR available.

3. PHARMACEUTICAL FORM

Solution for intravitreal injection.

AFQLIR 40 mg/mL is a sterile, clear, colourless to slightly brownish-yellow, preservative-free, iso-osmotic aqueous solution.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

AFQLIR (aflibercept) 2 mg 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

AFQLIR is for intravitreal injection only.

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

Dosage

The recommended dose for AFQLIR (40 mg/mL) is 2 mg aflibercept, equivalent to an injection volume of 50 µL.

Do **NOT** administer the 8 mg dosing of aflibercept using AFQLIR. There is **NO** 8 mg AFQLIR available. If the 8 mg dosing is required, other aflibercept products offering such an option should be used.

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, AFQLIR should be discontinued.

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

AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg 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)***

AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg 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)***

AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg 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)***

AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg 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 Pharmacodynamic properties, Clinical trials).

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

AFQLIR 2 mg treatment is initiated with one AFQLIR 2 mg injection (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.

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 'Instruction for use/handling'). Injecting the entire volume of the glass vial or the pre-filled syringe could result in overdose.

- AFQLIR 40 mg/mL (vial for 2 mg dosing): To administer 2 mg aflibercept (equivalent to 50 µL solution for injection), eliminate all bubbles and expel excess drug by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 mL (equivalent to 50 µL) on the syringe before injecting.

- AFQLIR 40 mg/mL (pre-filled syringe for 2 mg dosing): To administer 2 mg aflibercept (equivalent to 50 µL solution for injection), eliminate all bubbles and expel excess drug by slowly depressing the plunger to **align the plunger dome edge (not the tip of the dome) with the black dosing line on the syringe**. This will ensure a delivery equivalent to 50 µL i.e. 2 mg aflibercept.

After injection any unused product or waste material must be discarded.

- ***Instructions for use / handling***

Vial

The vial contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). **The excess volume must be discarded prior to administration.**

Storage and inspection

	Store AFQLIR in the refrigerator at 2°C - 8°C; do not freeze. Keep the vial in the outer carton to protect from light.
	Prior to use, the unopened vial of AFQLIR may be kept at room temperature below 30°C for up to 14 days. Store in original carton and do not open vial until time of use. After opening the vial, proceed under aseptic conditions.
	AFQLIR is a clear and colourless to slightly brownish-yellow solution.
	AFQLIR should be inspected visually for any particulates, cloudiness and/or discoloration or any variation in physical appearance prior to administration. In the event of any of these being observed, discard AFQLIR. Do not use if the packaging, vial and/or filter needle are damaged or expired.

Preparation and administration

Each glass vial is for one-time use in one eye only.

For preparation and intravitreal injection the following single use medical devices are needed:

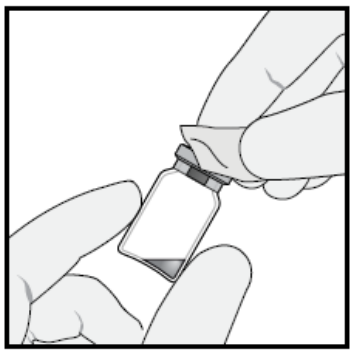
- A 5 µm blunt filter needle (18G x 1½ inch), sterile, supplied with the vial
- A 1 mL Luer-lock syringe with a 0.05 mL dose mark, sterile (not supplied)
- For the intravitreal injection, a sterile 30G x ½ inch injection needle should be used (not supplied)

Use aseptic technique to carry out the following steps.

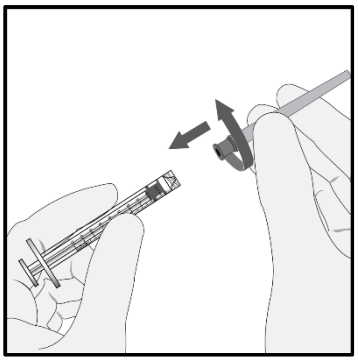
Injection procedure

1. Remove the protective plastic cap from the vial.

2. Clean the top of the vial with an alcohol wipe.

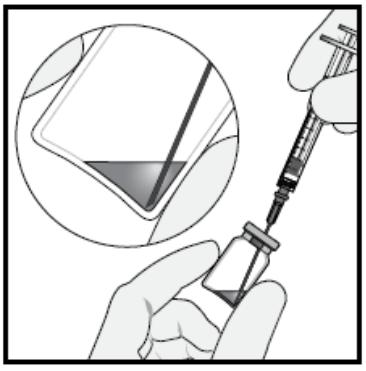


3. Attach the supplied 18G x 1½ inch, 5-micron filter needle to a 1 mL sterile, Luer-lock syringe by twisting it onto the syringe tip.



4. Push the filter needle into the centre 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.

5. Using aseptic technique withdraw all of the AFQLIR vial content into the syringe, keeping the vial in an upright position, **slightly inclined to ease complete withdrawal**. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.



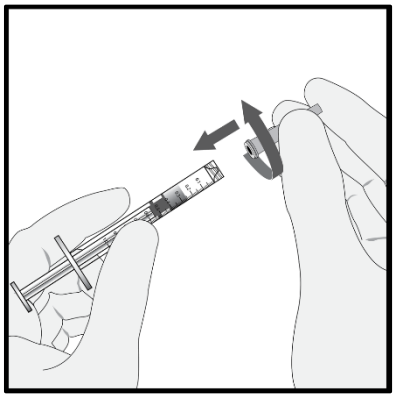
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle.

   Note: Filter needle is **not** to be used for intravitreal injection.

8. Attach the 30G x ½ inch injection needle to the syringe by firmly twisting the injection needle onto the Luer-lock syringe tip.

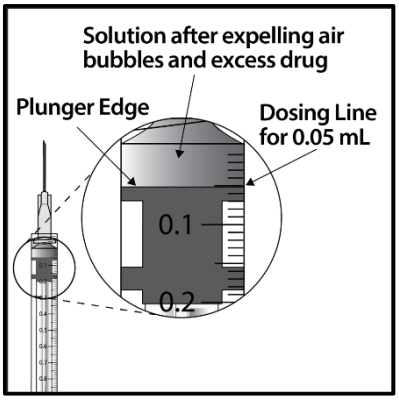
   Carefully remove the needle cap by pulling it straight off.



9. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

10. To eliminate all of the bubbles and to expel excess drug, **slowly** depress the plunger so that the flat plunger edge aligns with the line that marks **0.05 mL** on the syringe.

    Note: Inject immediately after preparation.



11. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. **Confirm delivery of the full dose** by checking that the rubber stopper has reached the end of the syringe barrel.

12. The vial is for one-time use in one eye only. Do not extract multiple doses from a single vial, as this may increase the risk of contamination and subsequent infection.

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

Pre-filled syringe

The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). **The excess volume must be discarded prior to administration.**

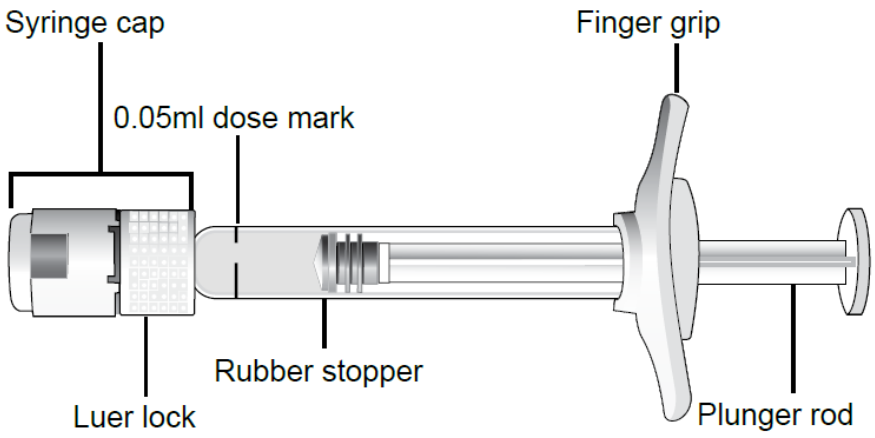
Storage and inspection

	Store AFQLIR in the refrigerator at 2°C - 8°C; do not freeze. Keep the pre-filled syringe in the outer carton to protect from light.
	Prior to usage, the unopened blister of AFQLIR may be stored at room temperature below 30°C for up to 14 days. Store in original carton and do not open sealed blister pack until time of use. After opening the blister, proceed under aseptic conditions.
	AFQLIR is a clear and colourless to slightly brownish-yellow solution.
	The solution should be inspected visually for any particulates, cloudiness and/or discoloration or any variation in physical appearance prior to administration. In the event of any of these being observed, discard the medicinal product. Do not use if the package is open or damaged. Do not use if any part of the pre-filled syringe is damaged, if the syringe cap is detached from the Luer lock, or if the pre-filled syringe is expired.

Preparation and administration

Each pre-filled syringe is for one-time use in one eye only.
Do not open the sterile pre-filled syringe blister outside the clean administration room.
For the intravitreal injection, a sterile 30G x ½ inch injection needle should be used (not supplied).
Use aseptic technique to carry out the following steps.

Pre-filled syringe description



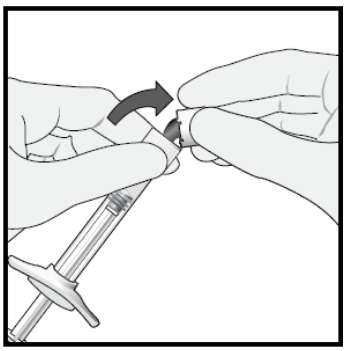
Injection procedure

1. When ready to administer AFQLIR, open the carton and remove sterilised blister pack. Carefully peel open the sterilised blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2. Using aseptic technique, remove the syringe from the sterilised blister pack.

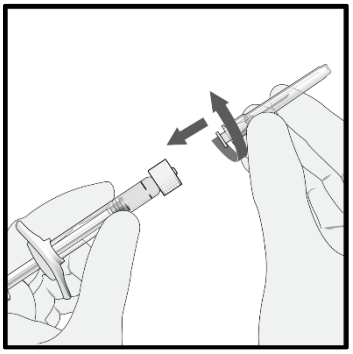
3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger. **Snap off** (do not turn or twist) the syringe cap.

   Note: To avoid compromising the sterility of the product, do not pull back on the plunger.

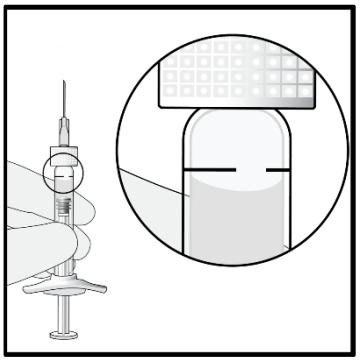


4. Using aseptic technique, firmly twist a 30G x ½ inch injection needle onto the Luer-lock syringe tip.

   Carefully remove the needle cap by pulling it straight off.

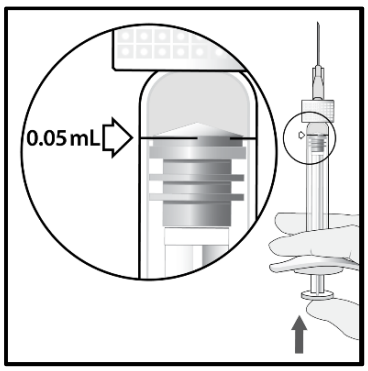


5. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



6. Eliminate all bubbles and expel excess drug by slowly depressing the plunger rod to align the plunger dome edge (not the tip of the dome) with the black dosing line on the syringe (equivalent to 50 microlitres).

   Note: Inject **immediately** after priming the syringe.



7. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel. Do not apply additional pressure once the end of the syringe is reached.

8. The pre-filled syringe is for one-time use in one eye only. Do not extract multiple doses from a pre-filled syringe, as this may increase the risk of contamination and subsequent infection. Any unused product or waste material should be disposed of in accordance with local requirements.

Dosage adjustment in:

- ***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).

For aflibercept 2 mg, 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***

Available data do not suggest a need for a dose adjustment with aflibercept 2 mg in these patients. (see Section 5.1 Pharmacodynamic properties, Clinical trials).

4.3. CONTRAINDICATIONS

- Known hypersensitivity to aflibercept or to any of the excipients of AFQLIR (see Section 6.1 List of excipients)
- Ocular or periocular infection
- Active severe intraocular inflammation

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Endophthalmitis, Retinal vasculitis and/or retinal occlusive vasculitis

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

Retinal detachment

Intravitreal injections, including those with aflibercept, have been associated with retinal detachment (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 Adverse effects (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 Adverse effects (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.

Bilateral treatment

Bilateral treatment with AFQLIR should be avoided. The safety and efficacy of bilateral treatment with aflibercept have not been systematically studied (see Section 5.1 Pharmacodynamic properties, Clinical trials). 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.

Retinal pigment epithelial tear

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.

Withholding treatment

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

There is only limited experience with aflibercept treatment in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy or Type 1 diabetes. Aflibercept has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with aflibercept in patients with uncontrolled hypertension. In myopic CNV there is no experience with aflibercept in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

This lack of information should be considered by the ophthalmologist when treating such patients.

Use in the elderly

Available data do not suggest a need for a dose adjustment with aflibercept 2 mg in these patients (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). There is limited experience in patients with DME aged 75 years and older.

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. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been performed with aflibercept.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in pregnancy

Category D

There are limited 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 2 mg.

AFQLIR should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. The treating ophthalmologist in consultation with the treating obstetrician need to consider the individual benefit-risk balance for each patient. This includes a consideration of timing of treatment, delaying treatment and other potential treatment options.

Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration.

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 embryofetal development was not established. At the lowest dose tested (0.1 mg/kg), the systemic exposures based on C_{max} and cumulative AUC for 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.

Use in lactation

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

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 Adverse effects (Undesirable effects)). Patients should not drive or use machinery until visual function has recovered sufficiently.

4.8. ADVERSE EFFECTS (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 DME, 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 with aflibercept 2 mg

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,	Endophthalmitis**, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye,	Blindness, Cataract traumatic, Vitritis, Hypopyon

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)
		Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia Ocular hyperaemia	Eyelid irritation, Anterior chamber flare, Corneal oedema	

* 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 2 mg, for which a frequency could not be estimated.

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

Eye disorders: retinal vasculitis and retinal occlusive vasculitis, scleritis

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 AFQLIR (aflibercept 2 mg) with EYLEA (aflibercept 2 mg) in terms of safety

The safety of AFQLIR was assessed over 52 weeks in patients with wet AMD in study CSOK583A12301 (see Section 5.1 Pharmacodynamic properties, Clinical trials). The mean number of study treatment injections was 7.6 in both the AFQLIR (n=244) and Eylea (n=240) arms. The frequency and severity of ocular treatment-emergent adverse events were broadly comparable between AFQLIR 2 mg and Eylea 2 mg.

Serious non-ocular adverse events were reported in 14.2% and 11.3% of patients treated with AFQLIR and Eylea, respectively. Arterial thromboembolic events, defined as nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause), were reported in 2.9% and 0.8% of patients treated with AFQLIR and Eylea, respectively.

Comparability of AFQLIR (aflibercept 2 mg) with EYLEA (aflibercept 2 mg) in terms of immunogenicity

Immunogenicity was evaluated in 465 subjects in study CSOK583A12301. No clinically meaningful difference was found between AFQLIR and Eylea in terms of the incidence of treatment-emergent anti-drug antibodies (ADAs).

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems

4.9. OVERDOSE

Overdosing with increased injection volume may increase intraocular pressure.

Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating ophthalmologist, adequate treatment should be initiated (see section 4.2 Dose and method of administration, Method of administration).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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-A121 is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

• Pharmacodynamic effects

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 2: 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						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**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						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**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 thickness from baseline	-169	-449	-219	-424	-306	-389
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 3: Pharmacodynamic parameter at week 24 and at week 52 (Full Analysis Set with LOCF) in VIBRANT study

VIBRANT				
	24 Weeks		52 Weeks	
Efficacy Outcomes	**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 (DME)

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

VIVID^{DME}						
	52 Weeks			100 Weeks		
Efficacy Outcomes	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}						
	52 Weeks			100 Weeks		
Efficacy Outcomes	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 5: Pharmacodynamic parameter at week 24 and week 48 in MYRROR study (Full Analysis Set with LOCF[a])

MYRROR				
	24 Weeks		48 Weeks	
Efficacy Outcomes	**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.

Clinical trials

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

The safety and efficacy of aflibercept 2mgwere assessed in two pivotal phase III randomised, multi-centre, 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 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.

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 6 and Figure 1 below.

Table 6: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW 1 and VIEW 2 studies[b)]

	Aflibercept 2 mg Q4 (N = 613)		Aflibercept 2 mg Q8[e)] (N = 607)		Ranibizumab 0.5 mg Q4 (N = 595)	
Efficacy Outcomes	**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 BCVA[a)] 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 ETDRS[a)] 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.

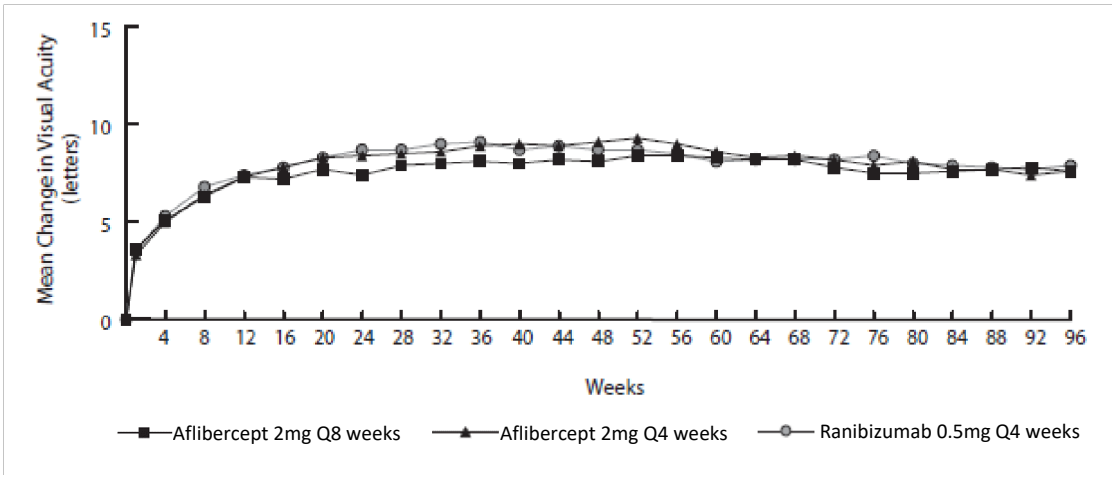
d) Confidence Interval (CI) calculated by normal approximation

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 2mg 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 maximum 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 the 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.

- ***Macular oedema secondary to central retinal vein occlusion (CRVO)***

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 VFQ25 total score at week 24 compared to baseline.

Detailed results from the analysis of both studies (primary* and secondary[#] endpoints) are shown in Table 2 (see Section 5.1 Pharmacodynamic properties, Pharmacodynamic effects), Table 7 and Figure 2 below.

Table 7: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[c]) in COPERNICUS and GALILEO studies

COPERNICUS						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**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)

COPERNICUS						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**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)**
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						
	24 Weeks		52 Weeks		76 Weeks	
Efficacy Outcomes	**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%

GALILEO						
	24 Weeks		52 Weeks		76 Weeks	
Efficacy Outcomes	**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)**
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
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

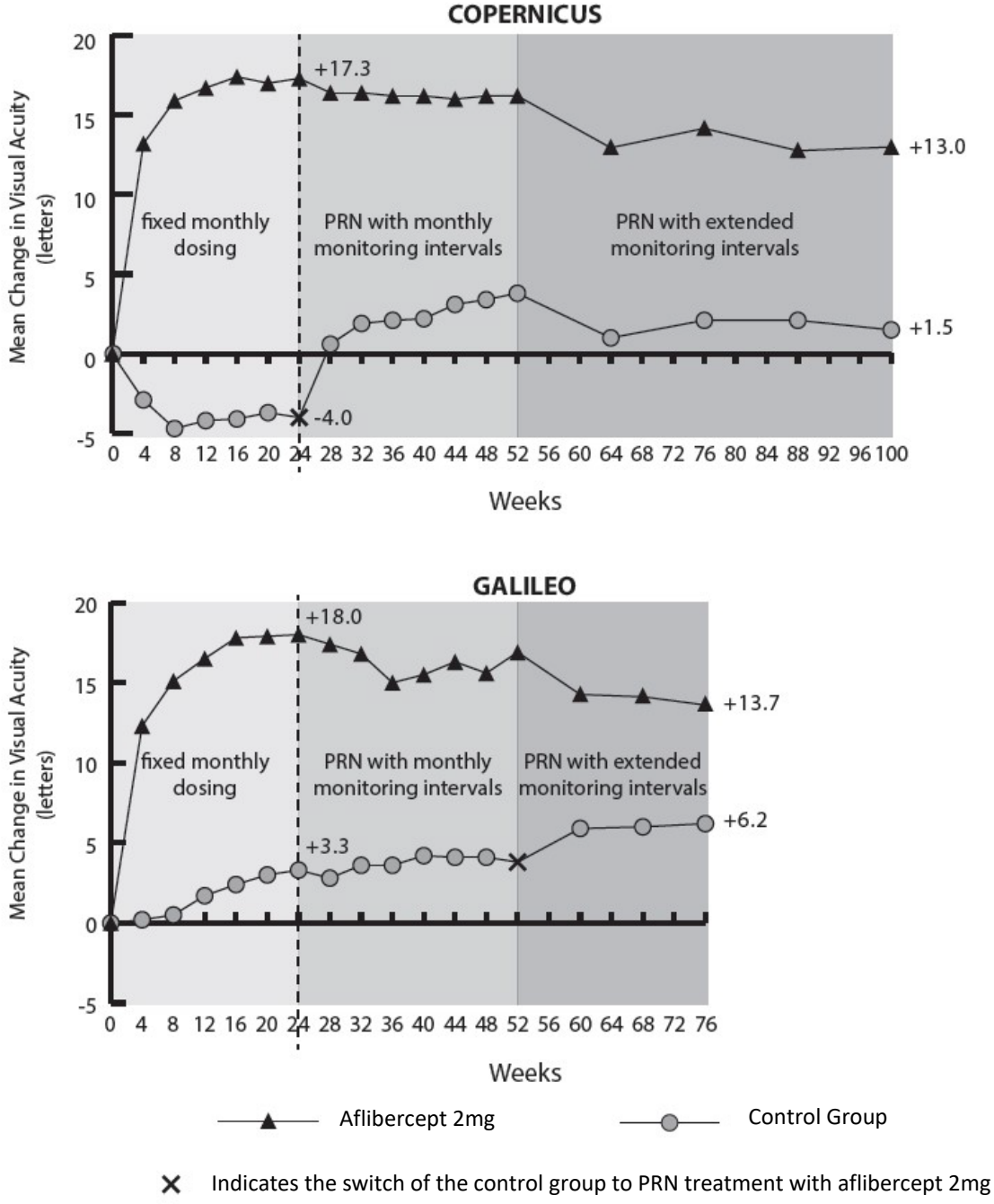
g) In GALILEO study, both control group and aflibercept 2 mg patients received aflibercept 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks

* 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 2mg 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 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 8 and Figure 3 below.

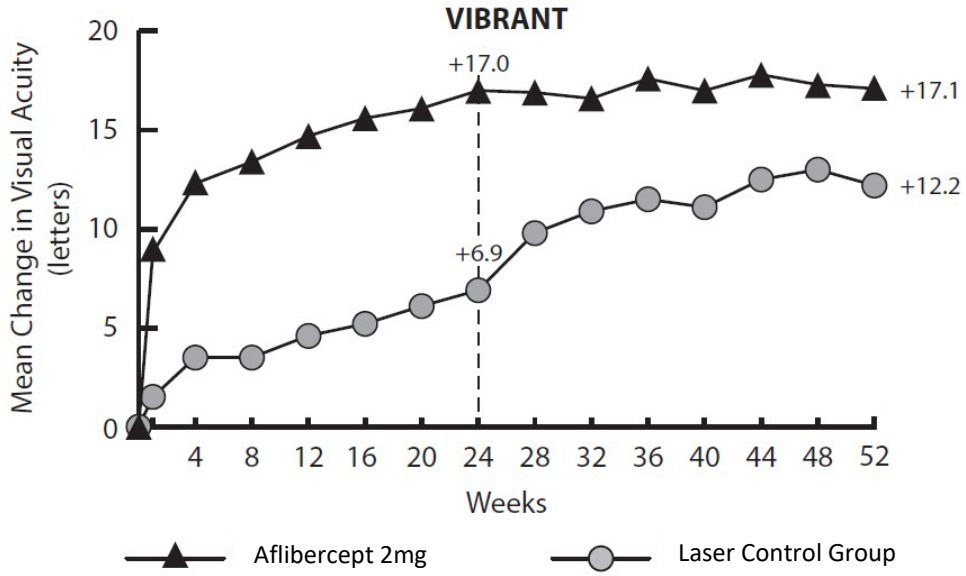
Table 8: Efficacy outcomes at week 24, and week 52 (Full Analysis Set LOCF) in the VIBRANT study

	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) (aflibercept 2mg)***

The safety and efficacy of aflibercept 2mg 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 9 and Figure 4 below.

Table 9: Efficacy outcomes at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} and VISTA^{DME} studies

VIVID^{DME}						
	52 Weeks			100 Weeks		
Efficacy Outcomes	**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	

VIVID[DME]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	**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)**
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 4 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]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	**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 4 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	

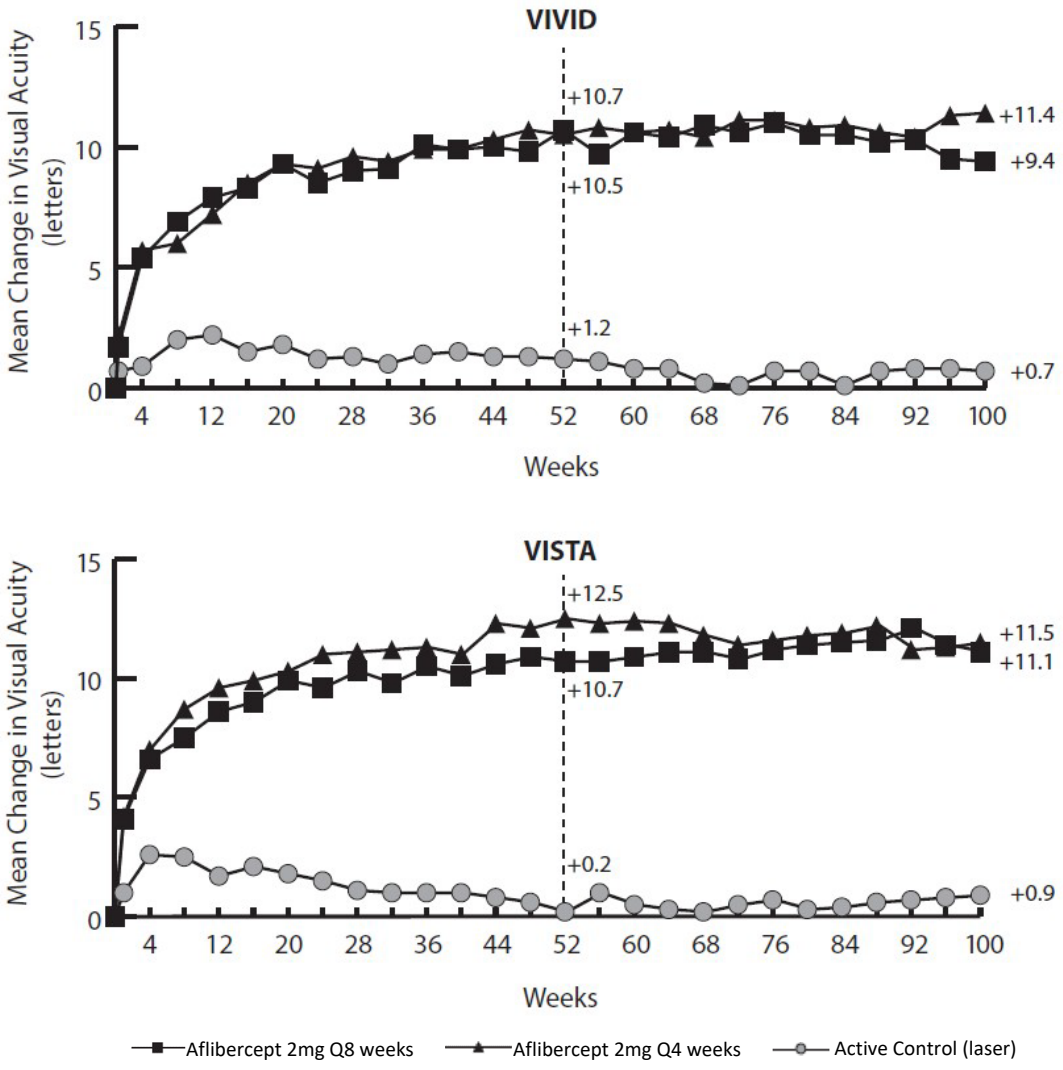
a) After treatment initiation with 5 monthly injections
b) LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as a factor for VIVID[DME], and history of MI and/or CVA 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 9).

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} (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 2mg 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.

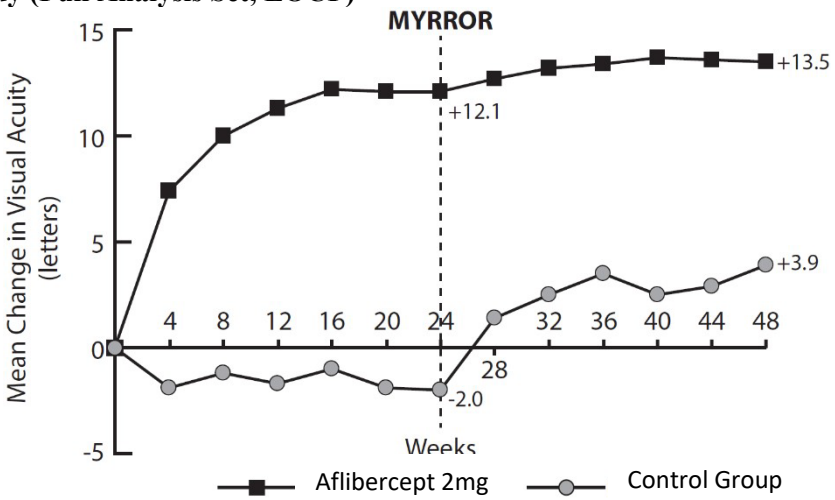
Detailed results from the analyses are shown in Table 10 and Figure 5 below.

Table 10: Efficacy outcomes at week 24 (primary analysis) and in week 48 in MYRROR study (Full Analysis Set with LOCF[a])

MYRROR				
	24 Weeks		48 Weeks	
Efficacy Outcomes	**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.

Comparative non-clinical pharmacology and toxicology

Pharmacodynamic comparability between AFQLIR and Eylea was demonstrated in *in vitro* studies.

Pharmacodynamic comparability of AFQLIR (aflibercept 2 mg) with EYLEA (aflibercept 2 mg)

No clinical comparative pharmacodynamic studies have been performed with AFQLIR.

Comparability of AFQLIR (aflibercept 2 mg) with EYLEA (aflibercept 2 mg) in terms of efficacy

Study CSOK583A12301 was an international, multicentre, randomised, double-masked, 2-arm parallel study in subjects with wet AMD, with a total duration of 52 weeks. The eligible subject population comprised male and female subjects who were 50 years of age or older, anti-VEGF treatment naive for both eyes, and diagnosed with active CNV secondary to AMD in the study eye.

A total of 485 subjects were randomised 1:1 to receive either AFQLIR or Eylea, and 484 subjects were treated. 461 subjects were included in the Per-protocol Set (PPS) for analysis of the primary efficacy endpoint. Only 1 eye was selected as the study eye. Subjects received a single intravitreal injection of AFQLIR 2 mg or Eylea 2 mg in the study eye every 4 weeks at 3 consecutive visits (Baseline, Week 4, and Week 8), and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48.

The overall mean age in the PPS was 76 years (range 53 to 94), and 59% of subjects were 75 years or older. 56% of subjects were female and 89% were white. At baseline, the overall median time since diagnosis of nAMD in the PPS was 12 days, and less than 30 days had passed since diagnosis in 74% of patients. The overall mean BCVA score at baseline, as measured using ETDRS charts, was 59.7 letters. At baseline, 81% and 75% of subjects in the PPS had the occult lesion type in the AFQLIR arm and the Eylea arm, respectively.

Primary efficacy was assessed at Week 8 after subjects have received two injections of either AFQLIR 2 mg or Eylea 2 mg. At Week 8 the difference between AFQLIR and Eylea in the LS mean changes in BCVA score from baseline was −0.3 letters for the PPS. The 95% CI (−1.8, 1.3) was contained within the prespecified interval [−3.5, +3.5]. Similar efficacy in terms of change in BCVA score from baseline was concluded.

Table 11: Primary efficacy analysis (PPS) - Summary statistics and ANCOVA for change in BCVA score from baseline to Week 8 in study CSOK583A12301

	AFQLIR 2 mg (n = 235)	**Eylea 2 mg** (n = 226)
Mean change in BCVA score from baseline to Week 8 as measured using ETDRS testing charts (SD)	6.5 (8.98)	6.8 (7.46)
ANCOVA LS mean difference (95% CI)	-0.3 (-1.8, 1.3)	

Baseline was the pre-dose BCVA score prior to the first aflibercept (AFQLIR or Eylea) injection. ANCOVA included treatment as a factor and baseline BCVA and age as continuous covariates. ANCOVA: Analysis of covariance; BCVA: Best-corrected visual acuity; CI: confidence interval; ETDRS: Early treatment diabetic retinopathy study; LS mean: least-squares mean; PPS: per-protocol set; SD: standard deviation

5.2. PHARMACOKINETIC PROPERTIES

Aflibercept 2 mg 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 12: Tabulated summary of free aflibercept in plasma by indication

Indication	Mean C_{max} 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.

Metabolism

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

Excretion

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.

Pharmacokinetic comparability of AFQLIR (aflibercept 2 mg) with EYLEA (aflibercept 2 mg)

A dedicated study to demonstrate pharmacokinetic comparability was not conducted due to the low systemic exposure of aflibercept after intravitreal injection.

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

Histidine

Histidine hydrochloride monohydrate

Trehalose dihydrate

Polysorbate 20

Hydrochloric acid

Sodium hydroxide

Water for injections

6.2. INCOMPATIBILITIES

AFQLIR must not be mixed with other medicinal products.

6.3. SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the ARTG.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

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

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

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

Prior to usage, the unopened vial or pre-filled syringe blister pack of AFQLIR may be stored outside the refrigerator below 30°C for up to 14 days. Store in original carton and do not open vial or sealed blister pack until time of use. After opening the vial or blister pack, proceed under aseptic conditions.

6.5. NATURE AND CONTENTS OF CONTAINER

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

- ***Vial***

Each carton includes a type I glass vial containing approximately 240 µL of solution, which provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept. The vial is sealed with an elastomeric rubber stopper, and is provided with an 18 G filter needle.

- ***Pre-filled syringe***

Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe, containing approximately 165 µL of solution, which provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept. The syringe is 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 grip.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure

The secondary and tertiary structures of aflibercept as well as the amino acid structure are shown in Figure 6 and Figure 7.

Figure 6: Aflibercept secondary and tertiary structures

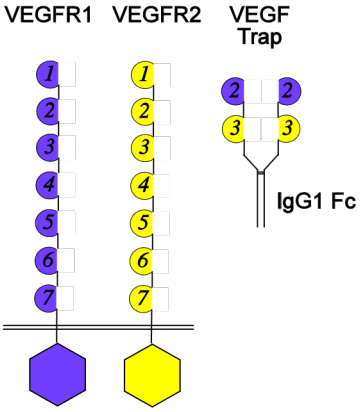
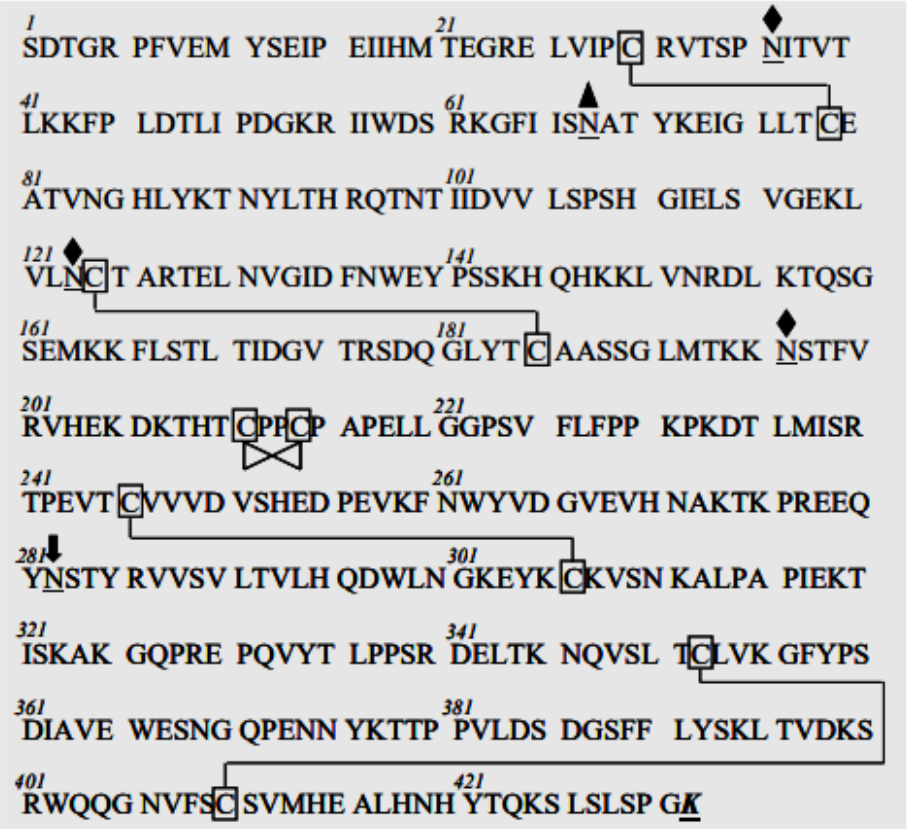


Figure 7: Aflibercept amino acid structure



Chemical names: Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine[human vascular endothelial growth factor receptor 1-(103-204)peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

Molecular weight: 97 kDa (protein molecular weight)

115 kDa (total molecular weight)

CAS number

862111-32-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Sandoz Pty Ltd
100 Pacific Highway
North Sydney, NSW 2060
Australia

Tel 1800 726 369

9. DATE OF FIRST APPROVAL

DD/MM/YYYY

10. DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

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Annexure C

AUSTRALIAN PRODUCT INFORMATION
ENZEEVU® AFLIBERCEPT SOLUTION FOR INTRAVITREAL INJECTION (2 MG)

1. NAME OF THE MEDICINE

ENZEEVU (aflibercept) 2 mg is a biosimilar medicine to EYLEA® (aflibercept) 2 mg. The comparability of ENZEEVU (aflibercept) with EYLEA® (aflibercept) has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes (see sections; 5.1 Pharmacodynamic Properties, Clinical trials and 4.8 Adverse Effects (Undesirable Effects)). The evidence for comparability supports the use of ENZEEVU for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see Section 6.1 List of excipients.

ENZEEVU 40 mg/mL (vial for 2 mg dosing): Each 1 mL of ENZEEVU solution contains 40 mg aflibercept. Each vial contains approximately 240 µL of solution. This amount is sufficient to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

ENZEEVU 40 mg/mL (pre-filled syringe for 2 mg dosing): Each 1 mL of ENZEEVU solution contains 40 mg aflibercept. Each pre-filled syringe contains approximately 165 µL of solution. This amount is sufficient to deliver a single dose of 50 µL solution for intravitreal injection containing 2 mg aflibercept.

2 mg is the only dose of ENZEEVU available. There is **NO** 8 mg ENZEEVU available.

3. PHARMACEUTICAL FORM

Solution for intravitreal injection.

ENZEEVU 40 mg/mL is a sterile, clear, colourless to slightly brownish-yellow, preservative-free, iso-osmotic aqueous solution.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

ENZEEVU (aflibercept) 2 mg 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

ENZEEVU is for intravitreal injection only.

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

Dosage

The recommended dose for ENZEEVU (40 mg/mL) is 2 mg aflibercept, equivalent to an injection volume of 50 µL. Do **NOT** administer the 8 mg dosing of aflibercept using ENZEEVU. There is **NO** 8 mg ENZEEVU available. If the 8 mg dosing is required, other aflibercept products offering such an option should be used.

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, ENZEEVU should be discontinued.

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

ENZEEVU 2 mg treatment is initiated with one ENZEEVU 2 mg injection per month for three consecutive months, followed by one injection every two months.

Based on the ophthalmologist'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)***

ENZEEVU 2 mg treatment is initiated with one ENZEEVU 2 mg 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)***

ENZEEVU 2 mg treatment is initiated with one ENZEEVU 2 mg 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)***

ENZEEVU 2 mg treatment is initiated with one ENZEEVU 2 mg injection per month for five consecutive months.

Following the initiation period and based on the ophthalmologist'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 Pharmacodynamic properties, Clinical trials).

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

ENZEEVU 2 mg treatment is initiated with one ENVEEZU 2 mg injection (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.

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 'Instruction for use/handling'). Injecting the entire volume of the glass vial or the pre-filled syringe could result in overdose.

- ENZEEVU 40 mg/mL (vial for 2 mg dosing): To administer 2 mg aflibercept (equivalent to 50 µL solution for injection), eliminate all bubbles and expel excess drug

by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 mL (equivalent to 50 µL) on the syringe before injecting.

- ENZEEVU 40 mg/mL (pre-filled syringe for 2 mg dosing): To administer 2 mg aflibercept (equivalent to 50 µL solution for injection), eliminate all bubbles and expel excess drug by slowly depressing the plunger to **align the plunger dome edge (not the tip of the dome) with the black dosing line on the syringe**. This will ensure a delivery equivalent to 50 µL i.e. 2 mg aflibercept.

After injection any unused product or waste material must be discarded.

- ***Instructions for use / handling***

Vial

The vial contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). **The excess volume must be discarded prior to administration.**

Storage and inspection

	Store ENZEEVU in the refrigerator at 2°C - 8°C; do not freeze. Keep the vial in the outer carton to protect from light.
	Prior to use, the unopened vial of ENZEEVU may be kept at room temperature below 30°C for up to 14 days. Store in original carton and do not open vial until time of use. After opening the vial, proceed under aseptic conditions.
	ENZEEVU is a clear and colourless to slightly brownish-yellow solution.
	ENZEEVU should be inspected visually for any particulates, cloudiness and/or discoloration or any variation in physical appearance prior to administration. In the event of any of these being observed, discard ENZEEVU. Do not use if the packaging, vial and/or filter needle are damaged or expired.

Preparation and administration

Each glass vial is for one-time use in one eye only.

For preparation and intravitreal injection the following single use medical devices are needed:

- A 5 µm blunt filter needle (18G x 1½ inch), sterile, supplied with the vial

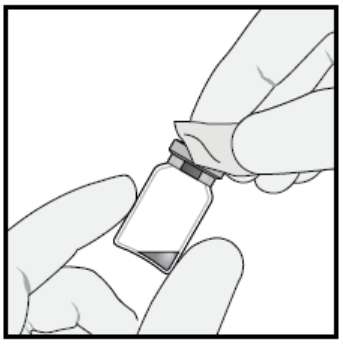
- A 1 mL Luer-lock syringe with a 0.05 mL dose mark, sterile (not supplied)
- For the intravitreal injection, a sterile 30G x ½ inch injection needle should be used (not supplied)

Use aseptic technique to carry out the following steps.

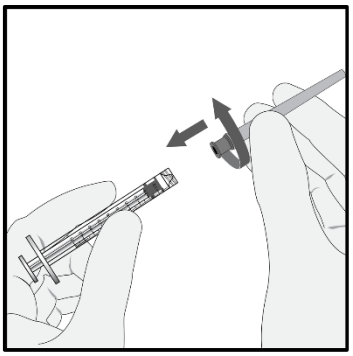
Injection procedure

1. Remove the protective plastic cap from the vial.

2. Clean the top of the vial with an alcohol wipe.

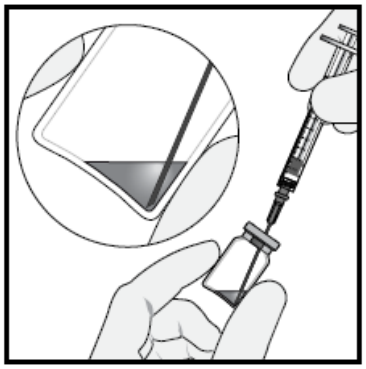


3. Attach the supplied 18G x 1½ inch, 5-micron filter needle to a 1 mL sterile, Luer-lock syringe by twisting it onto the syringe tip.



4. Push the filter needle into the centre 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.

5. Using aseptic technique withdraw all of the ENZEEVU vial content into the syringe, keeping the vial in an upright position, **slightly inclined to ease complete withdrawal**. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.



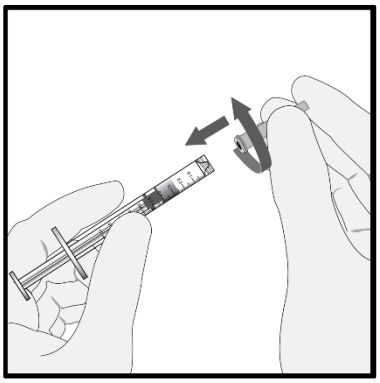
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

7. Remove the filter needle from the syringe and properly dispose of the filter needle.

   Note: Filter needle is **not** to be used for intravitreal injection.

8. Attach the 30G x ½ inch injection needle to the syringe by firmly twisting the injection needle onto the Luer-lock syringe tip.

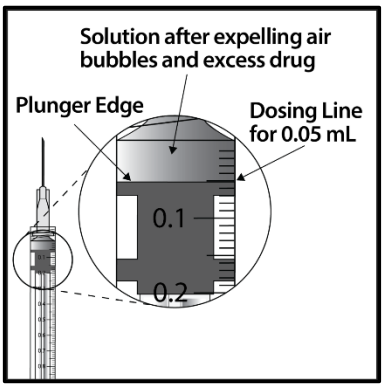
   Carefully remove the needle cap by pulling it straight off.



9. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

10. To eliminate all of the bubbles and to expel excess drug, **slowly** depress the plunger so that the flat plunger edge aligns with the line that marks **0.05 mL** on the syringe.

    Note: Inject immediately after preparation.



11. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. **Confirm delivery of the full dose** by checking that the rubber stopper has reached the end of the syringe barrel.

12. The vial is for one-time use in one eye only. Do not extract multiple doses from a single vial, as this may increase the risk of contamination and subsequent infection.

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

Pre-filled syringe

The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). **The excess volume must be discarded prior to administration.**

Storage and inspection

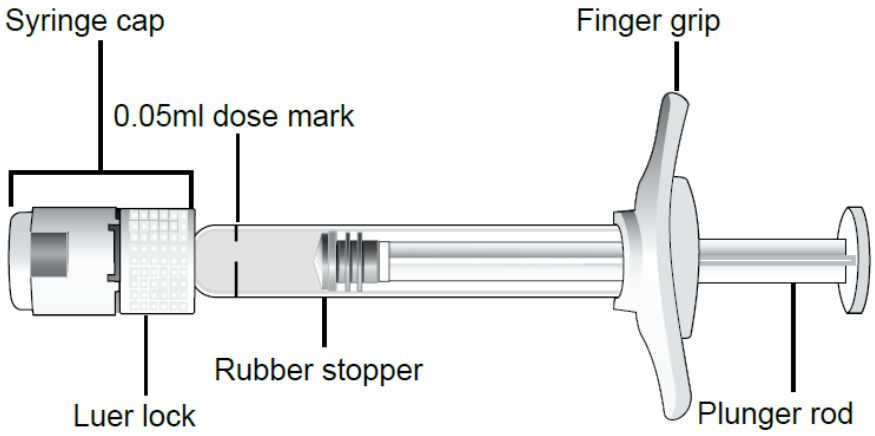
	Store ENZEEVU in the refrigerator at 2°C - 8°C; do not freeze. Keep the pre-filled syringe in the outer carton to protect from light.
	Prior to usage, the unopened blister of ENZEEVU may be stored at room temperature below 30°C for up to 14 days. Store in original carton and do not open sealed blister pack until time of use. After opening the blister, proceed under aseptic conditions.
	ENZEEVU is a clear and colourless to slightly brownish-yellow solution.
	The solution should be inspected visually for any particulates, cloudiness and/or discoloration or any variation in physical appearance prior to administration. In the event of any of these being observed, discard the medicinal product.

	Do not use if the package is open or damaged. Do not use if any part of the pre-filled syringe is damaged, if the syringe cap is detached from the Luer lock, or if the pre-filled syringe is expired.

Preparation and administration

Each pre-filled syringe is for one-time use in one eye only.
Do not open the sterile pre-filled syringe blister outside the clean administration room.
For the intravitreal injection, a sterile 30G x ½ inch injection needle should be used (not supplied).
Use aseptic technique to carry out the following steps.

Pre-filled syringe description



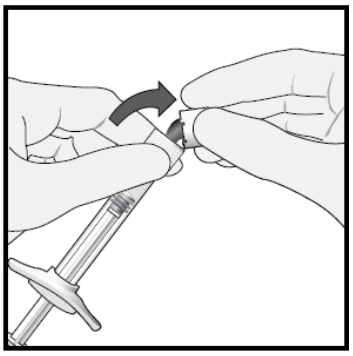
Injection procedure

1. When ready to administer ENZEEVU, open the carton and remove sterilised blister pack. Carefully peel open the sterilised blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2. Using aseptic technique, remove the syringe from the sterilised blister pack.

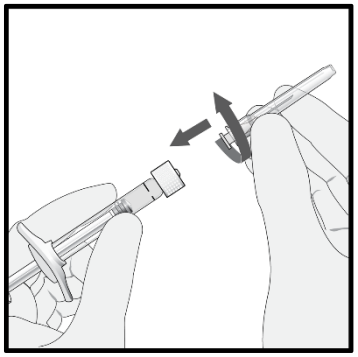
3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and forefinger. **Snap off** (do not turn or twist) the syringe cap.

   Note: To avoid compromising the sterility of the product, do not pull back on the plunger.



4. Using aseptic technique, firmly twist a 30G x ½ inch injection needle onto the Luer-lock syringe tip.

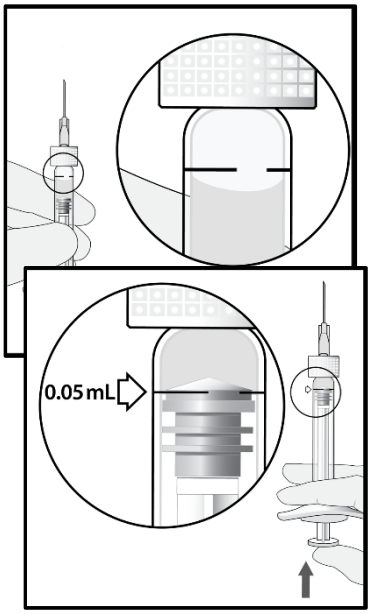
   Carefully remove the needle cap by pulling it straight off.



5. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

6. Eliminate all bubbles and expel excess drug by slowly depressing the plunger rod to align the plunger dome edge (not the tip of the dome) with the black dosing line on the syringe (equivalent to 50 microlitres).

   Note: Inject **immediately** after priming the syringe.



7. Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.05 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel. Do not apply additional pressure once the end of the syringe is reached.

8. The pre-filled syringe is for one-time use in one eye only. Do not extract multiple doses from a pre-filled syringe, as this may increase the risk of contamination and subsequent infection. Any unused product or waste material should be disposed of in accordance with local requirements.

Dosage adjustment in:

- **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).

For aflibercept 2 mg, 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**

Available data do not suggest a need for a dose adjustment with aflibercept 2 mg in these patients. (see Section 5.1 Pharmacodynamic properties, Clinical trials).

4.3. CONTRAINDICATIONS

- Known hypersensitivity to aflibercept or to any of the excipients of ENZEEVU (see Section 6.1 List of excipients)
- Ocular or periocular infection
- Active severe intraocular inflammation

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Endophthalmitis, Retinal vasculitis and/or retinal occlusive vasculitis

Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and more rarely, with retinal vasculitis and/or retinal occlusive vasculitis (see Section 4.8 Adverse effects (Undesirable effects)). Proper aseptic injection technique must always be used when administering ENZEEVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis, retinal vasculitis or retinal occlusive vasculitis without delay and should be managed appropriately.

Retinal detachment

Intravitreal injections, including those with aflibercept, have been associated with retinal detachment (see Section 4.8 Adverse effects (Undesirable effects)).

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 Adverse effects (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 Adverse effects (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.

Bilateral treatment

Bilateral treatment with ENZEEVU should be avoided. The safety and efficacy of bilateral treatment with aflibercept have not been systematically studied (see Section 5.1 Pharmacodynamic properties, Clinical trials). 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.

Retinal pigment epithelial tear

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.

Withholding treatment

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

There is only limited experience with aflibercept treatment in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy or Type 1 diabetes. Aflibercept has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with aflibercept in patients with uncontrolled hypertension. In myopic CNV there is no experience with aflibercept in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions.

This lack of information should be considered by the ophthalmologist when treating such patients.

Use in the elderly

Available data do not suggest a need for a dose adjustment with aflibercept 2 mg in these patients (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). There is limited experience in patients with DME aged 75 years and older.

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. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been performed with aflibercept.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in pregnancy

Category D

There are limited 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 2 mg.

ENZEEVU should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. The treating ophthalmologist in consultation with the treating obstetrician need to consider the individual benefit-risk balance for each patient. This includes a consideration of timing of treatment, delaying treatment and other potential treatment options.

Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration.

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 embryofetal development was not established. At the lowest dose tested (0.1 mg/kg), the systemic exposures based on C_{max} and cumulative AUC for 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.

Use in lactation

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

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 Adverse effects (Undesirable effects)). Patients should not drive or use machinery until visual function has recovered sufficiently.

4.8. ADVERSE EFFECTS (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 DME, 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 with aflibercept 2 mg

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***	

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)
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 2 mg, for which a frequency could not be estimated.

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

Eye disorders: retinal vasculitis and retinal occlusive vasculitis, scleritis

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 ENZEEVU (aflibercept 2 mg) with EYLEA (aflibercept 2 mg) in terms of safety

The safety of ENZEEVU was assessed over 52 weeks in patients with wet AMD in study CSOK583A12301 (see Section 5.1 Pharmacodynamic properties, Clinical trials). The mean number of study treatment injections was 7.6 in both the ENZEEVU (n=244) and Eylea (n=240) arms. The frequency and severity of ocular treatment-emergent adverse events were broadly comparable between ENZEEVU 2 mg and Eylea 2 mg.

Serious non-ocular treatment-emergent adverse events were reported in 14.2% and 11.3% of patients treated with ENZEEVU and Eylea, respectively. Arterial thromboembolic events, defined as nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause), were reported in 2.9% and 0.8% of patients treated with ENZEEVU and Eylea, respectively.

Comparability of ENZEEVU (aflibercept 2 mg) with EYLEA (aflibercept 2 mg) in terms of immunogenicity

Immunogenicity was evaluated in 465 subjects in study CSOK583A12301. No clinically meaningful difference was found between ENVEEZU and Eylea in terms of the incidence of treatment-emergent anti-drug antibodies (ADAs).

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems

4.9. OVERDOSE

Overdosing with increased injection volume may increase intraocular pressure.

Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating ophthalmologist, adequate treatment should be initiated (see section 4.2 Dose and method of administration, Method of administration).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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-A121 is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

• Pharmacodynamic effects

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 2: 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						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**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						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**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 thickness from baseline	-169	-449	-219	-424	-306	-389
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 3: Pharmacodynamic parameter at week 24 and at week 52 (Full Analysis Set with LOCF) in VIBRANT study

VIBRANT				
	24 Weeks		52 Weeks	
Efficacy Outcomes	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 (DME)

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 4: Pharmacodynamic parameter at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID[DME] and VISTA[DME]

VIVID[DME]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	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]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	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 5: Pharmacodynamic parameter at week 24 and week 48 in MYRROR study (Full Analysis Set with LOCF[a)])

MYRROR				
	24 Weeks		48 Weeks	
Efficacy Outcomes	**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.

Clinical trials

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

The safety and efficacy of aflibercept 2 mg were assessed in two pivotal phase III randomised, multi-centre, 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 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.

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 6 and Figure 1 below.

Table 6: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW 1 and VIEW 2 studies[b)]

	Aflibercept 2 mg Q4 (N = 613)		Aflibercept 2 mg Q8[e)] (N = 607)		Ranibizumab 0.5 mg Q4 (N = 595)	
Efficacy Outcomes	**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 BCVA[a)] 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 ETDRS[a)] 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

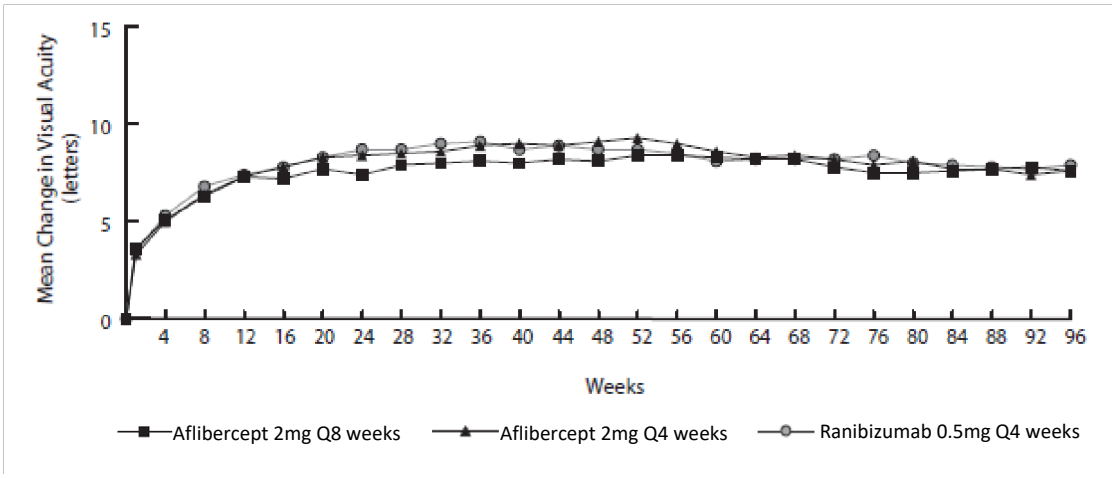
FA: Fluorescein angiography

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 2 mg 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 maximum 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 the 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.

- ***Macular oedema secondary to central retinal vein occlusion (CRVO)***

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 VFQ25 total score at week 24 compared to baseline.

Detailed results from the analysis of both studies (primary* and secondary# endpoints) are shown in Table 2 (see Section 5.1 Pharmacodynamic properties, Pharmacodynamic effects), Table 7 and Figure 2 below.

Table 7: Efficacy outcomes at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF[c]) in COPERNICUS and GALILEO studies

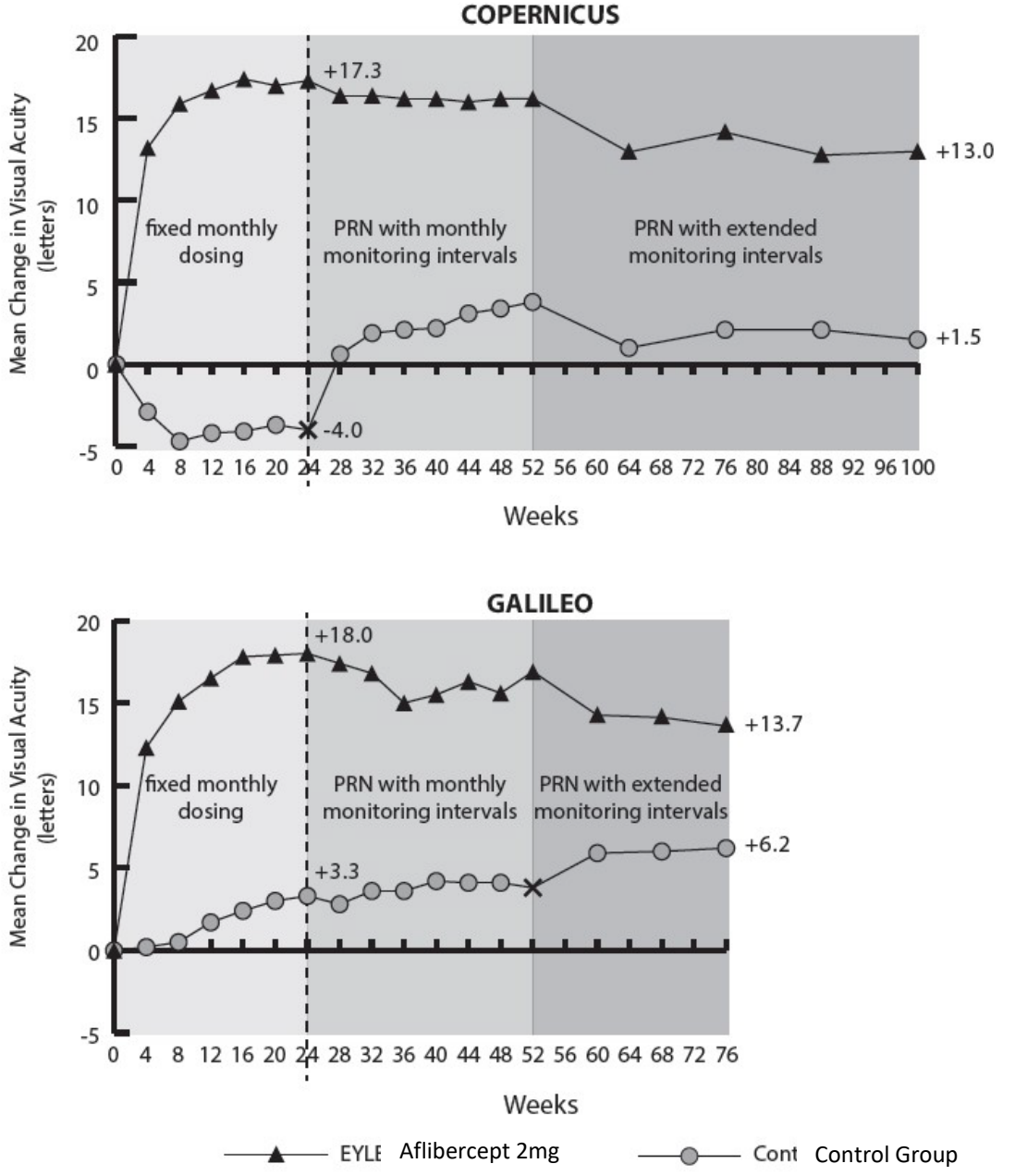
COPERNICUS						
	24 Weeks		52 Weeks		100 Weeks	
Efficacy Outcomes	**Control (N = 73)**	**Aflibercept 2 mg Q4 (N = 114)**	**Control[e] (N = 73)**	**Aflibercept 2 mg (N = 114)**	**Control[e,f] (N = 73)**	**Aflibercept[f] 2 mg (N = 114)**
Proportion of patients who gained at least 15 letters in BCVA[c] 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						
	24 Weeks		52 Weeks		76 Weeks	
Efficacy Outcomes	**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

GALILEO						
	24 Weeks		52 Weeks		76 Weeks	
Efficacy Outcomes	**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)**
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 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
* 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 2 mg 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 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 8 and Figure 3 below.

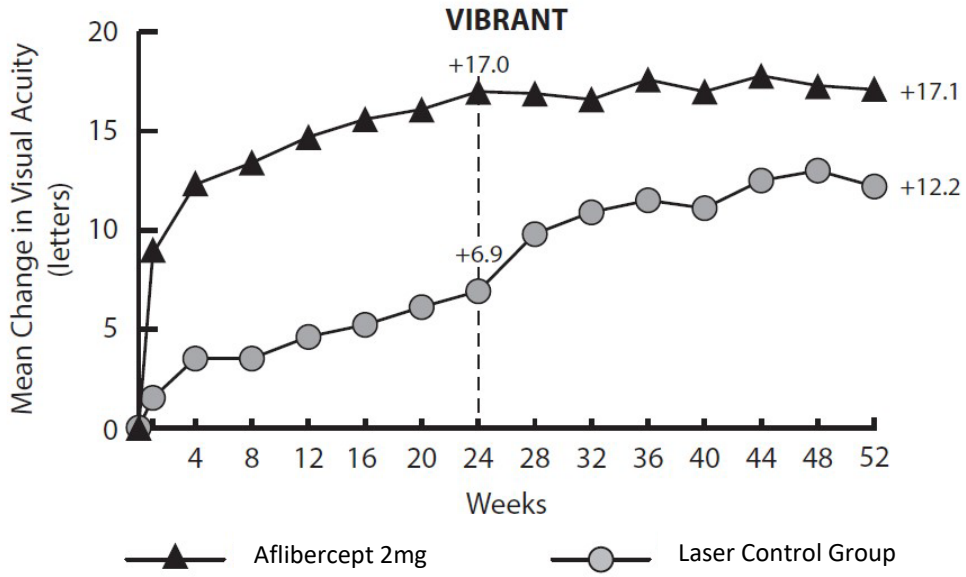
Table 8: Efficacy outcomes at week 24, and week 52 (Full Analysis Set LOCF) in the VIBRANT study

	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) (aflibercept 2 mg)***

The safety and efficacy of aflibercept 2 mg 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 9 and Figure 4 below.

Table 9: Efficacy outcomes at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} and VISTA^{DME} studies

VIVID^{DME}						
	52 Weeks			100 Weeks		
Efficacy Outcomes	**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)]	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	

VIVID[DME]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	**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)**
(97.5% CI) p-value						
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 4 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)	-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	

VIVID[DME]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	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)
p-value						

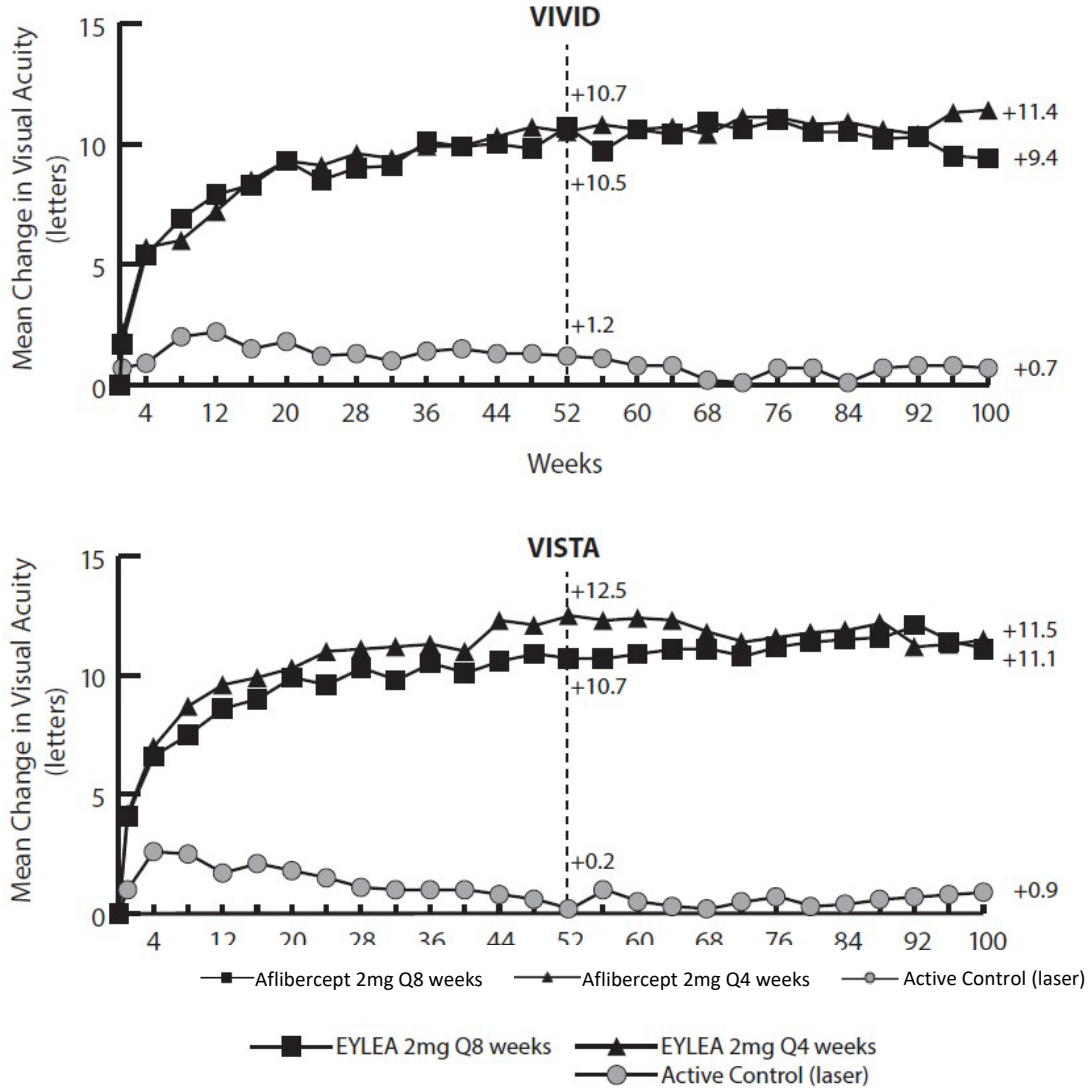
VISTA[DME]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	Aflibercept 2 mg Q8[a)] (N = 151)	Aflibercept 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)	Aflibercept 2 mg Q8[a)] (N =151)	Aflibercept 2 mg Q4 (N =154)	Active Control (laser) (N =154)
Mean change in BCVA as measured by ETDRS[e] letter 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 4 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	

VIVID[DME]						
	52 Weeks			100 Weeks		
Efficacy Outcomes	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 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

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 9).

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} (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 2mg 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 10 and Figure 5 below.

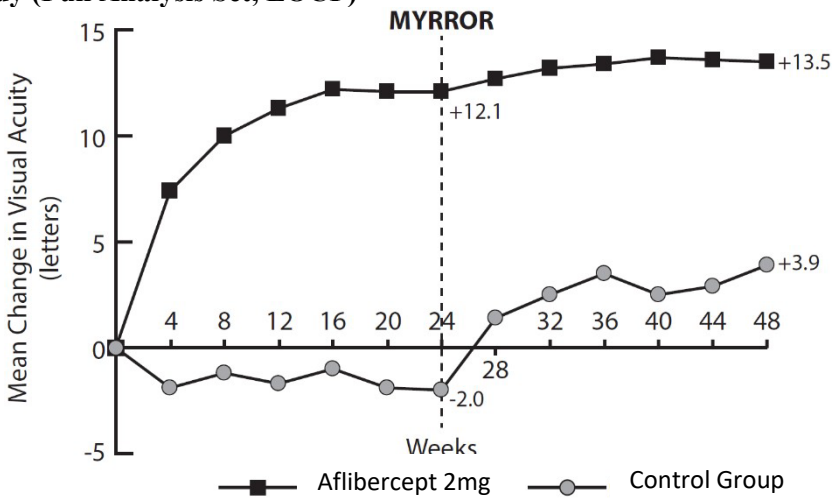
Table 10: Efficacy outcomes at week 24 (primary analysis) and in week 48 in MYRROR study (Full Analysis Set with LOCF[a)])

MYRROR				
	24 Weeks		48 Weeks	
Efficacy Outcomes	**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
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.

Pharmacodynamic comparability of ENZEEVU (aflibercept 2 mg) with EYLEA (aflibercept 2 mg)

No clinical comparative pharmacodynamic studies have been performed with ENZEEVU.

Comparability of ENZEEVU (aflibercept 2 mg) with EYLEA (aflibercept 2 mg) in terms of efficacy

Study CSOK583A12301 was an international, multicentre, randomised, double-masked, 2-arm parallel study in subjects with wet AMD, with a total duration of 52 weeks. The eligible subject population comprised male and female subjects who were 50 years of age or older, anti-VEGF treatment naive for both eyes, and diagnosed with active CNV secondary to AMD in the study eye.

A total of 485 subjects were randomised 1:1 to receive either ENZEEVU or Eylea, and 484 subjects were treated. 461 subjects were included in the Per-protocol Set (PPS) for analysis of the primary efficacy endpoint. Only 1 eye was selected as the study eye. Subjects received a single intravitreal injection of ENZEEVU 2 mg or Eylea 2 mg in the study eye every 4 weeks at 3 consecutive visits (Baseline, Week 4, and Week 8), and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48.

The overall mean age in the PPS was 76 years (range 53 to 94), and 59% of subjects were 75 years or older. 56% of subjects were female and 89% were white. At baseline, the overall

median time since diagnosis of nAMD in the PPS was 12 days, and less than 30 days had passed since diagnosis in 74% of patients. The overall mean BCVA score at baseline, as measured using ETDRS charts, was 59.7 letters. At baseline, 81% and 75% of subjects in the PPS had the occult lesion type in the Primary efficacy was assessed at Week 8 after subjects have received two injections of either ENZEEVU 2 mg or Eylea 2 mg. At Week 8 the difference between ENZEEVU and Eylea in the LS mean changes in BCVA score from baseline was −0.3 letters for the PPS. The 95% CI (−1.8, 1.3) was contained within the prespecified interval [−3.5, +3.5]. Similar efficacy in terms of change in BCVA score from baseline was concluded.

Table 11: Primary efficacy analysis (PPS) - Summary statistics and ANCOVA for change in BCVA score from baseline to Week 8 in study CSOK583A12301

	ENZEEVU 2 mg (n = 235)	**Eylea 2 mg (n = 226)**
Mean change in BCVA score from baseline to Week 8 as measured using ETDRS testing charts (SD)	6.5 (8.98)	6.8 (7.46)
ANCOVA LS mean difference (95% CI)	-0.3 (-1.8, 1.3)	

Baseline was the pre-dose BCVA score prior to the first aflibercept (ENZEEVU or Eylea) injection. ANCOVA included treatment as a factor and baseline BCVA and age as continuous covariates. ANCOVA: Analysis of covariance; BCVA: Best-corrected visual acuity; CI: confidence interval; ETDRS: Early treatment diabetic retinopathy study; LS mean: least-squares mean; PPS: per-protocol set; SD: standard deviation.

5.2. PHARMACOKINETIC PROPERTIES

Aflibercept 2 mg 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 12: Tabulated summary of free aflibercept in plasma by indication

Indication	Mean C_{max} 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.

Metabolism

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

Excretion

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.

Pharmacokinetic comparability of ENZEEVU (aflibercept 2 mg) with EYLEA (aflibercept 2 mg)

A dedicated study to demonstrate pharmacokinetic comparability was not conducted due to the low systemic exposure of aflibercept after intravitreal injection.

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

Histidine

Histidine hydrochloride monohydrate

Trehalose dihydrate

Polysorbate 20

Hydrochloric acid

Sodium hydroxide

Water for injections

6.2. INCOMPATIBILITIES

ENZEEVU must not be mixed with other medicinal products.

6.3. SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the ARTG.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

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

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

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

Prior to usage, the unopened vial or pre-filled syringe blister pack of ENZEEVU may be stored outside the refrigerator below 30°C for up to 14 days. Store in original carton and do not open vial or sealed blister pack until time of use. After opening the vial or blister pack, proceed under aseptic conditions.

6.5. NATURE AND CONTENTS OF CONTAINER

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

- ***Vial***

Each carton includes a type I glass vial containing approximately 240 µL of solution, which provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept. The vial is sealed with an elastomeric rubber stopper, and is provided with an 18 G filter needle.

- ***Pre-filled syringe***

Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe, containing approximately 165 µL of solution, which provides a usable amount to deliver a single dose of 50 µL containing 2 mg aflibercept. The syringe is 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 grip.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure

The secondary and tertiary structures of aflibercept as well as the amino acid structure are shown in Figure 6 and Figure 7.

Figure 6: Aflibercept secondary and tertiary structures

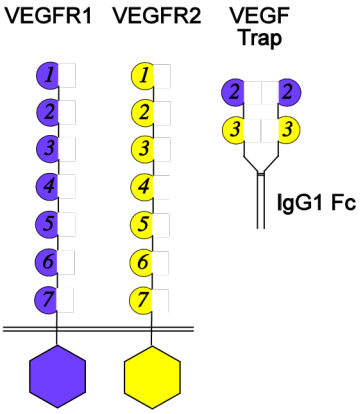
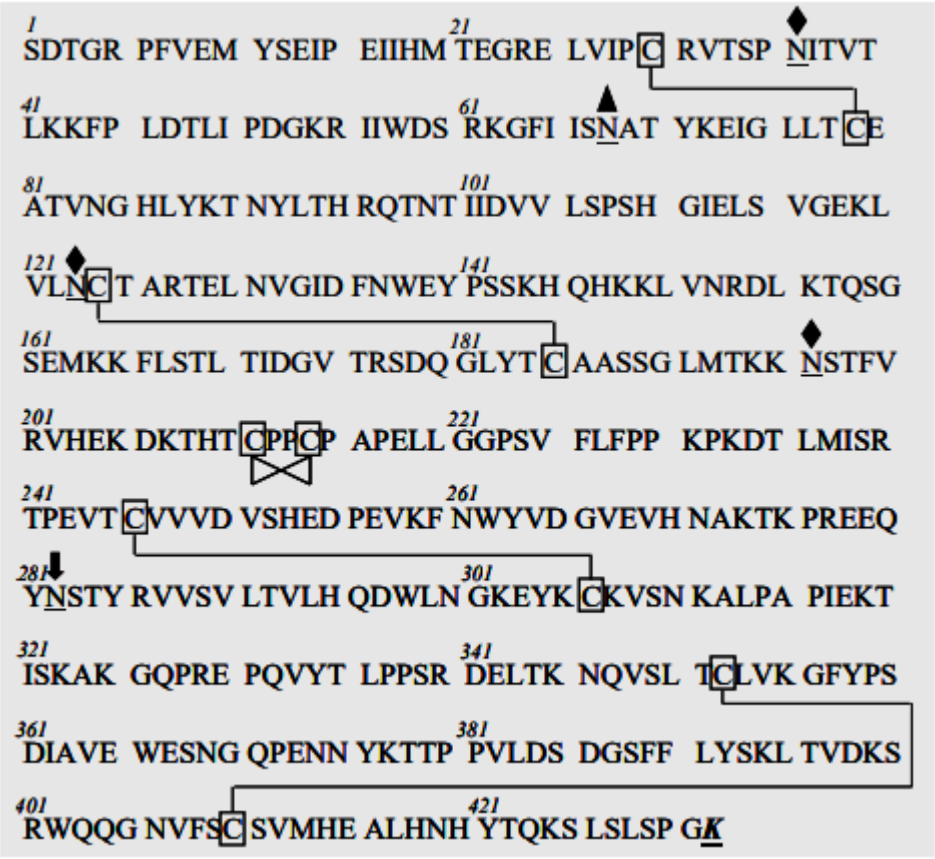


Figure 7: Aflibercept amino acid structure



Chemical names: Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine[human vascular endothelial growth factor receptor 1-(103-204)peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain

fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

Molecular weight: 97 kDa (protein molecular weight)

115 kDa (total molecular weight)

CAS number

862111-32-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Sandoz Pty Ltd
100 Pacific Highway
North Sydney, NSW 2060
Australia

Tel 1800 726 369

9. DATE OF FIRST APPROVAL

DD/MM/YYYY

10. DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

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