NOTICE OF FILING

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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.

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Form 17
Rule 15.06(1)(a)

Statement of Cross-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

Sandoz Pty Ltd (ACN 075 449 553)
Cross-claimant

Regeneron Pharmaceuticals, Inc and another
Cross-respondents

Definitions

In this Statement of Cross-claim, the following definitions apply:

(a) **Asserted AU'599 Claims** means claims 1, 3, 4, 5 and 12 of the AU'599 Patent.

(b) **AU'599 Patent** means Australian Patent number 2012205599 titled "*Use of a VEGF antagonist to treat angiogenic eye disorders*".

(c) ***Patents Act*** means the *Patents Act 1990* (Cth) as it applies to the AU'599 Patent.

(d) ***Patents Regulations*** means the *Patents Regulations 1991* (Cth) as it applies to the AU'599 Patent.

Filed on behalf of (name & role of party) Sandoz Pty Ltd, the Cross-Claimant and Respondent
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A. Parties

1. The Cross-claimant is, and has been at all material times, a company incorporated under the *Corporations Act 2001* (Cth) and is entitled to sue in its corporate name.

2. The First Cross-respondent, Regeneron Pharmaceuticals Inc:

   (a) is, and has been at all material times, a company incorporated under the laws of the United States of America;

   (b) is registered on the Australian Register of Patents as a proprietor of the AU'599 Patent; and

   (c) is entitled to be sued in its corporate name.

3. The Second Cross-respondent, Bayer Consumer Care AG:

   (a) is, and has been at all material times, a company incorporated under the laws of the Swiss Confederation;

   (b) is alleged in the Applicants' Amended Statement of Claim to be, since 10 June 2025, the exclusive licensee of the AU'599 Patent; and

   (c) is entitled to be sued in its corporate name.

B. Deferred priority date

4. The priority date of each of the Asserted AU'599 Claims is (or is no earlier than) the date at which the AU'599 Patent was filed, being 11 January 2012 (**Deferred Priority Date**).

Particulars

   (a) The patent application for the AU'599 Patent was filed as PCT Application Number US2012/020855 and asserts priority from each of United States of America patent application numbers:

      (i) 61/561,957 (**US'957**) filed on 21 November 2011;

      (ii) 61/434,836 (**US'836**) filed on 21 January 2011;

(iii) 61/432,245 (**US'245**) filed on 13 January 2011 (the **Earliest Asserted Priority Date**),

collectively, the **US Priority Documents**.

(b) Each of the Asserted AU'599 Claims encompass methods of using a VEGF antagonist, wherein:

(i) save for claim 3, the number of secondary doses administered is not defined or limited in any way and encompasses a broad range, ranging for example, from administration of a small number of secondary doses (e.g., 1, 2, 3 or 4) to a large number of secondary doses (e.g., 100, 200, 300 or 400);

(ii) the number of tertiary doses administered is not defined or limited in any way and includes, for example, only one dose or otherwise a small number of doses;

(iii) save for claim 12, the dose of the VEGF antagonist administered is not defined or limited in any way and encompasses a broad range, ranging for example, from a small dose (e.g., 1mg) to a large dose (e.g., 100mg); and

(iv) save for claim 5, the disease to be treated is not limited to, and thereby encompasses diseases other than, neovascular (wet) age related macular degeneration (**wet AMD**) or diabetic macular oedema (**DME**).

(c) Each of the US Priority Documents does not disclose the invention claimed in each of the Asserted AU'599 Claims to the extent of the scope identified in paragraphs (b)(i) to (b)(iv) above:

(i) *per se*; and

(ii) further or in the alternative, in a manner which was clear enough and complete enough for the invention to be performed by a person skilled in the relevant art,

as required by section 43(2)(a) of the *Patents Act* and regs 3.12 and 3.13A of the *Patent Regulations*.

(d) Further to (c), above, in each of the US Priority Documents, the "Examples" insofar as they concern the administration of a single initial dose of a VEGF antagonist followed by secondary doses and then tertiary doses:

(i) concern a defined number of secondary doses;

(ii) are limited to a defined number of tertiary doses over a minimum period;

(iii) are limited to doses of the VEGF antagonist of 2 mg; and

(iv) are limited to treatment of wet AMD and DME.

(e) Further particulars may be provided, including after evidence.

C. Lack of novelty

5. The alleged invention the subject of each of the Asserted AU'599 Claims is not a patentable invention within the meaning of section 18(1)(b)(i) of the *Patents Act* because, when compared with the prior art base as it existed before the priority date, the alleged invention is not novel.

Particulars

(a) If the priority date is the Earliest Asserted Priority Date, the Cross-Claimant relies on the information made publicly available in each of the following documents:

(i) Adis Data Information BV, "Aflibercept," (2008):9(4) Drugs R&D, page 261–269, published in 2008 (**Adis**), a copy of which is **Annexure A** to this document, at pages 9 to 18 of this document.

(ii) Press Release, Regeneron, "Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)", published on or about 20 December 2010 (the **December 2010 Press Release**), a copy of which is **Annexure B** to this document, at pages 19 to 22 of this document.

(iii) Press Release, Regeneron, "Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related

Macular Degeneration", published on or about 22 November 2010 (the **November 2010 Press Release**), a copy of which is **Annexure C** to this document, at pages 23 to 26 of this document.

(iv) Press Release, Regeneron, "Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)", published on or about 14 September 2009 (the **2009 Press Release**), a copy of which is **Annexure D** to this document, at pages 27 to 28 of this document.

(v) Dixon, J.A., *et al*., "VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration", (2009):18(10) *Expert Opin. Investig. Drugs*, 1573-1580, published in 2009 (**Dixon**), a copy of which is **Annexure E** to this document, at pages 29 to 37 of this document.

(b) If the priority date is the Deferred Priority Date, the Cross-Claimant relies on the information made publicly available in each of the documents identified in (a), above.

(c) The Cross-Claimant reserves the right to seek leave to add any additional prior art that comes to light during the course of the proceeding.

D. Lack of inventive step

6. The alleged invention the subject of each of the Asserted AU'599 Claims is not a patentable invention within the meaning of section 18(1)(b)(ii) of the *Patents Act* as the alleged invention did not involve an inventive step when compared with the prior art base as it existed before the priority date of each claim.

Particulars

(a) The alleged invention the subject of each of the Asserted AU'599 Claims was obvious before the Earliest Asserted Priority Date and the Deferred Priority Date (as the case may be) in light of the common general knowledge alone.

(b) Further or in the alternative, the alleged invention the subject of each of the Asserted AU'599 Claims was obvious before:

(i) the Earliest Asserted Priority Date; and

(ii) the Deferred Priority Date (as the case may be),

in light of the common general knowledge when considered together with each of the documents referred to in the particulars to paragraph 5(a) and 5(b) above, respectively.

(c) The Cross-Claimant reserves the right to seek leave to add any additional prior art that comes to light during the course of the proceeding.

E. Section 40(2)(a) - Disclosure

7. Further or in the alternative to paragraph 4 above, each of the Asserted AU'599 Claims is invalid in that it, or the complete specification of the AU'599 Patent, does not comply with section 40(2)(a) of the *Patents Act*.

Particulars

(a) The Cross-claimant refers to and repeats paragraph 4(b), above.

(b) The complete specification of the AU'599 Patent does not disclose the invention claimed in each of the Asserted AU'599 Claims to the extent of the scope identified in paragraphs 4(b)(i) to 4(b)(iv) above:

(i) *per se*; and

(ii) further or in the alternative, in a manner which was clear enough and complete enough for the invention to be performed by a person skilled in the relevant art.

(c) Further to (b), above, in the complete specification of the AU'599 Patent, the "Examples" insofar as they concern the administration of a single initial dose of a VEGF antagonist followed by secondary doses and then tertiary doses:

(i) concern a defined number of secondary doses;

(ii) are limited to a defined number of tertiary doses over a minimum period;

(iii) are limited to doses of the VEGF antagonist of 2 mg; and

(iv) are limited to treatment of wet AMD and DME.

(d) Further particulars may be provided, including after evidence.

F. Section 40(3) - Support

8. Each of the Asserted AU'599 Claims is invalid in that it is not supported by the matter disclosed in the complete specification as required by section 40(3) of the *Patents Act*.

Particulars

(a) The Cross-claimant refers to and repeats paragraph 4(b) and 7(c), above.

(b) Each of the Asserted AU'599 Claims is not supported by the matter disclosed in the complete specification, to the extent of the scope identified in paragraphs 4(b)(i) to 4(b)(iv) above.

(c) Further particulars may be provided, including after evidence.

G. Revocation

9. In the premises, each of the Asserted AU'599 Claims is liable to be revoked pursuant to section 138 of the *Patents Act.*

AND the Cross-claimant claims the relief specified in the Notice of Cross-claim.

Date: 26 June 2025

Signed by Robert Cooper
Lawyer for the Cross-claimant

This pleading was prepared and settled by Tom Cordiner, David Larish and Amy Surkis of counsel.

Certificate of lawyer

I, Robert Cooper, certify to the Court that, in relation to the Statement of Cross-claim filed on behalf of the Cross-claimant, the factual and legal material available to me at present provides a proper basis for each allegation in the pleading.

Date: 26 June 2025

Signed by Robert Cooper
Lawyer for the Cross-claimant

ADIS R&D PROFILE

Drugs R D 2008; 9 (4): 261-269
1174-5886/08/0004-0261/$48.00/0

Aflibercept

AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye

Abstract

Aflibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human IgG_1. Aflibercept is in clinical development with Regeneron Pharmaceuticals and sanofi-aventis for the treatment of cancer, while Regeneron and Bayer are developing the agent for eye disorders. Aflibercept binds to all VEGF-A isoforms as well as placental growth factor (PIGF), thereby preventing these factors from stimulating angiogenesis. Blockade of VEGF can also prevent blood vessel formation and vasuclar leakage associated with wet age-related macular degeneration (AMD). Aflibercept is a member of Regeneron's proprietary family of 'Trap' product candidates that catch, hold and block (i.e. trap) certain harmful cytokines or growth factors.

Regeneron and Bayer HealthCare entered into a collaboration agreement in October 2006 to develop and commercialize aflibercept for the treatment of eye disorders outside the US. The companies will share equally in profits from this market, while Regeneron will retain exclusive commercialization rights and profits from sales in the US.[1]

Regeneron and sanofi-aventis amended their aflibercept collaboration agreement to include Japan. Under the terms of the amended agreement, reported in December 2005, the two companies will jointly develop and commercialize aflibercept worldwide in all indications, except for intraocular delivery to the eye. sanofi-aventis paid $US25 million to Regeneron for the inclusion of Japan and will pay milestone payments linked to Japanese regulatory approvals, plus royalties on Japanese sales. sanofi-aventis will lead Japanese development and will pay all development costs; however, Regeneron will repay 50% of these expenses out of profits generated through the commercialization of aflibercept.[2]

sanofi-aventis reaffirmed its commitment to the aflibercept programme in oncology in January 2005, while the exclusive rights to develop and commercialize the agent for eye diseases through local delivery systems reverted to Regeneron. A $US25 million clinical development milestone payment to Regeneron was also triggered in connection with this agreement.[3]

Aventis (now sanofi-aventis) and Regeneron entered into a global (excluding Japan) agreement in September 2003 to jointly develop and commercialize aflibercept. Under the terms of the agreement, Aventis was to pay Regeneron $US125 million and fund development costs. An additional early clinical milestone payment of $US25 million was also outlined in the agreement. The two companies will share promotional rights equally, and profits globally. Aventis will also pay Regeneron up to $US360 million at identified milestones related to the receipt of marketing approvals for up to eight indications in Europe and the

US. The companies initially agreed to jointly develop aflibercept in oncology, ophthalmology and possibly in other indications.[4]

Originally, aflibercept was being developed under a research and development alliance between Regeneron and Procter & Gamble. However, in 2000 this agreement was restructured and Regeneron regained all rights.

An NCI-sponsored phase II trial (NCT00407654) of aflibercept, involving 80 patients with previously treated metastatic colorectal cancer, is also underway in the US and Canada. The trial was initiated in October 2006 and is evaluating the efficacy of aflibercept in this patient group, as measured by objective tumour response and progression-free survival at 4 months.

In September 2006, a phase II trial in 82 patients with locally advanced, unresectable or metastatic gynaecological soft tissue sarcoma was initiated by NCI and Regeneron in the US and Canada. This ongoing trial (NCT00390234) will evaluate the efficacy of aflibercept, as measured by progression-free survival and tumour response rate.

Regeneron and sanofi-aventis are conducting a phase II trial of intravenously (IV) administered aflibercept in patients with advanced ovarian cancer who have recurrent symptomatic malignant ascites (SMA). The trial (NCT00327444) began in July 2006 and was continuing to recruit a total of 54 patients at centres in the US, Canada, India and the EU (Austria, Belgium, Hungary, Spain and the UK) in April 2007.

In October 2006, the companies initiated a second small phase II trial of aflibercept (NCT00396591) in 15 patients with malignant ascites associated with ovarian cancer. The study will assess the efficacy, safety, pharmacokinetics and immunogenicity of aflibercept IV given every 2 weeks in the US and EU (Italy and Sweden) and was recruiting patients in May 2007.

Regeneron and sanofi-aventis are also conducting a single-agent phase II study of aflibercept in non-small-cell lung adenocarcinoma (NSCLA). The open-label, single-arm study (NCT00284141) has completed enrolment of approximately 100 patients with platinum- and erlotinib-resistant, locally advanced or metastatic NSCLA to receive aflibercept (4.0 mg/kg IV) in the US, France and Canada. Results from the first 37 evaluable patients have been reported showing aflibercept was generally well tolerated and two partial reponses were noted.[5,6]

Regeneron has completed an open-label phase I trial in patients with solid tumours and non-Hodgkin's lymphoma (NHL) at three sites in the US. The study enrolled 38 patients with incurable, relapsed or refractory solid tumours who received subcutaneous injections. In total, the trial enrolled patients with 15 different types of cancer who were treated with seven subcutaneous doses of aflibercept over 10 weeks. In June 2004, Regeneron presented results from this study showing that the aflibercept was well tolerated and had a good safety profile. The maximum tolerated dose was not established. The company has not conducted any further trials in this indication with aflibercept as a monotherapy, although the NCI has ongoing trials of aflibercept in patients with solid tumours and NHL (e.g. NCT0008283).[7]

In May 2005, Regeneron announced initiation of a phase I safety and tolerability study with aflibercept in combination with the FOLFOX-4 regimen (oxaliplatin, 5-fluorouracil and leucovorin) in patients with advanced solid tumours. As at

August 2006, the maximum tolerated dose had not been reached and dose-escalation was continuing in this study.[8,9]

The NCI/Regeneron trial in patients with metastatic or unresectable kidney cancer began in September 2007 with continued recruitment in April 2008. This trial (NCT00357760) is anticipated to recruit 120 patients in the US to evaluate the efficacy of two doses of aflibercept.

Regeneron and Bayer inititiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007. The non-inferiority, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) study will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and 2.0 mg at an 8-week dosing interval, compared with 0.5 mg ranibizumab administered every 4 weeks. The randomized, double-blind trial will be conducted at more than 200 centres throughout the US and Canada, pursuant to a Special Protocol Assessment (SPA) issued by the the US FDA. Patients will continue to be treated and followed for an additional year, after the first year of treatment. The VIEW 1 study is the first in a phase III global development programme in wet AMD, which is expected to be conducted in the US, Europe and other nations. Regeneron received a $US20 million milestone payment from Bayer HealthCare in August 2007 following dosing of the first patient.[10,11]

A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008. The VIEW 2 trial will enrol approximately 1200 patients from the EU, Asia Pacific, Japan and Latin America. This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. The primary endpoint will be the proportion of patients treated with aflibercept who maintain vision at the end of 1 year compared with ranibizumab patients.[12,13]

Regeneron has completed a 12-week, phase II trial in patients with wet AMD, to evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens. Two patient groups received monthly doses of 0.5 or 2.0 mg, and three groups received quarterly doses of 0.5, 2.0 or 4.0 mg (baseline and week 12). Analysis of data demonstrated that all five doses of aflibercept met the primary study endpoint of a statistically significant reduction in retinal thickness after 12 weeks and 32 weeks of treatment compared with baseline. The study commenced in April 2006 and enrolled 157 patients at sites in the US. Preliminary phase I trial results in 21 patients have also been presented.[14-16]

Additionally, Regeneron has conducted a phase I trial of aflibercept in five patients with diabetic macular oedema (DME) in the US. Results presented in May 2007 indicated that a single 4 mg injection resulted in a marked decrease in mean central retinal thickness and mean macular volume throughout the 6-week observation period. The VEGF Trap-Eye was generally well tolerated, and there were no drug-related serious adverse events.[17] Regeneron plans to conduct advanced studies of the VEGF Trap-Eye in DME.

Previously, sanofi-aventis and Regeneron had been collaborating on the development of aflibercept for eye diseases through local delivery systems. However, the exclusive rights to develop and commercialize aflibercept for eye diseases

through local delivery systems reverted to Regeneron in January 2005. Additionally, Regeneron chose to pursue intravitreal inection as a route of administration, instead of systemic delivery.[18]

Results from an earlier phase I trial assessing the safety and tolerability of intravenous infusions of aflibercept in patients with wet AMD have been reported. Preliminary results from the trial showed that the efficacy endpoint was met. Furthermore, systemic delivery of aflibercept was associated with a dose-dependent increase in blood pressure.[19]

Table I. Features and properties

CAS number	862111-32-8
WHO ATC code	A10X (Other Drugs Used in Diabetes) S01X (Other Ophthalmologicals) L01 (Antineoplastic Agents)
EphMRA ATC code	A10X (Other Drugs Used in Diabetes) S1X (Other Ophthalmologicals) L1 (Antineoplastics)
Originator	Regeneron Pharmaceuticals: USA
Licensee companies	Bayer HealthCare: world; sanofi-aventis: world
Highest development phase	Phase III (World)
Properties	
Mechanism of action	Vascular endothelial growth factor A antagonists
Pharmacodynamics	Halts new blood vessel growth and stopped leakage from existing blood vessels in mice; inhibits VEGF and abolishes mature, pre-existing vasculature of tumours in mice; inhibits development of ascites and decreases tumour burden in animal models of ovarian cancer
Route	IV

1. Profile

1.1 Pharmacokinetics

Clinical studies: Preliminary results of an open-label, phase I trial of a single dose of subcutaneous VEGF Trap (25, 50, 100 or 200 μg/kg) followed 4 weeks later by six weekly doses in patients with solid tumours or lymphoma showed that VEGF Trap binds to VEGF in plasma and has an apparent elimination half-life ($t_{1/2}$) of ≈17 days.[20]

Results of a phase I, open-label, dose-escalation trial of 38 patients with relapsed or refractory solid tumours showed that VEGF Trap has a long $t_{1/2}$ and binds to both VEGF 121 and VEGF 165 in patient plasma. Plasma VEGF Trap levels that were associated with antitumour activity in animal models were approached in patients receiving the two highest dose groups or 800 μg/kg once or twice weekly. In the trial patients received one or two initial doses of VEGF Trap followed 4 weeks later by six weekly or twice-weekly doses. Seven dose groups were evaluated in the trial ranging from 25 to 800 μg/kg weekly or 800 μg/kg twice weekly. Values for t_{max}, C_{max}, $t_{1/2}$, AUC_{28} and CL/F were 84 ± 60 hours, 3 ± 1 μg/mL, 25.3 ± 9.3 days, 1304 ± 256 μg • h/mL and 0.4 ± 0.1 mL/h/kg, respectively.[21]

1.2 Adverse Events

Solid tumours: Results of a phase I, open-label, dose-escalation trial of VEGF Trap in 38 patients with relapsed or refractory solid tumours showed that the drug had a good safety profile and was well tolerated overall. The maximum tolerated dose was not reached in the study, which reached the highest planned dose level of 800 μg/kg twice weekly. The majority of adverse events reported were grade 1 or

Table II. Drug development history

May 2000	Preclinical development for Cancer in the US (Unknown route)
Nov 2001	Phase-I for Non-Hodgkin's lymphoma in the US (Unknown route)
Nov 2001	Phase-I for Solid tumours in the US (Unknown route)
Jun 2003	Prein Age-related macular degeneration in the US (IV)
Jun 2003	Prein Eye disorders in the US (Intravitreous)
Jun 2003	Prein Wilms' tumour in the US (Intraperitoneal)
Sep 2003	Aflibercept has been licensed to Aventis worldwide (excluding Japan)
Mar 2004	Phase-I in Age-related macular degeneration in the US (IV)
Apr 2004	Regeneron has initiated enrolment in a phase I trial for cancer in the US
Aug 2004	Aventis has merged with Sanofi-Synthelabo to form sanofi-aventis
Feb 2005	Aflibercept received Fast Track designation for Malignant ascites [IV] in the US
Feb 2005	Discontinued – Phase-I for Age-related macular degeneration in the US (IV-infusion)
May 2005	Regeneron has initiated the safety and tolerability study with VEGF Trap in combination with the FOLFOX-4 regimen (oxaliplatin, 5-fluorouracil and folinic acid) in patients with advanced tumours
May 2005	Phase-I in Solid tumours in the US (IV)
Jul 2005	Phase-I in Age-related macular degeneration in the US (Intravitreous)
Jul 2005	Prein Eye disorders in the US (Intravitreous)
Dec 2005	Regeneron has licensed aflibercept to sanofi-aventis in Japan
Dec 2005	Phase-II in Non-small cell lung cancer in France (IV)
Dec 2005	Phase-II in Non-small cell lung cancer in Canada (IV)
Dec 2005	Phase-II in Non-small cell lung cancer in the US (IV)
May 2006	Phase-I in Diabetic macular oedema in the US (Intravitreous)
May 2006	Phase-II in Age-related macular degeneration in the US (Intravitreous)
Jun 2006	Phase-II in Ovarian cancer in the US (IV)
Jun 2006	Phase-II in Ovarian cancer in Australia (IV)
Jun 2006	Phase-II in Ovarian cancer in Canada (IV)
Jun 2006	Phase-II in Ovarian cancer in Europe (IV)
Jul 2006	Phase-II/III in Malignant ascites in India (IV)
Jul 2006	Phase-II/III in Malignant ascites in the US (IV)
Jul 2006	Phase-II/III in Malignant ascites in Canada (IV)
Jul 2006	Phase-II/III in Malignant ascites in Europe (IV)
Aug 2006	Phase-II in Glioma in the US (IV)
Sep 2006	Phase-II in Sarcoma in Canada (IV)
Sep 2006	Phase-II in Sarcoma in the US (IV)
Oct 2006	Aflibercept has been licensed to Bayer HealthCare for the treatment of eye disorders
Oct 2006	Phase-II in Colorectal cancer in Canada (IV)
Oct 2006	Regeneron and sanofi-aventis initiate enrolment in a second phase II trial in Malignant ascites in the EU and US
Oct 2006	Phase-II in Colorectal cancer in the US (IV)
Nov 2006	Phase-II in Bladder cancer in the USA (IV)
Dec 2006	Phase-II in Multiple myeloma in the US (IV)
Jan 2007	Phase-II in Gynaecological cancer in the US (IV)
Jan 2007	Phase-II in Breast cancer in the US (IV)

Continued next page

Table II. Contd

Mar 2007	Interim results from a phase II clinical trial in wet Age-related macular degeneration added to the Eye Disorders therapeutic trials section
Mar 2007	Phase-I in Cancer in Japan (IV)
Jun 2007	Final results from a phase I clinical trial in patients with diabetic macular oedema added to the adverse events and Eye Disorders therapeutic trials sections
Jun 2007	Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO-2007) added to the adverse events and Cancer therapeutic trials sections
Jun 2007	Phase-II in Malignant melanoma in the US (IV)
Jul 2007	Suspended – Phase-II for Colorectal cancer in Canada (IV)
Jul 2007	Suspended – Phase-II for Colorectal cancer in the US (IV)
Aug 2007	Phase-III in Age-related macular degeneration in the US (Intravitreous)
Aug 2007	Regeneron initiates patient dosing in a phase III trial for Age-related macular degeneration in the US
Aug 2007	Phase-III in Prostate cancer in the US (IV)
Aug 2007	Phase-III in Prostate cancer in Canada (IV)
Aug 2007	Phase-III in Prostate cancer in European Union (IV)
Aug 2007	Phase-III in Prostate cancer in Switzerland (IV)
Aug 2007	Phase-III in Prostate cancer in South Africa (IV)
Aug 2007	Phase-III in Prostate cancer in South America (IV)
Aug 2007	Phase-III in Prostate cancer in Asia (IV)
Aug 2007	Phase-III in Non-small cell lung cancer in the US (IV)
Aug 2007	Phase-III in Non-small cell lung cancer in France (IV)
Aug 2007	Phase-III in Prostate cancer in Australia (IV)
Oct 2007	Results from a phase II clinical trial in age-related macular degeneration added to the Eye Disorders therapeutic trials section
Dec 2007	Phase-III in Pancreatic cancer in World (IV)
Dec 2007	Phase-III in Colorectal cancer in World (IV)
Dec 2007	Phase-III in Non-small cell lung cancer in World (IV)
Dec 2007	Phase-III in Prostate cancer in World (IV)
Dec 2007	Suspended – Phase-II for Breast cancer in the US (IV)
Apr 2008	Interim efficacy data from a phase II trial in wet AMD released by Regeneron
May 2008	Bayer and Regeneron initiates enrolment in the VIEW 2 trial for Age-related macular degeneration in EU, Asia Pacific, Japan, and Latin America

2, including fatigue, nausea and vomiting. Observed grade 3 and 4 adverse events that were potentially drug related were grade 3 leukopenia, afebrile neutropenia and proteinuria, and grade 3 and 4 thromboembolic events including a transient cerebral ischaemia and a pulmonary embolism. Dose-related adverse events included hypertension and grade 1 hoarseness and anorexia. All patients who discontinued participation in the extension study withdrew due to disease progression, except one patient who developed grade 3 hypertension and proteinuria and was withdrawn after 22 weeks.[21]

The VEGF Trap administered intravenously every 2 weeks was generally well tolerated in a phase I, open-label, dose-ascending study in 27 patients with advanced solid tumours. The maximum tolerated dose has not been reached. The most frequently reported adverse events included fatigue, pain and constipation. The majority of adverse events were mild to moderate by nature. Occasional adverse events, including hypertension, were manageable and reversible. There were no anti-VEGF Trap antibodies detected.[9]

1.3 Pharmacodynamics

1.3.1 Cancer

Preclinical studies: VEGF Trap inhibited VEGF and destroyed mature, pre-existing vasculature in nude mice bearing established Wilms' tumour (SK-NEP-1) xenografts. This could provide an alternative therapeutic option for patients with bulky, metastatic cancers. Destruction of blood vessels was followed by marked tumour regression that included regression of lung micrometastases. The size of pulmonary metastases was significantly smaller in the lungs of VEGF Trap-treated animals compared with controls. These observations indicated that VEGF inhibition by VEGF Trap had interrupted cell signalling of the endothelial-vascular wall essential for the protection of tumours from apoptosis. Thus, it was concluded that even low levels of VEGF could be critical to the integrity of blood vessels and the maintenance of even the smallest tumour masses.[22]

VEGF Trap inhibited the development of ascites and decreased tumour burden in animal models of ovarian cancer. Findings indicated that VEGF Trap's activity was facilitated by inhibition of tumour angiogenesis as well as reduction in vascular permeability. In the first model, SKOV-3 ovarian carcinoma cells were engineered to overexpress VEGF (SKOV-VEGF) and then injected into the peritoneum of female nude mice. The animals were then administered subcutaneous (SC) VEGF Trap 25 mg/kg or control solution twice weekly until they had lost >10% of bodyweight or had persistent ascites. In the second model, OVCAR-3 ovarian cancer cells were injected into the peritoneum of athymic Balb/C nude mice. Fourteen days later, twice-weekly treatment with subcutaneous VEGF Trap 25 mg/kg or control solution was initiated and continued for 5 weeks. Ascites developed considerably earlier in control animals injected with SKOV-VEGF cells, compared with those injected with unaltered SKOV-3 cells. In contrast, the majority of mice administered VEGF Trap did not develop ascites, and those that did develop ascites had much lower volumes of fluid, compared with controls, according to the researchers. The mean volume of ascites in the OVCAR-3 model was also significantly lower in the VEGF Trap group, compared with controls. In fact, VEGF Trap completely inhibited the development of measurable ascites. Furthermore, tumour burden was reduced by 56% in the VEGF Trap group, compared with the controls.[23]

1.3.2 Eye Disorders

Preclinical studies: Administration of VEGF Trap (either subcutaneously or directly into the eye) resulted in significantly less new blood vessel growth, and also blocked leaking of blood vessels usually caused by VEGF, in two groups of mice. In the first group, mice with laser-induced rupture of Bruch's membrane received a single intravitreous injection of VEGF Trap. In the second group, mice genetically engineered to express VEGF in the retina received subcutaneous injections of VEGF Trap. No adverse effects were observed in these studies.[24]

1.4 Therapeutic Trials

1.4.1 Cancer

Ovarian cancer: Preliminary results of an open-label, phase I trial of a single dose of subcutaneous aflibercept (25, 50, 100 or 200 μg/kg) followed 4 weeks later by six weekly doses in patients with solid tumours or lymphoma (n = 14 treated to date) showed stable disease in patients with renal cell carcinoma (up to 15 weeks) and colon cancer.[20]

Preliminary efficacy data of the aflibercept administered intravenously every 2 weeks showed the reduction of tumour size and prolonged stable disease in some patients. A partial response with disappearance of ascites has been achieved in one patient, two patients had minor responses, and a stable disease was maintained in one patient for more than 11 months.[9]

1.4.2 Eye Disorders

Age-related macular degeneration (AMD): At 32 weeks, the 157 patients receiving either 0.5 or 2.0 mg followed by as-needed (PRN) dosing achieved mean improvements in visual acuity of 8.0 and 10.1 letters, respectively, and mean decreases in retinal thickness of 141 and 162 microns, respectively.

While PRN dosing also maintained the improvements versus baseline following a fixed dosing regimen (quarterly dosing at baseline and week 12), the results achieved were generally not as robust as those achieved with initial fixed monthly dosing. After the last fixed-dose administration at week 12, patients from all dose groups required on average only one additional injection over the following 20 weeks to maintain visual acuity gain achieved. Fifty-five percent of patients receiving 2.0 mg monthly for 12 weeks did not require any additional treatment throughout the next 20-week PRN dosing period.[14]

Preliminary results from a phase I trial in 20 patients with wet AMD have shown rapid, substantial and prolonged (≥4 weeks) reductions in retinal thickness with single-dose intravitreal injections of VEGF Trap. Ninety-five percent of patients had stabilization or improvement in visual acuity.[16,25]

Preliminary results from a phase I trial in 25 patients with advanced AMD showed a statistically significant decrease in excess retinal thickness with VEGF Trap (0.3, 1.0 and 3.0 mg/kg) compared with placebo.[19]

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Annexure B

REGENERON
science to medicine®

December 20, 2010

Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)

In Phase 3 study in CRVO, 56 percent of VEGF Trap-Eye patients gained at least 15 letters of vision compared to 12 percent in control group; VEGF Trap-Eye patients on average gained 17 letters of vision compared to mean loss of 4 letters in control group

In Phase 2 study in DME, patients in all VEGF Trap-Eye dose groups, including VEGF Trap-Eye dosed every two months, maintained or increased vision gains through 52-weeks

Regeneron to receive $20 million in milestone payments in connection with VEGF Trap-Eye program

Tarrytown, NY, USA, and Berlin, Germany, December 20, 2010 -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Bayer HealthCare today announced positive top-line results for VEGF Trap-Eye (aflibercept ophthalmic solution) in the COPERNICUS study, which is led by Regeneron, the first of two Phase 3 studies in patients with macular edema due to central retinal vein occlusion (CRVO). In this trial, 56.1 percent of patients receiving VEGF Trap-Eye 2 milligrams (mg) monthly gained at least 15 letters of vision from baseline, compared to 12.3 percent of patients receiving sham injections ($p<0.0001$), the primary endpoint of the study. Patients receiving VEGF Trap-Eye 2mg monthly gained, on average, 17.3 letters of vision compared to a mean loss of 4.0 letters with sham injections ($p<0.001$), a secondary endpoint. The second Phase 3 study, GALILEO, is currently ongoing and is led by Bayer HealthCare.

VEGF Trap-Eye was generally well tolerated and the most common adverse events were those typically associated with intravitreal injections or the underlying disease. A total of 114 patients were randomized to receive VEGF Trap-Eye and 73 patients to the control arm. Serious ocular adverse events in the VEGF Trap-Eye group were uncommon (3.5%) and were more frequent in the control group (13.5%). The incidence of non-ocular serious adverse events was generally well-balanced between the treatment arms. There were no deaths among the 114 patients treated with VEGF Trap-Eye and two in the 73 (2.7%) patients treated with sham injections.

"In the COPERNICUS trial, patients treated with VEGF Trap-Eye experienced a marked improvement in vision," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "If these results are confirmed by data from the GALILEO study, expected in the second quarter of 2011, VEGF Trap-Eye could provide patients and physicians with a new treatment option for central retinal vein occlusion."

"After reporting positive results from our global Phase 3 program (VIEW 1 and VIEW 2 studies) for the treatment of the neovascular form of age related macular degeneration (wet AMD), we are pleased to also have a positive Phase 3 trial with VEGF Trap-Eye in central retinal vein occlusion, a potential second indication," said Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee. "We are working diligently with Regeneron to prepare regulatory filings for VEGF Trap-Eye in wet AMD to submit in the first half of 2011."

Detailed results for COPERNICUS will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

Regeneron will receive a $10 million milestone payment from Bayer HealthCare in connection with the COPERNICUS trial meeting its primary endpoint and received a $10 million milestone payment in December 2010 for the positive VIEW 1 and VIEW 2 trial results in wet AMD.

Phase 2 DME Results
Regeneron and Bayer HealthCare also reported 52 week follow-up results from the Phase 2 DA VINCI study in patients with diabetic macular edema (DME). In this study, the previously reported visual acuity gains achieved with VEGF Trap-Eye treatment over 24 weeks (the primary endpoint of the study) were maintained or numerically improved up to completion of the study at week 52 in all VEGF Trap-Eye study groups, including 2mg dosed every other month. Based on these positive results, Regeneron and Bayer HealthCare are discussing plans to initiate Phase 3 studies.

In this double-masked, prospective, randomized, multi-center Phase 2 trial, entitled **DA VINCI** (**D**ME **A**nd **V**EGF Trap-Eye: **IN**vestigation of **C**linical Impact), 221 patients with clinically significant DME with central macular involvement were randomized and 219 patients were treated with balanced distribution over five groups. The control group received macular laser therapy at baseline, and patients were eligible for repeat laser treatments, but no more frequently than at 16 week intervals. Two groups

received monthly doses of 0.5 or 2mg of VEGF Trap-Eye throughout the 12-month dosing period. Two groups received three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by either every two months dosing or PRN (as-needed) dosing with very strict repeat dosing criteria. Mean gains in visual acuity versus baseline were as follows:

	Laser	0.5mg monthly	2mg monthly	2mg every two months*	2mg PRN*
n	44	44	44	42	45
Mean change in visual acuity at week 24 versus baseline[1] (letters)	2.5	8.6**	11.4**	8.5**	10.3**
Mean change in visual acuity at week 52 versus baseline (letters)	-1.3	11.0**	13.1**	9.7**	12.0**

*Following 3 initial monthly doses
**p<0.01 versus laser
[1] Primary endpoint

No significant differences among the VEGF Trap-Eye arms were observed. Approximately 80 percent of the VEGF Trap-Eye patients and 75 percent of the laser patients remained in the study through 52 weeks.

VEGF Trap-Eye was generally well-tolerated, and there were no ocular or non-ocular drug-related serious adverse events reported in the study.* The most common adverse events reported were those typically associated with intravitreal injections or the underlying disease. The most frequent ocular adverse events reported among patients receiving VEGF Trap-Eye included conjunctival hemorrhage, eye pain, ocular redness (hyperemia), and increased intraocular pressure. The incidence of non-ocular serious adverse events was generally well balanced between all treatment arms. There were six deaths (3.4%) among the 175 patients treated with VEGF Trap-Eye and one (2.3%) in the 44 patients treated with laser over 12 months. Detailed results for DA VINCI will be presented at the Angiogenesis Conference in Miami, Florida in February 2011.

About the Phase 3 CRVO Program
Patients in the COPERNICUS (Controlled Phase 3 Evaluation of Repeated intravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) and the identical GALILEO (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) studies receive six monthly injections of either VEGF Trap-Eye at a dose of 2mg or sham injections. Patients in the COPERNICUS trial were randomized in a 3:2 ratio with 114 patients randomized to receive VEGF Trap-Eye and 73 randomized to the control arm. At the end of the initial six months, all patients randomized to VEGF Trap-Eye are dosed on a PRN (as needed) basis for another six months. In the COPERNICUS trial, patients randomized to sham injections in the first six months are eligible to cross over to VEGF Trap-Eye PRN dosing in the second six months. During the second six months of the studies, all patients are eligible for rescue laser treatment. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity.

About Central Retinal Vein Occlusion (CRVO) Over 100,000 people in the United States and more than 66,000 people in key European countries are estimated to suffer from CRVO. CRVO is caused by obstruction of the central retinal vein that leads to a back up of blood and fluid in the retina. This causes retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new, inappropriate blood vessels that can cause further vision loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the inappropriate growth of new blood vessels in the retina in patients with CRVO.

About Diabetic Macular Edema (DME)
DME is the most prevalent cause of moderate vision loss in patients with diabetes. DME is a common complication of Diabetic Retinopathy (DR), a disease affecting the blood vessels of the retina. Clinically significant DME is a leading cause of blindness in younger adults (under 50). Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness.

Approximately 370,000 Americans currently suffer from clinically significant DME, with 95,000 new cases arising each year. According to the American Diabetes Association, more than 18 million Americans currently suffer from diabetes, and many other people are at risk for developing diabetes. With the incidence of diabetes steadily climbing, it is projected that up to 10 percent of all patients with diabetes will develop DME during their lifetime.

About VEGF Trap-Eye
VEGF Trap-Eye is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Regeneron and Bayer HealthCare are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age related macular degeneration (wet AMD), diabetic macular edema (DME), central retinal vein occlusion (CRVO), and other eye diseases and disorders. In November 2010, Regeneron and Bayer HealthCare announced positive top-line results from two parallel Phase 3 studies in patients with wet AMD, VIEW 1 and VIEW 2. In these trials, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab. A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies. There were no notable differences in non-ocular adverse events among the study arms. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval for the treatment of wet AMD in Europe and the U.S. in the first-half of 2011.

Bayer HealthCare will market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States.

About Regeneron Pharmaceuticals
Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

About Bayer HealthCare
The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward Looking Statement
This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with Astellas, the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2009 and Form 10-Q for the quarter ended September 30, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statements
This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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*As noted during our investor teleconference on December 20, 2010, the press release inadvertently omitted certain information, which

Regeneron does not consider to be material. To reflect inclusion of such omitted information, this sentence would be replaced with the following: "In this study, VEGF Trap-Eye was generally well-tolerated and no patients experienced ocular drug-related serious adverse events. With respect to the number of patients with non-ocular serious adverse events judged by investigators to be drug-related, there were none during the first six months of the study and one in the second six months."

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Annexure C

REGENERON
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November 22, 2010

Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration

In both studies, all regimens of VEGF Trap-Eye, including VEGF Trap-Eye dosed every two months, achieved primary endpoint compared to ranibizumab dosed every month
Regulatory applications for marketing approval planned in first-half of 2011

TARRYTOWN, N.Y. and BERLIN, Nov. 22, 2010 /PRNewswire-FirstCall/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) and Bayer HealthCare today announced that in two parallel Phase 3 studies in patients with the neovascular form of age-related macular degeneration (wet AMD), all regimens of VEGF Trap-Eye (aflibercept ophthalmic solution), including VEGF Trap-Eye dosed every two months, successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month. The primary endpoint was statistical non-inferiority in the proportion of patients who maintained (or improved) vision over 52 weeks compared to ranibizumab.

Further results will be presented at the Angiogenesis Conference in February 2011. Bayer HealthCare and Regeneron are planning to submit regulatory applications for marketing approval in Europe and the U.S. in the first-half of 2011 based on the positive results of the VIEW 1 and VIEW 2 trials.

In the North American VIEW 1 study, 96 percent of patients receiving VEGF Trap-Eye 0.5mg monthly, 95 percent of patients receiving VEGF Trap-Eye 2mg monthly, and 95 percent of patients receiving VEGF Trap-Eye 2mg every two months achieved maintenance of vision compared to 94 percent of patients receiving ranibizumab 0.5mg dosed every month. In the international VIEW 2 study, 96 percent of patients receiving VEGF Trap-Eye 0.5mg monthly, 96 percent of patients receiving VEGF Trap-Eye 2mg monthly, and 96 percent of patients receiving VEGF Trap-Eye 2mg every two months achieved maintenance of vision compared to 94 percent of patients receiving ranibizumab 0.5mg dosed every month. Visual acuity was measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity, over 52 weeks. Maintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS eye chart.

"The currently available anti-VEGF therapies have significantly advanced the treatment of wet AMD, actually improving vision in many patients. However, monthly injections are required to optimize and maintain vision gain over the long-term," said Ursula Schmidt-Erfurth, M.D., Professor and Chair of the Department of Ophthalmology at the University Eye Hospital in Vienna, Austria and the VIEW 2 Principal Investigator. "The results of the VIEW studies indicate that VEGF Trap-Eye could establish a new treatment paradigm for the management of patients with wet AMD --- predictable every-other-month dosing without the need for intervening monitoring or dosing visits."

"In an effort to avoid the inconvenience of monthly office visits and the burden of monthly injections into the eye for their wet AMD patients, retinal specialists have tried to extend the benefits of the existing anti-VEGF therapy with less frequent dosing. A growing body of data suggests that this practice may result in inconsistent visual acuity outcomes," said Jeffrey Heier, M.D., a clinical ophthalmologist and retinal specialist at Ophthalmic Consultants of Boston, Assistant Professor of ophthalmology at Tufts School of Medicine, and Chair of the Steering Committee for the VIEW 1 trial. "A critical goal of these studies was to demonstrate that VEGF Trap-Eye could achieve robust improvements in vision and maintain them over time with a more convenient every-other-month dose. Achievement of this goal could be important for patients, care givers, and physicians."

In the VIEW 1 study, patients receiving VEGF Trap-Eye 2mg monthly achieved a statistically significant greater mean improvement in visual acuity at week 52 versus baseline (secondary endpoint), compared to ranibizumab 0.5mg monthly; patients receiving VEGF Trap-Eye 2mg monthly on average gained 10.9 letters, compared to a mean 8.1 letter gain with ranibizumab 0.5mg dosed every month ($p<0.01$). All other dose groups of VEGF Trap-Eye in the VIEW 1 study and all dose groups in the VIEW 2 study were not statistically different from ranibizumab in this secondary endpoint.

A generally favorable safety profile was observed for both VEGF Trap-Eye and ranibizumab. The incidence of ocular treatment emergent adverse events was balanced across all four treatment groups in both studies, with the most frequent events associated with the injection procedure, the underlying disease, and/or the aging process. The most frequent ocular adverse events were conjunctival hemorrhage, macular degeneration, eye pain, retinal hemorrhage, and vitreous floaters. The most frequent serious non-ocular adverse events were typical of those reported in this elderly population who receive intravitreal treatment for wet AMD; the most frequently reported events were falls, pneumonia, myocardial infarction, atrial fibrillation,

breast cancer, and acute coronary syndrome. There were no notable differences among the study arms.

In the second year of the studies, patients in VIEW 1 and VIEW 2 will continue to be treated with the same dose per injection as in the first year but administered only every three months, or more often for any worsening of AMD, based on protocol-defined criteria (called "quarterly capped PRN" dosing).

About the VIEW Program

The VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) program consists of two randomized, double-masked, Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD). The VIEW 1 study, which randomized 1217 patients, is being conducted in the United States and Canada by Regeneron under a Special Protocol Assessment (SPA) with the U.S. Food and Drug Administration. The VIEW 2 study, which randomized 1240 patients, is being conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. The study designs are essentially identical. The primary endpoint evaluation was conducted at 52 weeks.

In each of the studies, VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5mg monthly, 2mg monthly, or 2mg every two months (following three monthly loading doses), as compared with intravitreal ranibizumab administered 0.5mg every month during the first year of the studies. As-needed (PRN) dosing with both agents, with a dose administered at least every three months (but not more often than monthly), is being evaluated during the second year of each study. These studies are part of the global development program for VEGF Trap-Eye being conducted by Bayer HealthCare and Regeneron.

The primary endpoint of these non-inferiority studies is the proportion of patients treated with VEGF Trap-Eye who maintain visual acuity at the end of one year, compared to ranibizumab patients. Visual acuity is measured as a score based on the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity, over 52 weeks. Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart.

The following table summarizes the VIEW 1 and VIEW 2 results for the primary and the first secondary endpoint pre-specified for testing:

	Ranibizumab 0.5mg monthly	VEGF Trap-Eye 0.5mg monthly	VEGF Trap-Eye 2mg monthly	VEGF Trap-Eye 2mg every 2 months
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
VIEW 1	94.4%	95.9%**	95.1%**	95.1%**
VIEW 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value versus ranibizumab 0.5mg monthly)***				
VIEW 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
VIEW 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)

*Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart
**Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)
*** Test for superiority
NS=non-significant

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating distortion and/or blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for people over the age of 65 in the U.S. and Europe.

About VEGF Trap-Eye

VEGF Trap-Eye is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. VEGF Trap-Eye is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

VEGF Trap-Eye is also in Phase 3 development for the treatment of Central Retinal Vein Occlusion (CRVO), another major cause of blindness, in two identical studies. The COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study is being led by Regeneron and the GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. Initial data from the CRVO program are anticipated in early 2011.

VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). In February 2010, Regeneron and Bayer HealthCare announced that treatment with VEGF Trap-Eye in the Phase 2 DA VINCI (DME And VEGF Trap-Eye: INvestigation of Clinical Impact) study demonstrated a statistically significant improvement in visual acuity versus baseline after six months of treatment compared to focal laser therapy, the primary endpoint of the study. Initial one-year results from this trial will be available before the end of this year.

About Regeneron Pharmaceuticals

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in Phase 3 clinical trials for the potential treatment of gout, diseases of the eye (wet age-related macular degeneration and central retinal vein occlusion), and certain cancers. Additional therapeutic candidates developed from proprietary Regeneron technologies for creating fully human monoclonal antibodies are in earlier stage development programs in rheumatoid arthritis and other inflammatory conditions, pain, cholesterol reduction, allergic and immune conditions, and cancer. Additional information about Regeneron and recent news releases are available on Regeneron's web site at www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of more than EUR 15.9 billion (2009), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 53.400 employees and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

Regeneron Forward Looking Statement

This news release includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties. These include, among others, risks and timing associated with preclinical and clinical development of Regeneron's drug candidates, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize its product and drug candidates, competing drugs that are superior to Regeneron's product and drug candidates, uncertainty of market acceptance of Regeneron's product and drug candidates, unanticipated expenses, the availability and cost of capital, the costs of developing, producing, and selling products, the potential for any license or collaboration agreement, including Regeneron's agreements with Astellas, the sanofi-aventis Group and Bayer HealthCare, to be canceled or terminated without any product success, and risks associated with third party intellectual property. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2009 and Form 10-Q for the quarter ended September 30, 2010. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise, unless required by law.

Bayer Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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SOURCE Regeneron Pharmaceuticals, Inc.

Annexure D

REGENERON

Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)

September 14, 2009

TARRYTOWN, N.Y., Sept 14, 2009 /PRNewswire-FirstCall via COMTEX News Network/ -- Regeneron Pharmaceuticals, Inc. (Nasdaq: REGN) today announced the completion of patient enrollment in two randomized, double-masked, Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD). In each study of the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) program, VEGF Trap-Eye is being evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of 0.5 milligram (mg) every four weeks, 2.0 mg every four weeks, or 2.0 mg every eight weeks (following three monthly doses), as compared with intravitreal ranibizumab (Lucentis((R)), a registered trademark of Genentech, Inc.) administered 0.5 mg every four weeks during the first year of the studies. As-needed (PRN) dosing with both agents is being evaluated during the second year of each study. These studies are part of the global development program for VEGF Trap-Eye being conducted by Regeneron and Bayer HealthCare AG. Each study has enrolled in excess of the targeted 1,200 patient goal. One-year primary endpoint data from both studies are expected in the fourth quarter of 2010.

VEGF Trap-Eye, an investigational drug, is being developed by Regeneron and Bayer HealthCare AG for the potential treatment of eye diseases, including wet AMD, diabetic macular edema (DME), and Central Retinal Vein Occlusion (CRVO). Regeneron maintains exclusive rights to VEGF Trap-Eye in the United States. Bayer HealthCare has exclusive rights to market VEGF Trap-Eye outside the United States, where the companies will share equally in profits from any future sales of VEGF Trap-Eye.

"Even with recent advances in the treatment of wet AMD, vision is not improved or stabilized in all patients despite monthly office visits and examinations that are inconvenient for these often elderly patients," said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "This Phase 3 program is exploring various doses and dosing schedules with our novel anti-VEGF investigational agent to evaluate whether further improvements in vision and/or longer dosing intervals than monthly administration are possible."

About the VIEW Program

The VIEW 1 study is being conducted in the United States and Canada by Regeneron and the VIEW 2 study is being conducted in Europe, Asia Pacific, Japan, and Latin America by Bayer HealthCare. In the first year of the studies, the safety and efficacy of VEGF Trap-Eye at doses of 0.5 mg and 2.0 mg administered at four-week intervals and 2.0 mg at an eight-week dosing interval following one additional 2.0 mg dose at week four are being evaluated. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every four weeks. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more often than every four weeks until the end of the study.

The primary endpoint of these non-inferiority studies is the proportion of patients treated with VEGF Trap-Eye who maintain vision at the end of one year, compared to ranibizumab patients. Visual acuity is defined as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, a standard chart used in research to measure visual acuity. Maintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart. Key secondary endpoints include the mean change from baseline in visual acuity as measured by ETDRS and the proportion of patients who gained at least 15 letters of vision at week 52.

About VEGF Trap-Eye

Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body whose normal role is to trigger the formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs. It has also been associated with the abnormal growth and fragility of new blood vessels in the eye, which lead to the development of wet AMD. VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PlGF). Investigational VEGF Trap-Eye is a specific blocker of VEGF-A and PlGF that has been demonstrated in preclinical models to bind these growth factors with greater affinity than their natural receptors. Blockade of VEGF can prevent abnormal blood vessel formation as well as vascular leak and has proven beneficial in the treatment of wet AMD.

VEGF Trap-Eye is also in Phase 3 development for the treatment of Central Retinal Vein Occlusion (CRVO), another cause of blindness. The COPERNICUS (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) study is being led by Regeneron and the GALILEO (General Assessment Limiting InfiLtration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) study is being led by Bayer HealthCare. Patients in both studies will receive six monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 mg or sham control injections. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. At the end of the initial six months, patients will be dosed on a PRN (as needed) basis for another six months. All patients will be eligible for rescue laser treatment. Initial data from the program are anticipated in early 2011.

VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses is being compared to focal laser treatment, the current standard of care in DME. The primary efficacy endpoint evaluation is mean improvement in visual acuity at six months. Patient enrollment has been completed with initial data expected in the first half of 2010.

About Wet AMD

Age-related Macular Degeneration (AMD) is a leading cause of acquired blindness. Macular degeneration is diagnosed as either dry (non-exudative) or wet (exudative). In wet AMD, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes disruption and dysfunction of the retina creating blind spots in central vision, and it can account for blindness in wet AMD patients. Wet AMD is the leading cause of blindness for

people over the age of 65 in the U.S. and Europe.

About Regeneron

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST((R))(rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, inflammatory diseases, and pain, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's Web site at www.regeneron.com.

Forward Looking Statement - Regeneron Pharmaceuticals, Inc.

This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of VEGF Trap-Eye, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize VEGF Trap-Eye, competing drugs that may be superior to VEGF Trap-Eye, uncertainty of market acceptance of VEGF Trap-Eye, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2008 and Form 10-Q for the quarter ending June 30, 2009. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.

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Annexure E

Expert Opinion on Investigational Drugs

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VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration

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Expert Opinion

VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration

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Background: Age-related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 90% of patients with AMD have the dry form, neovascular AMD accounts for the vast majority of patients who develop legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD. In addition to two anti-VEGF drugs currently in widespread use, ranibizumab and bevacizumab, a number of medications that interrupt angiogenesis are currently under investigation. One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2. *Objective*: To review the current literature and clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD. *Methods*: Literature review. *Results/conclusion*: VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD. Two Phase III clinical trials (VIEW-1 and VIEW-2) comparing VEGF Trap-Eye to ranibizumab are currently continuing and will provide vital insight into the clinical applicability of this drug.

Keywords: aflibercept, AMD, angiogenesis, neovascularization, VEGF, VEGF inhibition, VEGF Trap

Expert Opin. Investig. Drugs (2009) 18(10):1573-1580

1. Introduction

Age-related macular degeneration (AMD) affects > 1.75 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million [1]. Worldwide, AMD is estimated to affect 14 million people [2]. While the vast majority of patients suffering from AMD have the dry form, ~ 80 – 90% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease [3]. Until recently, healthcare professionals had few options when it came to treating neovascular AMD. For many years, subfoveal choroidal neovascularization (CNV) was treated with argon laser therapy according to guidelines from the Macular Photocoagulation Study [4-12]. This treatment, in the setting of subfoveal disease, was unsatisfactory for a number of reasons, including the limited benefits in visual stabilization and the high risk of inducing central vision deficits [13]. Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photosensitizing dye (verteporfin) to selectively target CNV. While more efficacious than previous treatments, patients receiving PDT failed to recover vision and continued to experience a decline in visual acuity [14] and the treatment was of questionable cost effectiveness [15].

The more recent development of agents that inhibit VEGF has largely supplanted these previous treatments. The pathogenesis of CNV in the setting of

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AMD is complex; however, there is overwhelming evidence that VEGF is a predominant mediator in its genesis. VEGF receptors are expressed by a number of important cell types in the eye, including vascular endothelial cells, choroidal fibroblasts, retinal pigment epithelial cells and inflammatory cells attracted by hypoxia [16-19]. Higher levels of VEGF expression have been demonstrated in animal models [20,21] and human studies of eyes with AMD [17,22-24] and antagonism of VEGF in both settings have definitively demonstrated inhibition of neovascularization and vascular permeability. VEGF-A is the predominant member of the VEGF family targeted by drugs currently in widespread use; however, the group is also comprised of VEGF-B, VEGF-C, VEFG-D and placental growth factors-1 and -2.

Systemic administration of bevacizumab is effective against neovascular AMD; however, systemic complications limit its use [25]. Accordingly, all anti-VEGF agents for neovascular AMD are administered only by intravitreal injection. The two largest studies examining anti-VEGF therapy, the MARINA [26] and the ANCHOR [27,28] trials, were randomized, controlled, double-masked Phase III clinical trials that together evaluated monthly ranibizumab for the treatment of all types of neovascular AMD. In both trials, 94% of patients with neovascular AMD lost fewer than 15 letters of visual acuity at 12 and 24 months when treated with ranibizumab. Surprisingly, as many as 40% of patients in the two trials improved by > 15 letters from baseline at 2 years. Ranibizumab received the FDA approval for all types of neovascular AMD in 2006. Based on the results of these two landmark studies, anti-VEGF therapies for neovascular AMD have largely replaced previous treatment modalities.

2. Background

2.1 Overview of the market (unmet needs, competitor compounds/in clinical development)

By far the most commonly used anti-VEGF drugs currently in use for neovascular AMD are ranibizumab and bevacizumab. Pegaptanib was the first anti-VEGF drug approved by the FDA for the treatment of AMD; however, it proved less efficacious than current treatments [13] (possibly due to its selective binding of VEGF-165) and is no longer widely used in most countries. Ranibizumab is the only drug in widespread use currently approved by the FDA for treatment of neovascular AMD and is by far the most extensively studied [26,27,29,30]. It is a recombinant monoclonal antibody fragment with a high binding affinity for all isotypes of VEGF-A. Bevacizumab, currently being used off-label for the treatment of AMD in the US, is a humanized whole antibody to VEGF-A used in oncology regimens that also binds all isotypes of VEGF-A. Although ranibizumab has been shown to have a higher affinity for VEGF-A, it is not clear if ranibizumab has superior efficacy to bevacizumab. Retrospective and small randomized studies have suggested similar efficacy profiles [31,32]. The Comparisons of Age-Related Macular Degeneration Treatment Trial (CATT) is a 2-year, multi-centered, randomized clinical trial comparing ranibizumab and bevacizumab for neovascular AMD. Enrollment began in February 2008. Despite the off-label status of bevacizumab, it continues to be a popular treatment choice in the US because of the significantly reduced price of treatment ($ 50 – 100 for bevacizumab versus $ 2000 for ranibizumab (2008 pricing)).

As previously mentioned, the MARINA [26] and the ANCHOR [27,28] trials examined the efficacy of ranibizumab when administered monthly. The time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules. In the PIER study [30], patients initially received monthly injections of ranibizumab for 3 months followed by quarterly injections. Although patient visual acuities actually improved at 3 months, during the quarterly dosing segment visual acuity returned to baseline. The PrONTO study [29] looked at as needed (p.r.n.) dosing of ranibizumab after three consecutive monthly doses. The need for further injections was made on the basis of recurrent CNV as evidenced by worsening vision, retinal thickening on ocular coherence tomography (OCT) or abnormalities on fluorescein angiogram (FA). At 2 years of follow up, 78% of patients had maintained vision and vision had improved by > 3 lines in 43% of patients with an average of five injections a year. These later studies seem to indicate that quarterly dosing is associated with poorer outcomes but it may be possible to extend the time between injections if the patient is frequently monitored. However, even with the p.r.n. dosing utilized in the PrONTO study, patients are still required to make monthly visits to the office with frequent and expensive testing.

The development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action. Most new compounds in development are targeted toward inhibition of various steps in the VEGF signaling pathway. There are a number of drugs in development that inhibit the downstream tyrosine kinase cascade activated by the binding of VEGF with its receptor (VEGFR). Vatalanib is an oral formulation that binds to all three VEGFRs and has recently completed Phase I/II study as adjuvant to PDT and ranibizumab [33]. Topical tyrosine kinase inhibitors currently undergoing Phase II clinical studies include pazopanib [34] and TG100801 [35]. Another approach utilizes siRNA to silence genes which express proteins involved in angiogenesis. Bevasiranib, an siRNA that targets VEGF-A mRNA, showed encouraging Phase I and II data, but the Phase III trial was halted in March 2009 for projected failure to meet the primary end point [36]. An extra antiangiogenic target being developed is pigment epithelium-derived factor (PEDF), a potent inhibitor of new vessel growth. AdGVPEDF.11D uses an adenovector to deliver the PEDF gene to target cells, resulting in the local production of PEDF in the treated eye. AdGVPEDF.11D has recently completed Phase I clinical trials [37]. Another

recently discovered alternative pathway for decreasing angiogenesis involves inhibition of nicotinic acetylcholine receptors. ATG3 (mecamylamine), a topical formulation that inhibits the nicotinic acetylcholine receptors, has shown promising results in animal and Phase I trials and is currently undergoing a Phase II study [25].

2.2 Introduction to compound

VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA) in the US and in collaboration with Bayer HealthCare (Leverkusen, Germany) in global markets. Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (**Figure 1**). Functionally, VEGF Trap-Eye acts as a receptor decoy with high affinity for all VEGF isoforms, binding more tightly than their native receptors. Unlike anti-VEGF drugs currently in use, VEGF Trap-Eye is designed to inhibit placental growth factors-1 and -2 in addition to all isoforms of VEGF-A.

2.3 Chemistry

VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations. Both aflibercept and VEGF Trap-Eye are manufactured in bioreactors from industry standard Chinese hamster ovary cells that overexpress the fusion protein. However, VEGF Trap-Eye undergoes further purification steps during manufacturing to minimize risk of irritation to the eye. VEGF Trap-Eye is also formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.

2.4 Pharmacodynamics

The aflibercept dose that is administered in oncology settings is either 4 mg/kg every 2 weeks or 6 mg/kg every 3 weeks, which corresponds to 2 mg/(kg week) with either schedule. The highest intravitreal dose being used in pivotal trials for VEGF Trap-Eye is 2 mg/month, which corresponds to at least a 280-fold lower potential systemic exposure than in the oncology setting. Early trials with aflibercept administered intravenously for AMD indicated that doses of 0.3 mg/kg (21 mg total) were inadequate to fully capture systemic VEGF. Thus, the low intravitreal dose of 2 mg allows for extended blocking of VEGF in the eye, but would be predicted to give negligible systemic activity as it will be rapidly bound to VEGF and inactivated.

2.5 Pharmacokinetics and metabolism

Aflibercept is cleared from circulation through two pathways: by binding to VEGF to form an inactive VEGF–aflibercept complex and by Fc-receptor or pinocytotic mediated pathways that end in proteolysis, which are presumed to be similar to pathways that metabolize antibodies. At very high doses, free aflibercept has a terminal half-life of ~ 17 days in the circulation. The half-life of human intravitreal doses is unknown. Intravitreal primate doses of ranibizumab have a half-life of ~ 3 days [38]. At low blood levels, clearance of free aflibercept is rapid as a result of binding to VEGF with picomolar affinity [39].

2.6 Clinical efficacy

2.6.1 Phase I

A Phase I, randomized, double-blind, placebo-controlled trial of intravenous aflibercept (oncology formulation) was completed in 25 patients with AMD. Although systemic aflibercept did demonstrate a dose-dependent decrease in retinal thickness, the study was halted due to concerns of dose-dependent toxicity when one patient developed hypertension and another proteinuria [40].

The safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the two-part Clinical Evaluation of Anti-angiogenesis in the Retina-1 (CLEAR-IT-1) study [41]. The first part was a sequential cohort dose-escalation study in which 21 patients were monitored for safety, changes in foveal thickness on OCT, best corrected visual acuity (BCVA) and lesion size on FA for 6 weeks. No adverse systemic or ocular events were noted and visual acuity remained stable or improved ≥ 3 lines in 95% of patients with a mean increase in BCVA of 4.6 letters at 6 weeks [42]. Patients showed substantially decreased foveal thickness [41].

In the second part, 30 patients received a single intravitreal injection of either 0.5 or 4 mg of VEGF Trap-Eye and were followed for 8 weeks. All patients were evaluated for their rates of retreatment, changes in BCVA, foveal thickness as well as change in total lesion size and area of CNV. Patients had ETDRS (Early Treatment of Diabetic Retinopathy Study) BCVA ranging from 20/40 to 20/320 with any angiographic subtype of CNV at baseline. No serious adverse events or ocular inflammation was identified during the study. At 8 weeks, the mean decrease in retinal thickness in the low dose group was 63.7 µm compared to 175 µm for the high dose group. Of the first 24 patients to complete the study, 11 out of 12 patients in the 0.5 mg dose group required retreatment in a median of 64 days, compared with 4 out of 12 in the 4 mg dose group who required retreatment in a median of 69 days [43].

VEGF Trap-Eye has also undergone a small open-label safety study for the treatment of diabetic macular edema (DME) [44]. The drug was administered as a single 4 mg intravitreal injection to five patients with longstanding diabetes and several previous treatments for DME. The single injection resulted in a median decrease of central macular thickness measured by OCT of 79 µm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks.

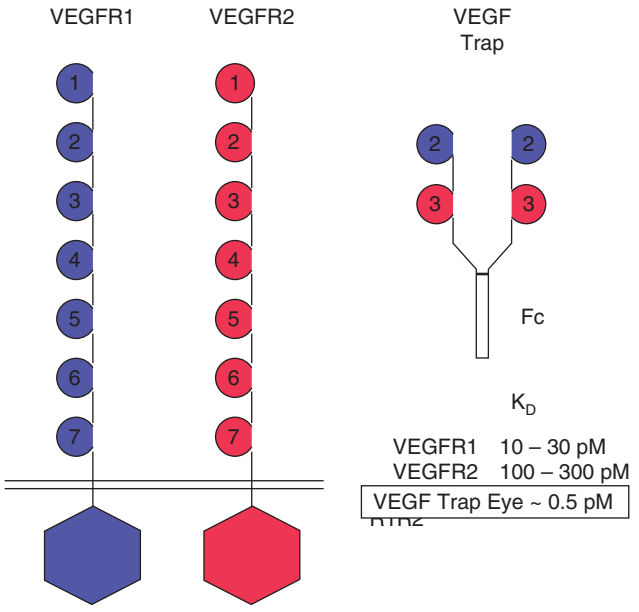

Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.

2.6.2 *Phase II*

CLEAR-IT-2 trial [45] was a prospective, randomized, multi-center, controlled dose- and interval-ranging Phase II trial in which 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. The mean age of the group was 78.2 years and all angiographic subtypes of CNV were represented at baseline. The mean ETDRS BCVA in letters at baseline was 56. Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12) and three groups received quarterly doses of either 0.5, 2.0 or 4.0 mg for 12 weeks (at weeks 0 and 12). Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for re-dosing included an increase in central retinal thickness of ≥ 100 µm by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

Patients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks. During the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections. The median time to first reinjection in all groups was 110 days and 19% of patients required no more injections at week 52. Patients in these two monthly dosing groups also displayed mean decreases in retinal thickness versus baseline of 143 µm ($p < 0.0001$) in the 2.0 mg group and 125 µm ($p < 0.0001$) in the 0.5 mg group at 52 weeks as measured by OCT [45].

Patients in the three quarterly dosing groups also showed mean improvements in BCVA and retinal thickness; however, they were generally not as profound as the monthly injection group [45].

2.6.3 *Phase III*

A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) [46] will enroll ~ 1200 patients with neovascular AMD in the US and Canada. This non-inferiority study will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation. The VIEW 2 [47] study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America. In both trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).

2.7 Safety and tolerability

Based on Phase II study data, VEGF Trap-Eye seems to be generally well tolerated with no serious drug-related adverse events. In the 157 patients enrolled in CLEAR-IT 2 trial, there was one reported case of culture-negative endophthalmitis not deemed to be related to the study drug. There were also two deaths (one from pre-existing pulmonary hypertension and one from pancreatic carcinoma) and one arterial thromboembolic event (in a patient with a history of previous stroke) that occurred during the study period, but no serious systemic adverse events were deemed related to VEGF Trap-Eye administration. The most common adverse events reported in the study included conjunctival hemorrhage (38.2%), transient increased intraocular pressure (18.5%), refraction disorder (15.9%), retinal hemorrhage (14.6%), subjective visual acuity loss (13.4%), vitreous detachment (11.5%) and eye pain (9.6%) [45].

3. Conclusion

Anti-VEGF therapy has vastly improved the treatment of neovascular AMD in terms of both safety and efficacy. The ANCHOR [26] and MARINA [27,28] trials have established ranibizumab as an effective therapy when dosed monthly. It has been shown to stabilize vision in 94% of patients and in almost 40% of patients vision will actually improve by 3 or more lines. However, the monthly dosing schedules used in these trials present a financial and time burden to patients and healthcare practitioners. The more recent PIER [30] and

PrONTO [29] trials have shown that ranibizumab is less effective when dosed quarterly, but it may be possible to extend the time between injections when patients are followed closely with frequent examinations and ancillary testing. The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established but new treatments are aimed at extending and improving on the efficacy of ranibizumab. VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and its blockage of placental growth factors-1 and -2. Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD. In Phase II study data, patients dosed in a similar fashion to the PrONTO trial demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year. Of the greatest interest, patients dosed at 2.0 mg during the initial monthly dosing period required 1.6 injections on average during the p.r.n. dosing phase. While this number is difficult to compare directly to the number of injections required during the p.r.n. phase of the PrONTO ranibizumab study, it is promising. A direct comparison of the efficacy of VEGF Trap-Eye versus ranibizumab will be possible with the completion of two Phase III trials, the VIEW-1 and -2 studies.

4. Expert opinion

The advent of anti-VEGF therapy for treatment of neovascular AMD has revolutionized therapy for a common blinding disease. Before the development of pegaptanib, ranibizumab and bevacizumab, the diagnosis of neovascular AMD portended a prognosis of nearly universal decline in vision, and frequently loss of useful vision in the affected eye.

Current treatment regimens with either ranibizumab or bevacizumab now afford stabilization of vision in > 90% of patients, with significant vision gain in one-third of all patients treated. There have been no significant, proven adverse systemic effects with the intraocular use of either drug. However, limitations of current therapy include the need for frequent intraocular injections, as often as monthly, without a defined stopping point. Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis. A significant time and financial burden falls on patients during their treatment course.

Desirable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and decreased dosing intervals. For other indications, time-release delivery methods have met with some success, including the following agents: intraocular steroids, including polymeric fluocinolone and dexamethasone, lasting 3 years and 6 months, respectively [48-50], and for a single biologically active cytokine, ciliary neurotrophic factor, which is released for a period greater than 1 year by encapsulated, bioengineered, implanted cells [51]. While efforts are underway to develop encapsulated cell technology for sustained-release anti-VEGF therapy, no investigational drugs or devices have progressed yet to clinical trial enrollment.

VEGF Trap-Eye represents the most promising anti-VEGF investigational drug that is currently in Phase III trial. VEGF Trap-Eye, a decoy VEGF receptor protein, binds all isoforms of free VEGF with high affinity, in addition to placental growth factor. In contrast to current anti-VEGF antibodies, which are rapidly cleared, the VEGF–VEGF Trap complex is relatively inert, and is degraded more slowly. Due to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye. Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye.

Data from the Phase II study with VEGF Trap-Eye were positive and the results from the non-inferiority Phase III trials will establish its efficacy versus ranibizumab. Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals. If effective at 4 week intervals only, VEGF Trap-Eye will be adopted into clinical practice if it offers a competitive price advantage over ranibizumab. If effective at 8 week intervals, VEGF Trap-Eye offers the opportunity to significantly reduce treatment burden on patients and physicians, and would probably find wide acceptance. The second p.r.n. dosing stage of the Phase III trial will also provide insight into whether VEGF Trap-Eye offers longer duration of treatment effectiveness than ranibizumab.

Data from the VIEW-1 and VIEW-2 trials will need to be interpreted by clinicians in the context of emerging adjuvant therapies that may extend the time between anti-VEGF therapy injections. Many clinicians now treat patients with anti-VEGF therapies in combination with verteporfin PDT. Randomized, open-label studies and one large retrospective case series database seem to indicate lower retreatment rates and improved visual outcomes when compared with monotherapy [52-55]. As a result, at least two prospective, randomized trials are currently underway to further examine combination verteporfin PDT and anti-VEGF treatments [56,57]. An extra combination treatment currently under study is the use of epiretinal brachytherapy with Strontium-90 combined with bevacizumab. A recently published small pilot study showed good safety and efficacy with a single application of epiretinal radiation and two bevacizumab injections after 12 months [58]. A larger, multi-center Phase III trial is underway [59].

Anti-VEGF agents are currently only approved for the treatment of exudative AMD. The multifactorial nature of DME, including non-VEGF mediated causes such as pericyte and endothelial cell damage and tractional mechanisms, has made treatment of this condition difficult using current modalities. Clinical studies are underway with anti-VEGF agents in DME and retinal vein occlusion. VEGF Trap-Eye is under Phase II investigation in DME and Phase III investigation in central retinal vein occlusion. The

FDA approval of VEGF Trap-Eye for these indications would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease.

Eventually, injectable agents targeting the VEGF pathway may be supplanted by implantable devices that deliver polymer-bound drug or manufacture the protein *in vivo*. Further therapies for neovascular AMD such as targeted radiation may confer extra treatment benefit. In the meantime, VEGF Trap-Eye is a promising investigational drug that, if approved, will improve ophthalmologists' ability to treat neovascular AMD.

Declaration of interest

SCN Oliver is a clinical investigator for Genentech and Alcon. JL Olson and N Mandava are clinical investigators for Genentech, Regeneron and Alcon.

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