

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., CELLTRION, INC., and
APOTEX, INC.,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Inter Partes Review No.: IPR2021-00880¹

U.S. Patent No. 9,669,069 B2
Filed: December 17, 2015
Issued: June 6, 2017
Inventor: George D. Yancopoulos

Title: USE OF A VEGF ANTAGONIST TO TREAT
ANGIOGENIC EYE DISORDERS

**PETITIONER'S CORRECTED DEMONSTRATIVES FOR ORAL
ARGUMENT**

¹ IPR2022-00257 and IPR2022-00301 have been joined with this proceeding.

***Mylan Pharmaceuticals Inc. v.
Regeneron Pharmaceuticals, Inc.***
IPR2021-00880 & IPR2021-00881
Petitioner, Mylan Pharmaceuticals Inc.
–Oral Argument–

August 10, 2022

'069 Patent: Anticipation Grounds 1-3

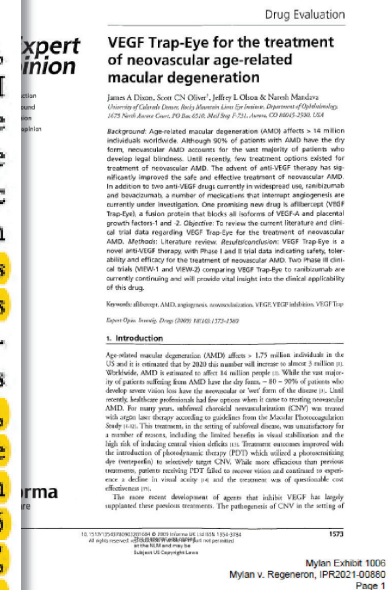
- The dosing regimen disclosures of Dixon, Heier-2009, and Regeneron April 2009 Press Release are undisputed.

- E.g., Dixon (Ground 2) discloses the VEGF Trap-Eye CLEAR-IT-2 trial: PRN dosing after 4 monthly loading doses (i.e., an initial dose and one or more secondary doses)
- Heier-2009 (Ground 1) discloses the same trial and regimen (Ex.1020)

(IPR2021-00880, Paper 1, 32-36, 45-50)

2.6.2 Phase II

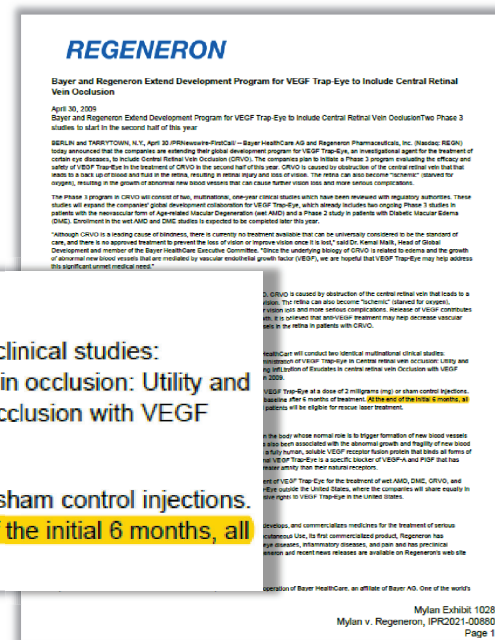
CLEAR-IT-2 trial [45] was a prospective, randomized, multi-center, controlled dose- and interval-ranging Phase II trial in which 157 patients were randomized to five dose groups and treated with VEGF Trap-Eye in one eye. The mean age of the group was 78.2 years and all angiographic subtypes of CNV were 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 $\geq 100 \mu\text{m}$ 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.**



Ex.1006, Dixon, 1576

'069 Patent: Anticipation Grounds 1-3

- The dosing regimen disclosures of Dixon, Heier-2009, and Regeneron April 2009 Press Release are undisputed.
 - The Press Release discloses the VEGF Trap-Eye Phase 3 CRVO trials - PRN dosing after six monthly loading doses (i.e., an initial dose and one or more secondary doses) (IPR2021-00880, Paper 1, 45-53)



About the Phase 3 CRVO Program

In the Phase 3 CRVO program for VEGF Trap-Eye, Regeneron and Bayer HealthCare will conduct two identical multinational clinical studies: **COPERNICUS** (COntrolled Phase 3 Evaluation of Repeated iNtravitreal administration of VEGF Trap-Eye In Central retinal vein occlusion: Utility and Safety) will be led by Regeneron and **GALILEO** (General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye) will be led by Bayer HealthCare. Enrollment will be initiated later in 2009.

Patients in both studies will receive 6 monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 milligrams (mg) or sham control injections. The primary endpoint of both studies is improvement in visual acuity versus baseline after 6 months of treatment. **At the end of the initial 6 months, all patients will be dosed on a PRN (as needed) basis for another 6 months.** All patients will be eligible for rescue laser treatment.

Ex.1028, Regeneron (30-April-2009)

'069 Patent: Anticipation Grounds 1-3

- Thus, Petitioner's asserted references cover each and every limitation of the claims

- It is undisputed that the references disclose the dosing regimen steps and the molecule, VEGF Trap-Eye, also known as aflibercept
- The sole dispute over Petitioner's anticipation grounds is over the sequence element

(IPR2021-00880, Paper 68, 25-36)

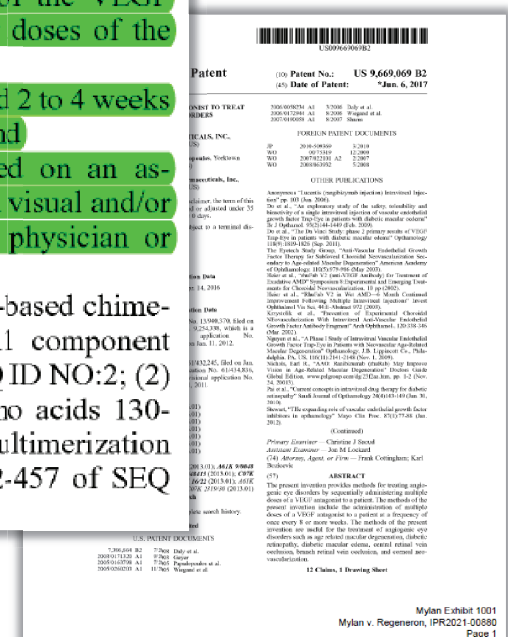
What is claimed is:

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.



Ex.1001, '069 patent, claim 1

'338 and '069 Patents: The claimed molecule

- No confusion among POSAs
 - Dixon discloses the use of VEGF Trap-Eye/aflibercept in AMD

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.

Drug Evaluation

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

A Dixon, Scott CN Oliver¹, Jeffrey L Olson & Nareh Mandava¹
¹U.S. Glaucoma Division, Regeneron Pharmaceuticals, Inc., 460 Route 9W, Tarrytown, NY 10593, USA

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: AMD, neovascularization, VEGF, VEGF inhibitors, VEGF Trap-Eye, Ranibizumab, Bevacizumab, Aflibercept, VEGF Trap-Eye

Drug: VEGF Trap-Eye (Ivance, Regeneron Pharmaceuticals, Inc.)

Introduction

Age-related macular degeneration (AMD) affects > 14 million individuals in the United States (1). It is estimated that by 2020 this number will increase to almost 3 million (2). AMD is estimated to affect 14 million people (3). While the vast majority 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.

© 2021 Regeneron Pharmaceuticals, Inc. All rights reserved. 1573

Regeneron Pharmaceuticals, Inc. 460 Route 9W, Tarrytown, NY 10593, USA

(IPR2021-00880, Paper 1, 26-34, 54-58; Paper 56, 10-15)
(IPR2021-00881, Paper 1, 23, 39-44; Paper 61, 23-27)

Ex.1006, Dixon, 1573

'338 and '069 Patents: The claimed molecule

- No confusion among POSAs
 - Adis discloses the use of VEGF Trap-Eye/aflibercept in AMD

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 IgG₁. 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 vascular leakage associated with wet age-related

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)

(IPR2021-00880, Paper 1, 26-34, 54-58; Paper 56, 10-15)

(IPR2021-00881, Paper 1, 23, 39-44; Paper 61, 23-28)

ADIS R&D PROFILE

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 IgG₁. 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 vascular 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.¹⁷

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 intracocular 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.¹⁸

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.¹⁹

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 \$US300 million at identified milestones related to the receipt of marketing approvals for up to eight indications in Europe and the

Mylan Exhibit 1007

Mylan v. Regeneron, IPR2021-00881

Page 1

Ex.1007, Adis, 261, 264

'338 and '069 Patents: The claimed molecule

- No confusion among POSAs
 - The aflibercept sequence was publicly available
(IPR2021-00880, Paper 1, 26-29, 38-39; Paper 56, 7-9, 13-15)
(IPR2021-00881, Paper 1, 24-25, 36-37; Paper 61, 22-28)

afliberceptum*
aflibercept

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

WHO Drug Information, Vol.20, No. 2, 2006

Proposed INN: List 95

C₄₃₁₈H₆₇₆₃N₁₁₆₄O₁₃₀₄S₃₂

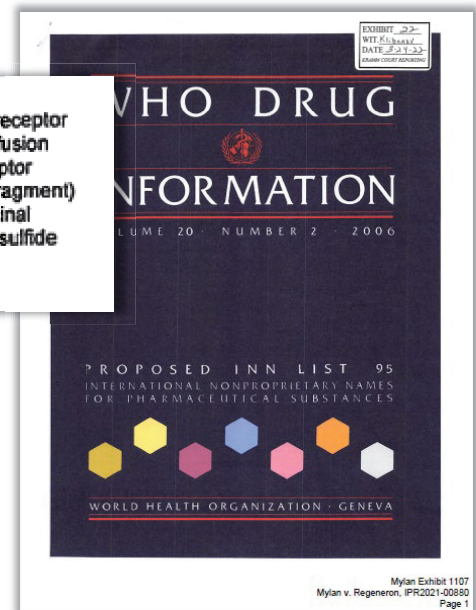
845771-78-0

Monomer / Monomère / Monómero

```

SDTGRPFVEH YSEIPEIIMH TEGRELYIPC RVTSPHITVT LKKFPLDTLI 50
PDGKRIIWDG RKGFIISMAT YKEIGLLTCE ATVNGHLYKT NYLTHROQNT 100
IDVVLSPSH GIELSVGERL VLNCTARTEL NVGIDFNHEY PSSKHQHKKL 150
VNRDLKTQSG SEMKKFLSTL TIDGVTESDQ GLYTCAASSG LMTKKNSTFV 200
RVNEKDKYHI CPPCPAPELL GGPSVLEFPF KPKDTLHISR TPEVTCVVVD 250
VSHEDPEVKF NMFVDOGVEVH NAKTKPREGQ YKSTYRVVSV LTVLHQDWLN 300
GKEYRCKVSN KALPAPIENT ISKANGQPRE PQVYTLPPSR DELTKNQVSL 350
TCLVKGFIYS DIAVEMESNG QPENNYKTFP FVLOS DGSPF LYSKLTVDKS 400
RHOQGNVESC SVMHEALHNN YTQKSLSLSP G 431
    
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
 36-79 39-79 124-183 124-183 211-211'
 214-214' 246-306 246-306' 352-410 352-410'



Mylan Exhibit 1107
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1107, WHO 2006 Drug Info, 118-119

'338 and '069 Patents: The claimed molecule

- No confusion among POSAs
 - The VEGF Trap-Eye/aflibercept sequence was available to interested POSAs

Ex.1004, Holash, 11397

Herein we describe the engineering of an anti-VEGF agent, termed **VEGF-Trap_{R1R2}**. VEGF-Trap_{R1R2} is a derivative of perhaps the most potent VEGF binder known, VEGFR1. Soluble forms of VEGFR1 suffer from poor pharmacokinetic properties, which seem to correlate with their nonspecific interactions with extracellular matrix. **VEGF-Trap_{R1R2}** was engineered to have minimal interactions with extracellular matrix, and this property apparently accounts for its satisfying pharmacokinetic profile. The combina-

(IPR2021-00880, Paper 1, 26-29, 38-39;
Paper 56, 7-9, 13-15)
(IPR2021-00881, Paper 1, 24-25, 36-37;
Paper 61, 22-28)

Ex.1008, '173 Patent, 1:48-52

... and VEGFR1R2-FcΔC1(a). In a specific and preferred embodiment, the VEGF trap is **VEGFR1R2-FcΔC1(a)** (also termed **VEGF trap_{R1R2}**) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2. The invention comprises

Ex.1010, '758 Patent, 10:15-17

FIG. 24A-24C. Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed **VEGFR1R2-FcΔC1(a)**.

Multiple VEGF Trap-Eye *and* aflibercept references refer back to Holash:

- Ex.2080, Heier (“**VEGF Trap-Eye** includes specific extracellular components of VEGF receptors 1 and 2 fused to the constant region (Fc) of IgG1,” and citing to, and presenting data from, Holash)
- *See also, e.g.*, Ex.1119 (referencing aflibercept and citing Holash); Ex.1120 (same); Ex.1123 (discussing VEGF Trap-Eye and citing Holash); Ex.1115, Gerritsen Reply Decl., ¶¶ 36-56

'338 and '069 Patents: The claimed molecule

- No confusion among POSAs
 - Ex.1122: '069/'338 claimed sequence = prior art 2006 WHO Drug Info aflibercept sequence (Ex.1107) = prior art '758/'959 Fig. 24 sequence of VEGFR1R2ΔC1(a) (SEQ ID NO: 16) (Ex.1010)
 - See also, e.g., Ex.1117 (aligning the '338 claimed sequence, the WHO aflibercept sequence, and the '173 patent, SEQ ID NO:2 sequence)
 - (IPR2021-00880, Paper 56, 13-15)
 - (IPR2021-00881, Paper 61, 27-28)

SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVI PCRVTS 60 -----SDTGRPFVEMYSEIPEIIHMTGRELVI PCRVTS 34 MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVI PCRVTS 60 MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVI PCRVTS 60
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNLYT 120 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNLYT 94 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNLYT 120 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNLYT 120
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSKHKHKKLVNRD 180 HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSKHKHKKLVNRD 154 HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSKHKHKKLVNRD 180 HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELVGIDFNWEYPSKHKHKKLVNRD 180
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC 240 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC 214 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC 240 LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC 240
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 274 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300 PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT 300
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	KPREEQYNSTYRVVSVLTVLHQDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360 KPREEQYNSTYRVVSVLTVLHQDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 334 KPREEQYNSTYRVVSVLTVLHQDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360 KPREEQYNSTYRVVSVLTVLHQDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY 360
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEHESNGQPENNYKTTTPPVLDSGDGSFFLYSK 420 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEHESNGQPENNYKTTTPPVLDSGDGSFFLYSK 394 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEHESNGQPENNYKTTTPPVLDSGDGSFFLYSK 420 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEHESNGQPENNYKTTTPPVLDSGDGSFFLYSK 420
SEQ ID 2 (338 & 069) Aflibercept (WHO 2006) 758 SEQ ID 16 959 SEQ ID 16	LTVDKSRWQQGNVFSCSVMHEALHNNHYTQKLSLSLSPGK 458 LTVDKSRWQQGNVFSCSVMHEALHNNHYTQKLSLSLSPG- 431 LTVDKSRWQQGNVFSCSVMHEALHNNHYTQKLSLSLSPGK 458 LTVDKSRWQQGNVFSCSVMHEALHNNHYTQKLSLSLSPGK 458

Ex.1122, Amino Acid Alignment (*see also*, e.g., Ex.1024 (Nucleic Acid Alignment))

'338 and '069 Patents: The claimed molecule

- PO's counter-arguments lack merit

- Dixon discloses that VEGF Trap-Eye and aflibercept have the "same molecular structure." Ex.1006, 1575
- Any other trap species would have a *different* molecular structure from aflibercept

(IPR2021-00880, Paper 56, 10-16)

(IPR2021-00881, Paper 61, 23-27)

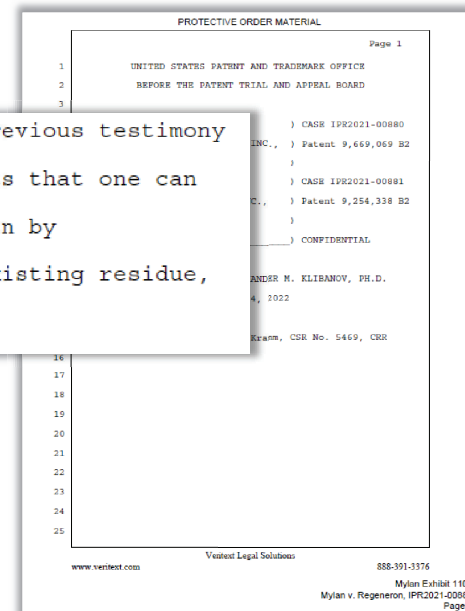
Q. Do you still agree with your previous testimony that: "It is understood among biochemists that one can change an amino acid sequence of a protein by substituting or chemically changing an existing residue, either way resulting in a new molecule"?

THE WITNESS: Yes, I agree with that statement.

BY MR. McLAUGHLIN:

Q. Do you also agree with the statement in the first sentence of paragraph 83 that says: "Changing even one bond in such a complex molecule as a protein, transforms it into a new molecular entity, with different (sometimes drastically so) chemical structure and properties"?

THE WITNESS: As a general proposition, I certainly agree with that. But, again, as I said before, it has to be read in the context of the entire document, as all other statements have to be.



Ex.1108, Klibanov Tr., 32-35; 184:1-189:10

Ex.1103, Klibanov Dep. Ex. 3, ¶¶ 76, 82-83

'338 and '069 Patents: The claimed molecule

- PO's counter-arguments lack merit

- VEGF Trap-Eye not a genus
- Dixon and Adis refer to the agent in the singular, and disclose it in Phase 2 and Phase 3 clinical trials
- Regeneron's public disclosures make clear the ophtho and onco products contained the same active ingredient (aflibercept)
(IPR2021-00880, Paper 56, 13-15; IPR2021-00881, Paper 61, 26-27)

1. Aflibercept (VEGF Trap) – Oncology

Aflibercept is a protein-based product candidate designed to bind all forms of Vascular Endothelial Growth Factor-A (called VEGF-A, also known as Vascular Permeability Factor or VPF), VEGF-B and the related Placental Growth Factor (called PlGF), and prevent their interaction with cell surface receptors. VEGF-A (and to a less validated degree, VEGF-B and PlGF) is required for the growth of new blood vessels (a process known as angiogenesis) that are needed for tumors to grow and is a potent regulator of vascular permeability and

2. VEGF Trap-Eye – Ophthalmologic Diseases

VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications. We and Bayer HealthCare are testing VEGF Trap-Eye in a Phase 3 program in patients with the neovascular form of age-related macular degeneration (wet AMD). We and Bayer HealthCare also are conducting a Phase 2 study of VEGF Trap-Eye in patients with diabetic macular edema (DME). Wet AMD and diabetic retinopathy (which includes DME) are two of the leading causes of adult blindness in the developed world. In both conditions, severe visual loss is caused by a combination of retinal edema and neovascular proliferation. We and Bayer HealthCare also initiated a Phase 3 program in Central Retinal Vein Occlusion (CRVO) in July 2009. In connection with the dosing of the first patient in a Phase 3 study in CRVO, we received a \$20.0 million milestone payment from Bayer HealthCare.

10-Q 1 regeneron_10q.htm QUARTERLY REPORT
UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
Form 10-Q
Check One
(X) QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the quarterly period ended September 30, 2009
OR
() TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from _____ to _____
Commission File Number 333-158074
REGENERON PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)
New York
(State or other jurisdiction of incorporation or organization) 113-015807
(G.S. Employer Identification No.)
777 Old Saw Kill Road
Parsippany, New Jersey 07054
1021-0202
(Zip Code)
Filed by Section 13 or 15(d) of the Securities Exchange Act of 1934
This report, with the information required by Item 12 of the Schedule, is incorporated by reference into the registrant's annual report on Form 10-K for the year ended September 30, 2009.
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1021, 2009 10-Q, 18-19

'338 and '069 Patents: The claimed molecule

- PO's counter-arguments lack merit

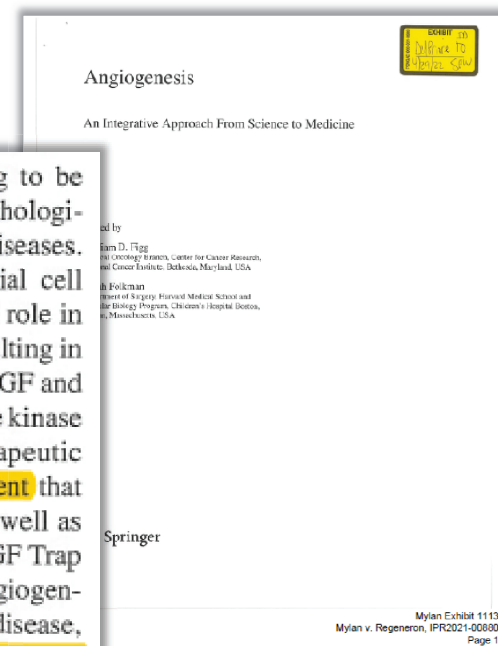
- Regeneron's public disclosures make clear the ophtho and onco products contained the same active ingredient (aflibercept)

- Ex.1113, Rudge 2008 at 417-418: *"promising results...supported the introduction of VEGF Trap into the clinic for treatment of both wet AMD and diabetic macular edema, using a version of VEGF Trap specifically formulated for intra-ocular administration, termed VEGF Trap-Eye."*

(IPR2021-00880, Paper 56, 13-15)

(IPR2021-00881, Paper 61, 26 n.13, 26-28)

Abstract: The inhibition of angiogenesis is proving to be an effective strategy in treating diseases involving pathological angiogenesis such as cancer and ocular vascular diseases. Since its discovery in the 1980s, vascular endothelial cell growth factor (VEGF) has been shown to play a vital role in both physiological and pathological angiogenesis, resulting in the development of numerous approaches to block VEGF and VEGF signaling, ranging from small molecule tyrosine kinase inhibitors to protein-based and RNA-based therapeutic candidates. VEGF Trap is one such protein-based agent that has been engineered to bind and sequester VEGF, as well as placental growth factor (PIGF), with high affinity. VEGF Trap has been shown to effectively inhibit pathological angiogenesis in numerous preclinical models of cancer and eye disease, and is now being evaluated in clinical trials in several types of cancer, as well as the 'wet' or neovascular form of age-related macular degeneration (AMD). This chapter will summarize the basic biology of VEGF and the progress of the VEGF Trap from the bench to the clinic.



Ex.1113, Rudge 2008, 415

IPR2021-00880 – Ground 4

- PO Should Be Held To Its Prosecution Representations
 - “In accordance with a dosage regimen as claimed in independent claim 1” (IPR2021-00880, Paper 56, 18-20)

The Heier et al. paper shows results of a treatment protocol of the type claimed on over 2,400 patients. The studies summarized in the Heier *et al.* paper correspond to the clinical trials disclosed in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or "VEGF Trap."¹ The results clearly show that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in independent claim 1, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible. This provides enormous benefits to patients, reduces health care cost,

Within the “Discussion” section of the Heier et al. paper, it is noted that the treatment group treated every two months achieved a visual acuity score within 0.3 letters of the group treated on a monthly basis. See also the results summarized in Table 1, page 15, of the present application. Thus, it is indicated that the treatment group which received the drug far less frequently than the monthly dosing arm achieved remarkably similar improvements without requiring the monthly monitoring and visits to the health care provider.

Electronically Filed	
PRELIMINARY AMENDMENT Under CFR 1.115	Amended Docket No. IPR2021-00880-IPCC03
	Confirmation No. To Be Assigned
	First Named Inventor YANCOPOULOS, GEORGE D.
	Application Number To Be Assigned
	Filing Date 17 December 2015
	Group Art Unit To Be Assigned
	Examiner Name To Be Assigned
	Title: "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders"

IPR2021-00880-IPCC03
Mylan v. Regeneron, IPR2021-00880
Mylan, VA 22113-1490

Prior to the examination of the above-referenced application on the merits, please enter the comments below.

Mylan Exhibit 1017
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1017, '069 PH, 136-137

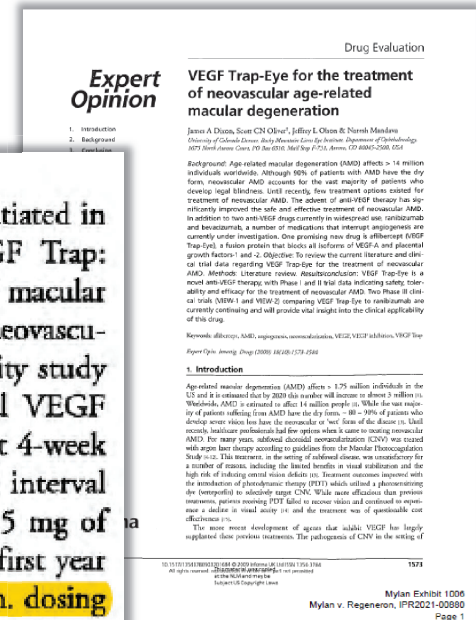
IPR2021-00880 – Ground 4

- Dixon Anticipates

- Dixon discloses VIEW's second year of PRN dosing (IPR2021-00880, Paper 56, 20-21)

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).



Ex.1006, Dixon, 1576

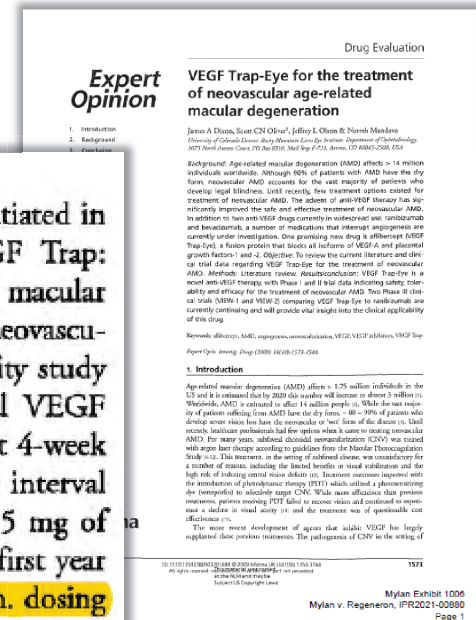
IPR2021-00880 – Ground 4

- Dixon Renders Obvious

- 3 monthly loading doses + PRN maintenance (IPR2021-00880, Paper 56, 21-24)

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).



Ex.1006, Dixon, 1576

IPR2021-00880 – Ground 4

- Dixon Renders Obvious

- Dixon sets forth motivation . . .
(IPR2021-00880, Paper 56, 21-24, 25-31)

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

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.**

Expert Opinion

Drug Evaluation

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

James A. Dixon, Scott CN Oliver, Jeffrey L. Olson & Norrish Mendras
University of Colorado Denver, Rocky Mountain Center for Ophthalmology, Department of Ophthalmology,
3875 North Arapahoe Court, PO Box 6510, Mail Stop F-751, Aurora, CO 80045-2504, USA

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 factor-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. **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 II clinical trials (VISION 1 and VISION 2) comparing VEGF Trap-Eye to ranibizumab are currently continuing and will provide vital insight into the clinical applicability of this drug.

Keywords: AMD, angiogenesis, ranibizumab, VEGF, VEGF inhibitors, VEGF Trap-Eye

Paper type: Review, Drug (2000) 1574B (17) 2000

1. Introduction

Age related macular degeneration (AMD) affects a 175 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million in. Wet AMD is estimated to affect 14 million people in. While the vast majority of patients suffering from AMD have the dry form (~80% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease). 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 (1). The treatment, in the setting of retinal disease, was considered for a number of reasons, including the limited benefits in visual stabilization and the high risk of inducing central macular atrophy. Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photocoagulating 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 (2) and the treatment was of questionable cost effectiveness (3).

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

informa
healthcare

Mylan Exhibit 1006
Mylan v. Regeneron, IPR2021-00880
Page 1

1574

Ex.1006, Dixon, 1574, 1577

IPR2021-00880 – Ground 4

- Dixon Renders Obvious

- Dixon provides motivation and a reasonable expectation of success . . .

(IPR2021-00880, Paper 56, 21-24)

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 $\geq 100 \mu\text{m}$ 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

Expert Opinion

Drug Evaluation

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

James A. Dixon, Scott CN Oliver¹, Jeffrey L. Olson B, Norrish Mansfield
Division of Ocular Disease, Retina-Macular-Lens-Epithelium, Department of Ophthalmology, UCSD Medical Center, P.O. Box 0316, Mail Stop F772, San Diego, CA 92161-0316, USA

1. Introduction
2. Background
3. Conclusion
4. Expert opinion

Background: Age-related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 60% 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 factor-1 and -2. Objectives: 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 II clinical trials (NEVO1 and NEVO2) comparing VEGF Trap-Eye to conventional care currently continuing and will provide vital insight into the clinical applicability of this drug.

Keywords: aflibercept, AMD, angiogenesis, macular degeneration, VEGF, VEGF inhibitors, VEGF Trap-Eye

Expert Opin Drug Saf (2015) 14(2)1576-1596

1. Introduction
Age-related macular degeneration (AMD) affects > 14 million individuals in the US and is estimated that by 2020 this number will increase to almost 20 million. Worldwide, AMD is estimated to affect 14 million people in. While the vast majority of patients suffering from AMD have the dry form, ~10-15% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease. Until recently, healthcare professionals had few options when it came to treating neovascular AMD. For many years, additional choroidal neovascularization (CNV) was treated with argon laser therapy according to guidelines from the Macula Therapeutics Study 610. This treatment, in the setting of advanced disease, was considered for a number of reasons, including the limited benefits in visual stabilization and the high risk of inducing central serous chorioretinopathy. Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photocoagulating dye (verteporfin) to selectively target CNV. While more efficacious than previous treatments, patients receiving PDT failed to receive vision and continued to experience a decline in visual acuity in and the emergence of questionable cost effectiveness [1].

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

informa
healthcare

1576
Mylan Exhibit 1006
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1006, Dixon, 1576

IPR2021-00880 – Ground 4

- **PO counter-arguments lack merit**
 - **Abundant evidence of motivation to minimize number of injections**
(IPR2021-00880, Paper 1, 58-59; Ex.1002, Dr. Albin Decl., ¶¶ 59-60, 168-171)
 - **Demonstrated ability to minimize injections using a PRN regimen**
 - **PRN Phase 2 = 5.6 injections in first year**
 - **Every-8-week dosing = 8 injections in first year**
 - **Monthly = 12 injections in first year**
- (IPR2021-00880, Paper 1, 60)
(IPR2021-00880, Paper 56, 21-24, 25-31)

59. Intravitreal treatment involves administering an injection directly into the vitreous of the eye. Because of this, patients can experience significant pain and discomfort. Soreness in the injected eye is a frequent side effect. In addition, potential complications that can occur include subconjunctival hemorrhage, infection, and inflammation. While the risk of infection is small, the consequences can be devastating. Lastly, the cost and inconvenience of monthly visits and injections can be a major drawback for patients, many of whom are elderly, cannot drive due to their deteriorating vision, and must rely on family, friends, or public transportation to get to their appointments—which can sometimes take 2-5 hours because of the assessments (optical coherence tomography (OCT) scan and visual acuity (VA)) that must be done, followed by the actual treatment, if necessary.

Ex.1002, Dr. Albin Decl., ¶ 59

171. For example, Dixon disclosed that PRN dosing in the Phase 2 trial (CLEAR-IT-2) had led to mean increases in visual acuity and mean decreases in retinal thickness. The one-year results discussed in Dixon show that in the randomized 157 patient trial, patients that were treated with 2.0 mg monthly doses at weeks 0, 4, 8, and 12, followed by PRN dosing, exhibited mean improvements of 9.0 letters in visual acuity and a mean decrease in retinal thickness of 143 µm. Further, the study showed that the median time to first reinjection after the loading dose phase was 110 days, and that patients that received monthly loading doses of 2.0 mg required on average only 1.6 more injections between weeks 12 and 52.

Ex.1002, Dr. Albin Decl., ¶ 171

IPR2021-00880 – Ground 4

- PO counter-arguments lack merit
 - PRN dosing not burdensome
 - Nothing in claims or specification about PRN requiring monthly visits
 - PO disregards PRN/as-needed regimens that did not involve monthly visits (Ex.2103, 2-3; Ex.1049, 24)

(IPR2021-00880, Paper 56, 21-24, 31-36)

Dr. Brown: For patients with good initial visual acuity or in whom we are dealing with the primary eye, I treat and extend from the start. I give 3 monthly injections and see them in 8 weeks. If fluid is absent at that visit, I give another injection and see them in 10 weeks.

Ex.2103, Retinal Physician, 2

15 | But our clinical practice, as was stated in the
16 | 2007 paper, was to give three monthly doses, and
17 | then assess how the patient is doing.

Ex.1110, Brown Tr., 149:15-17

IPR2021-00880 – Ground 4

- **PO counter-arguments lack merit**
 - '069 claims directed to the prevailing trend for treating AMD (Ex.2259, 17; Ex.2103, 2-3)
 - **Dr. Albini testified that minimizing injections was the primary focus** (IPR2021-00880, Paper 56, 18-35)

Albini, ¶¶61, 190). In any event, in my experience, while office visits could be burdensome, the much more serious burden, and risks, were related to the intravitreal injections. Imaging office visits might be time-consuming, but the injections themselves caused discomfort, anxiety, and brought with them potentially severe side effects, and in rare cases, complications and/or infections that could result in blindness. (Ex.1002, Albini, ¶59; Ex.1006, Dixon, 1577 (“Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.”)). Minimizing office visits was a goal, but by far the primary goal was to minimize intravitreal injections.

Ex.1114, Dr. Albini Reply Decl., ¶ 28

IPR2021-00880 – Ground 4

- **PO counter-arguments lack merit**
 - **Regeneron implemented PRN dosing in at least six clinical trials prior to 2010**
(IPR2021-00880, Paper 56, 20-24)

Trial	Disorder	Evidence
CLEAR-IT-2 (Phase 2)	AMD	Ex.1020; Ex.1006; Ex.1055
VIEW1 & VIEW2 (Phase 3)	AMD	Ex.1006
DME (Phase 2)	DME	Ex.1068
COPERNICUS (Phase 3)	CRVO	Ex.1028
GALILEO (Phase 3)	CRVO	Ex.1028

IPR2021-00880 – Ground 5

- Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious

- Heier-2009 = successful PRN dosing
- Heier-2009 showed significant increases in visual acuity with only 7.5 doses over 18 months (4 loading doses + 3.5 PRN doses over next 15 months)

(IPR2021-00880, Paper 56, 25-31)

CLEAR-IT 2 was a double-masked multicenter trial in which patients with neovascular AMD were randomly assigned to receive monthly intravitreal injections of VEGF Trap-Eye 0.5 mg or 2.0 mg or quarterly injections of 0.5, 2.0 or 4.0 mg for an initial 3-month fixed-dose period, after which they received the same doses on an as needed basis at monthly visits out to 1 year. Subgroups of patients were established based on age, best-corrected visual acuity (BCVA) at baseline, and treatment for neo-

At 1 year, for all treated groups combined (n=157), there was a significant improvement in BCVA from baseline (mean improvement 5.3 letters; $P < .0001$). Patients who received three monthly doses of 2.0 mg followed by as-needed dosing achieved mean improvements in BCVA of 9.0 letters from baseline ($P < .0001$ vs baseline). Those who received three monthly doses of

In the original study, the mean gain in BCVA from baseline for the 117 patients who entered the extension stage was 7.3 letters ($P < .0001$ vs baseline) at the 3-month primary endpoint of the original study, 8.4 letters ($P < .0001$ vs baseline) at 1 year, and 7.1 letters ($P < .0001$ vs baseline) at month 6 of the extension study. Over the 15-month course of the PRN dosing phase, from month 3 of the original study to month 6 of the extension phase, patients received a mean 3.5 injections of VEGF Trap-Eye.

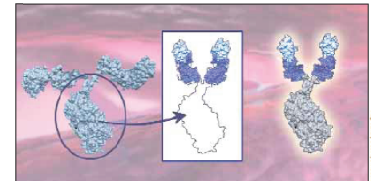
needed dosing achieved mean improvements in BCVA of 9.0 letters from baseline ($P < .085$ vs baseline) at 1 year. Patients who received initial loading doses followed by as-needed dosing also achieved mean improvements in BCVA of 9.0 letters from baseline but they were generally not as statistically significant as those with initial monthly dosing.

Intravitreal VEGF Trap for AMD: An Update

CLEAR-IT 2 Extension Study was presented at the annual meeting of the Association for Research in Vision and Ophthalmology.

BY JEFFREY S. HEIER, MD

CLEAR-IT 2 trial was a phase 2 study of the long-term efficacy of VEGF Trap-Eye (Eylea, Regeneron Pharmaceuticals) in patients with neovascular age-related macular degeneration (AMD). The results of the phase 2 trial were presented at the OASIS Society meeting. An extension of the CLEAR-IT 2 trial followed patients from the original trial. 6-month results of the extension stage of the study were presented at the Association for Research in Vision and Ophthalmology (ARVO) earlier this year. This article reviews results of the initial CLEAR-IT 2 as well as data from the extension stage.



Ex.1020, Heier-2009, 45

IPR2021-00880 – Ground 5

- Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious
 - Dixon = 3 monthly loading doses of aflibercept in AMD

(IPR2021-00880, Paper 56, 25-31)

2.6.3 Phase III

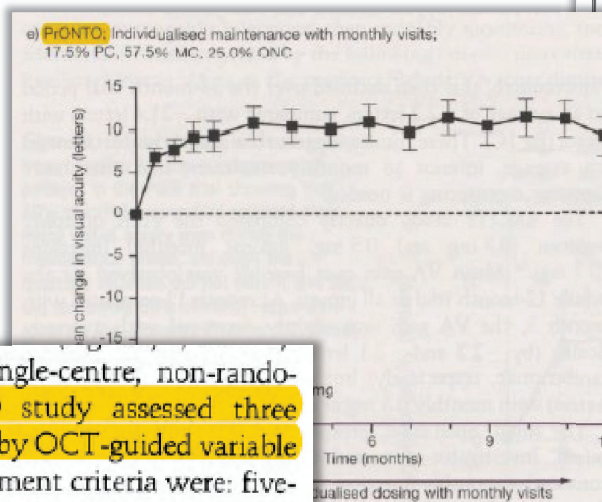
A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, **VIEW 1** (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) [46] will enroll ~ 1200 patients with neovascular AMD in the US and Canada. This non-inferiority study will 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).



Ex.1006, Dixon, 1576

IPR2021-00880 – Ground 5

- Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious
- Mitchell = 3 monthly loading doses of anti-VEGF therapy in AMD (IPR2021-00880, Paper 56, 25-31)



The small, open-label, prospective, single-centre, non-randomised, investigator-sponsored PrONTO study assessed three consecutive monthly injections followed by OCT-guided variable dosing (at ≥ 1 month intervals).³² Retreatment criteria were: five-letter loss in the presence of fluid at the macula detected by optical coherence tomography (OCT); $\geq 100 \mu\text{m}$ increase in central retinal thickness (CRT); new-onset classic choroidal neovascularisation (CNV); new macular haemorrhage; or persistent macular fluid detected by OCT. While similar VA outcomes to the MARINA and ANCHOR trials were demonstrated but with fewer intravitreal injections (figs 1E, 4; tables 2, 3), substantial trial design differences limit comparisons. Although small and open label, this study suggests that flexible OCT-guided retreatment could sustain visual gain with fewer injections.

Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials
 F Mitchell,¹ JF Corbeil,² P Lanzetta,³ F G Holz,⁴ C Picot,⁵ U Schriber-Erdem,⁶ Y Tano,⁷ S Wolf⁸

ABSTRACT Neovascular age-related macular degeneration (AMD) has a poor prognosis if left untreated. Ranibizumab (Lucentis) is a vascular endothelial growth factor (VEGF) inhibitor that has been shown to improve visual acuity in clinical trials. Although preliminary guidelines for anti-VEGF therapy are available, more comprehensive clinical practice guidelines on optimal maintenance are needed to optimise treatment outcomes.

Objective: To investigate the impact of individualised maintenance with monthly visits compared with standard maintenance (three consecutive monthly injections) on visual acuity, intravitreal injections, and the number of retreatments in patients with neovascular AMD.

Methods: We conducted a retrospective analysis of the PrONTO study, a single-centre, open-label, prospective study of individualised maintenance with monthly visits compared with standard maintenance (three consecutive monthly injections) in patients with neovascular AMD. The primary outcome was the number of intravitreal injections required to maintain visual acuity. Secondary outcomes included the number of retreatments and the number of patients who were lost to follow-up.

Results: The number of intravitreal injections required to maintain visual acuity was significantly lower in the individualised maintenance group compared with the standard maintenance group. The number of retreatments was also significantly lower in the individualised maintenance group. The number of patients who were lost to follow-up was similar between the two groups.

Conclusion: Individualised maintenance with monthly visits may be a more effective and cost-effective strategy for the treatment of neovascular AMD compared with standard maintenance (three consecutive monthly injections).

KEYWORDS: Ranibizumab, neovascular age-related macular degeneration, individualised maintenance, monthly visits, standard maintenance, intravitreal injections, retreatments, visual acuity, number of injections, number of retreatments, number of patients lost to follow-up.

INTRODUCTION Neovascular age-related macular degeneration (AMD) is a leading cause of blindness in developed countries. The disease is characterised by the growth of abnormal blood vessels in the macula, which can lead to vision loss. The standard of care for neovascular AMD is anti-vascular endothelial growth factor (VEGF) therapy. Ranibizumab (Lucentis) is a VEGF inhibitor that has been shown to improve visual acuity in clinical trials. Although preliminary guidelines for anti-VEGF therapy are available, more comprehensive clinical practice guidelines on optimal maintenance are needed to optimise treatment outcomes.

OBJECTIVE To investigate the impact of individualised maintenance with monthly visits compared with standard maintenance (three consecutive monthly injections) on visual acuity, intravitreal injections, and the number of retreatments in patients with neovascular AMD.

METHODS We conducted a retrospective analysis of the PrONTO study, a single-centre, open-label, prospective study of individualised maintenance with monthly visits compared with standard maintenance (three consecutive monthly injections) in patients with neovascular AMD. The primary outcome was the number of intravitreal injections required to maintain visual acuity. Secondary outcomes included the number of retreatments and the number of patients who were lost to follow-up.

RESULTS The number of intravitreal injections required to maintain visual acuity was significantly lower in the individualised maintenance group compared with the standard maintenance group. The number of retreatments was also significantly lower in the individualised maintenance group. The number of patients who were lost to follow-up was similar between the two groups.

CONCLUSION Individualised maintenance with monthly visits may be a more effective and cost-effective strategy for the treatment of neovascular AMD compared with standard maintenance (three consecutive monthly injections).

KEYWORDS Ranibizumab, neovascular age-related macular degeneration, individualised maintenance, monthly visits, standard maintenance, intravitreal injections, retreatments, visual acuity, number of injections, number of retreatments, number of patients lost to follow-up.

Mylan Exhibit 1030
 Mylan v. Regeneron, IPR2021-00880
 Page 4

Ex.1030, Mitchell, 5, 6

IPR2021-00880 – Ground 5

- Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious

- **Motivation: Reducing injection frequency**

(IPR2021-00880, Paper 56, 25-36)

Drug Evaluation

Expert Opinion

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

James A. Davis, Scott CN Olin, Jeffrey L. Olson & Nirmal Mishra
University of Colorado Denver, Rocky Mountain Eye Eye Institute, Department of Ophthalmology
1075 North Cooper Street, PO Box 6500, Mail Stop F-110, Aurora, CO 80046-2500, USA

Background: Age related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 60% 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 the disease.

Objective: The purpose of this review is to evaluate the safety and efficacy of anti-VEGF therapy for the treatment of neovascular AMD. Currently in widespread use, ranibizumab injections that interrupt angiogenesis are promising new drug in this category. Other anti-VEGF drugs in development include aflibercept (Eylea) and pegaptanib (Macugen). To review the current literature and describe the treatment of neovascular AMD with ranibizumab, aflibercept, and pegaptanib. We discuss the safety, efficacy, and quality of life data for these drugs. We also discuss the potential for VEGF Trap Eye to reduce the number of injections and improve the quality of life for patients with neovascular AMD.

Conclusion: VEGF Trap-Eye, VEGF Trap Eye, and pegaptanib are all well-tolerated and effective in the treatment of neovascular AMD.

informa
healthcare

10-11511 (24/08/2012) 048 © 2012 Informa UK Limited. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly.

1371

Mylan Exhibit 1006
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1006, Dixon, 1576

COVER STORY

Intravitreal VEGF Trap for AMD:

In the original study, the mean gain in BCVA from baseline for the 117 patients who entered the extension stage was 7.3 letters ($P < .0001$ vs baseline) at the 3-month primary endpoint of the original study, 8.4 letters ($P < .0001$ vs baseline) at 1 year, and 7.1 letters ($P < .0001$ vs baseline) at month 6 of the extension study. Over the 15-month course of the PRN dosing phase, from month 3 of the original study to month 6 of the extension phase, patients received a mean 3.5 injections of VEGF Trap-Eye.

in abnormal growth of new blood vessels.

44 | OCTOBER 2012 | OCTOBER 2012

Mylan Exhibit 1020
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1020, Heier-2009, 45

IPR2021-00880 – Ground 5

- Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious

- Reasonable expectation of success: improvements in visual acuity and retinal thickness in CLEAR-IT-2

(IPR2021-00880, Paper 1, 60-69, Paper 56, 27, 31-36); Ex.1002, Dr. Albini Decl., ¶¶ 95-96, n.15

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.l.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].

Drug Evaluation

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

Janis A. Dixon, Scott CN Oliver¹, Jeffrey L. Olson & Narmish Mendisa
Division of Clinical Ocular Drug Research, Department of Ophthalmology, 407 North Dearborn Street, Suite 1000, Chicago, IL 60610-5508, USA

Background: Age related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 60% 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 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 factor-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 1 and 2 trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD. Two Phase 3 clinical trials (MVO-1 and MVO-2) comparing VEGF Trap-Eye to ranibizumab are currently ongoing and will provide vital insight into the clinical applicability of this drug.

Keywords: aflibercept, AMD, angiogenesis, ranibizumab, VEGF, VEGF inhibitors, VEGF Trap-Eye

Expert Opin. Emerg. Drug (2009) 18(10) 1279-1290

1. Introduction

Age-related macular degeneration (AMD) affects > 175 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million in the UK. AMD is estimated to affect 14 million people in the US. While the vast majority of patients suffering from AMD have the dry form, ~10-15% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease. Until recently, ophthalmic professionals had few options when it came to treating neovascular AMD. For many years, additional choroidal neovascularization (CNV) was treated with argon laser therapy according to guidelines from the Macular Therapeutic Society (MTS). This treatment, in the setting of advanced disease, was considered only for a number of months, including the limited benefits in visual stabilization and the high risk of inducing central serous chorioretinopathy (CSC). Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photocoagulating (intercepted) to selectively target CNV. While some efficacious data permit treatment, patients receiving PDT failed to recover vision and continued to experience a decline in visual acuity over the treatment was of questionable cost effectiveness [1].

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

1571

Mylan Exhibit 1006
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1006, Dixon, 1576

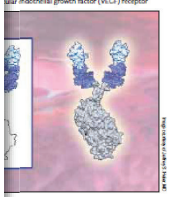
COVER STORY

At 1 year, for all treated groups combined (n=157), there was a significant improvement in BCVA from baseline (mean improvement 5.3 letters; $P < .0001$). Patients who received three monthly doses of 2.0 mg followed by as-needed dosing achieved mean improvements in BCVA of 9.0 letters from baseline ($P < .0001$ vs baseline). Those who received three monthly doses of 0.5 mg followed by as-needed dosing achieved mean improvements of 5.4 letters from baseline ($P < .085$ vs baseline) at the end of 1 year. Patients who received initial quarterly dosing followed by as-needed dosing also achieved gains in BCVA, but they were generally not as robust as those achieved with initial monthly dosing.

Patients receiving initial monthly doses of VEGF Trap-Eye achieved mean decreases in retinal thickness vs baseline at 1 year. In addition, treatment with VEGF Trap-Eye was associated with a reduction in the size of the total active choroidal neovascular membrane (CNV).

Annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) poster this year! The same results of the initial CLEAR-IT 2 as well as data for the extension study.

ARVO 2010
 2. Trap-Eye is a purified formulation of VEGF Trap, a soluble vascular endothelial growth factor (VEGF) receptor



Mylan Exhibit 1020
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1020, Heier-2009, 45

IPR2021-00880 – Ground 5

- PO arguments lack merit
 - CLEAR-IT-2 data would not discourage 3 monthly loading doses
 - Dixon disclosed the implementation of 3 loading doses for Phase 3 VIEW trials, i.e., dropping from 4 loading doses (Phase 2) to three loading doses (Phase 3)
- (IPR2021-00880, Paper 56, 20-26, 34-36)

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).

Expert Opinion

Drug Evaluation

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

Jason A. Dunn, Scott CH Ollivier, Jeffrey L Olson, R. Naveh Mendels
University of Colorado Denver, Aurora, Colorado; Denver, Colorado; Department of Ophthalmology
1677 16th Avenue, Suite 100, Box 6510, Mail Stop #121, Aurora, CO 80045-1208, USA

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 require legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the rate 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 inhibit angiogenesis are currently under investigation. One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that binds all isoforms of VEGF-A and placental growth factors¹ and is designed to receive the current literature and clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD. Methods: Literature review, meta-analysis. 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 inhibitors, VEGF Trap

Paper: *Optic. Amey. Drug* (2008) 18(2):179-186

1. Introduction

Age-related macular degeneration (AMD) affects ~ 1.75 million individuals in the US and is estimated that by 2025 this number will increase to almost 3 million in the US. Worldwide, AMD is estimated to affect 14 million people in 2010. While the vast majority of patients suffering from AMD have the dry form, ~ 10-15% of patients who develop severe vision loss have the neovascular or 'wet' form of the disease. 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 Therapeutic Study Group. This treatment, in the setting of subfoveal disease, was considered for a number of reasons, including the limited benefits of laser ablation and the high risk of inducing central vision deficits (8). Treatment outcomes improved with the introduction of photodynamic therapy (PDT) which utilized a photosensitizer that is beneficial to subfoveal CNV. While some efficacies that promote treatment, patients receiving PDT failed to recover vision and continued to experience a decline in visual acuity in and the treatment was of questionable cost effectiveness (9).

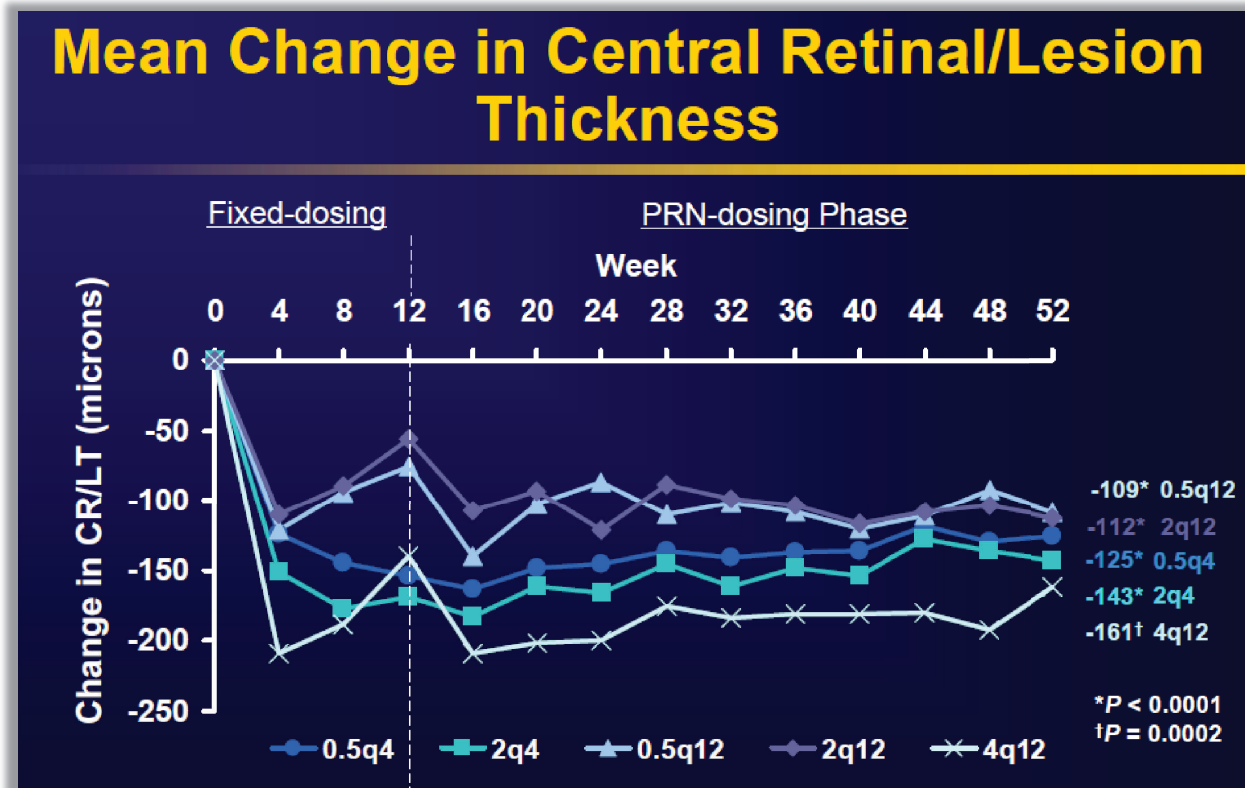
The more recent development of agents that inhibit VEGF has largely supplanted these previous treatments. The pathogenesis of CNV in the setting of

© 2010 Lippincott Williams & Wilkins. All rights reserved. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly. See the Terms and Conditions (http://www.lippincott.com) for more details. Mylan Exhibit 1006 IPR2021-00880 Page 1

Ex.1006, Dixon, 1576

IPR2021-00880 – Ground 5

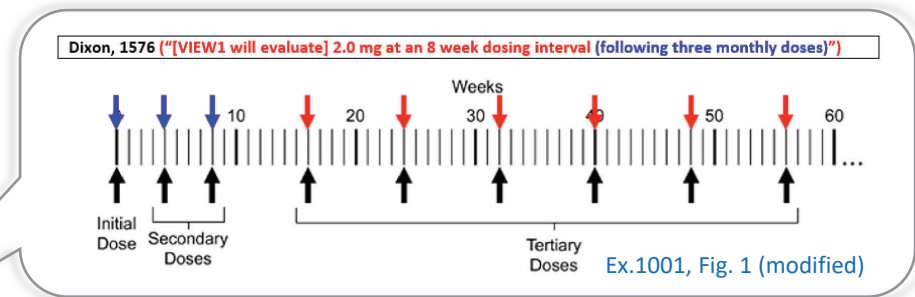
- PO arguments lack merit
 - CLEAR-IT-2 data would not discourage 3 monthly loading doses
 - Dr. Brown argues that the typical practice was to treat with loading doses until the retina was dry (Ex.2050, ¶¶ 141-142)
 - No significant change in retinal thickness after the first couple loading doses (Ex.1114, Albini Reply, ¶ 33)
(IPR2021-00880, Paper 56, 31-36)



Ex.1055, Retina Society, 18 (emphasis added)

IPR2021-00881 (U.S. Patent No. 9,254,338)

- **Challenged Claims: 1, 3-11, 13-14, 16-24, and 26**
 - **Claims broadly directed to administering VEGF Trap-Eye under a specific temporal sequences of doses (i.e., “Q8” dosing).**
 - **Clear, plain and ordinary meaning**
 - **Supported by and consistent with intrinsic record (including express definitions)**
 - **Prior art disclosed exact Q8 regimen (VIEW)** (E.g., Dixon (Ex.1006))
 - **PO now tries to rewrite the Claims / sow confusion over “VEGF Trap-Eye”**



Grounds 1-5 (Anticipation)	1. Dixon	4. NCT-795
	2. Adis	5. NCT-377
	3. REG (8-May-2008)	
Ground 6 (Obviousness)	6. Dixon (alone or combined with the '758 patent or Dix)	

Person of Ordinary Skill in the Art (“POSA”)

Patent Owner

- | | |
|---|---|
| <ul style="list-style-type: none">• Board: “Petitioner’s definition of [a POSA] is reasonable and consistent with the [challenged] patent and prior art of record.”
(Paper 21, 15)• Petitioner Reply: PO experts applied <i>different, incompatible</i> POSA perspectives; Inventor and Dr. Klibanov not a POSA under PO’s definition.
(Paper 61, 4-6) | <ul style="list-style-type: none">• POR and Dr. Do: Disagree with Petitioner’s definition; POSA must be a licensed physician (ophthalmologist).
(Ex.2051, Do Decl., ¶28)• Sur-reply: “[T]he Board need not make specific findings as to the level of the POSA.”
(Paper 73, 2) |
|---|---|

- **“The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis.”**
(Paper 21, 15 (citing *Al-Site Corp. v. VSI Int’l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999))).

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

	Patent Owner
<ul style="list-style-type: none">• Board: “[T]he preambles of the independent claims do not require the recited method steps to provide an effective treatment.” (Paper 21, 21)	<ul style="list-style-type: none">• “where a ‘method for treating’ is limiting, the claims require efficacy” (Paper 73, 2)
<ul style="list-style-type: none">• Petitioner: If limiting: “administering a therapeutic to a patient, without a specific degree of efficacy required” (Paper 1, 20-22)	
<ul style="list-style-type: none">• Petitioner: Claims encompass all levels of efficacy, not just a “high” one (Paper 61, 9)	<ul style="list-style-type: none">• “treating” requires a “high level of efficacy” (Paper 73, 3)
<ul style="list-style-type: none">○ Clear intrinsic record○ Preserves the intended scope and patent’s notice function○ Applies to all embodiments	<ul style="list-style-type: none">○ Extrinsic evidence○ Contradicts intrinsic record○ Eliminates notice function○ Excludes embodiments

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting: “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Claims

Plain language of the Claims do not set forth any efficacy requirement. (Paper 1, 20-22; see also Paper 61, 7-8 (quoting *Kaneka*) (“Claim construction begins with the language of the claims.”))

Ex.1001, '338 patent, 23:2-24:53 (claims)

Board: “Patent Owner does not direct us to any other portion of the claims ... that supports finding that the claimed method for treating ... requires such treatment method to have any particular level of effectiveness.” (Paper 21, 20)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting: “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Specification

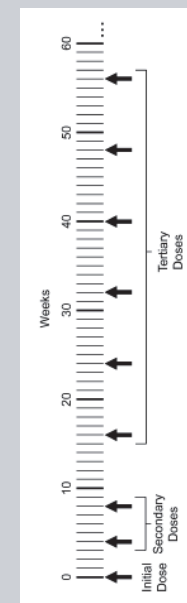
Intrinsic record describes the method as *sequentially administered doses* (no mention of efficacy)

immediately preceding dose. An example of a dosing regimen of the present invention is shown in FIG. 1. One advantage of

FIG. 1 shows an exemplary dosing regimen of the present invention. In this regimen, a single “initial dose” of VEGF antagonist (“VEGF”) is administered at the beginning of the treatment regimen (i.e. at “week 0”), two “secondary doses” are administered at weeks 4 and 8, respectively, and at least six “tertiary doses” are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc.).

Dosing Regimens

The present invention provides methods for treating angiogenic eye disorders. The methods of the invention comprise sequentially administering to a patient multiple doses of a VEGF antagonist. As used herein, “sequentially administer-



Ex.1001, '338 patent, 2:14-15, 54-55, Fig.1, 3:19-26 (Paper 61, 2, 9-10)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting: “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Specification

Intrinsic evidence expressly encompasses *all levels of efficacy*, not just a “high” one

complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. Thus, inhibiting the angiogenic-promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders.

Treatment Population and Efficacy

The methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder. Generally, the methods of the present invention demonstrate efficacy within 104 weeks of the initiation of the treatment regimen (with the initial dose administered at

Ex.1001, '338 patent, 1:44-48, 7:15-21

(Paper 61, 7-12)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting: “administering a therapeutic to a patient, without a specific degree of efficacy required”

(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Specification

Intrinsic evidence expressly encompasses *all levels of efficacy*, not just a “high” one

one or more tertiary doses of the VEGF antagonists. The present inventors have surprisingly discovered that **beneficial therapeutic effects can be achieved** in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks. Thus, according to the methods of the present inven-

Ex.1001, '338 patent, 2:3-10

(Paper 61, 7-12)

Board: “Without more, we do not find the disclosure that such effects ‘can be achieved’ demonstrates adequately that the claims *require* any particular level of efficacy.” (Paper 21, 21)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting, “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Specification

Intrinsic evidence expressly defines “therapeutically effective amount” as doses resulting in **all levels of efficacy**

The amount of VEGF antagonist administered to the patient in each dose is, **in most cases**, a therapeutically effective amount. As used herein, the phrase “**therapeutically effective amount**” means a dose of VEGF antagonist that results in a detectable improvement in one or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEGF antagonist that inhibits, prevents, **lessens, or delays** the progression of an angiogenic eye disorder. In the case of an anti-VEGF antibody or a VEGF receptor-based chimeric molecule such as VEGFR1R2-Fc Δ C1(a), a therapeutically effective amount can be from about **0.05 mg** to about 5 mg,

Ex.1001, '338 patent, 6:48-58

(Paper 61, 7-12)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting, “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Specification

“Efficacy” is expressly defined “[i]n the context of methods for treating” covered by the Challenged Claims (e.g., claim 6)

week 48, by the end of week 56, etc. In the context of methods for treating angiogenic eye disorders such as AMD, CRVO, and DME, “efficacy” means that, from the initiation of treatment, the patient exhibits a loss of 15 or fewer letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual

Ex.1001, '338 patent, 7:24-28

6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

(Paper 61, 2, 9-10)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting, “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Specification

Background “methods for treating” also make no mention of efficacy

Methods for treating eye disorders using VEGF antagonists are mentioned in, e.g., U.S. Pat. Nos. 7,303,746; 7,306,799; 7,300,563; 7,303,748; and US 2007/0190058. Nonetheless, there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy.

Ex.1001, '338 patent, 1:53-59

(Paper 61, 9-10, 13; Ex.1114, Albini, ¶ 23)

Only reference to a “high level of efficacy.”

Compare with Continental Circuits LLC v. Intel Corp., 915 F.3d 788, 798-99 (Fed. Cir. 2019)
(absent clear disavowal, a preferred embodiment does not limit claim construction).

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting, “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Prosecution History

PO emphasized **treatment protocols** and **dosing frequency**, not a “high level of efficacy”

Claims 1-20 were rejected under the judicially created doctrine of **obviousness-type double patenting** over claims 1-5 of U.S. Patent No. 7,303,746; claims 1-6 of U.S. Patent No. 7,303,747; claims 1-11 of U.S. Patent No. 7,306,799; and claims 1-15 of U.S. Patent No. 7,521,049.

In support of the rejection, it is argued that the claims of the cited patents claim methods of treating eye disorders. **Although the rejection points out that the patents do not disclose schedules set within the current claims, it is argued that where the general conditions of a claim are disclosed within the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.**

Due to all the above factors (1-5) **there was a need in the art for alternative treatment protocols** whereby the treatment would be carried out with less inconvenience and reduced safety risks to the patient. However, until the present invention once a month treatment remained the standard of care.

There are virtually an infinite number of different **treatment protocols** that could be tested. A drug could be administered **more frequently, or less frequently**, relative to the accepted standard of care. Further, **different variations in timing between dosing events** are possible. Due to the virtually infinite number of combinations, applicants do not believe that the claimed treatment protocol is *prima facie* obvious in view of the prior art standard of care which is administration of the drug once per month.

Ex.1017, '338 PH, 288-90 (Paper 1, 9-10; see also Paper 61, 9-10)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

Petitioner: If limiting, “administering a therapeutic to a patient, without a specific degree of efficacy required”
(Paper 1, 20-22; Paper 61, 7)

Ex.1001, '338 patent, claim 1

Intrinsic Evidence – The Prosecution History

PO emphasized **treatment protocols and dosing frequency, not** a “high level of efficacy”

The Heier et al. paper shows results of a treatment protocol of the type claimed on over 2,400 patients. The studies summarized in the Heier *et al.* paper correspond to the clinical trials disclosed in Example 4 of the present application which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept or “VEGF Trap.”¹ The results clearly show that by administering **the VEGF antagonist** in accordance with **a dosage regimen as claimed** in independent claims 1 and 21, **it is possible to treat** angiogenic eye disorders such as AMD **while administering doses on a less frequent basis** than previously thought possible. This provides enormous benefits to patients, reduces health care cost, reduces the pain and suffering of the patient, as well as the inconvenience to the patient and their family, and as such provides a major step forward in the treatment of patients suffering from angiogenic eye disorders, which is worthy of patent protection.

Ex.1017 , '338 PH, 288-90 (Paper 1, 9-10)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Requiring a “high level of efficacy” in the form of “visual acuity gains” excludes embodiments

acuity chart. In certain embodiments, “efficacy” means a gain of one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or more) letters on the ETDRS chart from the time of initiation of treatment.

Ex.1001, '338 patent, 7:29-32

- “[Courts] normally do not interpret claim terms in a way that excludes embodiments....” *Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276 (Fed. Cir. 2008)
- Absent clear disavowal, a preferred embodiment does not limit claim construction. *Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 798-99 (Fed. Cir. 2019)

Patent Owner’s Proposal:

1. A method for treating an angiogenic eye disorder in a patient [that achieves a high level of efficacy that is non-inferior to the standard of care, for that particular angiogenic eye disorder, at the time of patent filing], said

Ex.1138, Do Dep. Ex.4 (Paper 61, 7-8)

“treat[ing] **requires** a high level of efficacy”

“**visual acuity gains** became the new standard-of-care in treating wAMD”

(Paper 73, 3-4; Paper 40, 12-13; see also Paper 61, 13-14)

'338 Patent: Claim Construction

“method for treating an angiogenic eye disorder in a patient”

Requiring a “high level of efficacy” in the form of “visual acuity gains” excludes embodiments

Example 4

Phase III Clinical Trials of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGFT in Subjects with Neovascular Age-Related Macular Degeneration

TABLE 1

	Ranibizumab 0.5 mg monthly (RQ4)	VEGFT 0.5 mg monthly (0.5Q4)	VEGFT 2 mg monthly (2Q4)	VEGFT 2 mg every 8 weeks ^[a] (2Q8)
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
Study 1	94.4%	95.9%**	95.1%**	95.1%**
Study 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value vs RQ4)***				
Study 1	8.1	6.9 (NS)	10.9 (p < 0.01)	7.9 (NS)
Study 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)

^[a]Following three initial monthly doses

Patent Owner's Proposal:

1. A method for treating an angiogenic eye disorder in a patient [that achieves a high level of efficacy that is non-inferior to the standard of care, for that particular angiogenic eye disorder, at the time of patent filing], said

Ex.1138, Do Dep. Ex.4 (Paper 61, 7-8)

“treat[ing] *requires* a high level of efficacy”

“*visual acuity gains* became the new standard-of-care in treating wAMD”

(Paper 73, 3-4; Paper 40, 12-13; see also Paper 61, 13-14)

Dr. Brown (applying “high level of efficacy” construction):

Example 4 data does not “allow[] me to determine whether it’s a method of treatment.” Ex.1110, Brown Tr., 22:17-25:7 (Paper 61, 10)

'338 Patent: Claim Construction

“initial dose,” “secondary dose(s)” & “tertiary dose(s)”

Challenged Claim 1 ('338 Patent):

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

Board: “[W]e find that the Specification expressly defines the terms ‘initial dose,’ ‘secondary doses,’ and ‘tertiary doses.’”

(Paper 21, 22-23)

Ex.1001, '338 patent, Claim 1

Intrinsic Evidence – Lexicography

The terms “initial dose,” “secondary doses,” and “tertiary doses,” refer to the temporal sequence of administration of the VEGF antagonist. Thus, the “initial dose” is the dose which is administered at the beginning of the treatment regimen (also referred to as the “baseline dose”); the “secondary doses” are the doses which are administered after the initial dose; and the “tertiary doses” are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

Ex.1001, '338 patent, 3:31-45

'338 Patent: Claim Construction

“initial dose,” “secondary dose(s)” & “tertiary dose(s)”

NEW ARGUMENT. PO (Sur-reply): “[I]f the Board chooses to construe these terms, PO’s arguments regarding ‘tertiary dose’ apply with equal force to the ‘initial dose’ and ‘secondary dose’ terms.”

(Paper 73, 12; compare with Paper 40, 7 (“‘initial dose’ and ‘secondary doses’ need not be construed”))

Board: “[W]e do not find that the Specification requires the ‘tertiary doses’ to maintain any efficacy gain achieved after the initial and secondary doses, or that the term ‘connotes a specific level of efficacy’” (Paper 21, 22-23)

Patent Owner’s Proposal:

method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more [doses, administered after the initial and secondary doses, that maintain the efficacy gained after the initial and secondary doses] of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each [dose, administered after the initial and secondary doses, that maintains the efficacy gained after the initial and secondary doses] is administered at least 8 weeks after the immediately preceding

Ex.1138, Do Dep. Ex.4

'338 Patent: Claim Construction

“initial dose,” “secondary dose(s)” & “tertiary dose(s)”

PO does even not attempt to construe “tertiary dose(s)” separate from its arguments for “method for treating” (See Paper 40, 23-24 (incorporating by reference PO’s arguments regarding the “method for treating” preamble requiring a high level of efficacy); Paper 73, 12-13 (same))

PO offers only extrinsic evidence which contradicts the intrinsic record on “tertiary dose(s)”

Board: “[PO] has not directed us to any portion of the Specification that teaches differently or adds any efficacy requirement to that definition [of ‘tertiary doses’].”
(Paper 21, 23)

Patent Owner’s Proposal:

method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more [doses, administered after the initial and secondary doses, that maintain the efficacy gained after the initial and secondary doses] of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each [dose, administered after the initial and secondary doses, that maintains the efficacy gained after the initial and secondary doses] is administered at least 8 weeks after the immediately preceding

Ex.1138, Do Dep. Ex.4

Grounds 1-2 (Anticipation)

Dixon & Adis

- VIEW Q8 dosing regimen (with 3 loading doses) expressly disclosed

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).

Regeneron and Bayer initiated 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 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

Expert Opinion

1. Introduction
2. Background
3. Conclusion
4. Expert opinion

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

James A Dixon, Scott CN Olson¹, Jeffrey L Olson & Niall University of Colorado Denver, Denver, Colorado, USA
 1275 North Avenue, Suite 300, Denver, CO 80202, USA

Background: Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. Although 50% of patients with neovascular AMD account for the most rapid development of legal blindness, until recently, few treatment options were available. The advent of anti-VEGF agents has significantly improved the safety and efficacy of treatment. In addition to the anti-VEGF drugs currently in development, ranibizumab, a number of monoclonal antibodies are currently under investigation. One promising new drug is VEGF Trap-Eye, a fusion protein that blocks all isoforms of VEGF. To review the safety and efficacy of VEGF Trap-Eye for the treatment of neovascular AMD, a literature review, meta-analysis, and clinical trial data were analyzed. The primary outcome of this study was to compare the safety and efficacy of VEGF Trap-Eye with ranibizumab in the treatment of neovascular AMD. This study is currently continuing and will provide vital insight into the use of this drug.

Keywords: aflibercept, AMD, neovascular degeneration, VEGF Trap-Eye, ranibizumab, VEGF Trap-Eye (NCT00509795)

1. Introduction

46. Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) [ClinicalTrials.gov identifier: [NCT00509795](http://clinicaltrials.gov/ct2/show/NCT00509795)] [ClinicalTrials.gov [online]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00509795> [Accessed 28 Sep 2008].

47. VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2). [ClinicalTrials.gov identifier: [NCT00637377](http://clinicaltrials.gov/ct2/show/NCT00637377)] [ClinicalTrials.gov [online]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00637377> [Accessed 28 Sep 2008].

ADIS R&D PROFILE

Aflibercept
 AVE 0005, AVE 005, AVE 006, AVE 007, AVE 008, AVE 009, AVE 010, AVE 011, AVE 012, AVE 013, AVE 014, AVE 015, AVE 016, AVE 017, AVE 018, AVE 019, AVE 020, AVE 021, AVE 022, AVE 023, AVE 024, AVE 025, AVE 026, AVE 027, AVE 028, AVE 029, AVE 030, AVE 031, AVE 032, AVE 033, AVE 034, AVE 035, AVE 036, AVE 037, AVE 038, AVE 039, AVE 040, AVE 041, AVE 042, AVE 043, AVE 044, AVE 045, AVE 046, AVE 047, AVE 048, AVE 049, AVE 050, AVE 051, AVE 052, AVE 053, AVE 054, AVE 055, AVE 056, AVE 057, AVE 058, AVE 059, AVE 060, AVE 061, AVE 062, AVE 063, AVE 064, AVE 065, AVE 066, AVE 067, AVE 068, AVE 069, AVE 070, AVE 071, AVE 072, AVE 073, AVE 074, AVE 075, AVE 076, AVE 077, AVE 078, AVE 079, AVE 080, AVE 081, AVE 082, AVE 083, AVE 084, AVE 085, AVE 086, AVE 087, AVE 088, AVE 089, AVE 090, AVE 091, AVE 092, AVE 093, AVE 094, AVE 095, AVE 096, AVE 097, AVE 098, AVE 099, AVE 100, AVE 101, AVE 102, AVE 103, AVE 104, AVE 105, AVE 106, AVE 107, AVE 108, AVE 109, AVE 110, AVE 111, AVE 112, AVE 113, AVE 114, AVE 115, AVE 116, AVE 117, AVE 118, AVE 119, AVE 120, AVE 121, AVE 122, AVE 123, AVE 124, AVE 125, AVE 126, AVE 127, AVE 128, AVE 129, AVE 130, AVE 131, AVE 132, AVE 133, AVE 134, AVE 135, AVE 136, AVE 137, AVE 138, AVE 139, AVE 140, AVE 141, AVE 142, AVE 143, AVE 144, AVE 145, AVE 146, AVE 147, AVE 148, AVE 149, AVE 150, AVE 151, AVE 152, AVE 153, AVE 154, AVE 155, AVE 156, AVE 157, AVE 158, AVE 159, AVE 160, AVE 161, AVE 162, AVE 163, AVE 164, AVE 165, AVE 166, AVE 167, AVE 168, AVE 169, AVE 170, AVE 171, AVE 172, AVE 173, AVE 174, AVE 175, AVE 176, AVE 177, AVE 178, AVE 179, AVE 180, AVE 181, AVE 182, AVE 183, AVE 184, AVE 185, AVE 186, AVE 187, AVE 188, AVE 189, AVE 190, AVE 191, AVE 192, AVE 193, AVE 194, AVE 195, AVE 196, AVE 197, AVE 198, AVE 199, AVE 200, AVE 201, AVE 202, AVE 203, AVE 204, AVE 205, AVE 206, AVE 207, AVE 208, AVE 209, AVE 210, AVE 211, AVE 212, AVE 213, AVE 214, AVE 215, AVE 216, AVE 217, AVE 218, AVE 219, AVE 220, AVE 221, AVE 222, AVE 223, AVE 224, AVE 225, AVE 226, AVE 227, AVE 228, AVE 229, AVE 230, AVE 231, AVE 232, AVE 233, AVE 234, AVE 235, AVE 236, AVE 237, AVE 238, AVE 239, AVE 240, AVE 241, AVE 242, AVE 243, AVE 244, AVE 245, AVE 246, AVE 247, AVE 248, AVE 249, AVE 250, AVE 251, AVE 252, AVE 253, AVE 254, AVE 255, AVE 256, AVE 257, AVE 258, AVE 259, AVE 260, AVE 261, AVE 262, AVE 263, AVE 264, AVE 265, AVE 266, AVE 267, AVE 268, AVE 269, AVE 270, AVE 271, AVE 272, AVE 273, AVE 274, AVE 275, AVE 276, AVE 277, AVE 278, AVE 279, AVE 280, AVE 281, AVE 282, AVE 283, AVE 284, AVE 285, AVE 286, AVE 287, AVE 288, AVE 289, AVE 290, AVE 291, AVE 292, AVE 293, AVE 294, AVE 295, AVE 296, AVE 297, AVE 298, AVE 299, AVE 300, AVE 301, AVE 302, AVE 303, AVE 304, AVE 305, AVE 306, AVE 307, AVE 308, AVE 309, AVE 310, AVE 311, AVE 312, AVE 313, AVE 314, AVE 315, AVE 316, AVE 317, AVE 318, AVE 319, AVE 320, AVE 321, AVE 322, AVE 323, AVE 324, AVE 325, AVE 326, AVE 327, AVE 328, AVE 329, AVE 330, AVE 331, AVE 332, AVE 333, AVE 334, AVE 335, AVE 336, AVE 337, AVE 338, AVE 339, AVE 340, AVE 341, AVE 342, AVE 343, AVE 344, AVE 345, AVE 346, AVE 347, AVE 348, AVE 349, AVE 350, AVE 351, AVE 352, AVE 353, AVE 354, AVE 355, AVE 356, AVE 357, AVE 358, AVE 359, AVE 360, AVE 361, AVE 362, AVE 363, AVE 364, AVE 365, AVE 366, AVE 367, AVE 368, AVE 369, AVE 370, AVE 371, AVE 372, AVE 373, AVE 374, AVE 375, AVE 376, AVE 377, AVE 378, AVE 379, AVE 380, AVE 381, AVE 382, AVE 383, AVE 384, AVE 385, AVE 386, AVE 387, AVE 388, AVE 389, AVE 390, AVE 391, AVE 392, AVE 393, AVE 394, AVE 395, AVE 396, AVE 397, AVE 398, AVE 399, AVE 400, AVE 401, AVE 402, AVE 403, AVE 404, AVE 405, AVE 406, AVE 407, AVE 408, AVE 409, AVE 410, AVE 411, AVE 412, AVE 413, AVE 414, AVE 415, AVE 416, AVE 417, AVE 418, AVE 419, AVE 420, AVE 421, AVE 422, AVE 423, AVE 424, AVE 425, AVE 426, AVE 427, AVE 428, AVE 429, AVE 430, AVE 431, AVE 432, AVE 433, AVE 434, AVE 435, AVE 436, AVE 437, AVE 438, AVE 439, AVE 440, AVE 441, AVE 442, AVE 443, AVE 444, AVE 445, AVE 446, AVE 447, AVE 448, AVE 449, AVE 450, AVE 451, AVE 452, AVE 453, AVE 454, AVE 455, AVE 456, AVE 457, AVE 458, AVE 459, AVE 460, AVE 461, AVE 462, AVE 463, AVE 464, AVE 465, AVE 466, AVE 467, AVE 468, AVE 469, AVE 470, AVE 471, AVE 472, AVE 473, AVE 474, AVE 475, AVE 476, AVE 477, AVE 478, AVE 479, AVE 480, AVE 481, AVE 482, AVE 483, AVE 484, AVE 485, AVE 486, AVE 487, AVE 488, AVE 489, AVE 490, AVE 491, AVE 492, AVE 493, AVE 494, AVE 495, AVE 496, AVE 497, AVE 498, AVE 499, AVE 500, AVE 501, AVE 502, AVE 503, AVE 504, AVE 505, AVE 506, AVE 507, AVE 508, AVE 509, AVE 510, AVE 511, AVE 512, AVE 513, AVE 514, AVE 515, AVE 516, AVE 517, AVE 518, AVE 519, AVE 520, AVE 521, AVE 522, AVE 523, AVE 524, AVE 525, AVE 526, AVE 527, AVE 528, AVE 529, AVE 530, AVE 531, AVE 532, AVE 533, AVE 534, AVE 535, AVE 536, AVE 537, AVE 538, AVE 539, AVE 540, AVE 541, AVE 542, AVE 543, AVE 544, AVE 545, AVE 546, AVE 547, AVE 548, AVE 549, AVE 550, AVE 551, AVE 552, AVE 553, AVE 554, AVE 555, AVE 556, AVE 557, AVE 558, AVE 559, AVE 560, AVE 561, AVE 562, AVE 563, AVE 564, AVE 565, AVE 566, AVE 567, AVE 568, AVE 569, AVE 570, AVE 571, AVE 572, AVE 573, AVE 574, AVE 575, AVE 576, AVE 577, AVE 578, AVE 579, AVE 580, AVE 581, AVE 582, AVE 583, AVE 584, AVE 585, AVE 586, AVE 587, AVE 588, AVE 589, AVE 590, AVE 591, AVE 592, AVE 593, AVE 594, AVE 595, AVE 596, AVE 597, AVE 598, AVE 599, AVE 600, AVE 601, AVE 602, AVE 603, AVE 604, AVE 605, AVE 606, AVE 607, AVE 608, AVE 609, AVE 610, AVE 611, AVE 612, AVE 613, AVE 614, AVE 615, AVE 616, AVE 617, AVE 618, AVE 619, AVE 620, AVE 621, AVE 622, AVE 623, AVE 624, AVE 625, AVE 626, AVE 627, AVE 628, AVE 629, AVE 630, AVE 631, AVE 632, AVE 633, AVE 634, AVE 635, AVE 636, AVE 637, AVE 638, AVE 639, AVE 640, AVE 641, AVE 642, AVE 643, AVE 644, AVE 645, AVE 646, AVE 647, AVE 648, AVE 649, AVE 650, AVE 651, AVE 652, AVE 653, AVE 654, AVE 655, AVE 656, AVE 657, AVE 658, AVE 659, AVE 660, AVE 661, AVE 662, AVE 663, AVE 664, AVE 665, AVE 666, AVE 667, AVE 668, AVE 669, AVE 670, AVE 671, AVE 672, AVE 673, AVE 674, AVE 675, AVE 676, AVE 677, AVE 678, AVE 679, AVE 680, AVE 681, AVE 682, AVE 683, AVE 684, AVE 685, AVE 686, AVE 687, AVE 688, AVE 689, AVE 690, AVE 691, AVE 692, AVE 693, AVE 694, AVE 695, AVE 696, AVE 697, AVE 698, AVE 699, AVE 700, AVE 701, AVE 702, AVE 703, AVE 704, AVE 705, AVE 706, AVE 707, AVE 708, AVE 709, AVE 710, AVE 711, AVE 712, AVE 713, AVE 714, AVE 715, AVE 716, AVE 717, AVE 718, AVE 719, AVE 720, AVE 721, AVE 722, AVE 723, AVE 724, AVE 725, AVE 726, AVE 727, AVE 728, AVE 729, AVE 730, AVE 731, AVE 732, AVE 733, AVE 734, AVE 735, AVE 736, AVE 737, AVE 738, AVE 739, AVE 740, AVE 741, AVE 742, AVE 743, AVE 744, AVE 745, AVE 746, AVE 747, AVE 748, AVE 749, AVE 750, AVE 751, AVE 752, AVE 753, AVE 754, AVE 755, AVE 756, AVE 757, AVE 758, AVE 759, AVE 760, AVE 761, AVE 762, AVE 763, AVE 764, AVE 765, AVE 766, AVE 767, AVE 768, AVE 769, AVE 770, AVE 771, AVE 772, AVE 773, AVE 774, AVE 775, AVE 776, AVE 777, AVE 778, AVE 779, AVE 780, AVE 781, AVE 782, AVE 783, AVE 784, AVE 785, AVE 786, AVE 787, AVE 788, AVE 789, AVE 790, AVE 791, AVE 792, AVE 793, AVE 794, AVE 795, AVE 796, AVE 797, AVE 798, AVE 799, AVE 800, AVE 801, AVE 802, AVE 803, AVE 804, AVE 805, AVE 806, AVE 807, AVE 808, AVE 809, AVE 810, AVE 811, AVE 812, AVE 813, AVE 814, AVE 815, AVE 816, AVE 817, AVE 818, AVE 819, AVE 820, AVE 821, AVE 822, AVE 823, AVE 824, AVE 825, AVE 826, AVE 827, AVE 828, AVE 829, AVE 830, AVE 831, AVE 832, AVE 833, AVE 834, AVE 835, AVE 836, AVE 837, AVE 838, AVE 839, AVE 840, AVE 841, AVE 842, AVE 843, AVE 844, AVE 845, AVE 846, AVE 847, AVE 848, AVE 849, AVE 850, AVE 851, AVE 852, AVE 853, AVE 854, AVE 855, AVE 856, AVE 857, AVE 858, AVE 859, AVE 860, AVE 861, AVE 862, AVE 863, AVE 864, AVE 865, AVE 866, AVE 867, AVE 868, AVE 869, AVE 870, AVE 871, AVE 872, AVE 873, AVE 874, AVE 875, AVE 876, AVE 877, AVE 878, AVE 879, AVE 880, AVE 881, AVE 882, AVE 883, AVE 884, AVE 885, AVE 886, AVE 887, AVE 888, AVE 889, AVE 890, AVE 891, AVE 892, AVE 893, AVE 894, AVE 895, AVE 896, AVE 897, AVE 898, AVE 899, AVE 900, AVE 901, AVE 902, AVE 903, AVE 904, AVE 905, AVE 906, AVE 907, AVE 908, AVE 909, AVE 910, AVE 911, AVE 912, AVE 913, AVE 914, AVE 915, AVE 916, AVE 917, AVE 918, AVE 919, AVE 920, AVE 921, AVE 922, AVE 923, AVE 924, AVE 925, AVE 926, AVE 927, AVE 928, AVE 929, AVE 930, AVE 931, AVE 932, AVE 933, AVE 934, AVE 935, AVE 936, AVE 937, AVE 938, AVE 939, AVE 940, AVE 941, AVE 942, AVE 943, AVE 944, AVE 945, AVE 946, AVE 947, AVE 948, AVE 949, AVE 950, AVE 951, AVE 952, AVE 953, AVE 954, AVE 955, AVE 956, AVE 957, AVE 958, AVE 959, AVE 960, AVE 961, AVE 962, AVE 963, AVE 964, AVE 965, AVE 966, AVE 967, AVE 968, AVE 969, AVE 970, AVE 971, AVE 972, AVE 973, AVE 974, AVE 975, AVE 976, AVE 977, AVE 978, AVE 979, AVE 980, AVE 981, AVE 982, AVE 983, AVE 984, AVE 985, AVE 986, AVE 987, AVE 988, AVE 989, AVE 990, AVE 991, AVE 992, AVE 993, AVE 994, AVE 995, AVE 996, AVE 997, AVE 998, AVE 999, AVE 1000, AVE 1001, AVE 1002, AVE 1003, AVE 1004, AVE 1005, AVE 1006, AVE 1007, AVE 1008, AVE 1009, AVE 1010, AVE 1011, AVE 1012, AVE 1013, AVE 1014, AVE 1015, AVE 1016, AVE 1017, AVE 1018, AVE 1019, AVE 1020, AVE 1021, AVE 1022, AVE 1023, AVE 1024, AVE 1025, AVE 1026, AVE 1027, AVE 1028, AVE 1029, AVE 1030, AVE 1031, AVE 1032, AVE 1033, AVE 1034, AVE 1035, AVE 1036, AVE 1037, AVE 1038, AVE 1039, AVE 1040, AVE 1041, AVE 1042, AVE 1043, AVE 1044, AVE 1045, AVE 1046, AVE 1047, AVE 1048, AVE 1049, AVE 1050, AVE 1051, AVE 1052, AVE 1053, AVE 1054, AVE 1055, AVE 1056, AVE 1057, AVE 1058, AVE 1059, AVE 1060, AVE 1061, AVE 1062, AVE 1063, AVE 1064, AVE 1065, AVE 1066, AVE 1067, AVE 1068, AVE 1069, AVE 1070, AVE 1071, AVE 1072, AVE 1073, AVE 1074, AVE 1075, AVE 1076, AVE 1077, AVE 1078, AVE 1079, AVE 1080, AVE 1081, AVE 1082, AVE 1083, AVE 1084, AVE 1085, AVE 1086, AVE 1087, AVE 1088, AVE 1089, AVE 1090, AVE 1091, AVE 1092, AVE 1093, AVE 1094, AVE 1095, AVE 1096, AVE 1097, AVE 1098, AVE 1099, AVE 1100, AVE 1101, AVE 1102, AVE 1103, AVE 1104, AVE 1105, AVE 1106, AVE 1107, AVE 1108, AVE 1109, AVE 1110, AVE 1111, AVE 1112, AVE 1113, AVE 1114, AVE 1115, AVE 1116, AVE 1117, AVE 1118, AVE 1119, AVE 1120, AVE 1121, AVE 1122, AVE 1123, AVE 1124, AVE 1125, AVE 1126, AVE 1127, AVE 1128, AVE 1129, AVE 1130, AVE 1131, AVE 1132, AVE 1133, AVE 1134, AVE 1135, AVE 1136, AVE 1137, AVE 1138, AVE 1139, AVE 1140, AVE 1141, AVE 1142, AVE 1143, AVE 1144, AVE 1145, AVE 1146, AVE 1147, AVE 1148, AVE 1149, AVE 1150, AVE 1151, AVE 1152, AVE 1153, AVE 1154, AVE 1155, AVE 1156, AVE 1157, AVE 1158, AVE 1159, AVE 1160, AVE 1161, AVE 1162, AVE 1163, AVE 1164, AVE 1165, AVE 1166, AVE 1167, AVE 1168, AVE 1169, AVE 1170, AVE 1171, AVE 1172, AVE 1173, AVE 1174, AVE 1175, AVE 1176, AVE 1177, AVE 1178, AVE 1179, AVE 1180, AVE 1181, AVE 1182, AVE 1183, AVE 1184, AVE 1185, AVE 1186, AVE 1187, AVE 1188, AVE 1189, AVE 1190, AVE 1191, AVE 1192, AVE 1193, AVE 1194, AVE 1195, AVE 1196, AVE 1197, AVE 1198, AVE 1199, AVE 1200, AVE 1201, AVE 1202, AVE 1203, AVE 1204, AVE 1205, AVE 1206, AVE 1207, AVE 1208, AVE 1209, AVE 1210, AVE 1211, AVE 1212, AVE 1213, AVE 1214, AVE 1215, AVE 1216, AVE 1217, AVE 1218, AVE 1219, AVE 1220, AVE 1221, AVE 1222, AVE 1223, AVE 1224, AVE 1225, AVE 1226, AVE 1227, AVE 1228, AVE 1229, AVE 1230, AVE 1231, AVE 1232, AVE 1233, AVE 1234, AVE 1235, AVE 1236, AVE 1237, AVE 1238, AVE 1239, AVE 1240, AVE 1241, AVE 1242, AVE 1243, AVE 1244, AVE 1245, AVE 1246, AVE 1247, AVE 1248, AVE 1249, AVE 1250, AVE 1251, AVE 1252, AVE 1253, AVE 1254, AVE 1255, AVE 1256, AVE 1257, AVE 1258, AVE 1259, AVE 1260, AVE 1261, AVE 1262, AVE 1263, AVE 1264, AVE 1265, AVE 1266, AVE 1267, AVE 1268, AVE 1269, AVE 1270, AVE 1271, AVE 1272, AVE 1273, AVE 1274, AVE 1275, AVE 1276, AVE 1277, AVE 1278, AVE 1279, AVE 1280, AVE 1281, AVE 1282, AVE 1283, AVE 1284, AVE 1285, AVE 1286, AVE 1287, AVE 1288, AVE 1289, AVE 1290, AVE 1291, AVE 1292, AVE 1293, AVE 1294, AVE 1295, AVE 1296, AVE 1297, AVE 1298, AVE 1299, AVE 1300, AVE 1301, AVE 1302, AVE 1303, AVE 1304, AVE 1305, AVE 1306, AVE 1307, AVE 1308, AVE 1309, AVE 1310, AVE 1311, AVE 1312, AVE 1313, AVE 1314, AVE 1315, AVE 1316, AVE 1317, AVE 1318, AVE 1319, AVE 1320, AVE 1321, AVE 1322, AVE 1323, AVE 1324, AVE 1325, AVE 1326, AVE 1327, AVE 1328, AVE 1329, AVE 1330, AVE 1331, AVE 1332, AVE 1333, AVE 1334, AVE 1335, AVE 1336, AVE 1337, AVE 1338, AVE 1339, AVE 1340, AVE 1341, AVE 1342, AVE 1343, AVE 1344, AVE 1345, AVE 1346, AVE 1347, AVE 1348, AVE 1349, AVE 1350, AVE 1351, AVE 1352, AVE 1353, AVE 1354, AVE 1355, AVE 1356, AVE 1357, AVE 1358, AVE 1359, AVE 1360, AVE 1361, AVE 1362, AVE 1363, AVE 1364, AVE 1365, AVE 1366, AVE 1367, AVE 1368, AVE 1369, AVE 1370, AVE 1371, AVE 1372, AVE 1373, AVE 1374, AVE 1375, AVE 1376, AVE 1377, AVE 1378, AVE 1379, AVE 1380, AVE 1381, AVE 1382, AVE 1383, AVE 1384, AVE 1385, AVE 1386, AVE 1387, AVE 1388, AVE 1389, AVE 1390, AVE 1391, AVE 1392, AVE 1393, AVE 1394, AVE 1395, AVE 1396, AVE 1397, AVE 1398, AVE 1399, AVE 1400, AVE 1401, AVE 1402, AVE 1403, AVE 1404, AVE 1405, AVE 1406, AVE 1407, AVE 1408, AVE 1409, AVE 1410, AVE 1411, AVE 1412, AVE 1413, AVE 1414, AVE 1415, AVE 1416, AVE 1417, AVE 1418, AVE 1419, AVE 1420, AVE 1421, AVE 1422, AVE 1423, AVE 1424, AVE 1425, AVE 1426, AVE 1427, AVE 1428, AVE 1429, AVE 1430, AVE 1431, AVE 1432, AVE 1433, AVE 1434, AVE 1435, AVE 1436, AVE 1437, AVE 14

Grounds 3-5 (Anticipation)

REG (8-May-2008), NCT-795 (VIEW 1) & NCT-377 (VIEW 2)

- VIEW Q8 dosing regimen (with 3 loading doses) expressly disclosed (Paper 1, 31-36, 49-61)

“In the first year, the VIEW2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four.” (Ex.1013, REG (8-May-2008), 1-2)

REGENERON
REGENERON
 May 8, 2008

Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration

International study to evaluate efficacy and safety in treating a leading cause of blindness

Leverkusen, Germany, Monroville, NJ and Tarrytown, NY, May 8, 2008 - Bayer HealthCare AG and Regeneron Pharmaceuticals, Inc. (NASDAQ:REGN) today announced that the first patient has been dosed in the VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of the neovascular form of Age-related Macular Degeneration (wet AMD), a leading cause of blindness in adults.

VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients in up to 200 centers in Europe, Asia Pacific, Japan and Latin America. The first Phase 3 trial, VIEW 1, began enrolling patients in August 2007 in the United States and Canada. Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks. The development program will include visual acuity endpoints and anatomical endpoints, including retinal thickness, a measure of disease activity. The trial is intended to establish non-inferiority of VEGF Trap-Eye with Lucentis® (ranibizumab), an antiangiogenic agent approved for use in wet AMD in major markets globally.

Wet AMD accounts for about 80 percent of all severe AMD-related vision loss. It occurs when abnormal blood vessels in the eye leak fluid and blood into the macula, the area of the retina that allows for vision of fine details. This can lead to a rapid loss of central vision with continued progression.

“Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision,” said Pamela Malik, MD, Head of Global Development and member of the Bayer Healthcare Executive Committee. “Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide.”

“New therapies are still needed to provide optimal care to those patients with wet AMD,” said George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. “This global Phase 3 clinical program will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye using different dosing regimens.”

Bayer HealthCare and Regeneron are collaborating on the global development of VEGF Trap-Eye for treatment of wet AMD, diabetic eye diseases, and other ocular diseases and disorders. Once approved, Bayer HealthCare will market VEGF Trap-Eye outside the U.S., where the parties will share equally in profits from any future sales of VEGF Trap-Eye. Regeneron maintains exclusive rights to VEGF Trap-Eye in the U.S. VIEW 2 primary analyses results are anticipated in 2011.

About VIEW 2

In the first year, the VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (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 four. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. After the first year of treatment, patients will continue to be followed and treated for another year on a 4-week, once-dose extended regimen with 3 doses administered at least every 12 weeks, but not more often than every 4 weeks until the end of the study.

The primary endpoint of the study 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.

Phase 2 Clinical Data

In a Phase 2 trial in 157 patients, announced in October 2007 at the Retina Society Conference in Boston, VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity)

Mylan Exhibit 1013
 Mylan v. Regeneron, IPR2021-00881
 Page 1

“2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year.” (Ex.1014, NCT-795, 8; Ex.1015, NCT-377, 6)

10/20/2011 History of Changes for Study: NCT00509795
 U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT00509795
Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)
[Latest version submitted December 20, 2010 on ClinicalTrials.gov](#)

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merge" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in red.
- Study additions are displayed in green.

Version	A	B	Submitted Date	Changes
1	<input type="radio"/>	<input type="radio"/>	Jul 21, 2007	None (earliest Version on record)
2	<input type="radio"/>	<input type="radio"/>	August 17, 2007	Recruitment Status, Study Status and Contacts

12/20/2010 History of Changes for Study: NCT00637377
 U.S. National Library of Medicine
ClinicalTrials.gov archive

History of Changes for Study: NCT00637377
VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2).
[Latest version submitted November 28, 2010 on ClinicalTrials.gov](#)

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merge" or "Side-by-Side" comparison format to specify how the two study versions are to be displayed. The Side-by-Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to see a rendering of the study for that version.
- The yellow A/B choices in the table indicate the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in red.
- Study additions are displayed in green.

Version	A	B	Submitted Date	Changes
1	<input checked="" type="radio"/>	<input type="radio"/>	March 11, 2008	None (earliest Version on record)
2	<input type="radio"/>	<input type="radio"/>	April 24, 2008	Recruitment Status, Contacts/Locations, Study Status and Oversight
3	<input type="radio"/>	<input type="radio"/>	June 18, 2008	Contacts/Locations and Study Status

Mylan Exhibit 1015
 Mylan v. Regeneron, IPR2021-00881
 Page 1

Ex.1014,
 NCT-795

Ex.1013, REG (8-May-2008)

Ex.1015, NCT-377

Ground 6 (Obviousness)

Dixon (alone or combined with the '758 patent or Dix)

- VIEW Q8 dosing regimen (with 3 loading doses) expressly disclosed

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) 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

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

2.3 Chemistry

VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial dif-

Claim 1 ('338): A method for treating an angiogenic eye disorder in a patient

... administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist

... wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

... wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose...

FIG. 24A-24C. Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed VEGFR1R2-FcΔC1(a).

Ex.1010, '758 Patent, 10:15-17

Ex.1006, Dixon, 1575-76

(Paper 1, 36-37, 62-66)

Ground 6 (Obviousness)

Dixon (alone or combined with the '758 patent or Dix)

- VIEW Q8 dosing regimen (with 3 loading doses) expressly disclosed

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

ability and efficacy for the treatment of neovascular AMD. Two phase III clinical trials (VIEW-1 and VIEW-2) comparing VEGF TrapEye to ranibizumab are currently underway and will provide vital insights into the clinical applicability.

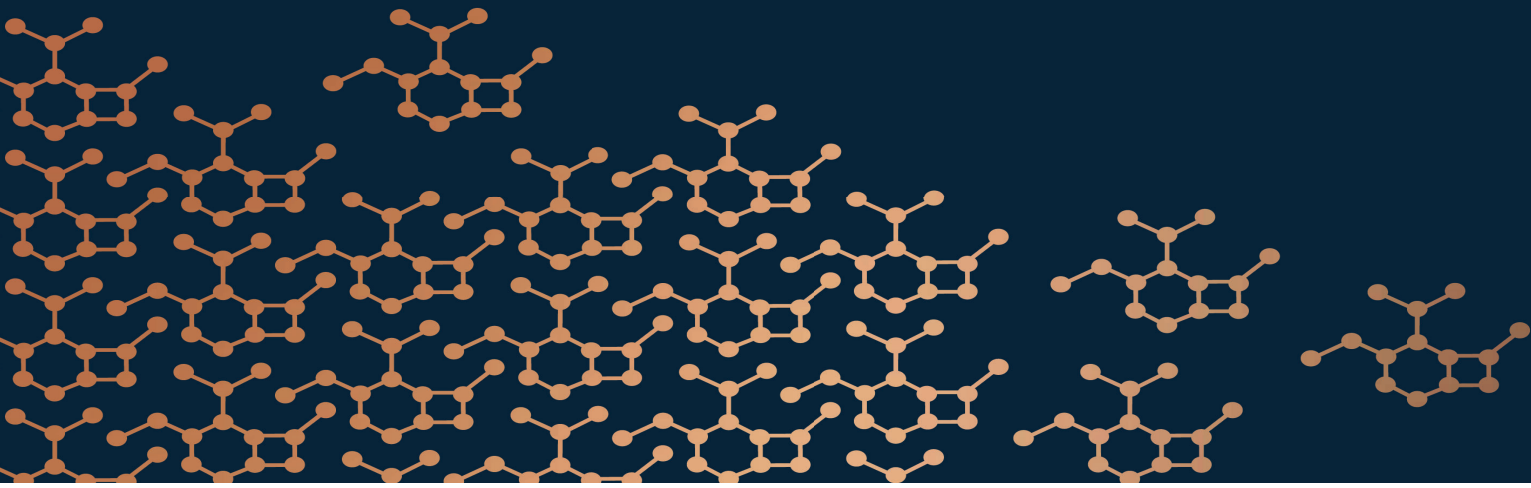
Patients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 (p < 0.0001) and 5.4 (p < 0.085) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks. During the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly 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

Reasonable Expectation of Success: Dixon discloses positive Phase 2 (“CLEAR-IT-2”) data which launched the VIEW trial. Ex.1006, Dixon, 1576 (after 52 weeks, Phase 2 patients required (on average) **only 1.6 additional injections** after four monthly loading doses) (Paper 1, 64-65; Paper 61, 32-33)

Motivation to Combine with the '758 patent or Dix: Dixon expressly discloses dosing VEGF Trap-Eye (Paper 1, 63-64)

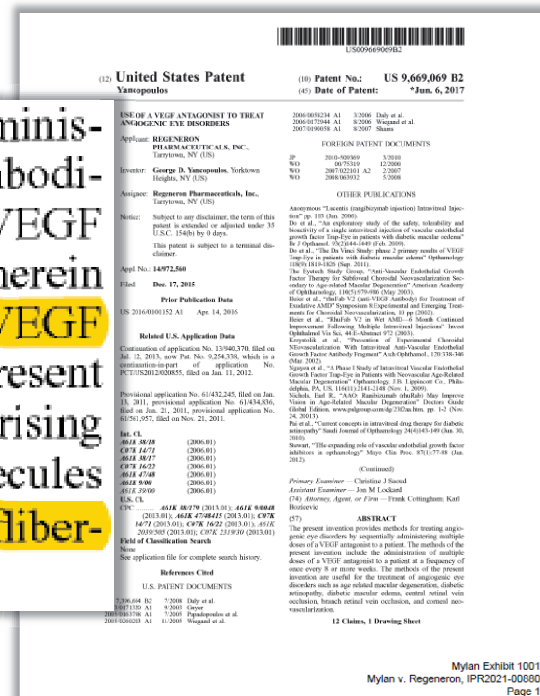
Ex.1006, Dixon, 1576

WWW.RMMSLEGAL.COM



'069 Patent

The methods of the present invention comprise administering any VEGF antagonist to the patient. In one embodiment, the VEGF antagonist comprises one or more VEGF receptor-based chimeric molecule(s), (also referred to herein as a “VEGF-Trap” or “VEGFT”). **An exemplary VEGF antagonist** that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as **“VEGFR1R2-FcΔC1(a)”** or **“aflibercept.”**



Ex.1001, '069 Patent, 2:30-38

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.

Dixon, Oliver, Olson & Mandava

recently discovered alternative pathway for decreasing angiogenesis involves inhibition of nicotinic acetylcholine receptors. A1033 (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 2 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 280-fold lower potential systemic exposure than in the oncology setting. Early trials with aflibercept administered intravitreally 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 placental growth factor

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 priming doses of ranibizumab have a half-life of ~3 days (26). At low blood levels, clearance of free aflibercept is rapid as a result of binding to VEGF with picomolar affinity (26).

2.6 Clinical efficacy
2.6.1 Phase I
A Phase I, randomized, double-blind, placebo-controlled trial of intravitreal 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 pneumonia (26).

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 (27). 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 (27). Patients showed substantially decreased foveal thickness (27).

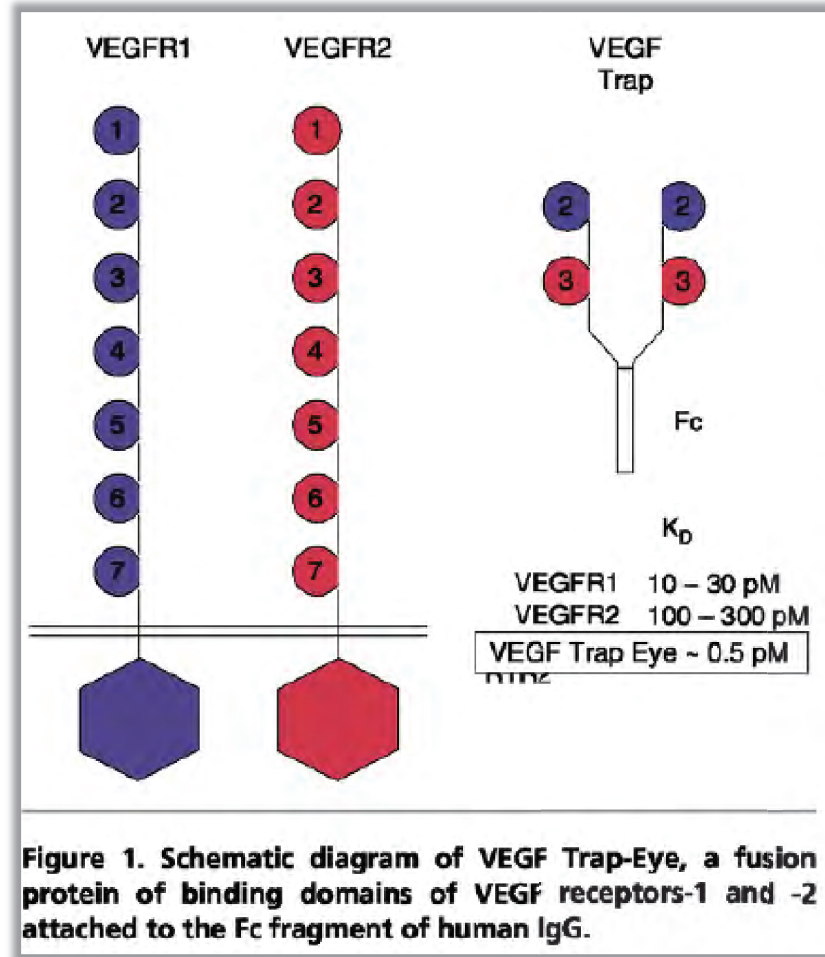
In the second part, 30 patients received a single intravitreal injection of either 0.5 or 4 mg of VEGF Trap-Eye and were followed for 8 weeks. All patients were evaluated for their rates of re-treatment, changes in BCVA, foveal thickness as well as change in total lesion size and area of CNV. Patients had ETDRS (Early Treatment of Diabetic Retinopathy Study) BCVA ranging from 20/40 to 20/20 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 re-treatment in a median of 64 days, compared with 4 out of 12 in the 4 mg dose group who required re-treatment in a median of 69 days (27).

VEGF Trap-Eye has also undergone a small open-label safety study for the treatment of diabetic macular edema (DME) (28). 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 improved to a 3 letter improvement at 6 weeks.

1575

Mylan Exhibit 1006
Mylan v. Regeneron, IPR2021-00880
Page 3

Ex.1006, Dixon, 1575



UP Trap-Eye

VEGFR1 VEGFR2 VEGF Trap

VEGFR1 10-30 pM
VEGFR2 100-300 pM
VEGF Trap Eye ~ 0.5 pM

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. Phase II

SMART-E and on as a prospective randomized, placebo-controlled dose- and interval-ranging Phase II trial in which 137 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 geographic types of CNV were represented as treated. The mean (SD) BCVA at baseline was 55. Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (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 (weeks 0 and 12). Following the final dosing period, patients were treated with the same dose of VEGF Trap-Eye in the contralateral eye. Criteria for re-dosing included an increase in retinal central thickness of $\geq 100 \mu\text{m}$ by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic macular edema, new or persistent leak on FA or new macular hemorrhage.

Patients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 5.0 ($p < 0.0001$) and 5.4 ($p < 0.0001$) ETDRS letters with 2.0 and 0.5 mg, respectively, at 52 weeks. During the re-dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections (1.4 were initially dosed on a 0.5 mg monthly schedule) and received an average of 1.5 injections. The median time to first injection in all groups was 11.0 days and 10% of patients given no more injections at week 52. Patients in dose two and three 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 assessed by OCT (10).

Patients in the three quarterly dosing groups also showed mean improvements in BCVA and retinal thickness; however, they were generally not as pronounced as the monthly injection group (10).

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-Eye [investigation of Efficacy and safety in Wet age-related macular degeneration] vs. wet 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 8 week dosing interval (following three monthly doses), compared with 0.5 mg of triamcinolone administered every 6 weeks. After the first year of the study, patients will cross a second year of open-label extension. The VIEW 2 (1) 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 137 patients enrolled in CLARITY 2 trial, there was one reported case of calcaneus-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 prostate cancer) and one serious thrombotic 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 (58.1%), transient increased intraocular pressure (18.3%), injection discomfort (12.9%), retinal hemorrhage (14.6%), subjective visual acuity loss (12.4%), vitreous detachment (11.3%) and eye pain (9.6%) (10).

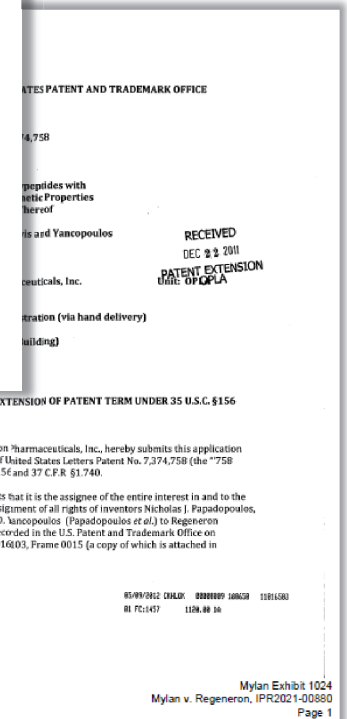
3. Conclusion

Anti-VEGF therapy has vastly improved the treatment of neovascular AMD in terms of both safety and efficacy. The RANIBICUMAB and MARIBICUMAB trials have established ranibizumab as an effective therapy when dosed monthly. It has been shown to stabilize vision in 79% of patients and in almost 40% of patients vision will actually improve by 3 or more lines. However, the monthly dosing schedule used in these trials presents a financial and time burden to patients and healthcare practitioners. The next generation (VEGF 10 and

'758 PTE Application

Holash further describes VEGFR1 and VEGFR2 on page 11393, in the second paragraph, as being “highly related transmembrane tyrosine kinases that use their ectodomains to bind VEGF.” The disclosure of the Flt1 and Flk1 components in the approved product and the construction of the expression vector used in making the active ingredient in the approved product is discussed in the '758 patent in Example 20, column 29, lines 41-56. **The amino acid sequence of both the Flt1 and Flk1 components of the approved product are disclosed in Figures 24A-24C. Flt1 Ig domain 2 spans amino acid residues 27 through 129 and Flk1 Ig domain 3 spans amino acid residues 130 through 231 of the fusion protein.**

Aflibercept comprises the Fc domain of human IgG1 fused to the extracellular domains from the VEGF receptors. See section 11 of EYLEA™ label, provided as Attachment B. A “multimerizing component” of the fusion protein of claim 1 can comprise an immunoglobulin domain, such as the Fc domain of IgG. See col. 5, lines 42-46 and col. 7, lines 25-30 of the '758 patent. Thus, aflibercept also includes a multimerizing component as defined in claim 1. The multimerizing component of the fusion protein, the Fc region of human IgG, is referenced throughout the '758 patent. **The disclosure of the Fc multimerizing component in the actual product is discussed in Example 20, column 29, lines 41-56, and its amino acid sequence is disclosed in Figures 24A-24C, from amino acid residue 232 through 458.**



Ex.1024, '758 PTE, 6-7 (Paper 1, 24-25)

'959 PTE Application

1. Identification of the Approved Product under 37 C.F.R. §1.740 (a)(1)

The name of the approved product is EYLEA™. The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}. Aflibercept is a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flt1 and an Ig domain 3 of a second VEGF receptor that is human Flk1; and (b) an Fc portion of human IgG1.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Number: 7,070,959
Serial No. 10/009,852

Reel Chimeric Polypeptides with
Improved Pharmacokinetic Properties
Papadopoulos, Davis and Yancopoulos
4,2006
Regeneron Pharmaceuticals, Inc.

RECEIVED
DEC 29 2011
PATENT EXTENSION
OPLA

Unit: OPLA

Patent Legal Administration (via hand delivery)
7025
Street (Madison Building)
VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Regeneron Pharmaceuticals, Inc., hereby submits this application
for extension of the term of United States Letters Patent No. 7,070,959 (the "'959
Patent") under 35 U.S.C. §156 and 37 C.F.R. §1.740.

The applicant represents that it is the assignee of the entire interest in and to the
'959 Patent, by virtue of assignment of all rights of inventors Nicholas J. Papadopoulos,
Samuel Davis and George D. Yancopoulos (Papadopoulos et al.) to Regeneron
Pharmaceuticals, Inc., as recorded in the U.S. Patent and Trademark Office on August
15, 2001, Reel 012077, Frame 0978 and on February 19, 2002, Reel 012639, Frame
0222 (a copy of each is attached in Attachment A).

85/99/2812 018.00 0000000 108608 707099
01 101107 1108.W 00

Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00960
Page 1

Ex.1102, '959 PTE, 2 (Paper 61, 30, 36)

'959 PTE Application

Aflibercept is also described in Holash *et al.* Proc. Natl. Acad. Sci. USA, August 20, 2002, Vol. 99, No. 17, pp. 11393-11398 ("Holash," Attachment G) as VEGF-Trap_{R1R2}, which has the Ig domain 2 of VEGF receptor 1 (VEGFR1; also known as Flt-1) fused to the Ig domain 3 of VEGF receptor 2 (VEGFR2; also known as Flk-1), which in turn is fused to the constant region (Fc) of human IgG1. See paragraph bridging pages 11393 and 11394 and Figure 1A. Moreover, Holash *et al.* demonstrate that aflibercept is a VEGF antagonist that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in various *in vitro* and *in vivo* assay systems.

UNITED STATES PATENT AND TRADEMARK OFFICE

7,070,959

(852)

Polypeptides with
Cokinetic Properties

Davis and Yancopoulos

Regeneron Pharmaceuticals, Inc.

Administration (via hand delivery)
Regeneron Building)

RECEIVED
DEC 22 2011
PATENT EXTENSION
OPLA

Unit: OPLA

EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Applicant, Regeneron Pharmaceuticals, Inc., hereby submits this application for extension of the term of United States Letters Patent No. 7,070,959 (the "'959 patent") under 35 U.S.C. §156 and 37 C.F.R. §1.740.

Applicant represents that it is the assignee of the entire interest in and to the "'959 patent by virtue of assignment of all rights of inventors Nicholas J. Papadopoulos, Samuel Davis and George D. Yancopoulos (Papadopoulos *et al.*) to Regeneron Pharmaceuticals, Inc., as recorded in the U.S. Patent and Trademark Office on August 13, 2001, Reel 012077, Frame 0978 and on February 19, 2002, Reel 012639, Frame 0222 (a copy of each is attached in Attachment A).

05/09/2012 09:40:00 00000010 108650 7870959
01 FC:1457 1120.00 DA

Ex.1102, '959 PTE, 5 (Paper 61, 30, 36)

'959 PTE Application

As noted in Section 11 of the EYLEA™ label (Attachment B), aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology. Holash (Attachment G) also describes the method of producing aflibercept (VEGF-Trap_{R1R2}) as expressing a recombinant DNA construct in Chinese hamster ovary cells (See “Engineering VEGF-Traps” in the Materials and Methods section on page 11393-11394).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Number: 7,070,959
Application No. 10/009,852

Revised Chimeric Polypeptides with Improved Pharmacokinetic Properties
Papadopoulos, Davis and Yancopoulos
Filed 4/20/06
Regeneron Pharmaceuticals, Inc.

RECEIVED
DEC 29 2011
PATENT EXTENSION
OPLA
Unit: OPLA

Patent Legal Administration (via hand delivery)
1000 West 71st Street (Madison Building)
Madison, VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Applicant, Regeneron Pharmaceuticals, Inc., hereby submits this application for extension of the term of United States Letters Patent No. 7,070,959 (the "'959 patent") under 35 U.S.C. §156 and 37 C.F.R. §1.740.

Applicant represents that it is the assignee of the entire interest in and to the "'959 patent" by virtue of assignment of all rights of inventors Nicholas J. Papadopoulos, Samuel Davis and George D. Yancopoulos (Papadopoulos et al.) to Regeneron Pharmaceuticals, Inc., as recorded in the U.S. Patent and Trademark Office on August 15, 2001, Reel 012077, Frame 0978 and on February 19, 2002, Reel 012639, Frame 0222 (a copy of each is attached in Attachment A).

85/99/2812 016.00 0000000 108608 700000
01 10/16/07 11/06/07

Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00960
Page 1

Ex.1102, '959 PTE, 5 (Paper 61, 30, 36)

'959 PTE Application

(2) Explanation Regarding Claim 11 Relative to Aflibercept

As explained below, a method for manufacturing aflibercept, the active ingredient of the approved product, is covered by at least claim 11.

Claim 11 reads as follows:

11. A method of producing a fusion polypeptide, comprising growing cells of the host-vector system of claim 8, under conditions permitting production of the fusion polypeptide and recovering the fusion polypeptide so produced.

Claim 11 depends from claim 8, which reads as follows:

8. A host-vector system for the production of a fusion

polypeptide comprising an expression vector encoding a fusion protein capable of binding VEGF, wherein the fusion protein consists of immunoglobulin-like (Ig) domain 2 of VEGF receptor human Flt1, Ig domain 3 of VEGF receptor human Flk1, and a multimerizing component, in a suitable isolated host cell.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent Number: 7,070,959
(Application No. 10/009,852)

For: Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties
Inventors: Papadopoulos, Davis and Yancopoulos
Issued: July 4, 2006
Assignee: Regeneron Pharmaceuticals, Inc.

RECEIVED
DEC 2 2 2011
PATENT EXTENSION
OPLA
Unit: OPLA

Office of Patent Legal Administration (via hand delivery)
Room MDW 7055
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Dear Sir,

Applicant, Regeneron Pharmaceuticals, Inc., hereby submits this application for extension of the term of United States Letters Patent No. 7,070,959 (the "'959 patent") under 35 U.S.C. §155 and 37 C.F.R. §1.740.

Applicant represents that it is the assignee of the entire interest in and to the '959 patent by virtue of assignment of all rights of inventors Nicholas J. Papadopoulos, Samuel Davis and George D. Yancopoulos (Papadopoulos et al.) to Regeneron Pharmaceuticals, Inc., as recorded in the U.S. Patent and Trademark Office on August 13, 2001, Reel 012077, Frame 0978 and on February 19, 2002, Reel 012639, Frame 0222 (a copy of each is attached in Attachment A).

85/09/2012 08:00 AM 00000000 100000
01 FC107 1100.W 00

Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00860
Page 1

Ex.1102, '959 PTE, 5-6
(Paper 61, 30, 36)

'959 PTE Application

Claim 11 describes a method of producing the fusion polypeptide encoded by the expression vector in the host-vector system of claim 8 comprising growing cells of the host-vector system under conditions permitting production of the fusion polypeptide and recovering the fusion polypeptide. As described above, aflibercept is a fusion polypeptide encoded by the expression vector in the host-vector system of claim 8. Therefore, growing cells of the host-vector system under conditions permitting production of the encoded fusion polypeptide according to claim 11 will produce aflibercept. Thus, claim 11 is directed to a method of manufacturing aflibercept, the active ingredient of the approved product.

Example 20 at col. 29, lines 13-29 of the '959 patent describes the construction of a nucleic acid (VEGFR1R2-FcΔC1(a)) encoding a fusion protein having the three components of aflibercept. The nucleic acid and amino acid sequence of VEGFR1R2-FcΔC1(a) is provided in Figures 24A-C. See col. 9, lines 65-67. Thus, aflibercept is a fusion

protein encoded by a nucleic acid sequence of SEQ ID NO: 15. The nucleotides encoding the various components of aflibercept are further described in Figures 24A-24C, whereby the Flt1 Ig domain 2 is encoded by nucleotide residues 80 through 389, the Flk1 Ig domain 3 is encoded by nucleotide residues 390 through 693 and the Fc component is encoded by nucleotide residues 694 through 1377.

UNITED STATES PATENT AND TRADEMARK OFFICE

7,070,959
(S2)

Polypeptides with
antibiotic Properties
Davis and Yancopoulos

RECEIVED
DEC 2 2 2011
PATENT EXTENSION
OPLA

macraceuticals, Inc. Unit: OPLA

Registration (via hand delivery)
on Building)

EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Applicant, Regeneron Pharmaceuticals, Inc., hereby submits this application for extension of the term of United States Letters Patent No. 7,070,959 (the "'959 patent") under 35 U.S.C. §156 and 37 C.F.R. §1.746.

Applicant represents that it is the assignee of the entire interest in and to the '959 patent by virtue of assignment of all rights of inventors Nicholas J. Papadopoulos, Samuel Davis and George D. Yancopoulos (Pseudopolos et al.) to Regeneron Pharmaceuticals, Inc., as recorded in the U.S. Patent and Trademark Office on August 15, 2001, Reel 012077, Frame 0978 and on February 19, 2002, Reel 012639, Frame 0222 (a copy of each is attached in Attachment A).

85/99/2812 C&A 8/8/08 10:08 AM 7/10/11
81 Fc107 11/26/11

Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00860
Page 1

Ex.1102, '959 PTE, 6-7 (Paper 61, 30, 36)

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing Petitioner's Corrected Demonstratives for Oral Argument was served on August 9, 2022, via electronic mail by agreement of the parties, to the following counsel for record of Patent Owners:

Deborah E. Fishman (Reg. No. 48,621)
David A. Caine (Reg. No. 52,683)
Arnold & Porter Kaye Scholer LLP
3000 El Camino Real
Five Palo Alto Square, Suite 500
Palo Alto, California 94306-3807
Telephone: 650.319.4519
Telephone: 650.319.4710
Facsimile: 650.319.4573
Deborah.Fishman@arnoldporter.com
David.Caine@arnoldporter.com
RegeneronEyleaIPRs@arnoldporter.com

Alice S. Ho (Lim. Rec. No. L1162)
Victoria Reines
Jeremy Cobb
Arnold & Porter Kaye Scholer LLP
601 Massachusetts Ave., N.W.
Washington D.C. 20001
Tel: 202.942.5000
Fax: 202.942.5999
Alice.Ho@arnoldporter.com
Victoria.Reines@arnoldporter.com
Jeremy.Cobb@arnoldporter.com

Daniel Reisner
Matthew M. Wilk
Arnold & Porter Kaye Scholer LLP
250 West 55th Street
New York, New York 10019-9710
Telephone: 212.836.8000
Fax: 212.836.8689
Daniel.Reisner@arnoldporter.com
Matthew.Wilk@arnoldporter.com

/Paul J. Molino/

Paul J. Molino (Reg. No. 45,350)