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.: IPR2021-00880[1]

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–

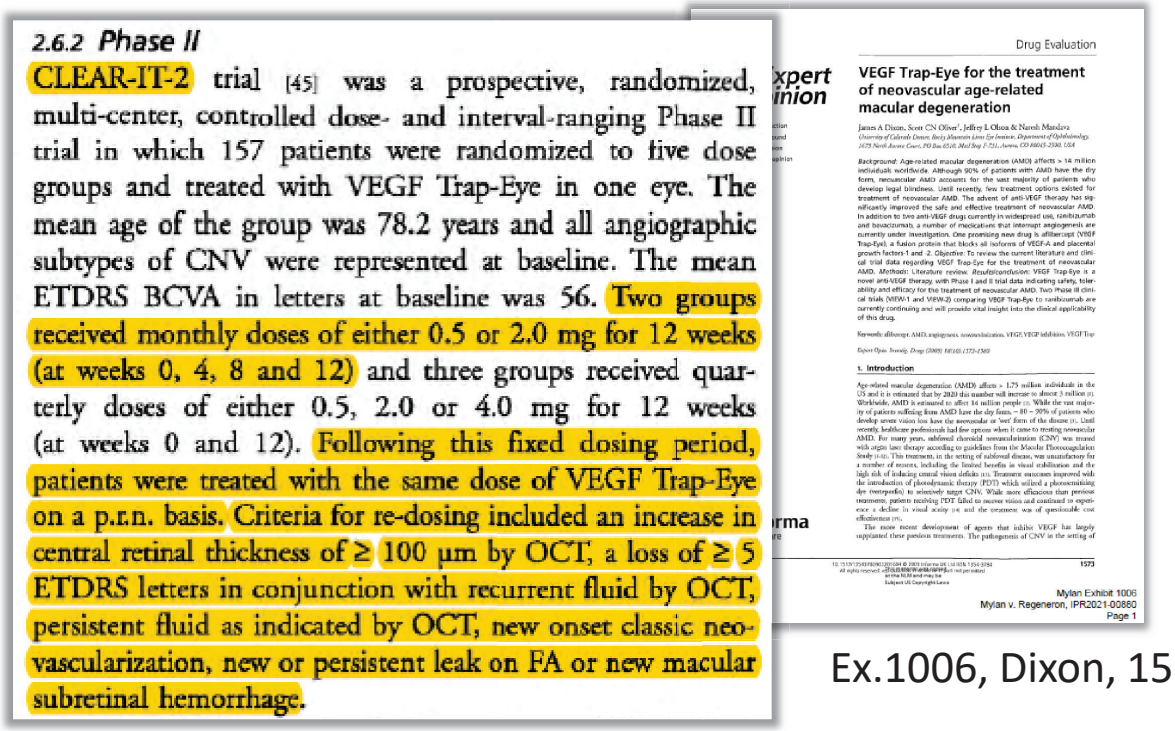
August 10, 2022

RMMS
LIFE SCIENCE LAW

’069 Patent: Anticipation Grounds 1-3

- **The dosing regimen disclosures of Dixon, Heier-2009, and Regeneron April 2009 Press Release are <u>undisputed</u>.**
  - **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 ≥ 100 µm by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

Drug Evaluation

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

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Ex.1006, Dixon, 1576

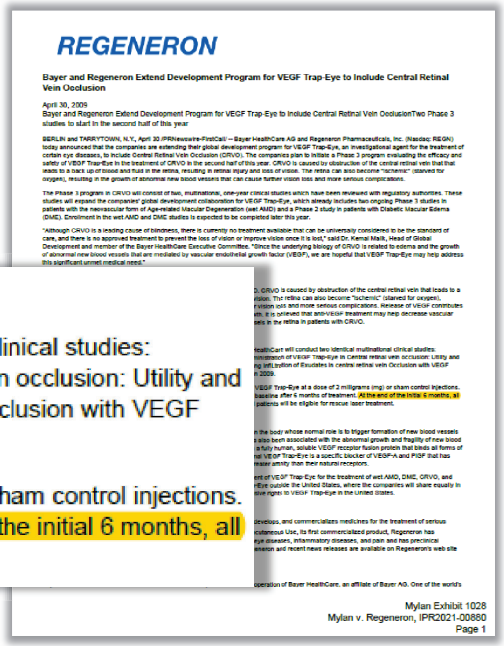
’069 Patent: Anticipation Grounds 1-3

- **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.


REGENERON

Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion

April 30, 2009
Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein OcclusionTwo Phase 3 studies to start in the second half of this year

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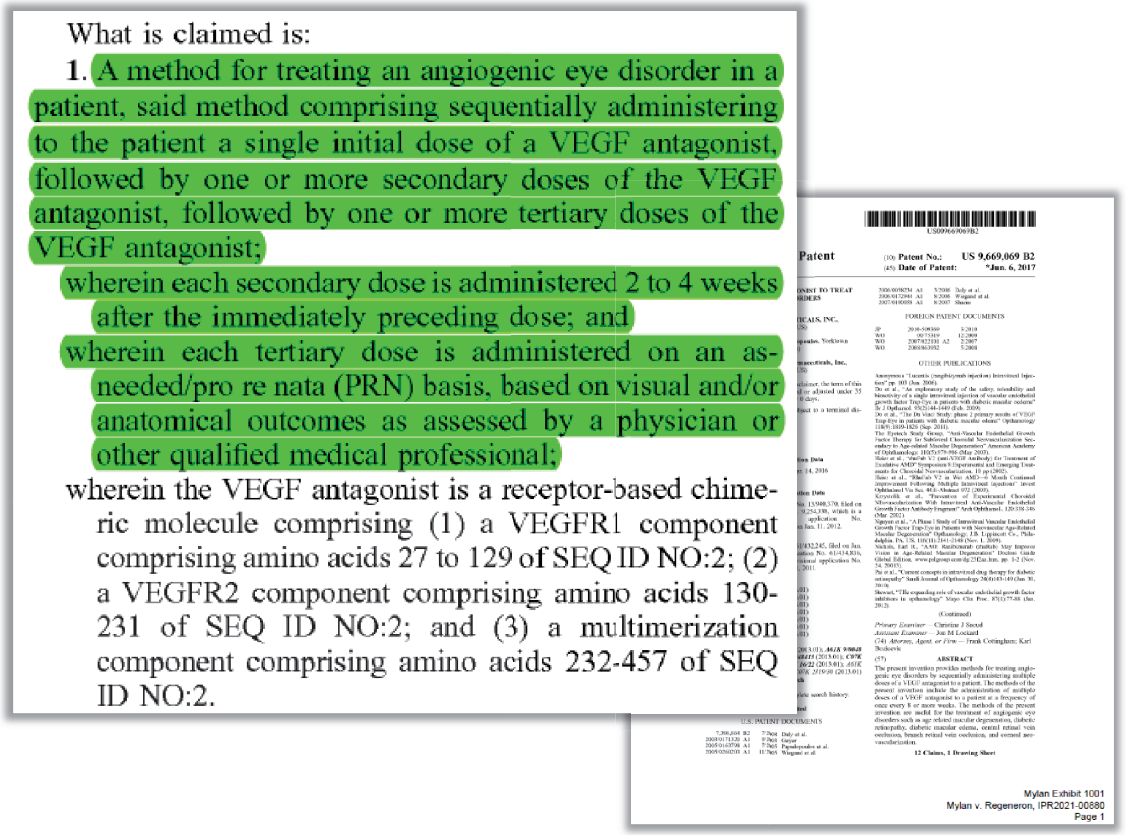
Ex.1028, Regeneron (30-April-2009)

’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.

Patent (10) Patent No.: US 9,669,069 B2 (45) Date of Patent: *Jun. 6, 2017

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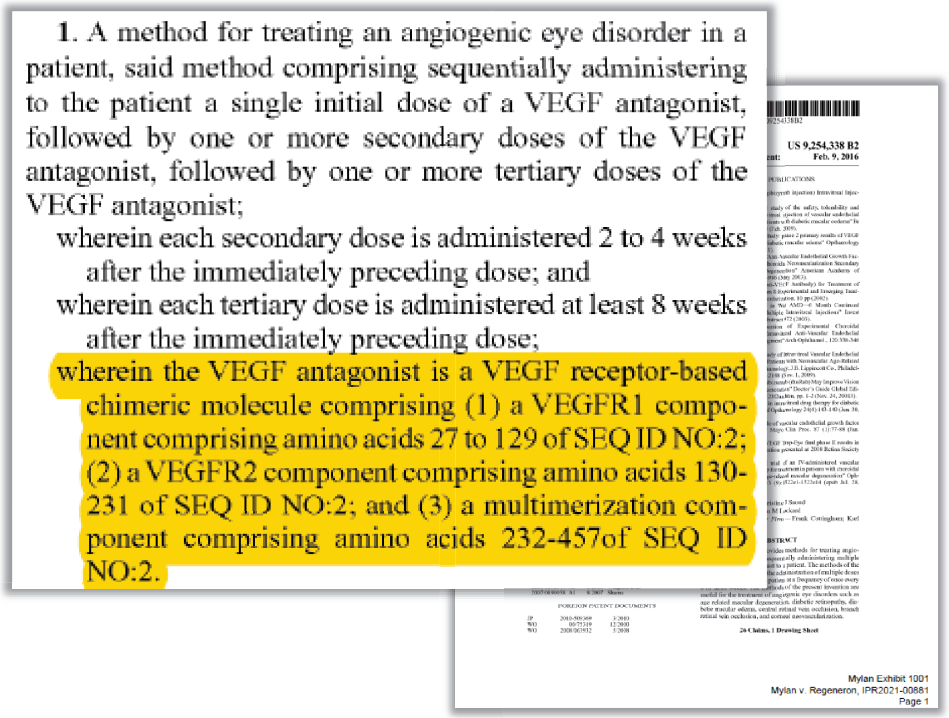
Ex.1001, ’069 patent, claim 1

’338 and ’069 Patents: The claimed molecule

- **Claim 1 of each patent sets forth the sequence of VEGF Trap-Eye/aflibercept**
  (IPR2021-00880, Paper 1, 45-50; IPR2021-00881, Paper 1, 39-44)



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;

wherein the VEGF antagonist is a VEGF 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 232-457of SEQ ID NO:2.

US 9,254,338 B2
Feb. 9, 2016

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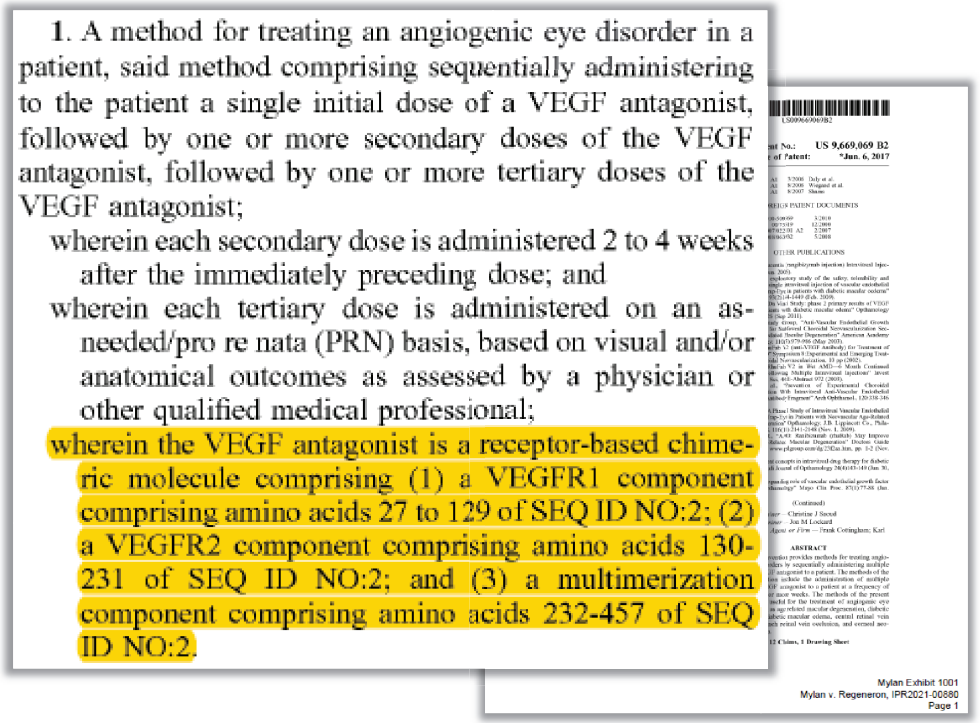
Ex.1001, ’338 patent, claim 1



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.

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Jun. 6, 2017

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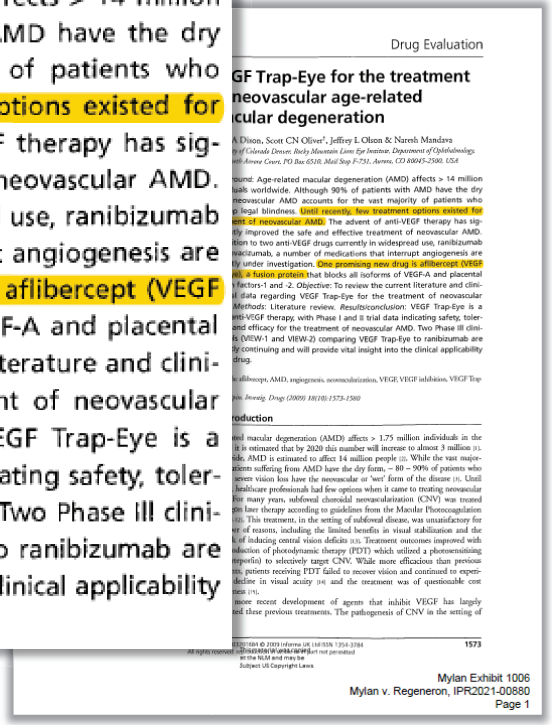
Ex.1001, ’069 patent, claim 1

’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

GF Trap-Eye for the treatment neovascular age-related cular degeneration

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(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 IgG_1. Aflibercept is in clinical development with Regeneron Pharmaceuticals and sanofi-aventis for the treatment of cancer, while Regeneron and Bayer are developing the agent for eye disorders. Aflibercept binds to all VEGF-A isoforms as well as placental growth factor (PIGF), thereby preventing these factors from stimulating angiogenesis. Blockade of VEGF can also prevent blood vessel formation and vasuclar leakage associated with wet age-related

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...trap) certain

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)

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

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

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

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

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

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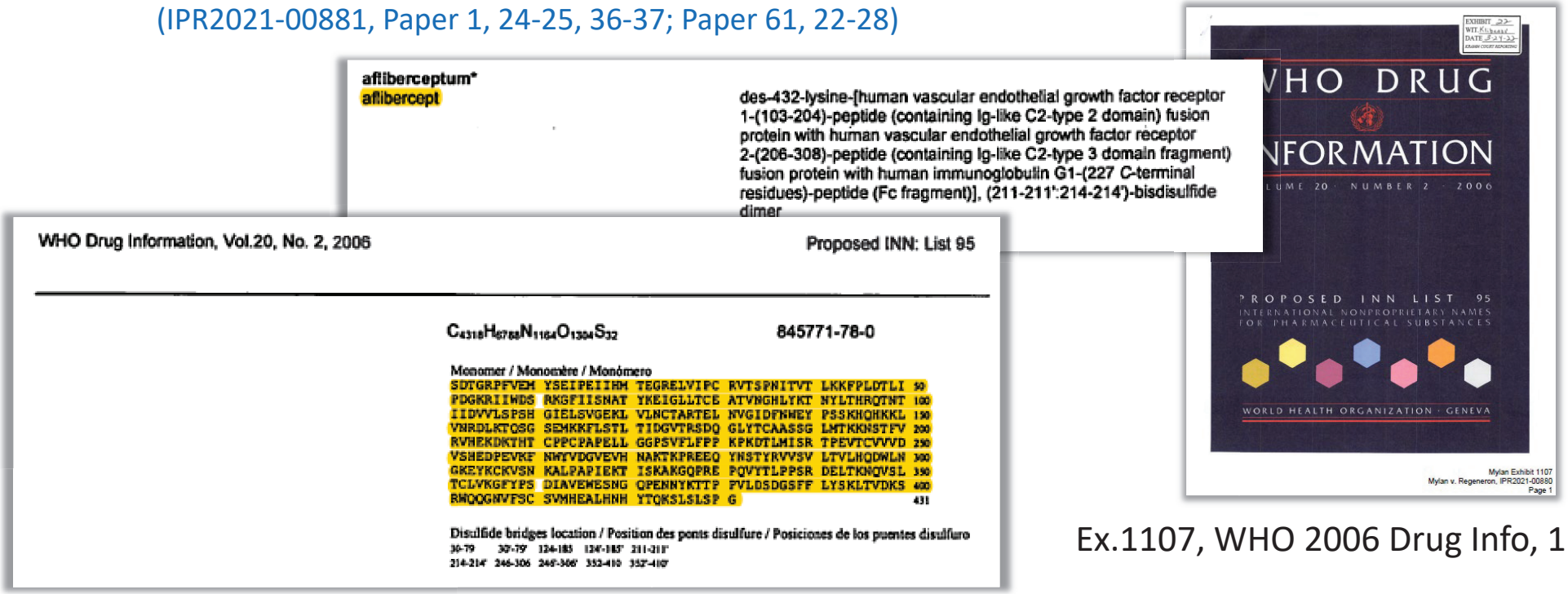
Ex.1007, Adis, 261, 264

(IPR2021-00880, Paper 1, 26-34, 54-58; Paper 56, 10-15)
(IPR2021-00881, Paper 1, 23, 39-44; Paper 61, 23-28)

’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)



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**

(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.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-

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).

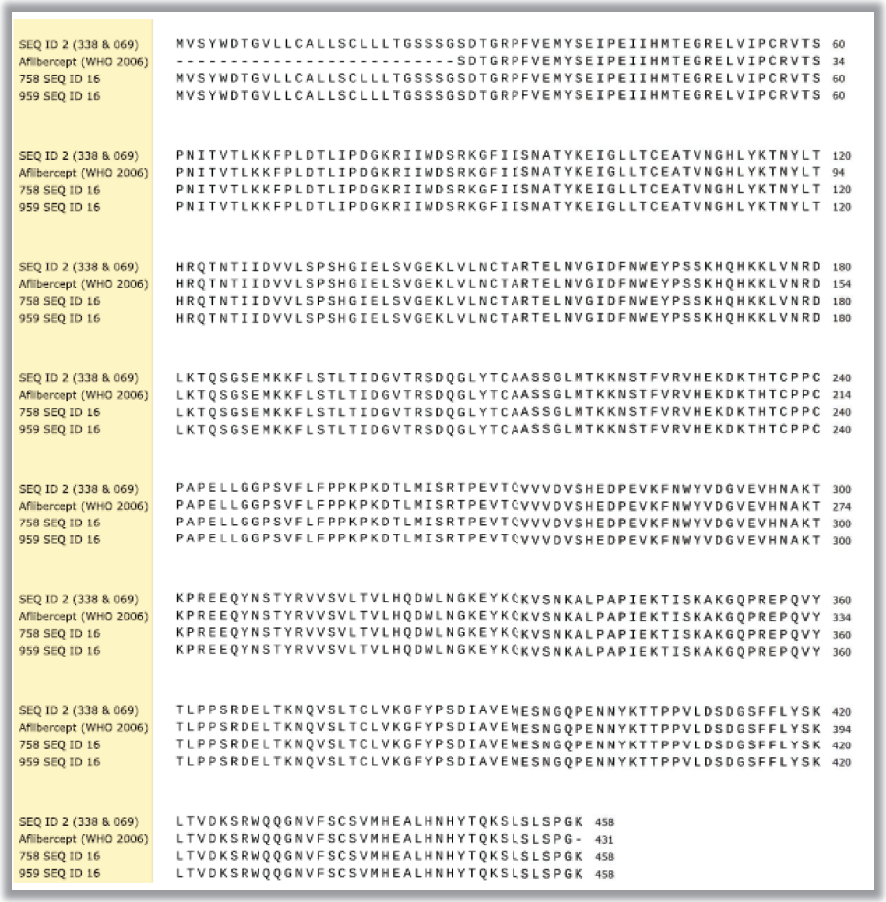
Multiple VEGF Trap-Eye ***and*** aflibercept references refer back to Holash:

- 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)

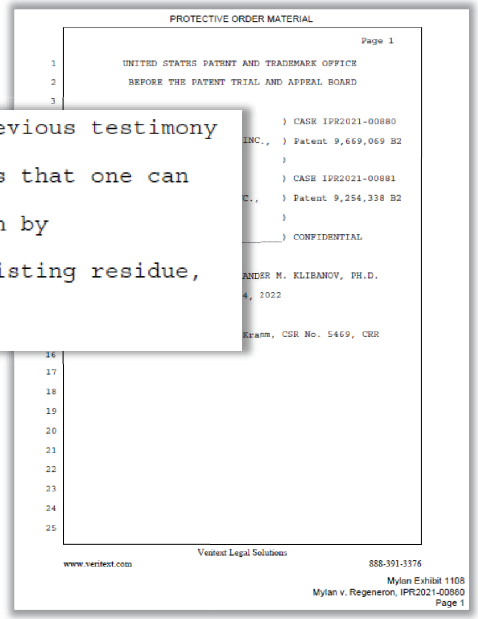


Ex.1122, Amino Acid Alignment (*see also, e.g.*, Ex.1024 (Nucleic Acid Alignment))

’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)


PROTECTIVE ORDER MATERIAL

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

) CASE IPR2021-00880
) Patent 9,659,069 B2
) CASE IPR2021-00881
) Patent 9,254,338 B2
) CONFIDENTIAL

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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"?

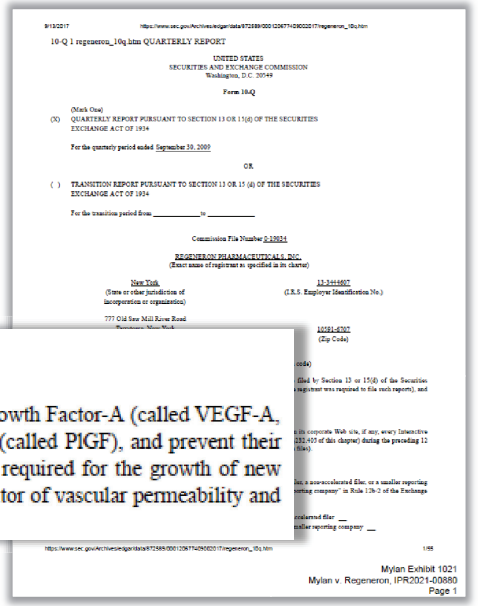
THE WITNESS: Yes, I agree with that statement.
BY MR. McLAUGHLIN:
Q. Do you also agree with the statement in the first sentence of paragraph 83 that says: "Changing even one bond in such a complex molecule as a protein, transforms it into a new molecular entity, with different (sometimes drastically 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)


10-Q 1 regeneron_10q.htm QUARTERLY REPORT

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-Q

(Mark 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 0-19034

REGENERON PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

New York
(State or other jurisdiction of incorporation or organization)

13-3444607
(I.R.S. Employer Identification No.)

777 Old Saw Mill River Road

10591-6707
(Zip Code)

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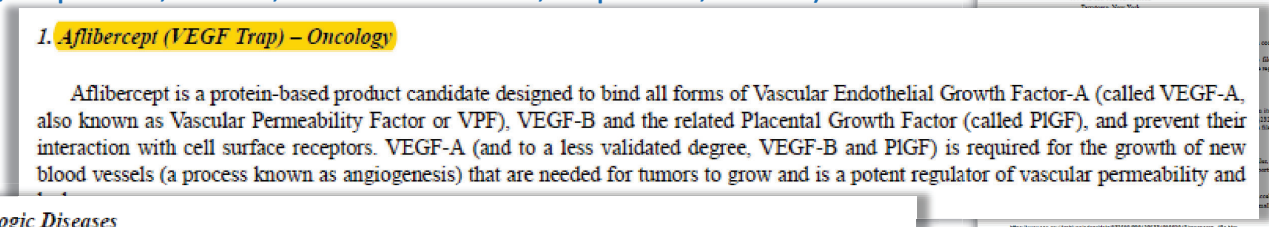
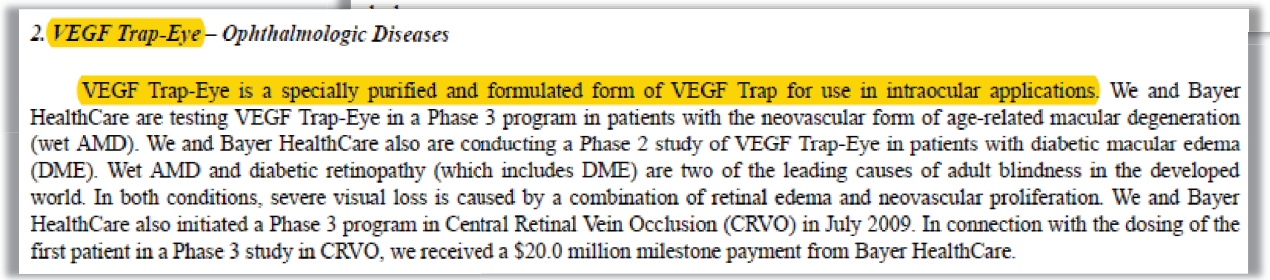
Page 1


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

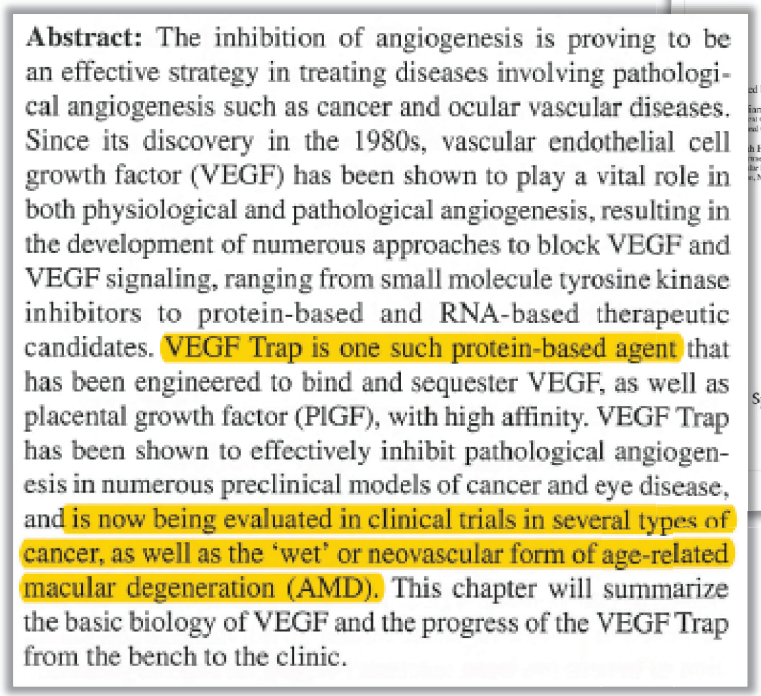
VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications. We and Bayer HealthCare are testing VEGF Trap-Eye in a Phase 3 program in patients with the neovascular form of age-related macular degeneration (wet AMD). We and Bayer HealthCare also are conducting 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.

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

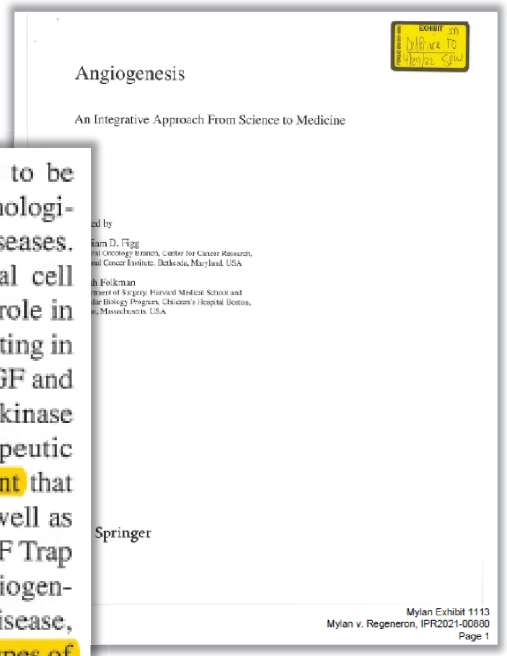
’338 and ’069 Patents: The claimed molecule

- **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 (PlGF), 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.



Angiogenesis

An Integrative Approach From Science to Medicine

Springer

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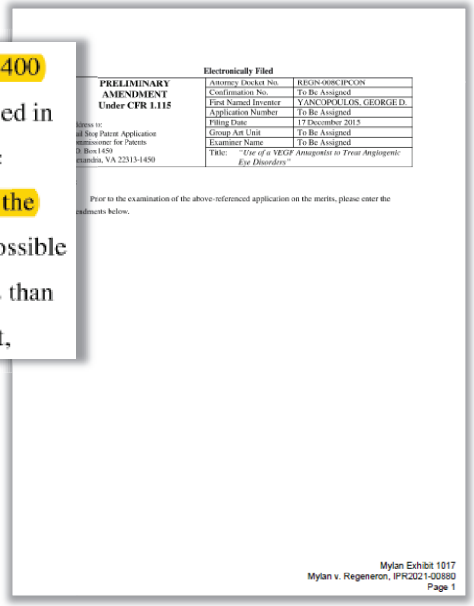
Ex.1113, Rudge 2008, 415

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

Attorney Docket No.	REGN-008CIPCON
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"*

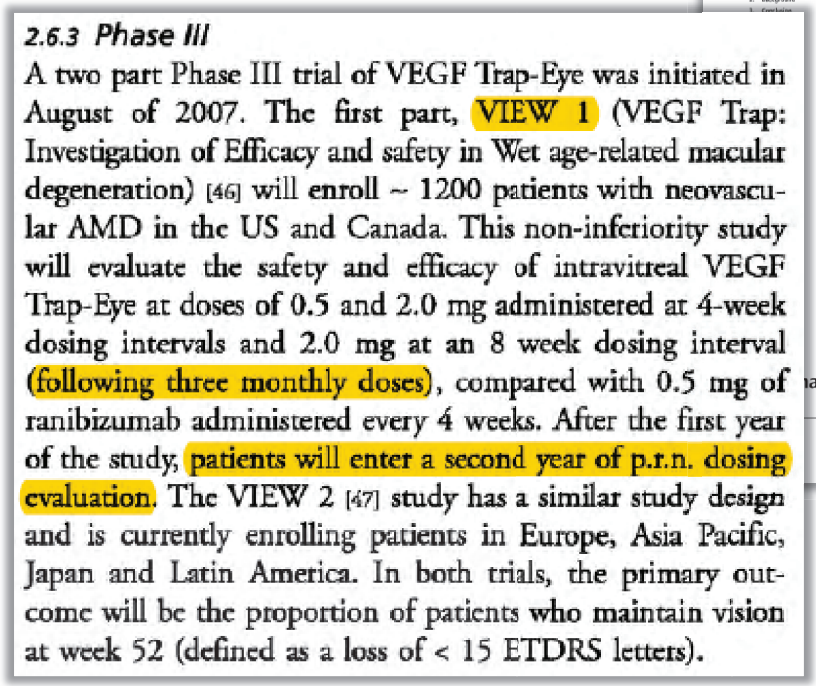
Prior to the examination of the above-referenced application on the merits, please enter the

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

Ex.1017, '069 PH, 136-137

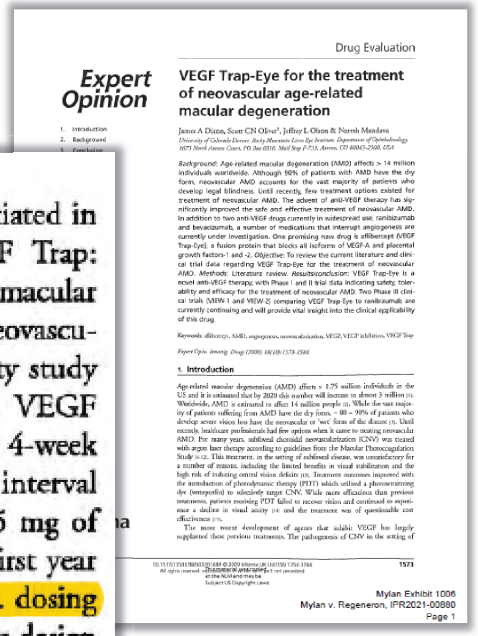
IPR2021-00880 – Ground 4

- **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).



Drug Evaluation

Expert Opinion

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

1. Introduction

Mylan Exhibit 1006
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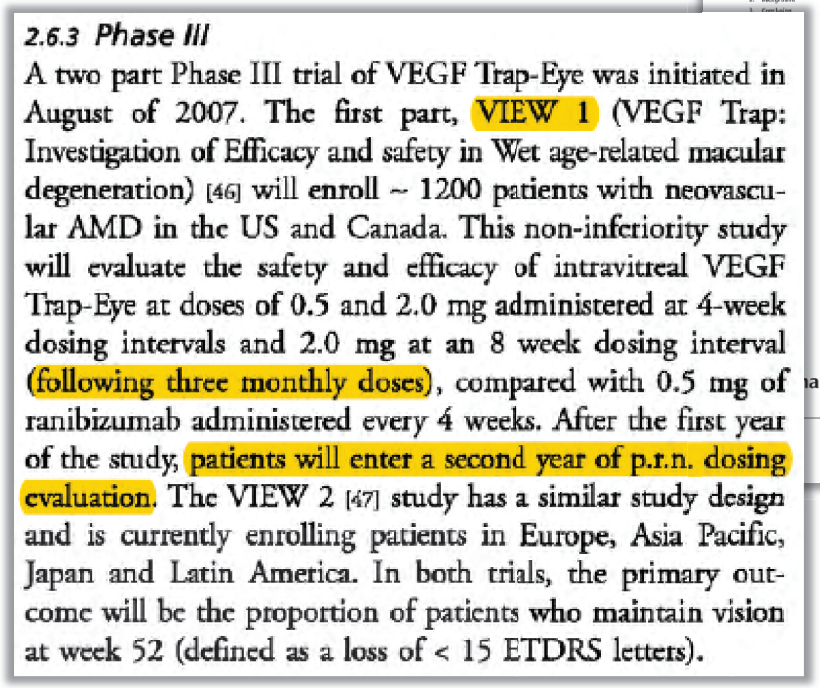
Ex.1006, Dixon, 1576

IPR2021-00880 – Ground 4

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



2.6.3 Phase III

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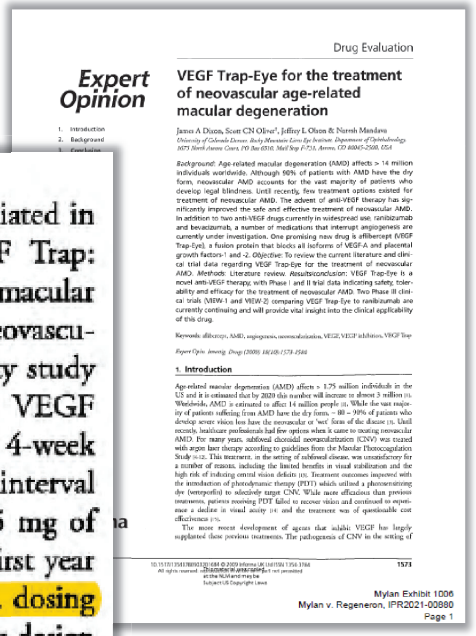

Drug Evaluation

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

1. Introduction

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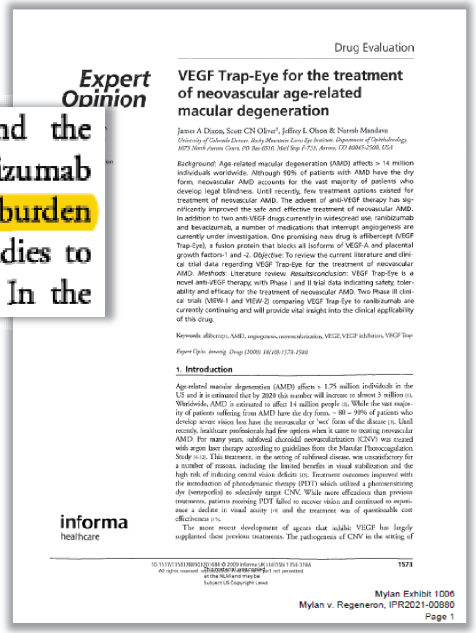
Ex.1006, Dixon, 1576

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.


Drug Evaluation

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

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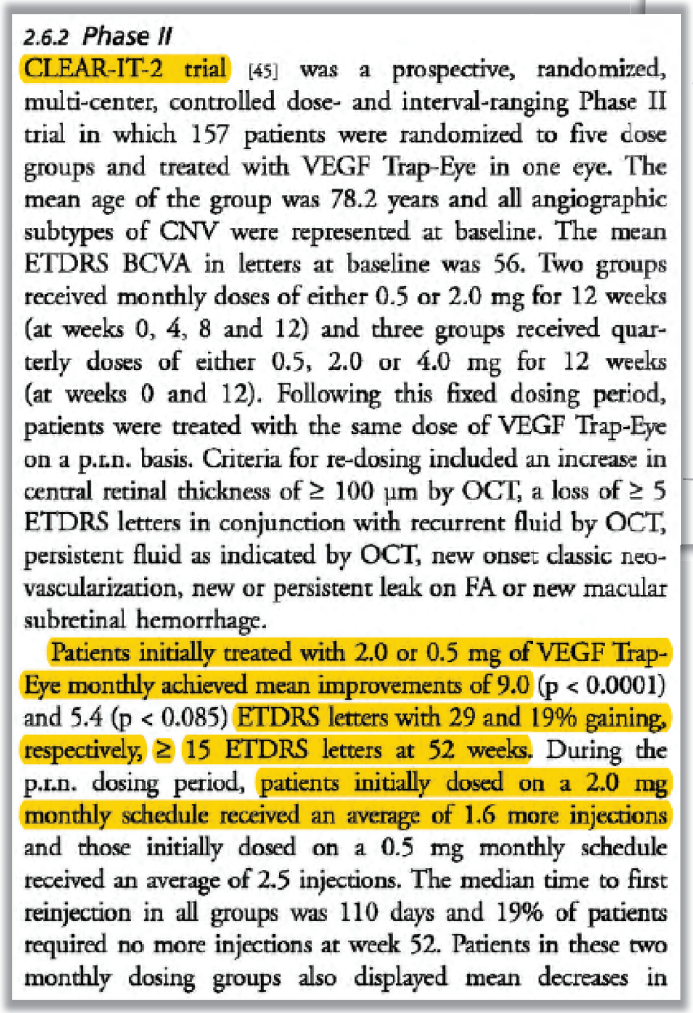
Ex.1006, Dixon, 1574, 1577

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 ≥ 100 µm by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

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

Drug Evaluation

Expert Opinion

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

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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. Albini 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. Albini 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. Albini 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.

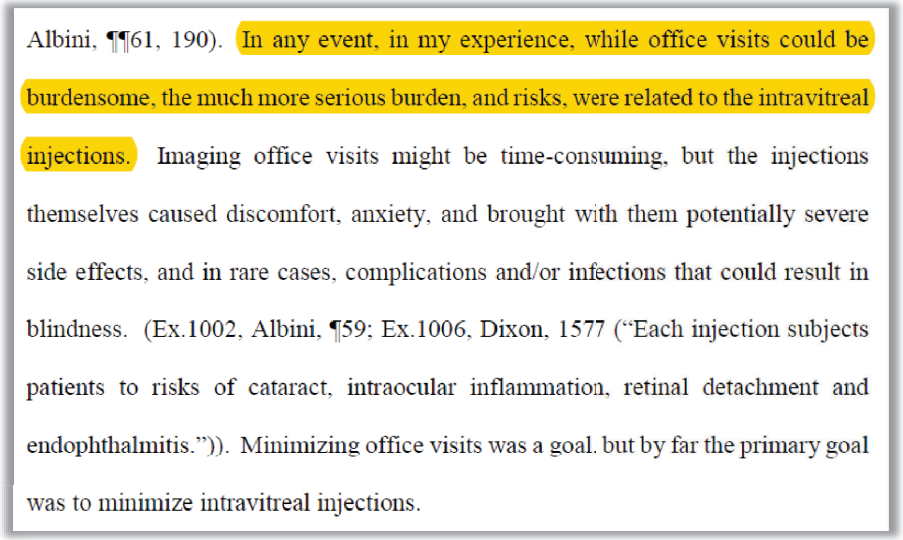
Ex.2103, Retinal Physician, 2

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

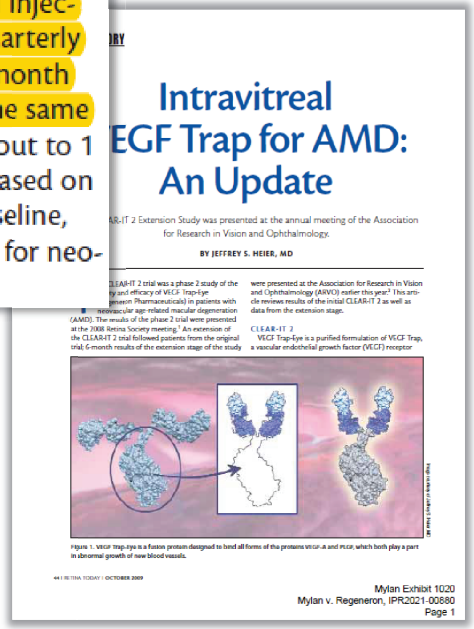
- **Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious**
  - **Heier-2009 = successful PRN dosing**
  - **Heier-2009 showed significant increases in visual acuity with only 7.5 doses over 18 months (4 loading doses + 3.5 PRN doses over next 15 months)**

(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, [illegible] 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 [illegible] eived three monthly doses of [illegible] eeded dosing achieved mean [illegible] ters from baseline ($P<.085$ vs [illegible] year. Patients who received initial [illegible] owed by as-needed dosing also [illegible] but they were generally not as [illegible] with initial monthly dosing.

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.


Intravitreal
EGF Trap for AMD:
An Update

BY JEFFREY S. HEIER, MD

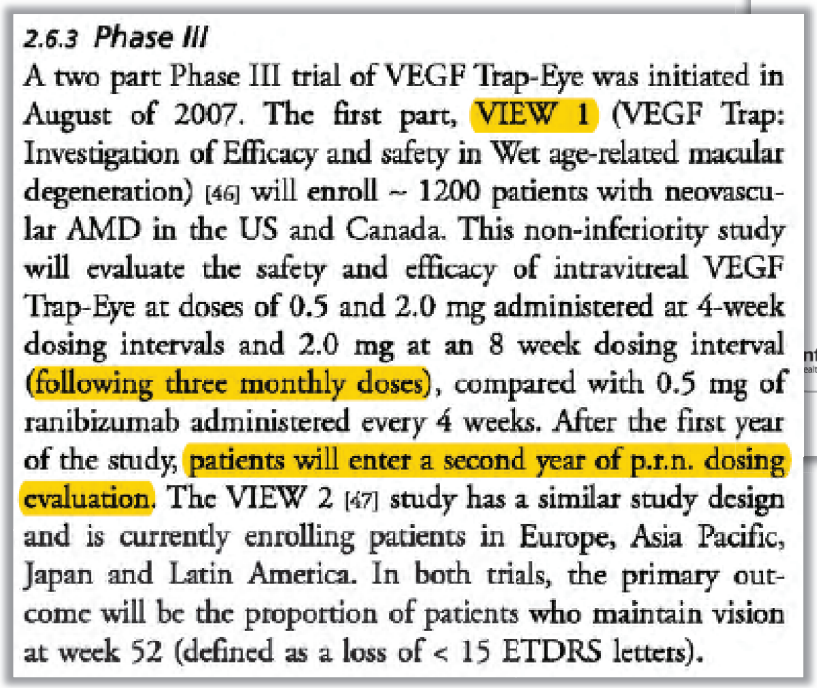
Mylan Exhibit 1020
Mylan v. Regeneron, IPR2021-00880
Page 1

Ex.1020, Heier-2009, 45

IPR2021-00880 – Ground 5

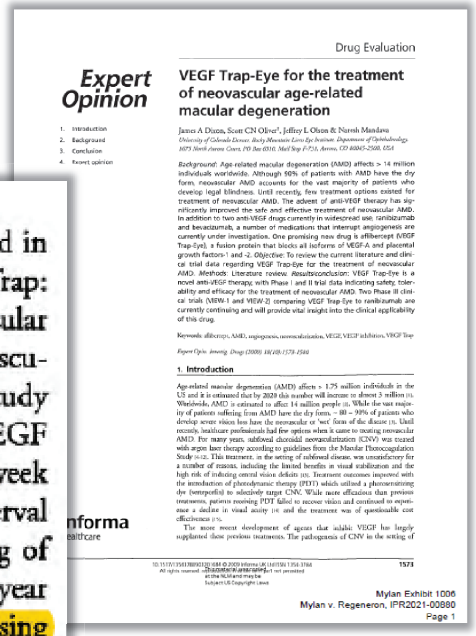
- **Heier-2009 (PRN dosing) + Dixon/Mitchell (3 monthly loading doses) render obvious**
  - **Dixon = 3 monthly loading doses of aflibercept in AMD**

(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).



Drug Evaluation

Expert Opinion

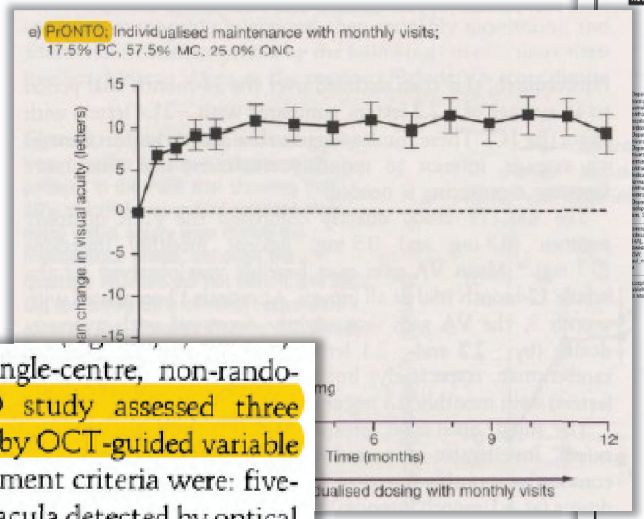
VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration

Ex.1006, Dixon, 1576

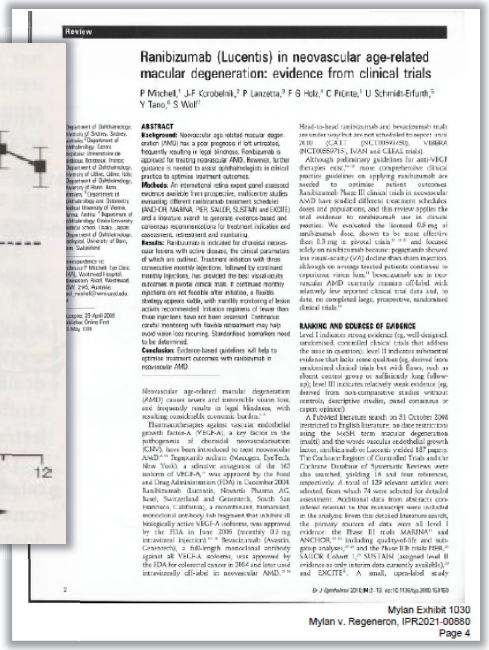
IPR2021-00880 – Ground 5

- **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); ⩾100 μm 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.


Review

Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials

P Mitchell,[1] J-F Korobelnik,[2] P Lanzetta,[3] F G Holz,[4] C Prünte,[5] U Schmidt-Erfurth,[6] Y Tano,[7] S Wolf[8]

ABSTRACT

RANKING AND SOURCES OF EVIDENCE

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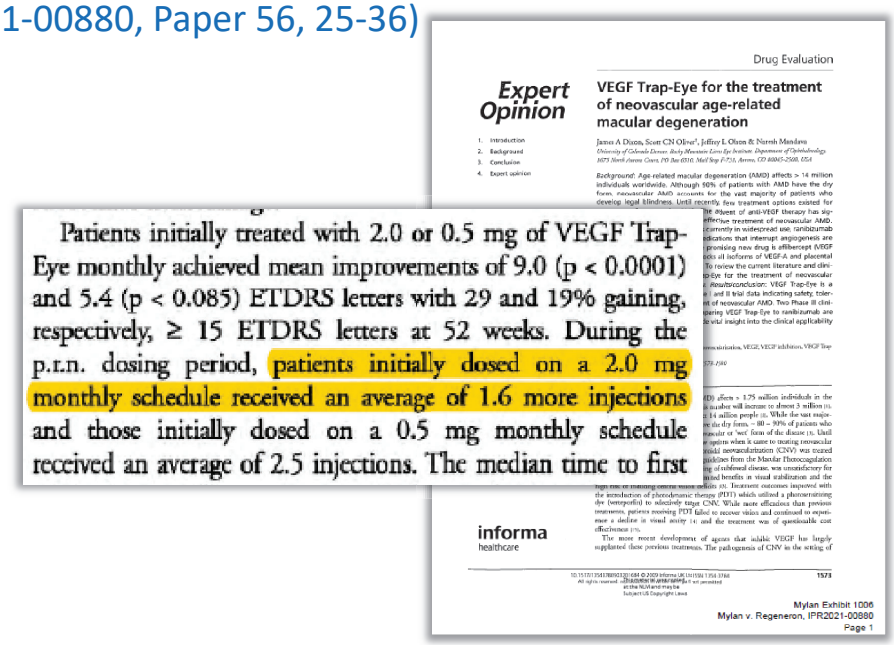
Ex.1030, Mitchell, 5, 6

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

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

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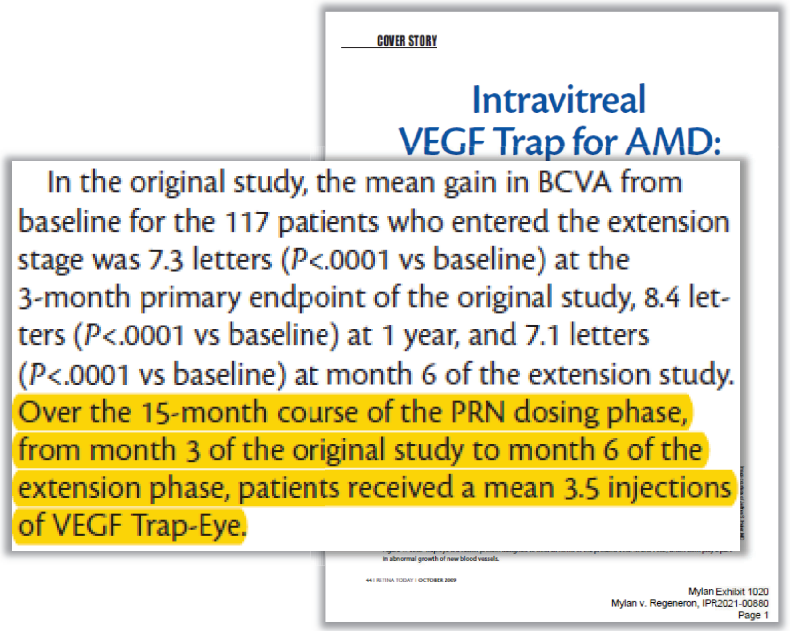
Ex.1006, Dixon, 1576



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.

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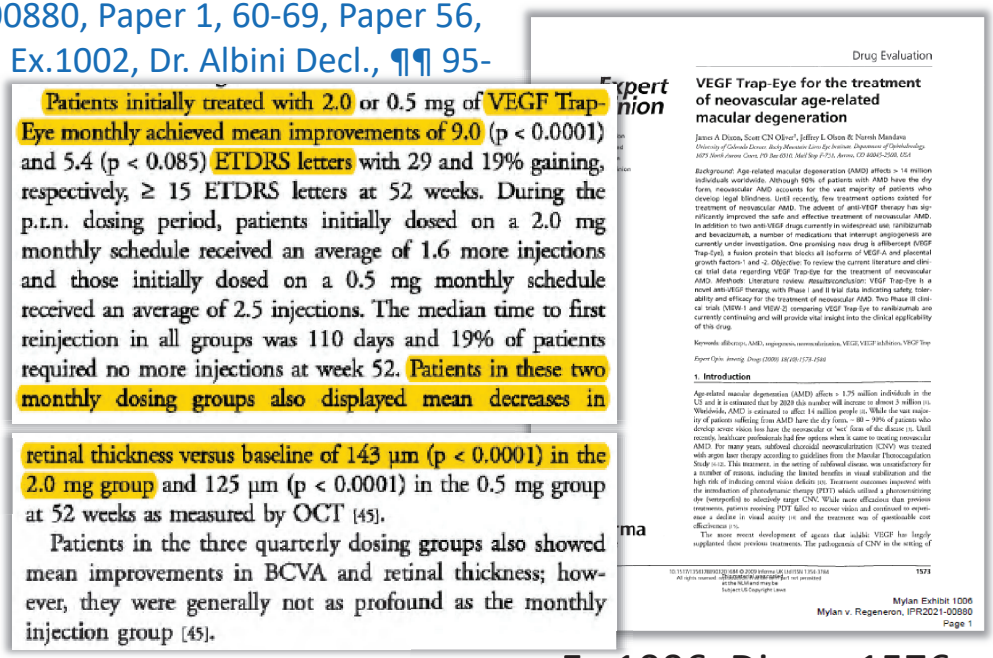
Ex.1020, Heier-2009, 45

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.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections. The median time to first reinjection in all groups was 110 days and 19% of patients required no more injections at week 52. Patients in these two monthly dosing groups also displayed mean decreases in retinal thickness versus baseline of 143 μm ($p < 0.0001$) in the 2.0 mg group and 125 μm ($p < 0.0001$) in the 0.5 mg group at 52 weeks as measured by OCT [45].

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

Drug Evaluation

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

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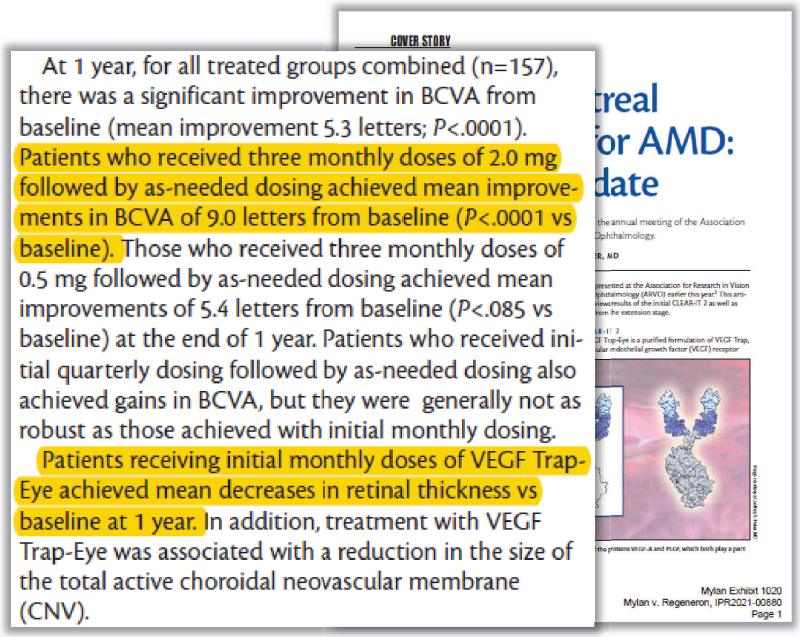
Ex.1006, Dixon, 1576



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).

Mylan Exhibit 1020
Mylan v. Regeneron, IPR2021-00880
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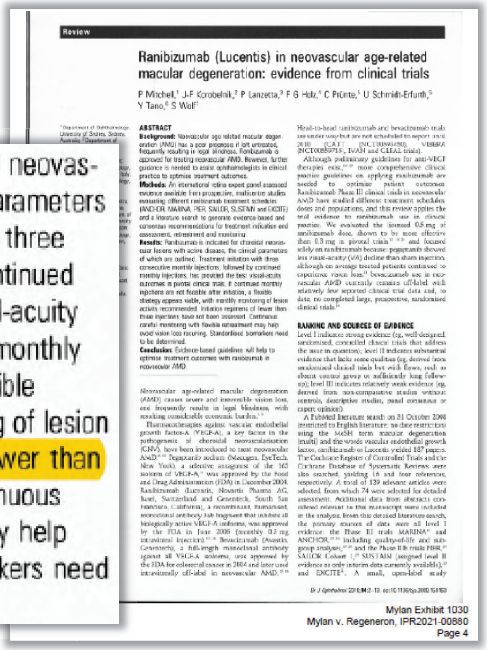
Ex.1020, Heier-2009, 45

IPR2021-00880 – Ground 5

- **PO counter-arguments lack merit**
  - **Motivation to reduce injections not limited to "chronic dosing"**
  - **Mitchell expressly suggested fewer loading doses**

    (IPR2021-00880, Paper 56, 25-28, 34-35)



Review

Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials

P Mitchell,[1] J-F Korobelnik,[2] P Lanzetta,[3] F G Holz,[4] C Prünte,[5] U Schmidt-Erfurth,[6] Y Tano,[7] S Wolf[8]

ABSTRACT

Results: Ranibizumab is indicated for choroidal neovascular lesions with active disease, the clinical parameters of which are outlined. Treatment initiation with three consecutive monthly injections, followed by continued monthly injections, has provided the best visual-acuity outcomes in pivotal clinical trials. If continued monthly injections are not feasible after initiation, a flexible strategy appears viable, with monthly monitoring of lesion activity recommended. Initiation regimens of fewer than three injections have not been assessed. Continuous careful monitoring with flexible retreatment may help avoid vision loss recurring. Standardised biomarkers need

RANKING AND SOURCES OF EVIDENCE

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

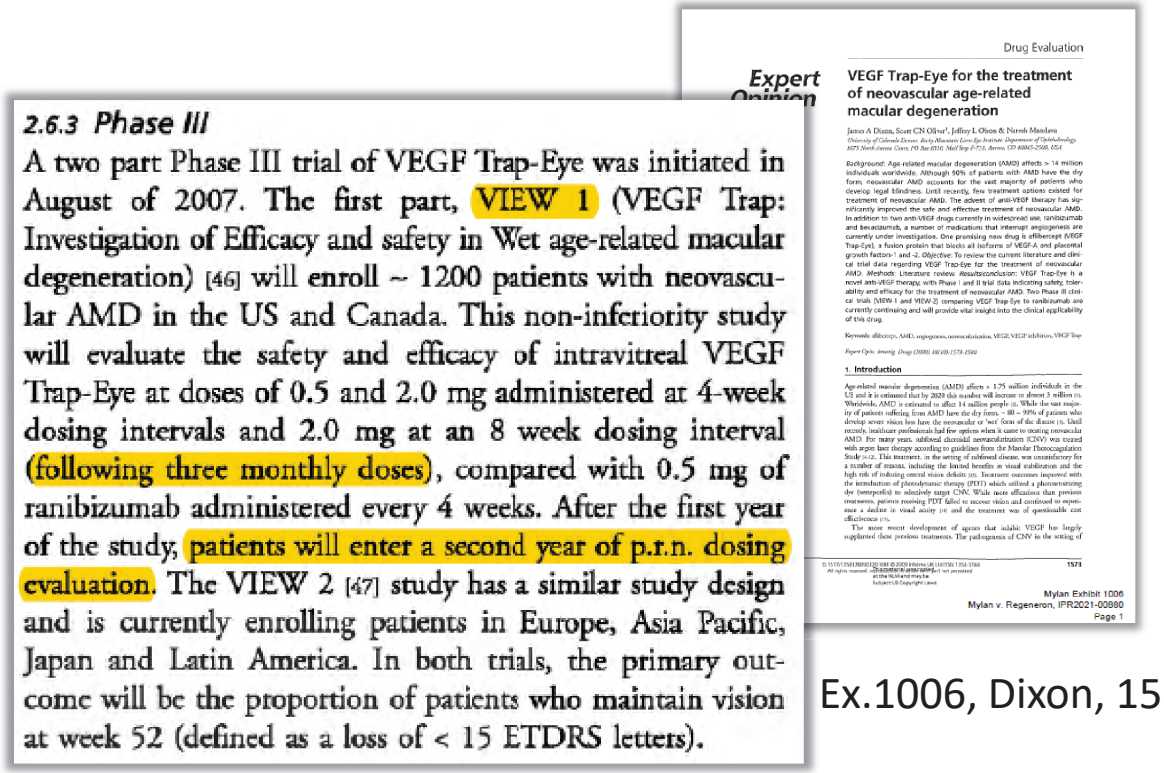
MARINA, ANCHOR[12 13 24] and the EXCITE ranibizumab active control arm[31] were the only Phase III studies with monthly injections throughout the whole treatment period. Most VA improvement was seen during the initial 3-month phase with subsequent injections appearing to maintain the achieved benefit (fig 2). Prospective clinical trials would be valuable for investigating fewer injections in the initiation phase.

Ex.1030, Mitchell, 2, 4

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

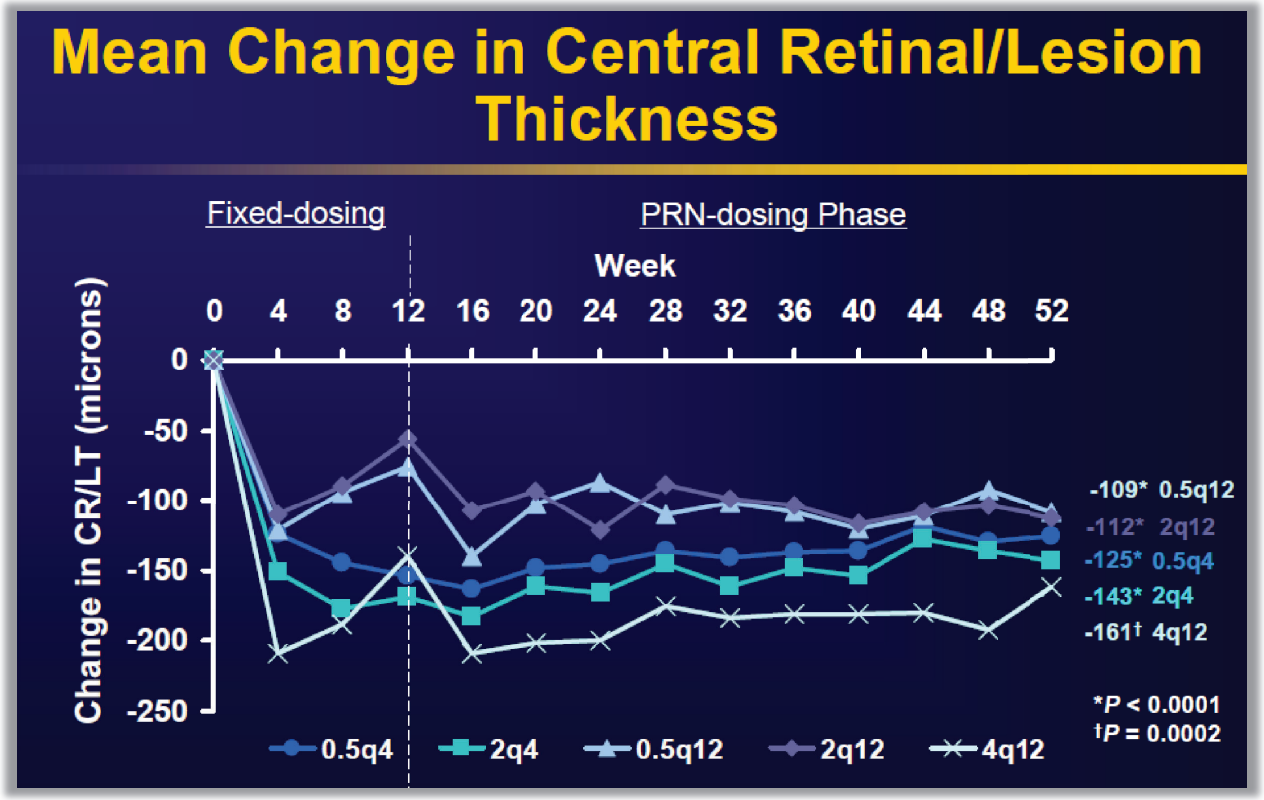
A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) [46] will enroll ~ 1200 patients with neovascular AMD in the US and Canada. This non-inferiority study will evaluate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

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)**

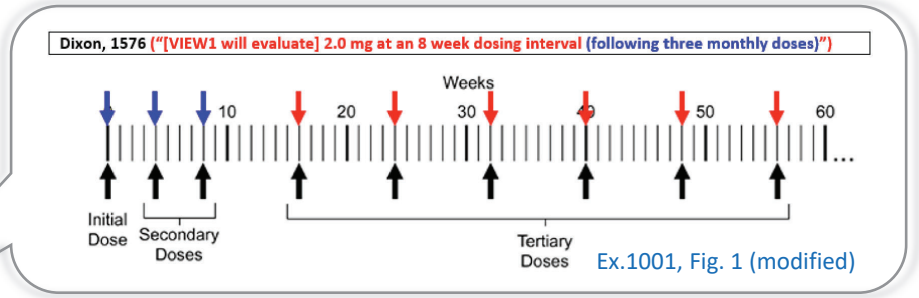
  (IPR2021-00880, Paper 56, 31-36)



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"***



Ex.1001, Fig. 1 (modified)

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

Person of Ordinary Skill in the Art ("POSA")

	Patent Owner
• **Board:** *"Petitioner's definition of [a POSA] is reasonable and consistent with the [challenged] patent and prior art of record."* (Paper 21, 15)	• **POR and Dr. Do:** Disagree with Petitioner's definition; POSA ***must*** be a licensed physician (ophthalmologist). (Ex.2051, Do Decl., ¶28)
• **Petitioner Reply:** PO experts applied *different, incompatible* POSA perspectives; Inventor and Dr. Klibanov not a POSA under PO's definition. (Paper 61, 4-6)	• **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
• **Board:** *“[T]he preambles of the independent claims do not require the recited method steps to provide an effective treatment.”* (Paper 21, 21)	• “where a ‘method for treating’ is limiting, the claims ***require*** efficacy” (Paper 73, 2)
• **Petitioner:** If limiting: “administering a therapeutic to a patient, without a specific degree of efficacy required” (Paper 1, 20-22)	
• **Petitioner:** Claims encompass all levels of efficacy, not just a “high” one (Paper 61, 9)	• “treating” requires a “high level of efficacy” (Paper 73, 3)
○ **Clear intrinsic record** ○ **Preserves the intended scope and patent’s notice function** ○ **Applies to all embodiments**	○ **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

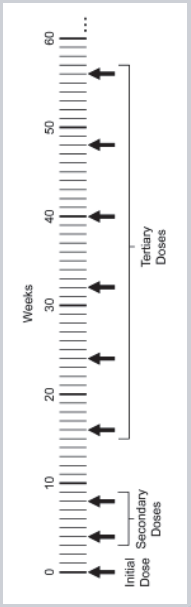
Intrinsic record describes the method as ***sequentially administered doses*** (no mention of efficacy)

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 (“VEGFT”) 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-

(Paper 61, 7-12)

Ex.1001, ’338 patent, 2:3-10

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-FcΔC1(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;

Ex.1001, ’338 patent, claim 1

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

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

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)

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

“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

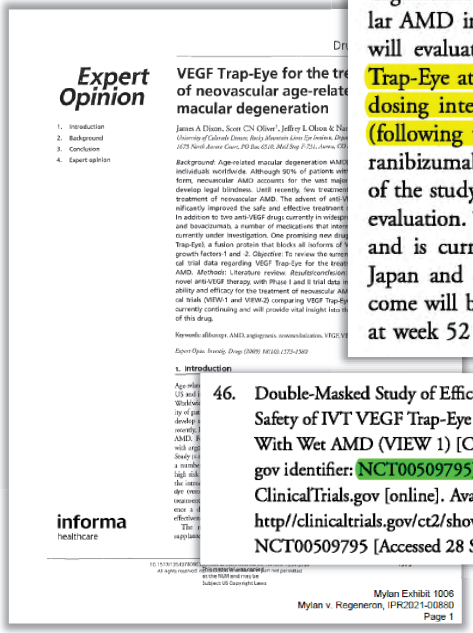
Grounds 1-2 (Anticipation)

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).


Expert Opinion

VEGF Trap-Eye for the tre… of neovascular age-relate… macular degeneration

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

informa healthcare

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

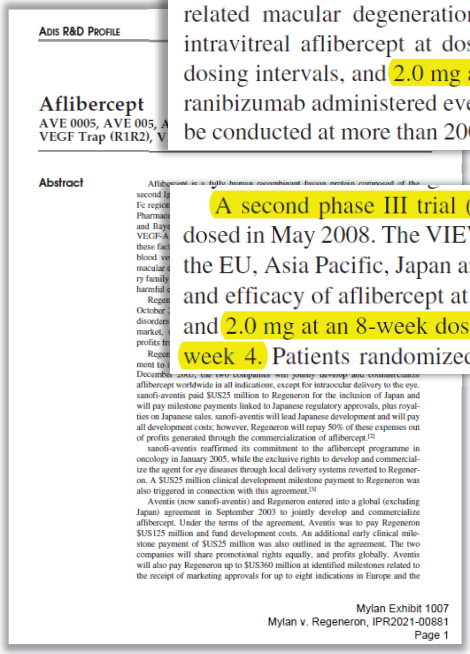
46. Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) [ClinicalTrials.gov identifier: NCT00509795] ClinicalTrials.gov [online]. Available http//clinicaltrials.gov/ct2/show/ NCT00509795 [Accessed 28 Sep 20…

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

Ex.1006, Dixon, 1576, 1579

Regeneron and Bayer inititiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007. The non-inferiority, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) study will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and 2.0 mg at an 8-week dosing interval, compared with 0.5 mg ranibizumab administered every 4 weeks. The randomized, double-blind trial will be conducted at more than 200 centres throughout the US and Canada, pursuant to

A 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


ADIS R&D PROFILE

Aflibercept
AVE 0005, AVE 005, …
VEGF Trap (R1R2), V…

Abstract

Mylan Exhibit 1007
Mylan v. Regeneron, IPR2021-00881
Page 1

Ex.1007, Adis, 263

(Paper 1, 27-30, 39-49)

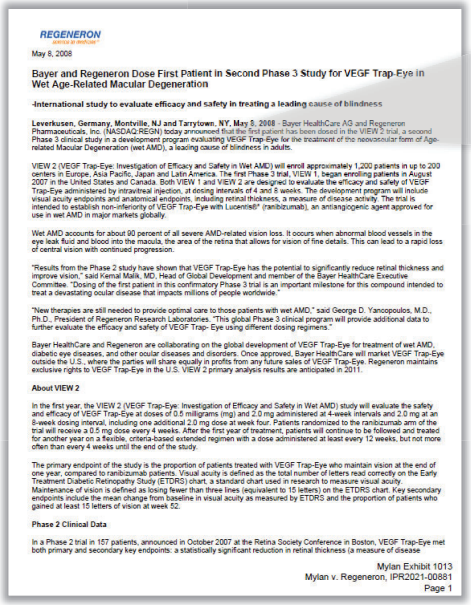
Grounds 3-5 (Anticipation)

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)

"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)



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, Montville, 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 anti-angiogenic agent approved for use in wet AMD in major markets globally.

Wet AMD accounts for about 90 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 Kemal 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 analysis 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 flexible, criteria-based extended regimen with a dose 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

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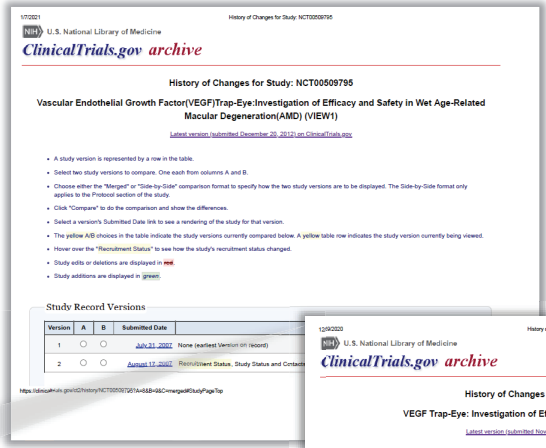
Mylan v. Regeneron, IPR2021-00881
Page 1

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



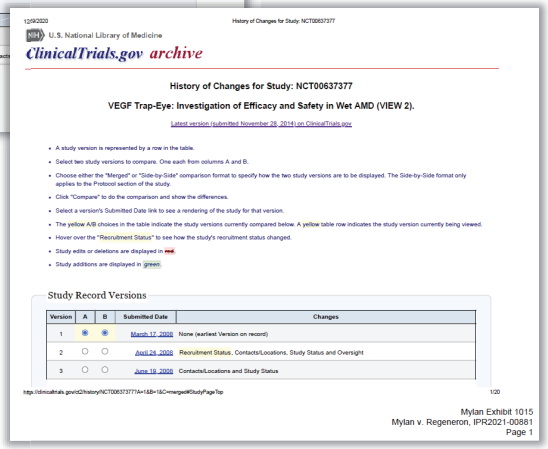
U.S. National Library of Medicine
ClinicalTrials.gov archive

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)

Study Record Versions

Ex.1014, NCT-795



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).

Study Record Versions

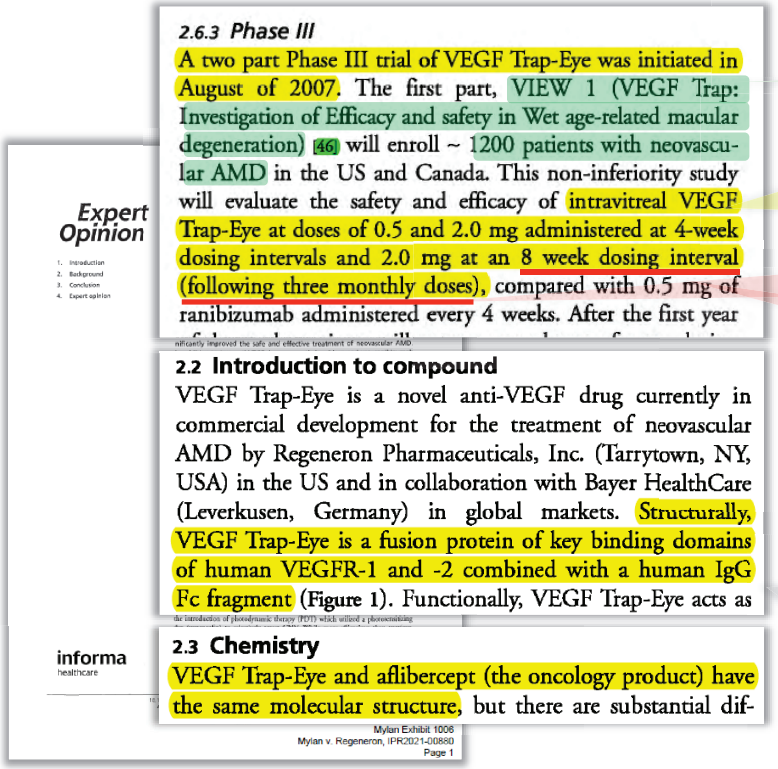
Mylan Exhibit 1015
Mylan v. Regeneron, IPR2021-00881
Page 1

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**



Expert Opinion

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

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

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-

informa healthcare

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

Ex.1006, Dixon, 1575-76

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).

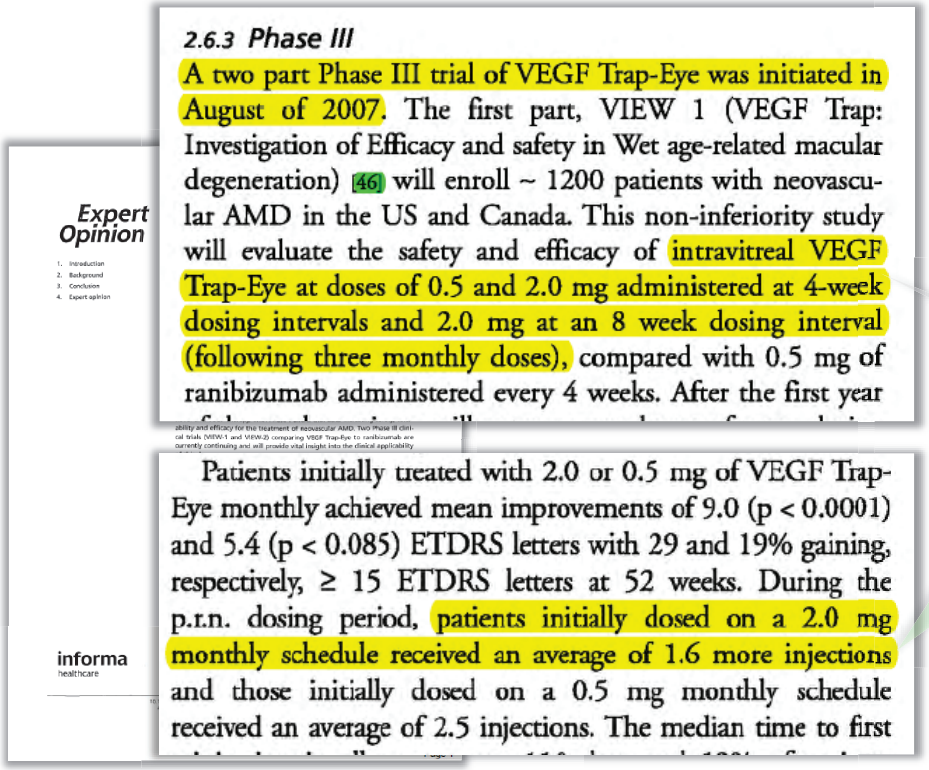
Ex.1010, '758 Patent, 10:15-17

(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



Expert Opinion

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

informa healthcare

2.6.3 Phase III

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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

Ex.1006, Dixon, 1576

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)

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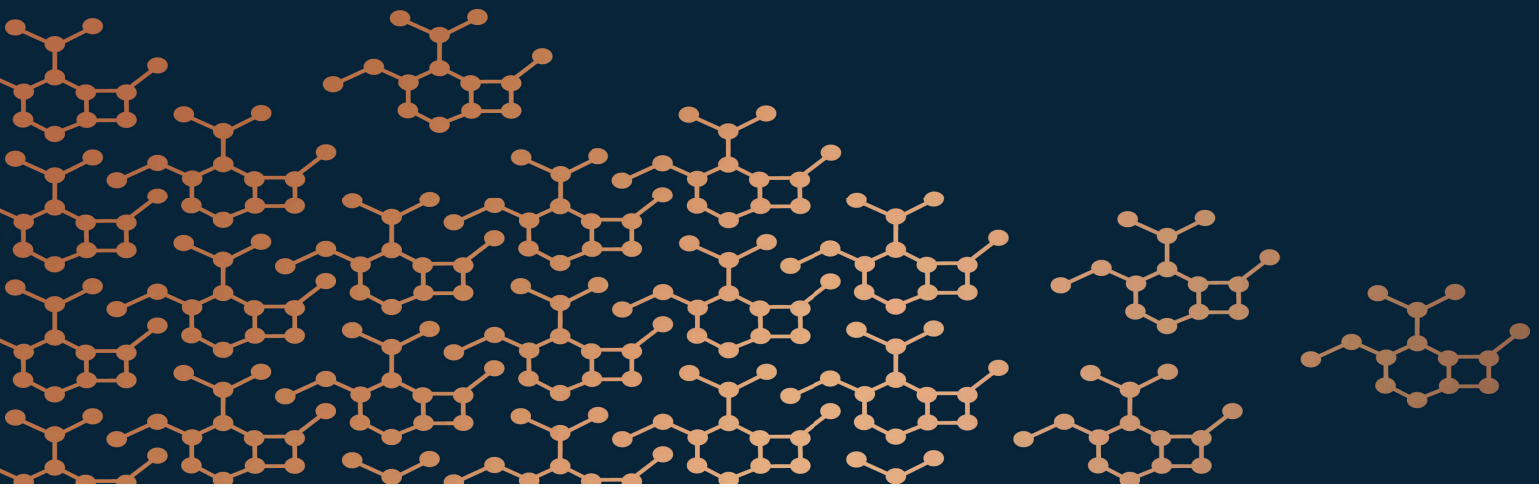
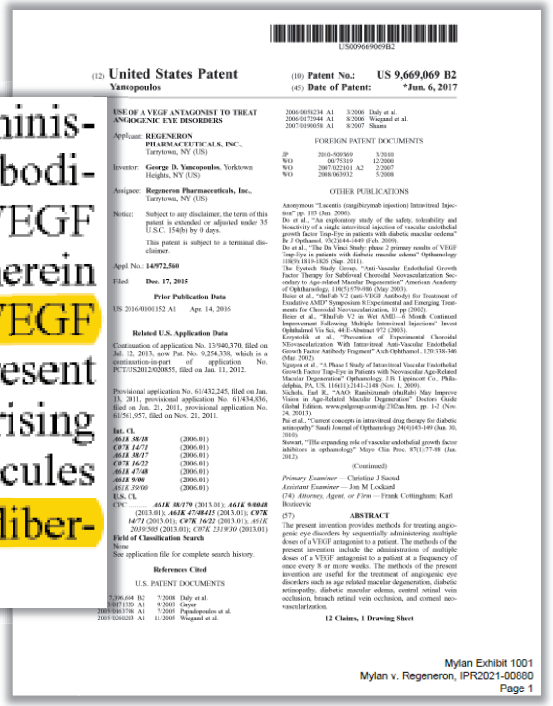


’069 Patent

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

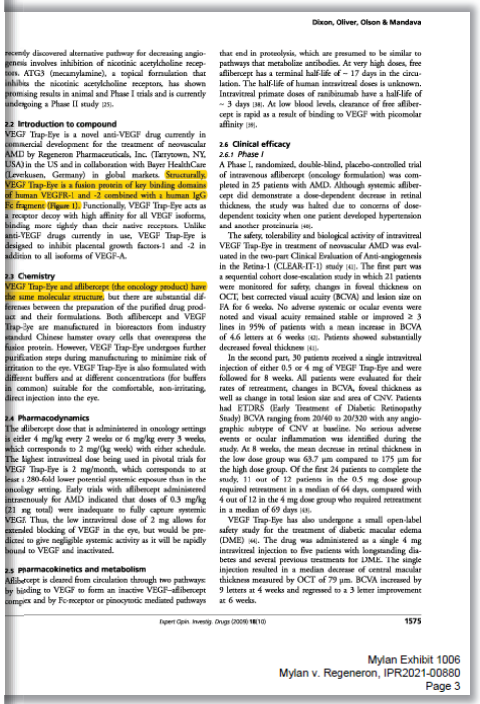
Dixon

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

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

Ex.1006, Dixon, 1575

Dixon

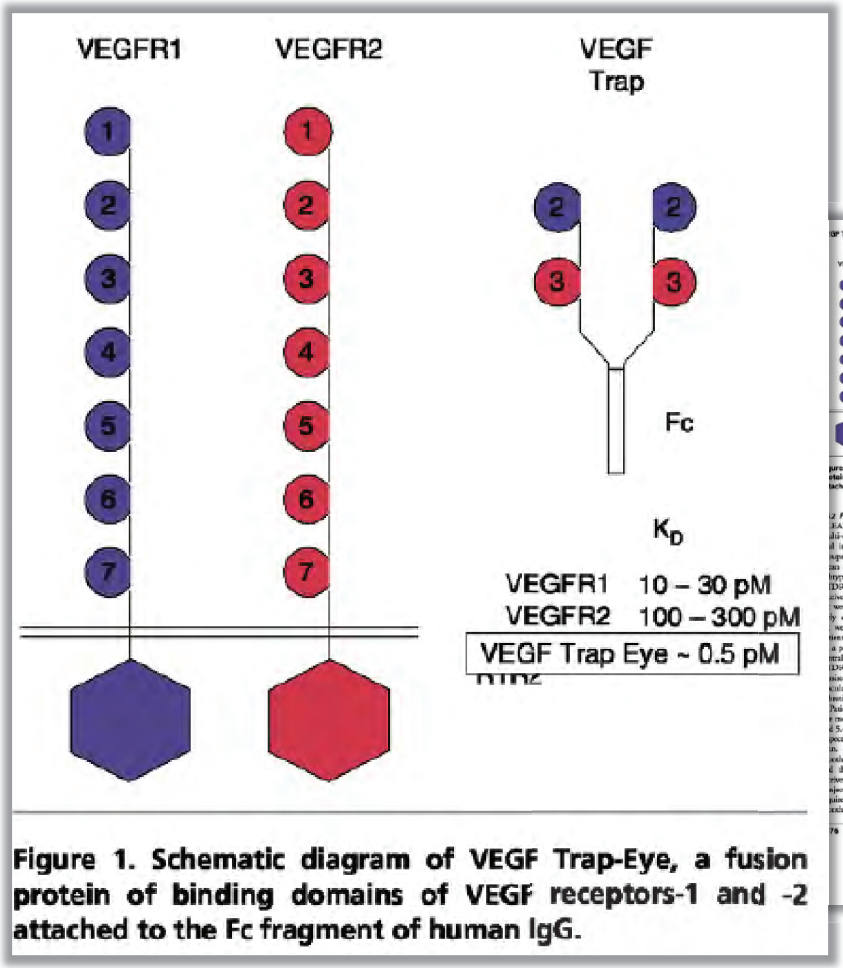
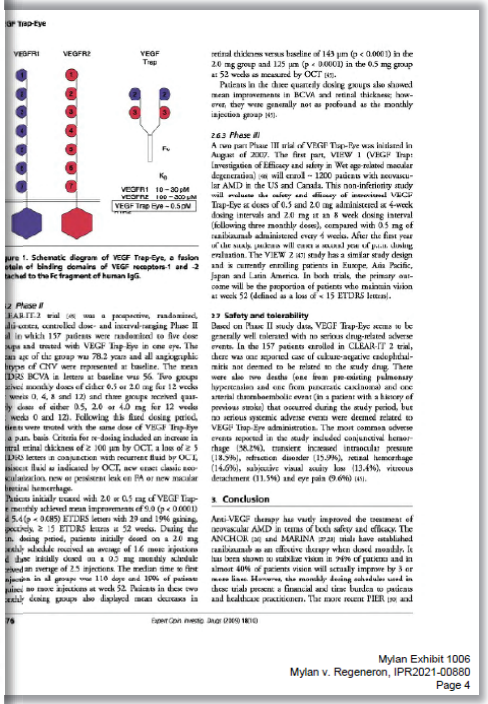


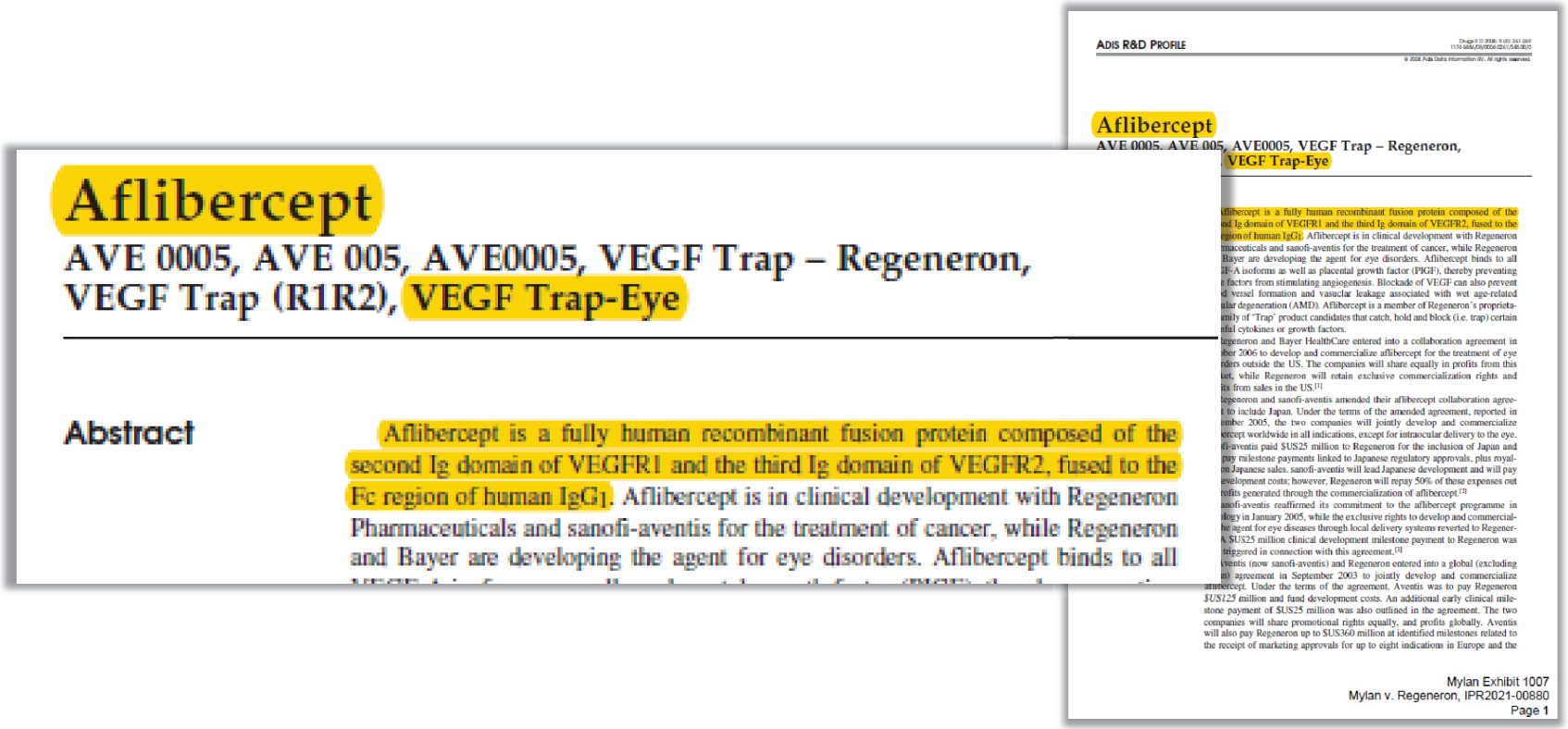
Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.



Mylan Exhibit 1006
Mylan v. Regeneron, IPR2021-00880
Page 4

Ex.1006, Dixon, 1576

Adis



ADIS R&D PROFILE

Aflibercept

AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap-Eye

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

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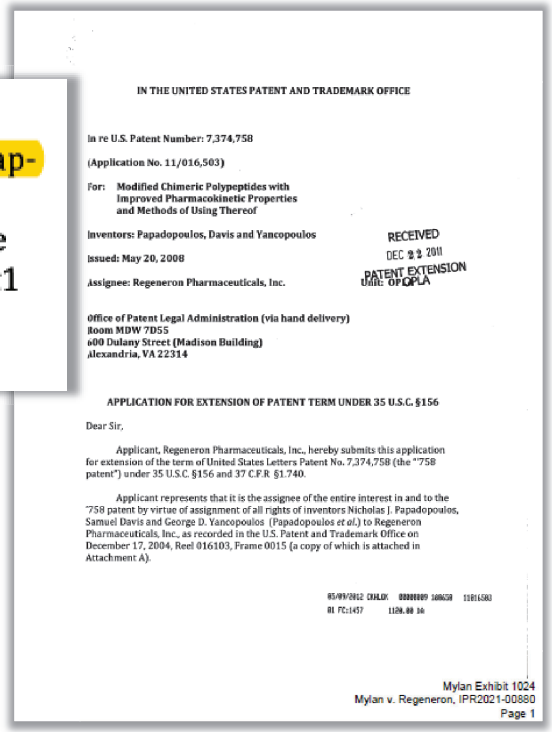
Page 1

Ex.1007, Adis, 261

’758 PTE Application

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

In re U.S. Patent Number: 7,374,758

(Application No. 11/016,503)

For: Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties and Methods of Using Thereof

Inventors: Papadopoulos, Davis and Yancopoulos

Issued: May 20, 2008

Assignee: Regeneron Pharmaceuticals, Inc.

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PATENT EXTENSION
UNIT: OPLA

Office of Patent Legal Administration (via hand delivery)
Room MDW 7D55
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. 7,374,758 (the "'758 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 '758 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 December 17, 2004, Reel 016103, Frame 0015 (a copy of which is attached in Attachment A).

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01 FC:1457 1120.00 DA

Mylan Exhibit 1024
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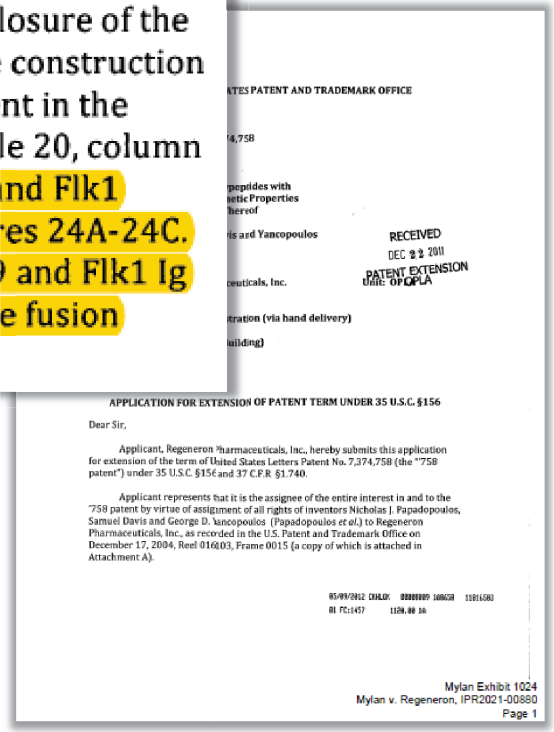
Page 1

Ex.1024, ’758 PTE, 2 (Paper 61, 22)

’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.



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PATENT EXTENSION
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...

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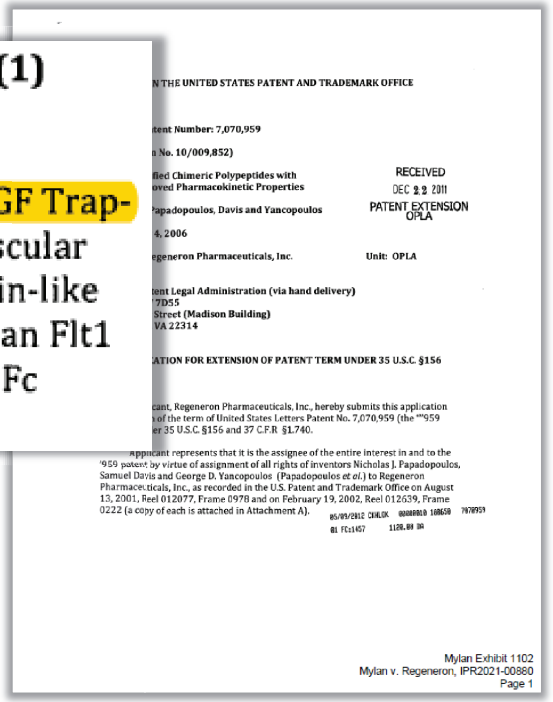
Page 1

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.


N THE UNITED STATES PATENT AND TRADEMARK OFFICE

tent Number: 7,070,959

No. 10/009,852)

fied Chimeric Polypeptides with
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OPLA

Papadopoulos, Davis and Yancopoulos

6, 2006

egeneron Pharmaceuticals, Inc.

Unit: OPLA

tent Legal Administration (via hand delivery)
7D55
Street (Madison Building)
VA 22314

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

cant, Regeneron Pharmaceuticals, Inc., hereby submits this application
of the term of United States Letters Patent No. 7,070,959 (the ""959
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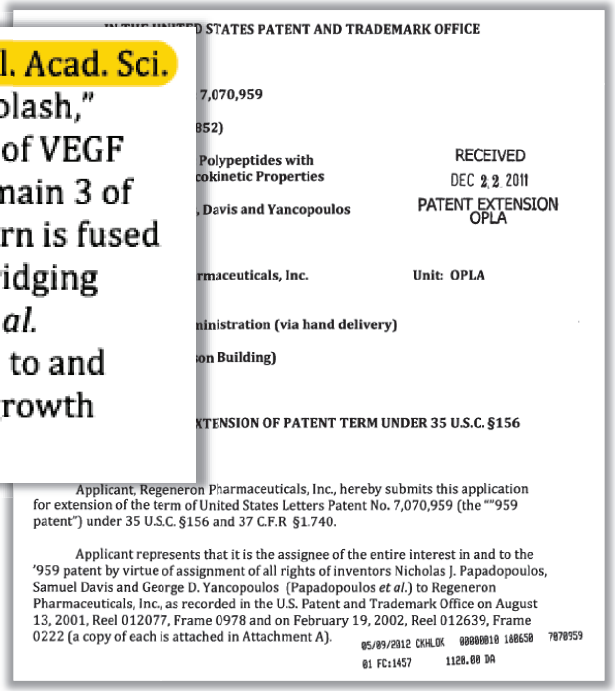
01 FC:1457 1120.00 DA

Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00880
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.



D STATES PATENT AND TRADEMARK OFFICE

7,070,959

852)

Polypeptides with
cokinetic Properties

Davis and Yancopoulos

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XTENSION 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.

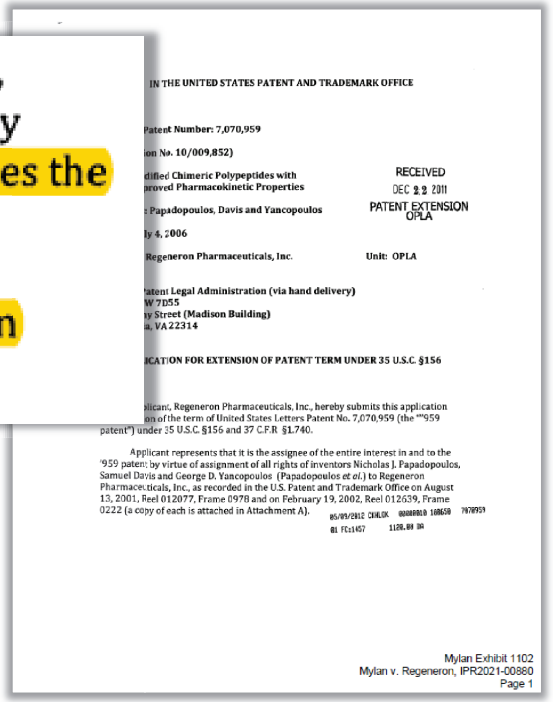
Applicant represents that it is the assignee of the entire interest in and to the '959 patent by virtue of assignment of all rights of inventors Nicholas J. Papadopoulos, Samuel Davis and George D. Yancopoulos (Papadopoulos *et al.*) to Regeneron Pharmaceuticals, Inc., as recorded in the U.S. Patent 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 CKHLOK 00000010 108650 7070959
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

on No. 10/009,852)

dified Chimeric Polypeptides with
proved Pharmacokinetic Properties

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PATENT EXTENSION
OPLA

: Papadopoulos, Davis and Yancopoulos

ly 4, 2006

Regeneron Pharmaceuticals, Inc.

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a, VA 22314

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0222 (a copy of each is attached in Attachment A).

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Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00880
Page 1

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

’959 PTE Application

(2) *Explanation Regarding Claim 11 Relative to Aflibercept*

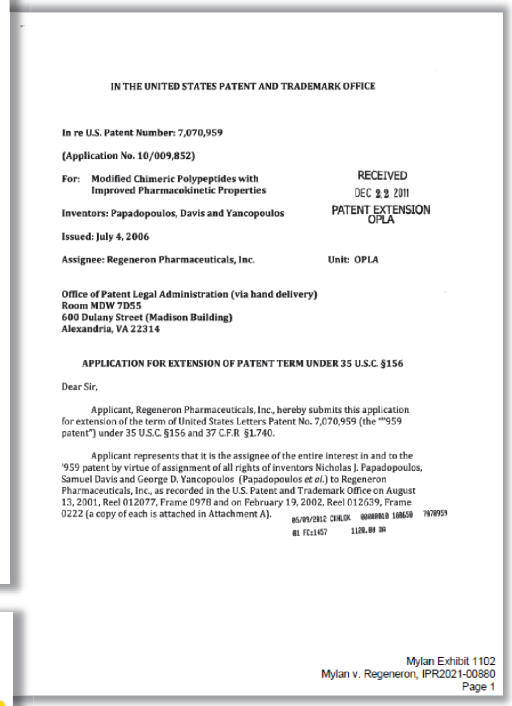
As explained below, a method for manufacturing aflibercept, the active ingredient of the approved product, is covered by at least claim 11.

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

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PATENT EXTENSION
OPLA

Inventors: Papadopoulos, Davis and Yancopoulos

Issued: July 4, 2006

Assignee: Regeneron Pharmaceuticals, Inc. Unit: OPLA

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

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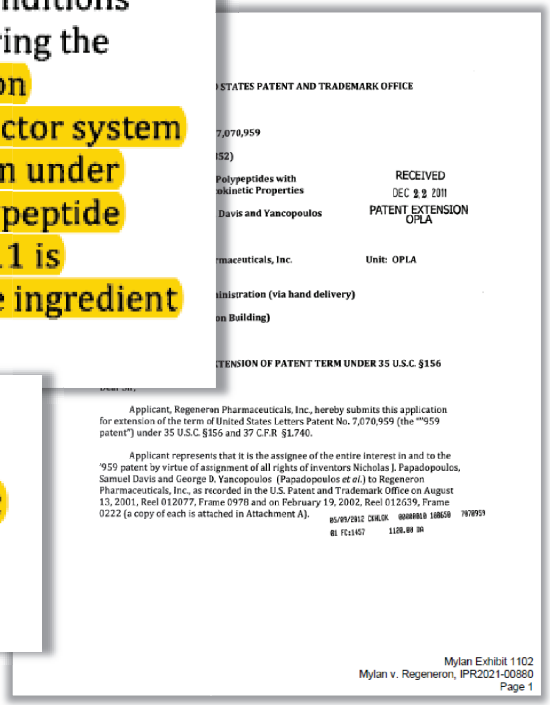
Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00880
Page 1

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.


STATES PATENT AND TRADEMARK OFFICE

7,070,959

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Mylan Exhibit 1102
Mylan v. Regeneron, IPR2021-00880
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:

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