

A u g u s t 1 0 , 2 0 2 2

IPR2021-00880, -00881

U.S. Patent Nos. 9,669,069 & 9,254,338

REGENERON[®]

Overview

- VEGF Trap-Eye: All Grounds, All Claims
- IPR2021-00880—U.S. Patent No. 9,669,069
 - Ground 4 – All Claims: No Anticipation or Obviousness Based on Dixon Disclosure of VIEW Dosing Regimen
 - Ground 5 – Claim 8: No Anticipation or Obviousness Based on Heier- of Mitchell or Dixon
- IPR2021-00881—U.S. Patent No. 9,234,338
 - Claim Construction
 - Grounds 1-5 – All Claims: No Anticipation Based on Lack of “Treatment
 - Ground 6 – All Claims: No Obviousness Based on Prospective VIEW Regimen



VEGF Trap-Eye

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Petitioner's Grounds Do Not Disclose the Recited Amino Acid or Nucleic Acid Sequences

Drug Evaluation

Expert Opinion

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

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Background: Age-related macular degeneration (AMD) is a leading cause of blindness in the developed world. Although 90% of patients with AMD are aged 50 years and older, neovascular AMD accounts for the vast majority of cases. Until recently, the treatment of neovascular AMD. The use of anti-VEGF agents, such as ranibizumab, bevacizumab, and aflibercept, has significantly improved the safety and efficacy of treatment. VEGF Trap-Eye is a novel, long-acting, intravitreal anti-VEGF agent. It is a dimeric protein consisting of two VEGF binding domains fused to a human IgG1 Fc domain. This structure allows for a long half-life in the eye, reducing the need for frequent injections. Clinical studies have shown that VEGF Trap-Eye is safe and effective in the treatment of neovascular AMD. Two Phase III clinical trials, CLEAR-IT 1 and CLEAR-IT 2, have demonstrated that VEGF Trap-Eye is non-inferior to ranibizumab in terms of visual acuity and safety. The results of these trials provide a vital insight into the clinical applicability of VEGF Trap-Eye as a treatment for neovascular AMD.

Introduction

1. Introduction

2. Background

3. Conclusion

4. Expert opinion

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Dixon Ex.1006

COVER STORY

Intravitreal VEGF Trap for AMD: An Update

The CLEAR-IT 2 Extension Study was presented at the Association for Research in Vision and Ophthalmology (ARVO) earlier this year. The results of the initial CLEAR-IT 2 as well as the extension study.

BY [Author Name]

Figure 1: VEGF Trap-Eye is a fusion protein designed to bind all forms of the proteins VEGF-A and PlGF, which both play a part in abnormal growth of new blood vessels.

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Heier-2009 Ex.1020

REGENERON

Bayer and Regeneron Extend Development Program for CRVO

April 30, 2009

Bayer and Regeneron Extend Development Program for CRVO to start in the second half of this year.

BERLIN and TARRYTOWN, N.Y., April 30 (PRNewswire) - Bayer and Regeneron today announced that the companies are extending their global development program for the treatment of Central Retinal Vein Occlusion (CRVO) with VEGF Trap-Eye. The extension of the program will include safety studies of VEGF Trap-Eye in the treatment of CRVO in the second half of 2009. The Phase 3 program in CRVO will consist of two, multicenter, randomized, controlled studies. The first study will evaluate the safety and efficacy of VEGF Trap-Eye compared to laser photocoagulation in the treatment of CRVO. The second study will evaluate the safety and efficacy of VEGF Trap-Eye compared to laser photocoagulation in the treatment of CRVO in patients with the neovascular form of CRVO. The extension of the program is a significant testament to the companies' commitment to the treatment of CRVO.

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Regeneron Ex.1020

Petitioner's Grounds Do Not Disclose the Recited Acid or Nucleic Acid Sequences

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 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 200 patients in 10 to 200 centers in Europe, Asia Pacific, Japan and Latin America. The first Phase 3 trial, VIEW 1, was completed in 2007 in the United States and Canada. Both VIEW 1 and VIEW 2 are designed to evaluate the safety and efficacy of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks, compared to standard of care. The primary endpoints are visual acuity endpoints and anatomical endpoints, including retinal thickness. Secondary endpoints include the proportion of patients who maintained vision at week 52. The study is intended to establish non-inferiority of VEGF Trap-Eye with Lucentis® in major markets globally.

Wet AMD accounts for about 90 percent of all severe AMD. It occurs when abnormal blood vessels in the eye leak fluid and blood into the macula, the area of the eye responsible for central vision. As the disease progresses, central vision with continued progression.

"Results from the Phase 2 study have shown that VEGF Trap-Eye significantly reduce retinal thickness and improve vision," said Kamel Malik, MD, PhD, President of Regeneron. "The Phase 3 clinical program will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye in different dosing regimens."

"New therapies are still needed for the treatment of wet AMD," said George D. Vancopoulos, M.D., Ph.D., President of Regeneron. "The Phase 3 clinical program will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye in different dosing regimens."

Bayer HealthCare and Regeneron are the global developers of VEGF Trap-Eye for treatment of wet AMD, diabetic macular edema and other eye diseases. Once approved, Bayer HealthCare will market VEGF Trap-Eye under the name Eylea. Regeneron will continue to be involved in the development of VEGF Trap-Eye. Regeneron maintains an ownership stake in the company. VIEW 2 primary analysis results are anticipated in 2011.

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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Regeneron (8-May-2008)
Ex.1013

177020 U.S. National Library of Medicine
History of Changes for Study: NCT00509795

ClinicalTrials.gov archive

Vascular Endothelial Growth Factor(VEGF)Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Study Record Versions

Version	A	B	Submitter
1			
2			

Changes

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NCT-795 Ex.1014

1099500 U.S. National Library of Medicine
History of Changes for Study: NCT00509795

ClinicalTrials.gov archive

VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW2)

Study Record Versions

Version	A	B	Submitter
1			
2			
3			

Changes

NCT-

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881 POR at 25-26; 881 Sur-reply at 14; Ex.2129 at 109:15-110:3; Ex.2130 at 341:13-16; Ex.2049 at Section IX; Ex.2048 at Section X; Ex.1114

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