High-Dose Aflibercept

Rationale & Clinical Studies

David M Brown MD

Houston, TEXAS USA

Take Home Messages

- Higher Dose Anti-VEGF improves anatomy /VA in historical RCTs
- Aflibercept (Like most anti-VEGFs) has a linear PK curve
- 8mg Aflibercept should provide two ½-lives more duration
- Variability in vitreous half-life makes standardized dosing/ clinical trial design challenging.

Disclosures

- Consultant / Clinical Trial Support from Regeneron & Competitors

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2006 VOL. 355 NO. 14

Ranibizumab for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boyer, M.D., Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D., for the MARINA Study Group*

ABSTRACT

BACKGROUND

Ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — has been evaluated for the treatment of neovascular age-related macular degeneration.

METHODS

In this multicenter, 2-year, double-blind, sham-controlled study, we randomly assigned patients with age-related macular degeneration with either minimally classic or occult (with no classic lesions) choroidal neovascularization to receive 24 monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

We enrolled 716 patients in the study. At 12 months, 94.5% of the group given 0.3 mg of ranibizumab and 94.6% of those given 0.5 mg lost fewer than 15 letters, as compared with 62.2% of patients receiving sham injections ($P<0.001$ for both comparisons). Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group ($P<0.001$ for both doses). Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group ($P<0.001$ for both comparisons). The benefit in visual acuity was maintained at 24 months. During 24 months, presumed endophthalmitis was identified in five patients (1.0%) and serious uveitis in six patients (1.3%) given ranibizumab.

CONCLUSIONS

Intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization secondary to age-related macular degeneration. (ClinicalTrials.gov number, NCT00056836.)

From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami (P.J.R.); Vitreoretinal Consultants, Methodist Hospital, Houston (D.M.B.); Ophthalmic Consultants of Boston, Boston (J.S.H.); Retina Vitreous Associates Medical Group, Los Angeles (D.S.B.); the Cole Eye Institute, Cleveland Clinic Foundation, Cleveland (P.K.K.); Retina Care Specialists, Palm Beach Gardens, FL (R.M.); the Clinique d'Ophtalmologie, University of Paris 8, Créteil, France (C.S.); Ophthalmic Consultants of Boston, Boston (J.S.H.); and Genentech, South San Francisco, CA (C.Y.C., R.Y.K.). Address reprint requests to Dr. Rosenfeld at the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami Miller School of Medicine, 900 NW 17th St., Miami, FL 33136, or at prosenfeld@med.miami.edu.

*Principal investigators in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) Study Group are listed in the Appendix.

N Engl J Med 2006;355:1419-31.

ORIGINAL ARTICLE

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

David M. Brown, M.D., Peter K. Kaiser, M.D., Mark Michels, M.D., Gisele Soubrane, M.D., Jeffrey S. Heier, M.D., Robert Y. Kim, M.D., Judy P. Sy, Ph.D., and Susan Schneider, M.D., for the ANCHOR Study Group*

ABSTRACT

From Vitreoretinal Consultants, Methodist Hospital, Houston (D.M.B.); the Cole Eye Institute, Cleveland Clinic Foundation, Cleveland (P.K.K.); Retina Care Specialists, Palm Beach Gardens, FL (M.M.); the Clinique d'Ophtalmologie, University of Paris 8, Créteil, France (G.S.); Ophthalmic Consultants of Boston, Boston (J.S.H.); and Genentech, South San Francisco, CA (J.P.S., S.S.). Address reprint requests to Dr. Brown at Vitreoretinal Consultants, 6560 Fannin St., Suite 750, Houston, TX 77030, or at dmbrown@houstonretina.com.

*Principal investigators in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) Study Group are listed in the Appendix.

N Engl J Med 2006;355:1432-44.

BACKGROUND

We compared ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — with photodynamic therapy with verteporfin in the treatment of predominantly classic neovascular age-related macular degeneration.

METHODS

During the first year of this 2-year, multicenter, double-blind study, we randomly assigned patients in a 1:1:1 ratio to receive monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin therapy or monthly sham injections plus active verteporfin therapy. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

Of the 423 patients enrolled, 94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg lost fewer than 15 letters, as compared with 64.3% of those in the verteporfin group ($P<0.001$ for each comparison). Visual acuity improved by 15 letters or more in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group, as compared with 5.6% of the verteporfin group ($P<0.001$ for each comparison). Mean visual acuity increased by 8.5 letters in the 0.3-mg group and 11.3 letters in the 0.5-mg group, as compared with a decrease of 9.5 letters in the verteporfin group ($P<0.001$ for each comparison). Among 140 patients treated with 0.5 mg of ranibizumab, presumed endophthalmitis occurred in 2 patients (1.4%) and serious uveitis in 1 (0.7%).

CONCLUSIONS

Ranibizumab was superior to verteporfin as intravitreal treatment of predominantly classic neovascular age-related macular degeneration, with low rates of serious ocular adverse events. Treatment improved visual acuity on average at 1 year. (ClinicalTrials.gov number, NCT00061594.)

The NEW ENGLAND JOURNAL of MEDICINE

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group*

ABSTRACT

BACKGROUND

Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS

In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

RESULTS

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, $P=0.03$ by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab ($P>0.20$). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.3% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

CONCLUSIONS

At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450.)

The members of the writing committee (Daniel F. Martin, M.D., Cleveland Clinic Cole Eye Institute, Cleveland; Maureen G. Maguire, Ph.D., Gui-shuang Ying, Ph.D., and Juan E. Grunwald, M.D., University of Pennsylvania, Philadelphia; Stuart L. Fine, M.D., University of Colorado Denver, Aurora; and Glenn J. Jaffe, M.D., Duke University, Durham, NC) assume responsibility for the integrity of the article. Address reprint requests to Dr. Maguire at the Scheie Eye Institute, University of Pennsylvania, 3535 Market St., Suite 700, Philadelphia, PA 19104, or at maguire@mail.med.upenn.edu.

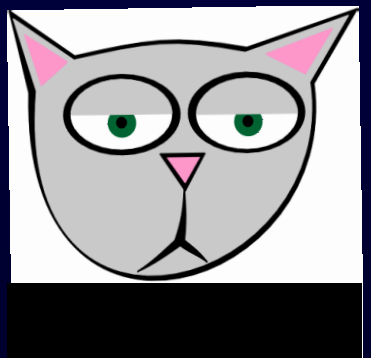
*The members of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) research group are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1102673) was published on April 28, 2011, at NEJM.org.

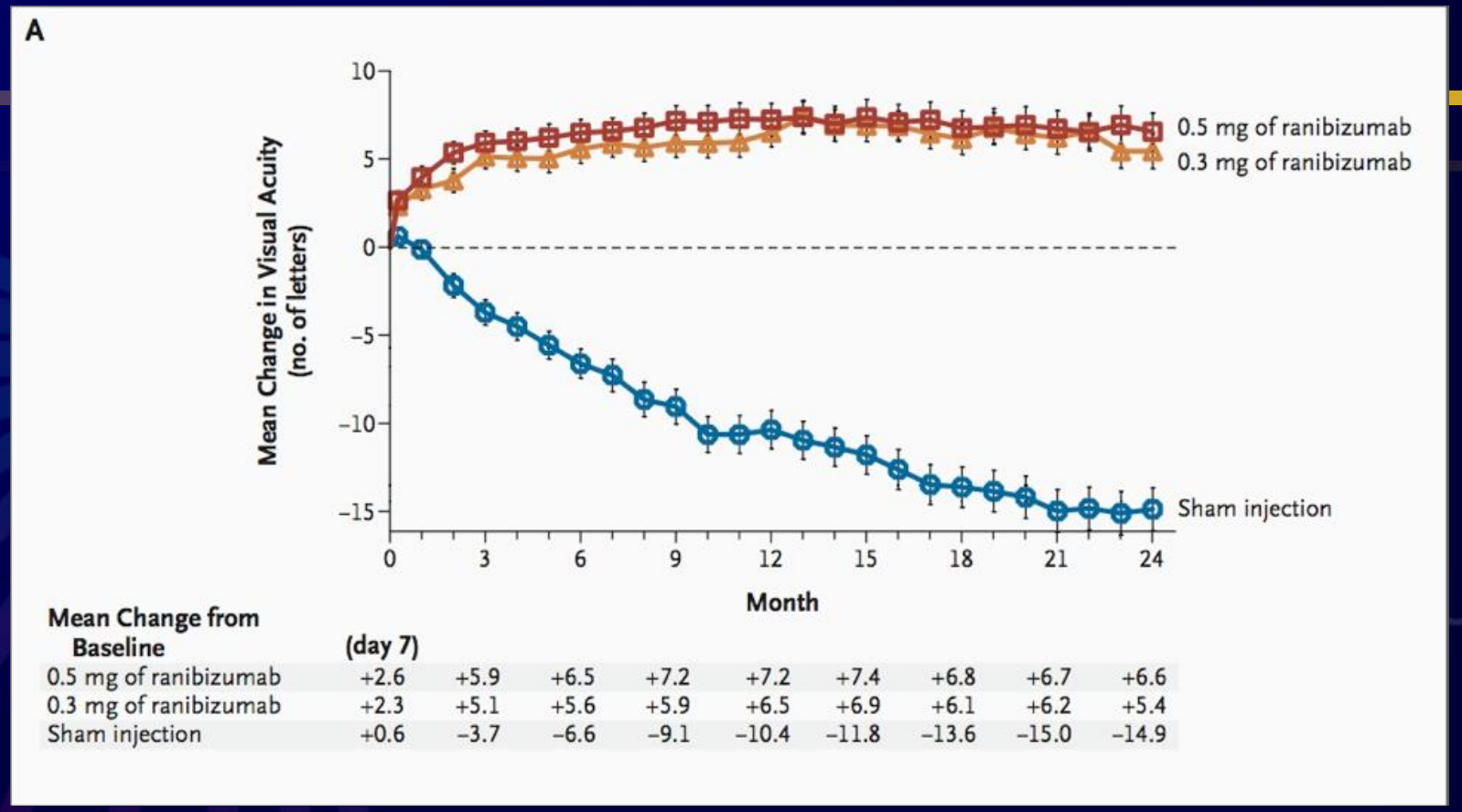
N Engl J Med 2011.

MARINA

ANCHOR



MARINA



Mean Change from Baseline	(day 7)								
0.5 mg of ranibizumab	+2.6	+5.9	+6.5	+7.2	+7.2	+7.4	+6.8	+6.7	+6.6
0.3 mg of ranibizumab	+2.3	+5.1	+5.6	+5.9	+6.5	+6.9	+6.1	+6.2	+5.4
Sham injection	+0.6	−3.7	−6.6	−9.1	−10.4	−11.8	−13.6	−15.0	−14.9


The NEW ENGLAND JOURNAL of MEDICINE

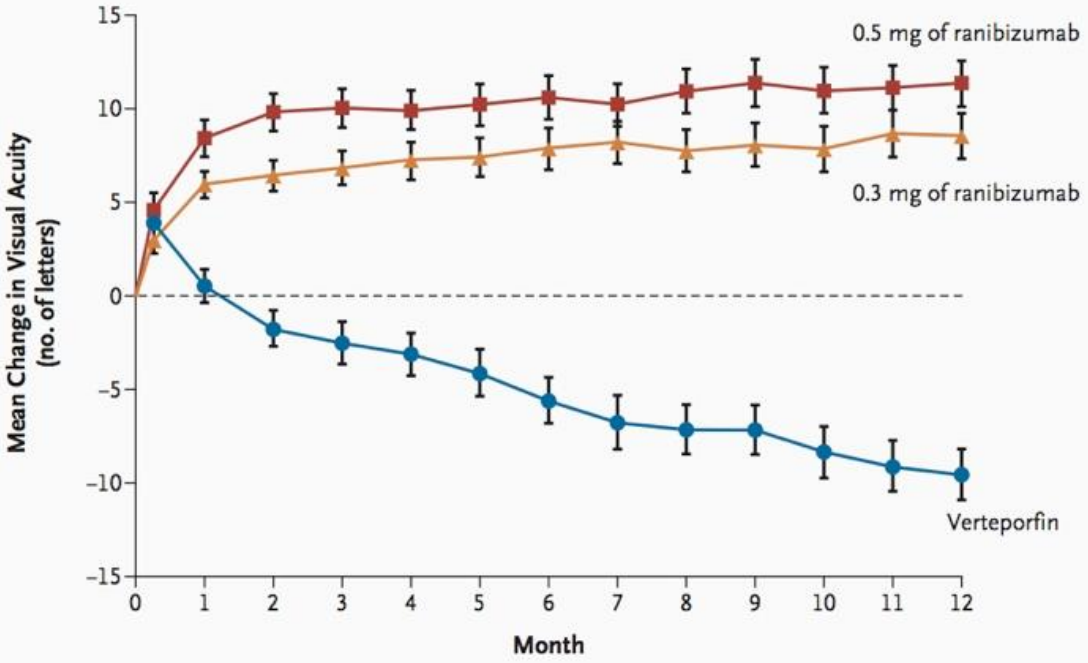
Ranibizumab for Neovascular Age-Related Macular Degeneration

ABSTRACT

NEJM, Rosenfeld et al 2006

MARINA

ANCHOR



Mean Change from Baseline	(day 7)												
0.5 mg of ranibizumab	+4.6	+8.4	+9.8	+10.0	+9.9	+10.2	+10.6	+10.2	+10.9	+11.4	+10.9	+11.1	+11.3
0.3 mg of ranibizumab	+2.9	+5.9	+6.4	+6.8	+7.2	+7.4	+7.9	+8.2	+7.7	+8.1	+7.8	+8.6	+8.5
Verteporfin	+3.9	+0.5	−1.8	−2.5	−3.1	−4.1	−5.6	−6.8	−7.1	−7.1	−8.3	−9.1	−9.5

ORIGINAL ARTICLE

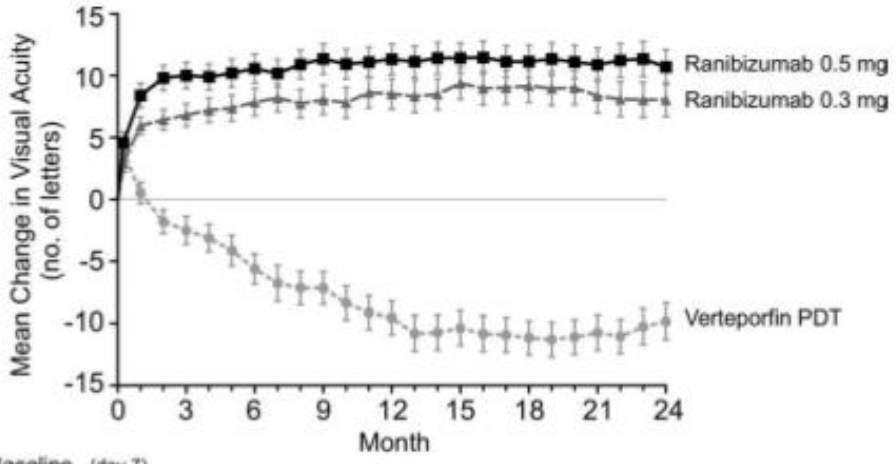
Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

ABSTRACT

NEJM, Brown et al 2006

ANCHOR

ANCHOR



Mean Change from Baseline	(day 7)								
Ranibizumab 0.5 mg (n=139)	+4.6	+10.0	+10.6	+11.4	+11.3	+11.4	+11.1	+10.9	+10.7
Ranibizumab 0.3 mg (n=140)	+2.9	+6.8	+7.9	+8.1	+8.5	+9.4	+9.2	+8.4	+8.1
Verteporfin PDT (n=143)	+3.9	-2.5	-5.6	-7.2	-9.6	-10.4	-11.2	-10.7	-9.8

Figure 1. Mean change from baseline visual acuity (VA) score (letters) over time. Vertical bars represent ±1 standard error of the mean. The mean change at some visits in the first year differed slightly from those previously reported[6] because the present analysis is based on the final data. $P<0.001$ for all comparisons versus verteporfin photodynamic therapy (PDT) at each month. Pairwise analysis of variance models adjusting for VA score at day 0 (<45 letters vs. ≥45 letters) were used to analyze mean VA change from baseline at each monthly assessment. The last-observation-carried-forward method was used to impute missing data. All tests were 2-sided.

Ophthalmology, Brown et al 2009

ANCHOR

CATT
FLUID on OCT @ 1 Year
Ranibizumab = 53.2%
Bevacizumab = 70.9%

Table 2. Outcome Measures at 1 Year.*

Outcome	Ranibizumab Monthly (N=284)	Bevacizumab Monthly (N=265)	Ranibizumab as Needed (N=285)	Bevacizumab as Needed (N=271)	P Value†
Fluid on optical coherence tomography — no. (%)					
Absent	124 (43.7)	69 (26.0)	68 (23.9)	52 (19.2)	<0.001
Present	151 (53.2)	188 (70.9)	203 (71.2)	214 (79.0)	


The NEW ENGLAND JOURNAL of MEDICINE

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group*

ABSTRACT

BACKGROUND

Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS

In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

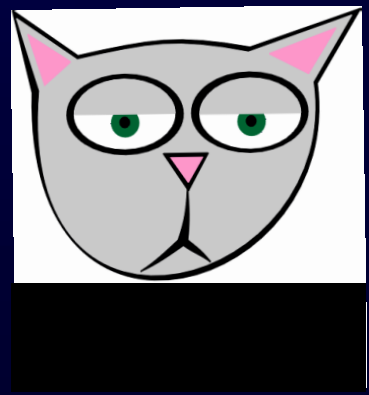
RESULTS

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm; P=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P=0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.2% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

CONCLUSIONS

At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; CLinicalTrials.gov number, NCT00593450.)

NEJM, Martin et al 2011



UPER DOSE ANTI-VEGF

(2.0 mg Ranibuzimab)

RECALCITRANT AMD

"Incomplete Responders"

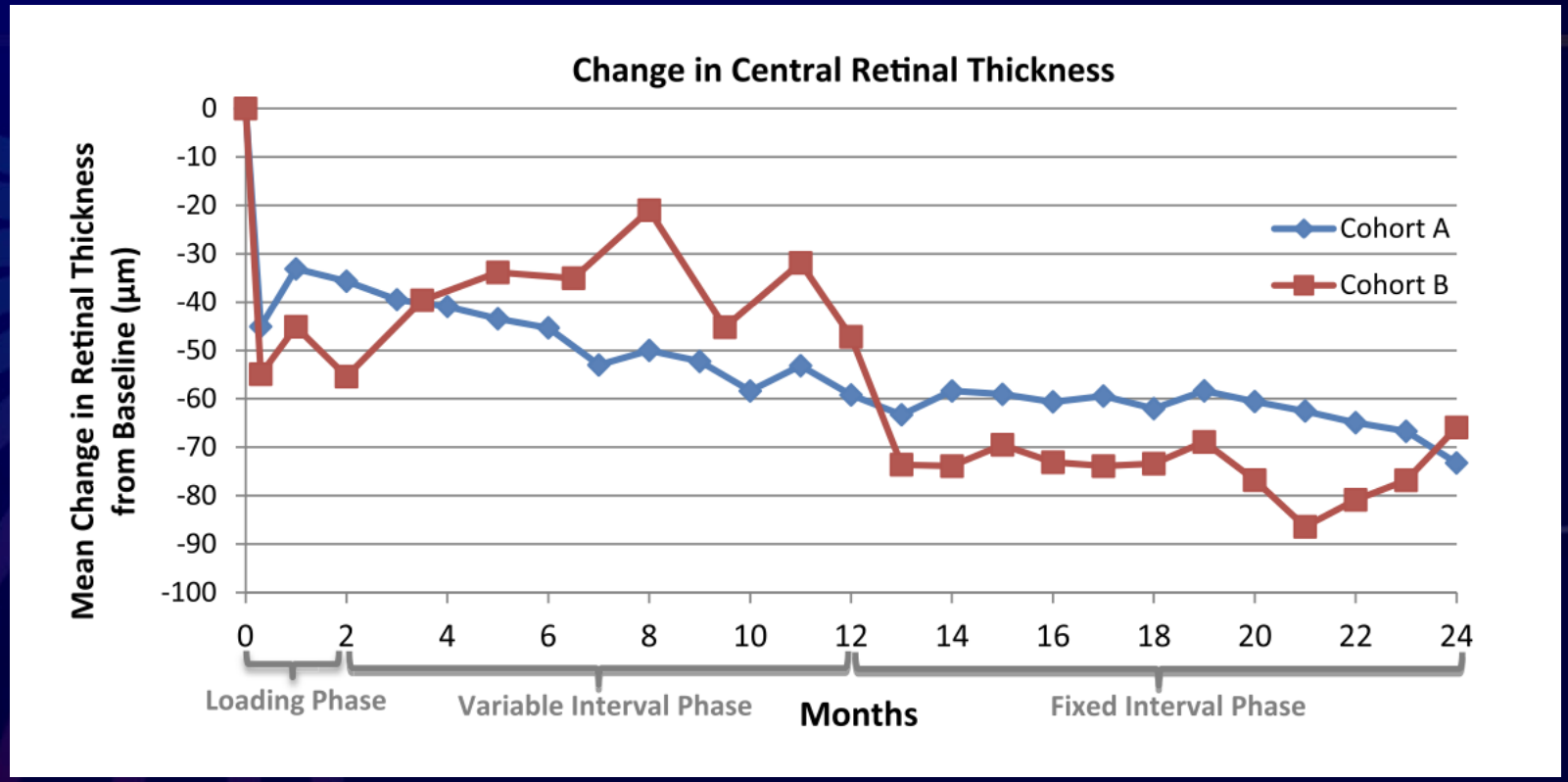
- **Persistent OCT or FFA activity on monthly therapy**
- **50 Patients followed for 24 months**
- **Patients randomized to q4w vs q6w f/u with "Capped" PRN therapy**

RECALCITRANT AMD

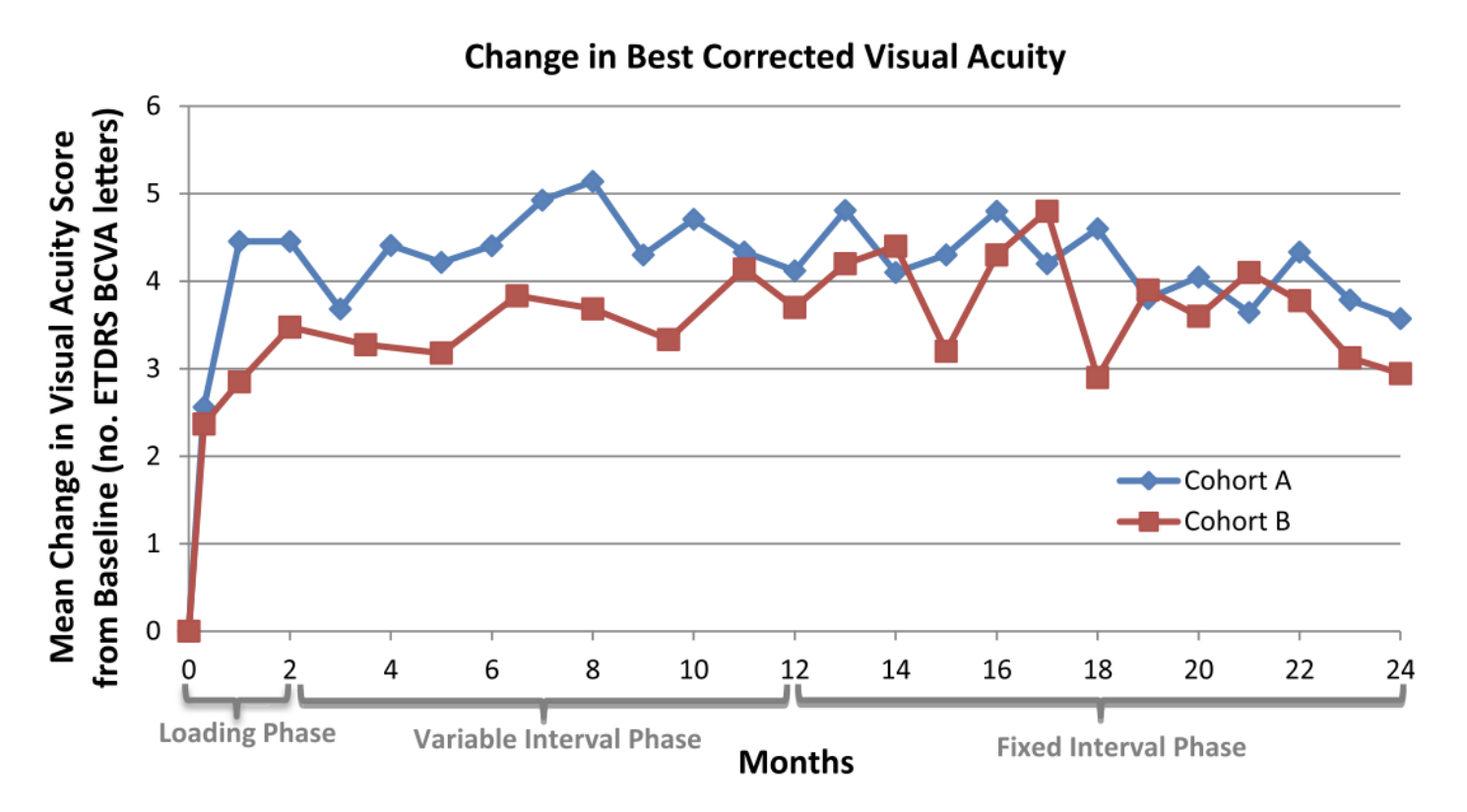
"Incomplete Responders"

- **Sex = 25 male, 25 female**
- **Mean age = 77.3**
- **Prior injections = 26.8 (mean)**
- **Prior injections past year = 10.5 (mean)**

SAVE 24 Month Anatomy



SAVE 24 Month Vision



Treatment Burden Reduction

- Q6 Week arm had loss of Anatomy and VA
- 11.2 / 12.0 PRN injections required year 2

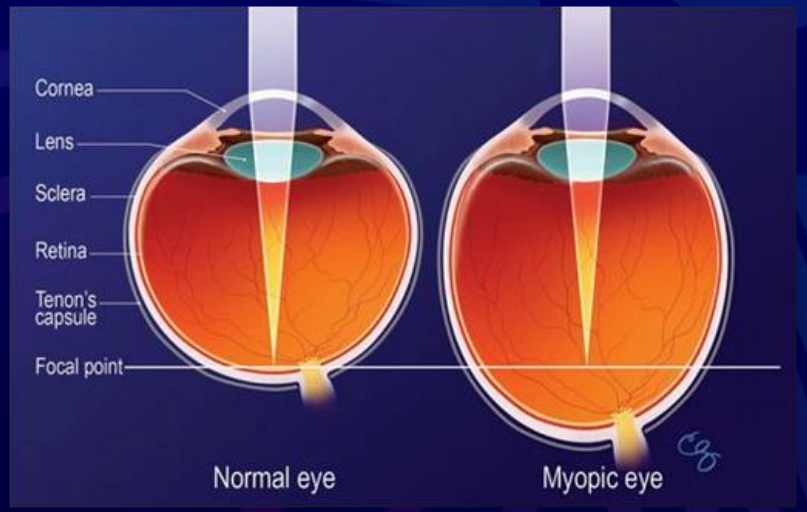
CONCLUSIONS

Will “Incomplete Responders” Respond with a higher dose?

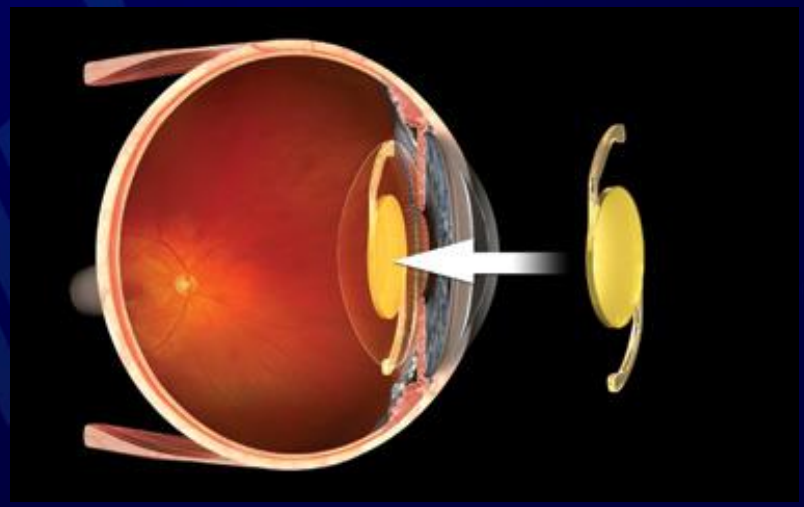
CONCLUSIONS

Can Treatment Frequency be Reduced?

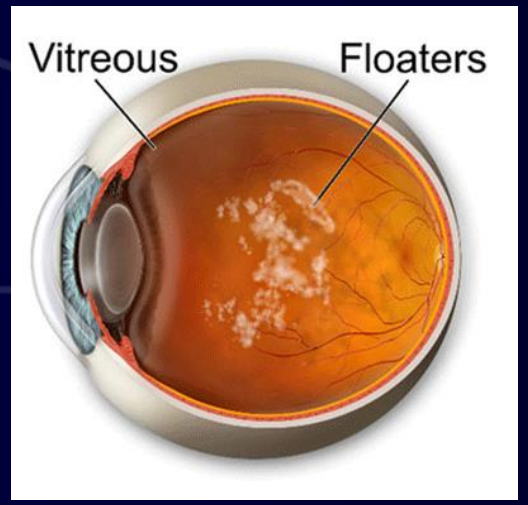
What Determines Drug Clearance?



Axial Eye Length



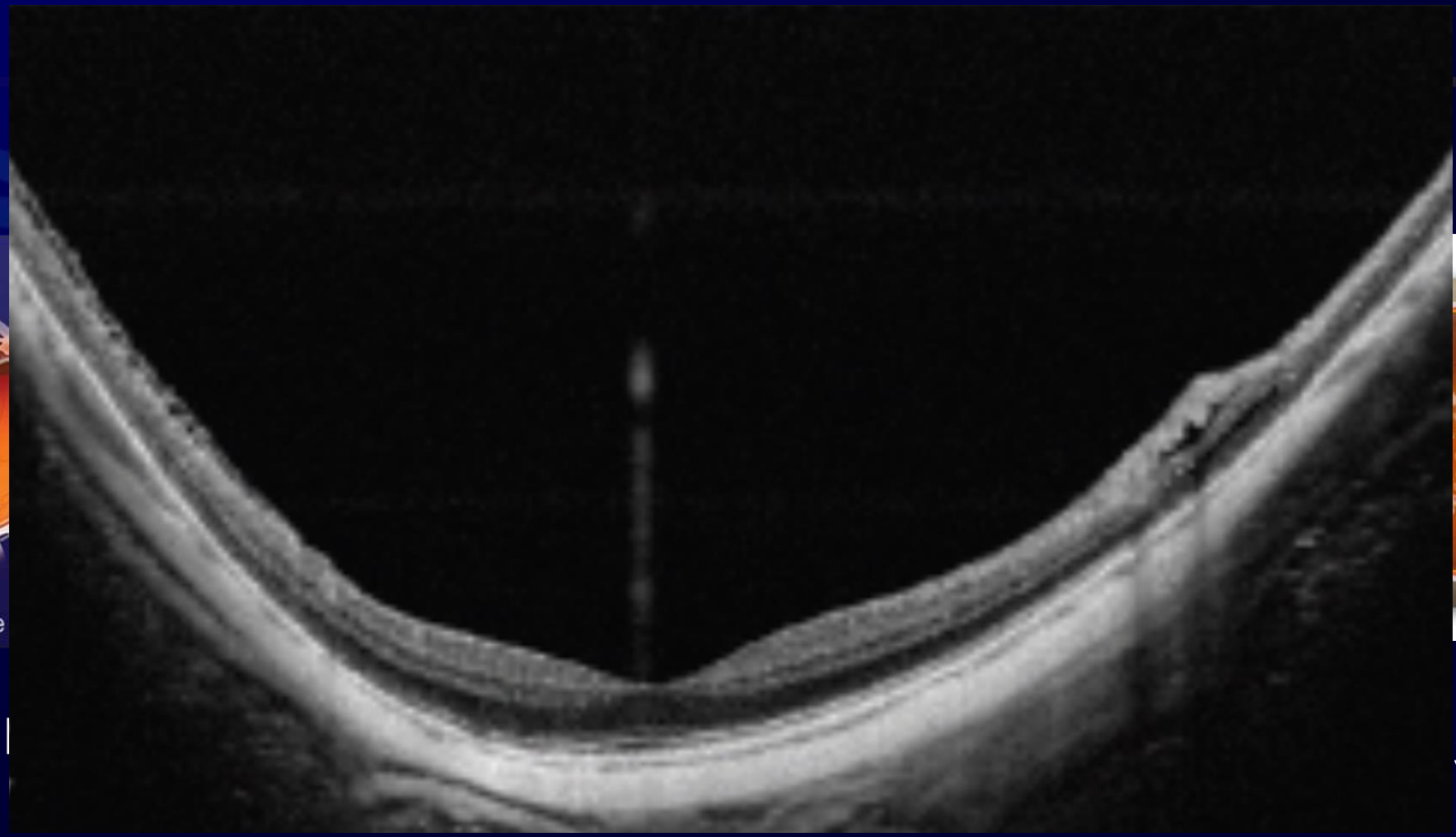
Psuedophakia



Vitreous Syneresis

What Determines Drug Clearance?

Axial



Syneresis

CLINICAL SCIENCE

SAVE (Super-dose Anti-VE Ranibizumab for Recalcitra Age-Related Macular Dege

Charles C. Wykoff, MD, PhD; David M. Brown, MD; Eric Croft, BA; Angeline Mariani, BA; Tien P. Wong, MD; SA

OBJECTIVES: To assess durability of visual and anatomic gains with 2.0 mg ranibizumab in recalcitrant neovascular age-related macular degeneration (AMD).

METHODS: Phase I-II trial of 88 patients with recalcitrant neovascular AMD treated as needed every 4 (cohort A) or 6 weeks (cohort B) following three monthly doses. ETDRS refraction and spectral-domain OCT–guided as-needed re-treatments.

RESULTS: Seventy-nine patients completed the 12-month endpoint and were given 11.6 (cohort A) and 8.6 (cohort B) mean treatments. Mean best corrected visual acuity gains of 4.1 letters following three monthly doses were sustained for 12 months for both cohorts. Anatomic improvements were sustained for 12 months for cohort A, but not for cohort B; cohort B demonstrated a gradual increase in mean central retinal thickness ($P = .03$).

CONCLUSION: Visual and anatomic gains achieved with 2.0 mg ranibizumab in recalcitrant neovascular AMD were sustained for 1 year with monthly treatment. In comparison, anatomic gains were diminished with less than monthly treatment.

[*Ophthalmic Surg Lasers Imaging Retina.* 2013;44:121-126]

From the Retina Consultants of Houston, the Methodist Hospital, Houston, Texas.

Originally submitted February 15, 2013. Accepted for publication February 20, 20
The authors received a research grant from Genentech. The funding organization

Address correspondence to Charles C. Wykoff, MD, PhD, 6560 Fannin Street, Suite
ccwmd@houstonretina.com.

doi: 10.3928/23258160-20130313-04

March/April 2013 • Vol. 44, No. 2

COMPARISON OF SPECTRAL-DOMAIN AND TIME-DOMAIN OPTICAL COHERENC TOMOGRAPHY IN THE DETECTION OF NEOVASCULAR AGE-RELATED MACULA DEGENERATION ACTIVITY

JAMES C. MAJOR, Jr., MD, PhD, CHARLES C. WYKOFF, MD, PhD, ANGELINE F. MARIANI, BA, ERIC CHEN, MD, DANIEL E. CROFT, BA, DAVID M. BROWN, MD

Purpose: To compare the sensitivity of commonly used time-domain (TD-OCT) and spectral-domain optical coherence tomography platforms and scanning modalities in the management of neovascular age-related macular degeneration in a population with a high prevalence of exudative disease activity.

Methods: Fifty consecutive patients within the prospective SAVE (Super-dose Anti-Vascular Endothelial growth factor) trial, which analyzed the utility of 2.0 mg intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration, were enrolled in a comparison trial of 3 different optical coherence tomography (OCT) platforms. Stratus TD-OCT radial scan (Carl Zeiss Meditec, Inc) was compared with 3 Heidelberg Spectralis Heidelberg Retinal Angiograph+OCT (Heidelberg Engineering) acquisition settings (radial, 7-line raster, volumetric) and 2 Cirrus high definition (HD)-OCT (Carl Zeiss Meditec, Inc) acquisition settings (5-line raster, volumetric).

Results: Using every imaging platform and acquisition setting, evidence of exudative disease activity was positively identified in 168 of 191 patient visits (87.9%). Intraretinal cysts were identified in 88 of 191 visits (46.5%), and subretinal fluid was identified in 116 of 191 visits (60.7%). Of these positive visits, the Stratus TD-OCT radial scanning technology demonstrated a significantly lower rate of detection (71.8%) when compared with the Spectralis HRA+OCT spectral domain scanning modalities (radial 87.1%, $P < 0.001$; 7-line raster 92.0%, $P < 0.001$; volumetric 94.5%, $P < 0.001$) or the Cirrus HD-OCT spectral domain scanning modalities (5-line raster 81.8%, $P = 0.001$; volumetric 92.0%, $P < 0.001$). Intraretinal cysts and subretinal fluid were identified in 83 visits (43.5%) and 116 visits (60.7%), respectively, with 36 eyes (18.8%) having fluid in both locations. No individual imaging modality demonstrated a diagnostic advantage for detecting subretinal fluid versus intraretinal cysts (e.g., Cirrus volume detected 86.7% of intraretinal cysts and 88.8% of subretinal fluid, $P = 0.35$).

Conclusions: In this neovascular age-related macular degeneration patient population, spectral-domain ocular coherence tomography was a superior diagnostic tool when compared with TD-OCT, with each spectral domain platform and acquisition setting identifying significantly more exudative disease activity. The two spectral domain platforms (Cirrus and Spectralis) were not directly compared because identical image acquisition parameters were not used. No individual imaging modality demonstrated a diagnostic advantage for detecting subretinal fluid versus intraretinal cysts.

RETINA 0:1–7, 2013

Age-related macular degeneration (AMD) is the leading cause of severe vision loss and blindness in elderly patients in the United States.[1] The last two decades have witnessed incredible advances in our understanding of and ability to treat neovascular AMD. These advances have stemmed from major innovations: the invention and clinical application of optical coherence tomography (OCT) and development of anti–vascular endothelial growth factor pharmaceuticals.

1

Two Year SAVE Outcomes: 2.0 mg Ranibizumab for Recalcitrant Neovascular AMD

The Super-dose Anti-VEGF (SAVE) trial assessed the et 2.0 mg ranibizumab (0.05 ml), a 4-fold higher dose than t dose approved by the US Food and Drug Administratio management of recalcitrant neovascular age-related degeneration (AMD) in 88 patients.[1,2] Primary outcome the 3-month, fixed-interval dosing period were rep *Ophthalmology*, and in this report we offer 2-year follow

Recalcitrant fluid despite monthly or near-monthly anti endothelial growth factor (VEGF) therapy is a commo scenario in the management of neovascular AMD. Inde than one half of patients treated with anti-VEGF prospective neovascular AMD trials manifest residual in subretinal, or subretinal pigment epithelium fluid despite anti-VEGF dosing.[3] This persistent macular edema lik maximal visual recovery in these challenging cases.[4]

Higher dose of existing anti-VEGF agents, as prospectively in SAVE, is a potential route for manag incomplete responders. At study entry, patients had re average of 24 previous intravitreal injections of anti-VEG including monthly dosing in the year before enrollment (n between injections of 31 days). After 3 monthly 2.0 m patients were evaluated every 4 weeks (cohort A) or every (cohort B) and retreated as needed (PRN) for any in subretinal, or subretinal pigment epithelium fluid de spectral domain optical coherence tomography (SD OCT

After 3 monthly treatments, mean Early Treatment Retinopathy Study (ETDRS) best-corrected visual acuity improved +3.3 letters ($P = 0.001$) and mean SD OCT cent subfield thickness (CST) improved −33.1 μm ($P = 0.01$ gains were maintained through month 12,[2] with cohorts gaining a mean of +4.1 and +3.7 ETDRS letters, respecti receiving a mean of 11.6 (cohort A) and 8.6 (cohort B) in Anatomically, monthly PRN retreatment led to continu detergescence through year 1, whereas every 6 we

Super-dose Anti-VEGF (SAVE) Trial: 2.0 mg Intravitreal Ranibizumab for Recalcitrant Neovascular Macular Degeneration–Primary End Point

David M. Brown, MD, Eric Chen, MD, Angeline Mariani, BA, James C. Major, Jr., MD, PhD, for the SAVE Study Group

Purpose: To determine whether a higher dose of intravitreal ranibizumab could improve the anatomy and best-corrected visual acuity (BCVA) in eyes with neovascular age-related macular degeneration (AMD) with persistent disease activity despite monthly intravitreal anti-vascular endothelial growth factor (VEGF) injections.
Design: Phase I to II multicenter, open-label, controlled clinical trial.
Participants: Eighty-seven patients with recalcitrant neovascular AMD, defined as having leakage on fundus fluorescein angiography or spectral domain optical coherence tomography (SD-OCT) despite monthly anti-VEGF injections.
Methods: Patients were treated with 2.0-mg ranibizumab injections monthly for 3 doses and monitored with Early Treatment Diabetic Retinopathy Study (ETDRS) 4-m refractions, clinical examinations, and SD-OCT.
Main Outcome Measures: The mean change in baseline visual acuity (VA), the percentage of patients who experienced a loss or gain of 15 or more letters in ETDRS BCVA, the mean change in central retinal thickness, and the incidence of adverse events.
Results: Eighty-seven patients with an average of 24 injections before enrollment and a mean of 10.4 injections in the preceding 12 months had a mean refracted VA of 69.2 ETDRS letters (20/41 Snellen) and a mean central subfield of 422 μm at baseline. Mean VA gain over baseline was +2.5 letters at day 7 (n = 82), +3.7 letters at month 1 (n = 87), +3.9 letters at month 2 (n = 87), and +3.3 letters at month 3 (20/36 Snellen; $P = 0.001$; n = 86). Anatomic outcomes showed a mean optical coherence tomography central subfield thickness improvement from baseline of −48.4 μm at day 7 (n = 84), −37.5 μm at month 1 (n = 87), −42.4 μm at month 2 (n = 85), and −33.1 μm at month 3 ($P = 0.01$; n = 86).
Conclusions: Intravitreal injections of 2.0 mg ranibizumab led to statistically significant VA gains and anatomic improvement in patients with persistent intraretinal, subretinal, or subretinal pigment epithelial fluid during a previous regimen of chronic monthly 0.5-mg ranibizumab injections.
Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2013;120:349–354 © 2013 by the American Academy of Ophthalmology.*

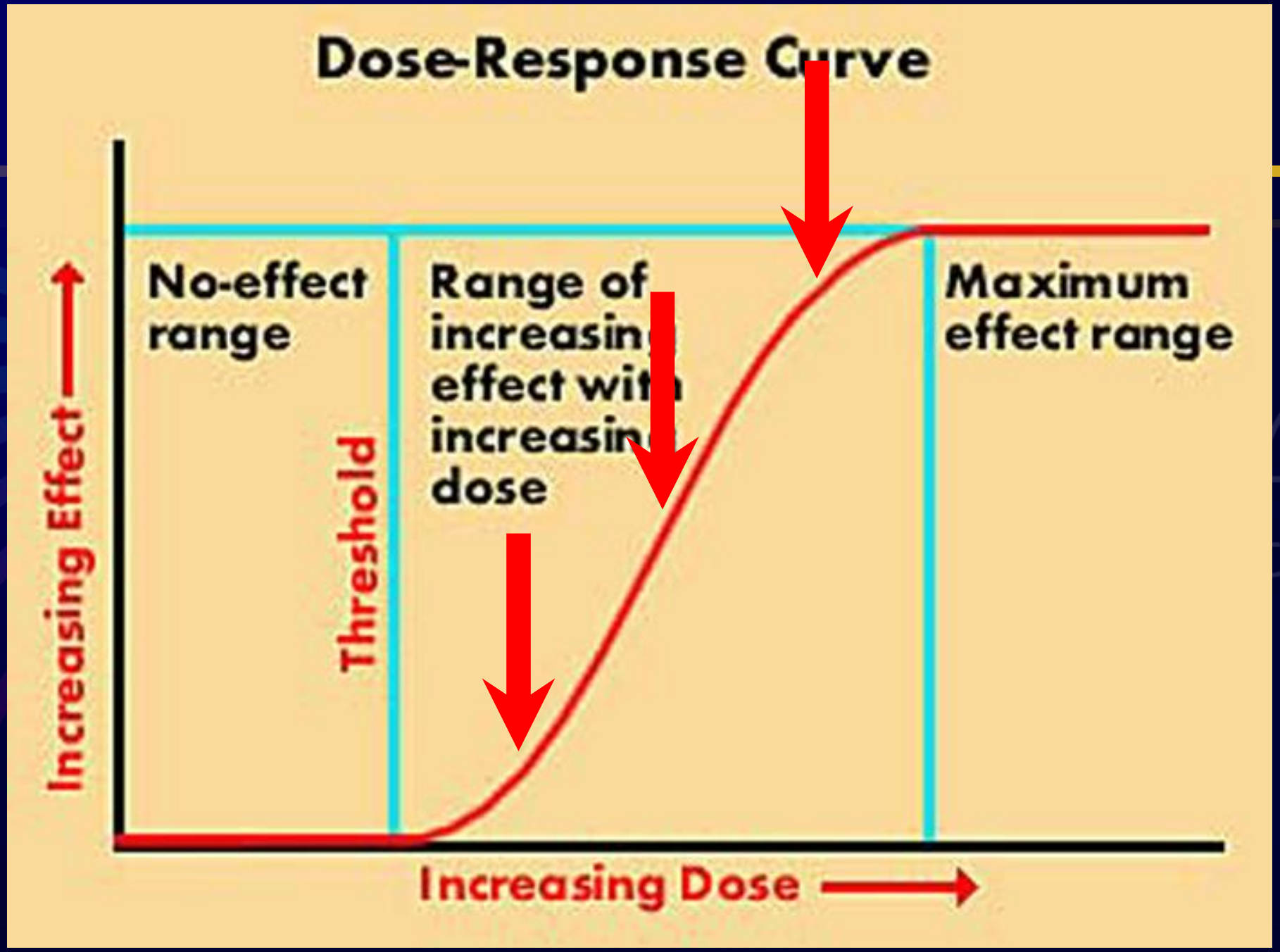
The standard of care treatment of neovascular age-related macular degeneration (AMD) is based on anti-vascular endothelial growth factor (VEGF) therapies with intravitreal ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA), bevacizumab (Avastin, Genentech, Inc.), or aflibercept (Eylea, Regeneron, Tarrytown, NY).[1,2] Despite monthly treatment, many patients continue to have persistent intraretinal, subretinal, or subretinal pigment epithelium fluid. The Comparison of Age-Related Treatments Trial (CATT) demonstrated persistent fluid with time domain optical coherence tomography (OCT) in 53.2% and 70.9% of patients treated monthly with standard dose ranibizumab and bevacizumab, respectively.[3] Because there are no other alternatives to treat these patients, there exists a significant unmet need for treatment that has increased potency, longer duration of action, or a complementary mechanism of action to eliminate fluid in these recalcitrant cases.

The pivotal phase III Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial seemed to demonstrate a dose-response curve with 0.5 mg ranibizumab being more efficacious in functional and anatomic outcomes compared with 0.3 mg ranibizumab. On the basis of the dose-response findings and unmet medical need, we hypothesize that a higher dose of ranibizumab might improve efficacy, leading to better outcomes for patients who are "incomplete responders" to conventional monthly therapy.

Materials and Methods

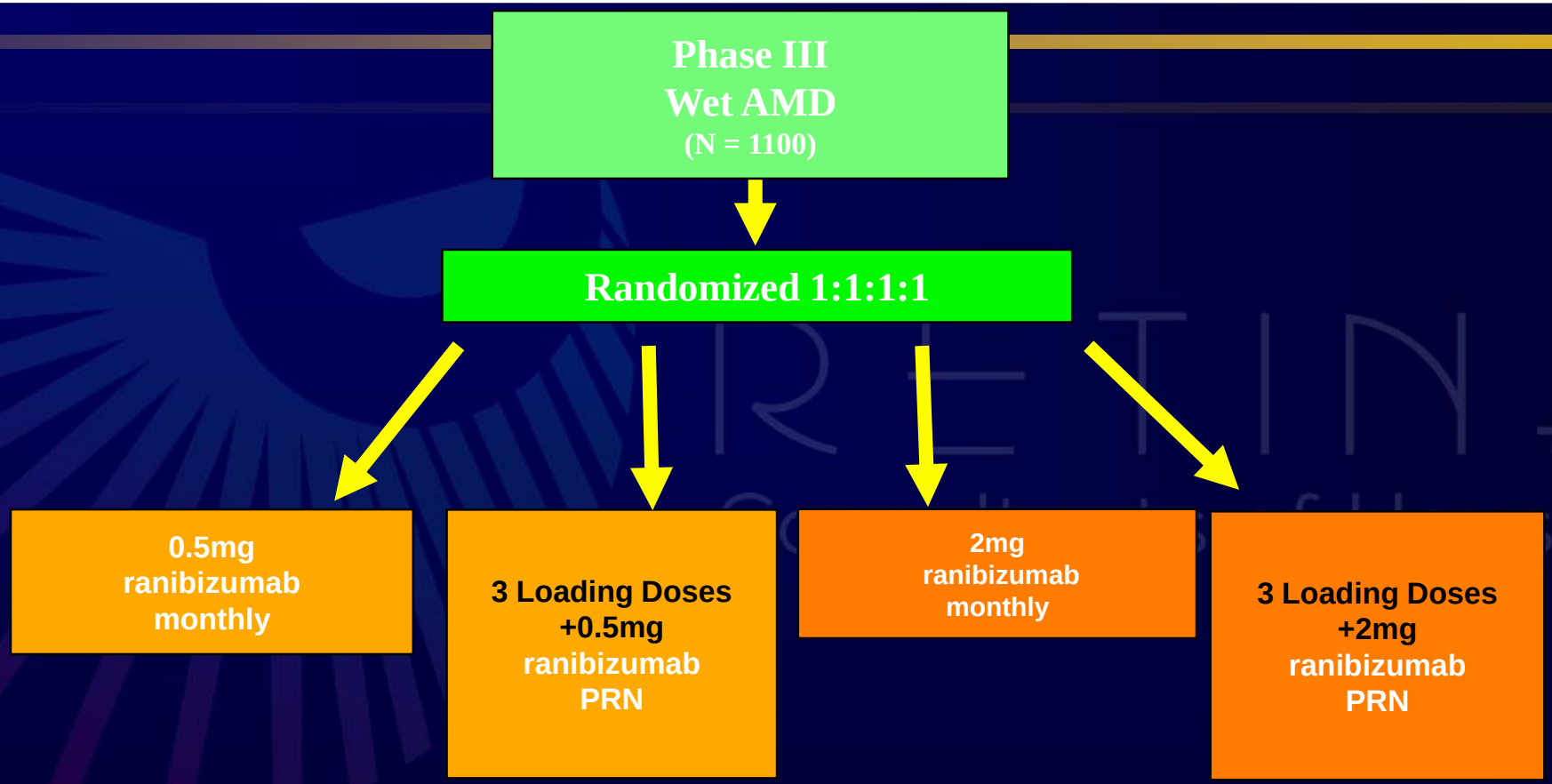
This study was a phase I to II multicenter, open-label, randomized, controlled clinical trial (Food and Drug Administration Investiga-

ISSN 0161-6420/13/$–see front matter
http://dx.doi.org/10.1016/j.ophtha.2012.08.008

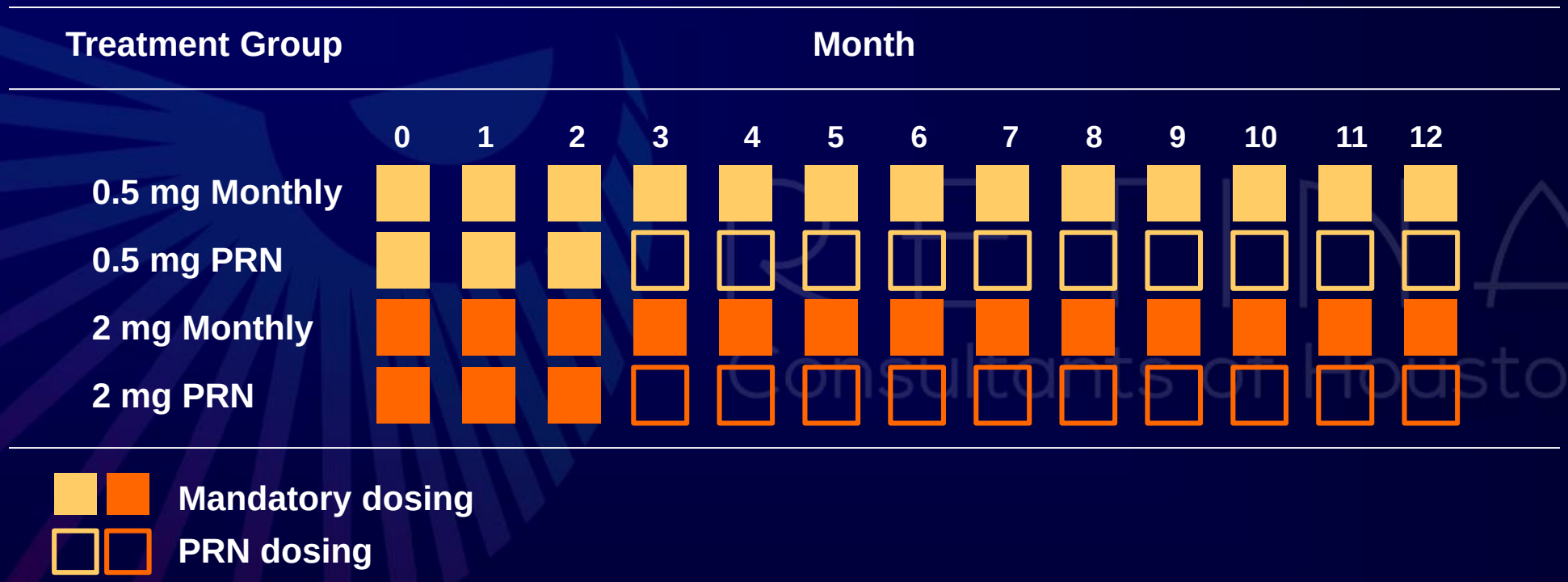

Dose-Response Curve
No-effect range
Range of increasing effect with increasing dose
Maximum effect range
Threshold
Increasing Effect
Increasing Dose

HARBOR Study Design

HARBOR will assess 2mg vs 0.5mg monthly and alternate dosing regimens



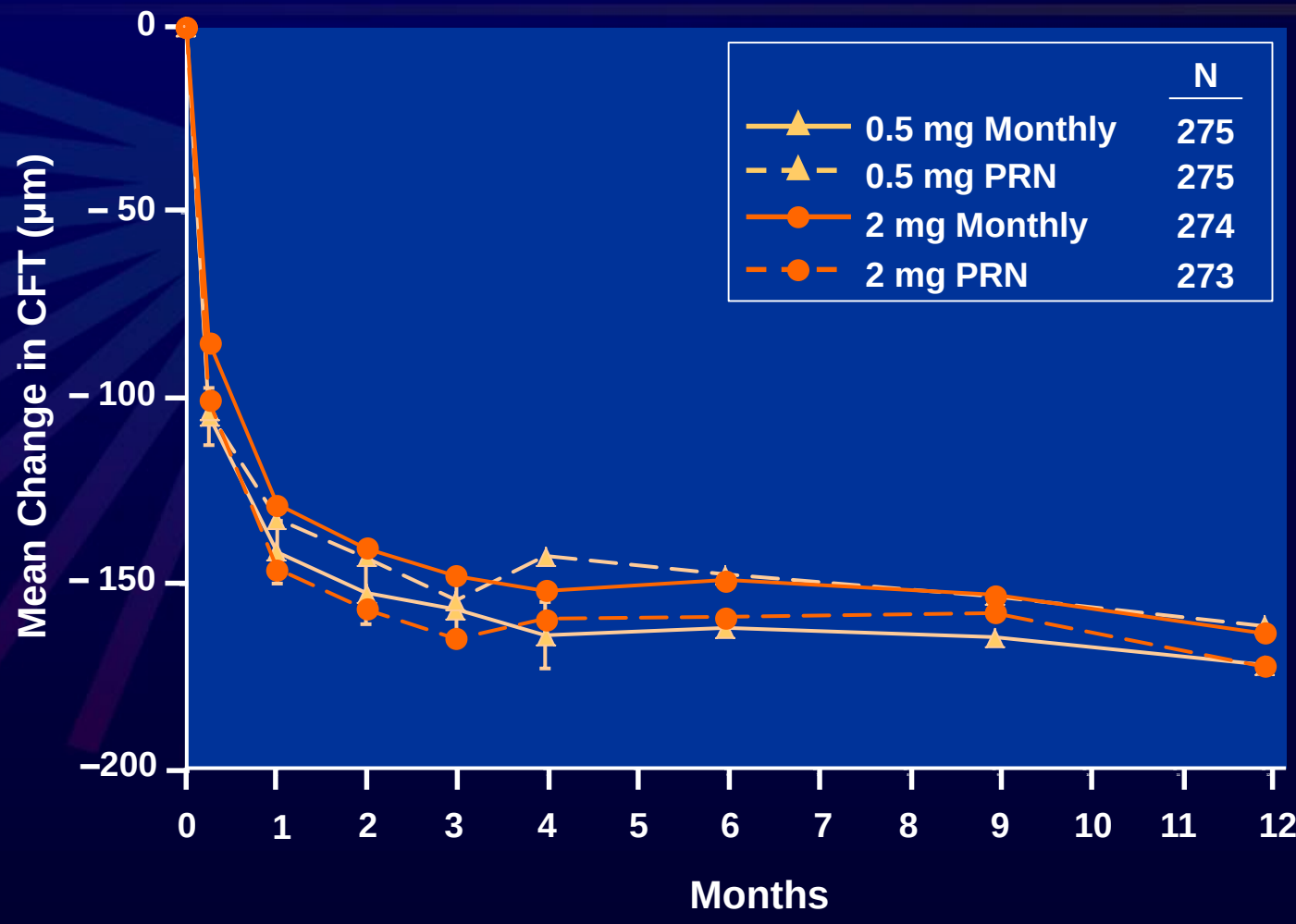
HARBOR Treatment Schema*



Starting at Month 3, PRN groups were evaluated for retreatment monthly and treated if there was a ≥5 letters decrease from previous visit OR any evidence of disease activity on SD-OCT

* All groups continued same treatment schedule through Month 24.

Mean Change from Baseline in CFT by SD-O to Month 12



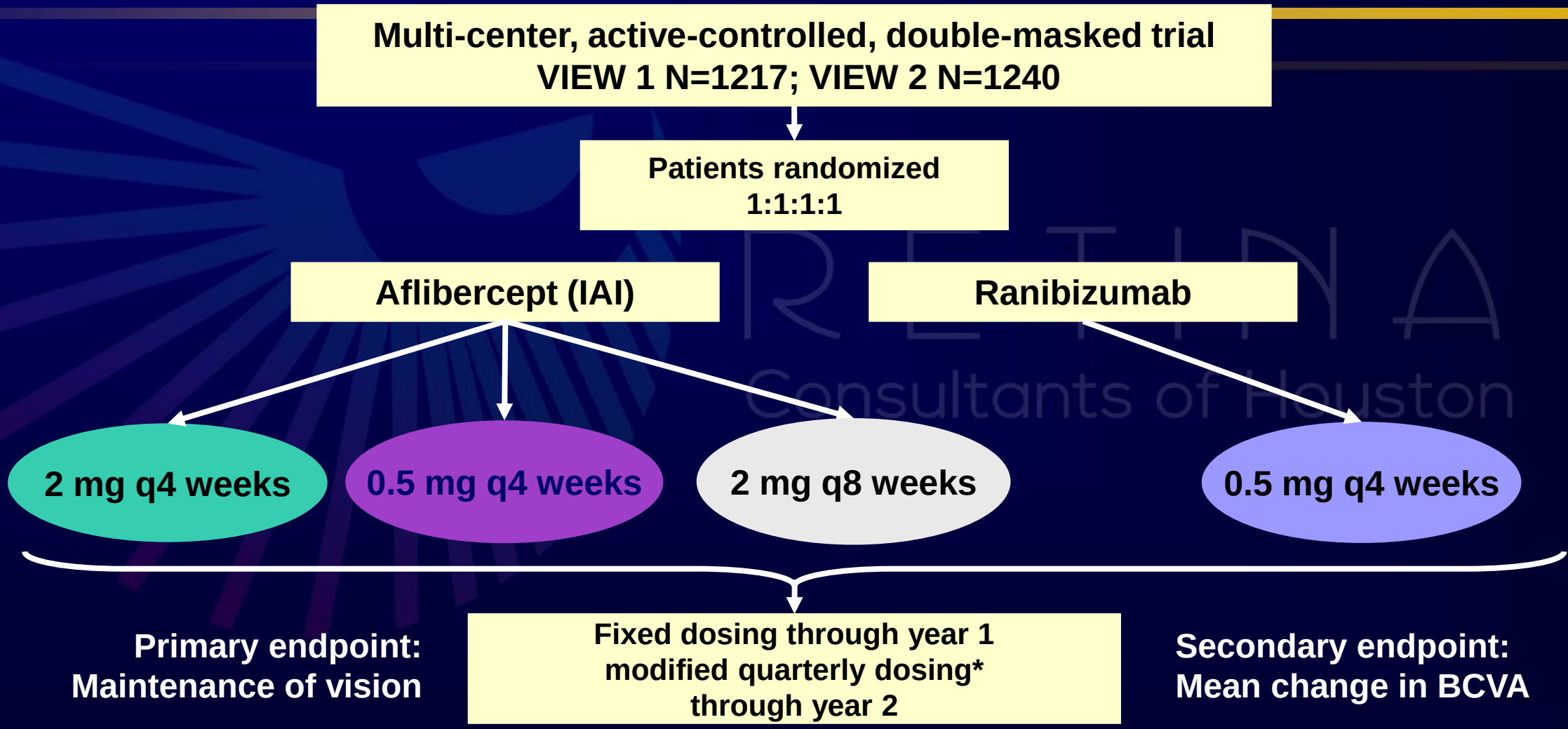
0.5 mg PRN –162.1 µm
2 mg Monthly –164.3 µm
0.5 mg Monthly –172.6 µm
2 mg PRN –173.3 µm

The last-observation-carried-forward (LOCF) method was used to impute missing

High-Dose Aflibercept

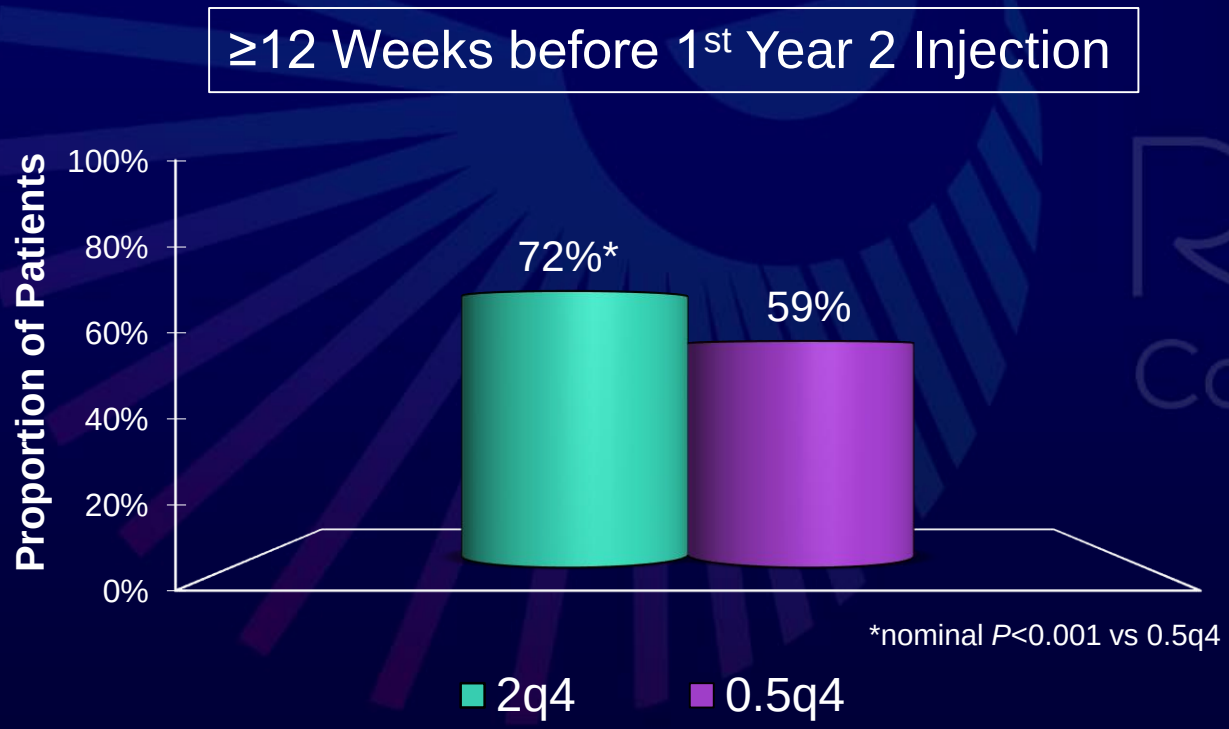
Rationale and Clinical Studies

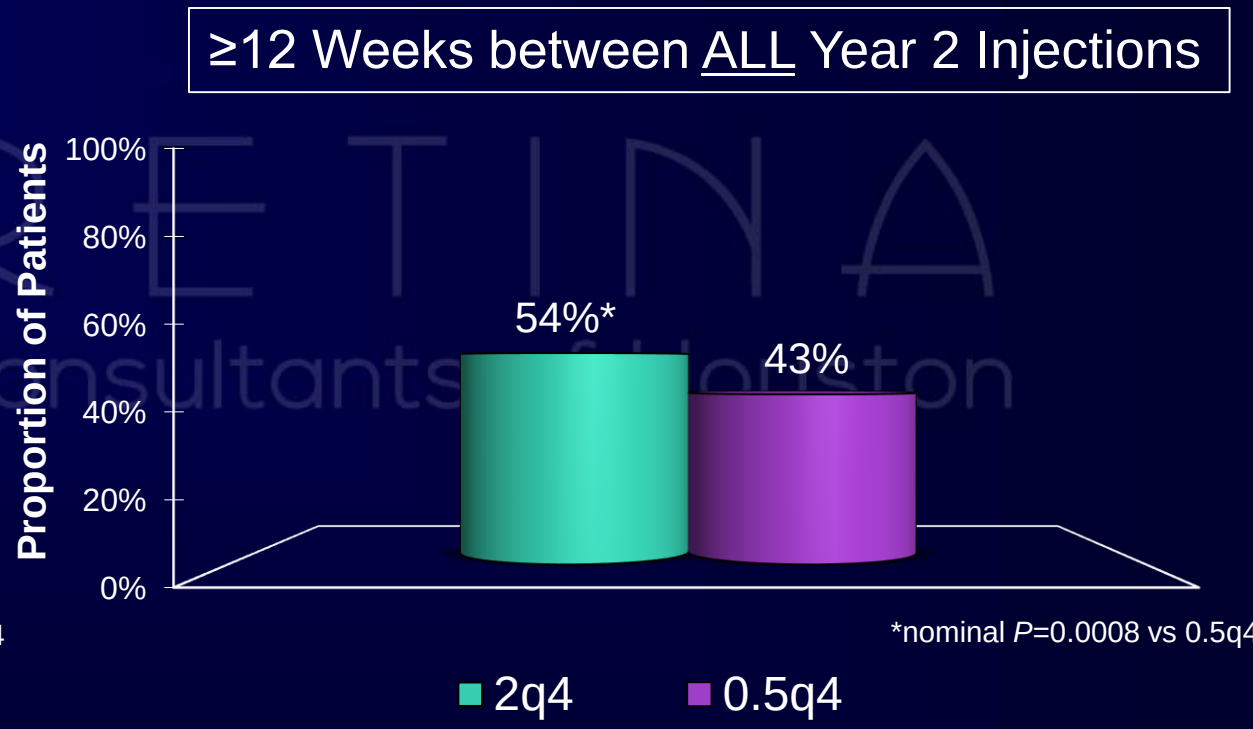
VIEW 1 and 2 (Phase 3 AMD) Study Designs



*During year 2, patients were evaluated every 4 weeks, and received doses at least every 12 weeks. Dosing could be as frequent as every 4 weeks.

VIEW: A 4X Increase in Aflibercept Dose Results in Significantly More Patients Achieving ≥12 Week Dosing

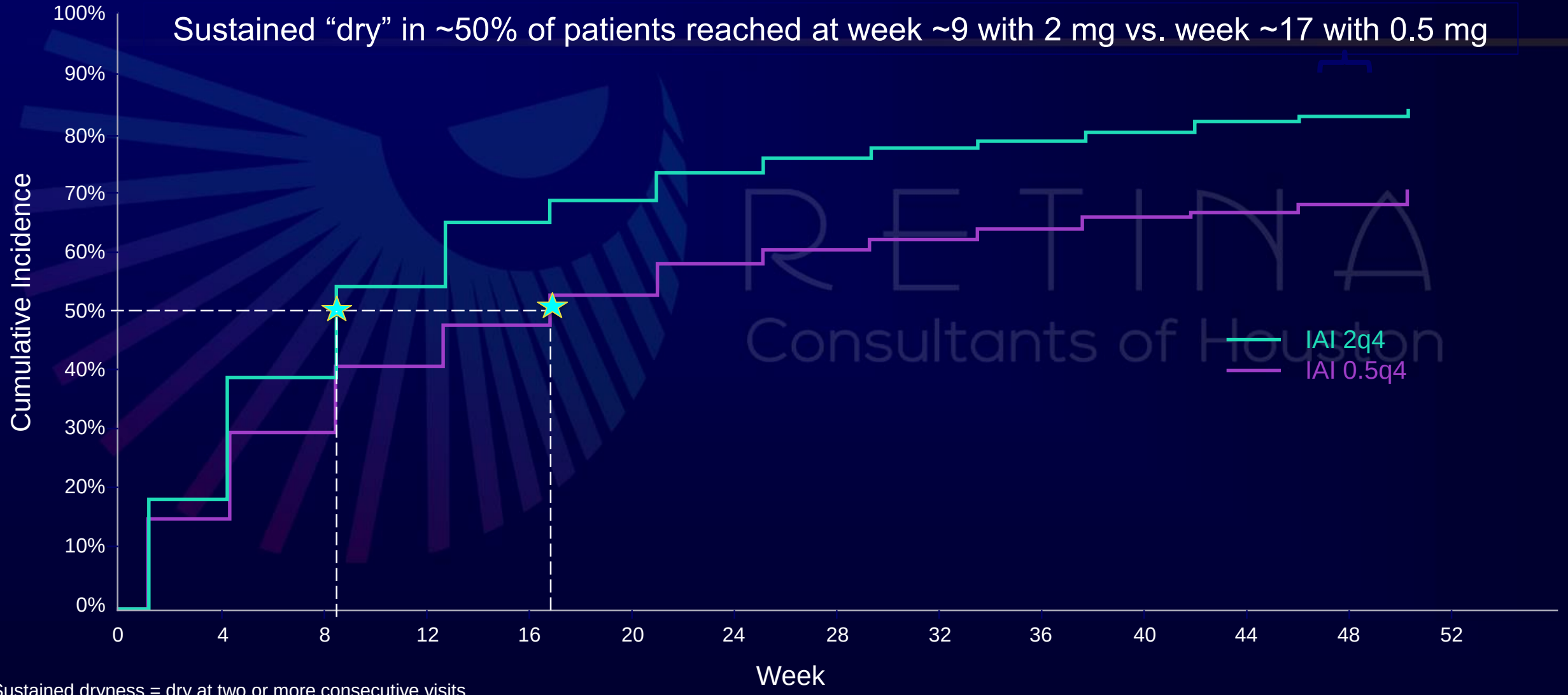




Observed; Full analysis set, 2Q4 n=613, 0.5Q4 n=597

Cumulative Incidence of Sustained* Dryness through Week 52

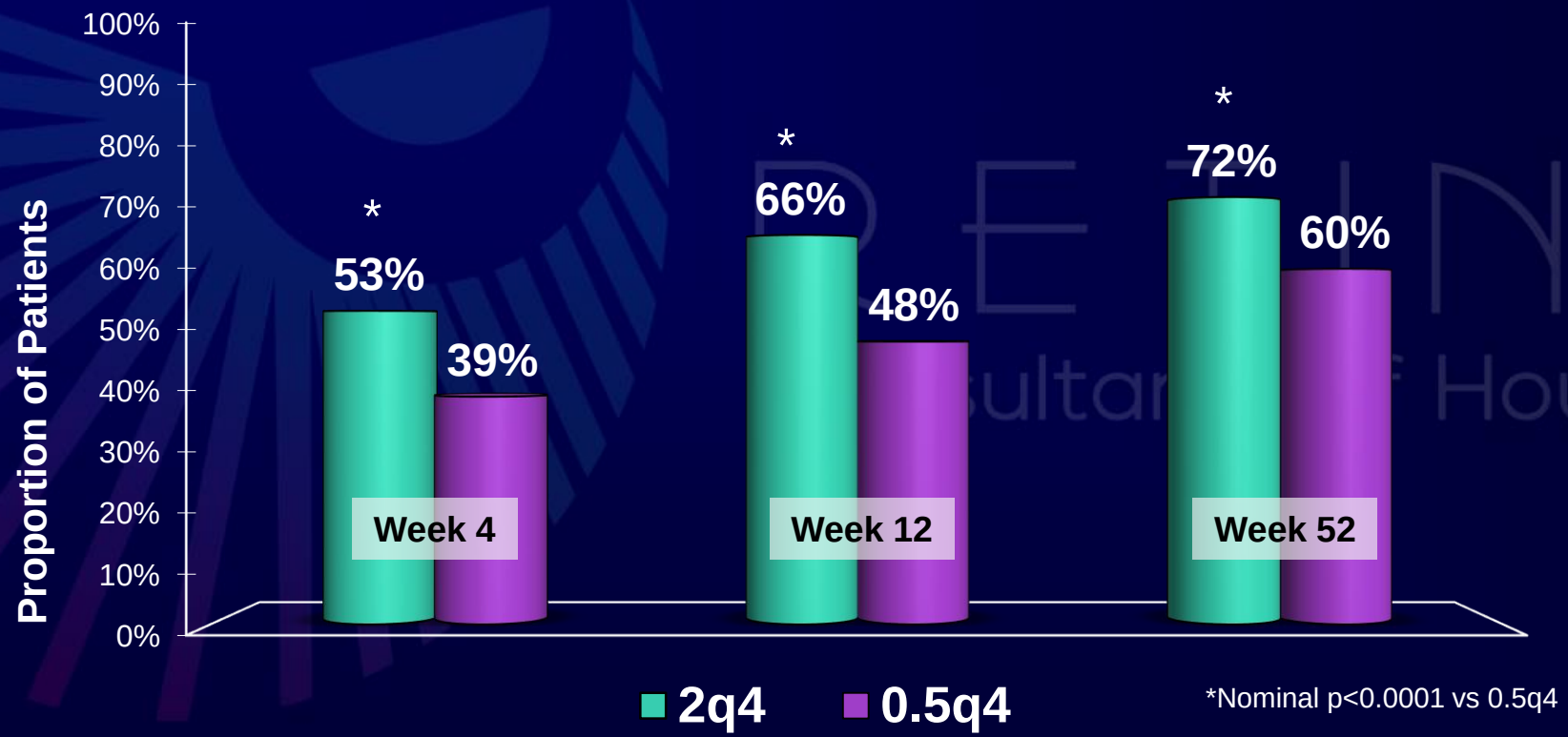
Sustained “dry” in ~50% of patients reached at week ~9 with 2 mg vs. week ~17 with 0.5 mg



*Sustained dryness = dry at two or more consecutive visits

“Dry” defined by masked reading center as absence of both cystic retinal edema and subretinal fluid **on Time Domain-OCT**

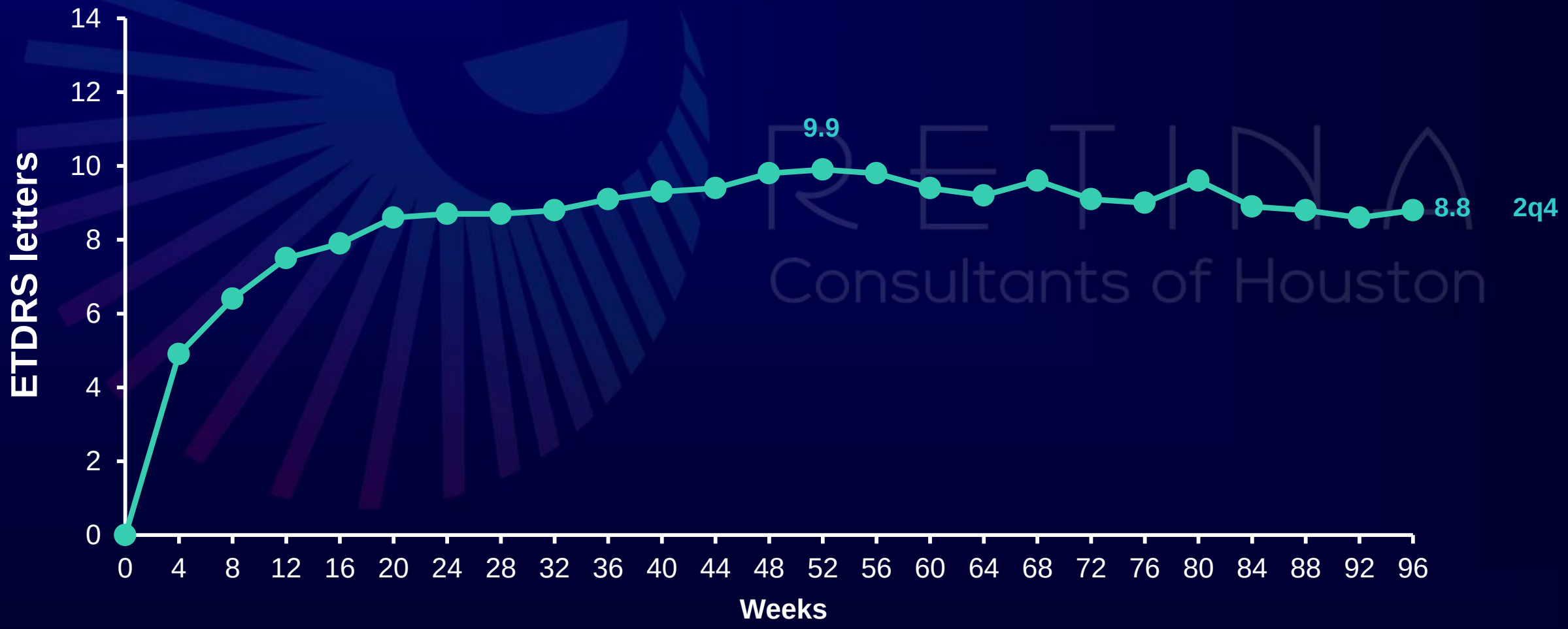
2 mg vs. 0.5 mg Aflibercept: Proportion of Patients without Fluid in the Center Subfield



^ "Without Fluid" defined by masked reading center as absence of both cystic retinal edema and subretinal fluid on **Time Domain-OCT**.

Observed; Full analysis set, 2Q4 n=613, 0.5Q4 n=597

VIEW: Visual Acuity for Patients Dosed ≥12 Weeks in Year 2 with 2 mg

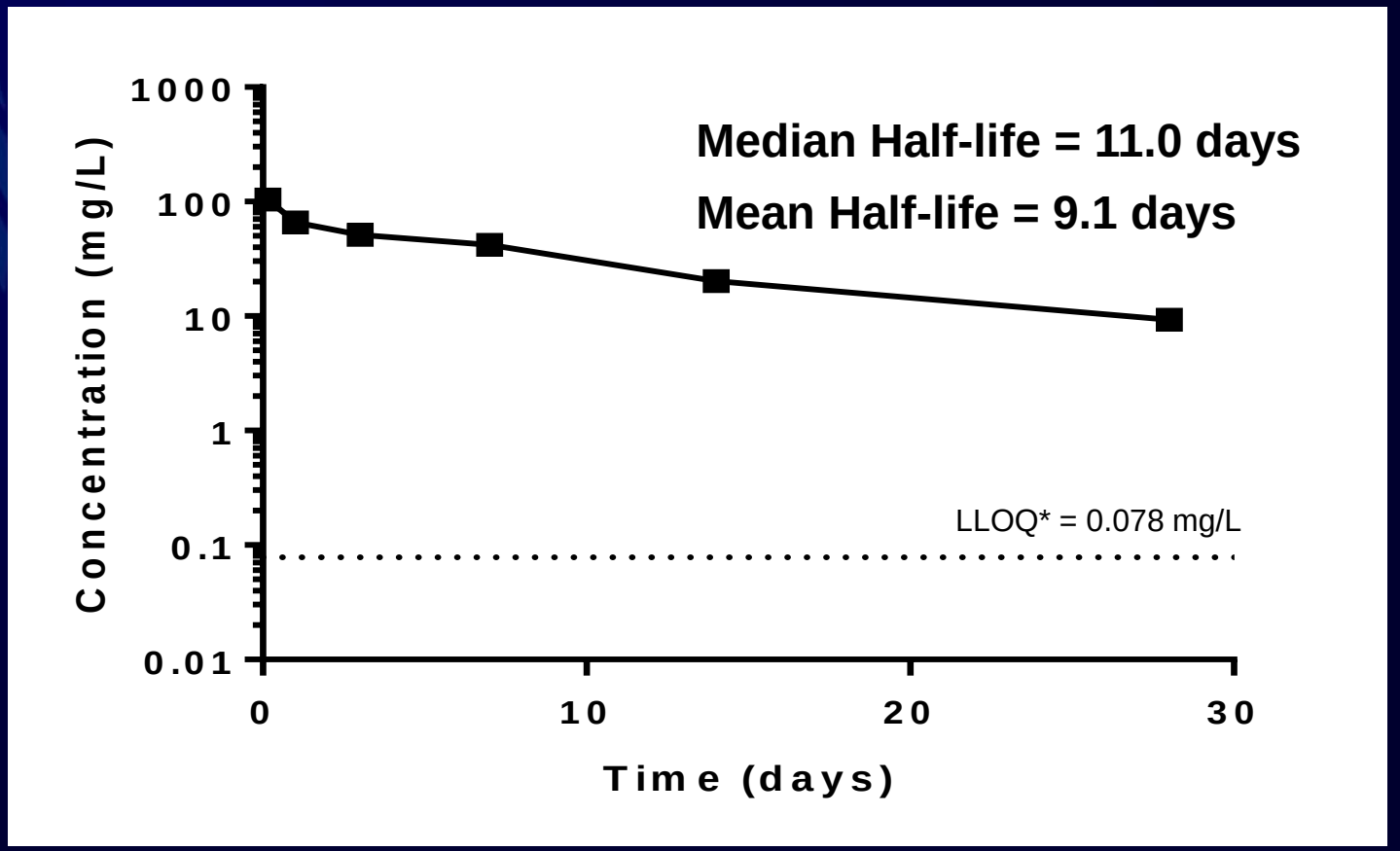


FAS, LOCF Pts Completing 2nd Year; 2q4 n=529;

Aqueous Humor Concentrations of Free Aflibercept Over Time

- Five subjects with new-onset nAMD received intravitreal 2mg aflibercept at Day 0
- Sampling of aqueous at 4 h post-dose and Days 1,3,7,14, and 28

Median Half-life of Free Aflibercept in Aqueous

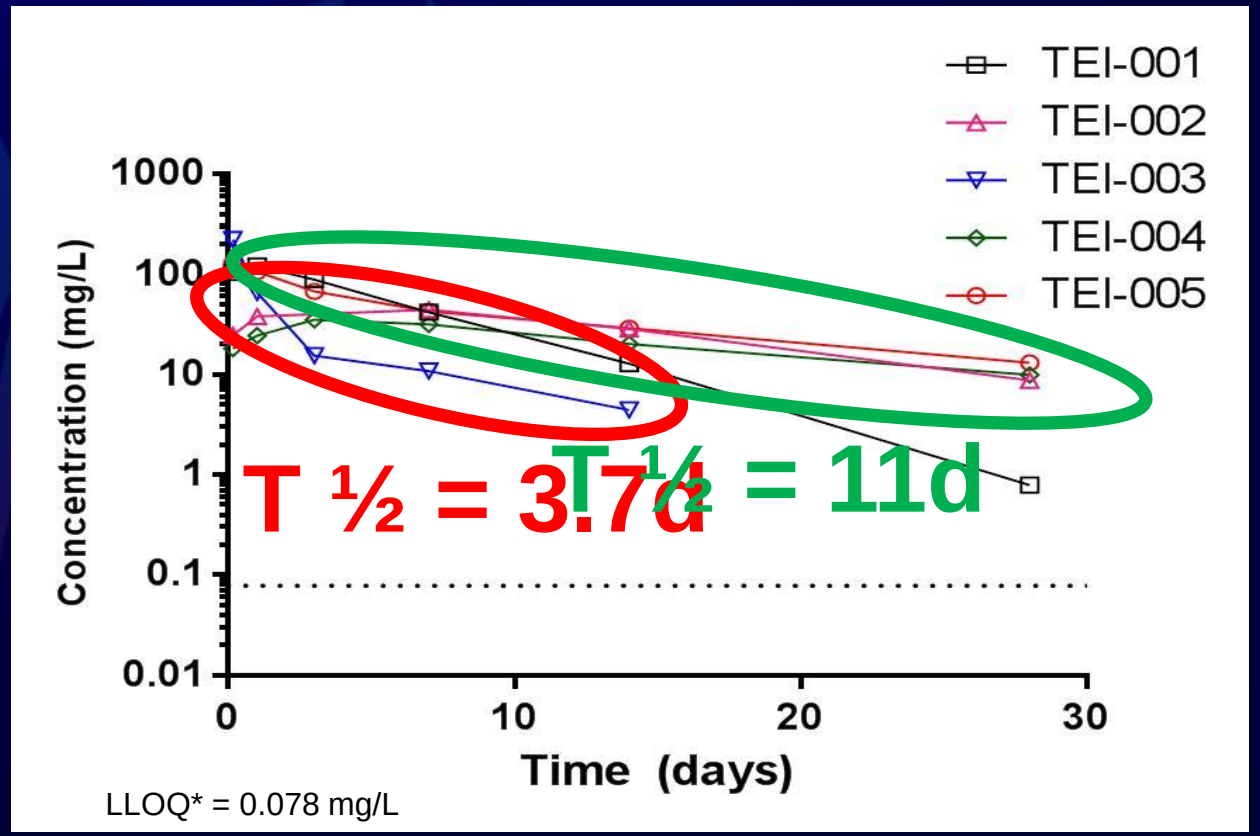


*LLOQ: lower limit of quantification

Do, D. Retina May 2019

Aqueous and Plasma Concentrations Vary Among Patients

Aqueous- Free Aflibercept Concentrations by Patient



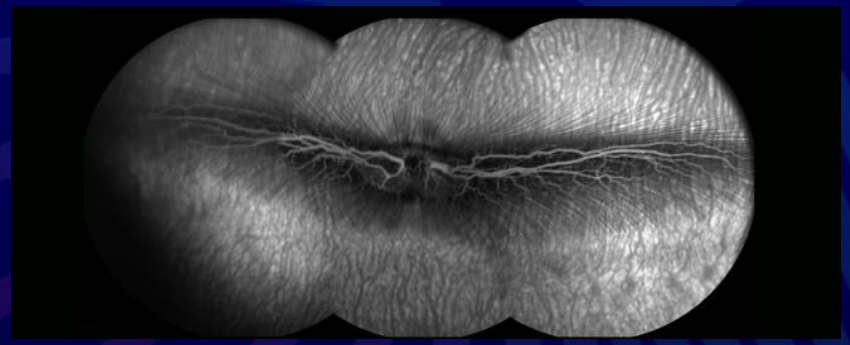
*LLOQ: Lower Limit Of Quantification

Do, D. Retina 00:1-5, 2019

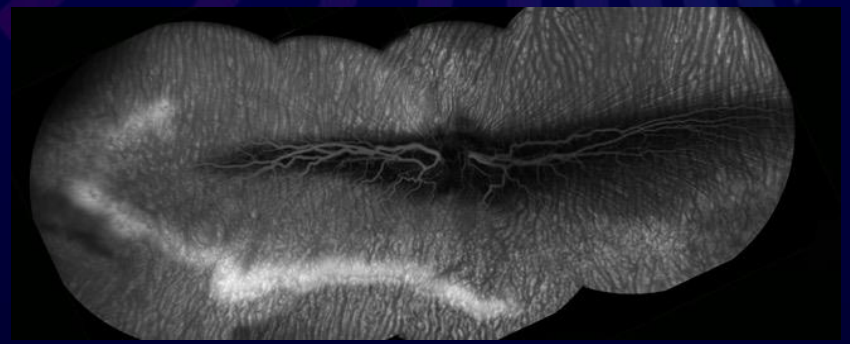
Preclinical Pharmacology Data of 8 mg Aflibercept Dose

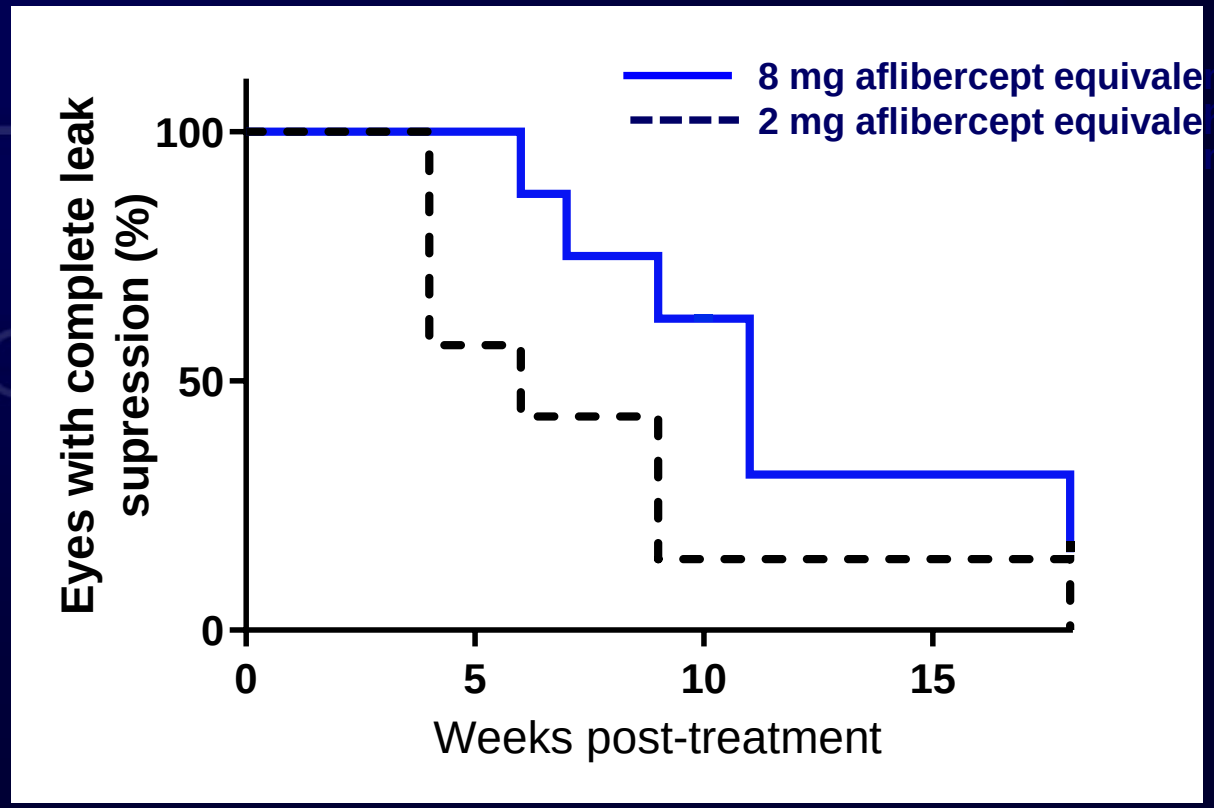
- *In the DL-α-aminoadipic acid (DL-AAA) rabbit model of chronic retinal vascular leak, the 8 mg equivalent dose of aflibercept increased duration of efficacy*

Normal rabbit fundus (FA)



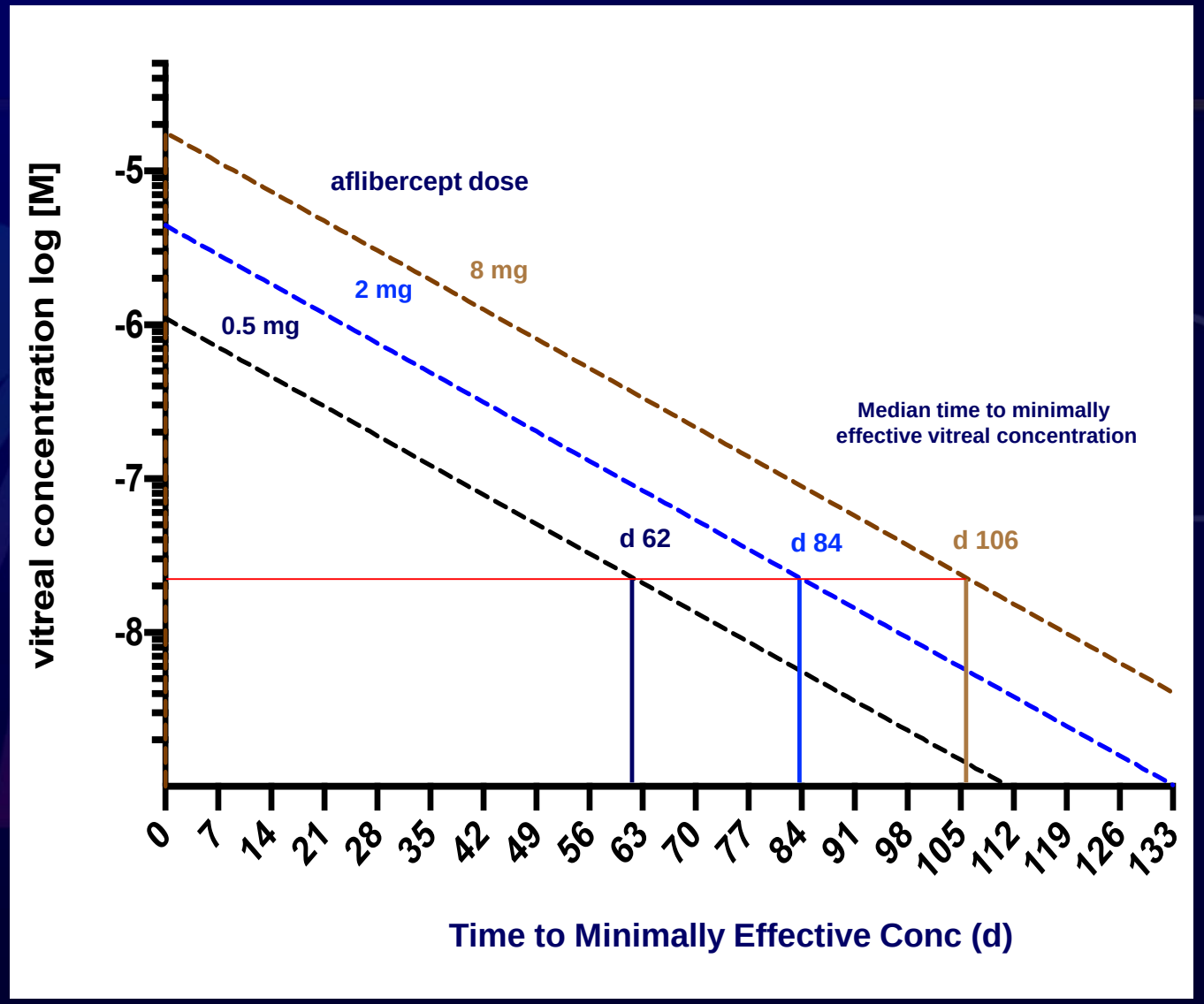
8 weeks post DL-AAA (FA)





Regeneron data on file

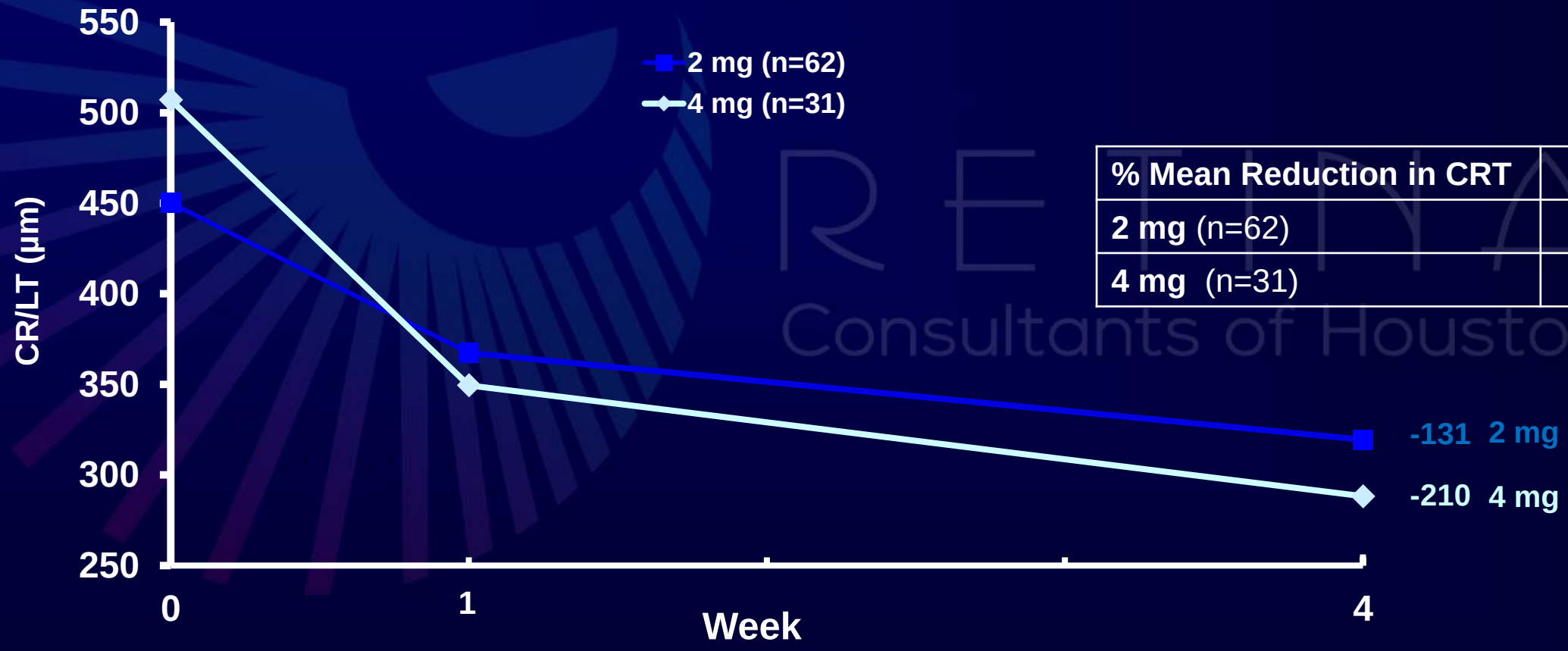
Duration of Aflibercept Activity is Directly Related to Dose



* Assumes 11 d median half-life

Do, D. Retina May 2019

CLEAR-IT 2 (Phase 2 AMD): Greater Reduction in CR/LT Through Week 4 After Single Dose of 4 mg



% Mean Reduction in CRT	Week 4
2 mg (n=62)	-29%
4 mg (n=31)	-42%

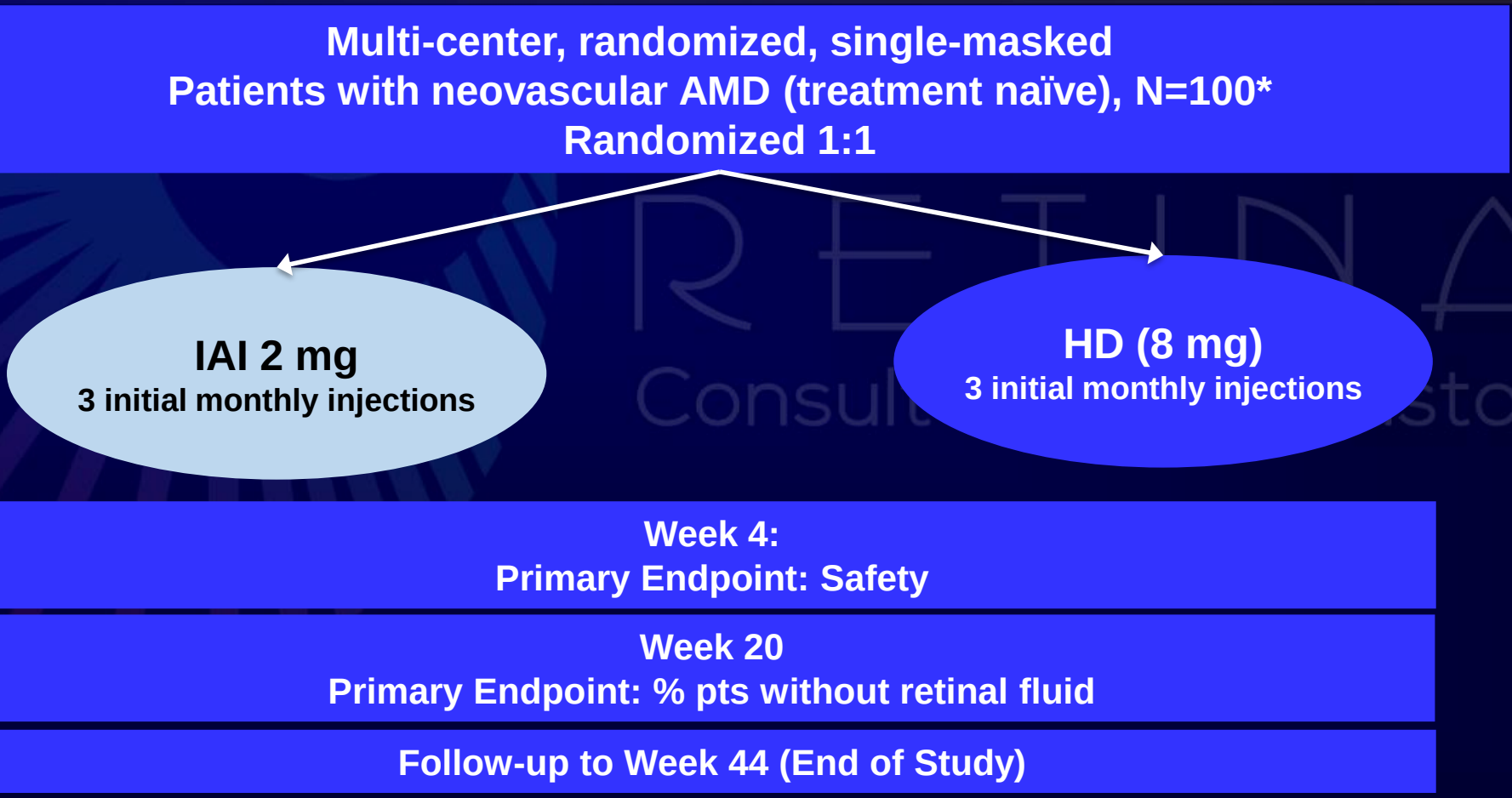
CR/LT: Central retinal/lesion thickness manually measured on posterior pole s**cans with time-domain OCT included the thickness of the RPE/choriocapillaris complex**
FAS, LOCF

4 mg Aflibercept: Safety

- No new ocular / systemic safety signals identified in combined group of AMD patients (n=81) treated with 4 mg aflibercept
- No serious ocular AEs of intraocular inflammation
  - Only serious ocular AEs were retinal hemorrhage (1 patient) and retinal detachment (1 patient)

- In Phase 1 DME (n=5), 4 mg aflibercept was well tolerated
  - Four patients had ocular AEs, all of which were mild (including conjunctival hemorrhage in 3 patients)

High-Dose Aflibercept Phase 2 in AMD



NCT04126317

*Phamacokinetic Substudy will include ~15 patients to be enrolled per treatment group

High-Dose Aflibercept Phase 2 Dosing Schedule

		Wk 4 Safety Analysis				Wk 20 Efficacy Analysis						Wk 44 Analysis EOS
	Day 1 (baseline)	Wk 4	Wk 8	Wk 12	Wk 16*	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44
IAI – 2 mg 50 µl	X	X	X			X	PRN	PRN	X	PRN	PRN	
HD – 8 mg 70 µl	X	X	X			X	PRN	PRN	X	PRN	PRN	

*Additional treatment allowed after discussion with sponsor

Aflibercept 8 mg Clinical Studies – Current Status

- Phase 2, single-masked, study of 8 mg aflibercept in neovascular AMD is currently enrolling
- Phase 3 studies in neovascular AMD and DME investigating dosing intervals of 12 weeks and longer will be initiated in 2020

VEGF = vascular endothelial growth fac
AMD = age-related macular degeneratio

Take Home Messages

- Higher Dose Anti-VEGF improves anatomy /VA in historical RCTs
- Aflibercept (Like most anti-VEGFs) has a linear PK curve
- 8mg Aflibercept should provide two ½-lives more duration
- Variability in vitreous half-life makes standardized dosing/ clinical trial design challenging