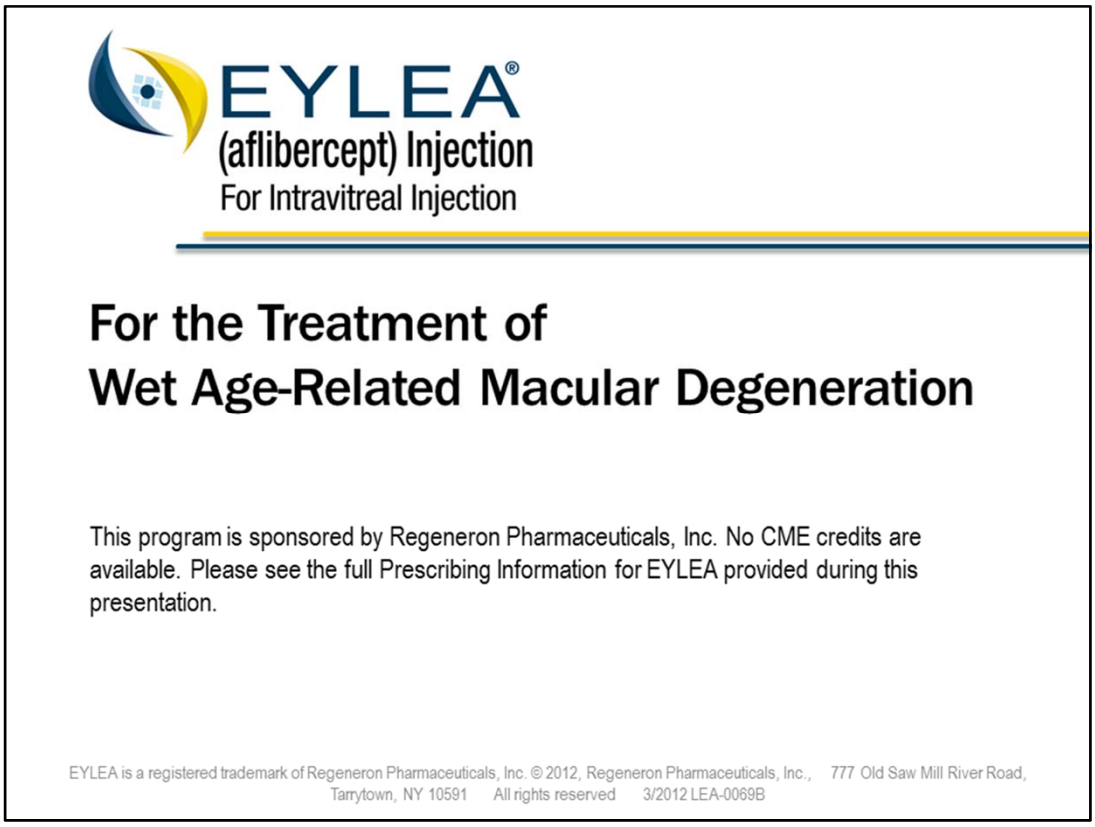


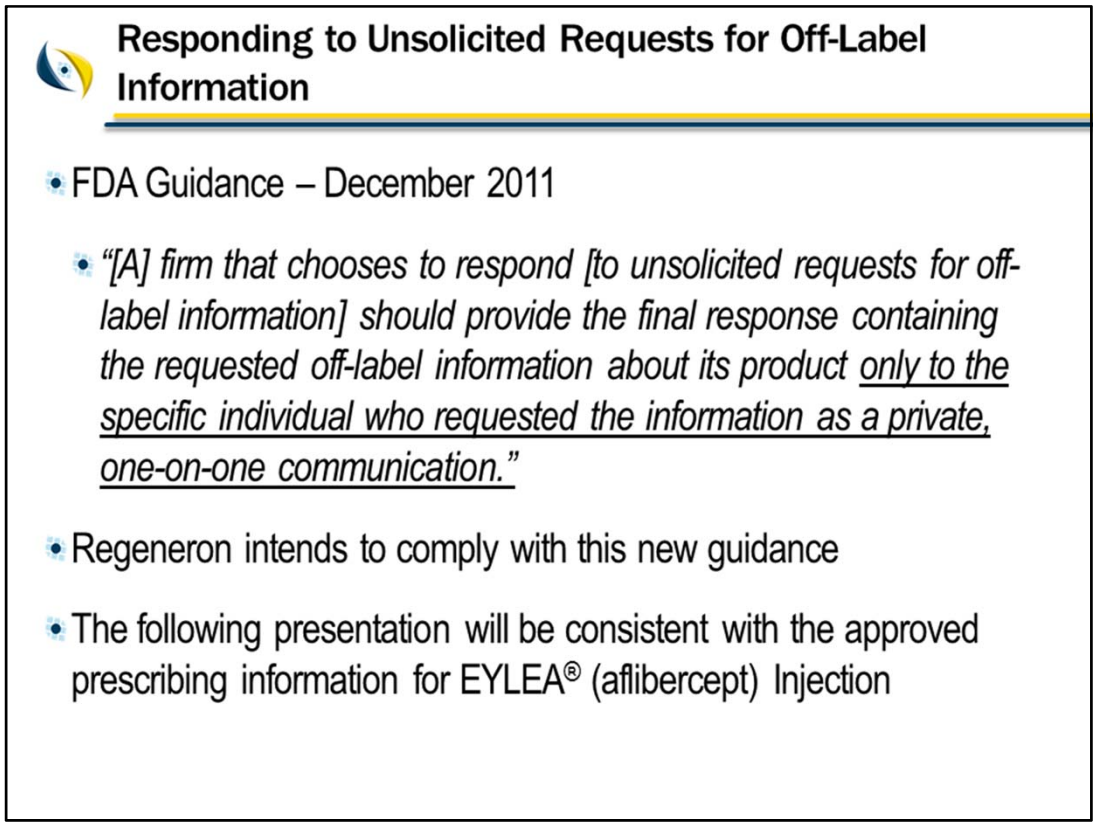
Note to Presenters: The text accompanying this set of slides is intended to be a guide. Unless otherwise highlighted in the notes section, presentations are not expected to be verbatim.

Thank you for joining us for this review of EYLEA® (aflibercept) Injection for the treatment of neovascular or wet age-related macular degeneration.

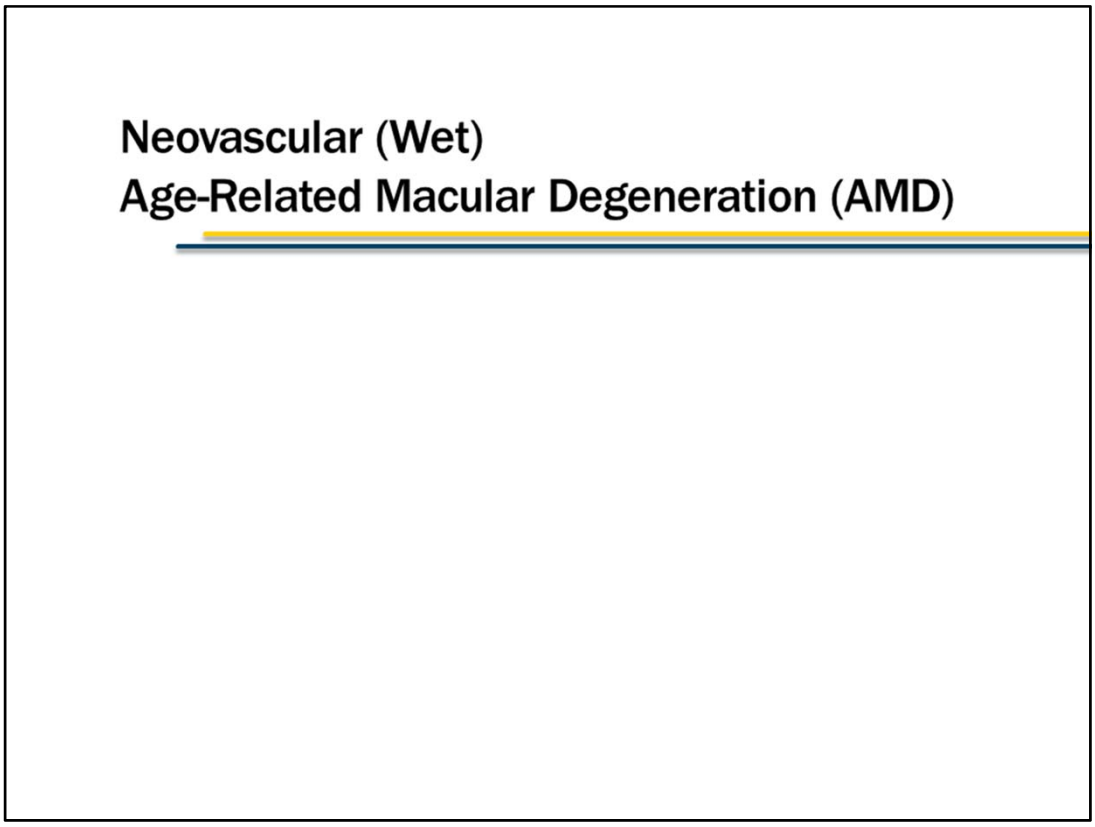
This program is sponsored by Regeneron Pharmaceuticals.

As a reminder, no CME credits are offered for this program. (CLICK)

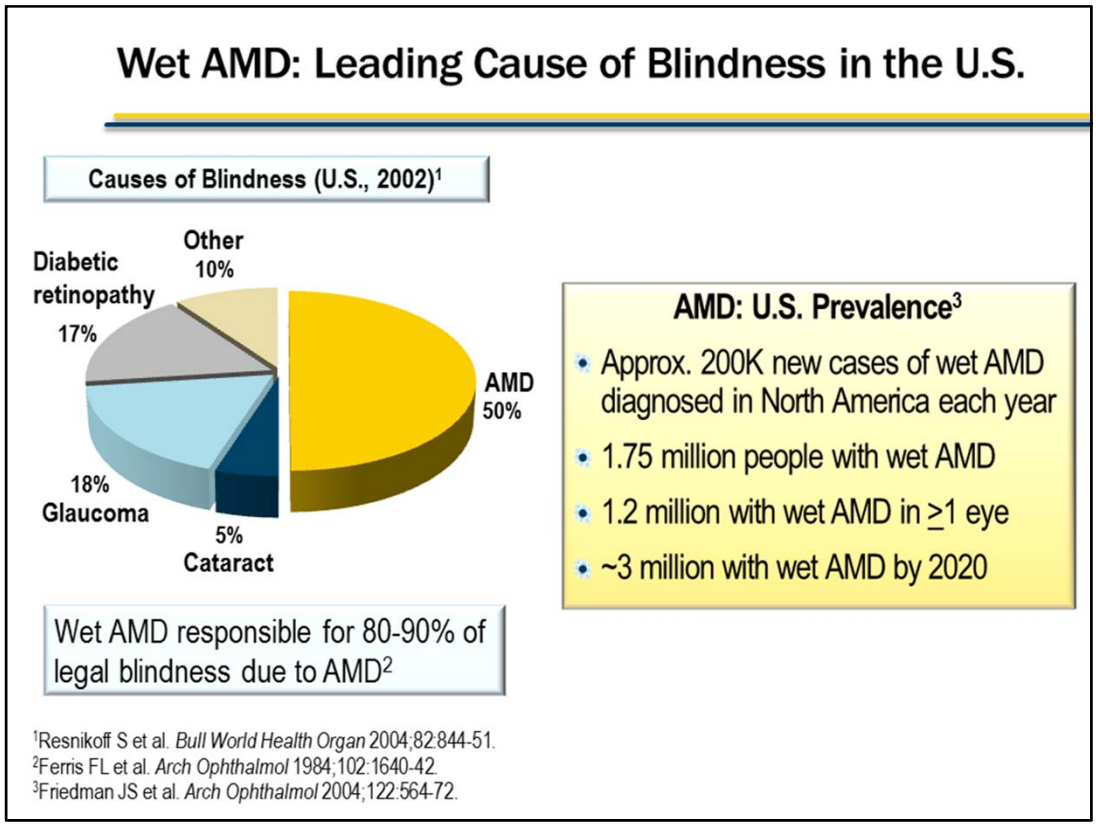
Samsung v. Regeneron
IPR2023-00442
U.S. Pat. 10,130,681
Exhibit 2139



Regeneron Medical Specialist to present, and then introduce presenting Physician.



Let's start by considering where we currently are with wet AMD and its management. (CLICK)



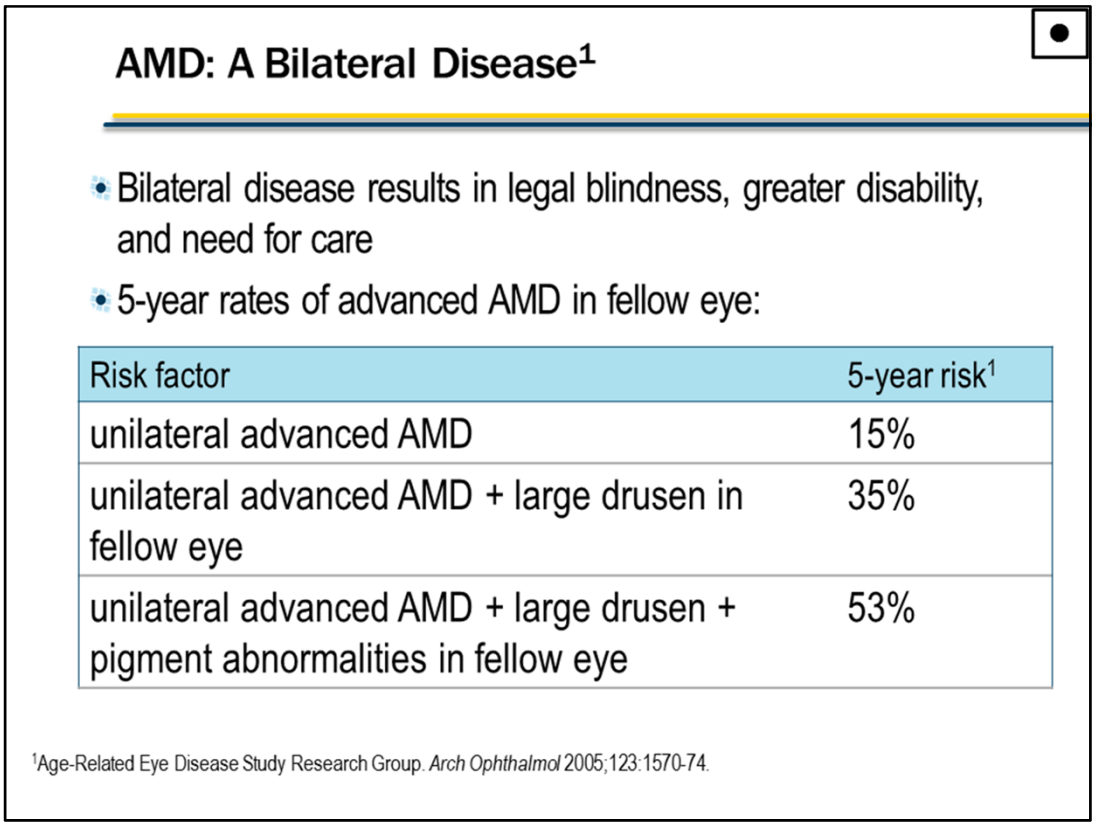
This pie chart reminds us that AMD is the leading cause of blindness in the U.S, accounting for half of all cases,[1] with wet AMD accounting for 80-90% of legal blindness among individuals with AMD.[2]

An estimate based on the 2000 U.S. Census was that nearly 2 million people in the U.S. had AMD, of which more than 1 million had wet AMD involving at least one eye, while another 7 million people had early-stage AMD.[3] Projections for 2020 are that nearly 3 million people will suffer from AMD. (CLICK)

[1]Resnikoff Set al. *Bull World Health Organ* 2004;82:844-51.

[2]Ferris FL et al. *Arch Ophthalmol* 1984;102:1640-42.

[3]Friedman DS et al. *Arch Ophthalmol* 2004;122:564-72.



(Optional Slide)

A survey by the National Eye Institute found that fear of blindness ranks second only to the fear of cancer among Americans.[1] Bilateral involvement is typical in AMD.[2,3] Vision loss due to neovascularization in one eye may be a harbinger of the future for the other eye – and the potential that patients with wet AMD will become legally blind and face even greater disability and increased need for care.

Based on the data from the Age-Related Eye Disease Study (AREDS),[4] 15% of patients with unilateral wet AMD will develop advanced AMD in the contralateral eye within 5 years. That risk increases to 53% when the contralateral eye exhibits large drusen and pigment abnormalities.

The propensity for wet AMD to be a bilateral disease means that we are going to be treating more patients with bilateral neovascularization as the population ages and the prevalence of wet AMD increases. For patients, bilateral wet AMD often means the loss of independence.[5] (CLICK)

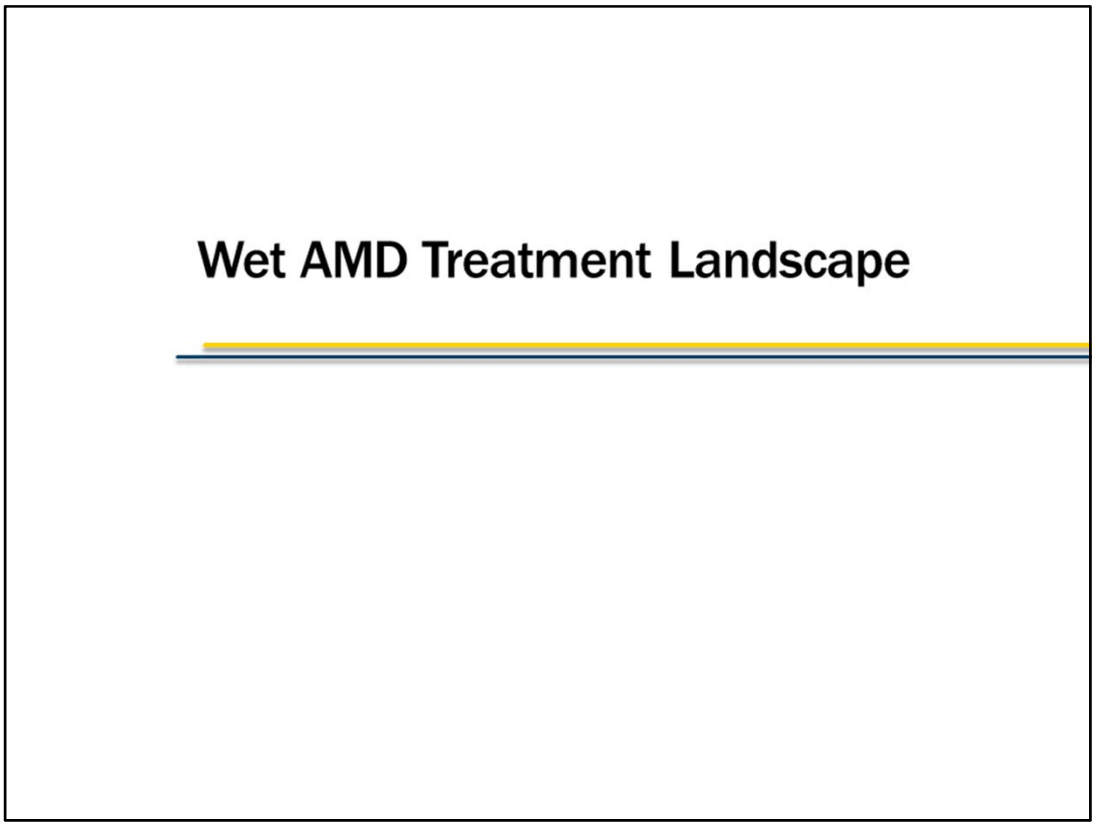
[1]Progress in Eye and Vision Research: U.S. Department of Health and Human Services, National Eye Institute. Accessed July 27, 2011, at: http://222.nei.nih.gov/strategicplanning/NEI_Progress-Doc.pdf.

[2]Pai AS-I et al. *Arch Ophthalmol* 2009;127:1339-44.

[3]Wang JJ et al. *Br J Ophthalmol* 1998;82:743–47.

[4]Age-Related Eye Disease Study Researc Group. *Arch Ophthalmol* 2005;123:1570-74.

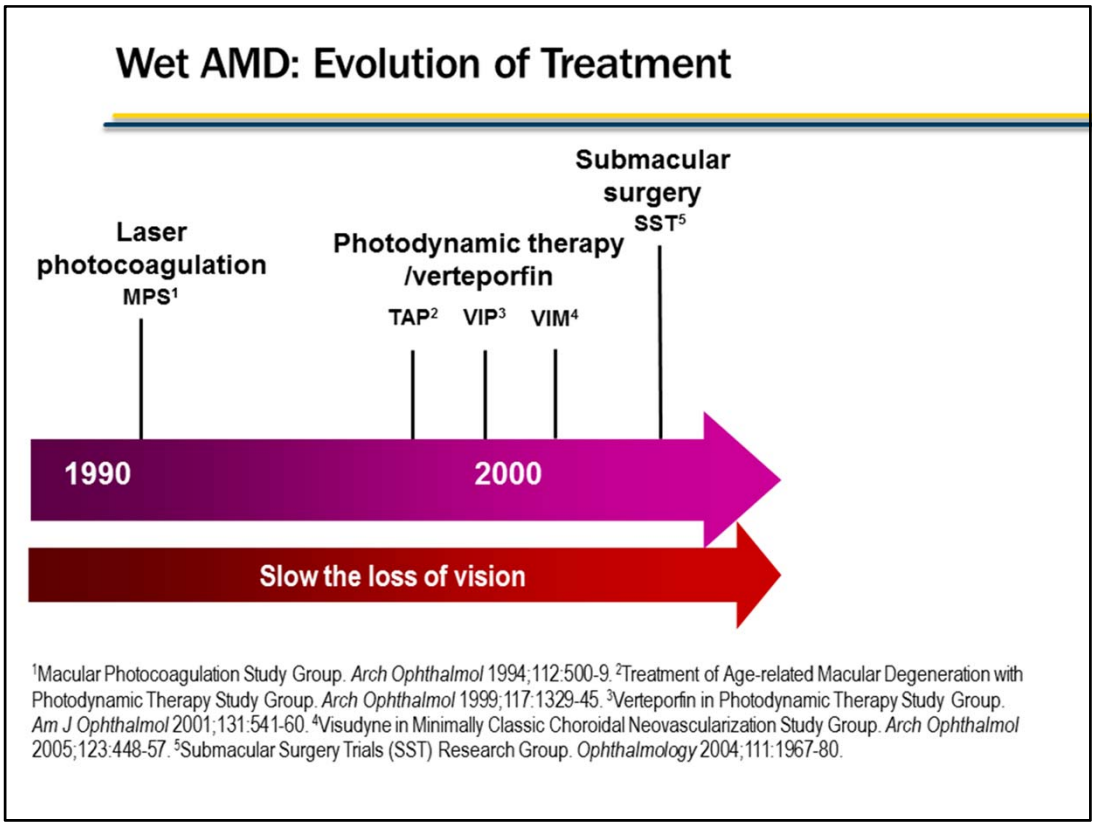
[5]Cruess AF et al. *Pharmacoeconomics*. 2008;26:57-73.



The speed with which neovascularization develops and visual acuity deteriorates in wet AMD makes prompt treatment an imperative.[1,2] So just how are we doing? (CLICK)

[1]Abraham P et al. *Am J Ophthalmol* 2010;150:315–24.

[2]Brown DM et al. *Ophthalmol* 2009;116:57-65.



We have certainly made considerable progress compared with where we were in the 1980s. In the 1990s, randomized trials showed that laser photocoagulation therapy could slow vision loss,[1] albeit at the expense of irreversible destruction of healthy macular tissue. In the late 1990s, photodynamic therapy or PDT, which was less destructive, was shown to have a modest effect in slowing vision loss.[2-4]

Although submacular surgery had looked promising, randomized studies funded by the National Eye Institute, had failed to show a benefit of surgically excising subfoveal CNV lesions that could not be treated with photocoagulation or PDT.[5]

In short, available treatments had limited or modest impact on the natural history of wet AMD. (CLICK)

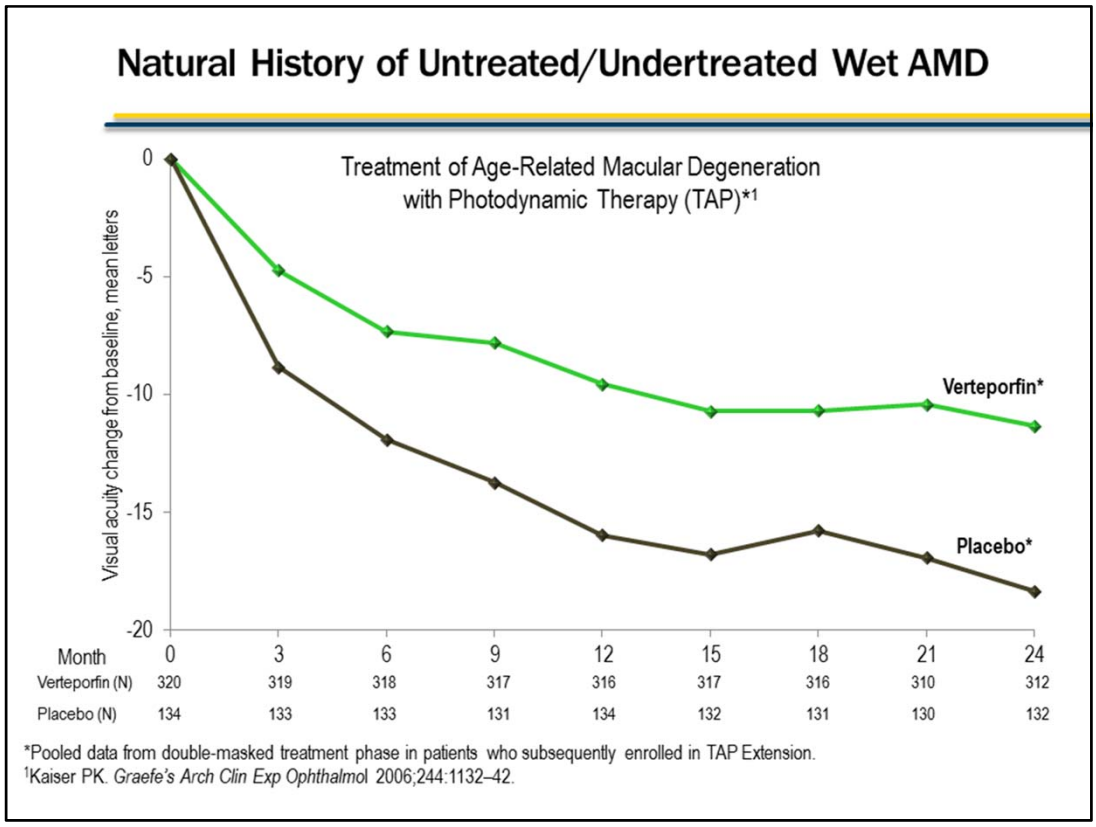
[1]Macular Photocoagulation Study Group. *Arch Ophthalmo*l 1994;112:500-9.

[2]Treatment of Age-related Macular Degeneration with Photodynamic Therapy Study Group. *Arch Ophthalmol* 1999;117:1329-45.

[3]Verteporfin in Photodynamic Therapy Study Group. *Am J Ophthalmol* 2001;131:541-60.

[4]Visudyne Minimally Classic Choroidal Neovascular Study Group. *Arch Ophthalmol* 2005;123:448-57.

[5]Submacular Surgery Trials (SST) Research Group. *Ophthalmology* 2004;111:1967-80.



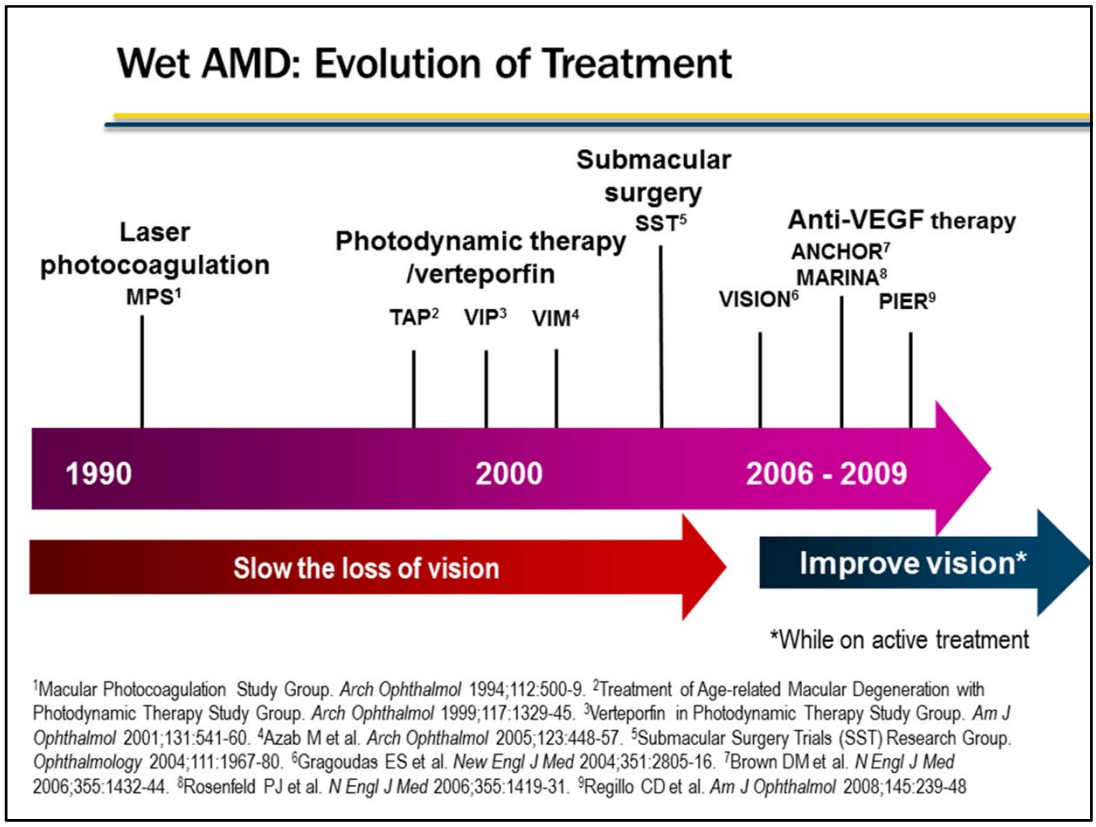
Results of the TAP study illustrate the prognosis of wet AMD when left untreated, as in the placebo arm, or is undertreated, as in the arm where patients were treated with verteporfin and photodynamic therapy (PDT). The data shown here are pooled data during the double-masked treatment phase in patients who subsequently enrolled in the TAP Extension.[1]

With no treatment, patients with wet AMD experienced a steady decline in visual acuity over time, losing approximately 18 letters over the 2-year period. Verteporfin slowed the progression of wet AMD but did not reverse vision loss. (CLICK)

Study Description:

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP): Two multicenter, double-masked, placebo-controlled, randomized clinical trials in patients with classic CNV treated/followed for 2 years. Data shown in slide are for the double-masked treatment phase in patients who subsequently enrolled in TAP Extension (80% of patients treated with verteporfin subsequently enrolled in the extension).[1]

[1]Kaiser PK. *Graefe's Arch Clin Exp Ophthalmol* 2006; 244:1132–42.



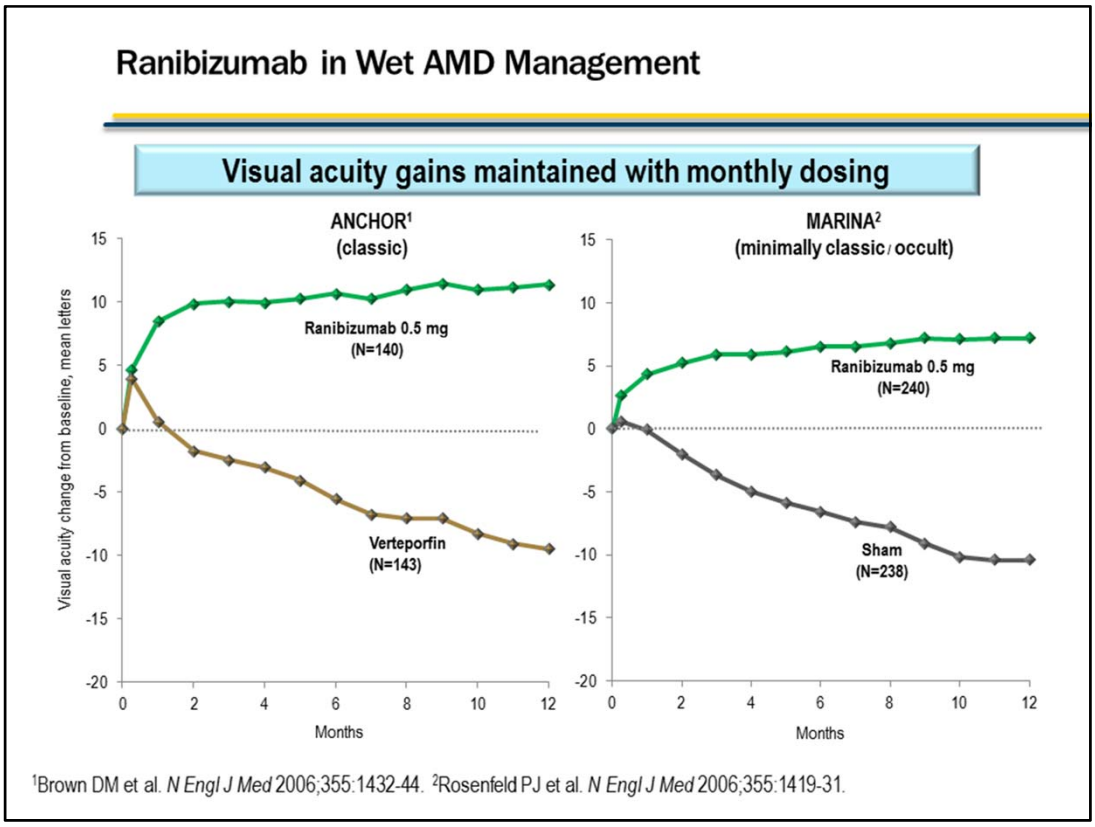
Pegaptinib provided the first evidence of the VEGF inhibitors' therapeutic potential in retinal neovascular disease.[1] With pegaptinib targeting VEGF-A_{165}, some patients gained vision.[1] In 2006, ranibizumab changed the treatment landscape.[2-4] (CLICK)

[1]Gragoudas ES et al. *New Engl J Med* 2004;351:2805-16.

[2]Brown DM et al. *N Engl J Med* 2006;355:1432-44.

[3]Rosenfeld PJ et al. *N Engl J Med* 2006;355:1419-31.

[4]Regillo CD et al. *Am J Ophthalmol* 2008;145:239-48



The ANCHOR[1] study of monthly ranibizumab in classic wet AMD and the MARINA[2] study of monthly ranibizumab in occult and minimally classic wet AMD showed a significant improvement in BCVA which were sustained for at least 24 months with monthly injections.(CLICK)

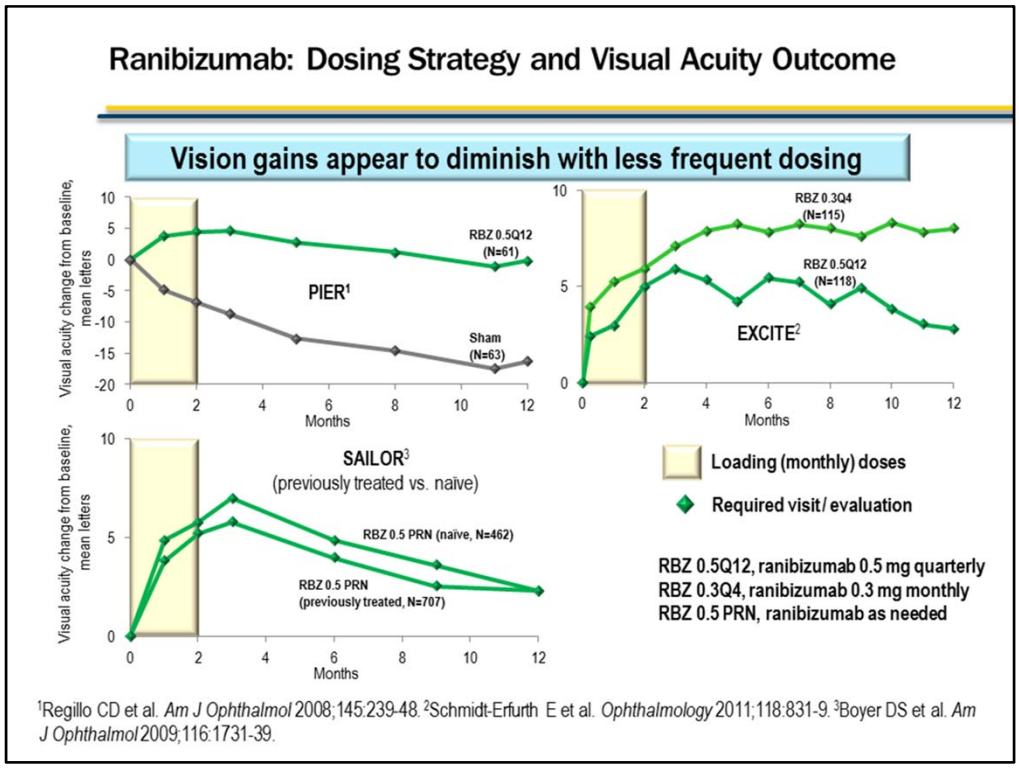
Study Description:

ANCHOR: Multicenter, double-masked randomized study comparing monthly ranibizumab in patients with predominantly classic wet AMD with the standard-of-care at the time of study initiation, verteporfin sodium, over 2 years (primary endpoint – maintenance of vision – evaluated at 1 year).[1]

MARINA: Multicenter, double-masked, sham-controlled randomized study of monthly ranibizumab in patients with minimally classic or occult lesions over 2 years (primary endpoint – maintenance of vision – evaluated at 1 year).[1]

[1]Brown DM et al. *N Engl J Med* 2006;355:1432-44.

[2]Rosenfeld PJ et al. *N Engl J Med* 2006;355:1419-31.



Monthly injections pose challenges for patients and physicians. As a result, studies were conducted to evaluate less frequent dosing schedules.

These are 3 of the major studies that evaluated alternatives to monthly ranibizumab dosing without monthly monitoring. In all 3 studies, ranibizumab was initiated with 3 injections at monthly intervals. However, after this loading dose phase, the studies had somewhat different approaches to dosing and monitoring.

The PIER[1] study evaluated the efficacy of fixed quarterly ranibizumab injections and showed that initial visual gains with 3 monthly doses all but disappeared by the end of Year 1, with patients reverting back, on average, to their baseline.

The 0.5 mg ranibizumab arm in the EXCITE study was also dosed at 3-month intervals.[2] Here, patients were seen at monthly intervals so the curve for ranibizumab has an up-and-down quality to it that was not apparent in the PIER study. But again, quarterly injections were not able to sustain visual gains achieved with initial monthly dosing.

The SAILOR[3] study evaluated a PRN dosing strategy in which retreatment was based on decreased visual acuity with or without OCT evidence of retinal fluid. Monthly monitoring during PRN dosing was not required. Once again, initial visual gains from monthly dosing could not be maintained.

In the SAILOR study, the inability of PRN dosing to maintain vision gained from three monthly doses was attributed to inadequate monitoring and undertreatment of active disease. (CLICK)

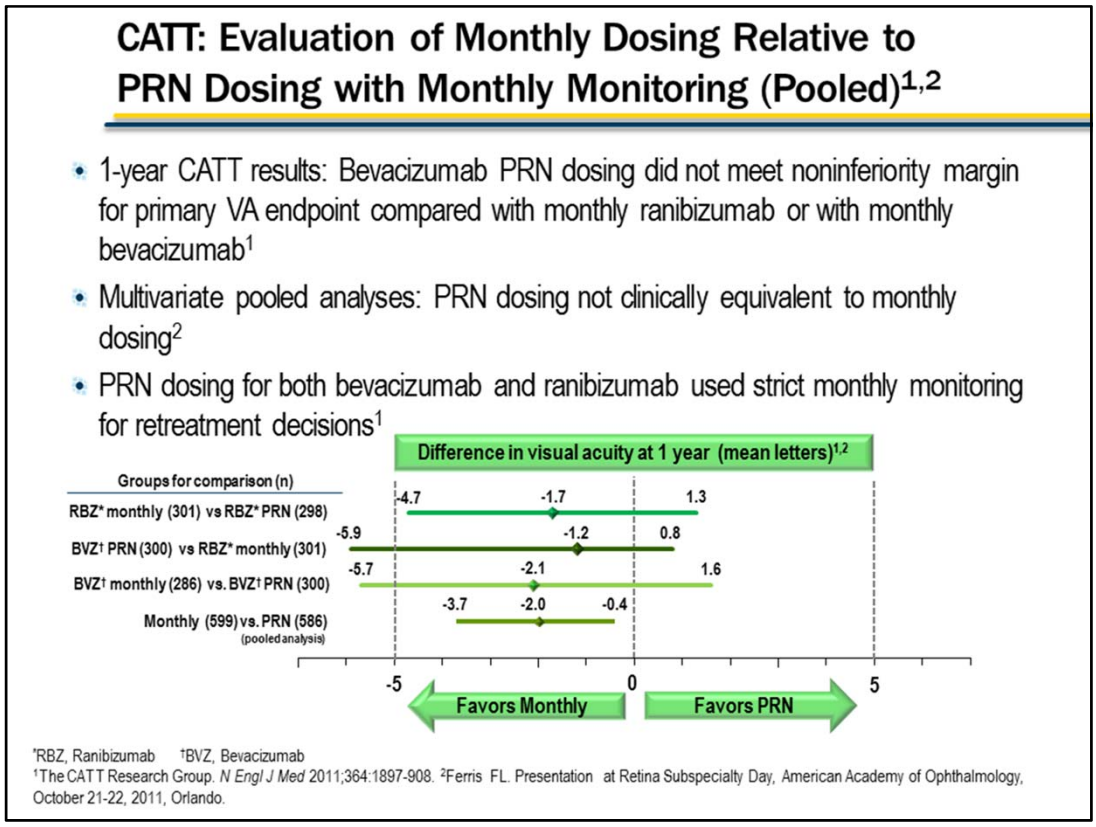
Study Descriptions:

PIER : Phase 3b, 2-year randomized, double-masked, sham-controlled trial of ranibizumab in all 3 CNV subtypes. Dosing: Monthly injections for the first 3 months; quarterly injections thereafter.[1]

EXCITE: Phase 3b, multicenter, randomized, 12-month, double-masked, active-control trial of ranibizumab 0.3 mg quarterly, 0.5 mg ranibizumab quarterly, or 0.3 mg ranibizumab monthly in all 3 CNV subtypes.[2]

SAILOR: Phase 3b, multicenter, open-label, 12-month trial included previously-treated and treatment-naïve patients with all 3 CNV sub-types. Dosing: Monthly injections for the first 3 months, then as-needed (PRN) based on vision and anatomical examinations.[3] *Visits for re-evaluation and possible retreatment were only required at quarterly intervals.*

[1]Brown DM, Regillo CD. *Am J Ophthalmol* 2007;144:627-37. [2]Schmidt-Erfurth E et al. Ophthalmology 2011;118:831-9. [3]Boyer DS et al. *Ophthalmology* 2009;116:1731-39.



The most rigorous evaluation of PRN versus monthly dosing was the CATT study.[1]

Just to briefly summarize the study design … Patients with wet AMD were randomized to one of four groups based on drug and dosing strategy – ranibizumab or bevacizumab administered as fixed monthly injections or fixed monthly injections for 3 months followed by as-needed dosing based on monthly monitoring for signs of active disease.

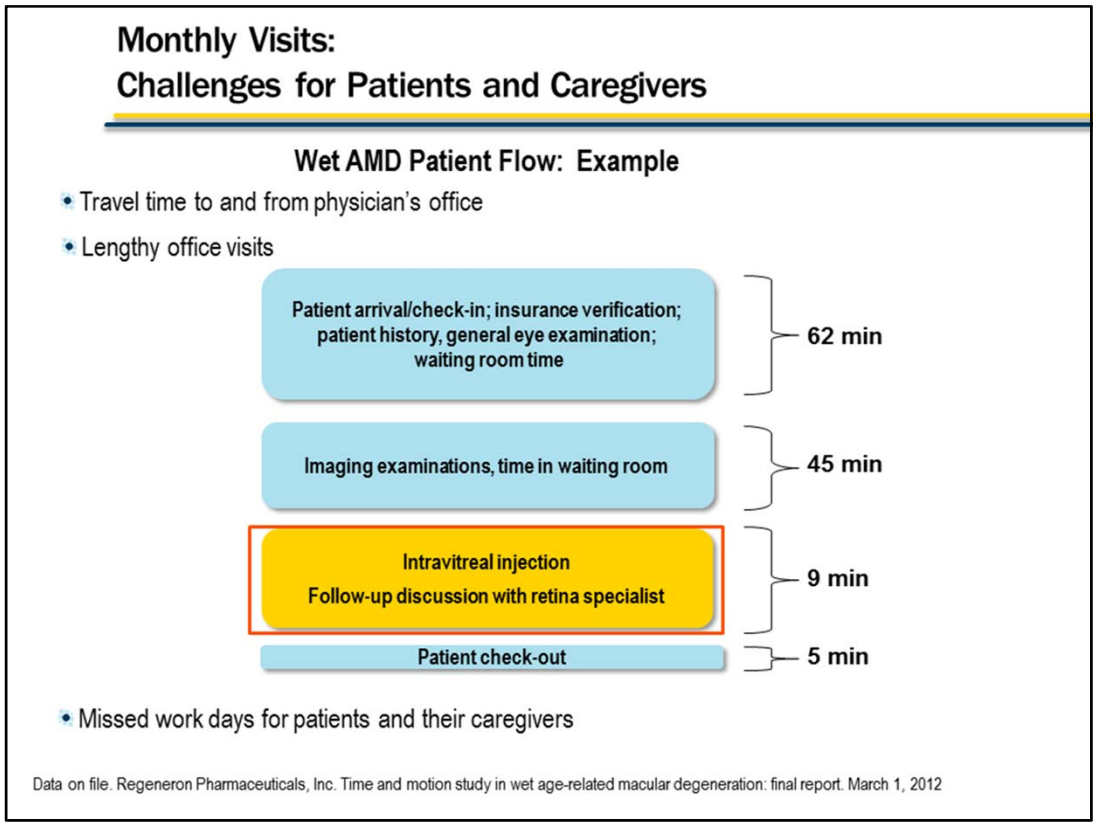
This was a noninferiority trial in which the primary outcome was mean change in visual acuity at 1 year, using a confidence interval approach to the noninferiority analysis. For PRN dosing to be noninferior to monthly dosing, the 95% confidence interval for the difference in mean visual acuity at 1 year had to be within 5 letters (1 line) on the ETDRS chart.

As the chart shows, PRN ranibizumab was shown to be noninferior to monthly ranibizumab at 1 year because the confidence interval fell within the 5-letter margin. However, the noninferiority of PRN bevacizumab to monthly ranibizumab was not established because the confidence interval exceeded the 5-letter margin to the left. This was also true for PRN bevacizumab versus monthly bevacizumab.

When monthly dosing groups and PRN dosing groups were pooled, PRN dosing was inferior to monthly dosing, as shown by the bottom plot in which the confidence interval lies entirely to the left of 0 and within the 5-letter margin statistically favoring monthly dosing.[2] (CLICK)

[1]The CATT Research Group. *N Engl J Med* 2011;364:1897-908.

[2]Ferris FL. Presentation at Retina Subspecialty Day, American Academy of Ophthalmology, October 21-22, 2011, Orlando.



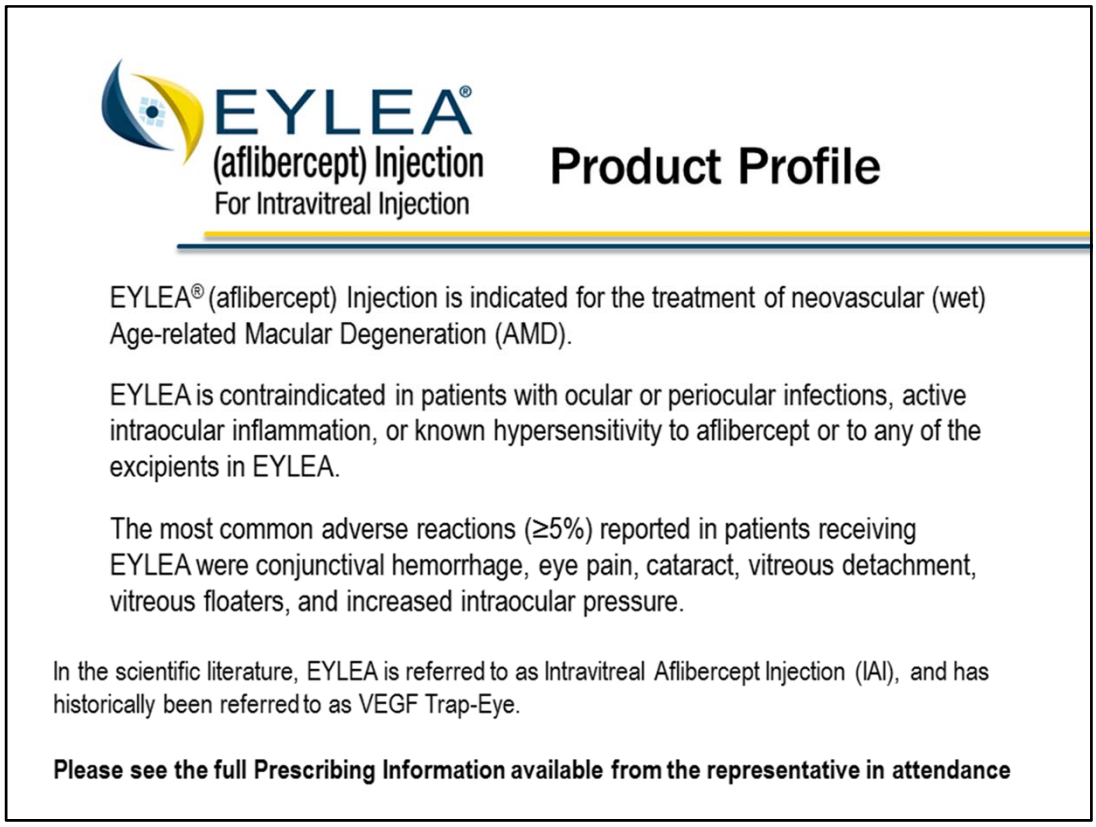
Wet AMD management still appears to require monthly office visits even if each office visit does not result in an injection. The data shown here are from a study in retinal specialists' offices, which collected information on the time associated with discrete steps of the wet AMD treatment process.[1]

Each visit requires a time commitment for not only office visits that can be quite lengthy, but also for travel to and from the office as well as time lost from work for the patients and their adult caregiver. (CLICK)

Study Description:

Time and motion study design: Multi-phase qualitative and quantitative observational study. Study integrated data from detailed interviews/surveys with retinal specialists, patients, and caregivers. Data on time involved with discrete steps of office procedures for wet AMD patients were collected from 201 patient records prospectively completed by retinal specialists.

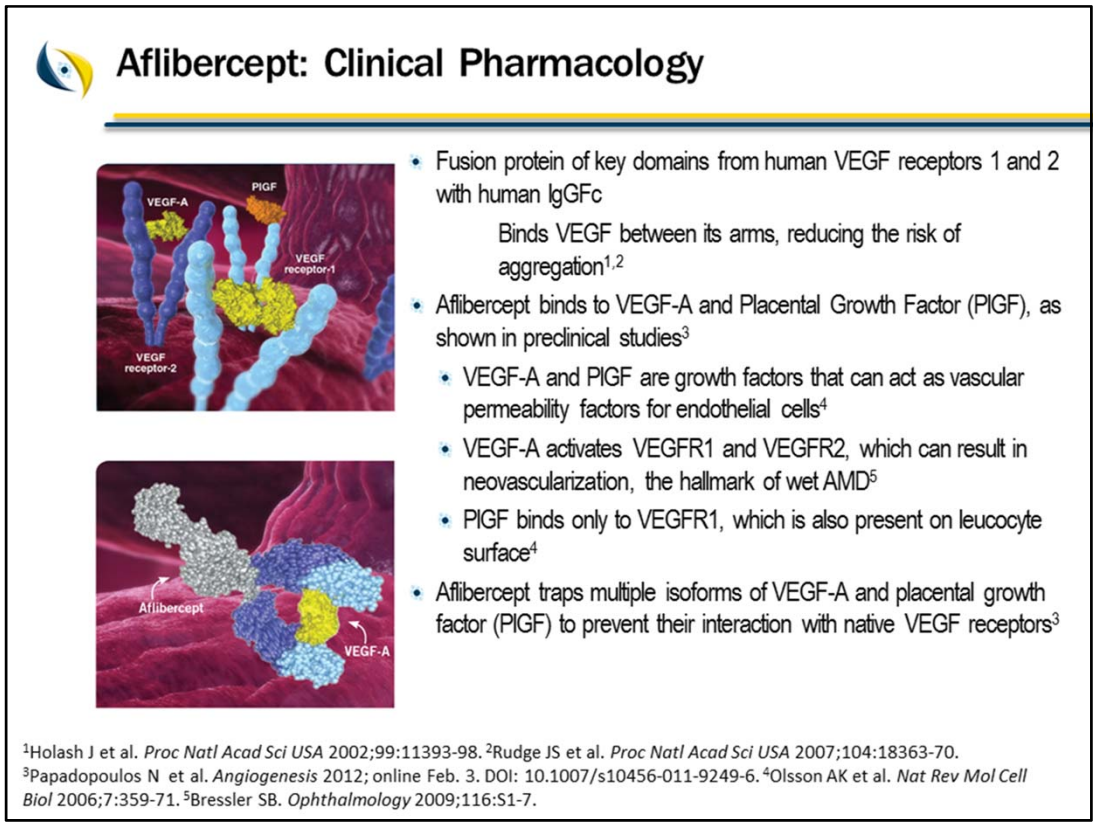
[1]Data on file. Regeneron Pharmaceuticals, Inc. Time and motion study in wet age-related macular degeneration: final report, March 1, 2012.



This brings us to EYLEA® (aflibercept) Injection, which is indicated for the treatment of wet AMD.

EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

In the scientific literature, EYLEA is referred to as Intravitreal Aflibercept Injection (IAI) and has historically been referred to as VEGF Trap-Eye. (CLICK)



Some therapeutic proteins derive their target specificity from antibody structures that recognize growth factors as antigens. Aflibercept uses Regeneron's trap technology to bind and block various VEGF ligands. This technology combines key components of multiple receptors into one molecule[1,2]
Aflibercept is a fusion protein that combines key binding domains from VEGF receptor 1 and VEGF receptor 2 and fuses this binding unit to the IgG1 constant region to create a 2-armed dimeric trap.[1] It simultaneously binds both poles of the VEGF dimer to form a stable, inactive complex for elimination.[2] By engaging both VEGF binding sites, no site is left open to interact with other molecules and form higher order complexes, thereby reducing the risk of aggregation.[2]

As shown in preclinical studies, aflibercept traps not only multiple VEGF-A isomers, which bind to both VEGF receptor 1 and VEGF receptor 2, it also traps placental growth factor (PlGF), which binds only to VEGF receptor 1.[3]

Preclinical studies have shown that VEGF receptors 1 and 2 have somewhat different distribution profiles.[4] For example, endothelial cells express both subtypes; leucocytes express only VEGF receptor 1.[4] The biologic implications of these differences are not clear. However, what we do know is that activation of both VEGF receptors 1 and 2 stimulate neovascularization and vascular permeability.[4,5] (CLICK)

[1]Holash J et al. *Proc Natl Acad Sci USA* 2002;99:11393-98.
[2]Rudge JS et al. *Proc Natl Acad Sci USA* 2007;104:18363-70.
[3]Papadopoulos N et al. *Angiogenesis* 2012; online Feb. 3. DOI: 10.1007/s10456-011-9249-6.
[4]Olsson AK et al. *Nat Rev Mol Cell Biol* 2006;7:359-71.
[5]Bressler SB. *Ophthalmology* 2009;116:S1-S7.

Aflibercept: Clinical Pharmacology

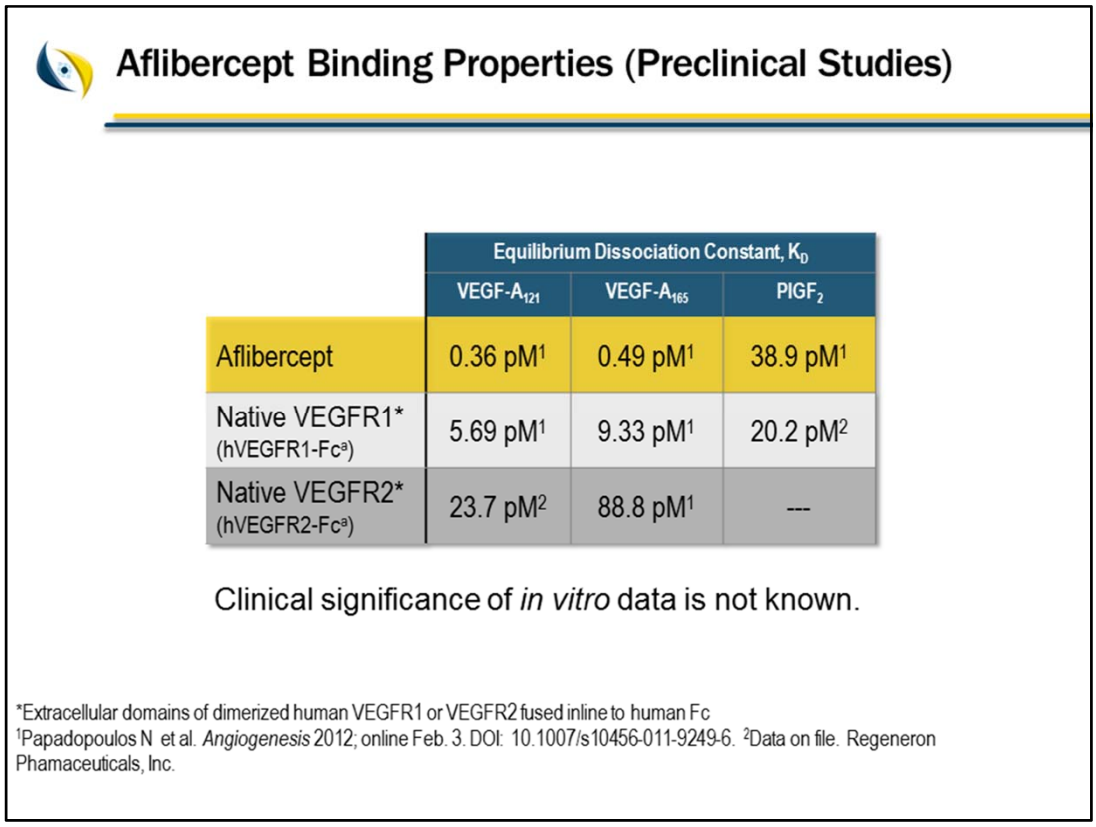


- Aflibercept has a low incidence of immunogenicity
  - Contains all human amino acid sequences[1]
  - Produced in recombinant Chinese hamster ovary (CHO) cells
- EYLEA® (aflibercept) Injection is a purified and formulated preparation of aflibercept, specifically for intravitreal injection[2]
  - Formulated as an iso-osmotic solution compatible with intraocular environment[2]
  - Purified form of aflibercept to reduce unnecessary ingredients in the eye[3]
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic technique must always be used when administering EYLEA.

[1]Holash J et al. *Proc Natl Acad Sci USA* 2002;99:11393-98. [2]Papadopoulos N et al. *Angiogenesis* 2012; online Feb. 3. DOI: 10.1007/s10456-011-9249-6. [3]Data on file. Regeneron Pharmaceuticals. BLA Sec 2.3.S Drug Substance.

EYLEA® (aflibercept) Injection is a purified and formulated preparation of afibercept, specifically for intravitreal administration. It is formulated as an iso-osmotic solution compatible with the intraocular environment. It is a purified form of aflibercept to reduce unnecessary ingredients in the eye.

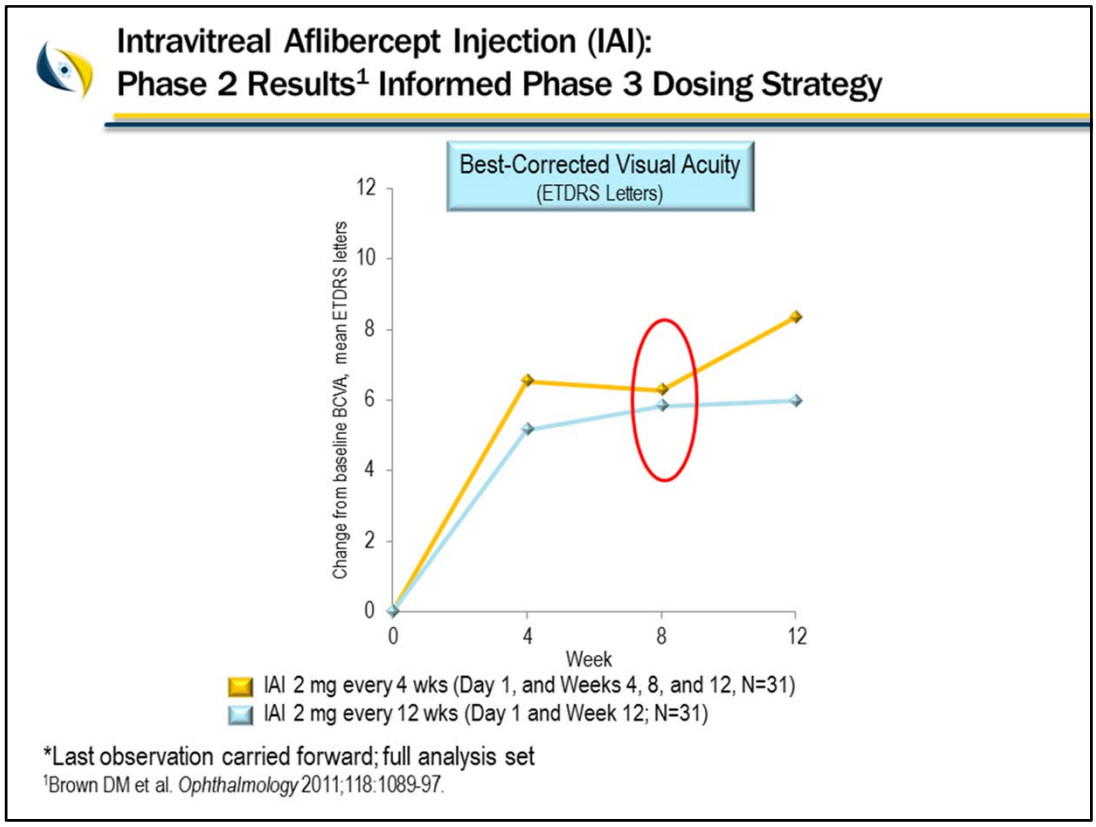
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. (CLICK)



The binding affinity derived from preclinical studies and expressed as the equilibrium dissociation constant, is shown here for aflibercept binding to VEGF-A_{121}, VEGF-A_{165}, and $PlGF_2$ compared with VEGF-A_{165} binding to experimental native VEGF receptors 1 and 2.

The clinical significance of *in vitro* data is not known. (CLICK)

[1]Papadopoulos N et al. *Angiogenesis* 2012; online Feb. 3. DOI: 10.1007/s10456-011-9249-6



CLEAR-IT 2 was a Phase 2 study designed to assess the efficacy of different doses and dose strategies for intravitreal aflibercept injection over a 12-week period.[1] The data displayed here are for the arms in which patients received 2 mg every 4 weeks (monthly) or 2 mg as a single injection on Day 1. The mean change in BCVA from baseline was a secondary efficacy variable.

At the end of 3 months, the 2Q4 group showed greater visual acuity improvement than the group receiving a single 2-mg intravitreal aflibercept injection on Day 1. This finding suggested that three doses at monthly intervals could be helpful in maximizing clinical benefit of EYLEA.

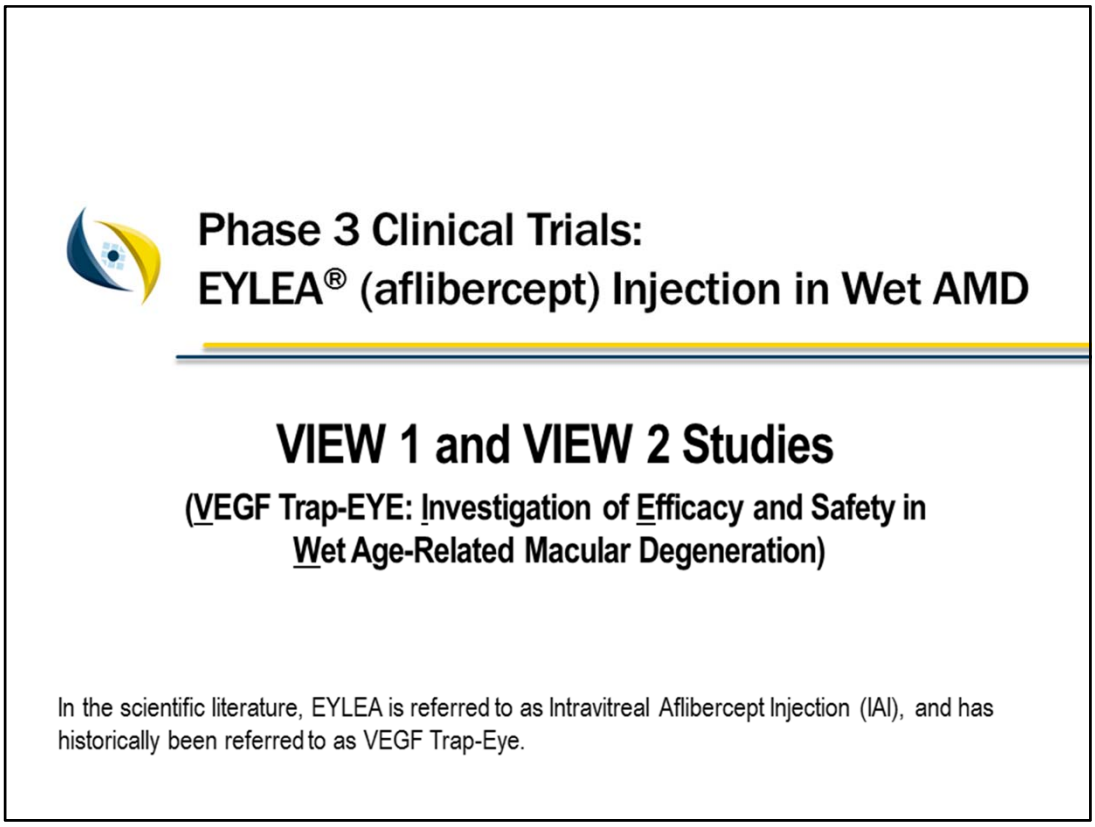
Although an 8-week dosing interval was not specifically evaluated in CLEAR-IT 2, vision improvements in the 2Q12 group extended to 8 weeks and began to wane at 12 weeks. These findings of sustained effects over 8 weeks were the foundation for dosing protocols that included an every 8-week (every 2-month) dosing interval in the pivotal Phase 3 studies.

After fixed-dose administration in CLEAR-IT 2, most adverse events were injection related. No serious ocular adverse events, clinically significant ocular inflammation, or endophthalmitis was reported in any study eyes. Most ocular adverse events were mild. (CLICK)

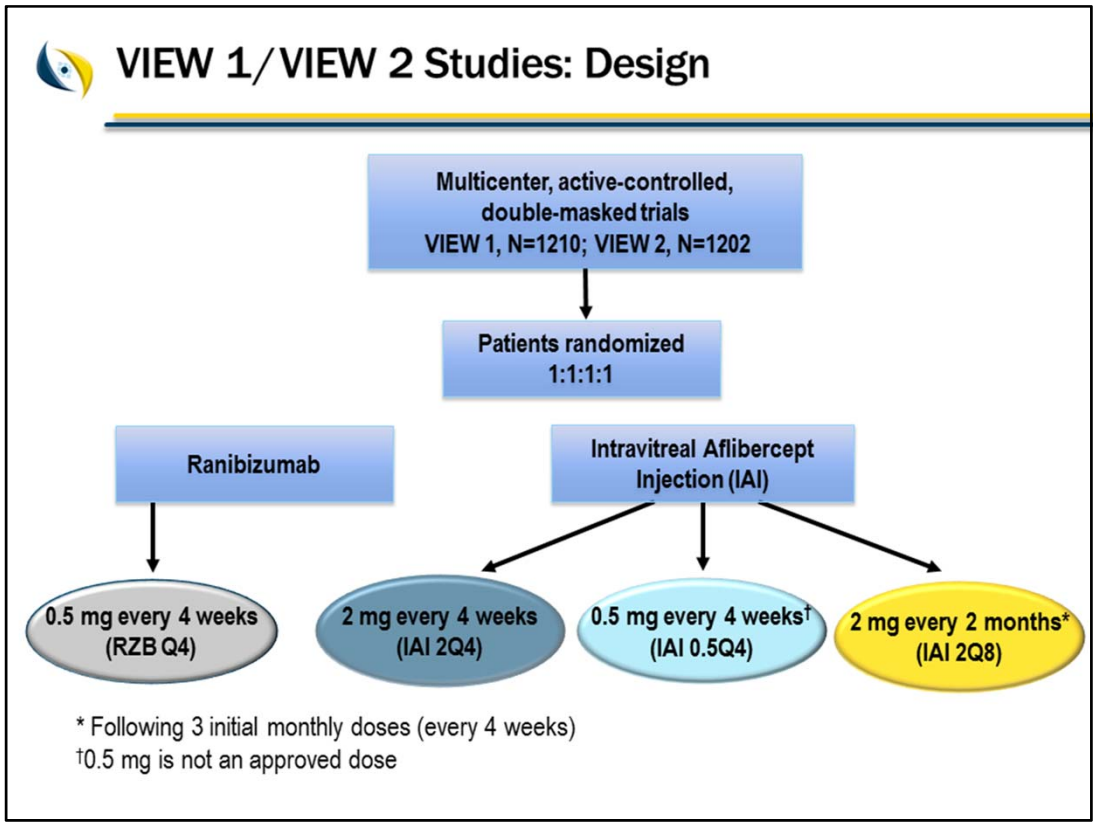
Study Description:

CLEAR-IT 2 (Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial) design: Multicenter, prospective, randomized, double-masked clinical trial with initial 12-week fixed dosing period. Patients were randomized 1:1:1:1:1 to IAI 0.5 or 2 mg every 4 weeks on day 1 and at weeks 4, 8, and 12; or 0.5, 2, or 4 mg every 12 weeks on day 1 and at week 12. For this discussion, only data for IAI 2Q4 and for IAI 2Q12 are presented.[1]

[1]Brown DM et al. *Ophthalmology* 2011;118:1089-97.



The Phase 3 clinical studies of EYLEA® (aflibercept) Injection are the VIEW 1 and VIEW 2 studies, with VIEW standing for VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration. (CLICK)



Phase 1 and 2 studies of intravitreal aflibercept injection (IAI) in patients with wet AMD helped define the dosing strategies that were subsequently evaluated in two larger Phase 3 studies – VIEW 1 and VIEW 2. VIEW 1 was conducted in the United States and Canada; VIEW 2 was conducted in 26 countries worldwide.[1]

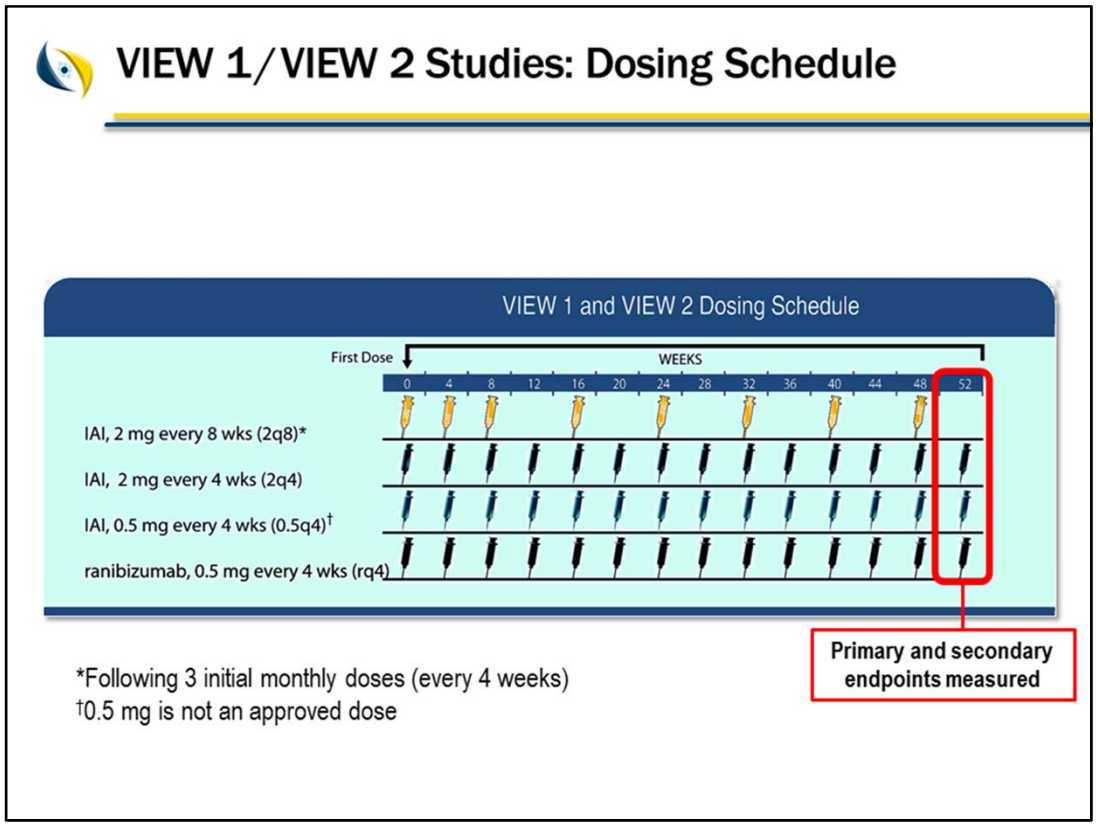
These studies enrolled 2412 patients. The trials were double-masked studies in which equal numbers of patients were randomized to one of 4 treatment arms.

The active control was ranibizumab 0.5 mg every 4 weeks – the recommended dose per the U.S. Prescribing Information.

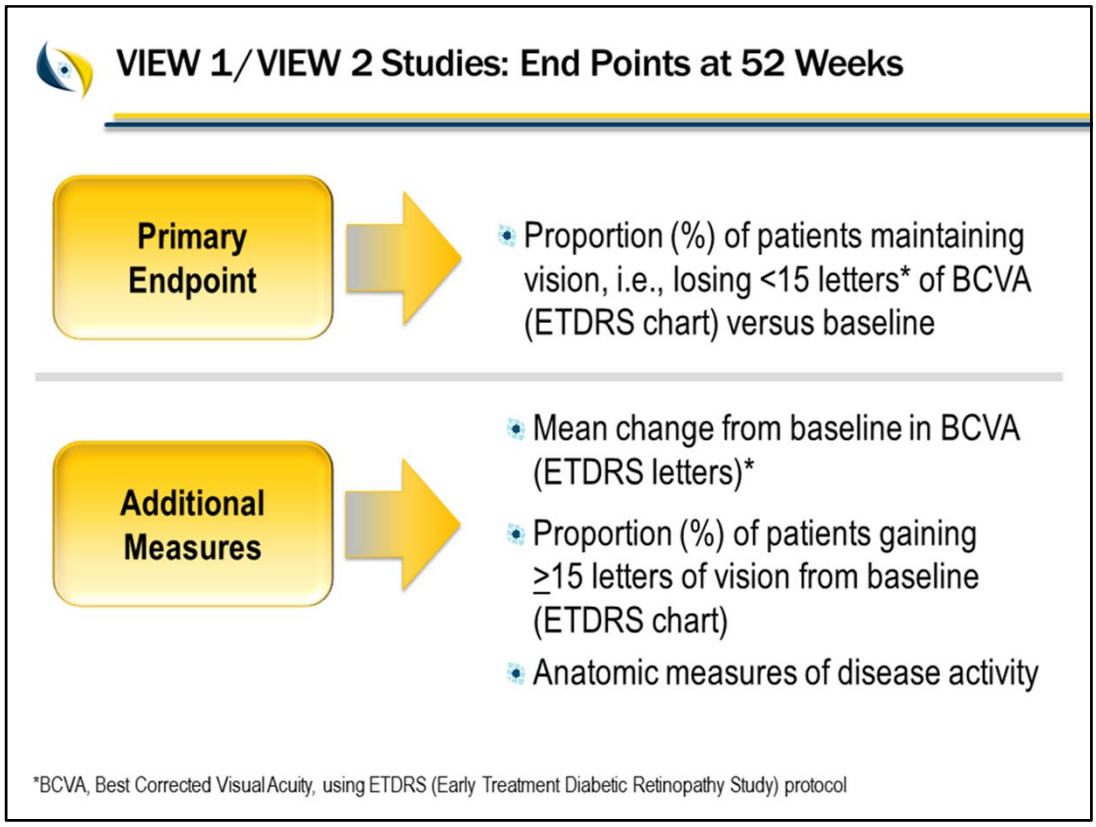
The other three arms of the trial were intravitreal aflibercept injection (IAI) dosed as 0.5 mg every 4 weeks, 2 mg every 4 weeks, or 2 mg every 8 weeks following 3 initial monthly doses.

0.5 mg aflibercept every 4 weeks is not an approved dose so we will not be presenting the efficacy results from this group. Safety information from this dosing arm are included in the integrated safety database that will be presented later. (CLICK)

[1]Data on file. Regeneron Pharmaceuticals, Inc.

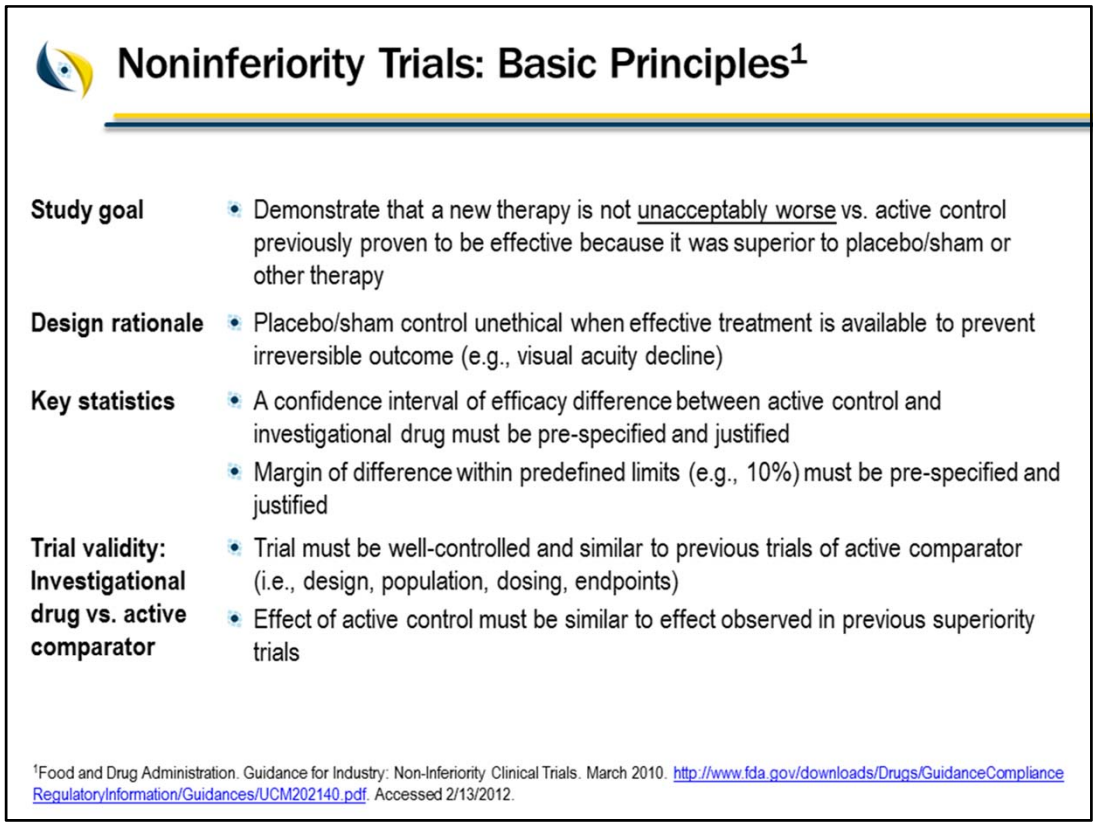


This schematic illustrates the dosing schedule for all 4 groups. Bear in mind that the group assigned to intravitreal aflibercept injection 2 mg every 8 weeks following 3 initial monthly injections received sham injections at the visits without active drug injections. However, no treatment decisions were allowed at the sham injection visits. Clinical assessments at week 52 were completed before the injection (or sham injection). (CLICK)



The primary endpoint was the proportion in whom vision was maintained, defined as losing <15 letters of best-corrected visual acuity on the ETDRS eye chart.

Other measures included mean change in visual acuity, proportion of patients who gained at least 15 letters or 3 lines of vision, and change in anatomic outcomes. (CLICK)



VIEW 1 and VIEW 2 were designed as noninferiority comparisons with ranibizumab. Just to review some key points about noninferiority studies[1] …

The objective of a noninferiority study is to show that a new treatment is not unacceptably less effective than a treatment previously proved effective in randomized controlled trials.

A noninferiority design is used when placebo or sham treatment would be unethical because patients would be at risk of irreversible harm that could be prevented with a therapy we know is effective.

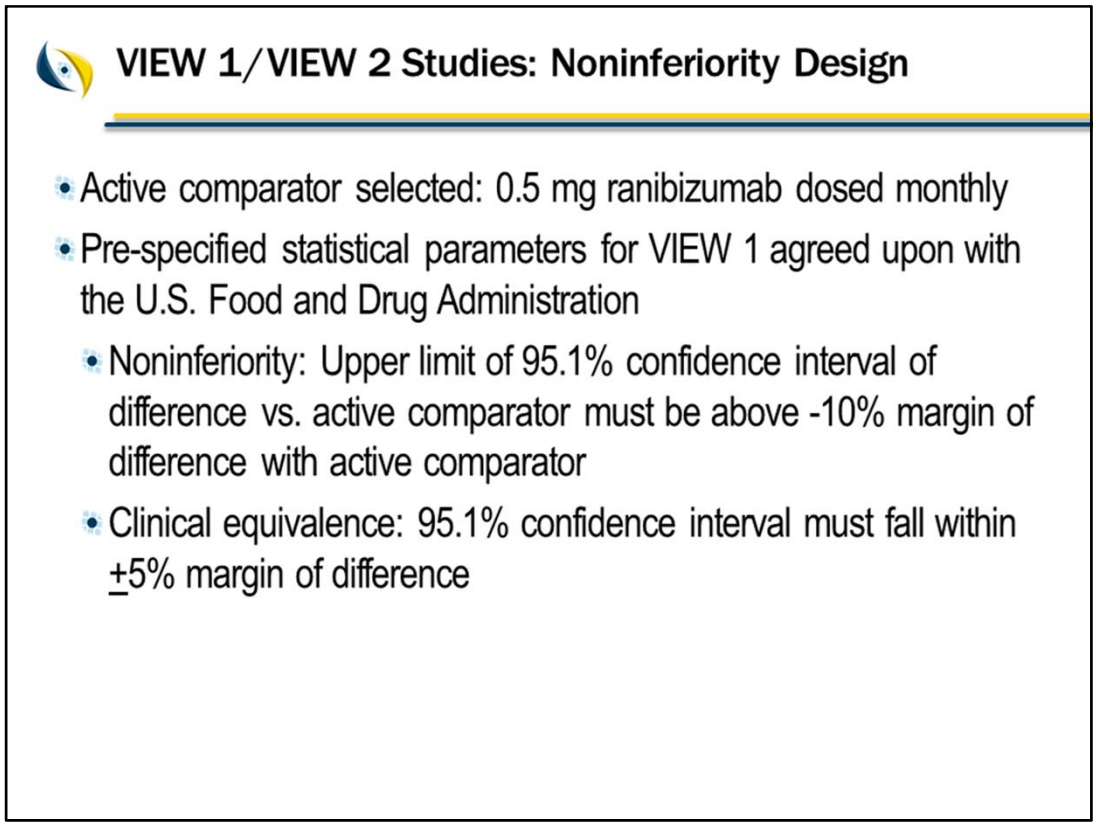
The statistical measure of interest is the confidence interval for the difference between the investigational drug and the active control. The margin of acceptable difference must be predefined.

Noninferiority studies must be conducted under similar conditions as the trials that established the efficacy of the active comparator in order to reliably conclude that the investigational drug is not less effective. That means similar designs, comparable populations, similar endpoints, and dosing of the active comparator.(CLICK)

[1]Food and Drug Administration. Guidance for Industry: Non-Inferiority Clinical Trials. March 2010. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM202140.pdf. Accessed 2/13/2012

[2]Brown DM et al. *N Engl J Med* 2006;355:1432-44.

[3]Rosenfeld PJ et al. *N Engl J Med* 2006;355:1419-31.

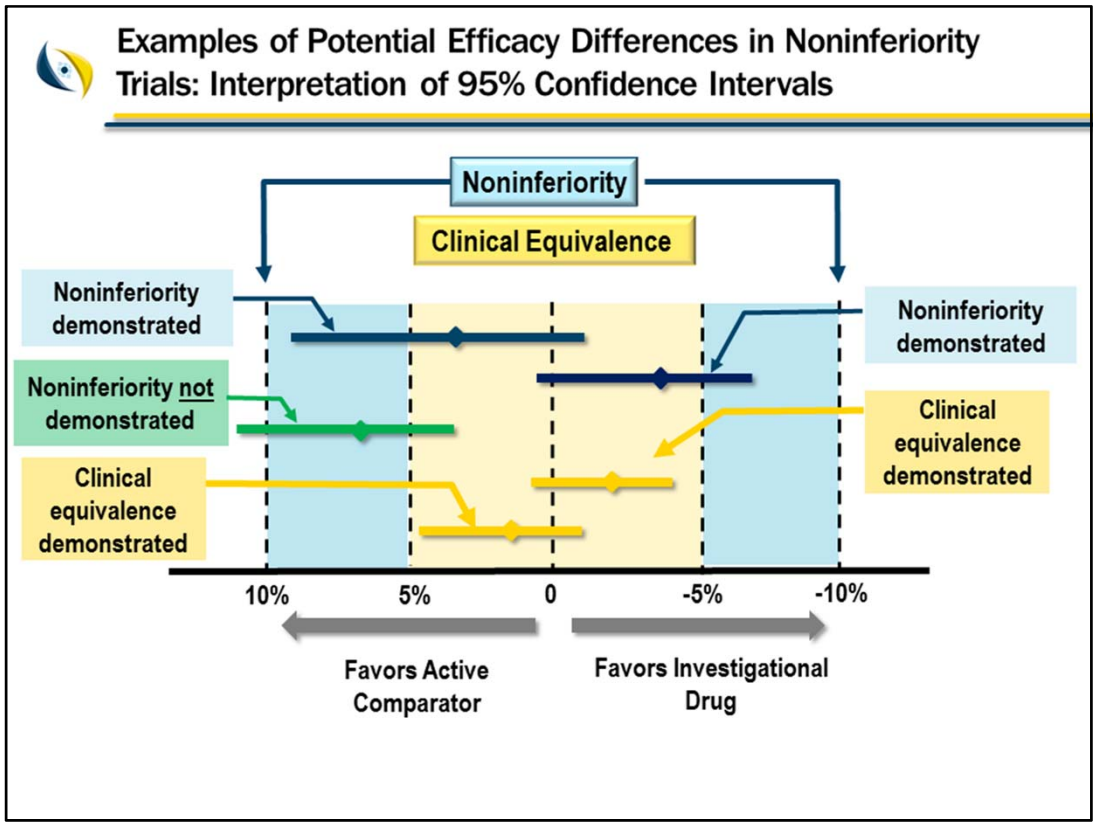


These principles account for the design of VIEW 1 and VIEW 2 in which intravitreal aflibercept injection was compared with ranibizumab 0.5 mg monthly under study conditions that were similar to the ANCHOR[2] and MARINA[3] studies.

At the time of the Phase 3 program for intravitreal aflibercept injection, ranibizumab 0.5 mg was the only pan-VEGF-A inhibitor previously proved effective in wet AMD in randomized, double-masked, controlled studies. Consequently, ranibizumab 0.5 mg dosed monthly was selected as the active comparator for VIEW 1 and VIEW 2 studies.

In consultation and agreement with the U.S. FDA, the prespecified statistical parameters for the noninferiority design of intravitreal aflibercept injection were a 95.1% confidence interval of the difference between intravitreal aflibercept injection and ranibizumab 0.5 mg had and 10% margin of difference. The confidence interval had to be above -10% in order for aflibercept to be proven noninferior to ranibizumab.

Clinical equivalence was defined as a 95.1% confidence interval being between ±5% for the primary endpoint. (CLICK)



This schematic illustrates the confidence interval approach for non-inferiority analyses. The statistical objective of VIEW 1 and VIEW 2 was to demonstrate that the 95% confidence interval of the difference between active comparator and investigational drug fell within a 10% margin for maintenance of visual acuity.

A statistical plan can also define a more narrow confidence interval margin within which active comparator and investigational drug can be considered clinically equivalent. In this case, we are showing a 5% margin for clinical equivalence. (CLICK)

These two plots show results that meet the specified noninferiority margin. The point estimate in the top plot favors active comparator, but the confidence interval does not cross the 10% margin on the left. In the second plot, the point estimate favors investigational drug but the confidence interval includes 0 so the investigational drug is noninferior to active comparator. (CLICK)

This plot shows a result that would fail to meet noninferiority criteria – the confidence interval crosses the 10% margin on the left. (CLICK)

Finally, these illustrate results that would be interpreted as demonstrating clinical equivalence since the confidence intervals around the point estimates for the efficacy difference fall within the 5% margins.

Now for the results from the VIEW 1 and VIEW 2 studies … (CLICK)

VIEW 1/VIEW 2 Studies: Baseline Demographics

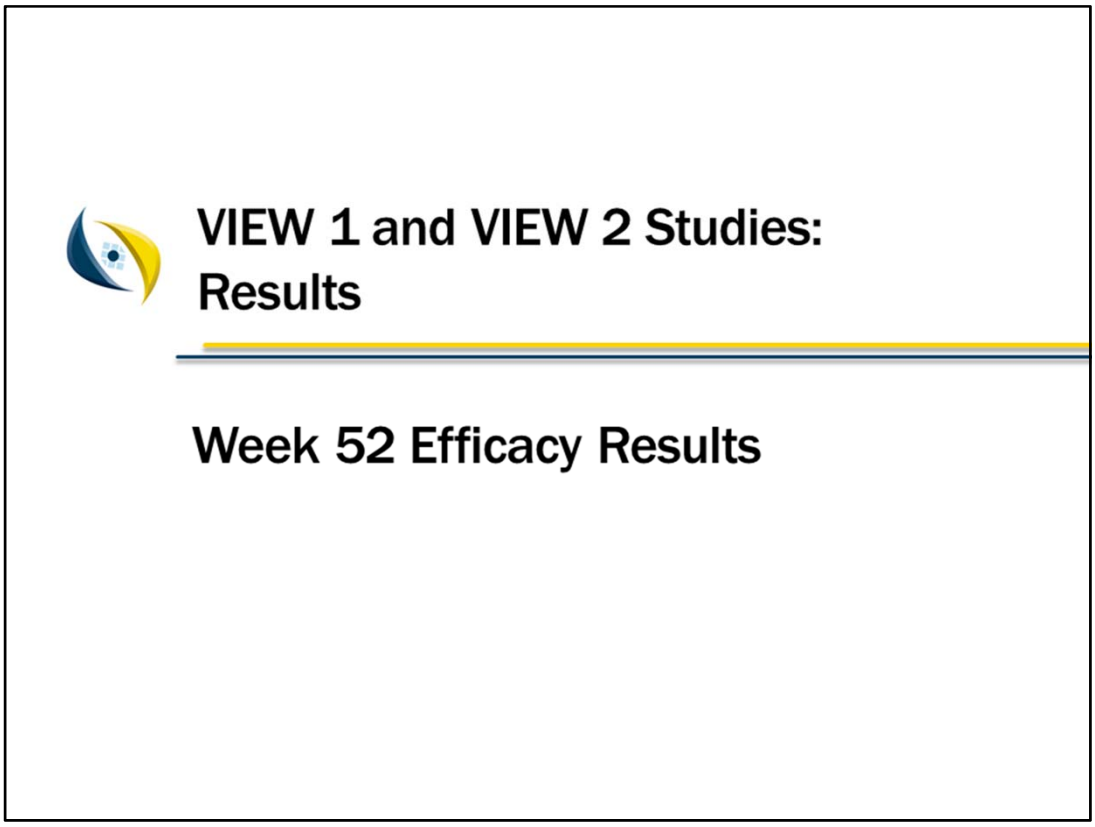
		RBZ Q4	IAI 0.5Q4	IAI 2Q4	IAI 2Q8
VIEW 1	N (full analysis set)	304	301	304	301
	Age, mean (SD)	78 (8) yrs	78 (8) yrs	78 (8) yrs	78 (8) yrs
	Women	57%	55%	64%	59%
	Race				
	White	97%	97%	97%	95%
	Asian	0	2%	1%	1%
	Black	<1%	0	<1%	<1%
	Other/not reported	2%	2%	2%	3%
VIEW 2	N (full analysis set)	291	296	309	306
	Age, mean (SD)	73 (9) yrs	75 (9) yrs	74 (8.5) yrs	74 (9) yrs
	Women	58%	50%	57%	57%
	Race				
	White	73%	74%	73%	71%
	Asian	21%	21%	22%	22.5%
	Black	<1%	<1%	0	1%
	Not reported	6%	5%	5%	6%

All treatment groups were well balanced in terms of age, gender, and race. Patient groups were demographically consistent with the overall population of patients with wet AMD in the countries where the studies were conducted. The higher proportion of Asian patients in VIEW 2 reflects the inclusion of study sites in Asia. (CLICK)

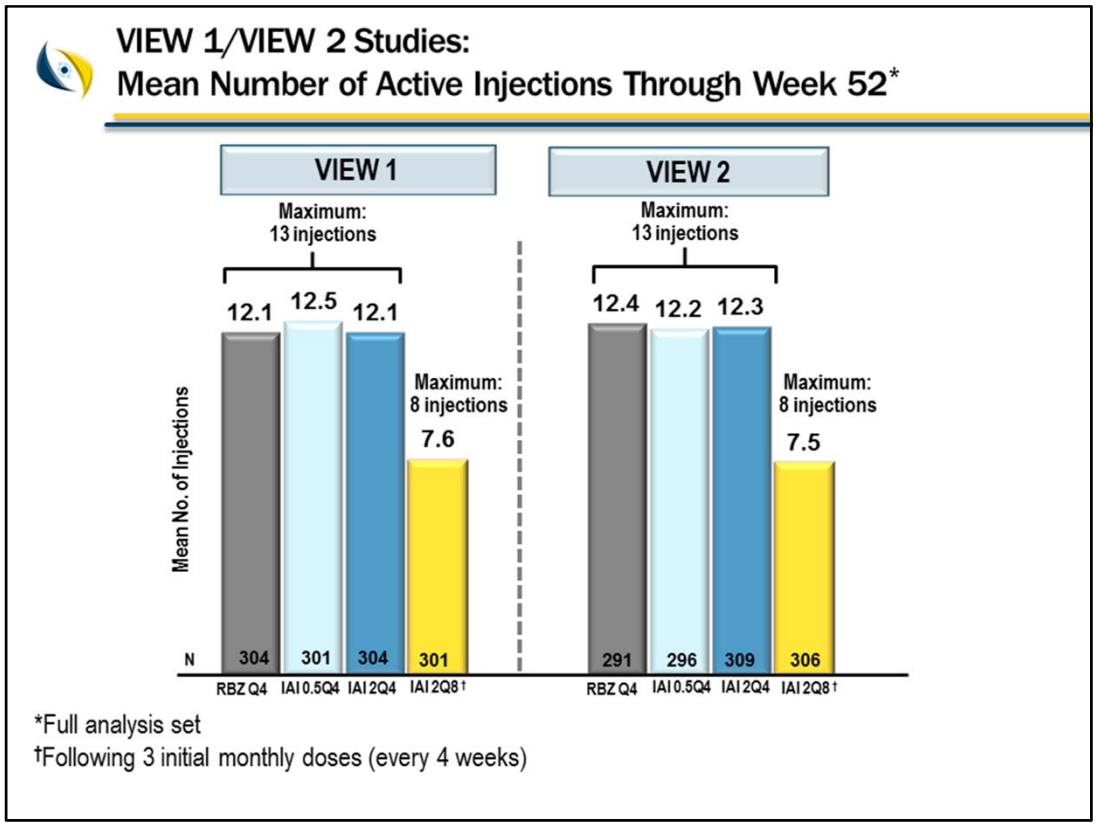
VIEW 1/VIEW 2 Studies: Baseline Disease Characteristics

		RBZ Q4	IAI 0.5Q4	IAI 2Q4	IAI 2Q8
VIEW 1	N (full analysis set)	304	301	304	301
	ETDRS BCVA letter score, mean (SD) Snellen Equivalent	54 (13) 20/80	56 (13) 20/80	55 (13) 20/80	56 (13) 20/80
	Lesion type				
	Predominantly classic	27%	27%	29%	24%
	Minimally classic	33%	32%	34.5%	36.5%
	Occult no classic	37%	40%	36%	39%
	Lesion size, mean (SD), mm^2	7 (5.5)	7 (5)	7 (5)	7 (5)
	Central retinal thickness, mean (SD), µm	315 (109)	313 (106)	314 (104)	324 (112)
VIEW 2	N (full analysis set)	291	296	309	306
	ETDRS BCVA letter score, mean (SD) Snellen Equivalent	54 (14) 20/80	52 (14) 20/80	53 (14) 20/80	52 (14) 20/80
	Lesion type				
	Predominantly classic	24%	27%	23%	29%
	Minimally classic	36%	35%	36%	35%
	Occult no classic	40%	38%	40%	36%
	Lesion size, mean (SD), mm^2	8 (6)	8 (5.5)	9 (6)	8 (6)
	Central retinal thickness, mean (SD), µm	326 (111)	327 (116)	335 (120)	343 (124)

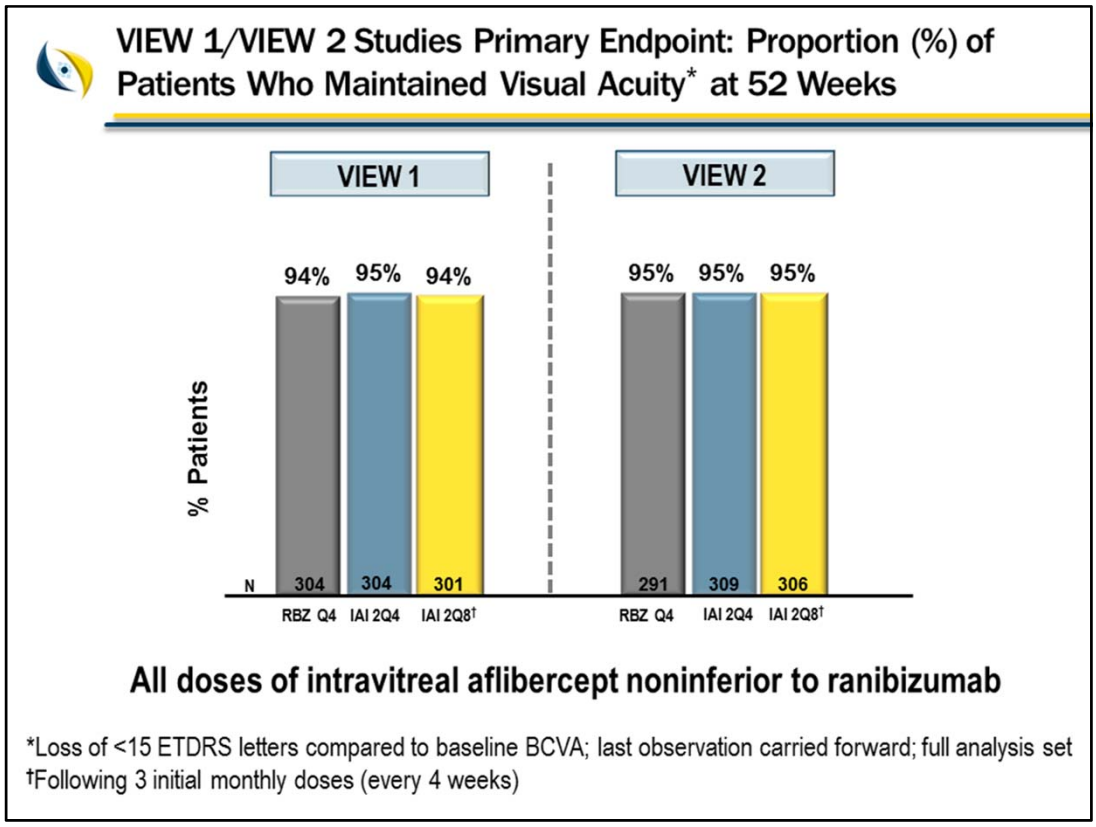
Baseline visual acuity, lesion type, lesion size and central retinal thickness were well balanced across all treatment groups and both studies. Patients were moderately impaired with an average BCVA (Snellen equivalent) of 20/80. All three types of lesions were roughly equally represented. (CLICK)



Let's now take a look at the efficacy results through week 52 of the VIEW 1 and VIEW 2 studies. (CLICK)



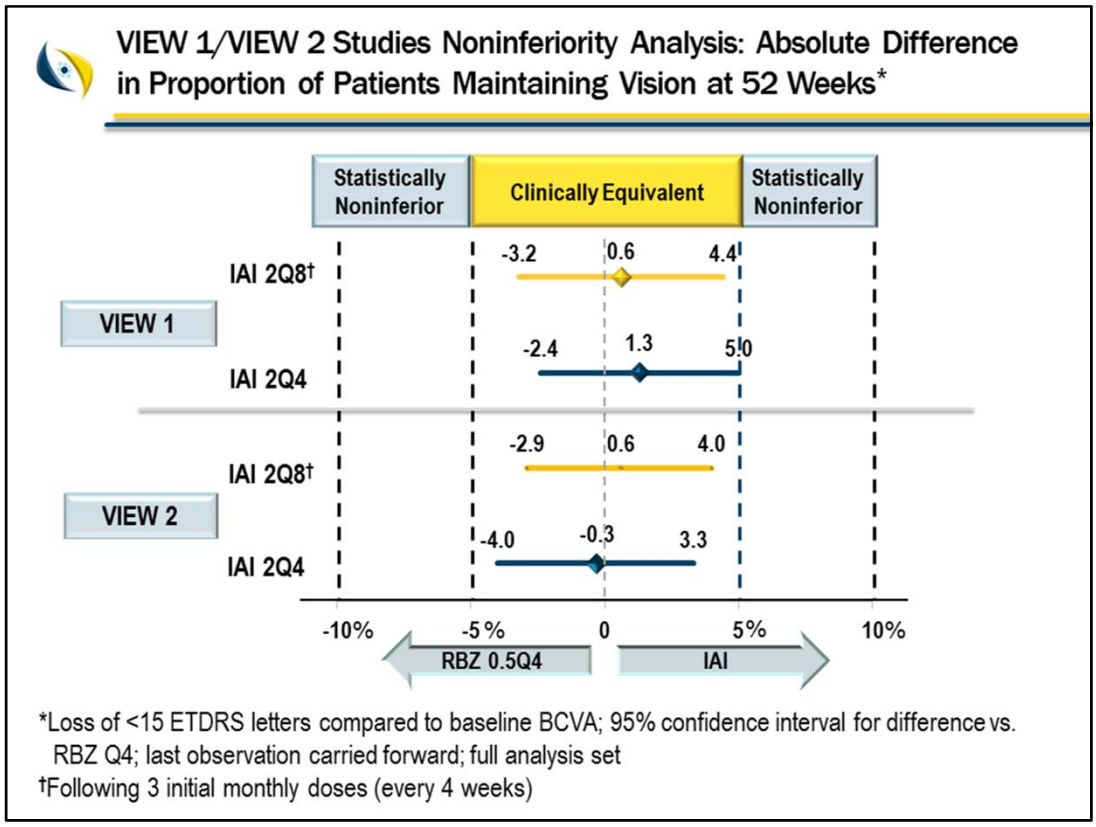
The protocols' dosing schedules called for 13 injections in the Q4 groups while the Q8 groups were scheduled for 8 injections. Compliance with each dosing regimen was well over 90%. As planned, the group assigned to intravitreal aflibercept injection 2Q8 received approximately 5 fewer injections than the Q4 groups. (CLICK)



The primary endpoint was the proportion of patients in whom best-corrected visual acuity on an ETDRS chart was maintained, defined as a loss of no more than 52 letters from baseline to week 52.

All treatment groups were numerically similar or virtually identical.

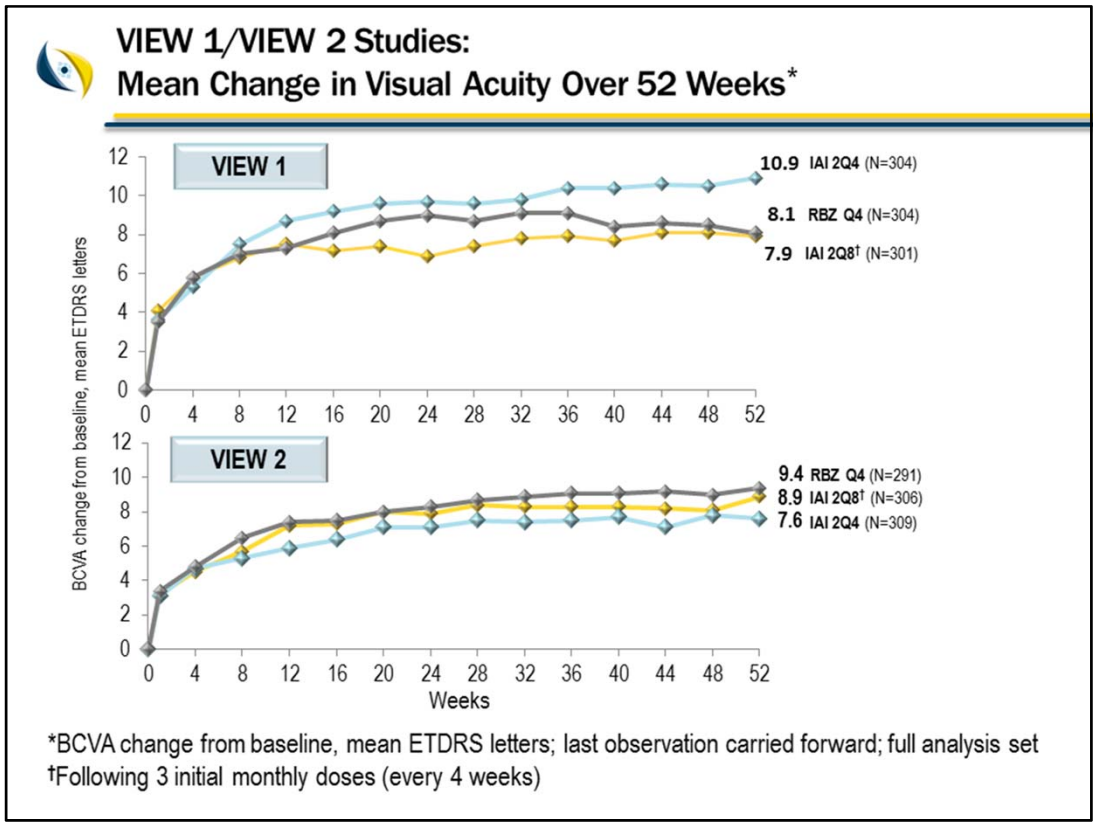
EYLEA 0.5 mg every 4 weeks (monthly) demonstrated similar efficacy and safety to EYLEA 2 mg every 4 weeks (monthly), but is not an approved dose. (CLICK)



The 95.1% confidence intervals for the difference between intravitreal aflibercept injection and ranibizumab were well within the noninferiority margin of 10%, showing that intravitreal aflibercept injection treatment arms, including the 2 mg every 8 weeks arm, achieved statistical noninferiority to monthly ranibizumab for the primary endpoint.

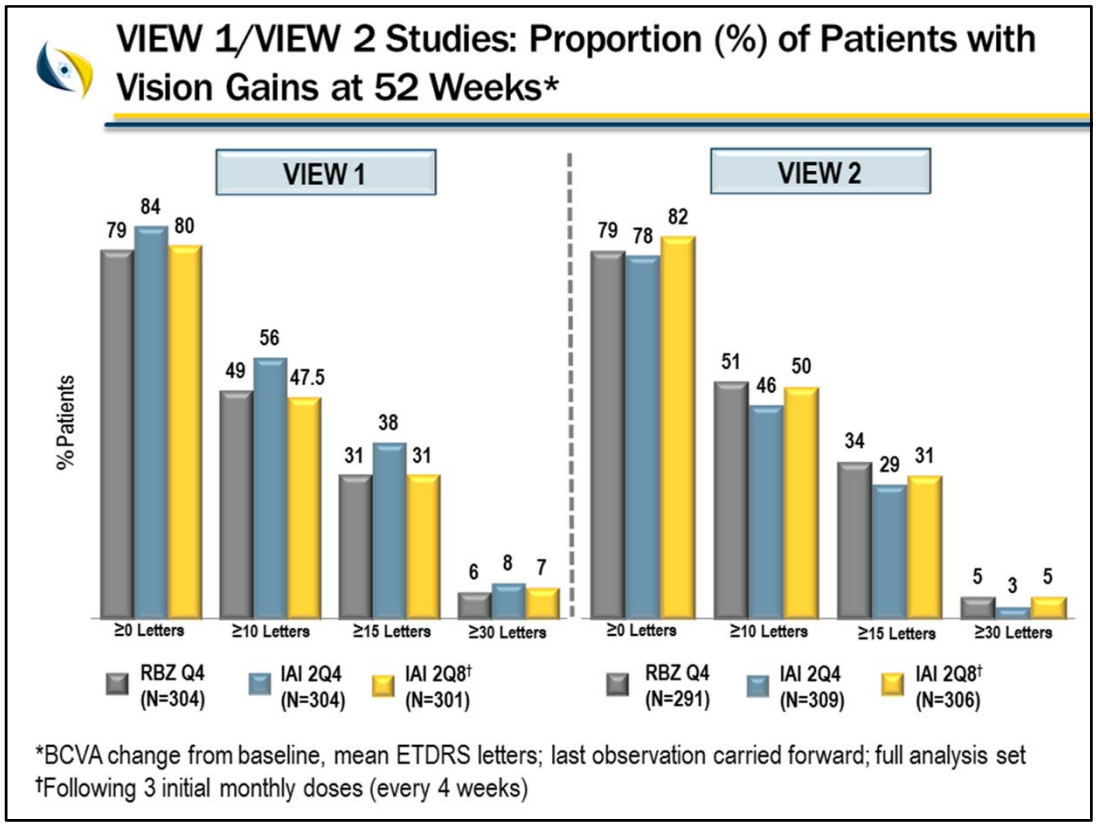
In addition, the confidence intervals around the mean difference were very tight and fell within ±5%.

Therefore, aflibercept injection administered as 2 mg every 8 weeks (following 3 initial monthly doses) or as 2 mg every 4 weeks is clinically equivalent to ranibizumab 0.5 mg dosed every 4 weeks in terms of the primary endpoint. (CLICK)



Again, with efficacy measured as mean change in best-corrected visual acuity, intravitreal aflibercept injection tracked closely with ranibizumab in both studies. Improvements in BCVA were observed as early as week 1 in all treatment groups, with an overall trend of continuing improvement to the week 52 visit.

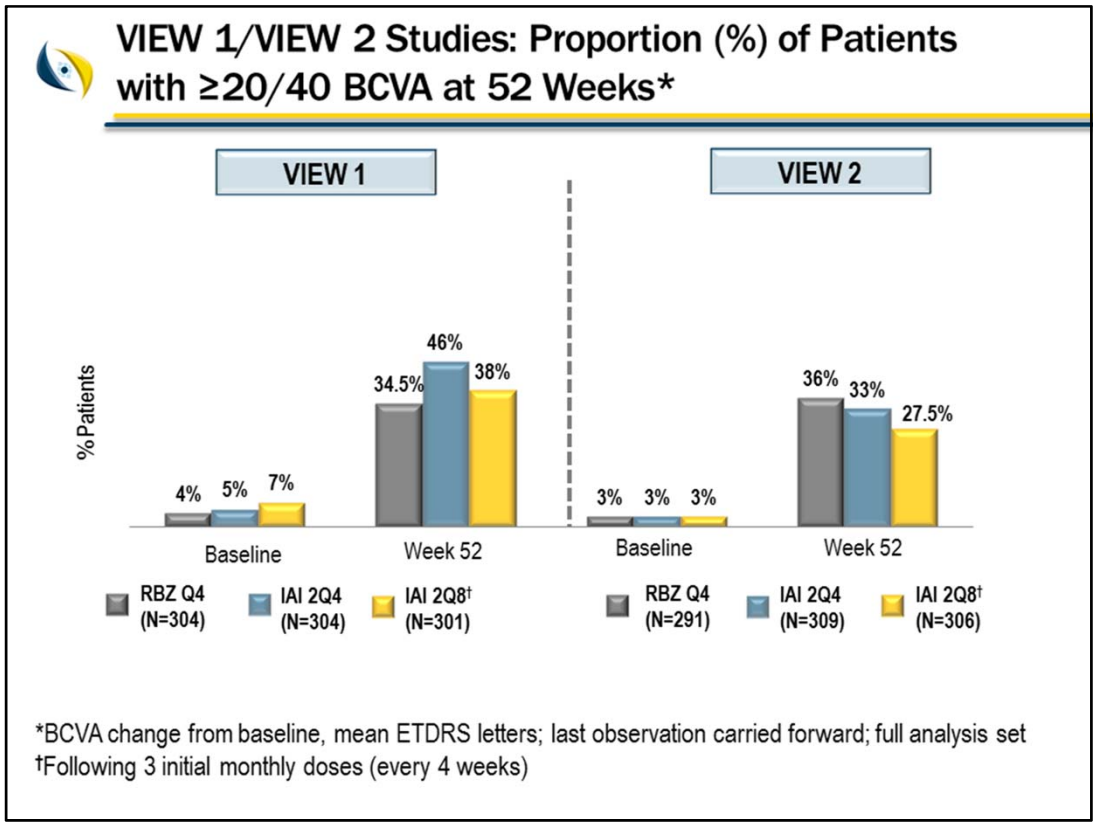
The minor differences between groups disappeared when data were combined across studies, showing that the mean change in BCVA at week 52 was within 1 letter for all study treatments (range, 8.3 to 9.3 letters). All intravitreal aflibercept injection groups, including the 2 mg every 8 weeks arm, were similar to monthly ranibizumab. (CLICK)



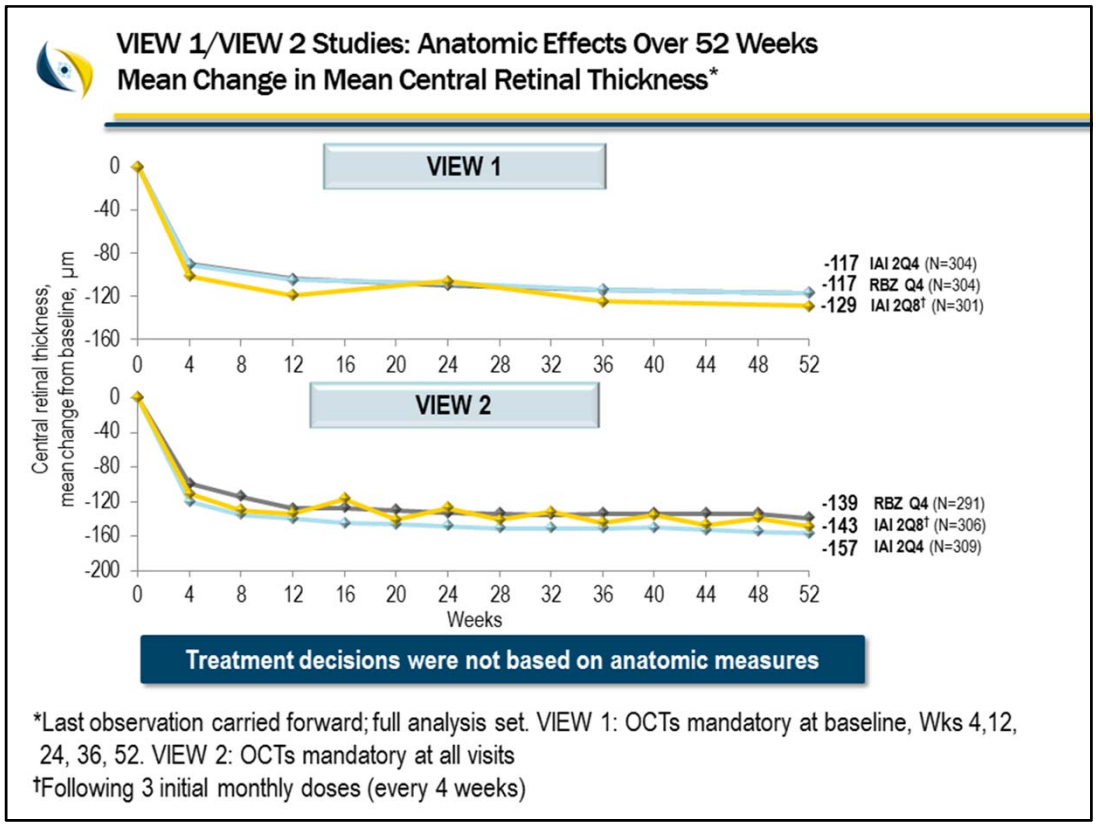
Most patients in both studies showed some improvement in visual acuity at 1 year. Proportions were numerically similar for all intravitreal aflibercept injection groups and ranibizumab monthly.

A gain of at least 15 letters or 3 lines in BCVA is considered a clinically significant increase in visual acuity. Similar proportions of patients treated with intravitreal aflibercept injection or monthly ranibizumab experienced improvements in vision.

Confidence intervals for differences between intravitreal aflibercept injection and ranibizumab in the individual studies as well as in combined data included zero, thereby showing no clinically relevant differences between groups in terms of patients gaining 15 or more letters. (CLICK)



Average BCVA at baseline was 20/80. At 1 year, visual acuity had improved to 20/40 or better in similar proportions across intravitreal aflibercept injection arms, including the 2 mg every 8 weeks group, and the monthly ranibizumab arm. (CLICK)

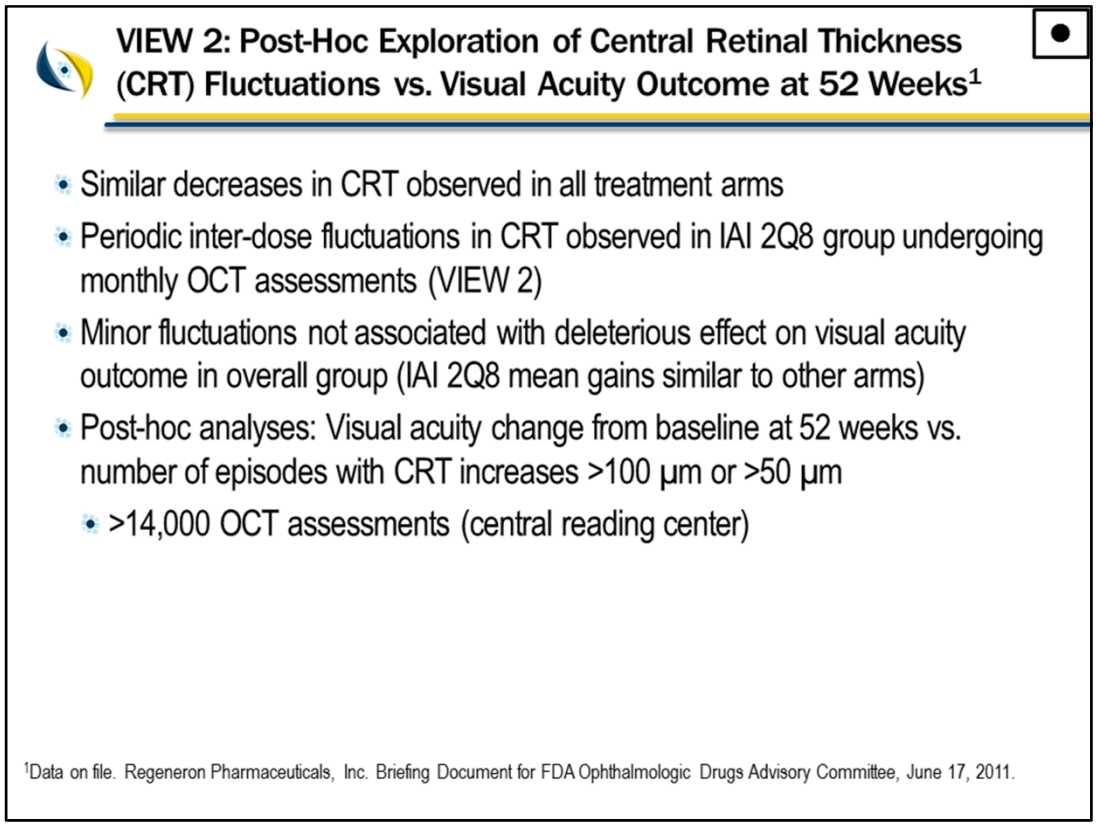


Changes in anatomic measures such as central retinal thickness as measured by OCT are regarded as pharmacodynamic indicators of VEGF inhibition in wet AMD.

Mean central retinal thickness was reduced by week 4. Reductions were maintained through the end of year 1. Reductions were similar across treatment groups.

Because OCTs were performed at all visits in VIEW 2, monthly data were available and showed minor inter-injection fluctuations in average retinal thickness in the 2 mg Q8 group. These fluctuations steadily diminished in the latter part of the study.

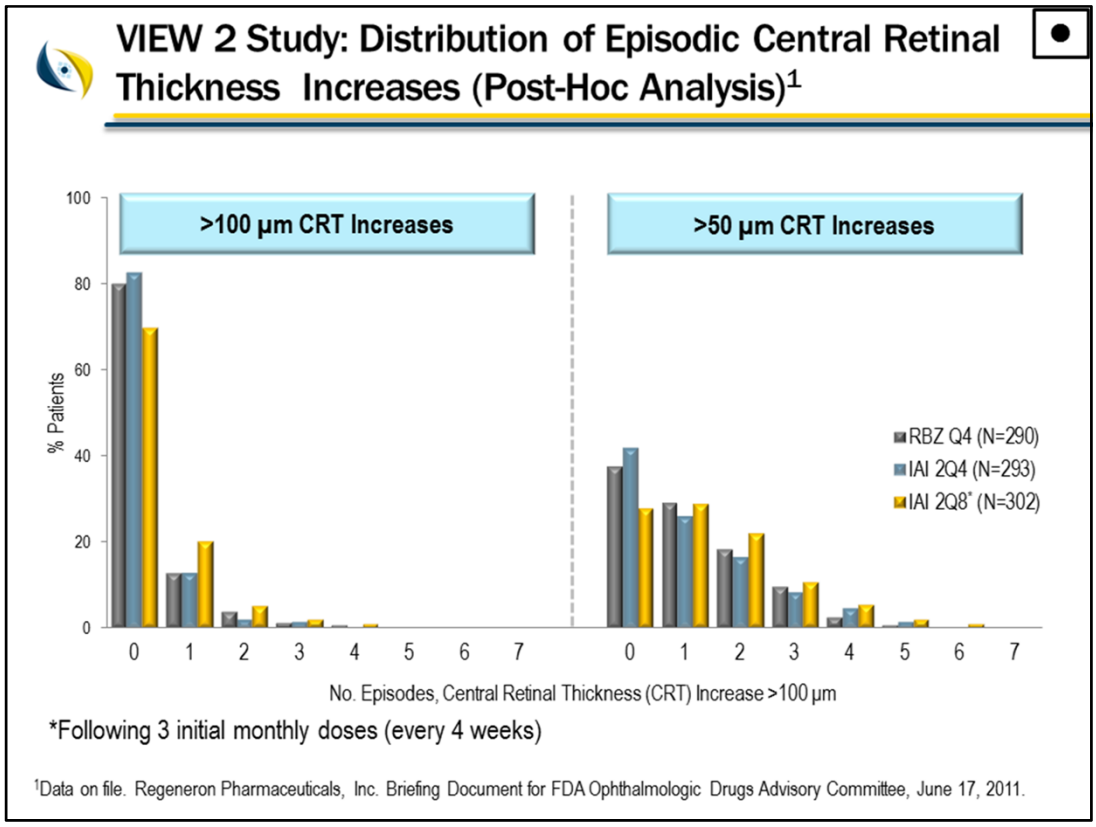
It should be noted that anatomic measures were not used to guide dosing decisions in these studies.(CLICK)



(Optional Slide)

The VIEW studies showed similar decreases in retinal thickness in all treatment arms over 52 weeks. However, in VIEW 2, monthly OCT data exhibited minor inter-dose fluctuations in central retinal thickness in the aflibercept 2Q8 group, prompting additional post-hoc exploration. Mean visual acuity changes from baseline in the intravitreal aflibercept 2Q8 group were similar to the gains achieved in the other arms, suggesting no overall deleterious effect associated with the CRT fluctuations.

Data on more than 14,000 OCT evaluations read by a central reading center were available for analysis. Patients in each arm were grouped according to the number of inter-visit CRT increases >100 µm or >50 µm. The mean visual acuity outcome for each group was then analyzed in these post-hoc investigations. (CLICK)

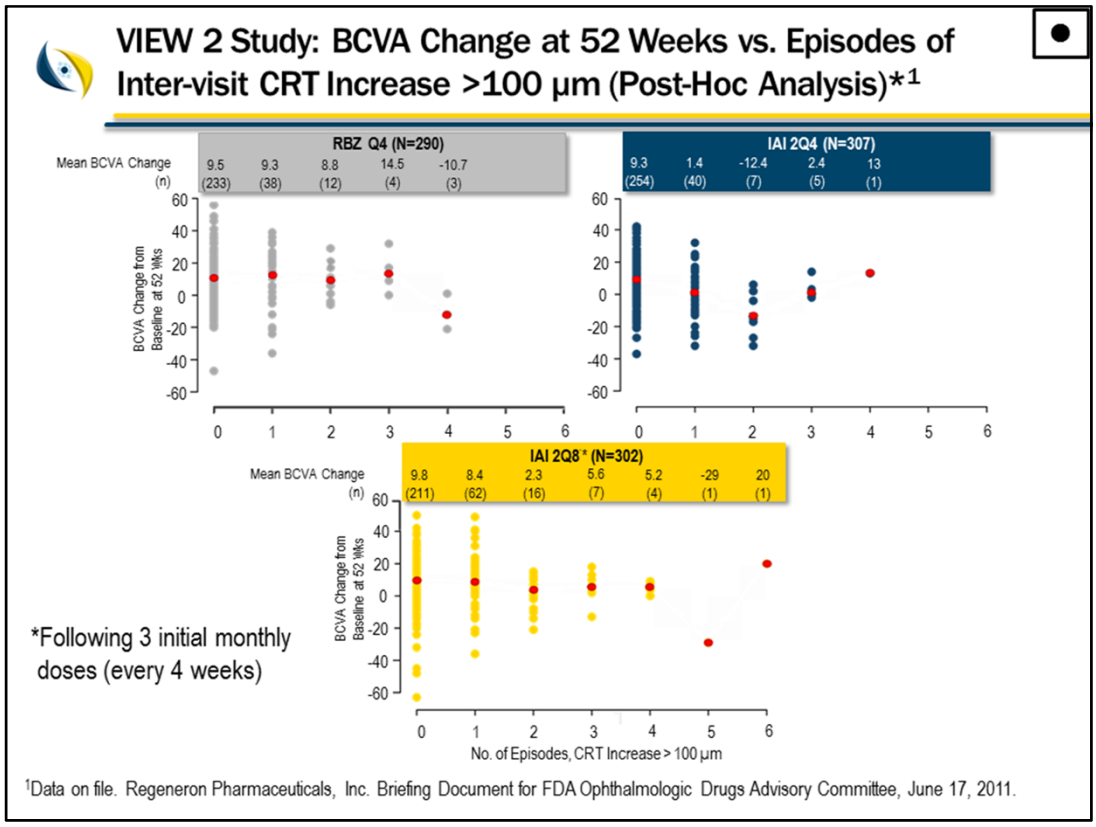


(Optional Slide)

Looking at inter-visit increases >100 µm in CRT, the post-hoc analyses showed that approximately 20-30% of patients in every group in VIEW 2 displayed at least one such episode.[1] However, relatively few patients in any group had more than one such occurrence. There was a small shift in the group receiving intravitreal aflibercept injection as 2 mg every 8 weeks.

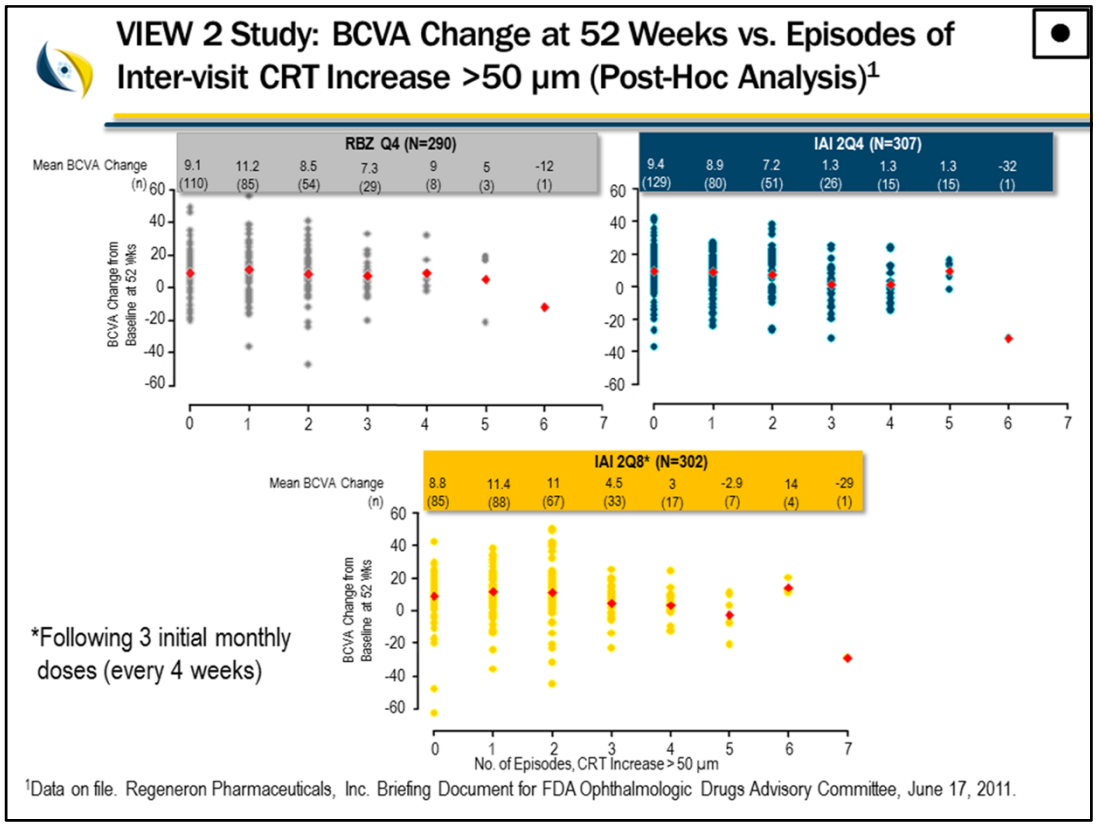
A similar pattern was observed among patients with inter-visit CRT increases >50 µm. (CLICK)

[1]Data on file. Regeneron Pharmaceuticals, Inc. Briefing Document for FDA Ophthalmologic Drugs Advisory Committee, June 17, 2011.



When number of episodes of inter-visit CRT increases > 100 µm was compared with best-corrected visual acuity at 52 weeks, the post-hoc analyses did not find a correlation between CRT increases and visual acuity outcome.[1] (CLICK)

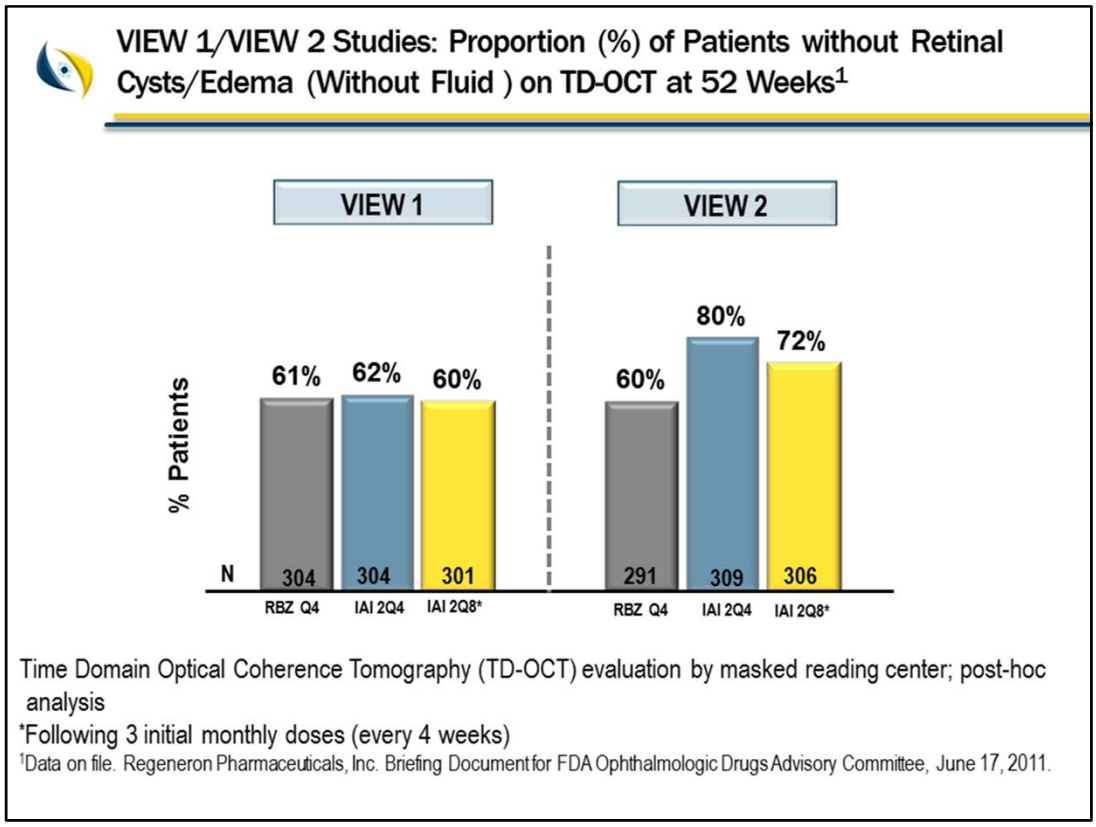
[1]Data on file. Regeneron Pharmaceuticals, Inc. Briefing Document for FDA Ophthalmologic Drugs Advisory Committee, June 17, 2011.



(Optional Slide)

When the cut-off for intervisit CRT increase was >50 µm, there was no correlation between episodic CRT increase and visual acuity outcome at 52 weeks.[1] (CLICK)

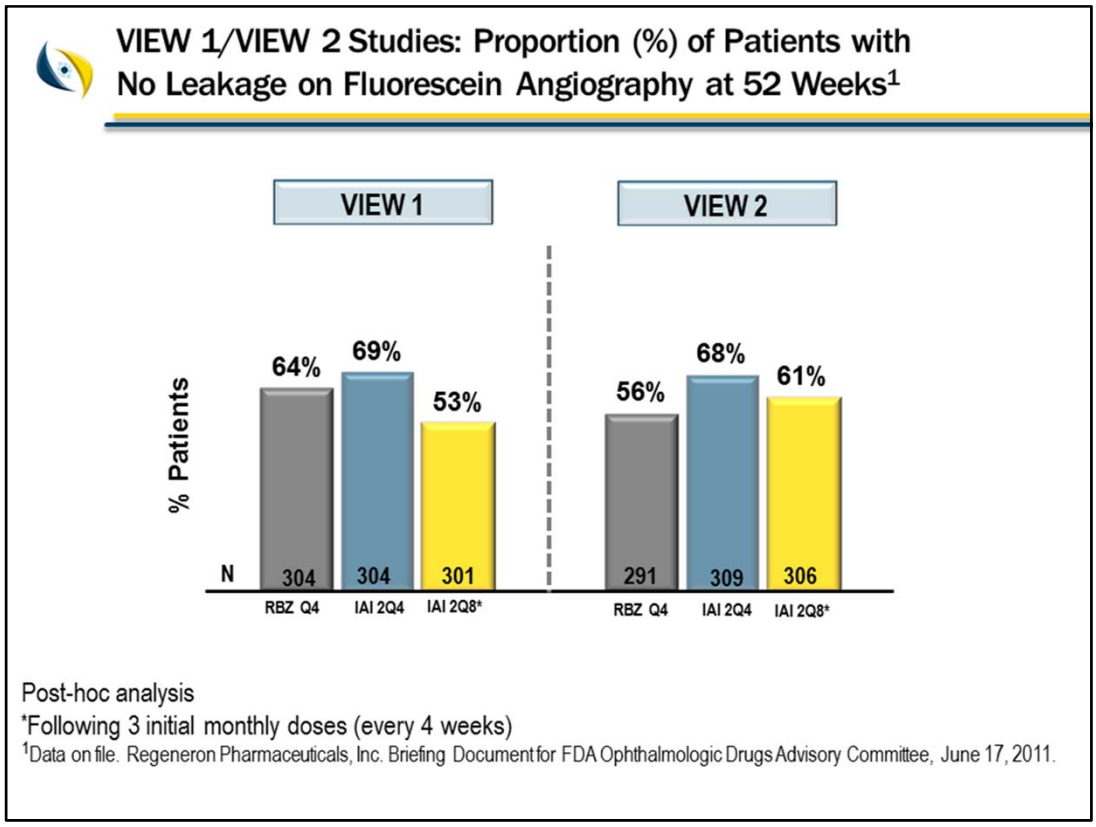
[1]Data on file. Regeneron Pharmaceuticals, Inc. Briefing Document for FDA Ophthalmologic Drugs Advisory Committee, June 17, 2011.



A post-hoc analysis was performed to determine the proportion of patients with no retinal cysts or edema on OCT.[1] Groups were generally numerically similar.

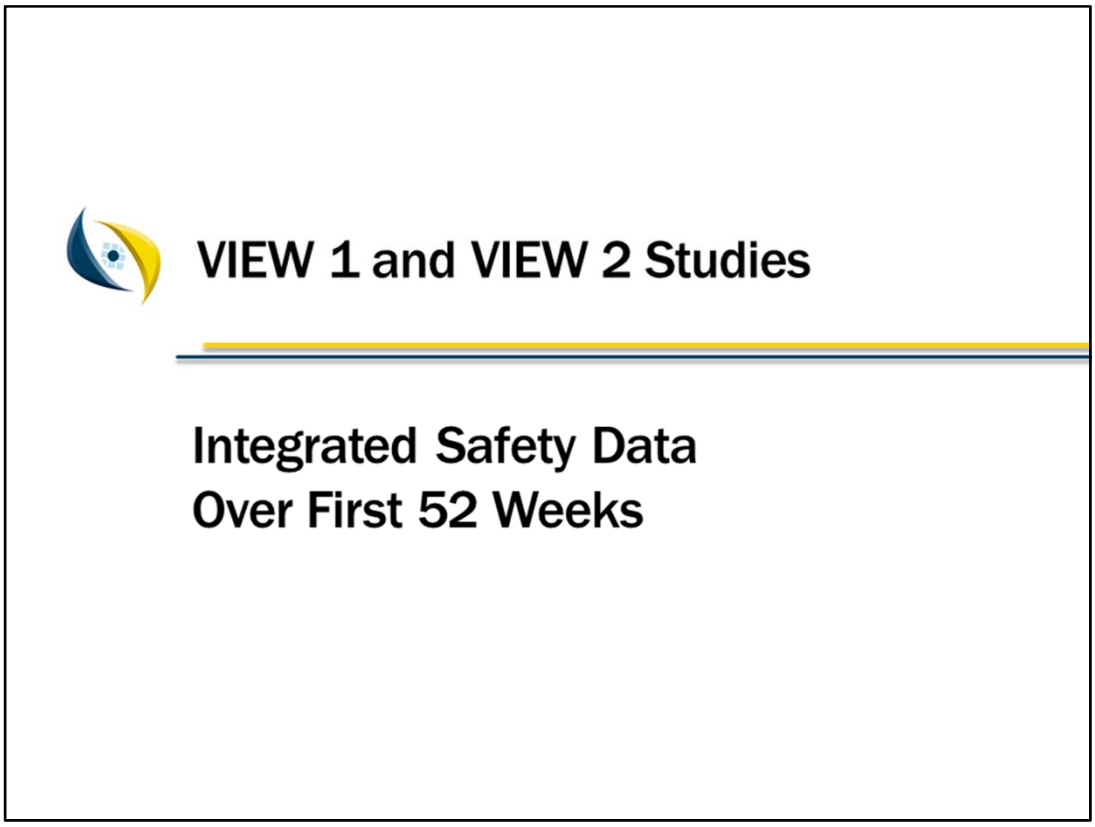
Their clinical significance in terms of vision benefits are not clear and they were not used to guide dosing decisions in these studies. (CLICK)

[1]Data on file. Regeneron Pharmaceuticals, Inc. Briefing Document for FDA Ophthalmologic Drugs Advisory Committee, June 17, 2011.

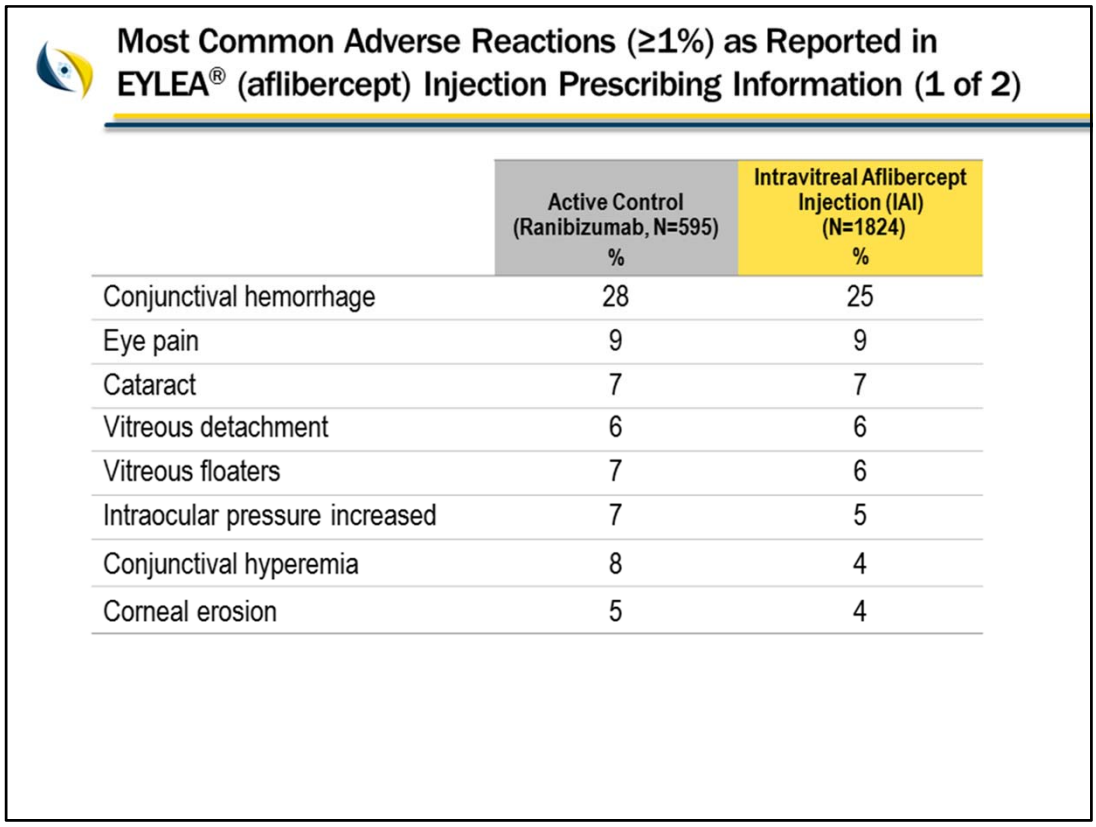


As with patients without retinal edema, the proportion of patients with no fluorescein leakage were comparable across treatment groups.[1] (CLICK)

[1]Data on file. Regeneron Pharmaceuticals, Inc. Briefing Document for FDA Ophthalmologic Drugs Advisory Committee, June 17, 2011.



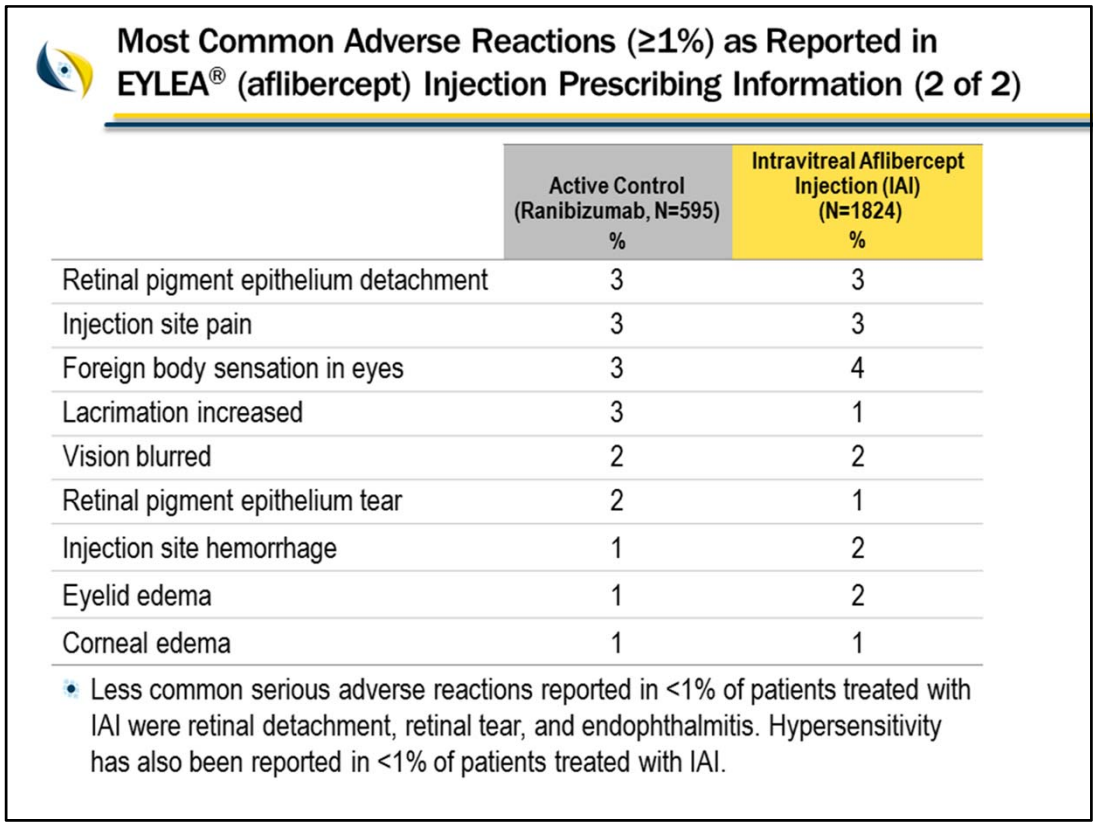
We'll now turn our attention to the safety data from the VIEW 1 and VIEW 2 trials, which pool all EYLEA® (aflibercept) Injection arms, including the EYLEA 0.5 mg monthly arm. (CLICK)



(Slide 1 of 2 slides)

The most common adverse reactions reported in ≥5% patients receiving intravitreal aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. Occurrence rates were similar for intravitreal aflibercept injection and active control ranibizumab. Combined data for all intravitreal aflibercept injection dosages are shown. No dose-related incidence or pattern of adverse reactions was seen in patients receiving intravitreal aflibercept injection.

Adverse reactions occurring in <5% but in ≥1% of patients receiving intravitreal aflibercept injection included corneal erosion … (CLICK)



Most Common Adverse Reactions (≥1%) as Reported in EYLEA® (aflibercept) Injection Prescribing Information (2 of 2)

	Active Control (Ranibizumab, N=595) %	Intravitreal Aflibercept Injection (IAI) (N=1824) %
Retinal pigment epithelium detachment	3	3
Injection site pain	3	3
Foreign body sensation in eyes	3	4
Lacrimation increased	3	1
Vision blurred	2	2
Retinal pigment epithelium tear	2	1
Injection site hemorrhage	1	2
Eyelid edema	1	2
Corneal edema	1	1

- Less common serious adverse reactions reported in <1% of patients treated with IAI were retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in <1% of patients treated with IAI.

(slide 2 of 2 slides)

Adverse reactions occurring in <5% but in ≥1% of patients receiving intravitreal aflibercept injection included RPE detachment, injection site pain, foreign body sensation in the eyes, increased lacrimation, blurred vision, RPE tear, injection site hemorrhage, eyelid edema, and corneal edema.

Less common serious adverse reactions reported in <1% of patients treated with intravitreal aflibercept injection were retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in <1% of patients treated with intravitreal aflibercept injection. (CLICK)

VIEW 1/VIEW 2 Studies: Serious Ocular Adverse Reactions Over First 52 Weeks*

	Active Control (Ranibizumab, N=595) %	Intravitreal Aflibercept Injection (IAI) (N=1824) %
Any serious ocular adverse event	3.4	2.1
Visual acuity reduced	0.5	0.5
Retinal hemorrhage	0.5	0.3
Endophthalmitis	0.5	0.2
Cataract	0.2	0.2
RPE Tear	0.2	0.2
IOP increased	0.2	0.1
Retinal detachment	0.2	0.1
Macular hole	0	0.1
Posterior capsular opacification	0.3	0

*Occurring in ≥2 patients in either group

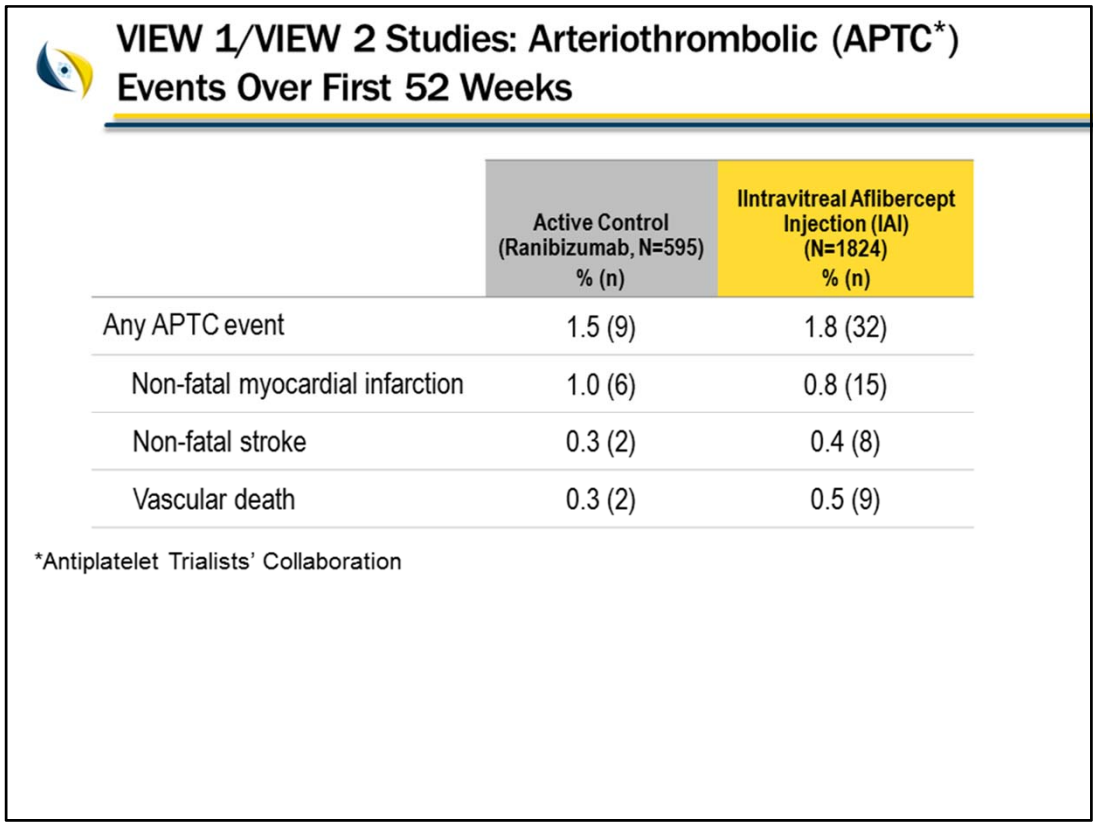
Serious ocular adverse events reported in 3.4% of patients in the ranibizumab group and 2.1% of patients in the intravitreal aflibercept injection arm. Rates of serious ocular adverse reactions were similar for active control ranibizumab and intravitreal aflibercept injection. Less common serious adverse reactions occurring in <1% of patients treated with intravitreal aflibercept injection were retinal detachment, retinal tear, and endophthalmitis.(CLICK)

VIEW 1/VIEW 2 Studies: Serious Non-ocular (Systemic) Adverse Reactions Over First 52 Weeks*

Disorder	Active Control (Ranibizumab, N=595) %	Intravitreal Aflibercept Injection (IAI) (N=1824) %
Any serious non-ocular adverse event	14	14
Infections/infestations	3.5	2
Cardiac	3	3
Neoplasms	2	2.5
Vascular disorders	1	1
Injury/poisoning/procedural complications	1	2
Musculoskeletal/connective tissue	1	0.5
Gastrointestinal	1	1.5
Respiratory/thoracic/mediastinal	1	1
General/administration site	1	1
Nervous system	0.5	2

*≥1% in either group

In both the ranibizumab and the intravitreal aflibercept injection arms the incidence of any serious non-ocular adverse reaction was 14%. (CLICK)



VIEW 1/VIEW 2 Studies: Arteriothrombolic (APTC*) Events Over First 52 Weeks

	Active Control (Ranibizumab, N=595) % (n)	IIntravitreal Aflibercept Injection (IAI) (N=1824) % (n)
Any APTC event	1.5 (9)	1.8 (32)
Non-fatal myocardial infarction	1.0 (6)	0.8 (15)
Non-fatal stroke	0.3 (2)	0.4 (8)
Vascular death	0.3 (2)	0.5 (9)

*Antiplatelet Trialists' Collaboration

There is a potential risk of arteriothrombolic events (ATEs) following the use of intravitreal VEGF inhibitors, including EYLEA. These are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs with EYLEA in clinical trials was 1.8% during the first year. (CLICK)

VIEW 1/VIEW 2 Studies: Deaths Over First 52 Weeks

	Active Control (Ranibizumab, N=595) % (n)	Intravitreal Aflibercept Injection (IAI) (N=1824) % (n)
All deaths	1.2 (7)	1.0 (19)
Cardiac disorders	0.5 (3)	0.4 (8)
General/administration site conditions	0	0.1 (2)
Neoplasms	0.5 (3)	0.1 (2)
Nervous system	0	0.2 (3)
Respiratory/thoracic/mediastinal	0.2 (1)	0.2 (3)
Vascular disorders	0	0.1 (2)

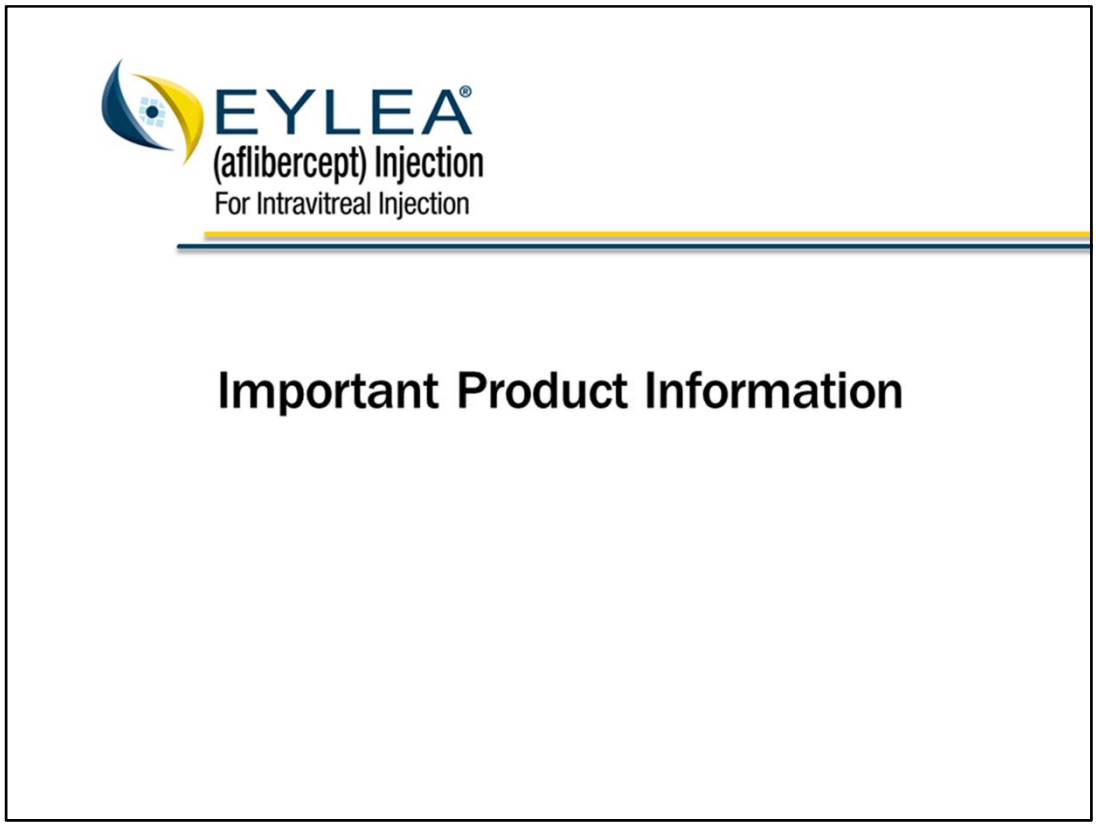
Deaths occurred in 1.2% of patients in the ranibizumab arm and 1.0% of the patients in the intravitreal aflibercept injection arm. (CLICK)

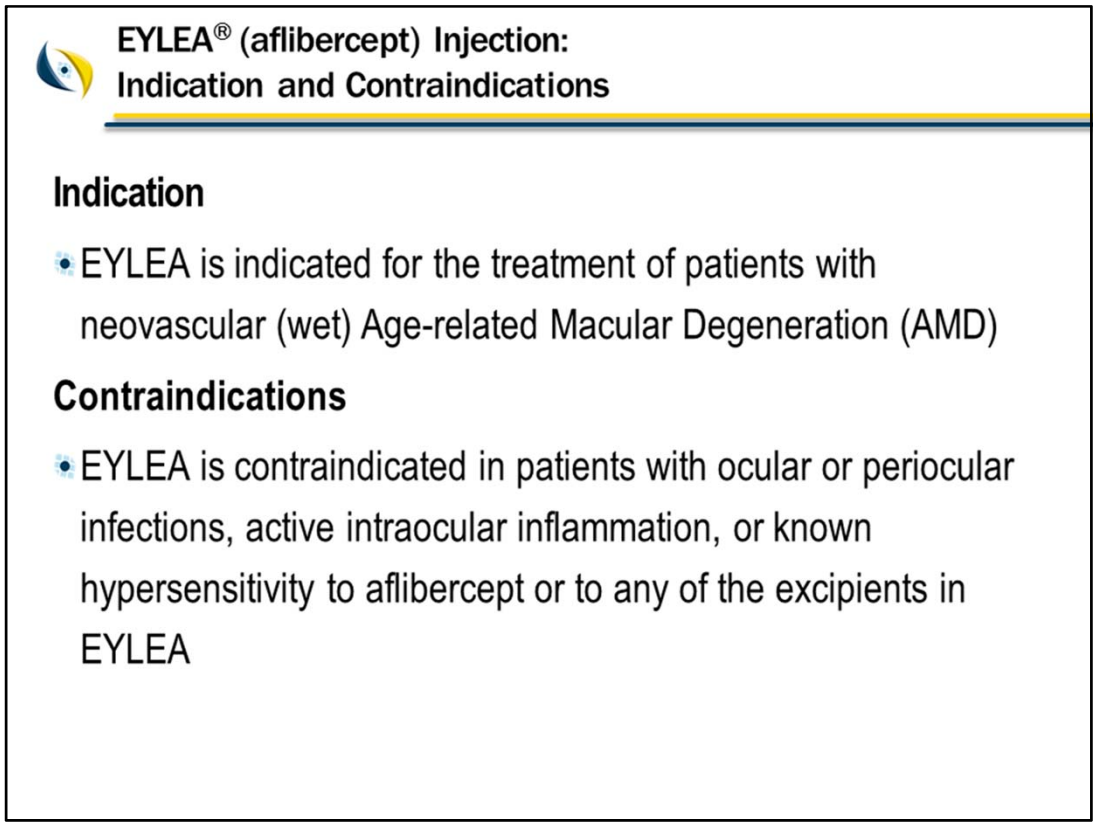
VIEW 1/VIEW 2 Studies: Intraocular Inflammation Events Over First 52 Weeks

	Active Control (Ranibizumab, N=595) % (n)	Intravitreal Aflibercept Injection (IAI) (N=1824) % (n)
Endophthalmitis*	0.5 (3)	0.2 (3)
Eye inflammation	0	<0.1 (1)
Iridocyclitis	0	0.1 (2)
Iritis	0.2 (1)	0
Retinal vasculitis	0	<0.1 (1)
Vitritis	0.2 (1)	<0.1 (1)

*Serious ocular adverse event

Intraocular inflammatory events occurred with similar frequency across treatment groups. (CLICK)


EYLEA®
(aflibercept) Injection
For Intravitreal Injection
Important Product Information



We reviewed the efficacy results from VIEW 1 and VIEW 2 which support the approved indication for EYLEA® (aflibercept) Injection ...

Namely, that EYLEA is indicated for the treatment of wet age-related macular degeneration.

EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.(CLICK)

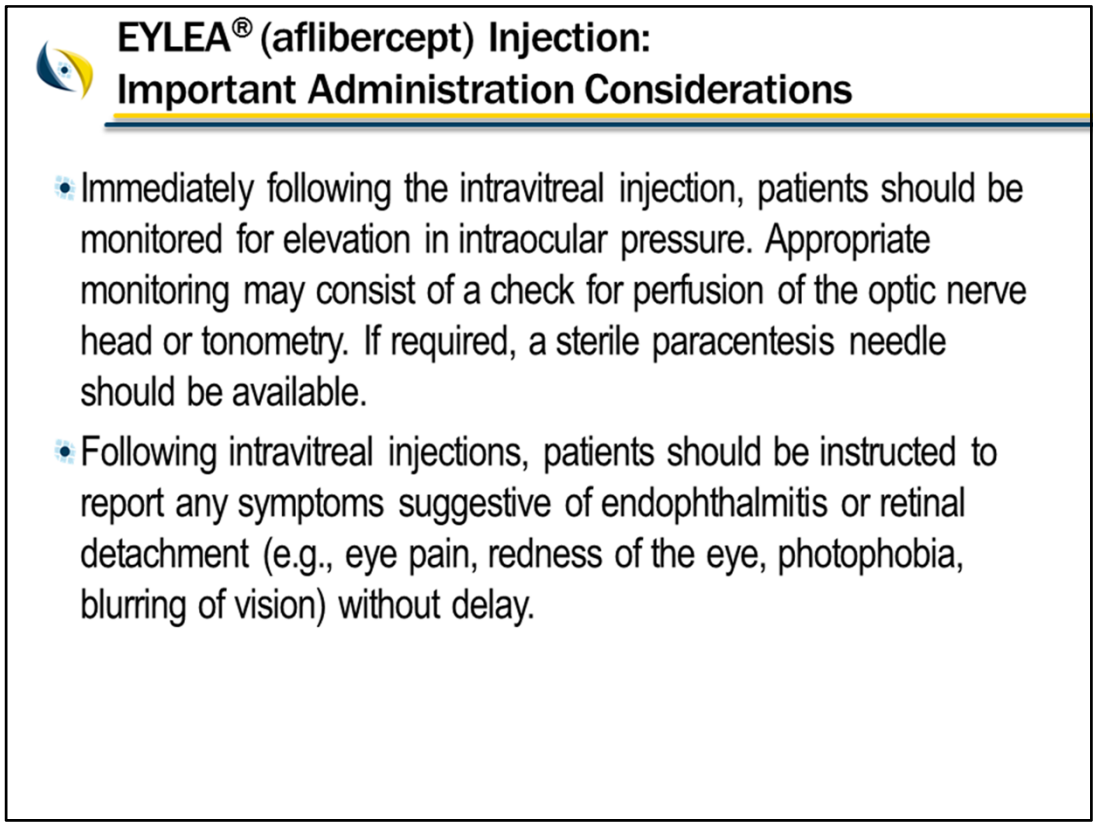
EYLEA® (aflibercept) Injection: Dosage and Administration

- The recommended dose for EYLEA is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months).



- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

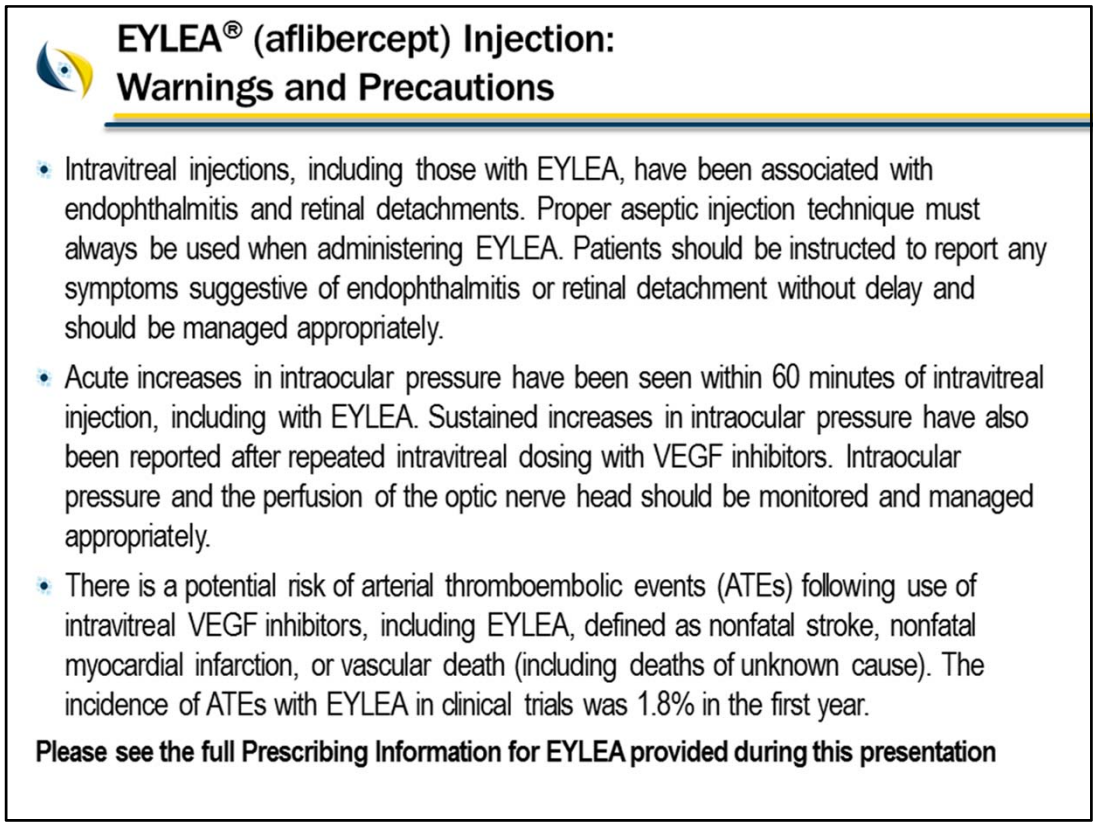
The recommended dose for EYLEA® (aflibercept) Injection is 2 mg administered by intravitreal injection every 4 weeks, or monthly, for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (CLICK)



Verbatim

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injections, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.



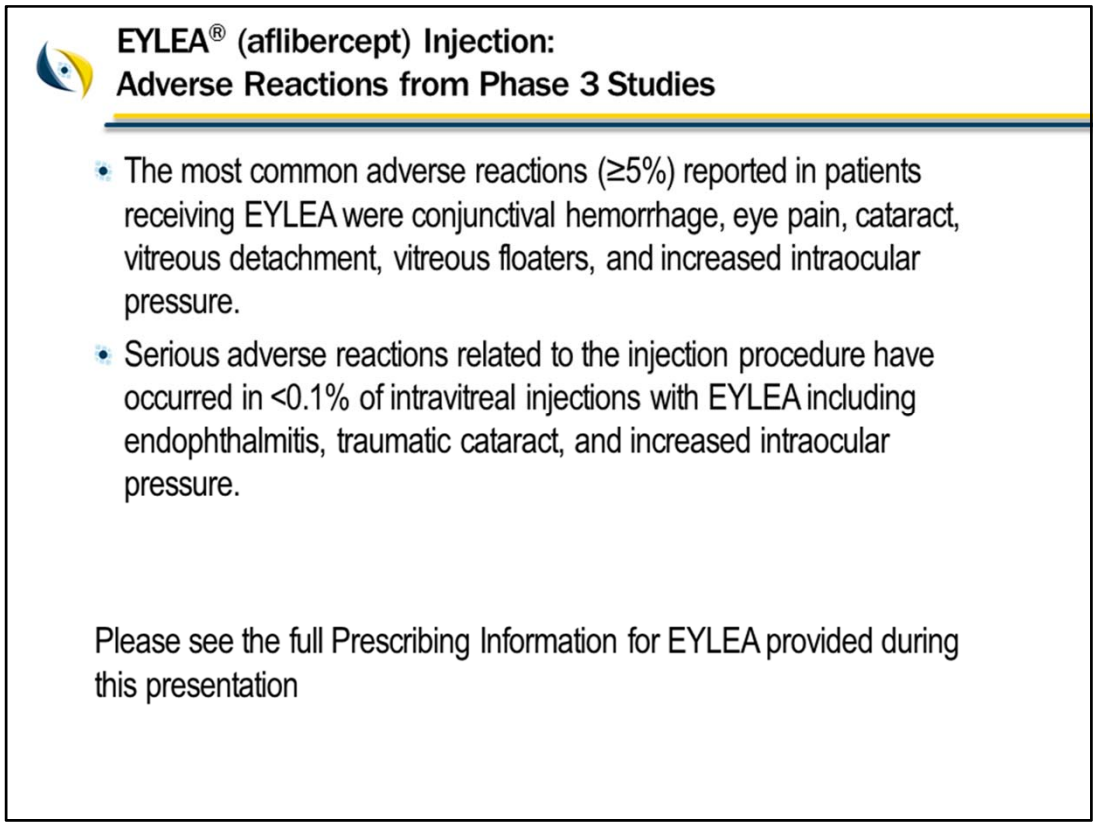
Verbatim

Important safety information to be aware of when considering the use of EYLEA® (aflibercept) Injection…

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

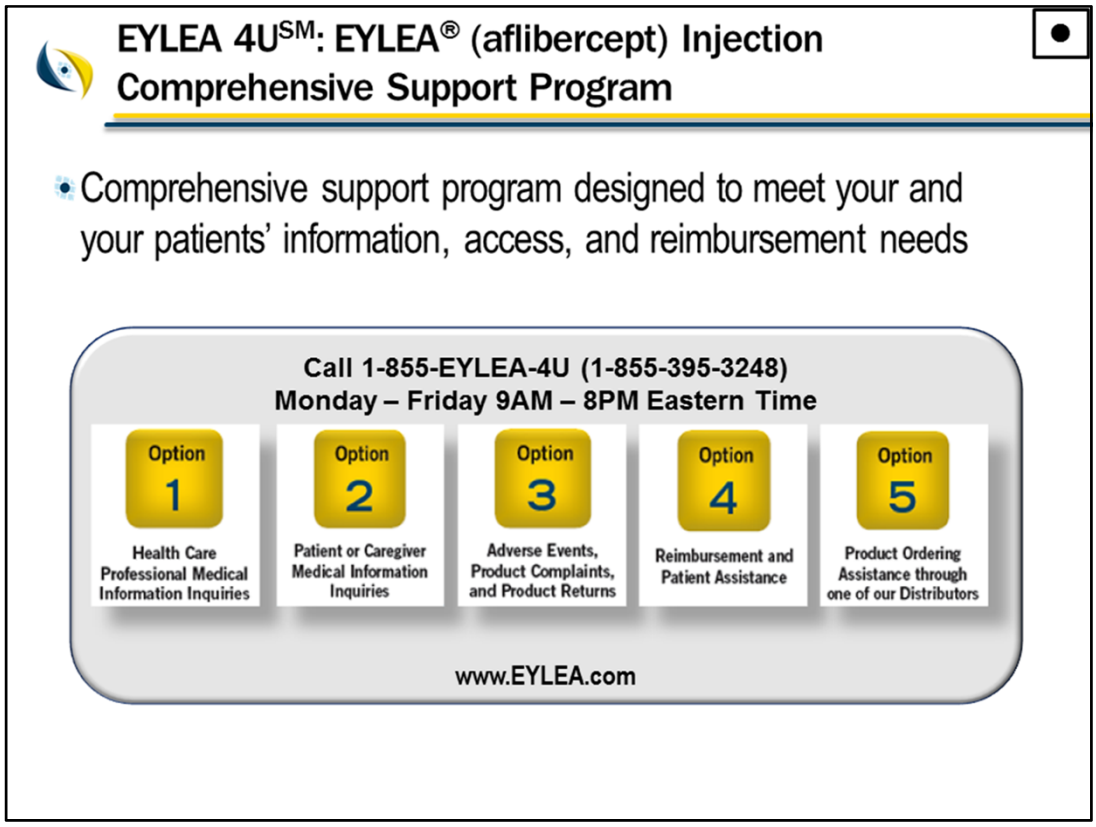
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

There is a potential risk of arterial thromboembolic events (ATEs) following use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs with EYLEA in clinical trials was 1.8% during the first year.(CLICK)



The most common adverse reactions (≥5%) reported in patients receiving EYLEA® (aflibercept) Injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, and increased intraocular pressure. (CLICK)



(Optional for presentation by Regeneron Medical Specialist at conclusion of the program)

Regeneron has established EYLEA 4U as a comprehensive support program for EYLEA® (aflibercept) Injection that can help you, your staff , and patients with various inquiries, including requests for medical information, reimbursement assistance, and product ordering assistance. (CLICK)

EYLEA® (aflibercept) Injection: Distribution

- Available through a broad network of specialty distributors and specialty pharmacies to help ensure access to all providers, including offices and hospitals

How Supplied	40 mg/mL solution for intravitreal injection in a single-use glass vial containing 1 dose (2 mg) of EYLEA
Doses Per Vial	1
NDC #	61755-0005-02
Wholesale Acquisition Cost (WAC)	$1,850



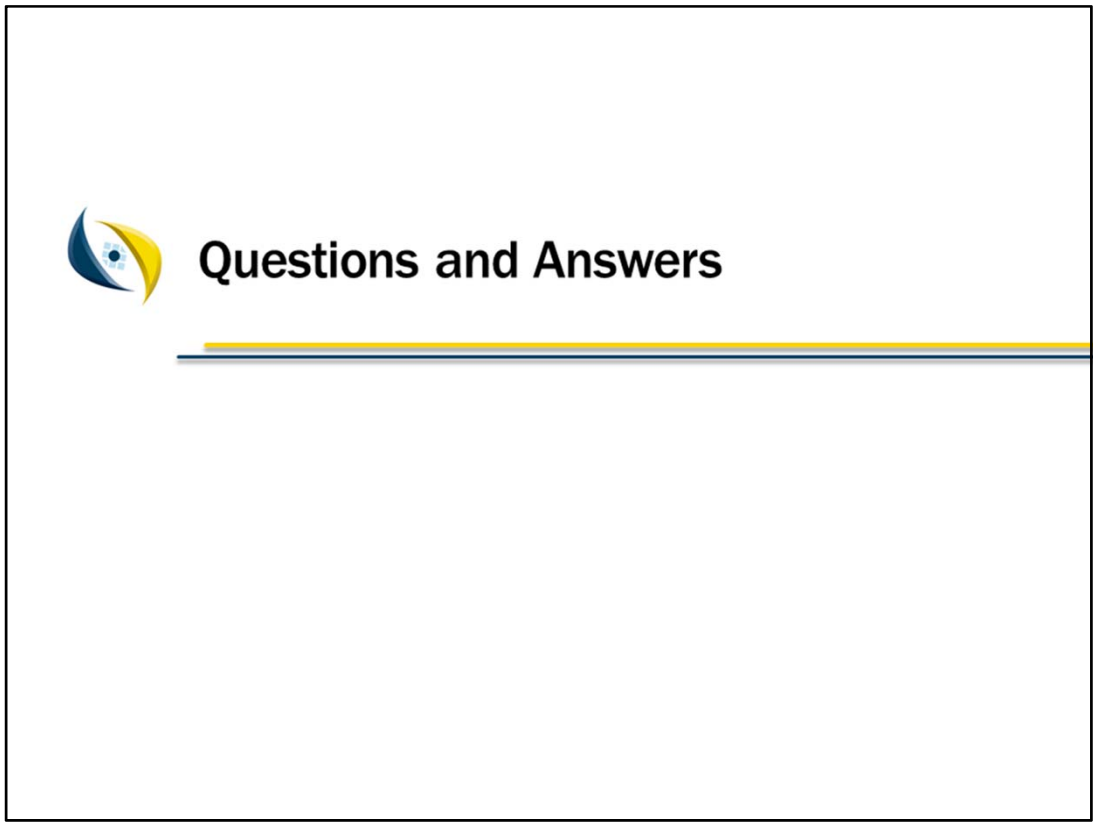
Please see full Prescribing Information available from the representative in attendance

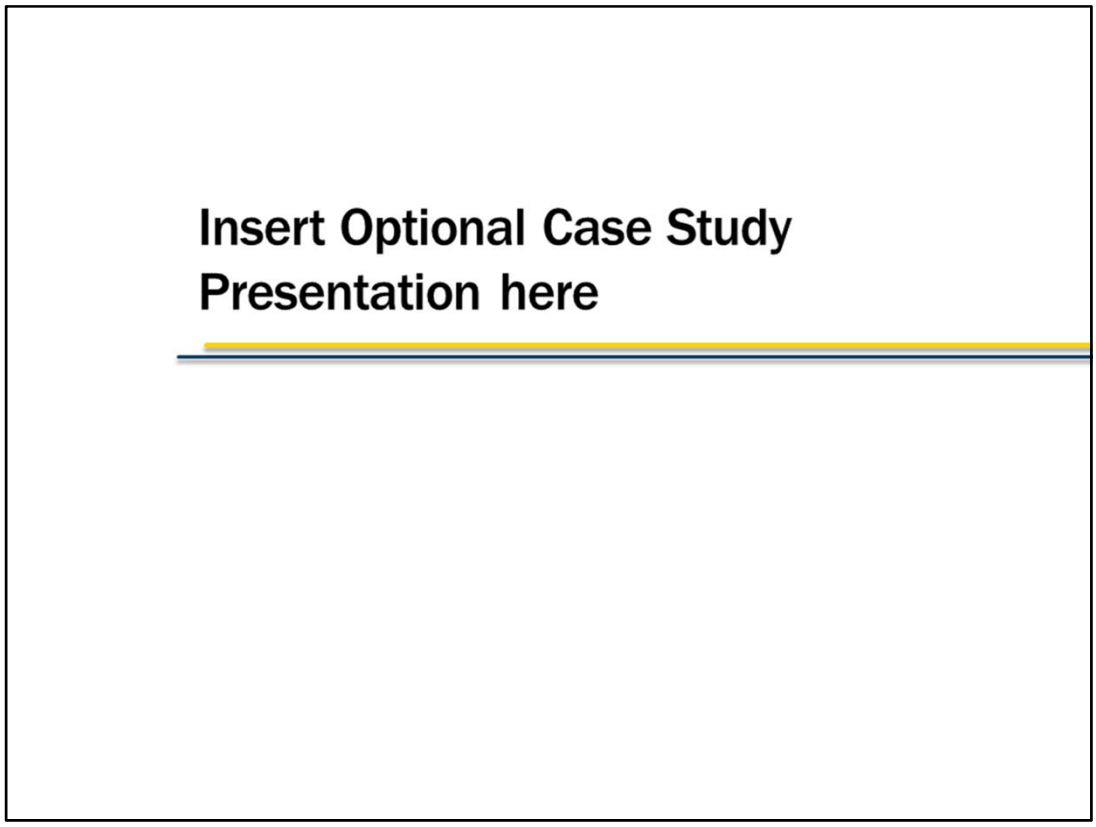
(Optional for presentation by Regeneron Medical Specialist at conclusion of the program)

EYLEA® (aflibercept) Injection is available through a number of different sources, including distributors – Besse Medical, CuraScript SD Specialty Distribution, and McKesson Specialty Health, and Apothecary Shoppe – and through a network of Specialty Pharmacy Providers. (CLICK)


EYLEA®
(aflibercept) Injection
For Intravitreal Injection
Please see Regeneron representative in attendance for Full Prescribing Information

Thank you.


Questions and Answers


Insert Optional Case Study
Presentation here