Disclosures

- Consulting: Regeneron, Genentech, Allergan, Visunex, Valeant, Spark
- Research funding: Regeneron, Genentech

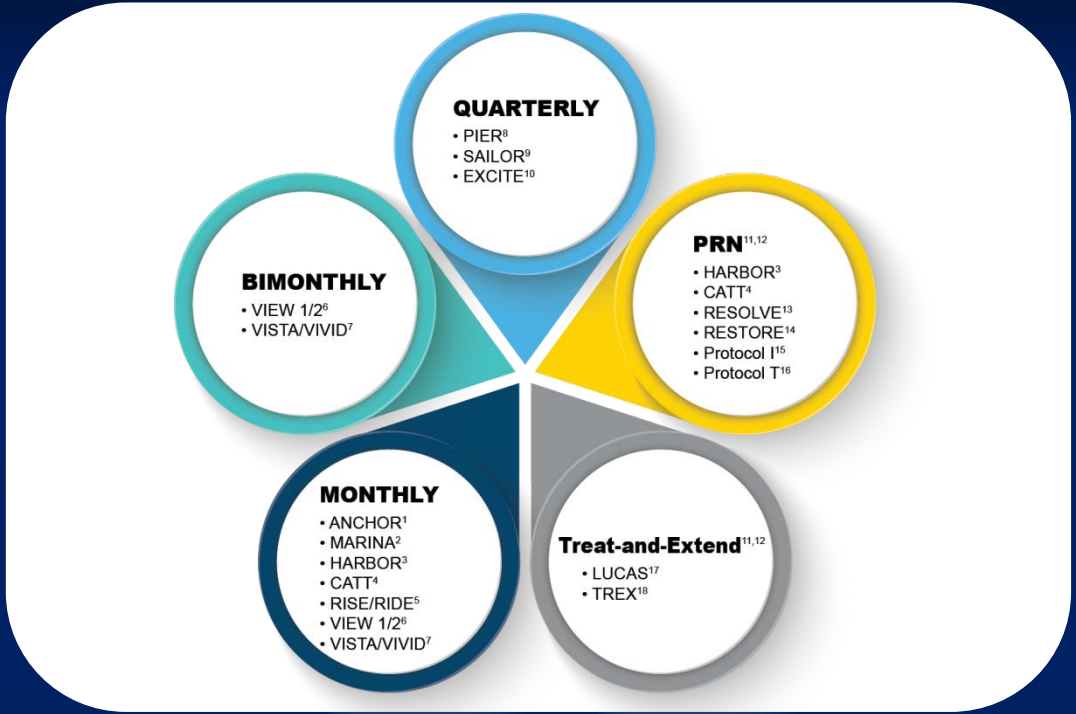
Impact of Injection Frequency on Visual Outcomes
A Real-world Analysis

Andrew A. Moshfeghi, MD, MBA
Director, Vitreoretinal Fellowship
Director, Clinical Trials Unit
Associate Professor of Clinical Ophthalmology
USC Roski Eye Institute
Keck School of Medicine
Los Angeles

Key Takeaways

- Consistent with results of clinical trials, in routine clinical practice, maintenance of visual gains was associated with more frequent anti-VEGF injections in patients with neovascular AMD or DME
- Patients with neovascular AMD or DME were more likely to receive more frequent injections ($\geq$ 7) rather than fewer injections ($\leq$ 6) during the first year of treatment
  - However, a substantial proportion (43%) of DME patients are receiving $\leq$ 6 injections during their first year of treatment
  - Annually, a trend towards more injections during the first year of treatment was observed in the neovascular AMD cohort
  - Low compliance with continuing treatment beyond the first year was observed

Dosing Approaches in Clinical Trials are Varied

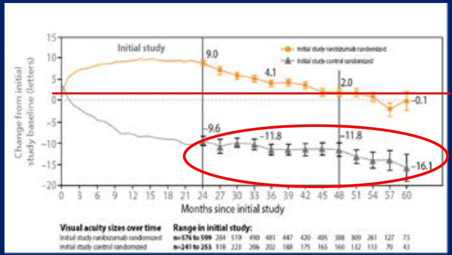


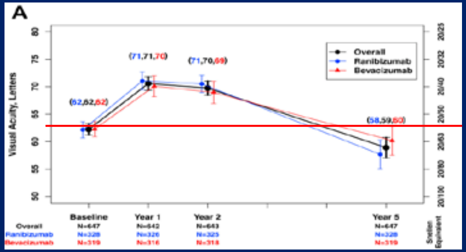
1. Brown DM et al. *N Engl J Med*. 2006;355(14):1432-1444. 2. Rosenfeld PJ et al. *N Engl J Med*. 2006;355(14):1419-1431. 3. CATT Research Group. *N Engl J Med.* 2011;364(20):1897-1908. 4. Heier JS et al. *Ophthalmology*. 2012;119(12):2537-2548. 5. Nguyen QD et al. *Ophthalmology*. 2012;119(4):789-801. 6. Busbee BG et al. *Ophthalmology*. 2013;120(5):1046-1056. 7. Korobelnik J-F et al. *Ophthalmology*. 2014;121(11):2247-2254. 8. Wykoff C et al. *Ophthalmology.* 2015;122(12):2514-2522. 9. Regillo CD et al. *Am J Ophthalmol*. 2008;145(2):239-248.e5. 10. Schmidt-Erfurth U et al. *Ophthalmology*. 2011;118(5):831-839. 11. Freund KB et al. *Retina*. 2015;35(8):1489-1506. 12. Mantel I. *Transl Vis Sci Technol*. 2015;4(3):6. 13. Boyer DS et al. *Ophthalmology*. 2009; 116(9):1731-1739. 14. Massin P et al. *Diabetes Care*. 2010;33(11):2399-2405. 15. Diabetic Retinopathy Clinical Research Network. *Ophthalmology*. 2010;117(6):1064-1077. 16. Mitchell P et al. *Ophthalmology*. 2011;118(4):615-625. 17. Diabetic Retinopathy Clinical Research Network. *N Engl J Med*. 2015;372(13):1193-1203. 18. Berg K et al. *Ophthalmology*. 2015;122(1):146-152.

Long-term Trials in AMD Demonstrate that …..

No Recovery of Vision Following Inadequate Treatment Over Long Period of Time

Deviations from Consistent Dosing Result in Decline of Visual Gains Over Time

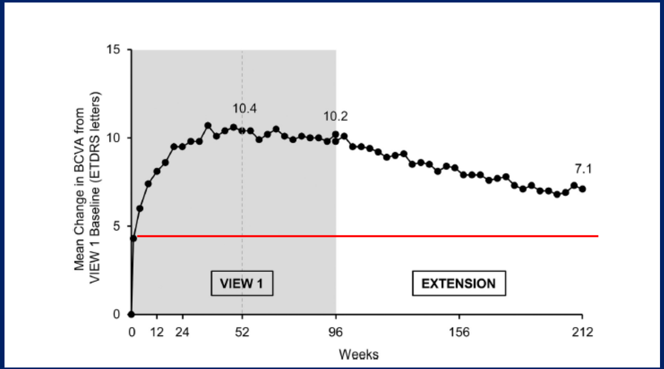




HORIZON	
Dosing Regimen in Extension Phase	PRN
Mean Number of Injections	
Year 3	2.2**
Year 4	2.0**

CATT	
Dosing Regimen in Extension Phase	Investigator Determined
Mean Number of Injections	
Year 3	4.8
Year 4	4.5
Year 5	4.0

And Vision Can Largely be Maintained When Patients with AMD are Treated Consistently



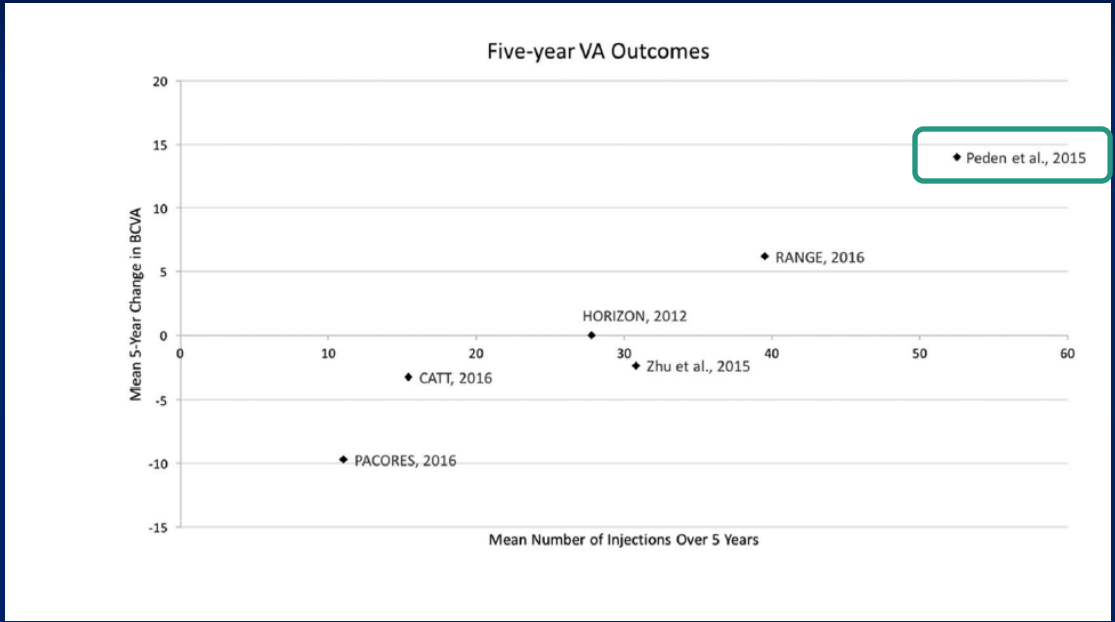
VIEW 1 Extension	
Dosing Regimen in Extension Phase	Modified Quarterly*
Mean Number of Injections	
Year 3	6.0
Year 4	5.5

All patients received IAI 2 mg on a modified quarterly dosing schedule until the amendment in June 2012 mandated q8 dosing

*Mandatory dosing at least every 12 weeks, up to monthly injections possible

**Calculated from the cumulative injection total

Five Year Visual Acuity Outcomes vs Injection Frequency in AMD



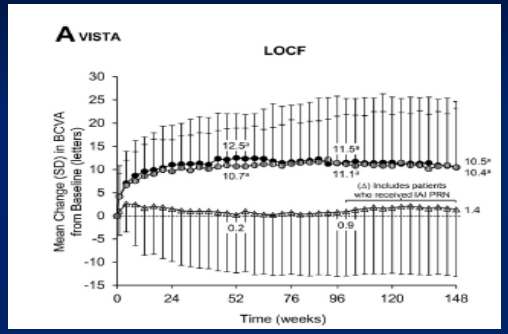
Fixed q4/q8 weeks (10.5 injs/year)

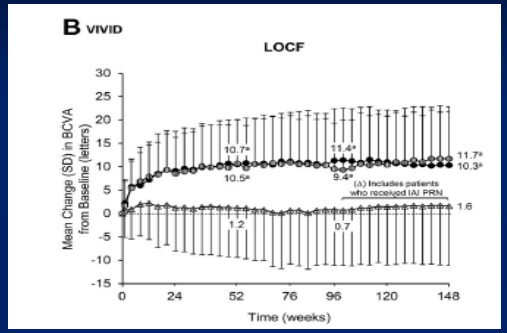
"The body of evidence to date regarding long-term anti-VEGF treatment indicates a variable course at greater than 36 months follow-up and seems to be dependent on the treatment protocol. Consistent dosing with fluid-free interval is suggested to maintain VA gains in patients with exudative age-related macular degeneration."

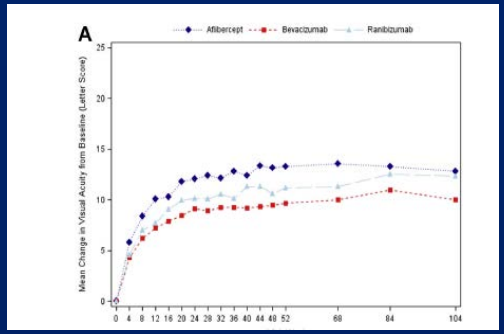
OUTCOMES OF PATIENTS WITH EXUDATIVE AGE-RELATED MACULAR DEGENERATION TREATED WITH ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR THREE OR MORE YEARS: A Review of Current Outcomes.

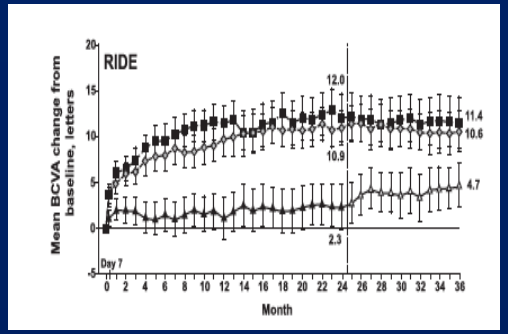
Qin VL, Young J, Silva FQ, Conti FF, Singh RP. Retina. 2017 Jun 30. doi: 10.1097/IAE.0000000000001753. [Epub ahead of print]

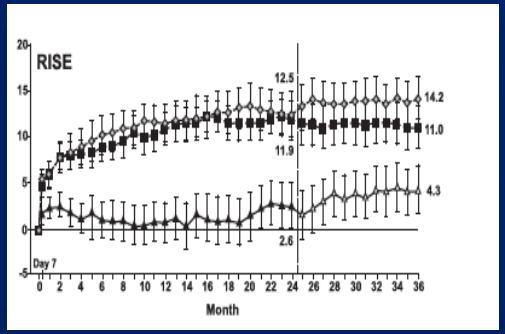
Similarly, Frequent Monitoring and Consistent Treatment Resulted in Optimal Outcomes in Clinical Trials for DME





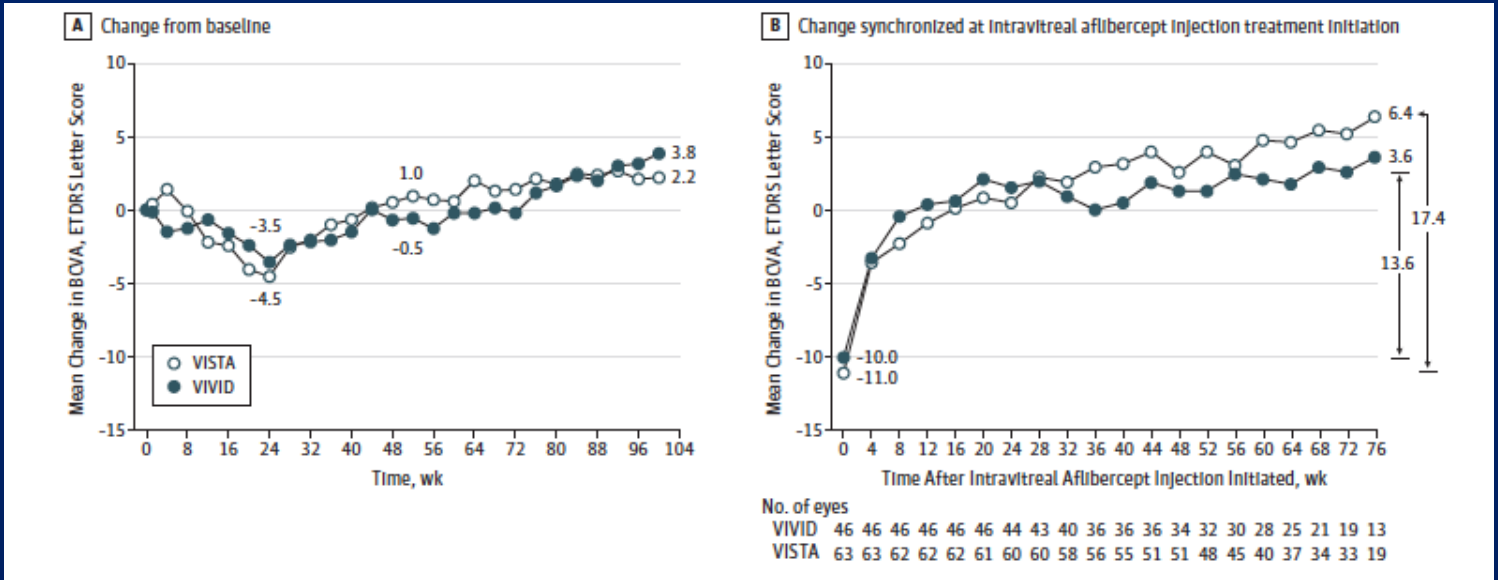






Limited Vision Improvement when Initial Treatment Approach is not Optimized in Patients with DME

- Final vision was limited in patients who were treated with intravitreal aflibercept following vision loss with initial laser treatment



Wykoff CC, Marcus DM, et al. Intravitreal Aflibercept Injection in Eyes With Substantial Vision Loss After Laser Photocoagulation for Diabetic Macular Edema Subanalysis of the VISTA and VIVID Randomized Clinical Trials. *JAMA Ophthalmol.* 2017;135(2):107–114.

Analysis of Outcomes in Routine Clinical Practice

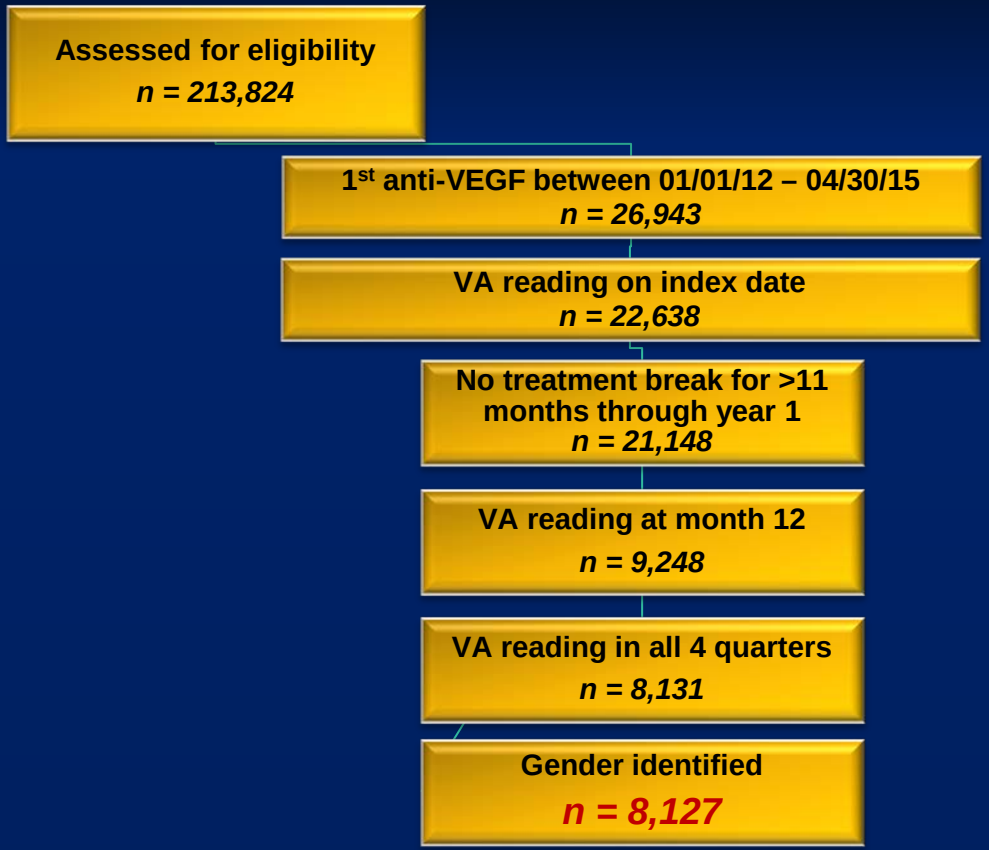
Study Design

- **Objective**
  - To evaluate visual acuity outcomes following treatment with intravitreal anti-VEGF agents in routine clinical practice through 2 years

- **Methods**
  - Electronic medical record data collected from 251 Retina Specialists for patients with –
    - *Neovascular age-related macular degeneration*
    - *Diabetic macular edema*
  - Anti-VEGF treatment naïve eyes
    - 1st anti-VEGF injection between January 1st, 2012 and April 30th, 2015
  - Two subgroups evaluated –
    - *Group 1: ≤6 injections/year*
    - *Group 2: ≥7 injections/year*

Neovascular Age-Related Macular Degeneration

Patient Selection
Year 1



Baseline Characteristics

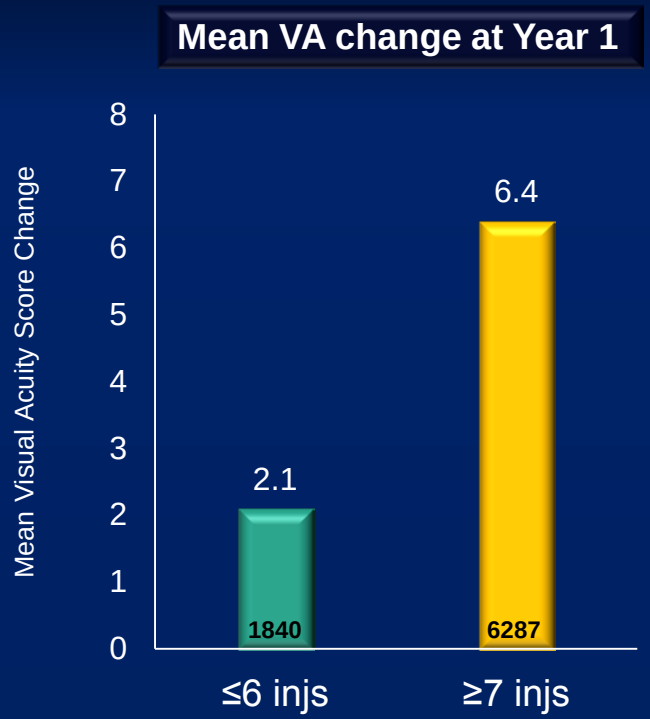
	Total *(n=8127)*	≤6 injections *(n=1840)*	≥7 injections *(n=6287)*
Mean Age, years	80	80	80
Female, %	64%	63%	65%
Mean VA, letters	65	61	66
Median VA, letters	74	72	74
VA Subgroups			
≥20/40	22%	23%	21%
<20/40 – 20/100	47%	39%	49%
<20/100 – 20/200	15%	13%	15%
<20/200	17%	24%	15%

Patients included in Year 1 analysis

Mean Visual Acuity Change By Injection Subgroups (*Year 1*)

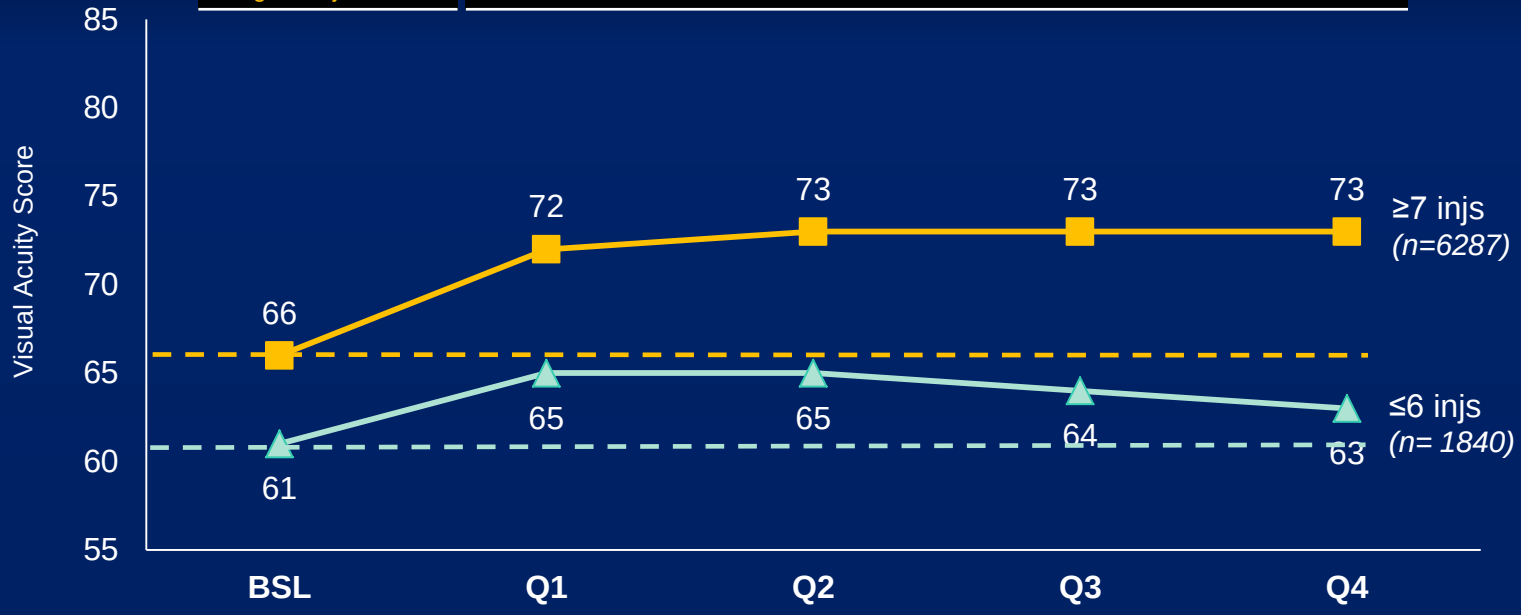
Subgroup	Mean BSL VA
≤6 injs *(n=1840)*	61
≥7 injs *(n=6287)*	66

Subgroup	Mean Number of Injections
≤6 injs *(n=1840)*	4.5
≥7 injs *(n=6287)*	9.1



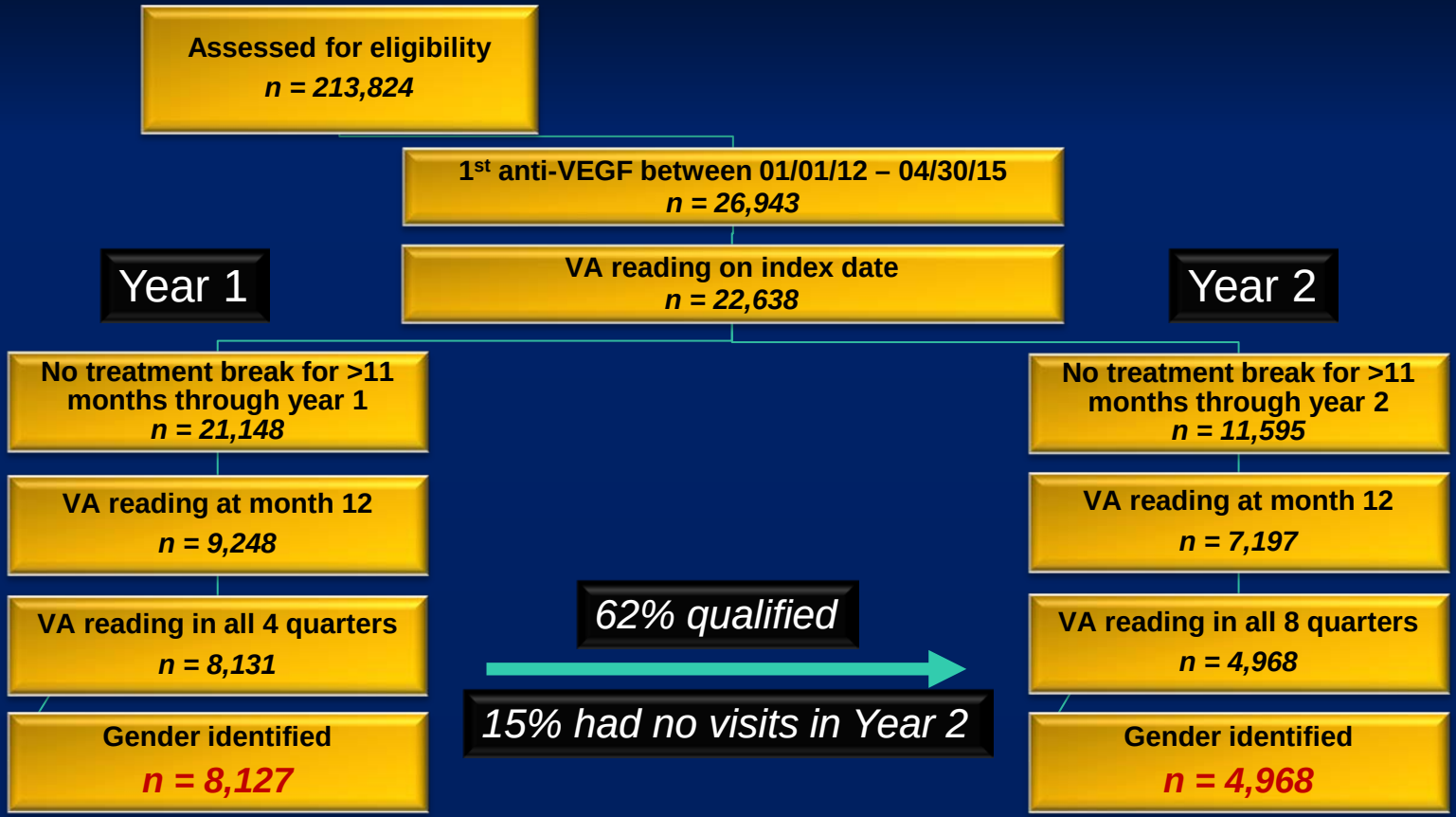
Mean Visual Acuity by Injection Subgroups (*Year 1*)

Mean # of Injections	3.1	2.1	1.9	2.0
Range of Injections	1-6	0-5	0-6	0-6



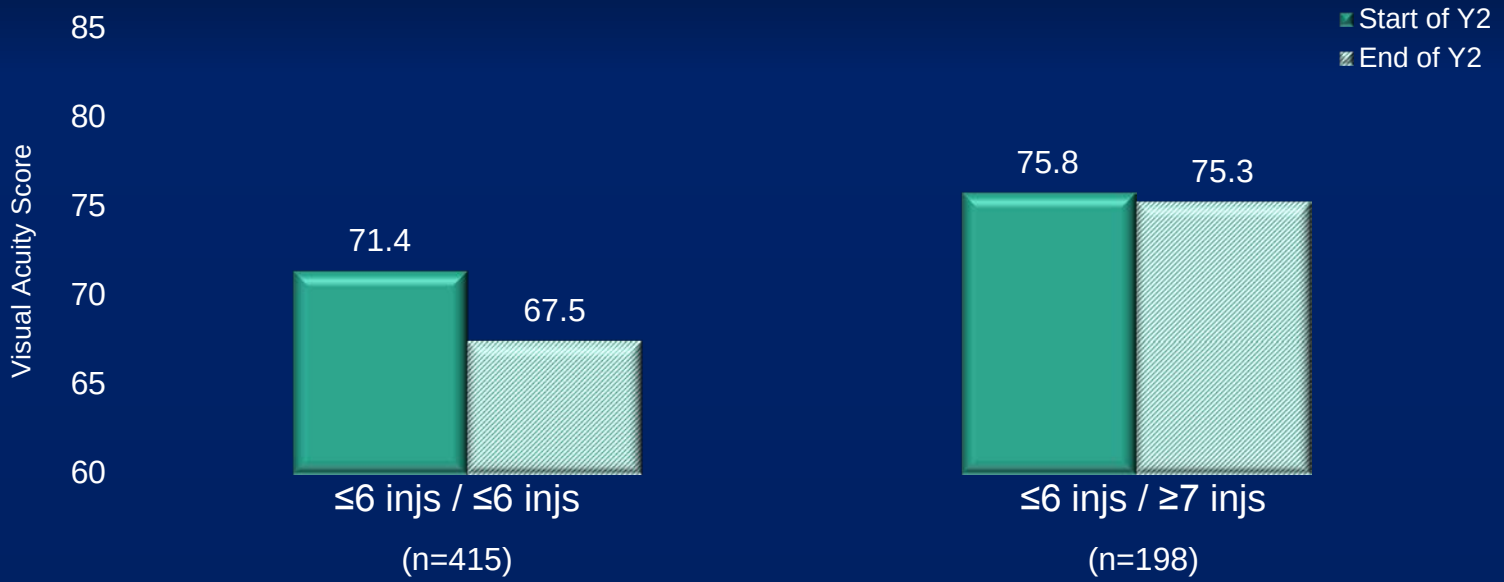
Mean # of Injections	2.4	0.8	0.6	0.7
Range of Injections	1-5	0-3	0-3	0-4

Patient Selection
Year 2



Mean Visual Acuity by Injection Subgroups *(Year 2)*

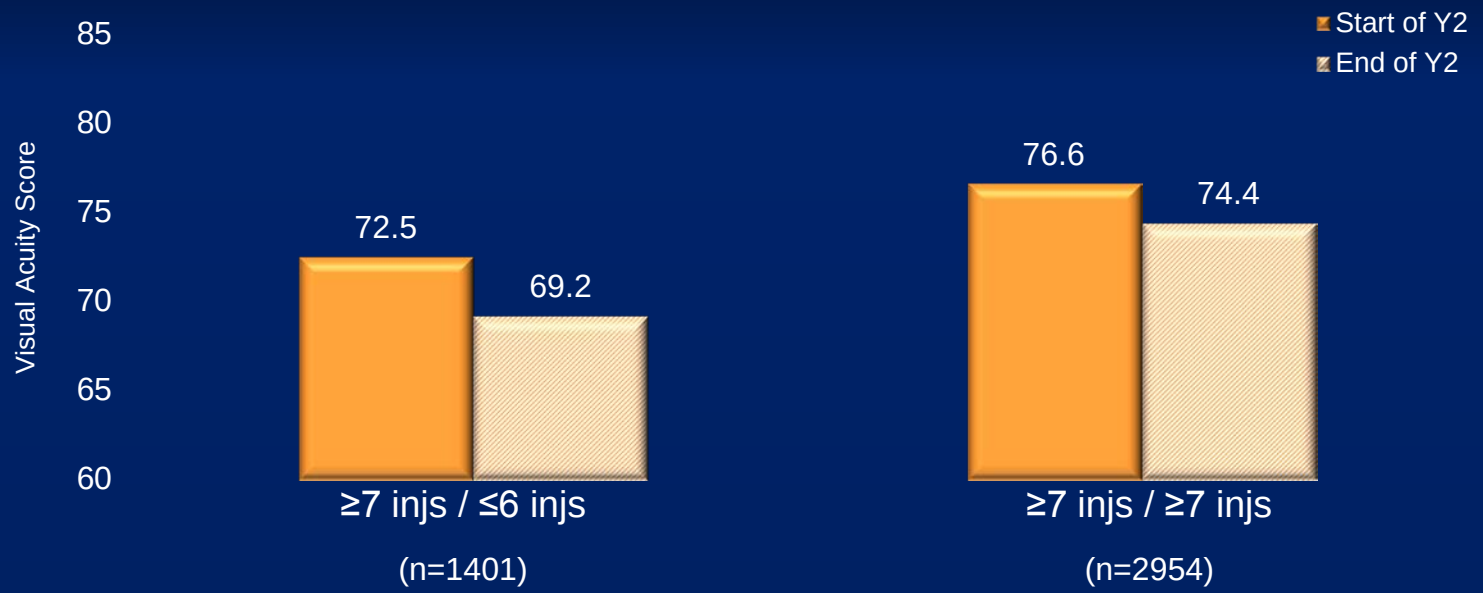
Patients Receiving ≤6 injections in Year 1



Mean number of injections		
Year 1	*5.2*	*5.3*
Year 2	*4.4*	*8.2*

Mean Visual Acuity by Injection Subgroups (Year 2)

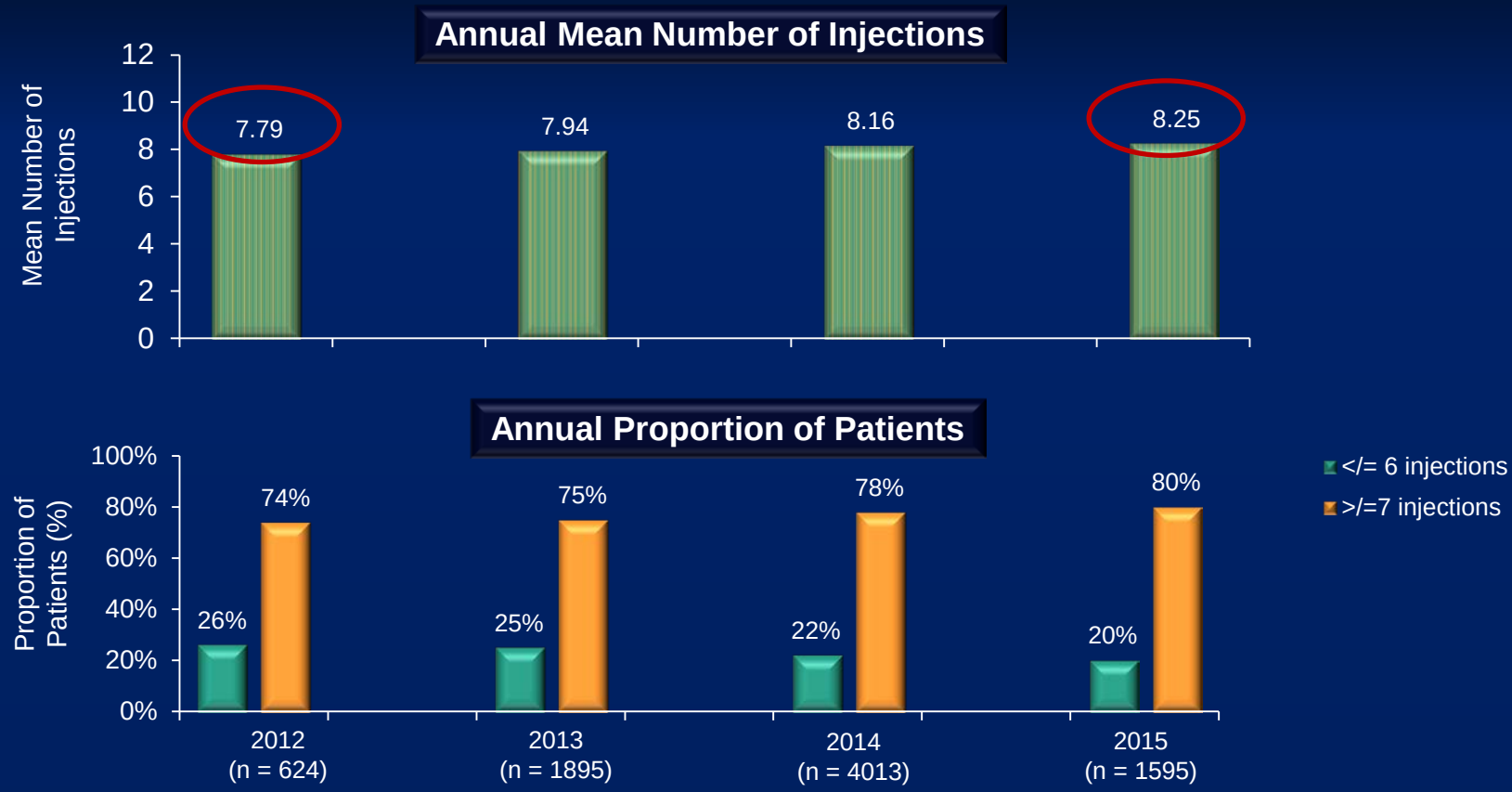
Patients Receiving ≥7 injections in Year 1



Mean number of injections		
Year 1	*8.5*	*9.7*
Year 2	*5.0*	*9.1*

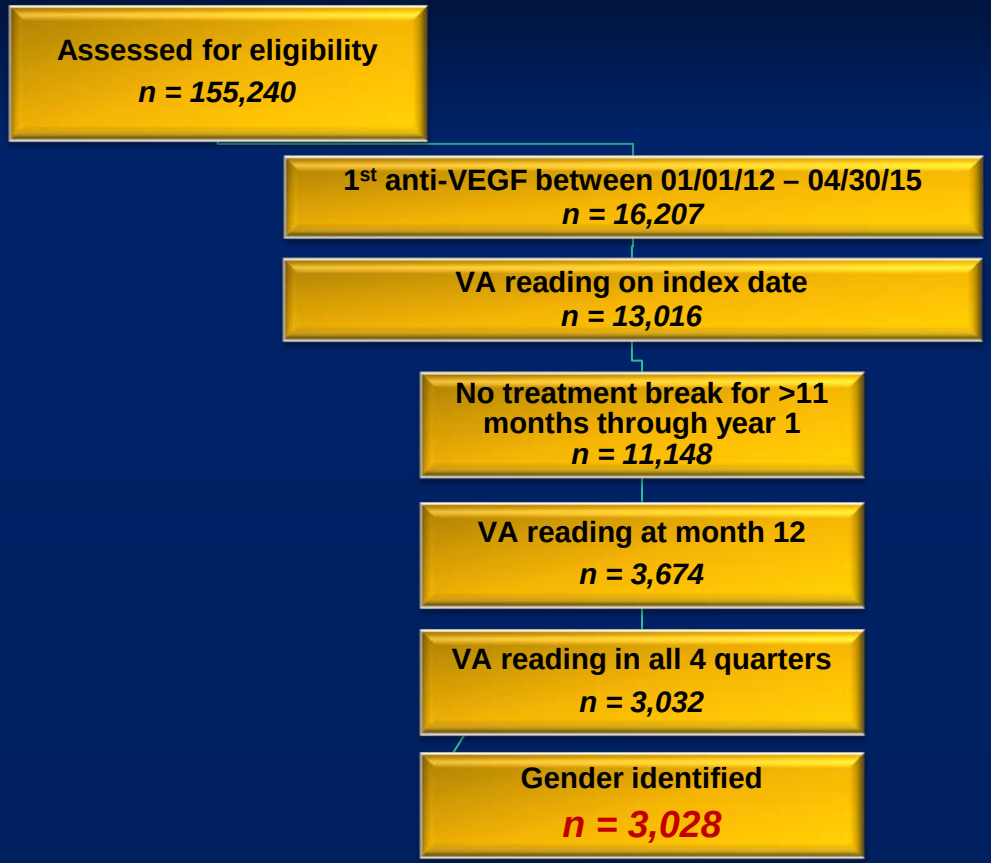
Change Over Time in Injection Frequency During Year 1 of Treatment

AMD



Diabetic Macular Edema

Patient Selection
Year 1



Baseline Characteristics

	Total *(n=3028)*	≤6 injections *(n=1303)*	≥7 injections *(n=1725)*
Mean age, years	62	61	63
Female, %	46%	47%	44%
Mean VA, letters	71	71	70
Median VA, letters	76	77	76
VA subgroups			
≥20/40	27%	29%	25%
<20/40 – 20/100	51%	50%	51%
<20/100 – 20/200	11%	11%	12%
<20/200	11%	10%	12%

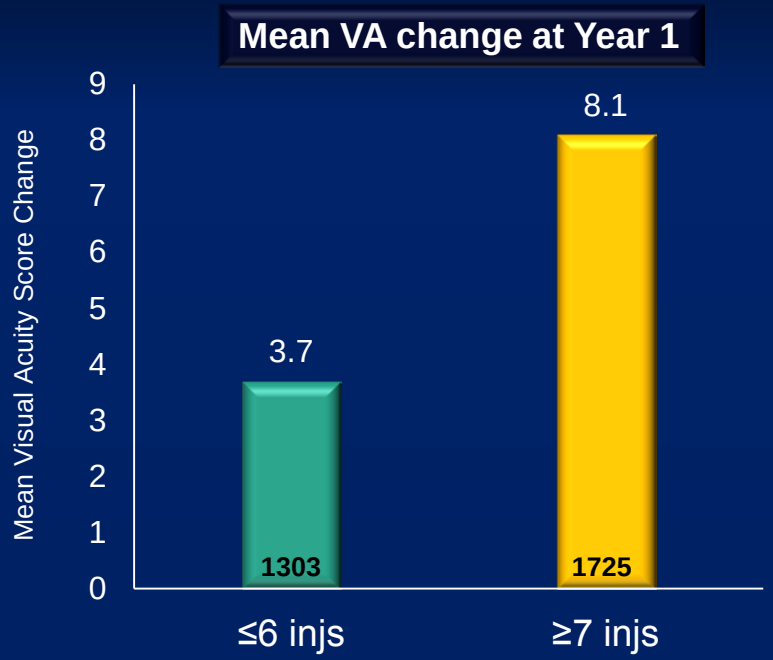
Patients included in Year 1 analysis

Mean Visual Acuity Change By Injection Subgroups (*Year 1*)

DME

Subgroup	Mean BSL VA
≤6 injs *(n=1303)*	71
≥7 injs *(n=1725)*	70

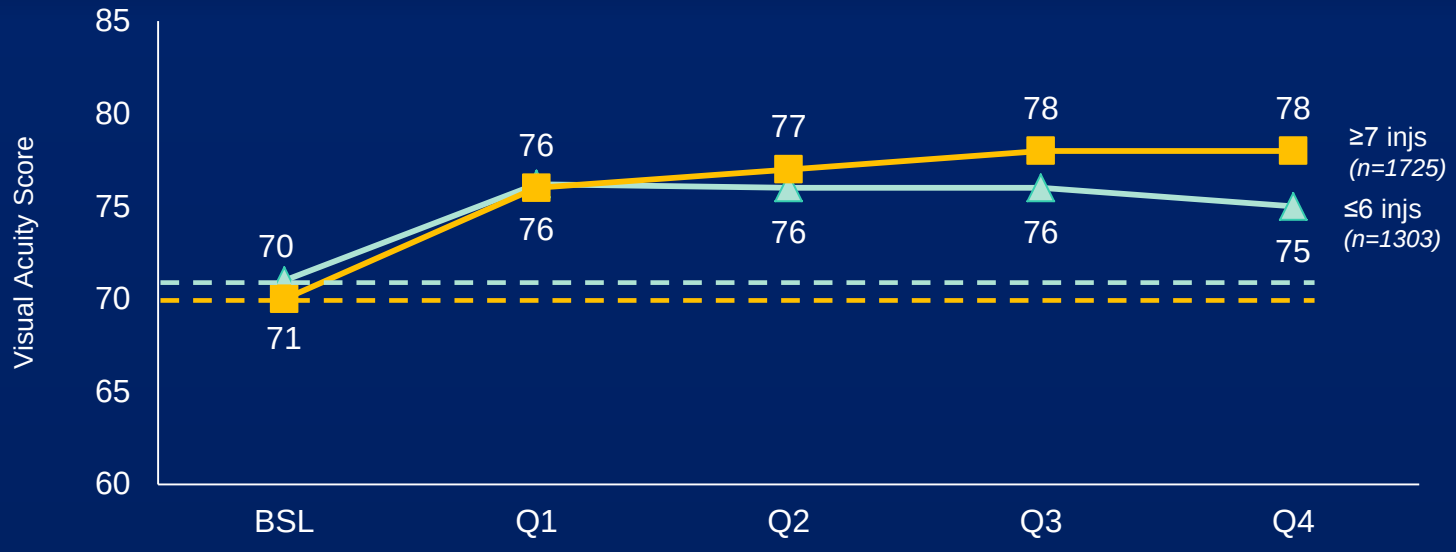
Subgroup	Mean Number of Injections
≤6 injs *(n=1303)*	4.0
≥7 injs *(n=1725)*	9.1



Patient had to have a VA reading in each quarter to be included in the analysis

Mean Visual Acuity by Injection Subgroups (*Year 1*)

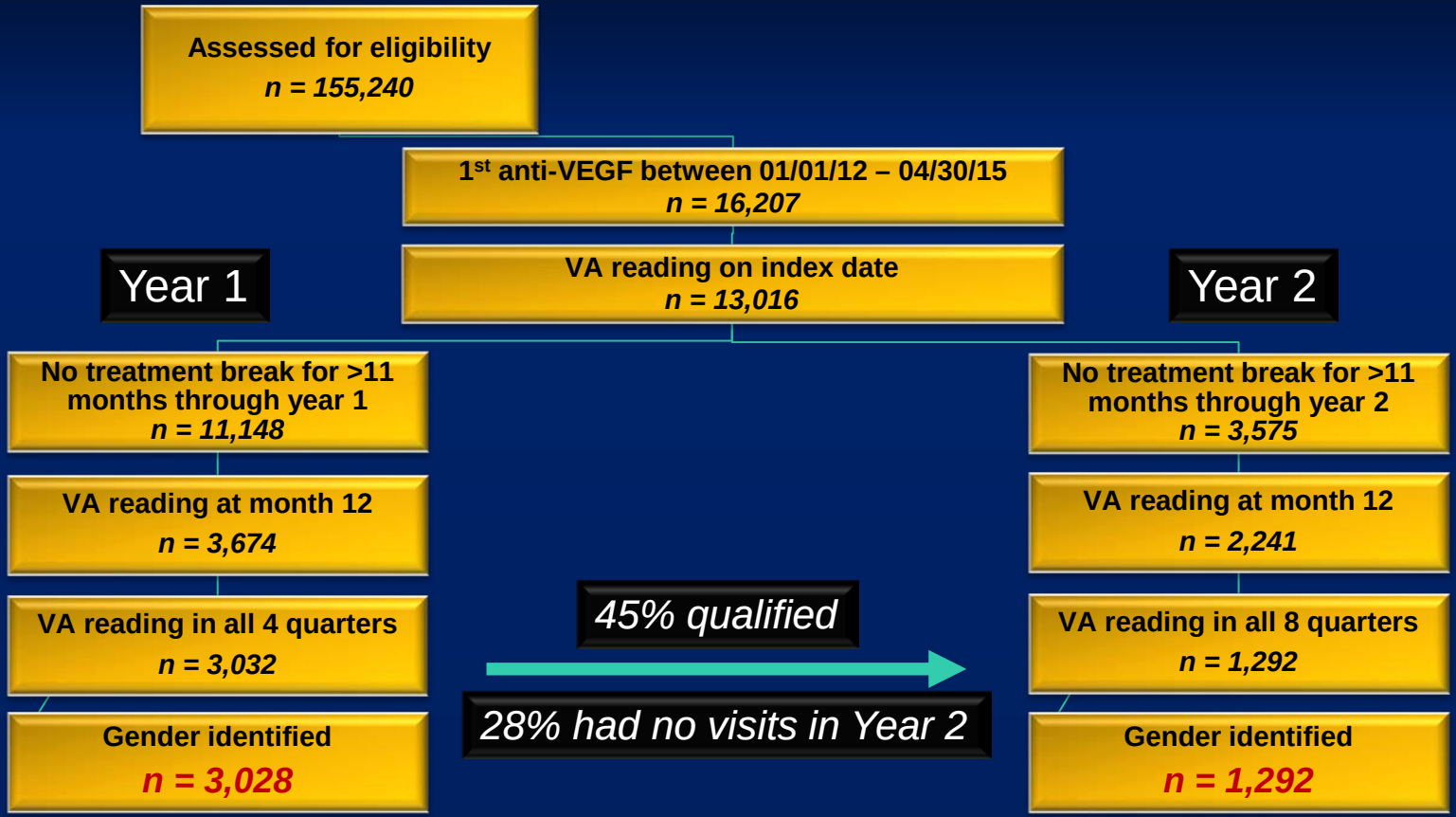
Mean # of Injections	3.0	2.2	2.0	2.0
Range of Injections	1-5	0-4	0-4	0-6



Mean # of Injections	2.0	0.7	0.6	0.7
Range of Injections	1-4	0-3	0-3	0-3

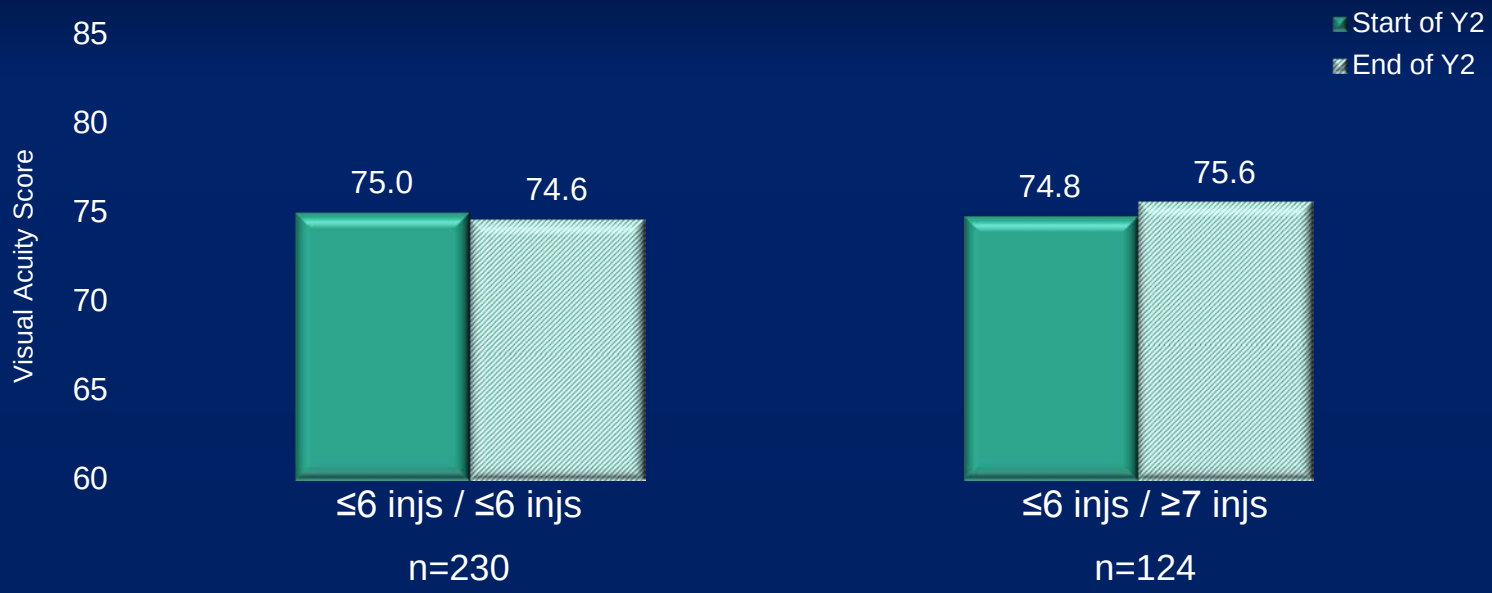
Patient had to have a VA reading in each quarter to be included in the analysis

Patient Selection
Year 2



Mean Visual Acuity by Injection Subgroups *(Year 2)*

Patients Receiving ≤6 injections in Year 1

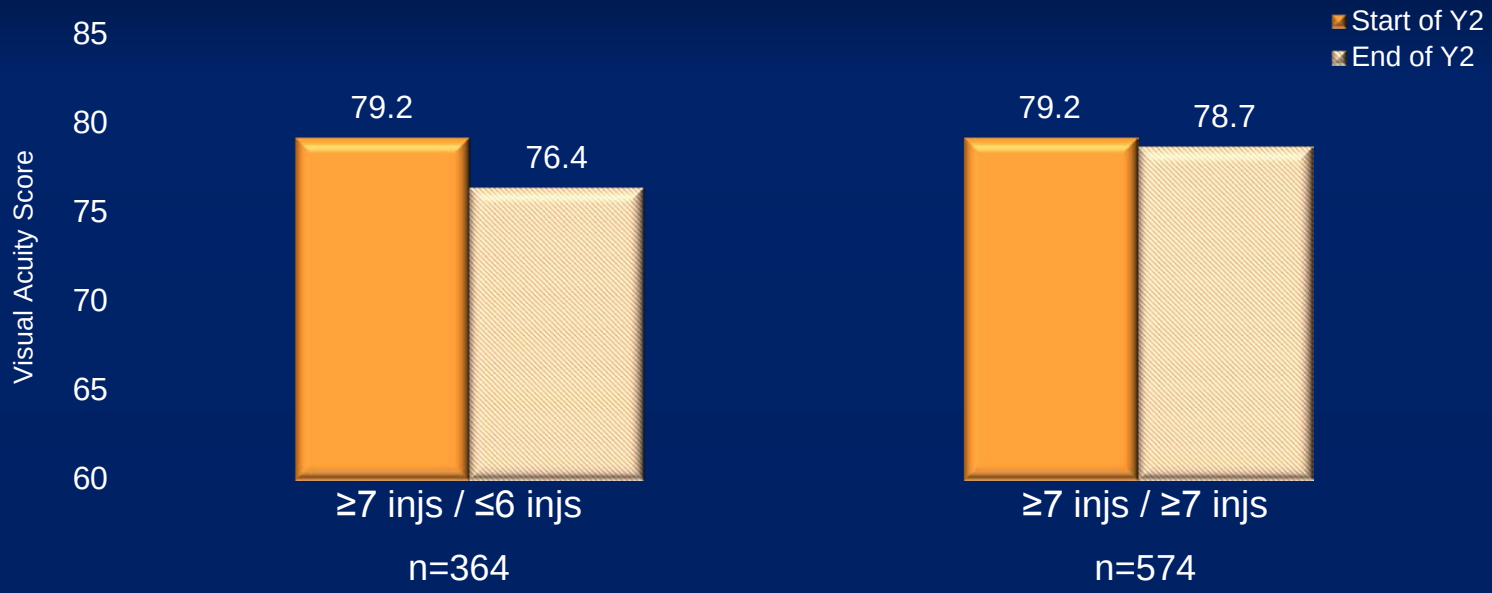


Mean number of injections

Year 1	*4.6*	*4.9*
Year 2	*4.3*	*8.2*

Mean Visual Acuity by Injection Subgroups (Year 2)

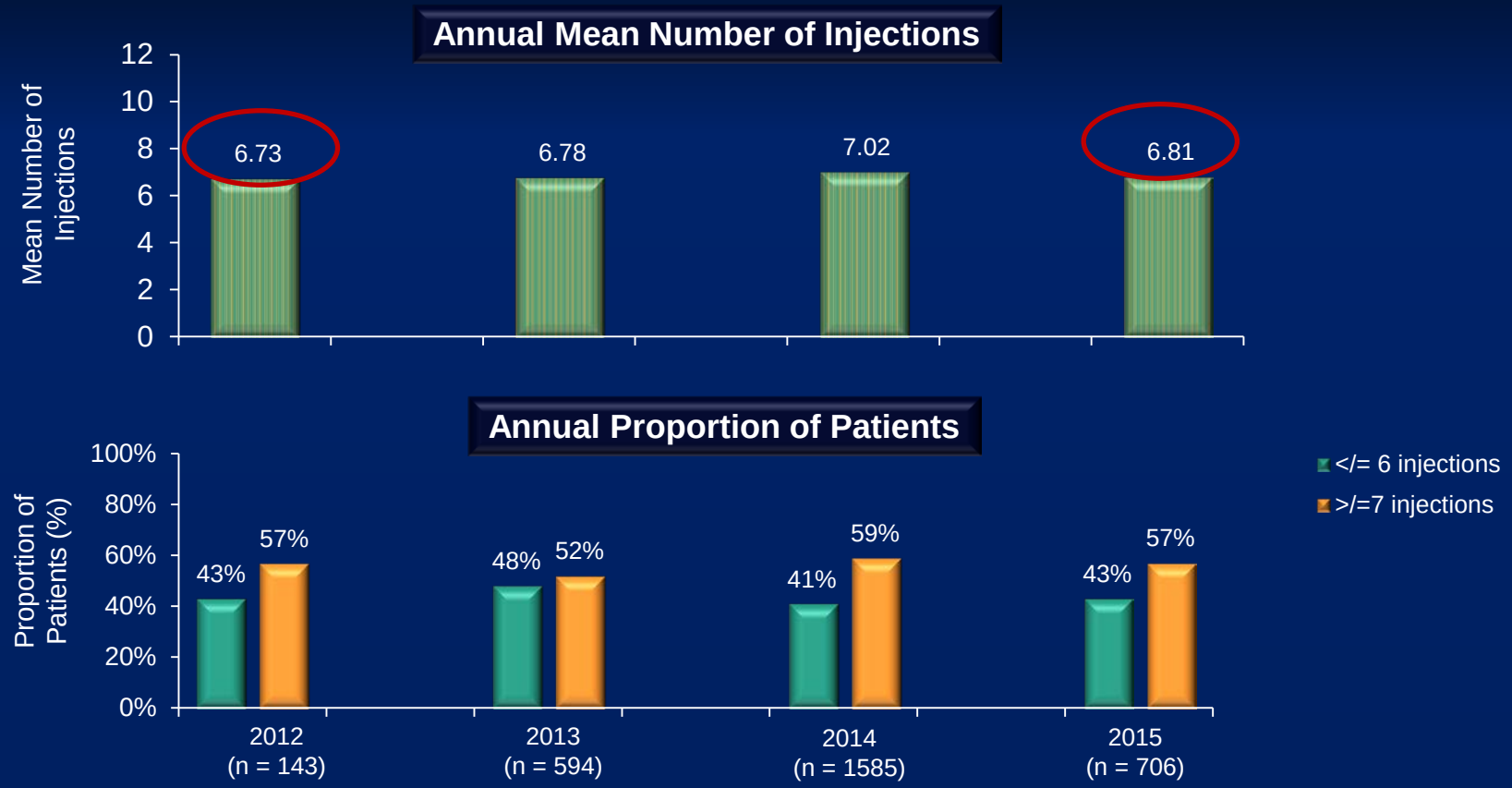
Patients Receiving ≥7 injections in Year 1



Mean number of injections

Year 1	*8.8*	*9.7*
Year 2	*4.7*	*9.0*

Change Over Time in Injection Frequency During Year 1 of Treatment



Summary

- Consistent with results of clinical trials, in routine clinical practice, maintenance of visual gains was associated with more frequent anti-VEGF injections in patients with neovascular AMD or DME
- Patients with neovascular AMD or DME were more likely to receive more frequent injections ($\geq$ 7) rather than fewer injections ($\leq$ 6) during the first year of treatment
  - However, a substantial proportion (43%) of DME patients are receiving $\leq$ 6 injections during their first year of treatment
  - Annually, a trend towards more injections during the first year of treatment was observed in the neovascular AMD cohort
  - Low compliance with continuing treatment beyond the first year was observed

Thank You

Back-Up

Overview of Trials
Neovascular Age-related Macular Degeneration

Trial	Treatment Groups	Mean Change in BCVA at Year 1	Long-Term Follow-up	Mean Change in BCVA (As compared to enrollment in original study)
MARINA	RBZ 0.5mg monthly	+7.2	HORIZON** (PRN) Annual: 2.0 -2.2 injs	Year 2: +9.0
	sham	-10.4		Year 3: +4.0
ANCHOR	RBZ 0.5mg monthly	+11.3		Year 4: +2.0
	PDT	-9.6		Year 5: -0.1
VIEW 1	IAI 2mg monthly	+10.9	VIEW 1 Extension (Modified Quarterly/ Bimonthly) Annual: 5.5-6 injs	Week 96: +10.2
	IAI 2mg bi-monthly*	+7.9		Week 212: + 7.1
	RBZ 0.5mg monthly	+8.1		
CATT	RBZ 0.5mg monthly	+8.5	Extension (Variable) Annual: 4.0-4.8 injs	Year 2: +8[#]
	RBZ 0.5mg PRN	+6.8		
	BVZ 1.25mg monthly	+8.0		Year 5: -11[#]
	BVZ 1.25mg PRN	+5.9		

RBZ=ranibizumab, IAI=intravitreal aflibercept injection, BVZ=bevacizumab
**following 3 initial monthly doses*
*** Also Included patients from the FOCUS study*
[#]Calculated mean change

Overview of Trials
Diabetic Macular Edema

Trial	Treatment Groups	Mean Change in BCVA at Year 2
RISE	RBZ 0.3mg monthly	+14.3
	sham	+5.1
RIDE	RBZ 0.3mg monthly	+13.1
	sham	+4.5
VISTA	IAI 2mg monthly	+12.5
	IAI 2mg bi-monthly*	+10.7
	laser	+0.2
VIVID	IAI 2mg monthly	+10.5
	IAI 2mg bi-monthly*	+10.7
	laser	+1.2
Protocol T	IAI 2mg PRN	+13
	RBZ 0.3mg PRN	+11
	BVZ 1.25mg PRN	+10

RBZ=ranibizumab, IAI=intravitreal aflibercept injection, BVZ=bevacizumab
**following 5 initial monthly doses*