

VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results

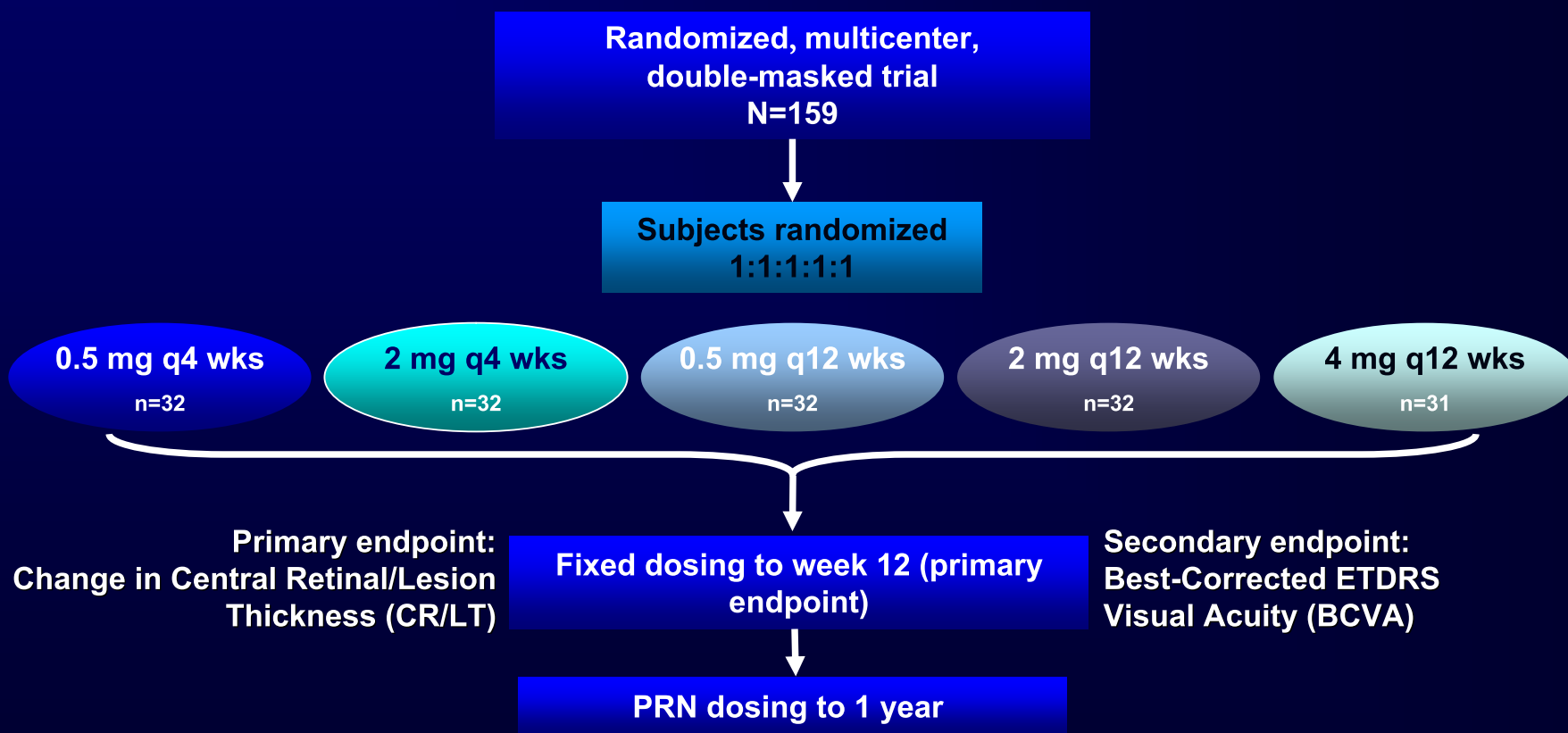
**Presented at 2008 Retina Society Meeting
Scottsdale, Arizona
September 28, 2008**

A Phase 2, Randomized, Controlled
Dose- and Interval-Ranging Study
of Intravitreal VEGF Trap-Eye
in Patients With Neovascular,
Age-Related Macular Degeneration

CLEAR-IT 2: Rationale

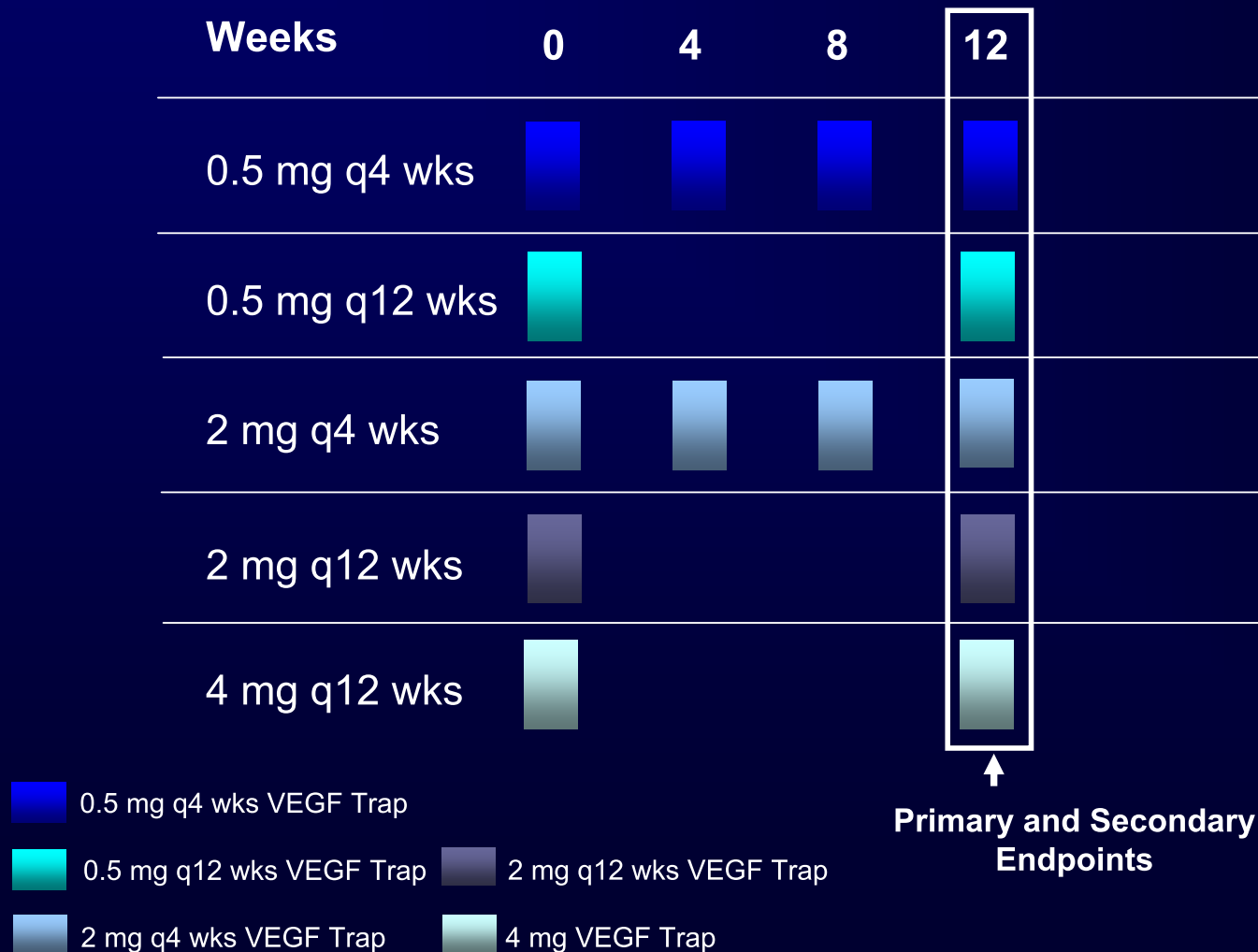
- Anti-VEGF therapy has dramatically changed the treatment paradigm for wet AMD
 - Improvement in visual acuity is now an achievable goal of treatment
- A potential limitation of anti-VEGF therapy is the unpredictable durability of vision gain initially achieved with monthly dosing when the treatment interval is prolonged
- VEGF Trap-Eye is a novel anti-VEGF therapy with high binding affinity for VEGF-A and placental growth factor (PIGF)
- CLEAR-IT 2 was designed to assess:
 - Response at 12 weeks to a range of doses administered monthly and quarterly
 - Durability of response with PRN (as-needed) dosing out to 1 year

CLEAR-IT 2: Study Design

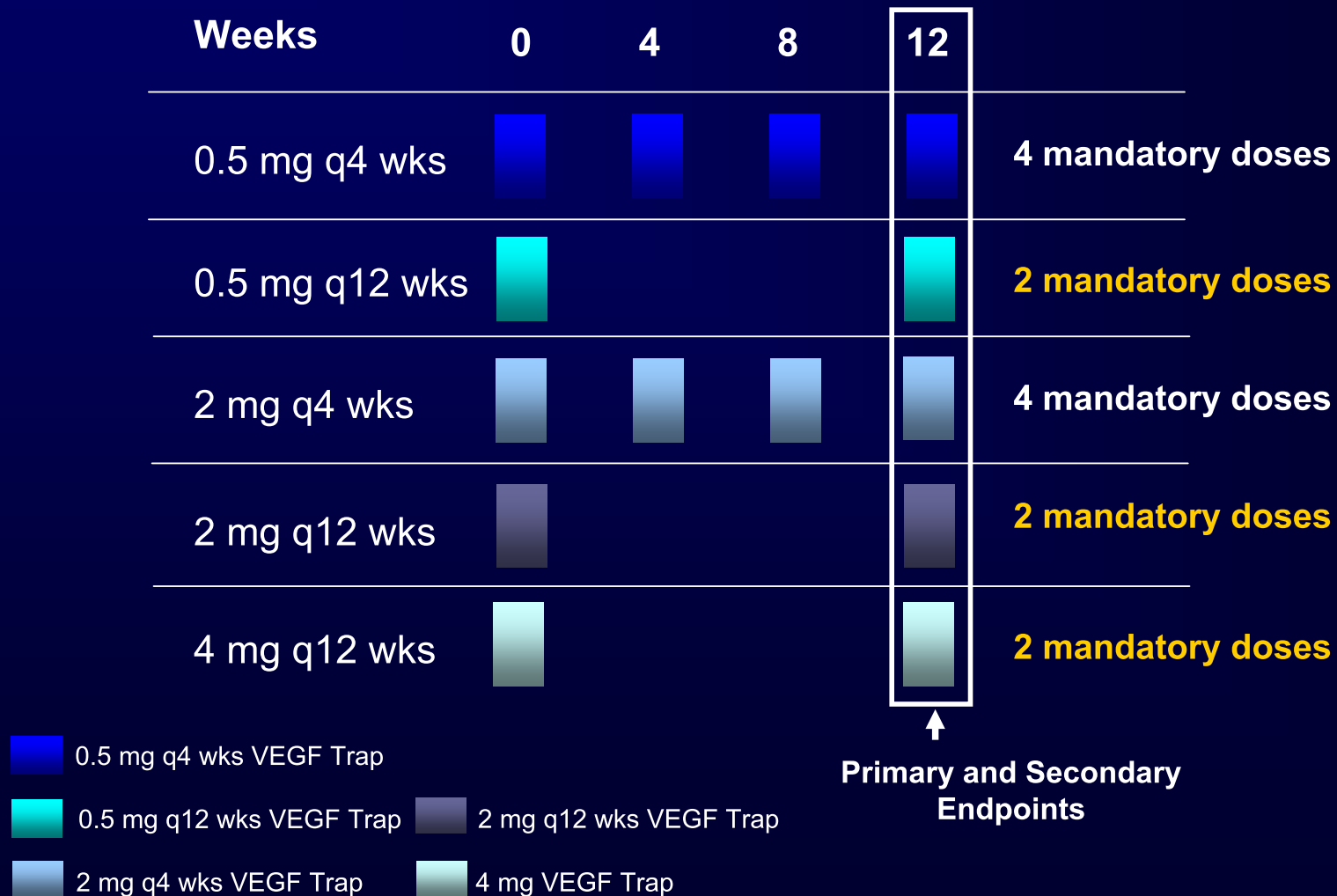


Patients were re-dosed at week 12; PRN dosing started at week 16

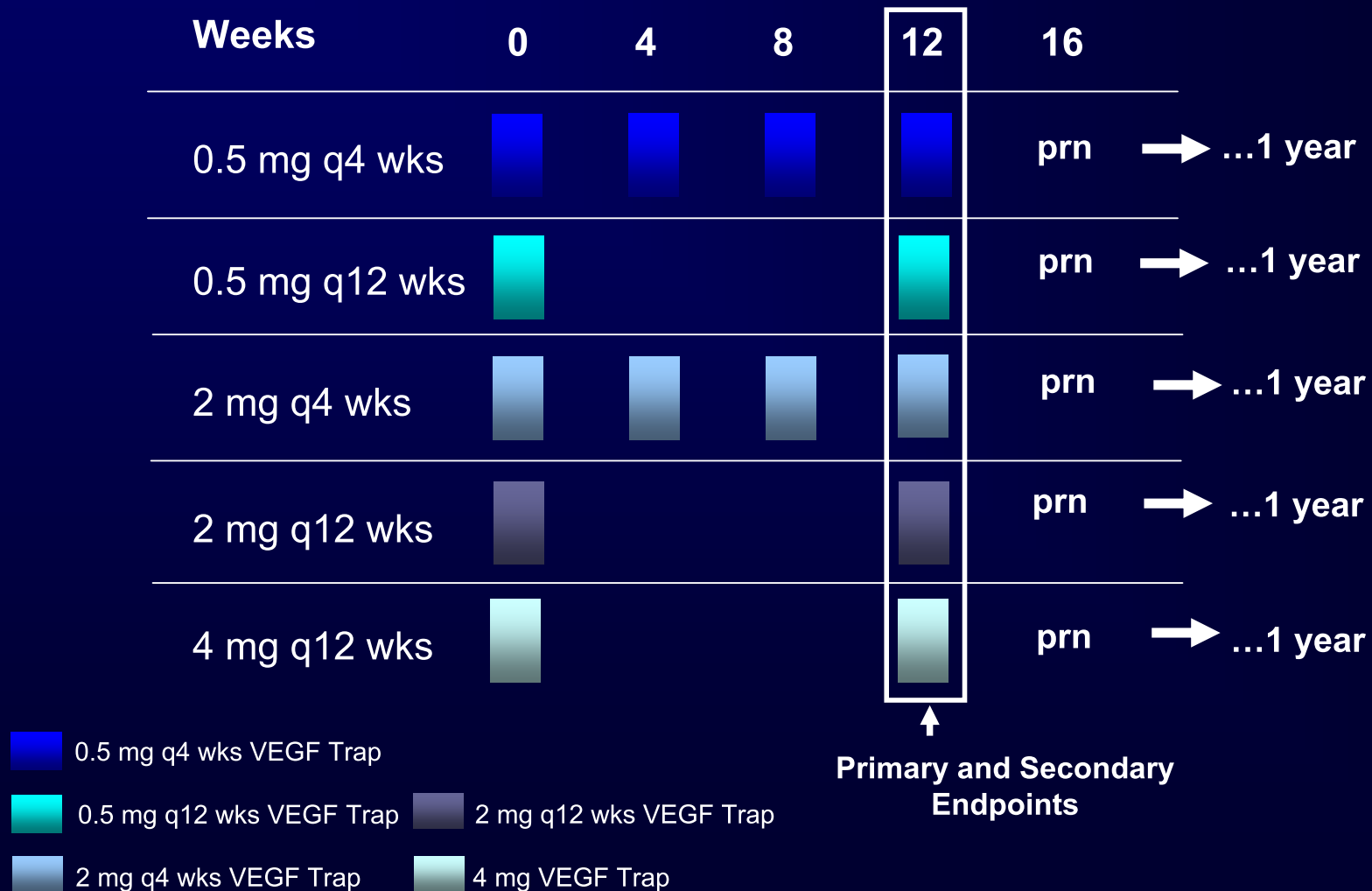
Study Schedule (fixed-dosing phase)



Study Schedule (fixed-dosing phase)



Study Schedule



Baseline Characteristics

(n=157*)	Mean	Range
Age (years)	78.2	53-94
Gender (% M:% F)	38:62	
Disease Duration (months)	3.9	0-67
Lesion Size (mean±SD) in disc areas	3.11±2.12	
Lesion Type: number (%)		
Classic	30 (19.1)	
Predominantly Classic	30 (19.1)	
Minimally Classic	37 (23.6)	
Occult Lesions	60 (38.2)	
Disease Status		
Central Retinal/Lesion Thickness	456 µm	186-1316 µm
Foveal Thickness	327 µm	116-1081 µm
ETDRS BCVA (letters)	56	27-83

*N=159 randomized; n=157 treated

Patient Disposition

No. of Patients	0.5 q4	0.5 q12	2 q4	2 q12	4 q12	All Patients
Screened						301
Randomized	32	32	32	32	31	159
Treated	32	32	31	31	31	157
Completed Wk 52	26	26	29	27	26	134 (84.3%)
Withdrawn by Wk 52	6	6	2	4	5	23 (14.5%)
Reason for Withdrawal						
Non-compliance					1	1 (0.6%)
Subject request	3			2	1	6 (3.8%)
Adverse event				1		1 (0.6%)
Investigator decision	1	1				2 (1.3%)
Sponsor decision	1	1			1	3 (1.9%)
Lost to follow-up		2	1			3 (1.9%)
Death			1		1	2 (1.3%)
Other	1	2		1	1	5 (3.1%)

Mylan Exhibit 1055

Mylan v. Regeneron, IPR2022-01226

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Primary Endpoint Results: Reported at 2007 Retina Society

At 12 weeks VEGF Trap-Eye:

- Significantly improved mean visual acuity
- Significantly reduced central retinal thickness
- Groups dosed at Baseline and at Week 12 showed improved visual acuity and retinal thickness
 - Effect was not as robust as with monthly dosing
- Maintained effect on visual acuity with a single dose to 8 weeks
- Was generally well tolerated with no drug-related serious adverse events

Number of Doses Administered

Re-dosing Criteria (starting at week 16)

- Increase in central retinal thickness of $\geq 100\mu\text{m}$ as measured by OCT, or;
- A loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or;
- Persistent fluid as indicated by OCT, or;
- New onset classic neovascularization, or;
- New or persistent leak on FA, or;
- New macular hemorrhage

Re-Treatment Outcome

Number of injections over PRN phase*

VEGF Trap-Eye	Mean	Median	Range
0.5 mg q4	2.52	2	0 – 9
2 mg q4	1.55	1	0 – 4
0.5 mg q12	1.84	2	0 – 4
2 mg q12	2.48	3	0 – 5
4 mg q12	1.7	1	0 – 7
All	2.01	2	0 – 9

* After the week 12 injection through week 52

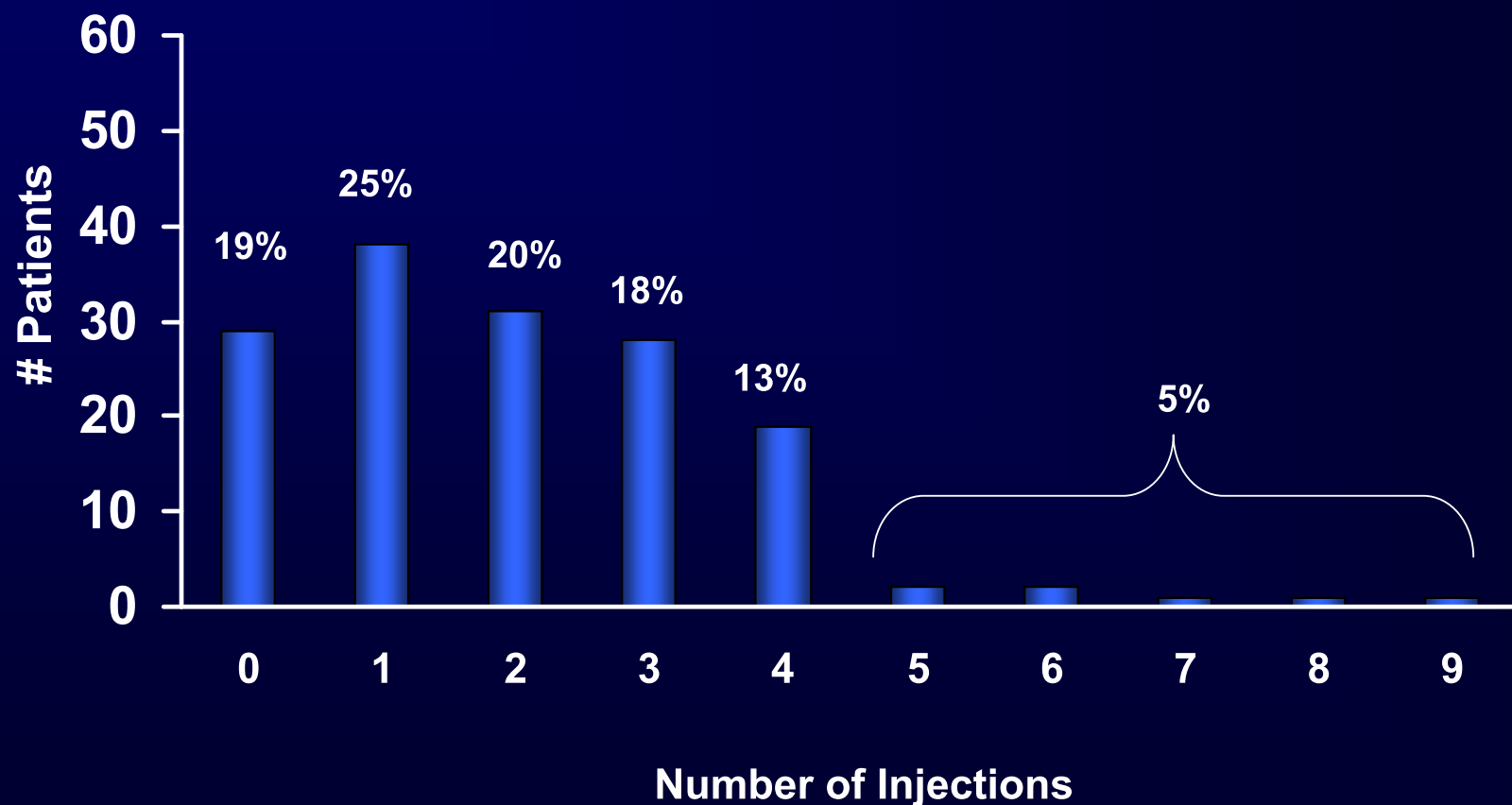
All patients, n=152

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Re-Treatment Outcome

VEGF Trap-Eye	Mean number of injections over PRN phase (week 12 – 52)	Mean number of days to first injection over PRN phase (week 12 – 52)	Median number of days to first injection over PRN phase (week 12 – 52)
0.5 mg q4	2.52	102	85
2 mg q4	1.55	160	150
0.5 mg q12	1.84	133	86
2 mg q12	2.48	113	86
4 mg q12	1.7	138	111
All	2.01	129	110

Distribution of Injections over PRN Phase (All groups combined)

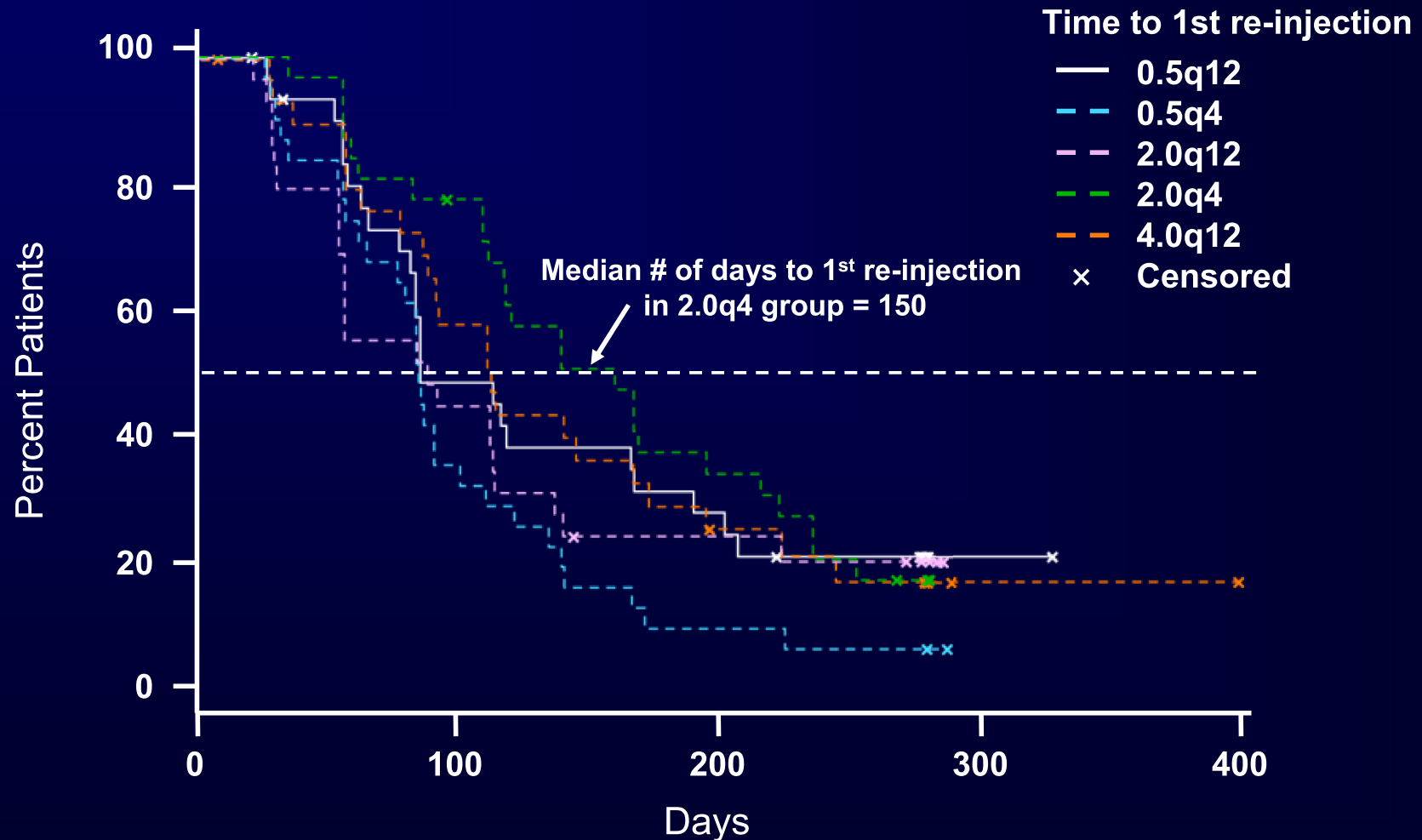


Percent of patients receiving an injection analyzed by number of injections, n=152

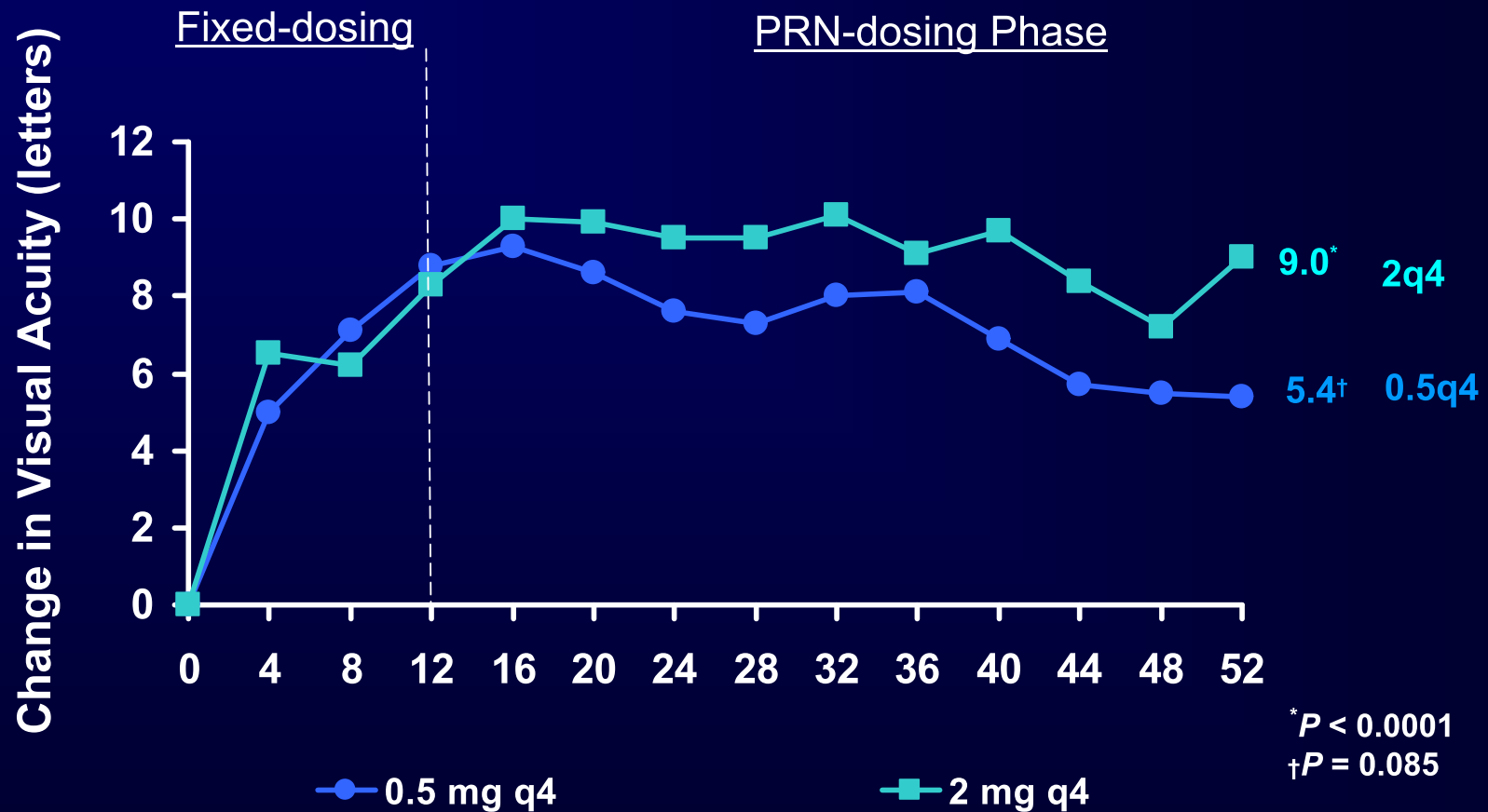
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Kaplan-Meier Curve

Time to Re-injection (by treatment group)

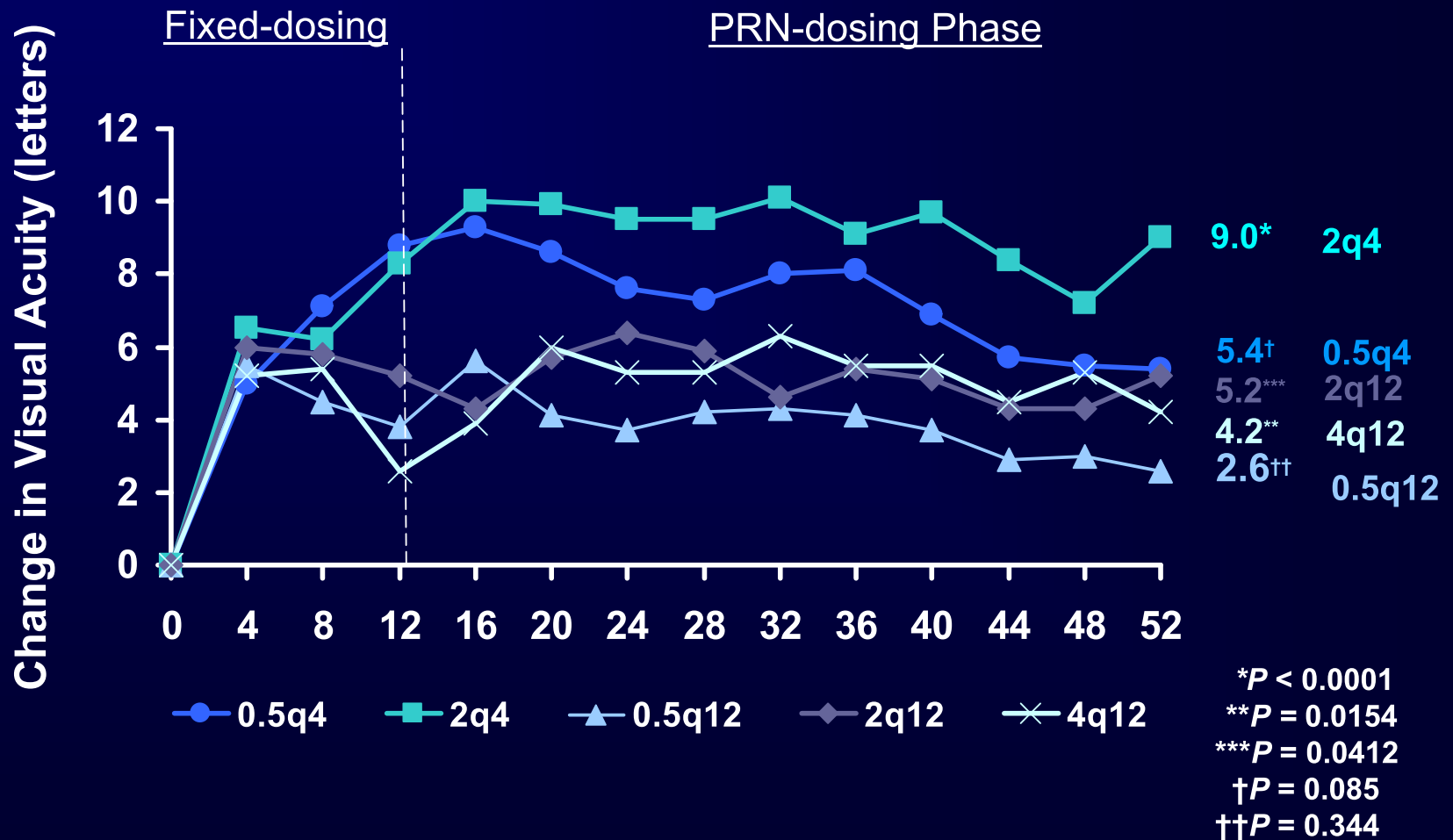


Mean Change in Visual Acuity



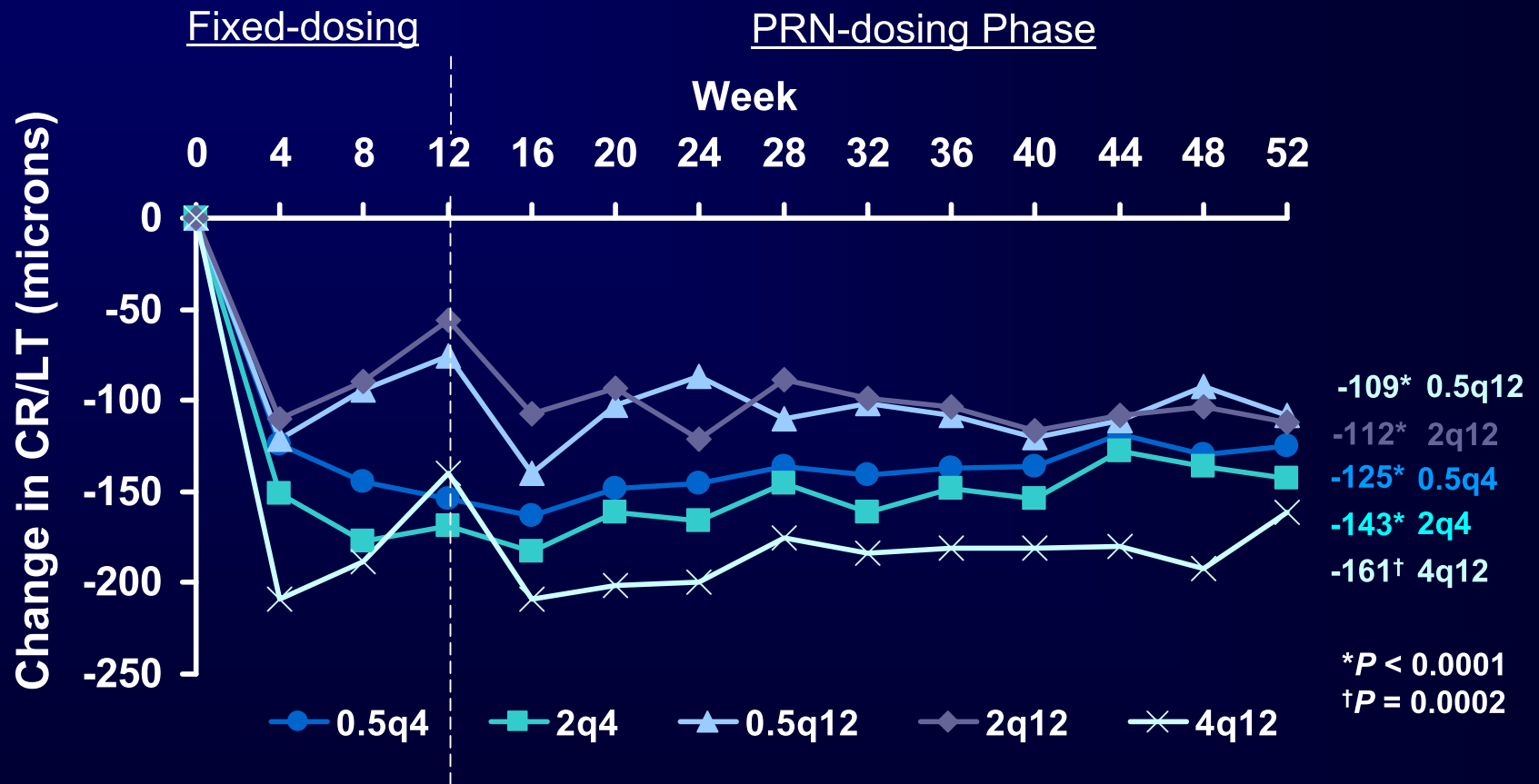
Last Observation Carried Forward (LOCF) analysis; paired t-test; 0.5q4 : n=32; 2q4: n=31

Mean Change in Visual Acuity



LOCF analysis; paired t-test; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

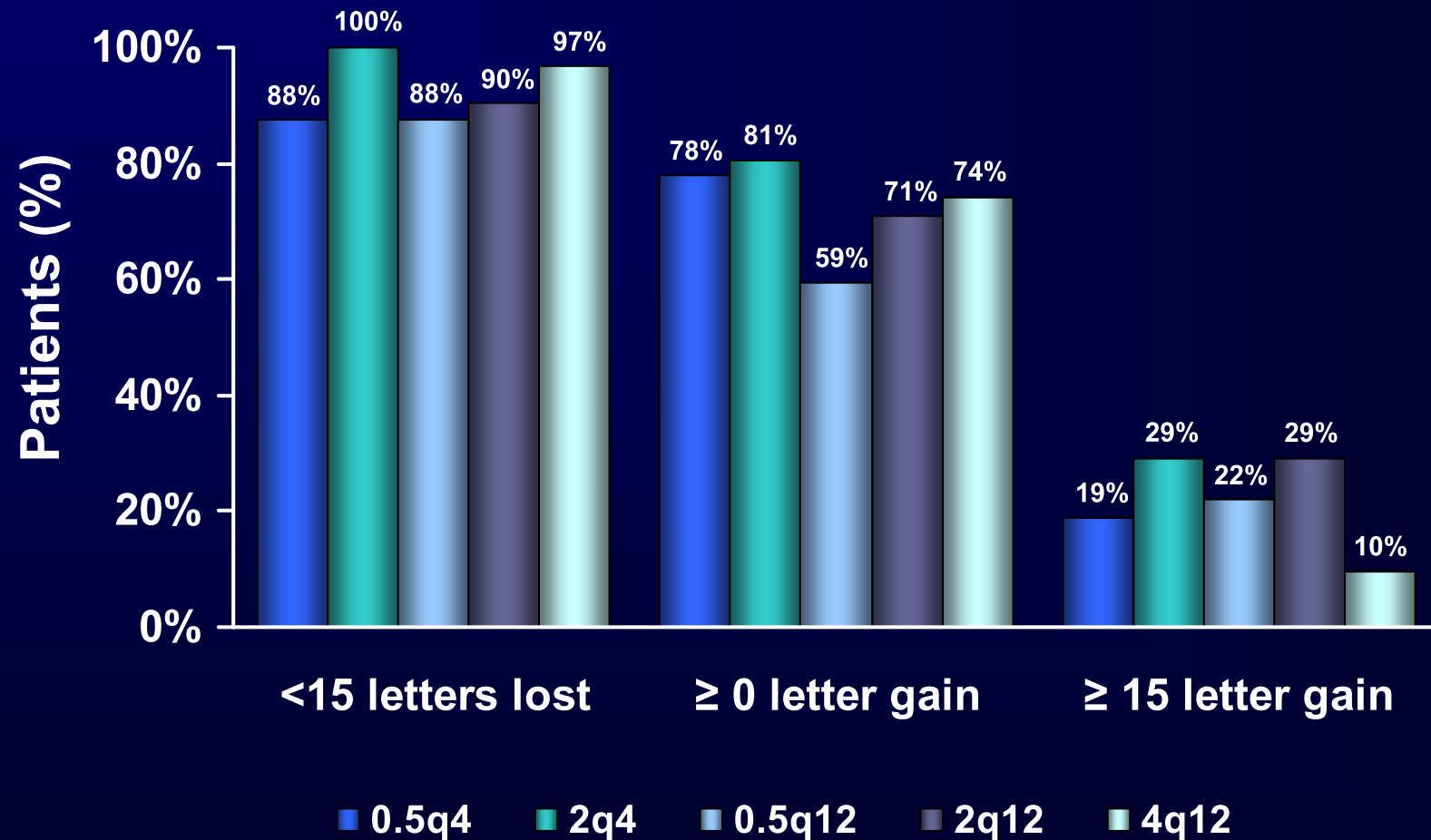
Mean Change in Central Retinal/Lesion Thickness



Posterior Pole Scans; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

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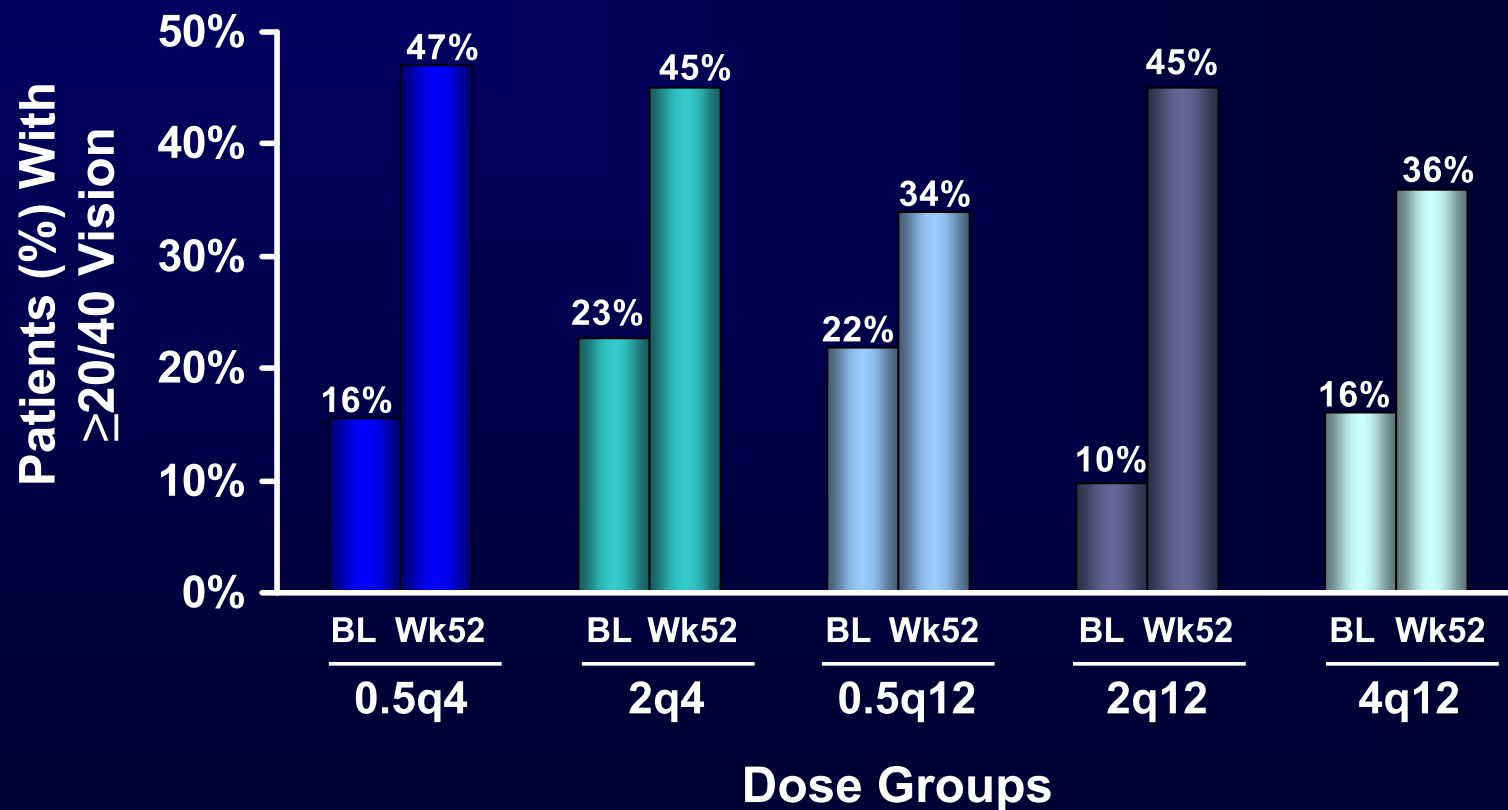
Visual Acuity at Week 52



LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

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Proportion of Patients With $\geq 20/40$ Vision

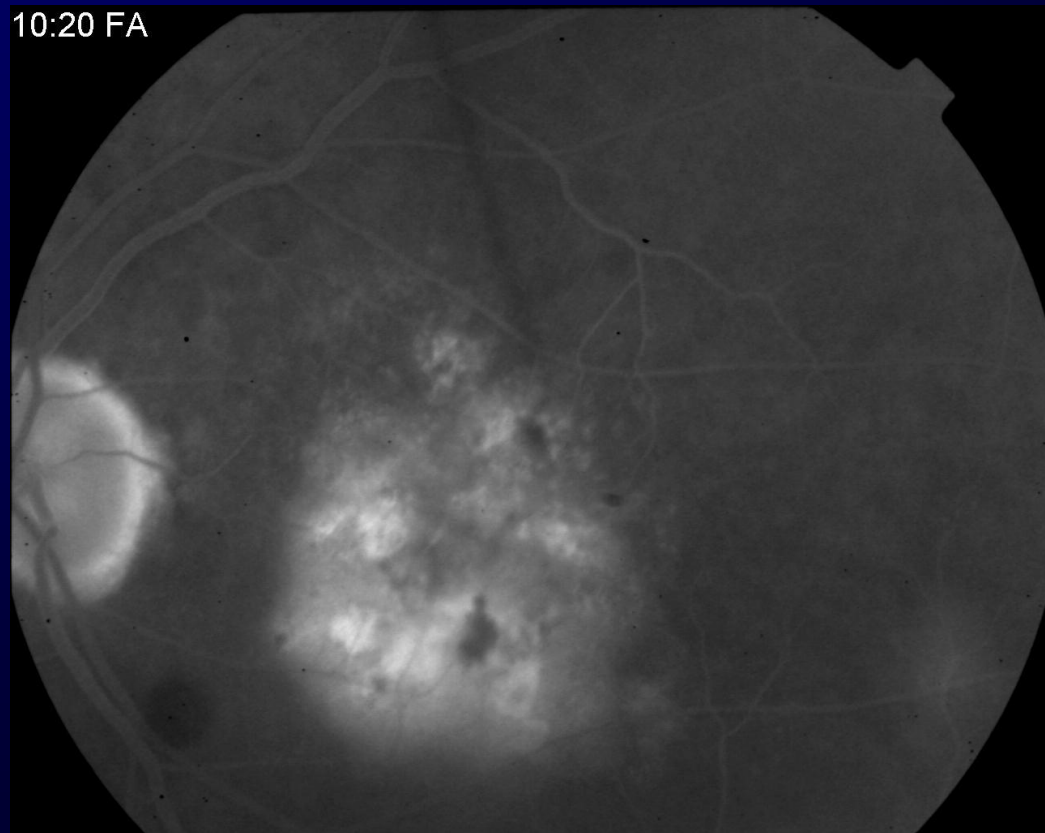


LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31; BL=baseline;

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Fluorescein Angiography

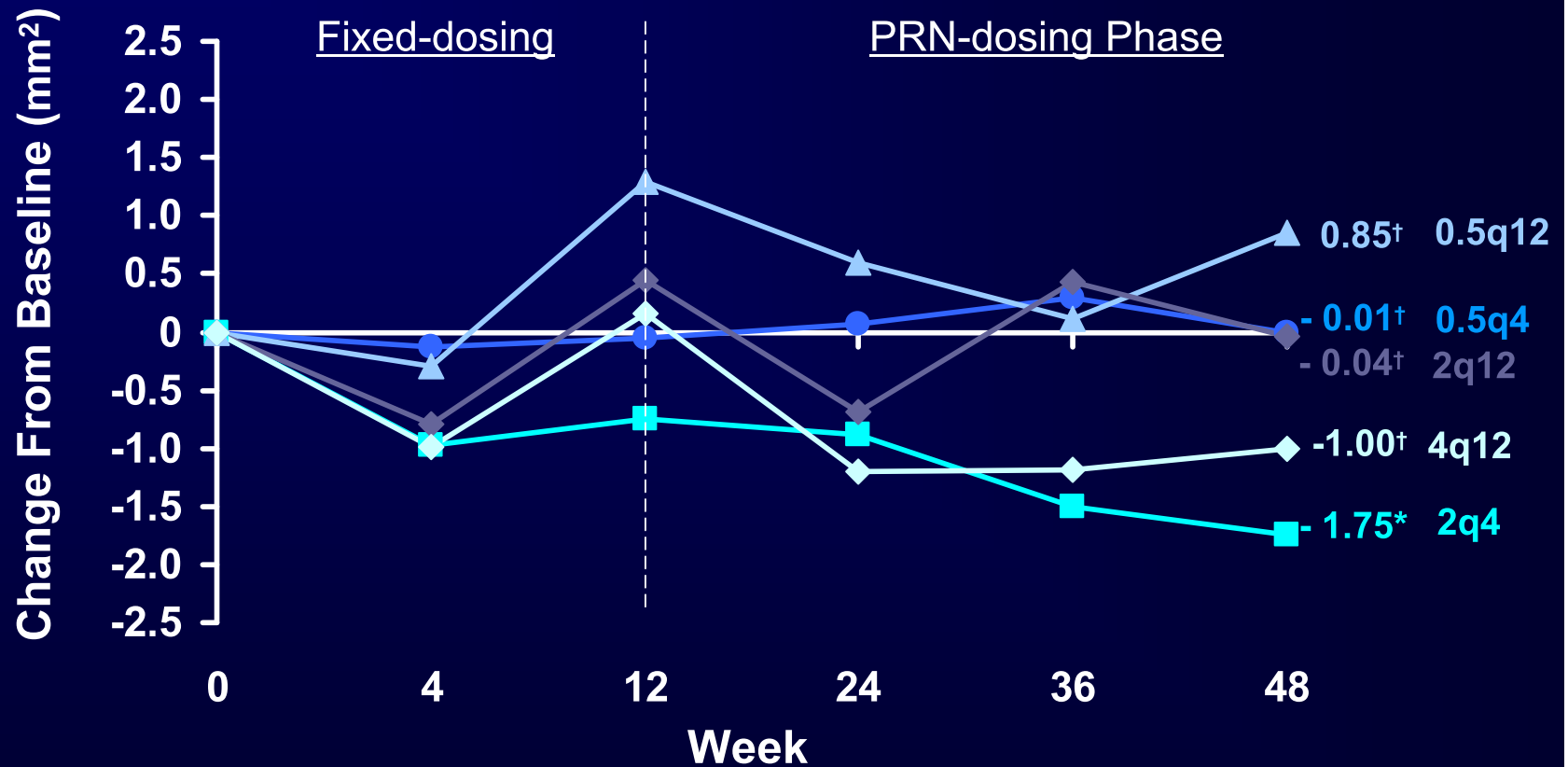
1-Year Outcomes



DARC Reading Center: Definitions

- Total Lesion Size
 - Measurement of entire lesion including the classic and occult neo-vascular component as well as contiguous areas of blood and/or blocked fluorescence and/or serous pigment epithelial detachment (PED)
- Total Active CNV Size
 - Area of visible CNV (classic and/or occult) which demonstrates angiographic evidence of late leakage or pooling of dye
- Classic CNV
 - Area of bright, well-demarcated hyper-fluorescence in early phase, with progressive dye leakage into overlying sub-sensory retinal space in late phase of angiogram (not a measurement of area of leakage, but rather extent of the classic neo-vascular complex)
- Occult CNV
 - Angiogram shows staining or leakage from fibro-vascular PED or hyper-fluorescent leakage at level of RPE that represents late leakage of undetermined source (leakage in late phase without classic CNV or fibro-vascular PED to account for leakage)

Mean Change in Total Lesion Size by Fluorescein Angiography



Lesion Size at Baseline (mm²)

0.5q4

2q4

0.5q12

2q12

4q12

**P* = 0.04

†*P* = NS

Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

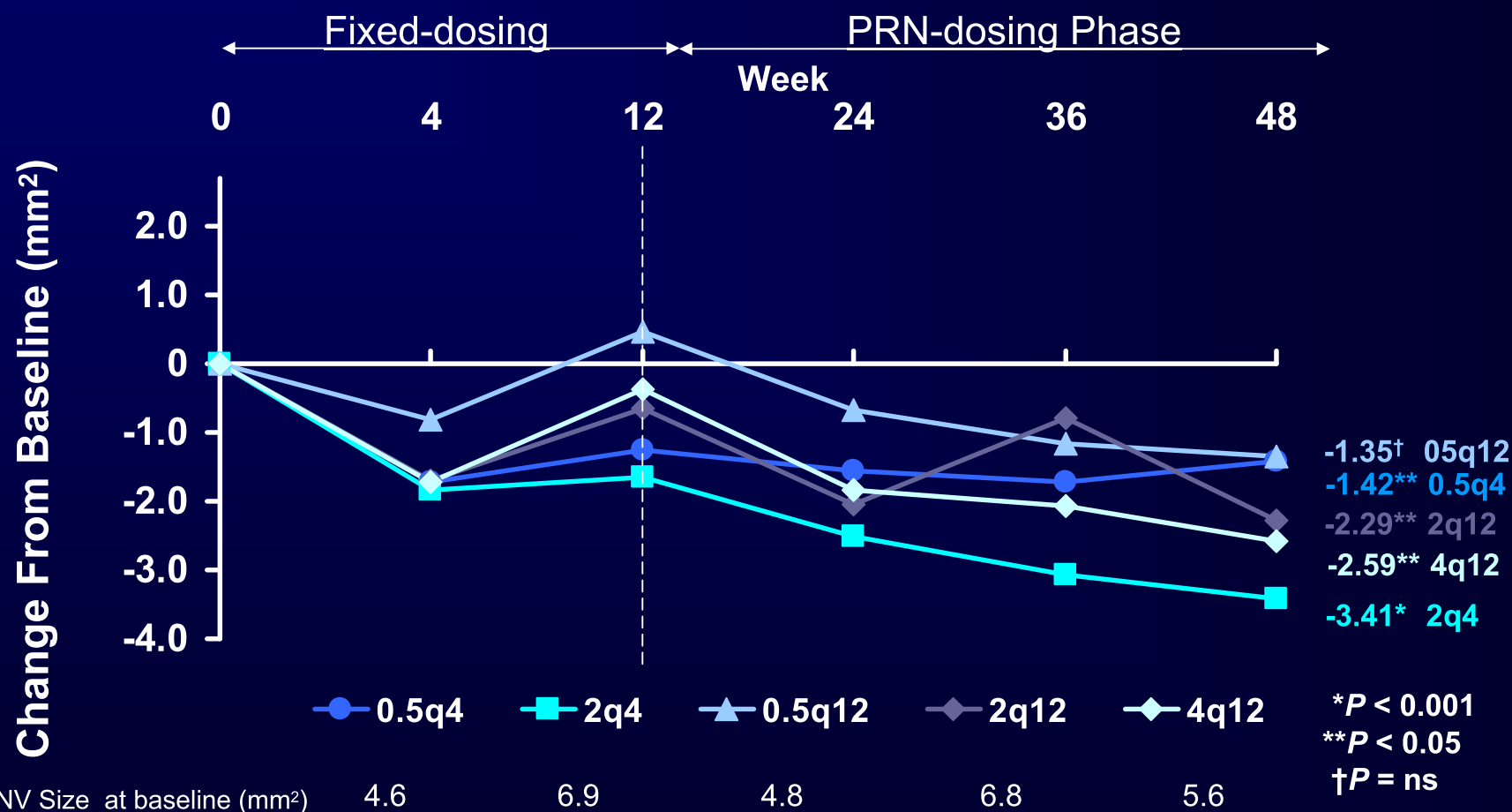
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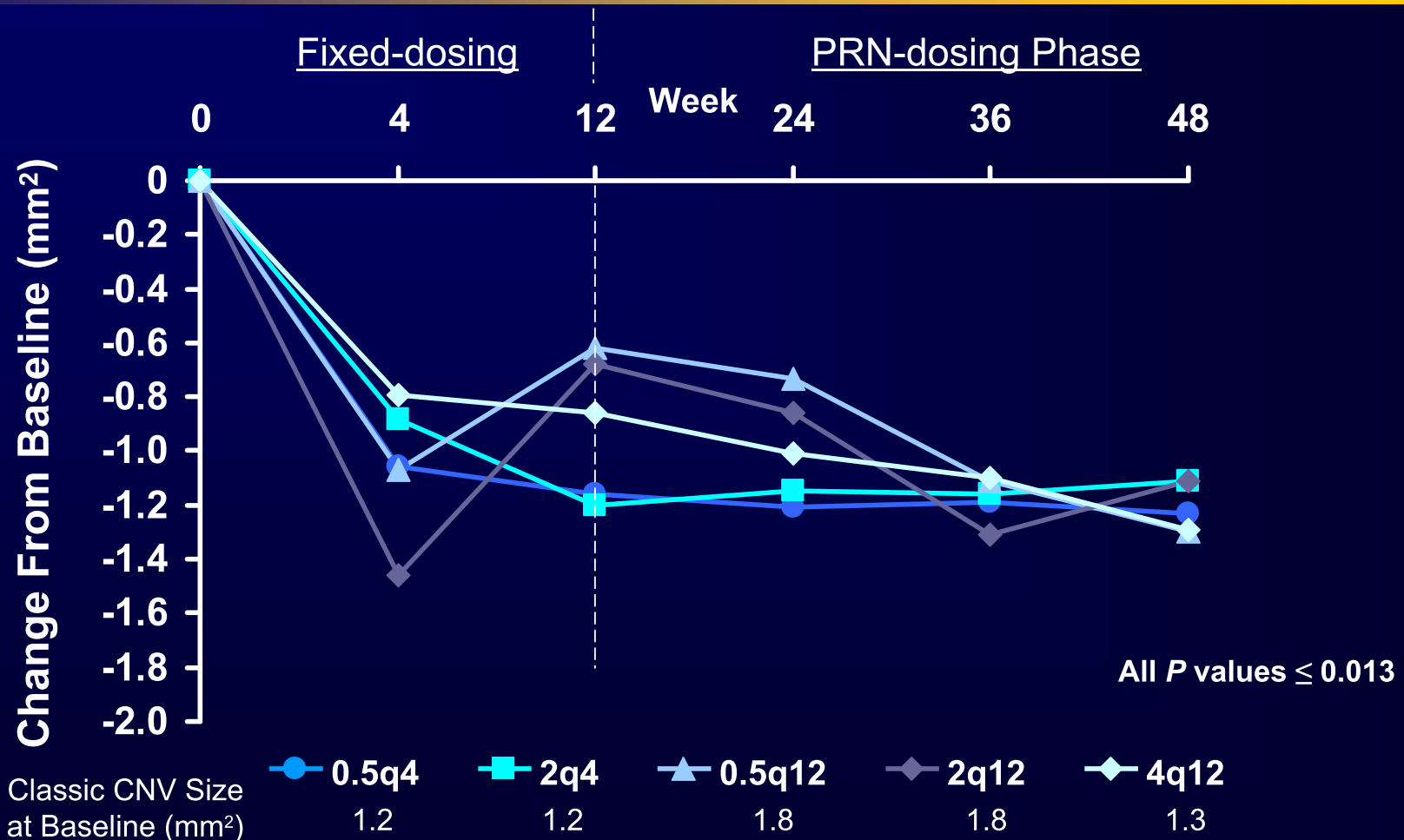
Mean Change in Total Active CNV Size by Fluorescein Angiography



Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

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Mean Change in Classic CNV Size by Fluorescein Angiography



Mandatory FA only; LOCF analysis; 0.5q4 and 0.5q12: n=32; 2q4, 2q12, and 4q12: n=31

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Safety: Serious Adverse Events

Ocular Serious Adverse Events in the study eye:

- 1 case of culture-negative endophthalmitis / uveitis (deemed not related to study drug)

Systemic Serious Adverse Events:

- None deemed to be drug-related
- 2 deaths
 - Pulmonary hypertension (pre-existing condition)
 - Pancreatic carcinoma
- Arterial Thromboembolic Events (ATE's): 1 case of hemorrhagic stroke
 - Subject had a history of prior stroke

Adverse Events

(Study eye, all groups combined $\geq 5\%$)

Adverse Event	Number (N=157)	Percent (%)
Conjunctival Hemorrhage	60	38.2
Increased IOP (transient post-injection)	29	18.5
Refraction Disorder	25	15.9
Retinal Hemorrhage	23	14.6
Visual Acuity Reduced (patient reported)	21	13.4
Vitreous Detachment	18	11.5
Eye Pain	15	9.6
Vitreous Floaters	14	8.9
Detachment of Retinal Pigment Epithelium	12	7.6
Retinal Edema	10	6.4
Visual Disturbance	9	5.7
Blepharitis	8	5.1
Cataract nuclear	8	5.1
Subretinal Fibrosis	8	5.1

IOP=intraocular pressure

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Conclusions

- Patients received, on average, only two additional injections over 40-week PRN-dosing phase (after a 12-week fixed dosing period)
 - 19% received no additional injections after Week 12
 - 110 days median time to first re-injection
- VEGF Trap-Eye achieved clinically meaningful and durable vision improvement over 1 year
 - Up to +9.0 mean letters gained at week 52
 - Up to -161 microns reduction in central retinal lesion thickness at week 52 as measured by OCT
- Generally well tolerated with no drug-related serious adverse events
 - Most common AE's typical of intravitreal injection

VIEW 1 & VIEW 2 Phase 3 Studies

(Dosing schedule-years 1 and 2)

