PANORAMA

A Phase 3, Double-Masked, Randomized Study Of The Efficacy And Safety Of Aflibercept In Patients With Moderately Severe To Severe NPDR

Week 100 Results

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Disclosures

- This study was funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY). The sponsors participated in the design and conduct of the study and analysis of the data
- CCW: Adverum (C, R); Bayer (C); Genentech/Roche (C, R); Novartis (C, R); Regeneron (C, R); Regenxbio (C, R); Takeda (C)
- Study Disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation.

PANORAMA Study Design

Phase 3, Double-masked, Randomized, Study of Efficacy & Safety of IAI in Patients with moderately severe to severe NPDR (DRSS Level 47 and 53)
N=402**

Sham
N=133

2q16
IAI 2 mg Q16 weeks⁺
N=135

2q8►PRN
IAI 2 mg Q8 weeks*
N=134

Week 24
Primary Endpoint: **Proportion of patients improving ≥ 2 steps on DRSS**
All IAI Combined versus Sham

Week 52
Primary Endpoint: **Proportion of patients improving ≥ 2 steps on DRSS**
2q16 and 2q8 individually versus Sham

Follow up through Week 100

Key Secondary endpoints
- % developing PDR/ASNV
- % developing CI-DME
- Time to development of PDR/ASNV or CI-DME

⁺After 3 initial monthly doses and 1 q8 interval *After 5 initial monthly doses, flexible treatment schedule after week 52 **Patients were stratified by baseline DRSS level
ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; DRSS, Diabetic Retinopathy Severity Score; NPDR, nonproliferative diabetic retinopathy;

Inclusion & Exclusion Criteria

- **Inclusion**
  - Anti-VEGF treatment naïve with moderately severe to severe NPDR (DRSS levels 47 or 53), confirmed by the central reading center, in whom PRP could be safely deferred for ≥6 months
  - BCVA ETDRS letter score of ≥69 letters (~ Snellen equivalent of ≥20/40)
- **Exclusion**
  - DME threatening the center of the macula
  - Evidence of retinal neovascularization
  - Any prior treatment with:
    - Focal or grid laser photocoagulation or PRP
    - Systemic or intravitreal anti-VEGF agents
    - Intraocular steroids
  - Current ASNV, vitreous hemorrhage, or traction retinal detachment
  - HbA1c >12% or HbA1c ≤12% with uncontrolled diabetes mellitus
  - Uncontrolled blood pressure
  - History of cerebrovascular accident or myocardial infarction within 6 months of study start

BCVA, best-corrected visual acuity; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, glycated hemoglobin; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

Dosing Schedule

Week:	BL	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100
Sham	O	O	O	O	O		O		O		O		O		O		O		O		O		O		O	-
2q16	X	X	X	O	X		O		X		O		X		O		X		O		X		O		X	-
2q8 ▶ PRN	X	X	X	X	X		X		X		X		X		+		+		+		+		+		+	-

+ = Aflibercept PRN:
Injection given unless DRSS is
Level 35 or better (mild NPDR)
as determined by the investigator

Patients progressing to PDR/ASNV or CI-DME were eligible for rescue treatment (IAI or laser) at the discretion of the investigator. Data for patients receiving rescue treatment was censored from the time of rescue.

X=active injection, O=sham injection

Baseline Demographics

	Sham	2q16	2q8▸PRN	Total
N (FAS/SAF)	133	135	134	402
Age (years (SD))	55.8 (10.31)	55.4 (11.13)	55.8 (10.19)	55.7 (10.53)
Women # (%)	64 (48.1%)	60 (44.4%)	53 (39.6%)	177 (44.0%)
Race # (%)				
White	107 (80.5%)	99 (73.3%)	104 (77.6%)	310 (77.1%)
Black or African American	13 (9.8%)	16 (11.9%)	12 (9.0%)	41 (10.2%)
Asian	4 (3.0%)	12 (8.9%)	7 (5.2%)	23 (5.7%)
Other	9 (6.8%)	8 (5.9%)	11 (8.2%)	28 (7.0%)
Hemoglobin A1C (%)	8.5 (1.54)	8.6 (1.69)	8.4 (1.64)	8.5 (1.62)
Duration of Diabetes (years (SD))	15.5 (9.34)	13.7 (8.61)	14.0 (9.67)	14.4 (9.23)
Diabetes Type 2	123 (92.5%)	121 (89.6%)	124 (92.5%)	368 (91.5%)

FAS, Full analysis set; SAF, Safety analysis set; SD, standard deviation

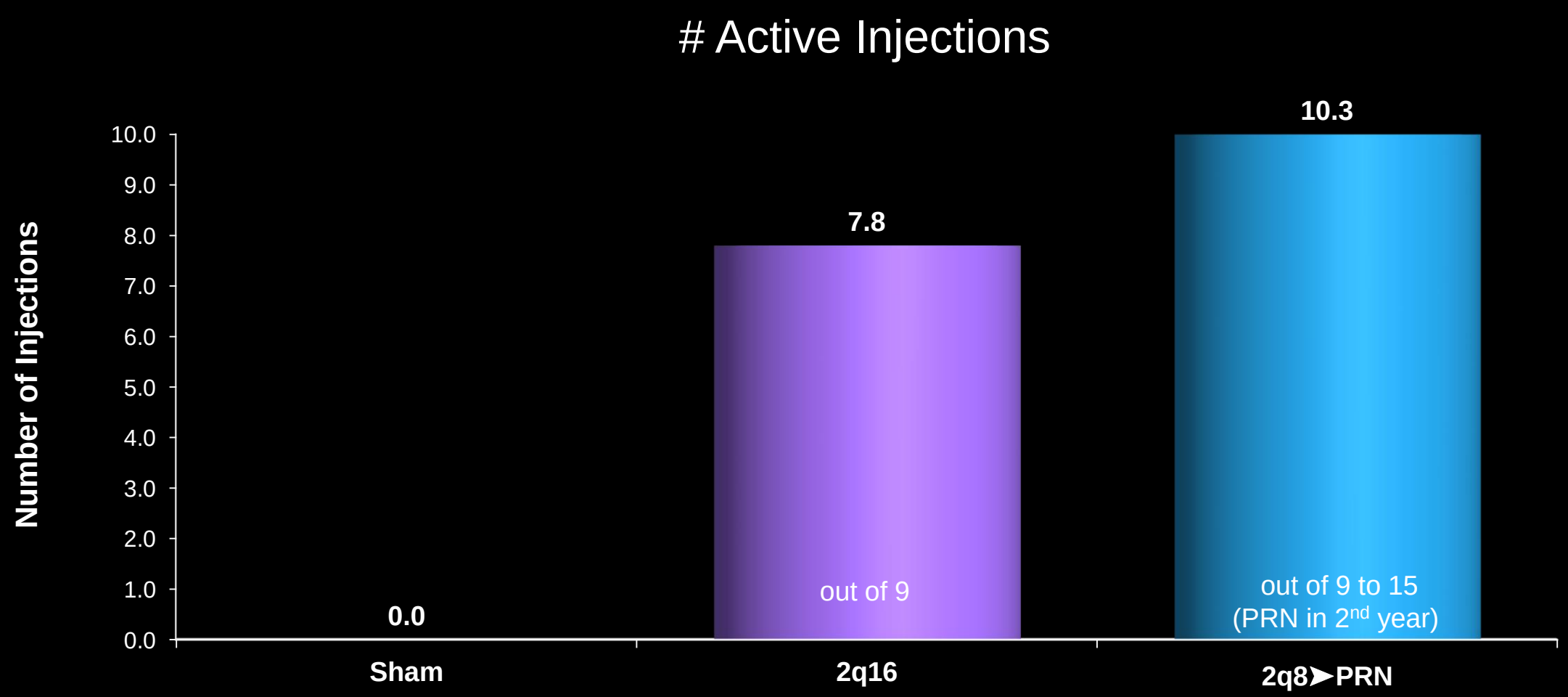
Baseline Disease Characteristics and Disposition

	Sham	2q16	2q8▸PRN	Total
N (FAS/SAF)	133	135	134	402
ETDRS BCVA (letters) Mean (SD) Snellen Equivalent	82.7 (6.03) 20/25	82.2 (6.63) 20/25	82.3 (5.15) 20/25	82.4 (5.96) 20/25
CRT(microns) Mean (SD)	249.4 (38.41)	246.0 (34.34)	246.8 (31.59)	247.4 (34.82)
Diabetic Retinopathy Severity Score (DRSS)				
Level 47	99 (74.4%)	102 (75.6%)	101 (75.4%)	302 (75.1%)
Level 53	34 (25.6%)	33 (24.4%)	33 (24.6%)	100 (24.9%)

# of Patients Completing Week 100	97 (72.9%)	111 (82.2%)	112 (83.6%)	320 (79.6%)
# of Patients Completing Week 52	109 (82.0%)	122 (90.4%)	124 (92.5%)	355 (88.3%)

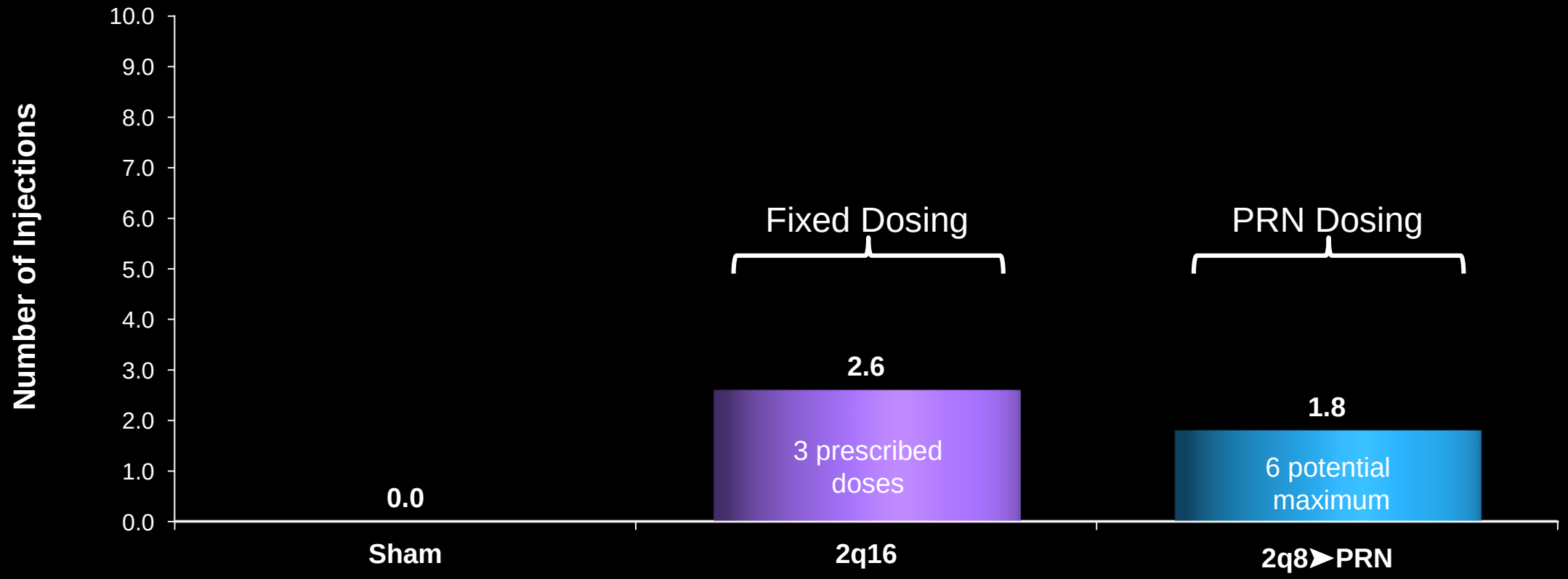
CRT, central retinal thickness.

Treatment Experience through Week 100



Sham n=133, 2q16 n=135, 2q8 n=134

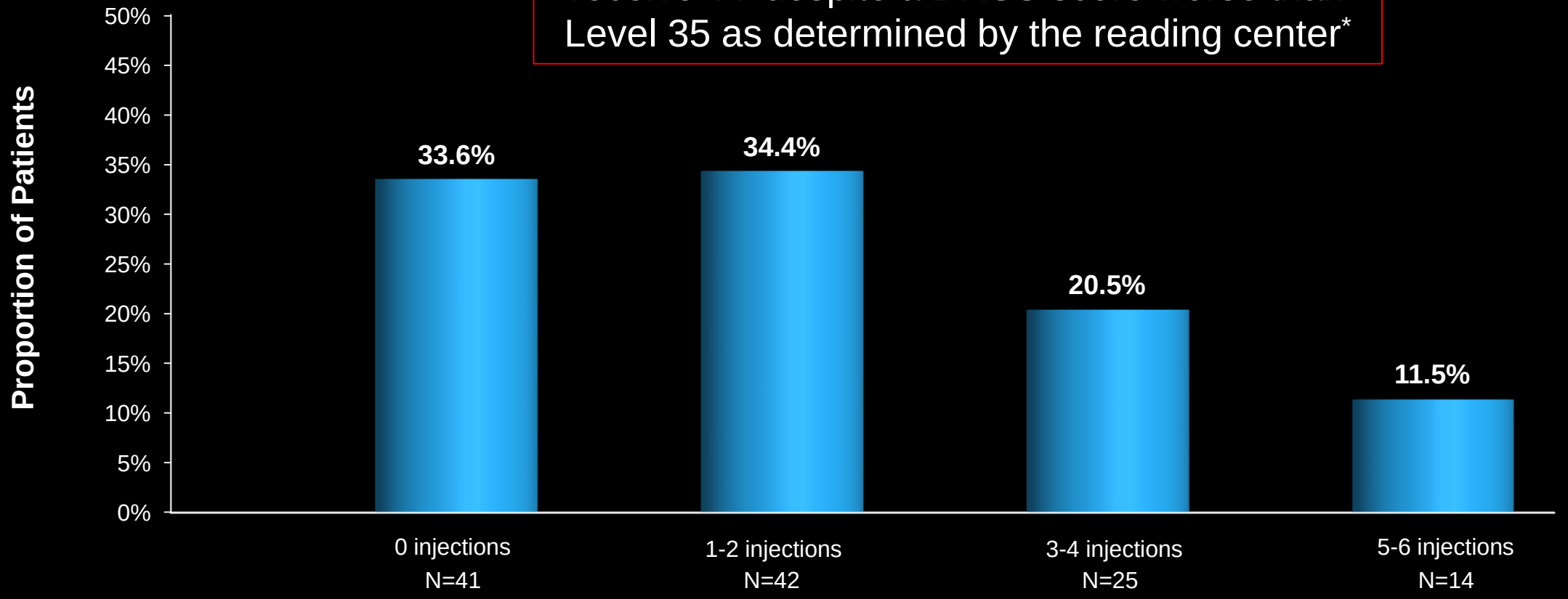
Treatment Experience* from Week 56 to 100



*Not including IAI rescue treatment.
Patients entering the 2nd year: Sham n=106, 2q16 n=121, 2q8 n=122 (41 patients in 2q8 group did not receive any injections in year 2)

% of Patients by Number of Injections in 2q8▸PRN Group in Year 2

≈30% of eyes at each PRN dosing visit did not receive IAI despite a DRSS score worse than Level 35 as determined by the reading center*

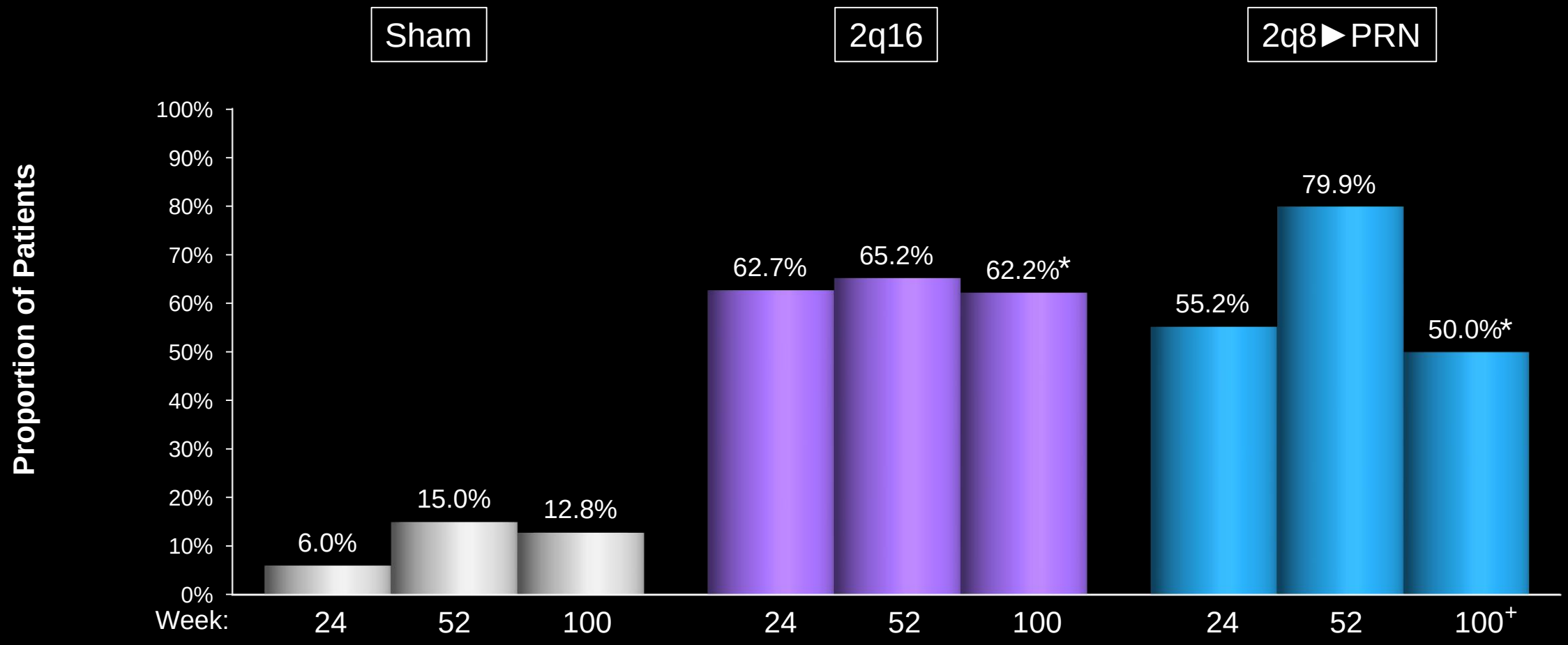


Patients in 2q8 group who entered the 2nd year; 2q8 n=122.

*At any visit, twice as many patients did not receive an injection that should have (based on analysis of reading center evaluations) compared to the reverse

Efficacy

Proportion of Patients with ≥2-step Improvement from Baseline in DRSS

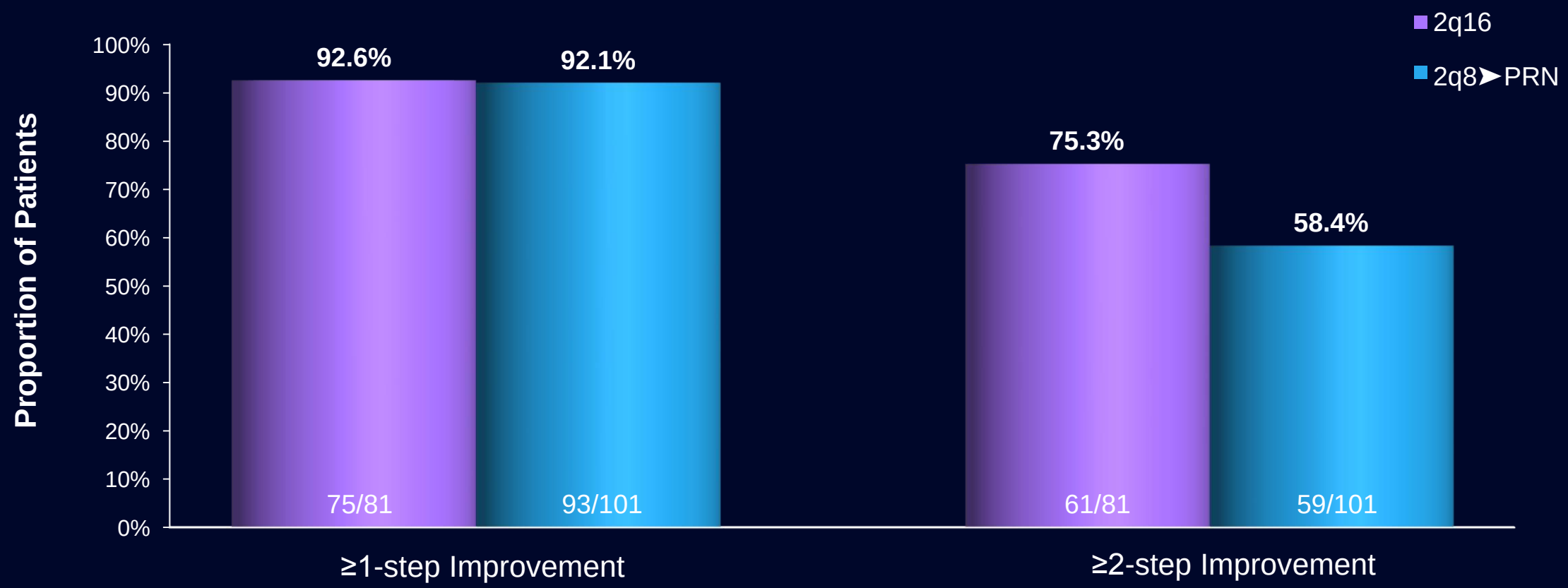


+Independent reading center review of investigator PRN decisions suggests under treatment during Year 2

Nominal p < 0.0001 vs. sham

Last observation carried forward (LOCF); Sham n=133, 2q16 n=135, 2q8 n=134

% of Patients with DRSS Improvement at Week 100 with ≥2-step Improvement in DRSS at Week 52

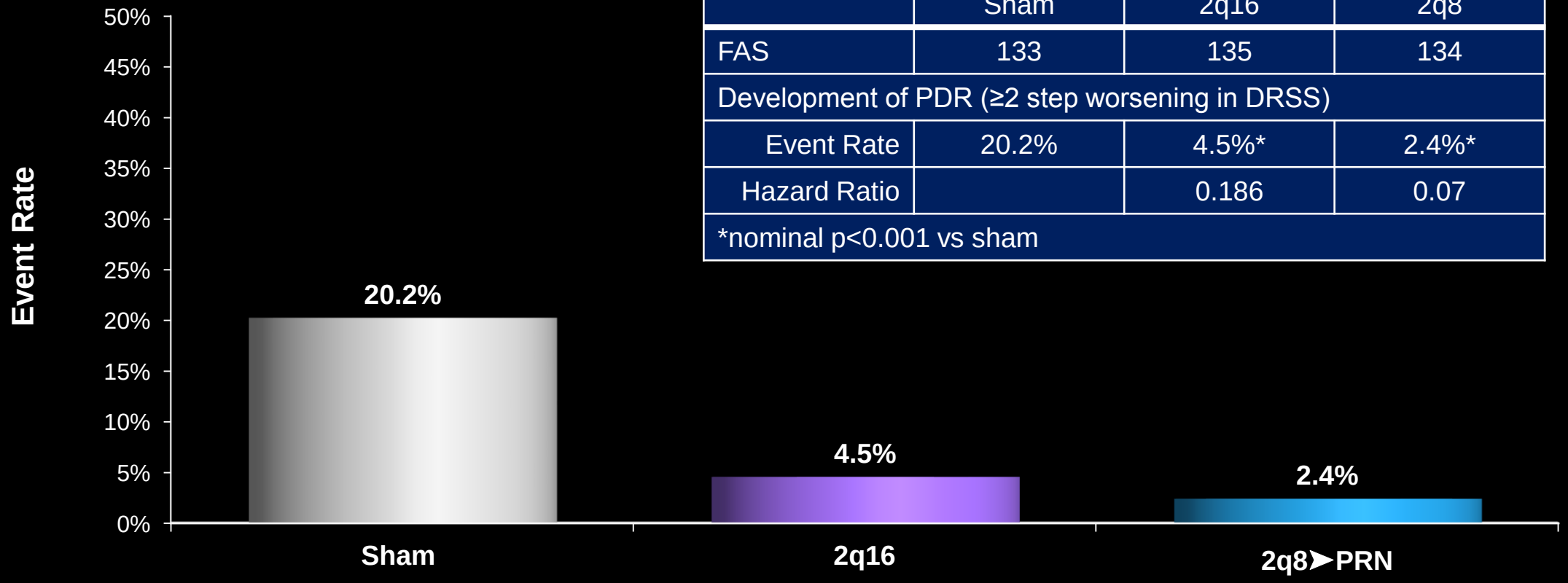


Of patients who had ≥2-step improvement in DRSS at week 52, >90% had ≥1-step improvement at week 100

Patients in 2q16 and 2q8 group who entered the 2nd year; 2q16 n=121; 2q8 ▶ PRN n=122

Proportion of Patients with ≥2-Step Worsening from Baseline in DRSS through Week 100

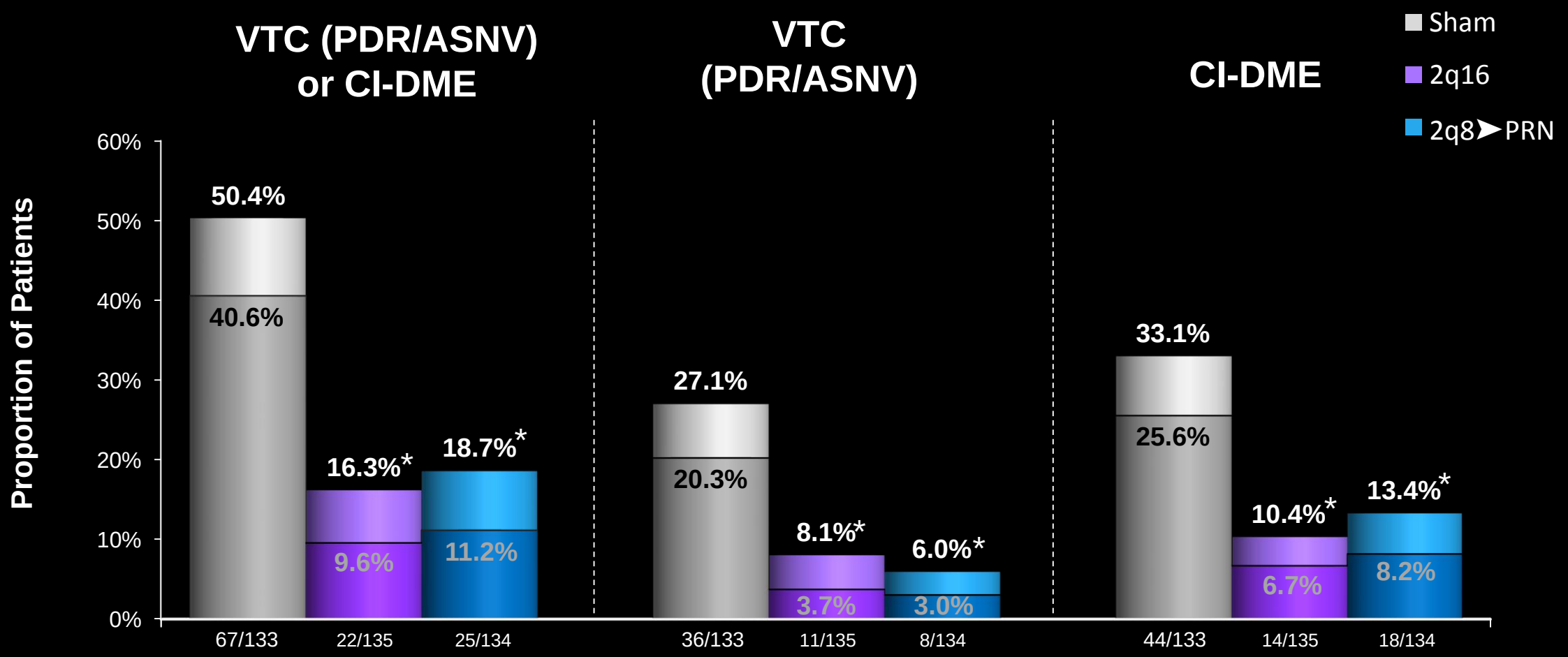
Kaplan-Meier Analysis



	Sham	2q16	2q8
FAS	133	135	134
Development of PDR (≥2 step worsening in DRSS)			
Event Rate	20.2%	4.5%*	2.4%*
Hazard Ratio		0.186	0.07
*nominal p<0.001 vs sham			

PDR, proliferative diabetic retinopathy
Sham n=133, 2q16 n=135, 2q8 n=134

Proportion of Patients Developing a VTC or CI-DME through Week 52^ and 100



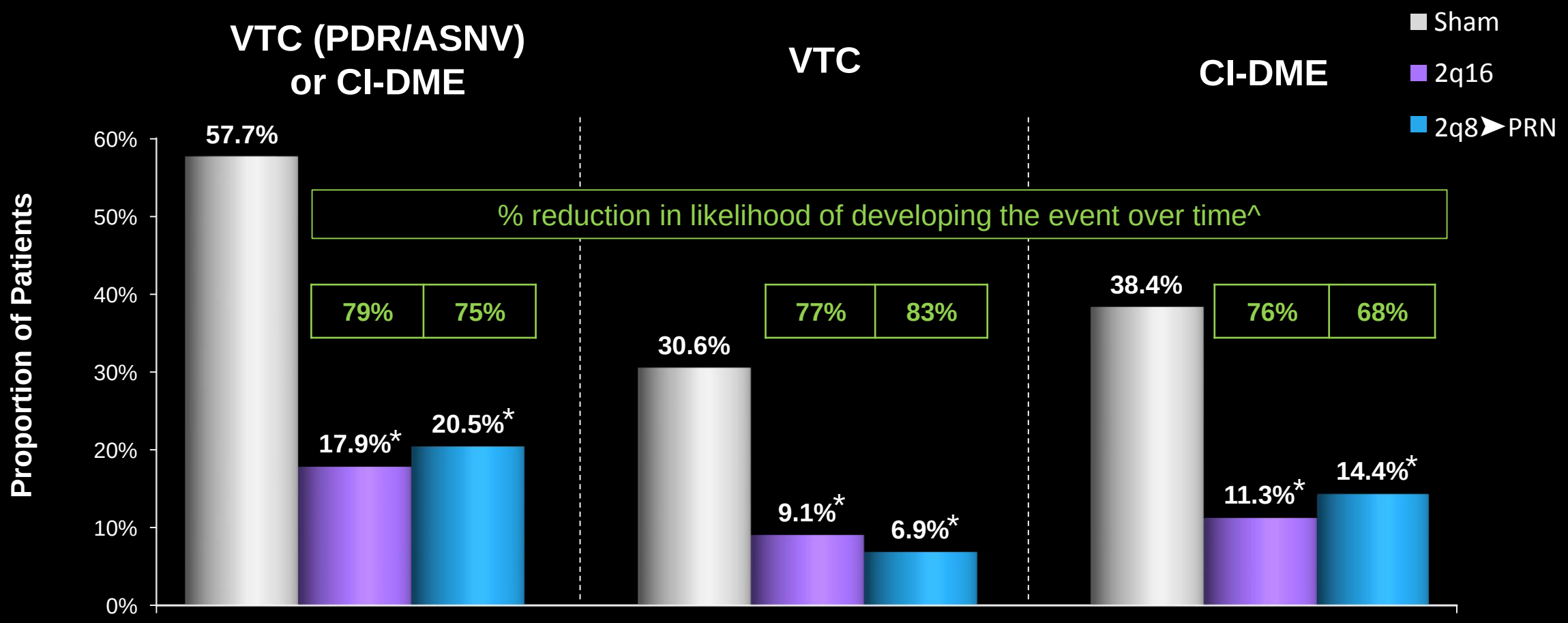
VTC = Vision threatening complication defined as PDR/ASNV;
CI-DME = center-involved DME
FAS; Sham n=133, 2q16 n=135, 2q8 n=134.

^Week 52 represented by shaded portion of columns and black font

Nominal p < 0.001 vs. sham

Proportion of Patients Developing a VTC or CI-DME through Week 100

Kaplan-Meier Analysis

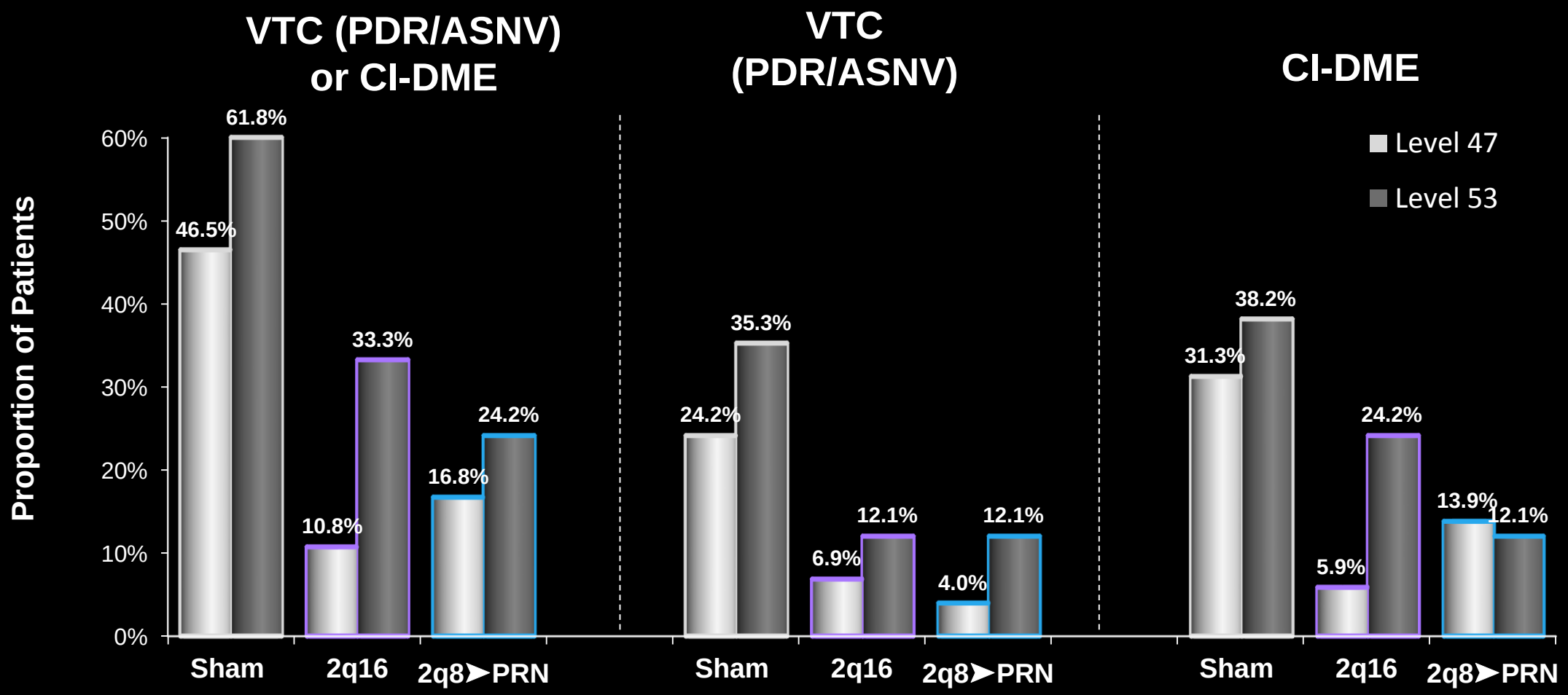


VTC = Vision threatening complication defined as PDR/ASNV
CI-DME = center involved DME
FAS; At baseline: Sham n=133, 2q16 n=135, 2q8 n=134

^Percentage reductions in risk derived from hazard ratios from Kaplan-Meier estimates.

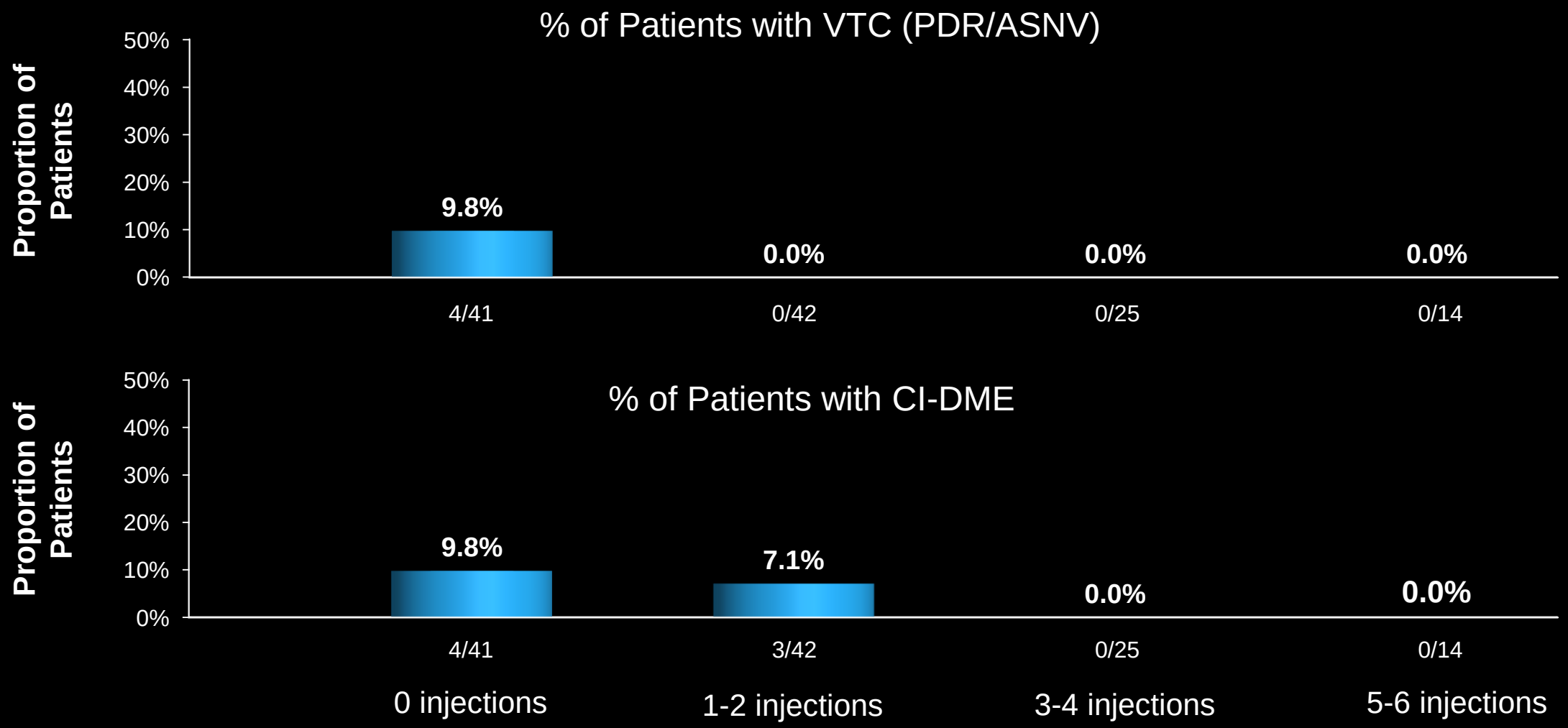
Nominal p < 0.001 vs. sham

Proportion of Patients Developing a VTC or CI-DME through Week 100 by Baseline DRSS



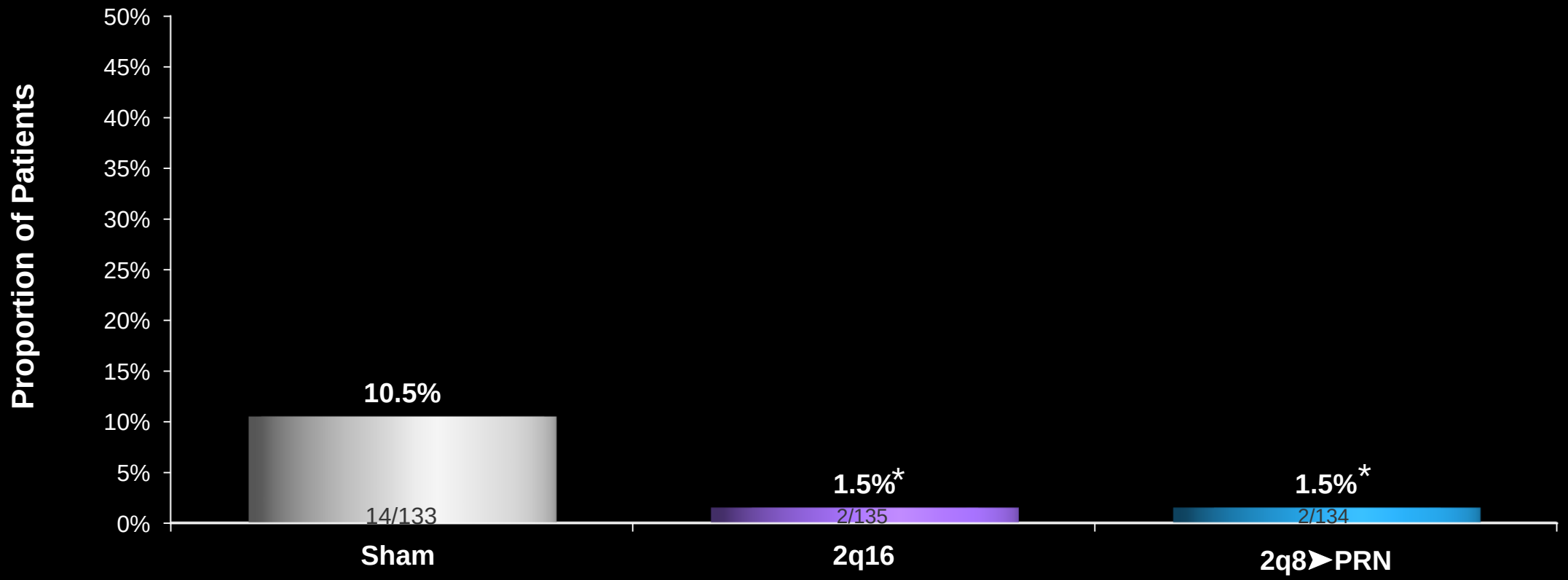
VTC = Vision threatening complication defined as PDR/ASNV
CI-DME = center involved DME
FAS; Sham n=133, 2q16 n=135, 2q8 n=134

% of Patients with Events in Year 2 in 2q8▸PRN Group by Number of Injections



Patients in 2q8 group who entered the 2nd year; 2q8 n=122

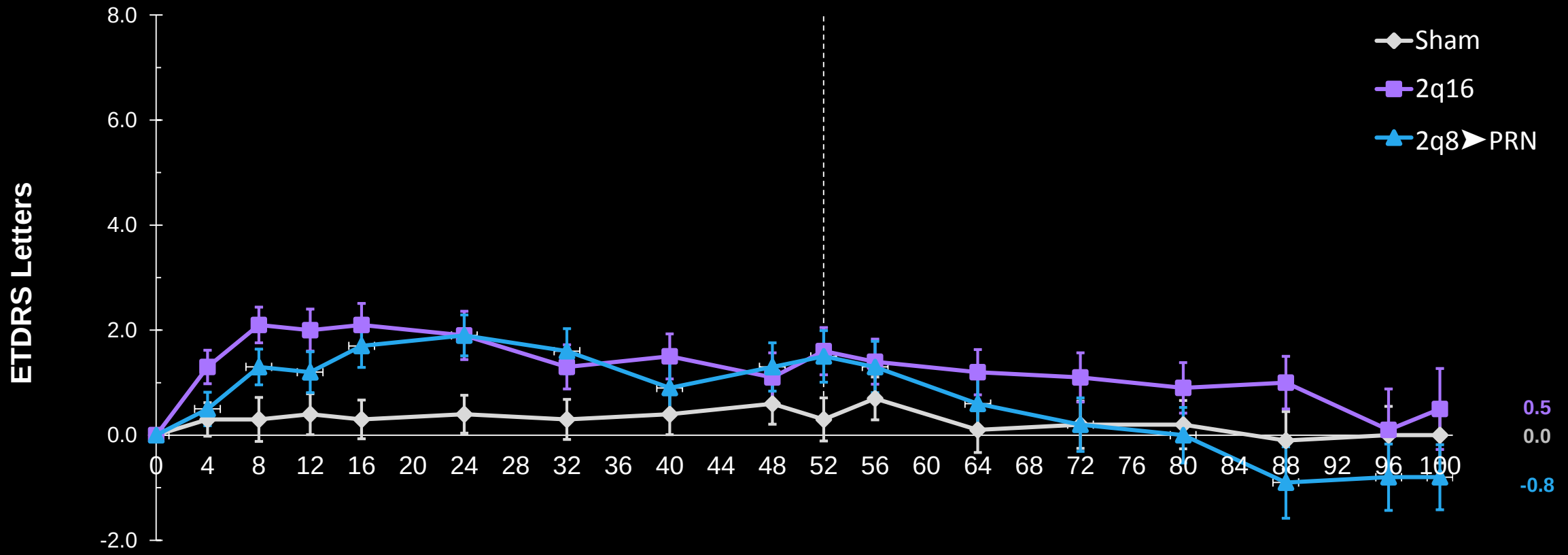
Proportion of Patients Receiving PRP or Vitrectomy through Week 100



Sham n=133, 2q16 n=135, 2q8 n=134

**Nominal p < 0.002 vs. sham*

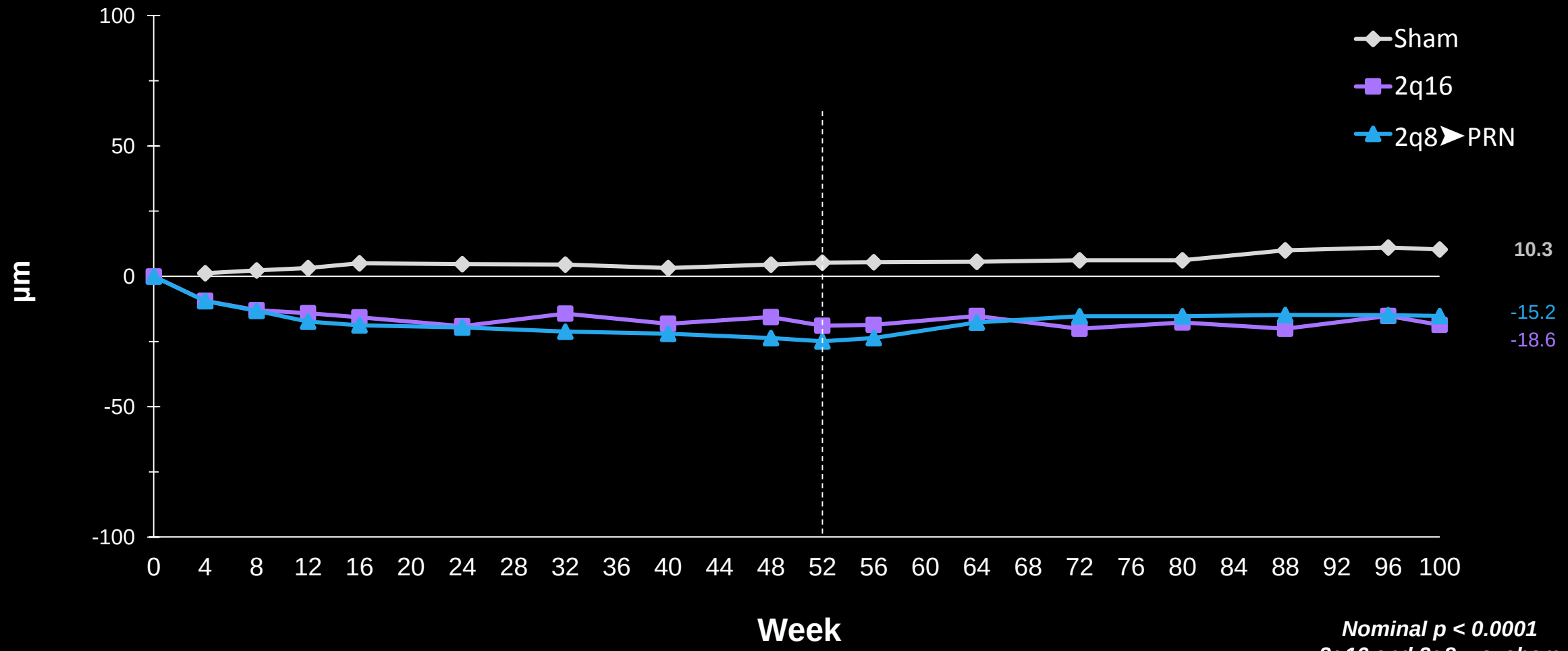
Mean Change in Best Corrected Visual Acuity



Nominal p = NS 2q16 vs. sham
Nominal p = NS 2q8 vs. sham

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

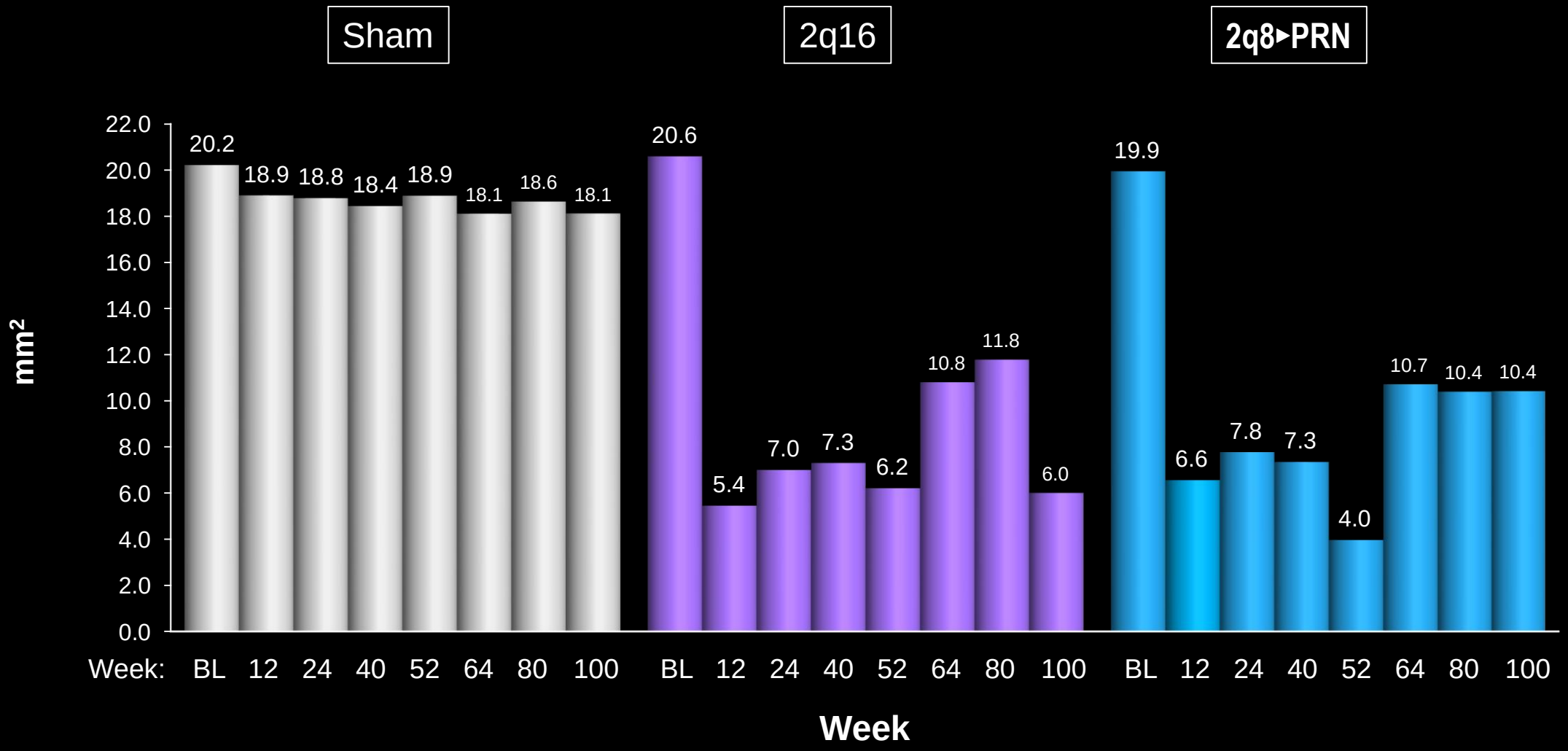
Mean Change in Central Retinal Thickness



Nominal p < 0.0001
2q16 and 2q8 vs. sham

LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

Absolute Leakage Area by Visit on Fluorescein Angiography



LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

Safety

Ocular TEAEs in Study Eye through Week 100
(≥3%)

	Sham	2q16	2q8▸PRN
N (FAS/SAF)	133	135	134
Number of patients ≥ 1 AE, n (%)	76 (57.1%)	77 (57.0%)	81 (60.4%)
Conjunctival hemorrhage	8 (6.0%)	18 (13.3%)	25 (18.7%)
Diabetic retinal edema	43 (32.3%)	14 (10.4%)	19 (14.2%)
Vitreous floaters	3 (2.3%)	7 (5.2%)	13 (9.7%)
Cataract	5 (3.8%)	8 (5.9%)	8 (6.0%)
Vision blurred	1 (0.8%)	1 (0.7%)	5 (3.7%)
Eye pain	6 (4.5%)	11 (8.1%)	5 (3.7%)
Retinal exudates	6 (4.5%)	5 (3.7%)	9 (6.7%)
Vitreous detachment	4 (3.0%)	7 (5.2%)	7 (5.2%)
Blepharitis	1 (0.8%)	2 (1.5%)	7 (5.2%)
Cataract subcapsular	1 (0.8%)	5 (3.7%)	4 (3.0%)
Diabetic retinopathy	22 (16.5%)	3 (2.2%)	5 (3.7%)
Dry eye	6 (4.5%)	3 (2.2%)	5 (3.7%)
Cataract nuclear	0	0	6 (4.5%)

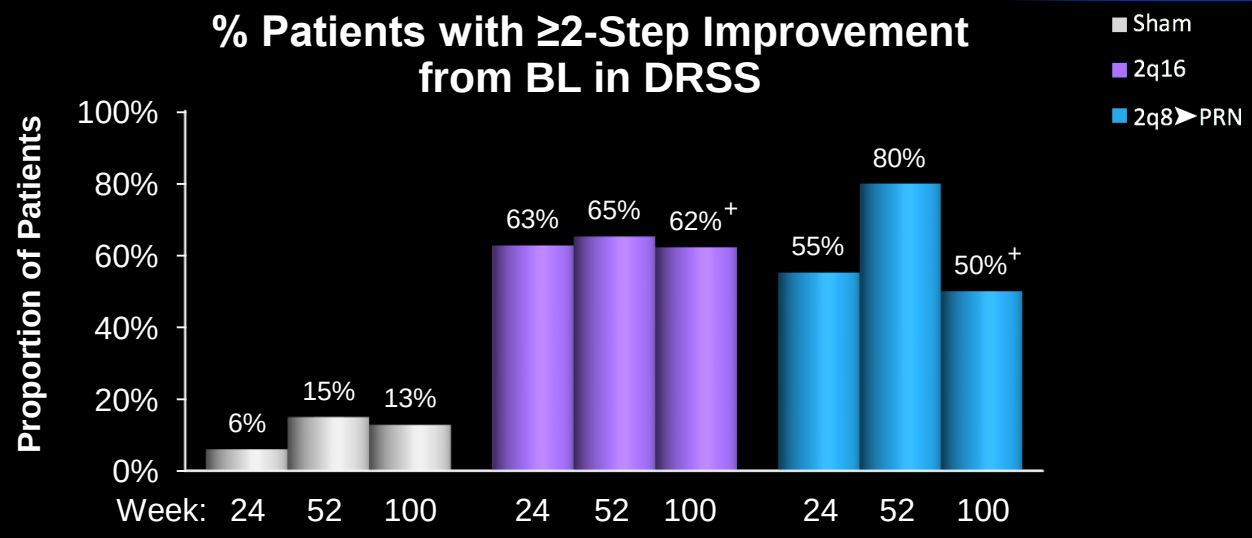
AE, adverse event; TEAE, treatment-emergent AE

APTC Events and Deaths through Week 100

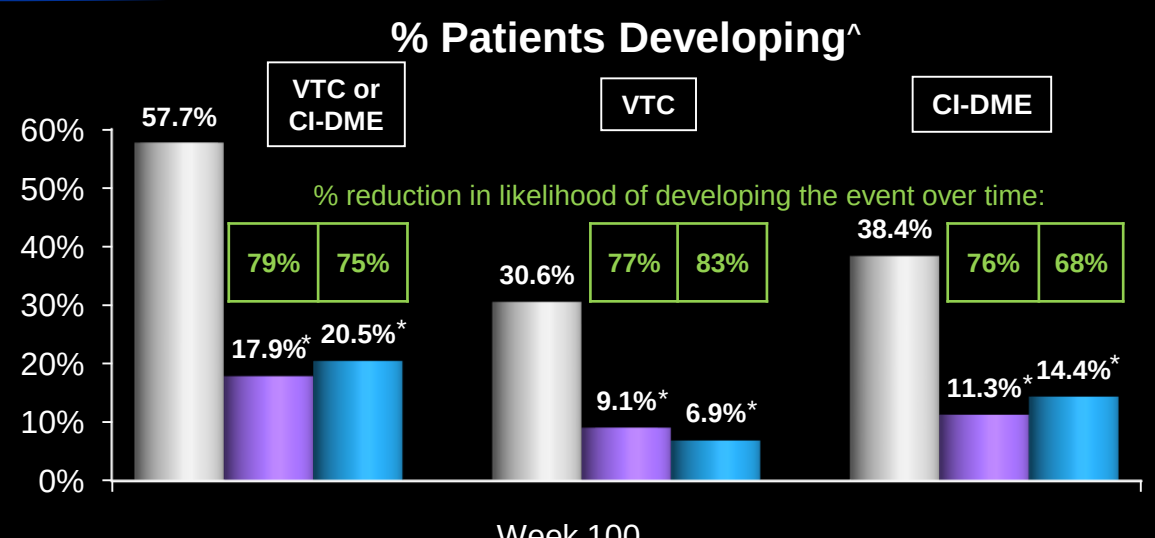
	Sham	2q16	2q8▸PRN
N (FAS/SAF)	133	135	134
Number of patients with at least one such AE, n (%)	7 (5.3%)	8 (5.9%)	4 (3.0%)
Non Fatal Stroke	3 (2.3%)	5 (3.7%)	1 (0.7%)
Non Fatal MI	0	3 (2.2%)	2 (1.5%)
Vascular Death	4 (3.0%)	0	1 (0.7%)
All Deaths	8 (6.0%)	1 (0.7%)	3 (2.2%)

APTC, Antiplatelet Trialists' Collaboration; MI, myocardial infarction.

PANORAMA 100 Week Conclusions



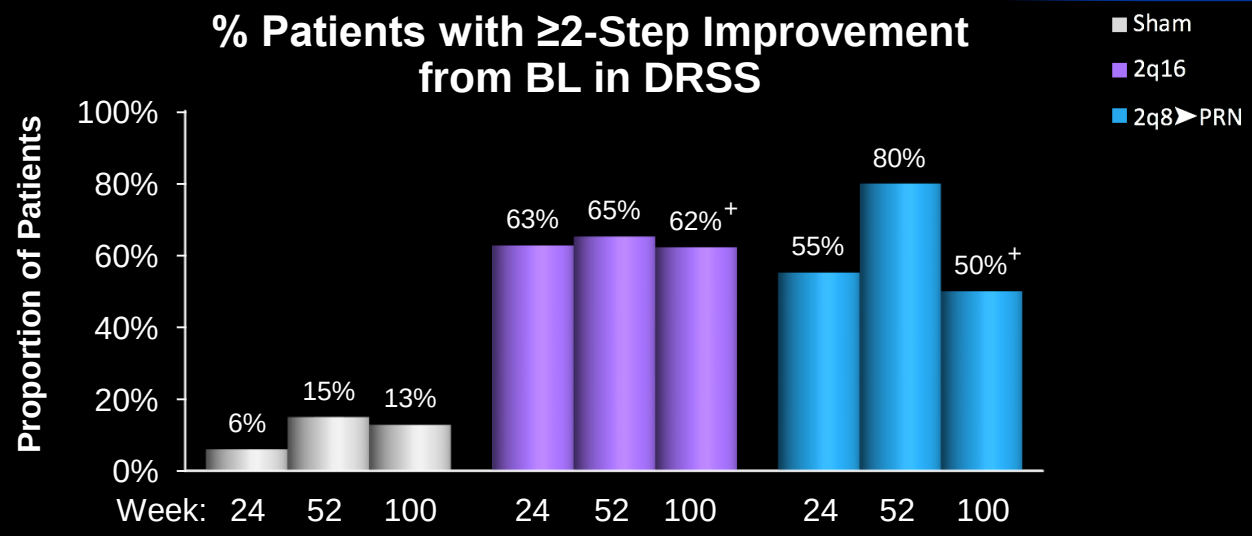
LOCF; Sham n=133, 2q16 n=135, 2q8 n=134



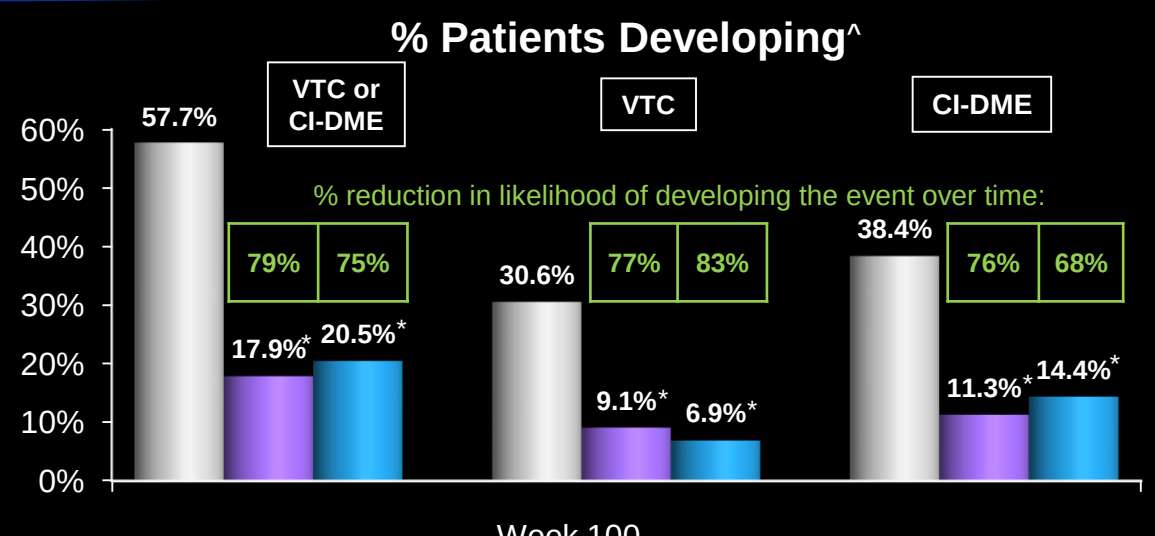
^Derived from hazard ratios from Kaplan-Meier estimates.

- Proportion of patients with a ≥2-step DRSS improvement remained significantly greater with aflibercept vs sham
- Vision threatening complications (PDR/ASNV) and CI-DME occurred in a substantially greater proportion of sham patients

PANORAMA 100 Week Conclusions



LOCF; Sham n=133, 2q16 n=135, 2q8 n=134



^Derived from hazard ratios from Kaplan-Meier estimates.

- >92% of eyes that achieved ≥ 2-step DRSS improvement at year 1 maintained DRSS improvements from baseline with decreased dosing through Week 100
- DR is a progressive disease and despite aflibercept therapy, some eyes still developed PDR or CI-DME
- Less frequent dosing in year 2 appeared to be associated with a higher rate of PDR+CI-DME development (although n's are small)
  - Physician assessment of DRSS scores was suboptimal; Independent reading center review of investigator PRN decisions suggests under treatment during the 2nd year

Thank You


Japan (6 sites)
Europe
Germany (3 sites)
Hungary (5 sites)
United Kingdom (2 sites)
USA
(71 sites)
PANORAMA Study Sites