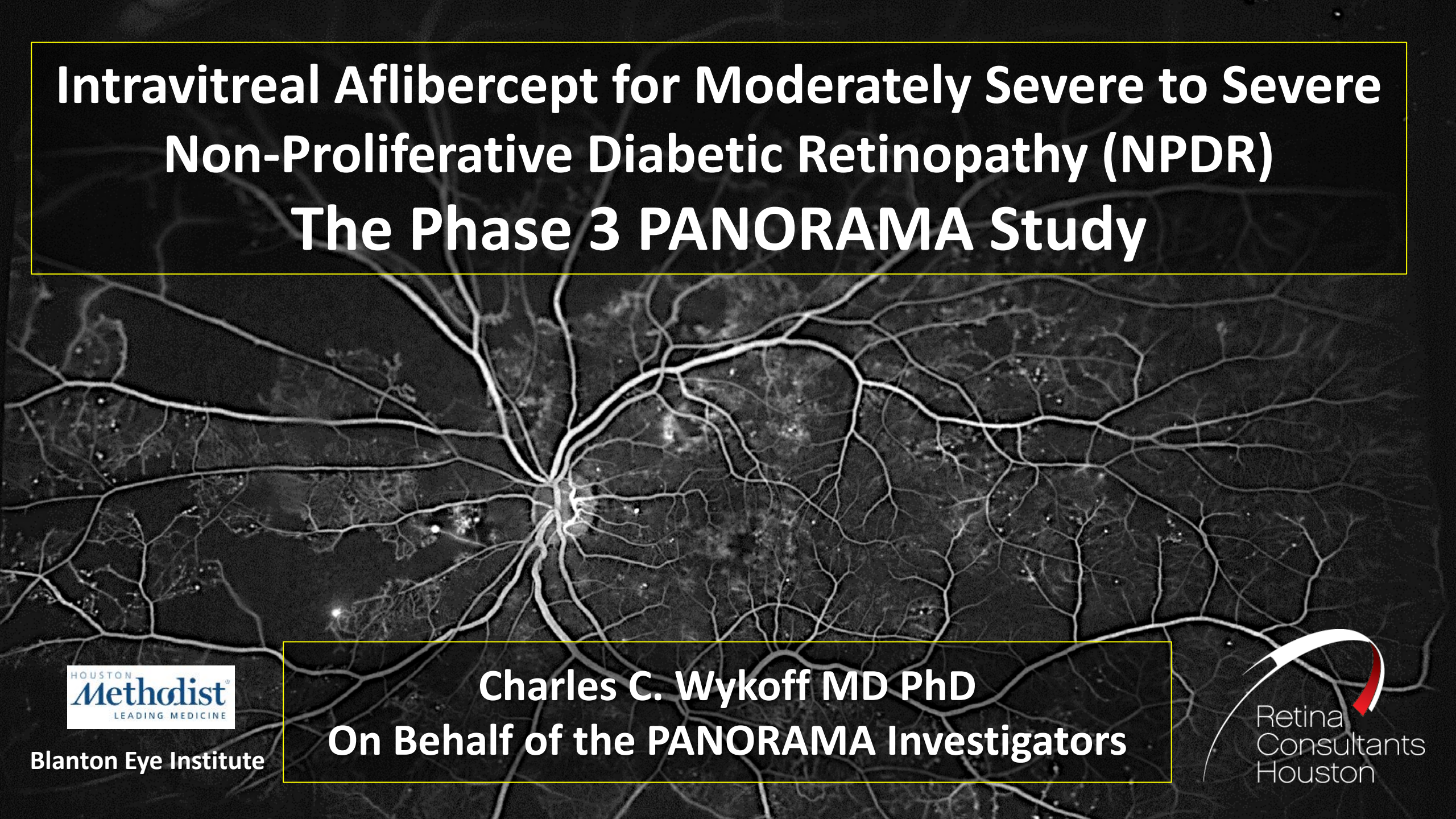
Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR)
The Phase 3 PANORAMA Study



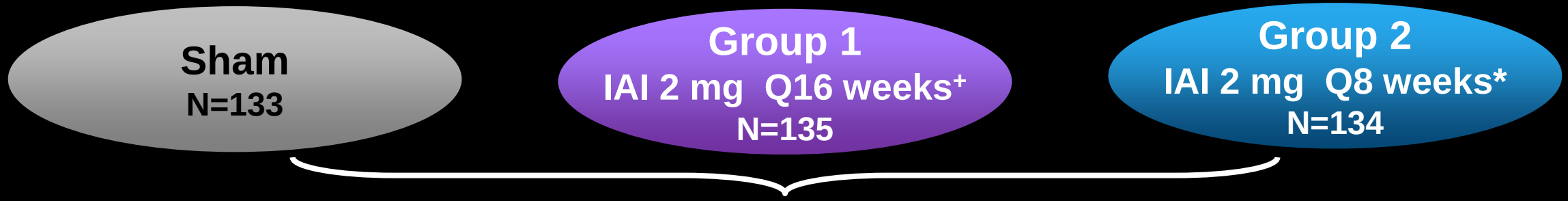
Charles C. Wykoff MD PhD
On Behalf of the PANORAMA Investigators

HOUSTON Methodist LEADING MEDICINE
Blanton Eye Institute

Retina Consultants Houston

PANORAMA Study Design

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



Week 24
Primary Endpoint
Proportion of patients improving ≥ 2 steps on DRSS
Groups 1 & 2 combined

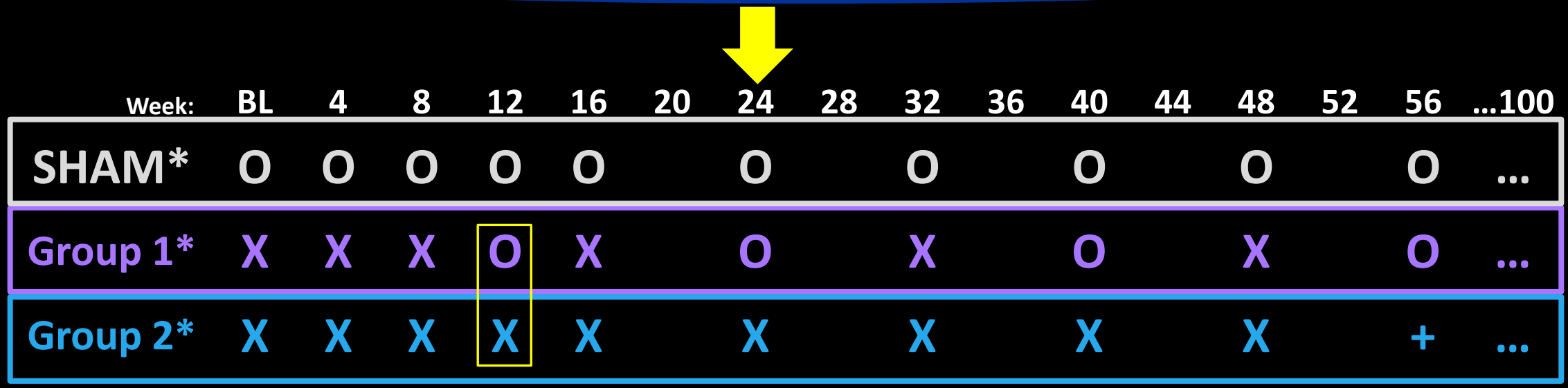
Follow up through Week 100

+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

Inclusion & Exclusion Criteria

- **Inclusion**
  - 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**
  - Presence of 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

Dosing Schedule



1 dose difference between Group 1 & 2 through week 24

+Group 2 (Q8) group continues PRN through Week 100 based on DRSS level

*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	Group 1	Group 2	All IAI	Total
N (FAS, SAF)	133	135	134	269	402
Age (years (SD))	55.8 (10.31)	55.4 (11.13)	55.8 (10.19)	55.6 (10.66)	55.7 (10.53)
Women # (%)	64 (48.1%)	60 (44.4%)	53 (39.6%)	113 (42.0%)	177 (44.0%)
Race # (%)					
White	107 (80.5%)	99 (73.3%)	104 (77.6%)	203 (75.5%)	310 (77.1%)
Black or African American	13 (9.8%)	16 (11.9%)	12 (9.0%)	28 (10.4%)	41 (10.2%)
Asian	4 (3.0%)	12 (8.9%)	7 (5.2%)	19 (7.1%)	23 (5.7%)
Other	9 (6.8%)	8 (5.9%)	11 (8.2%)	19 (7.1%)	28 (7.0%)
Hemoglobin A1C (%)	8.5 (1.54)	8.6 (1.69)	8.4 (1.64)	8.5 (1.66)	8.5 (1.62)
Duration of Diabetes (years (SD))	15.5 (9.34)	13.7 (8.61)	14.0 (9.69)	13.8 (9.15)	14.4 (9.24)
Diabetes Type 2	123 (92.5%)	121 (89.6%)	124 (92.5%)	245 (91.1%)	368 (91.5%)

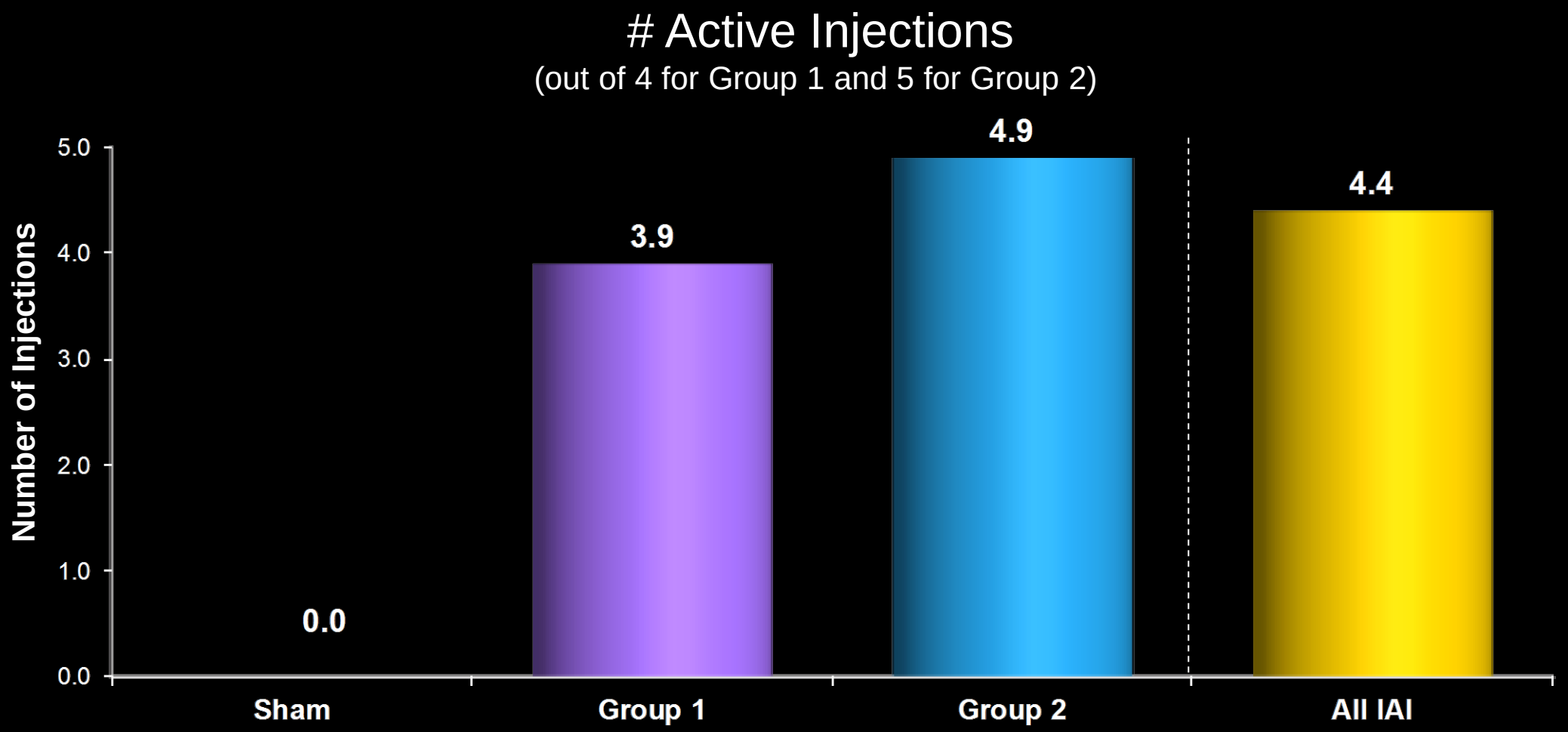
Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8

Baseline Disease Characteristics & Disposition

	Sham	Group 1	Group 2	All IAI	Total
N (FAS/SAF)	133	135	134	269	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	82.3 (5.93) 20/25	82.4 (5.96) 20/25
CRT(microns) Mean (SD)	249.4 (38.41)	246.0 (34.34)	246.8 (31.59)	246.4 (32.94)	247.4 (34.82)
Diabetic Retinopathy Severity Score (DRSS)					
Level 47	99 (74.4%)	102 (75.6%)	101 (75.4%)	203 (75.5%)	302 (75.1%)
Level 53	34 (25.6%)	33 (24.4%)	33 (24.6%)	66 (24.5%)	100 (24.9%)
Number of Patients who Completed at Week 24	119 (89.5%)	129 (95.6%)	132 (98.5%)	261 (97.0%)	380 (94.5%)

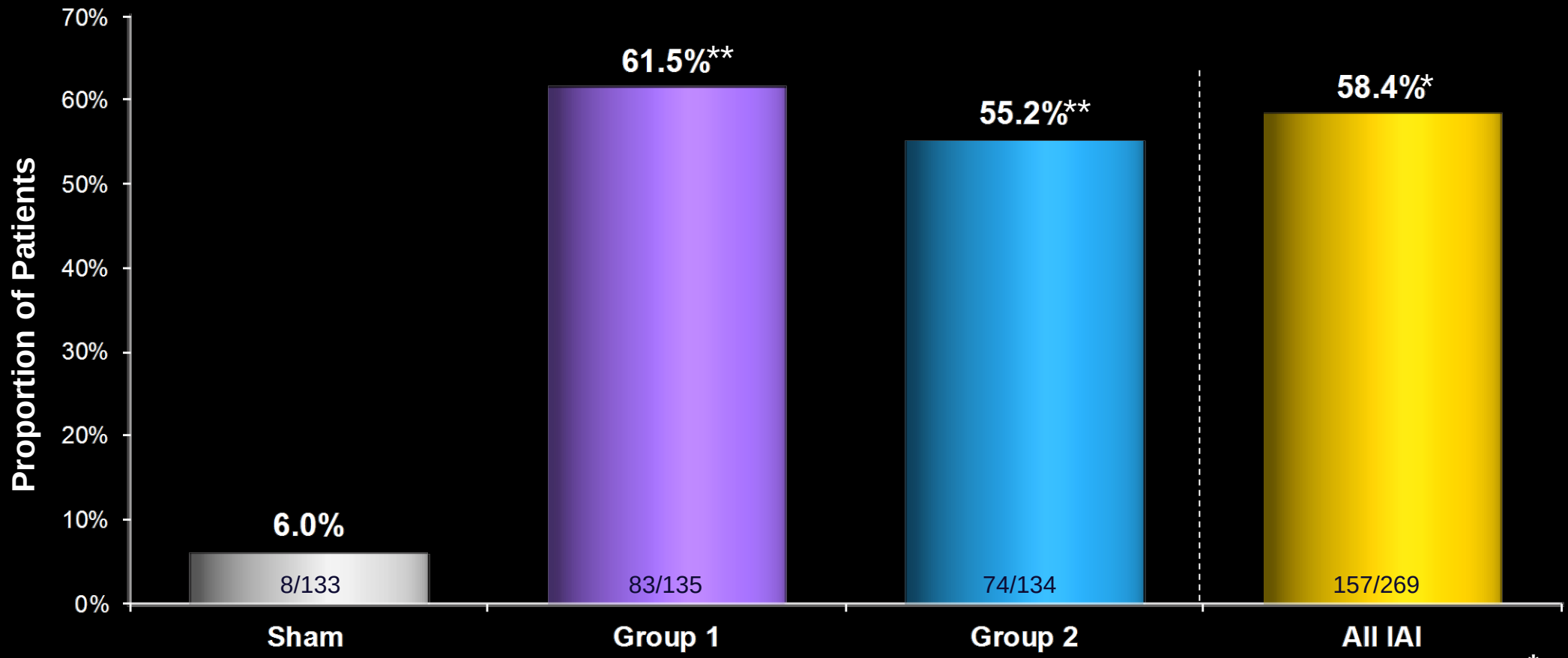
Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8

Treatment Experience



Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8
Sham n=133, Group 1 n=135, Group 2 n=134, All IAI n=269

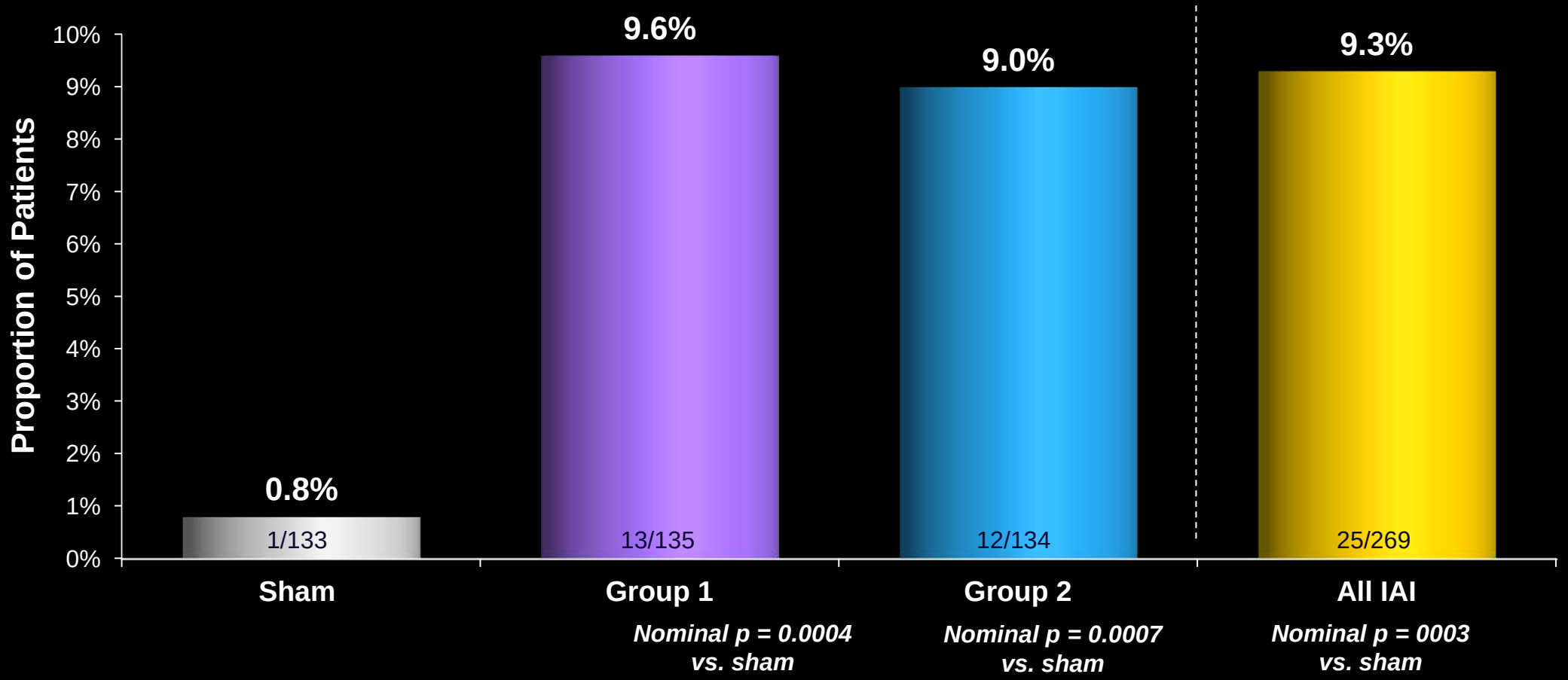
Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS



*p < 0.0001 vs. sham
** Nominal p < 0.0001 vs. sham

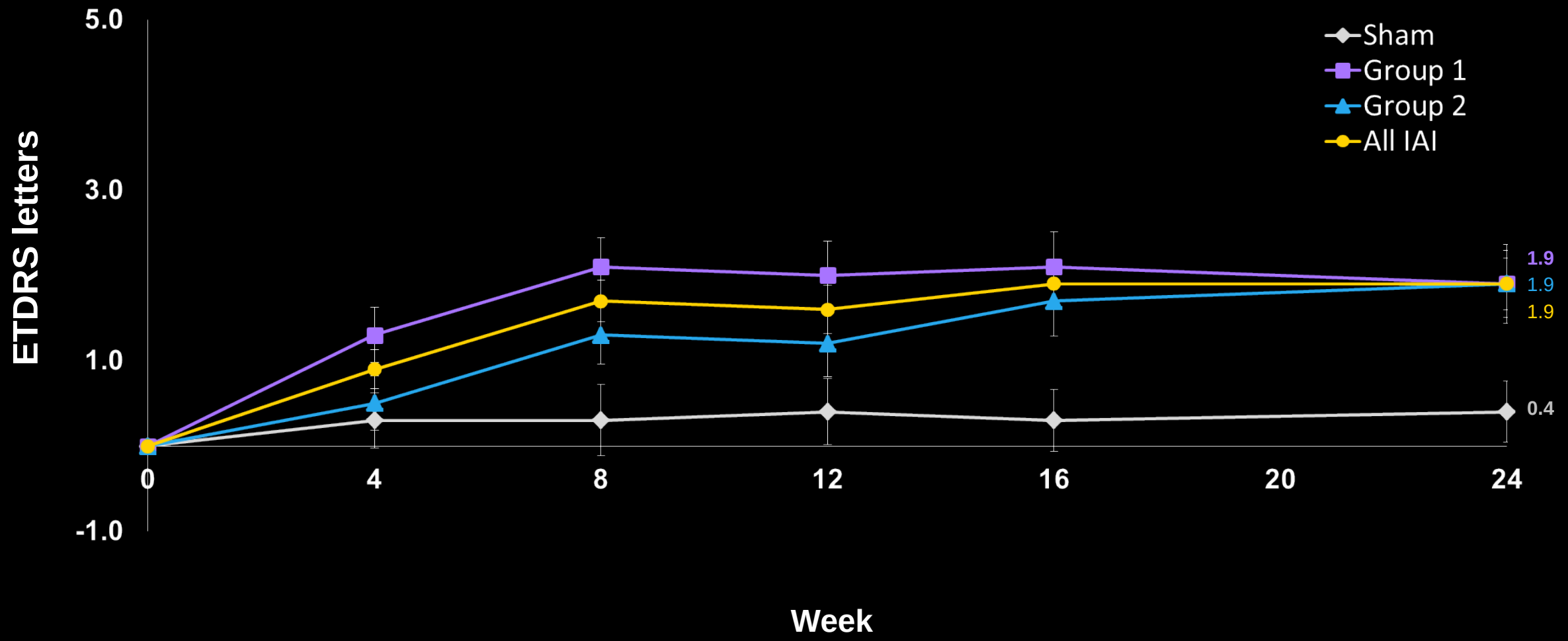
Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8
LOCF; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

Proportion of Patients with ≥3-Step Improvement from Baseline in DRSS



Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8
LOCF; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

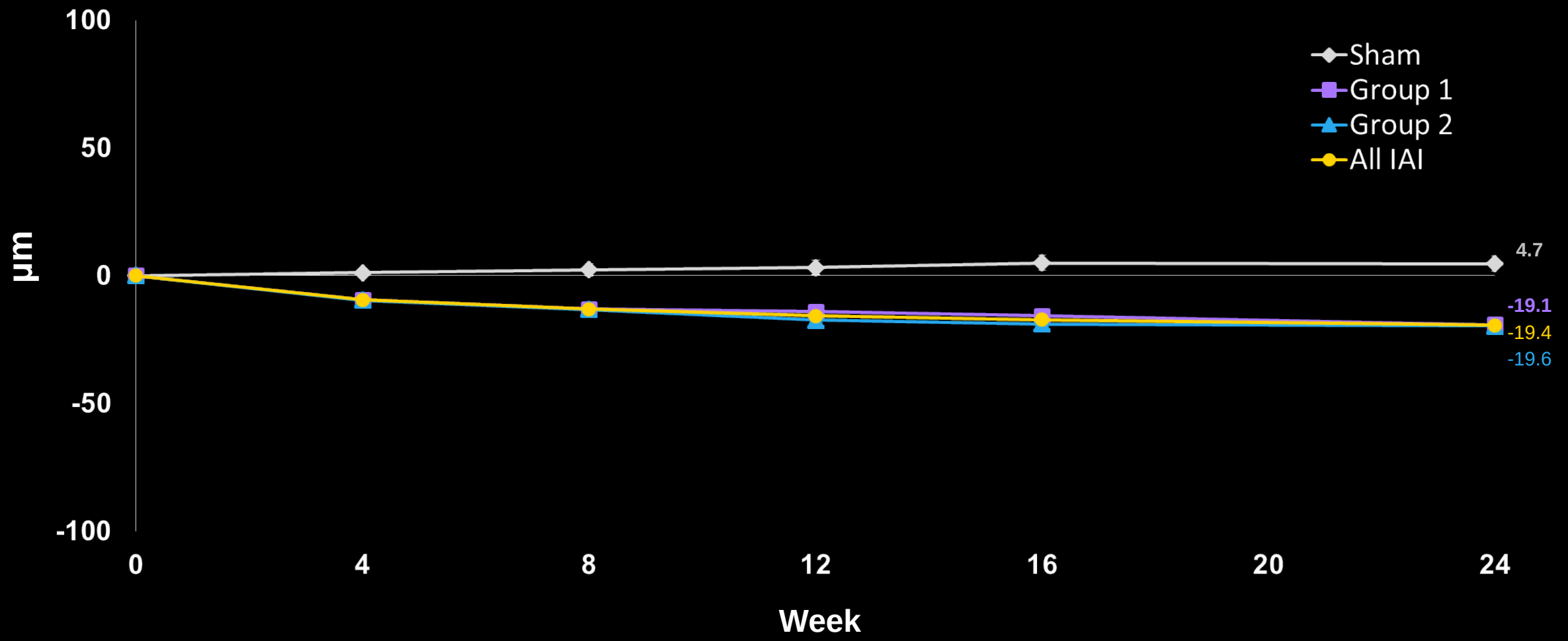
Mean Change in Best Corrected Visual Acuity



Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8
LOCF.; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

Nominal p = 0.0057 All IAI vs. sham
Nominal p = 0.0194 Group 1 vs. sham
Nominal p = 0.0139 Group 2 vs. sham

Mean Change in Central Retinal Thickness



Nominal p < 0.0001
All vs. sham

Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8
LOCF; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

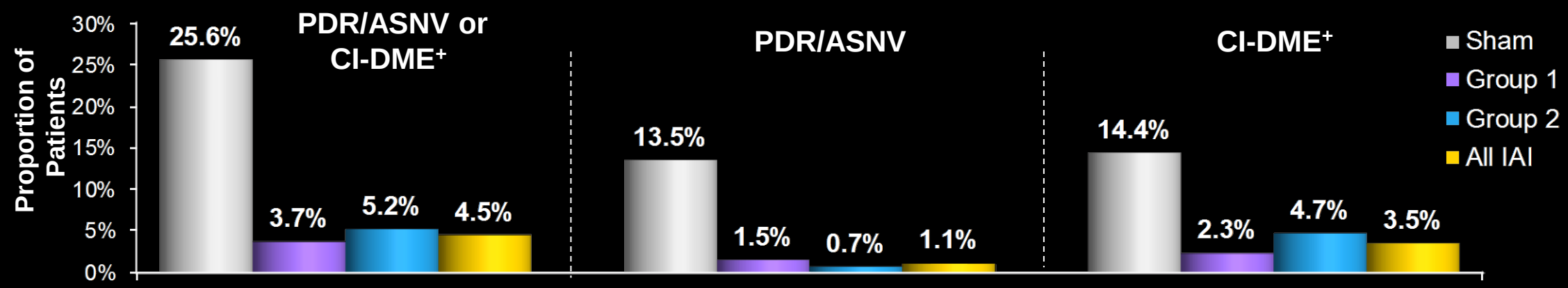
Safety Events through Week 24

	Sham	All IAI
N (FAS/SAF)	133	269
Ocular TEAEs (≥3%)		
Conjunctival hemorrhage	5 (3.8%)	32 (11.9%)
Vitreous floaters	1 (0.8%)	14 (5.2%)
Diabetic retinal edema	20 (15.0%)	11 (4.1%)
Eye pain	2 (1.5%)	11 (4.1%)
Diabetic retinopathy	4 (3.0%)	1 (0.4%)
Non Ocular Events		
Patients with ≥ 1 APTC, n (%)	2 (1.5%)	1 (0.4%)
Deaths	3 (2.3%)	0

- One Serious ocular AE of iris neovascularization occurred in 1 patient
- One ocular AE of vitreal cells occurred in 1 patient, which was considered mild

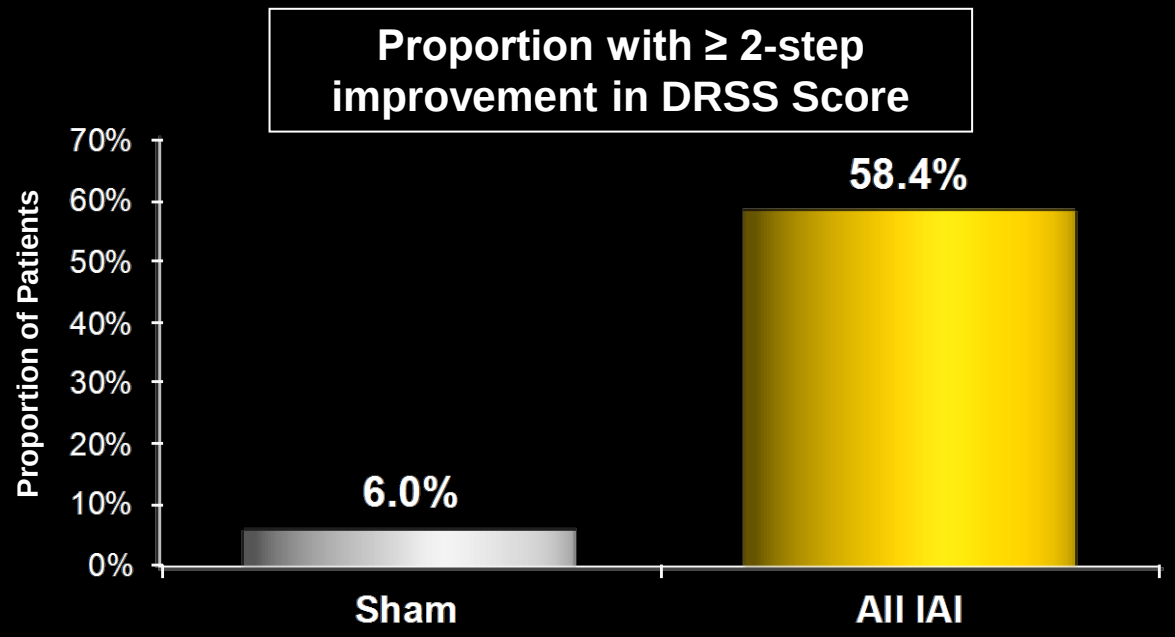
Proportion of Patients Developing a Vision Threatening Complication (VTC) or Center Involved (CI)-DME through Week 24

	Sham	Group 1	Group 2	All IAI
N (SAF)	133	135	134	269
% Patients Developing PDR/ASNV or CI-DME	34/133 (25.6%)	5/135 (3.7%)	7/134 (5.2%)	12/269 (4.5%)
% Developing PDR/ASNV	18/133 (13.5%	2/135 (1.5%)	1/134 (0.7%)	3/269 (1.1%)
% Developing CI-DME+	18/125 (14.4%)	3/128 (2.3%)	6/128 (4.7%)	9/256 (3.5%)

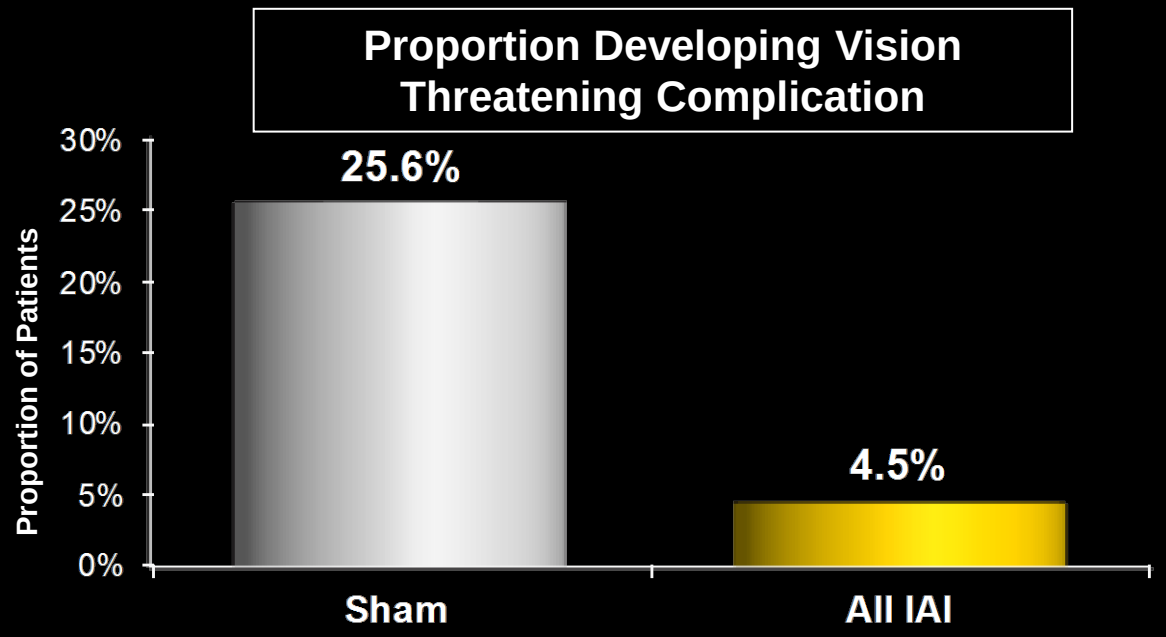


Group 1: 3 monthly doses followed by 1 Q8 interval then Q16, Group 2: 5 monthly doses then Q8. Exploratory analysis. VTC = PDR/ASNV
PDR/ASNV: Proliferative Diabetic Retinopathy/Anterior Segment Neovascularization; CI-DME: Central involved DME +CI-DME evaluable set excluded patients who, at baseline, both had CRT>300µm and qualitative evidence of CI-DME as assessed by the reading center.

PANORAMA 24 Week Results



LOCF; Sham n= 133, All IAI n=269



LOCF; Sham n= 133, All IAI n=269. Vision Threatening Complications: Proliferative Diabetic Retinopathy/Anterior Segment Neovascularization and central-Involved Diabetic Macular Edema

- The proportion of patients with ≥ 2-step DRSS improvement was significantly greater with aflibercept vs sham
- Diabetes related safety outcomes including PDR/ASNV and CI-DME occurred in a substantially greater proportion of sham patients
- No new safety signals identified with aflibercept