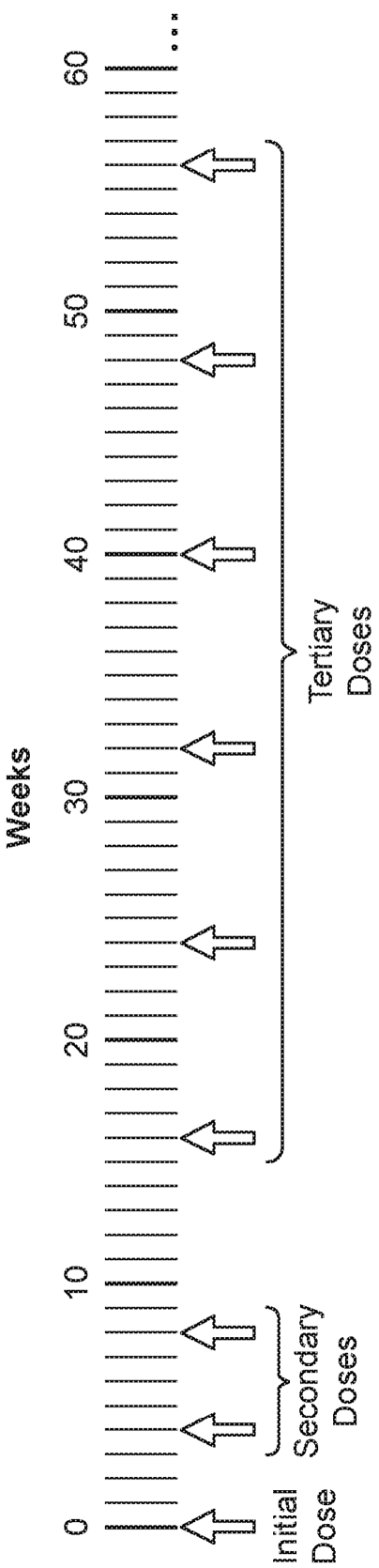

Weeks
0
10
20
30
40
50
60
...
Initial Dose
Secondary Doses
Tertiary Doses

FIG. 1

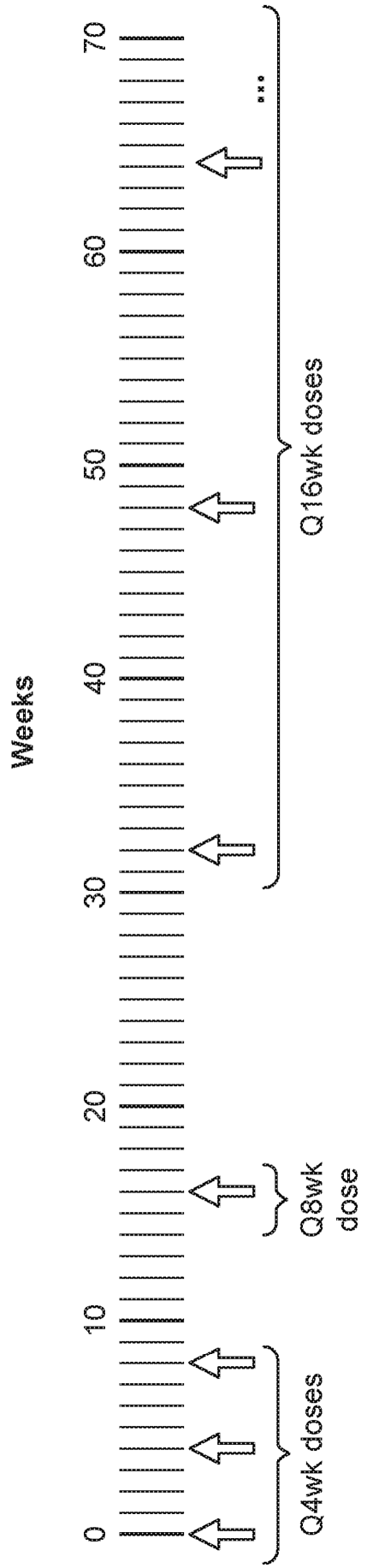


FIG. 2

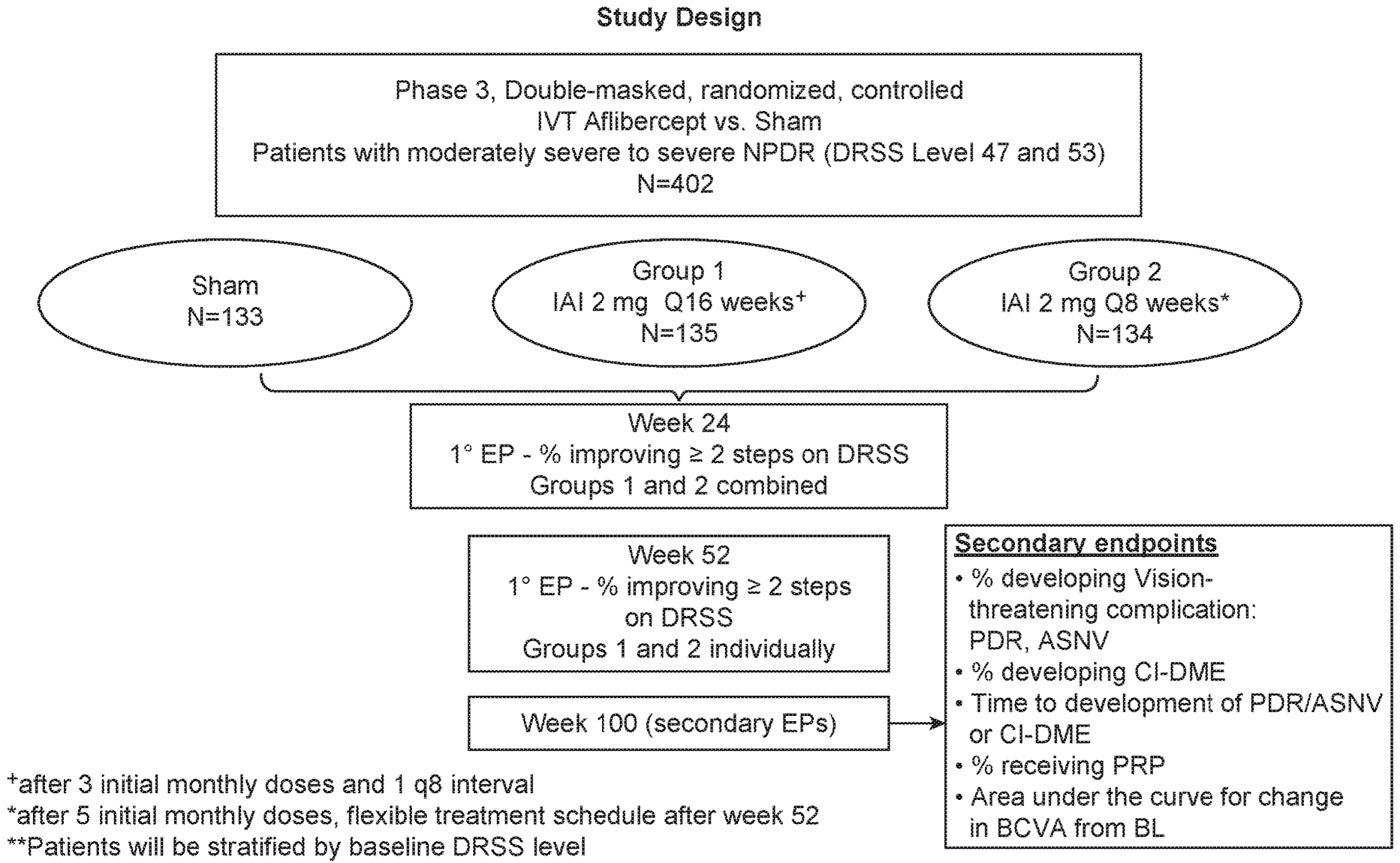
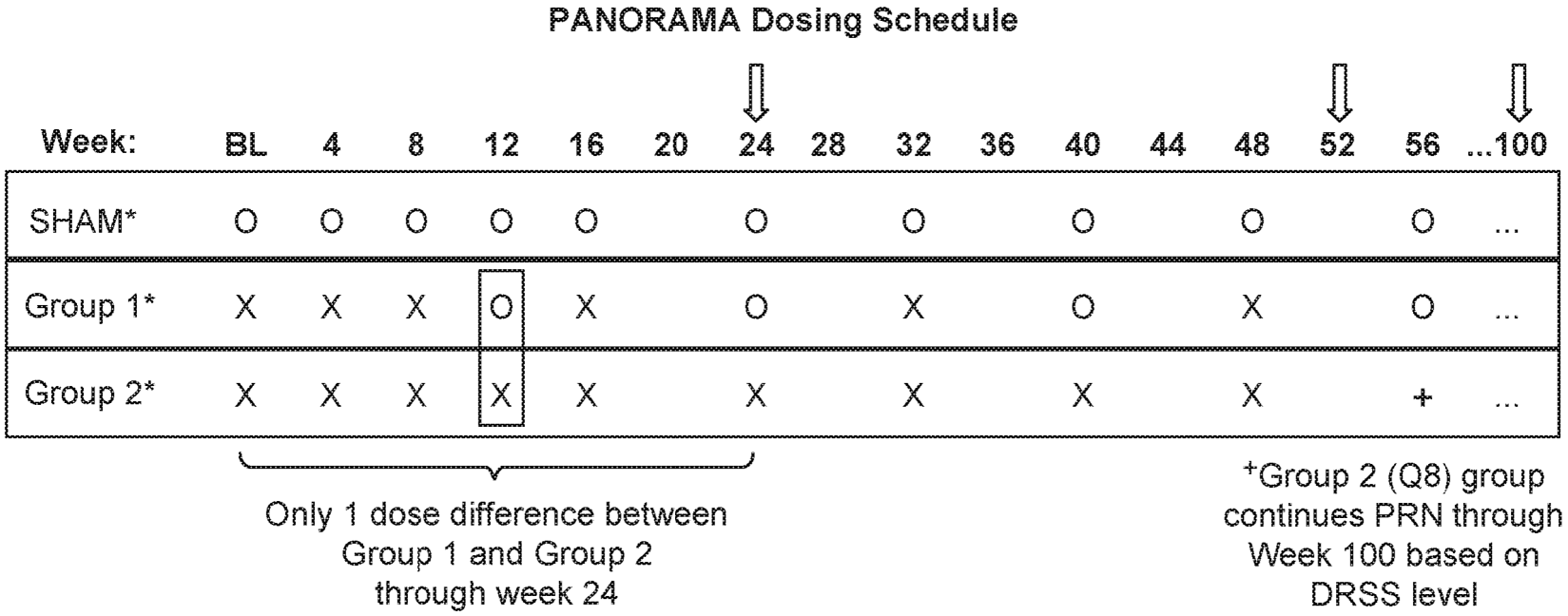

Study Design
Phase 3, Double-masked, randomized, controlled
IVT Aflibercept vs. Sham
Patients with moderately severe to severe NPDR (DRSS Level 47 and 53)
N=402
Sham
N=133
Group 1
IAI 2 mg Q16 weeks+
N=135
Group 2
IAI 2 mg Q8 weeks*
N=134
Week 24
1° EP - % improving ≥ 2 steps on DRSS
Groups 1 and 2 combined
Week 52
1° EP - % improving ≥ 2 steps on DRSS
Groups 1 and 2 individually
Week 100 (secondary EPs)
Secondary endpoints
• % developing Vision-threatening complication: PDR, ASNV
• % developing CI-DME
• Time to development of PDR/ASNV or CI-DME
• % receiving PRP
• Area under the curve for change in BCVA from BL
+after 3 initial monthly doses and 1 q8 interval
*after 5 initial monthly doses, flexible treatment schedule after week 52
**Patients will be stratified by baseline DRSS level

FIG. 3



*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

FIG. 4

Disposition and Baseline Demographics

	Sham	Group 1	Group 2	All IAI	Total
Number of Patients who Completed at Week 24	119 (89.5%)	129 (95.6%)	132 (98.5%)	261 (97.0%)	380 (94.5%)

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 intervals, Group 2: 5 monthly doses

FIG. 5

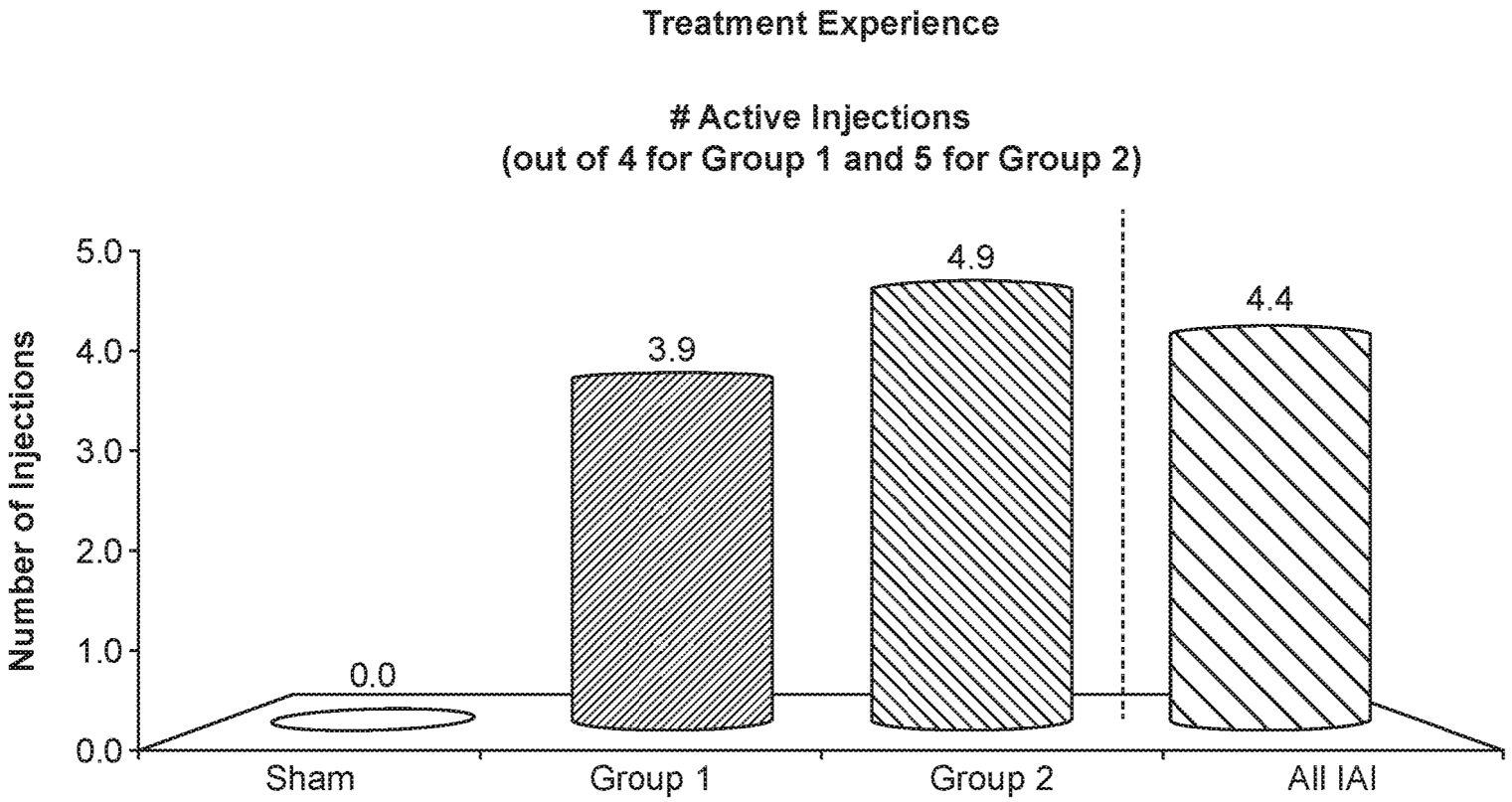
Baseline Disease Characteristics

— 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%)

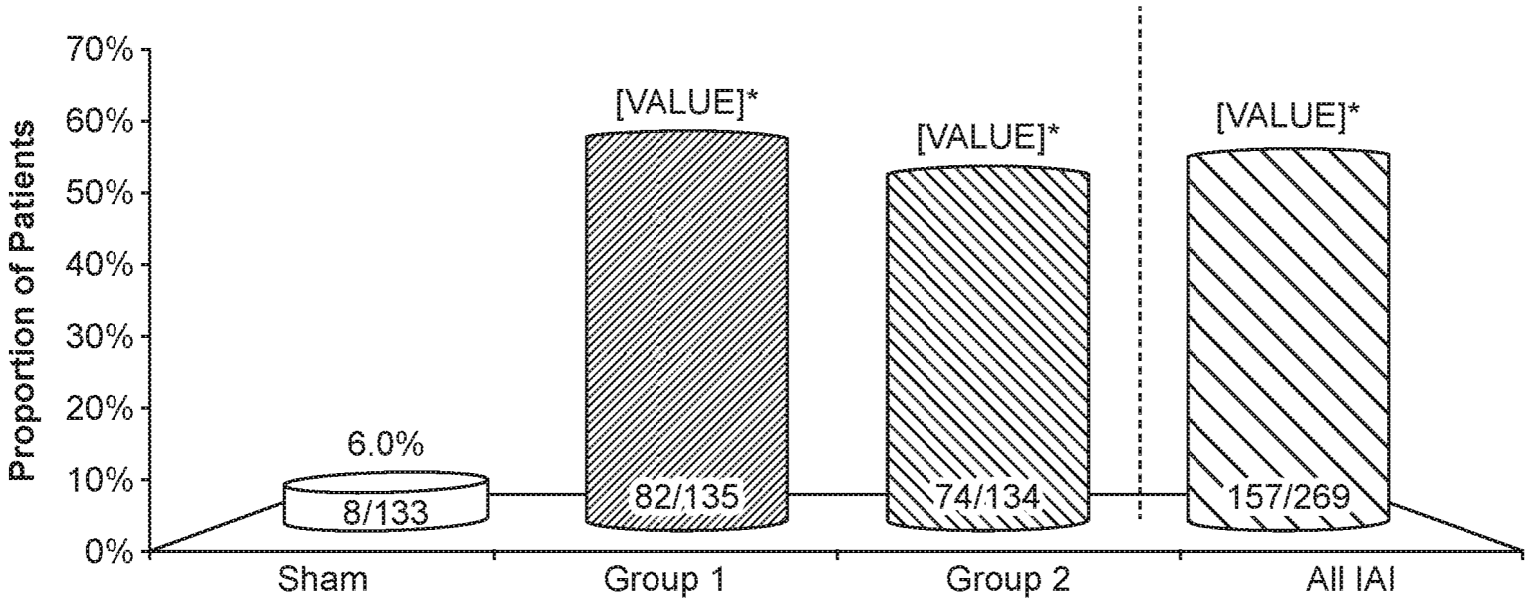
Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses

FIG. 6



Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses
Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

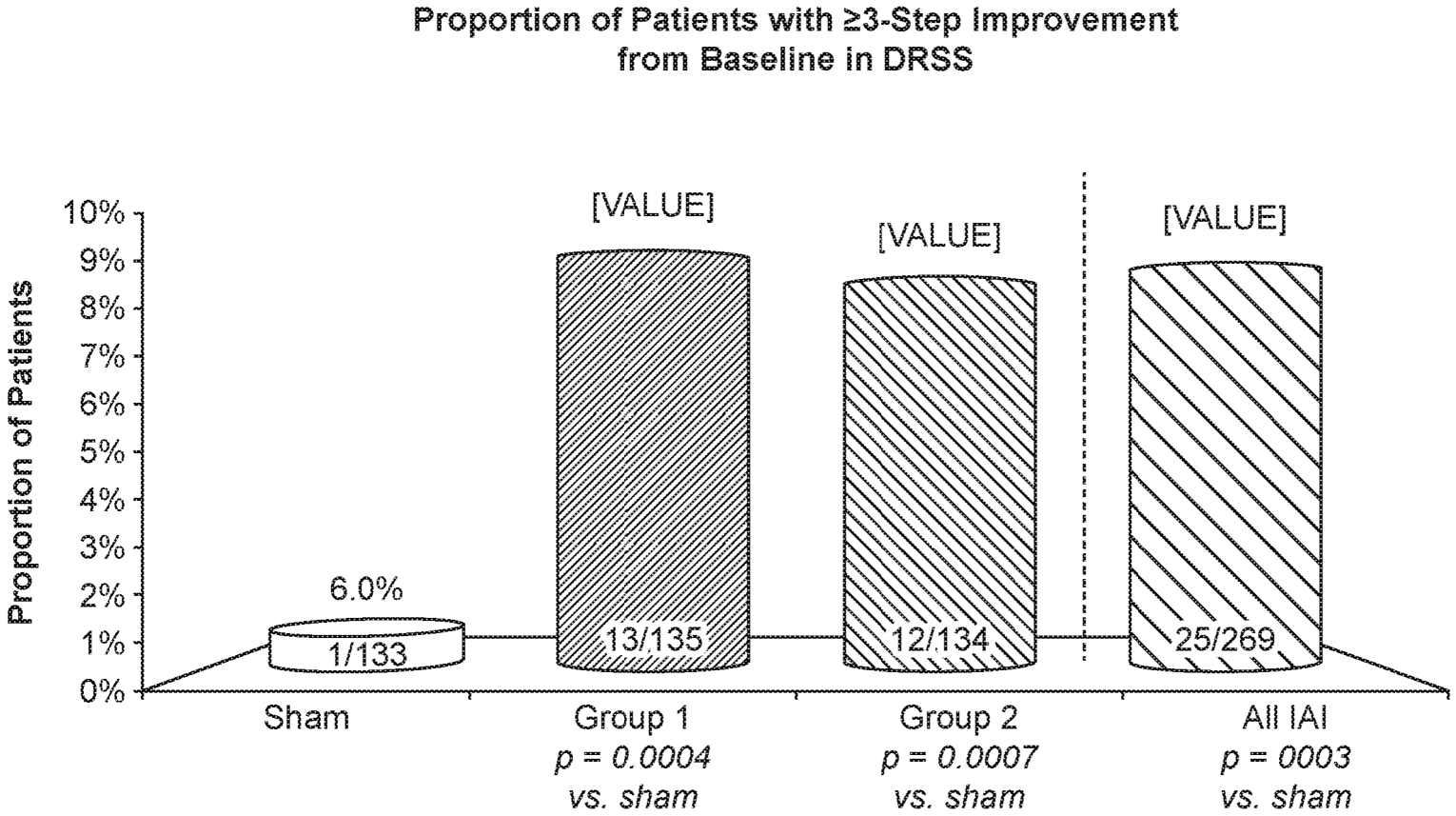
FIG. 7



Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses
LOCF; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

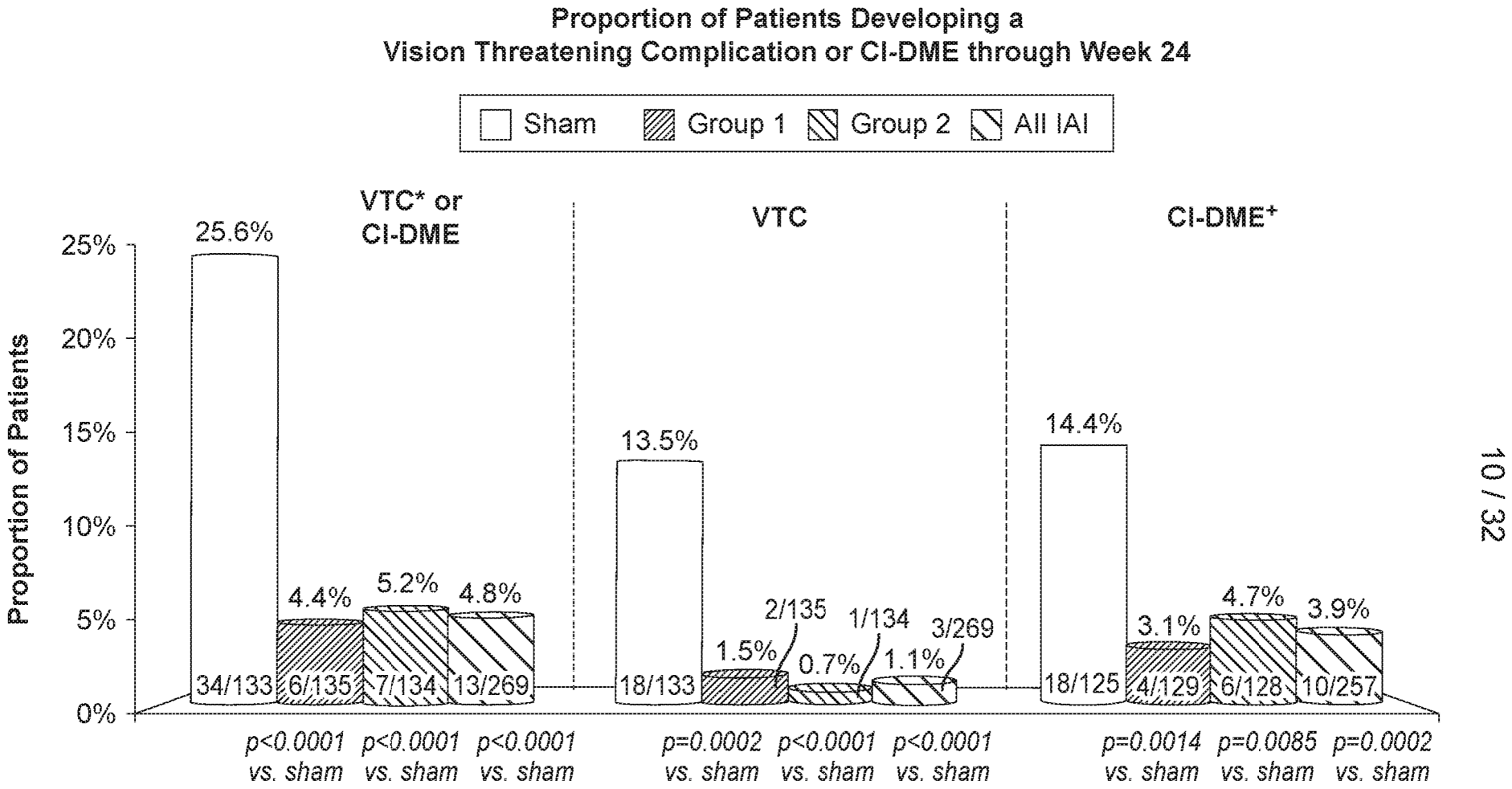
*$p < 0.0001$ vs. sham

FIG. 8



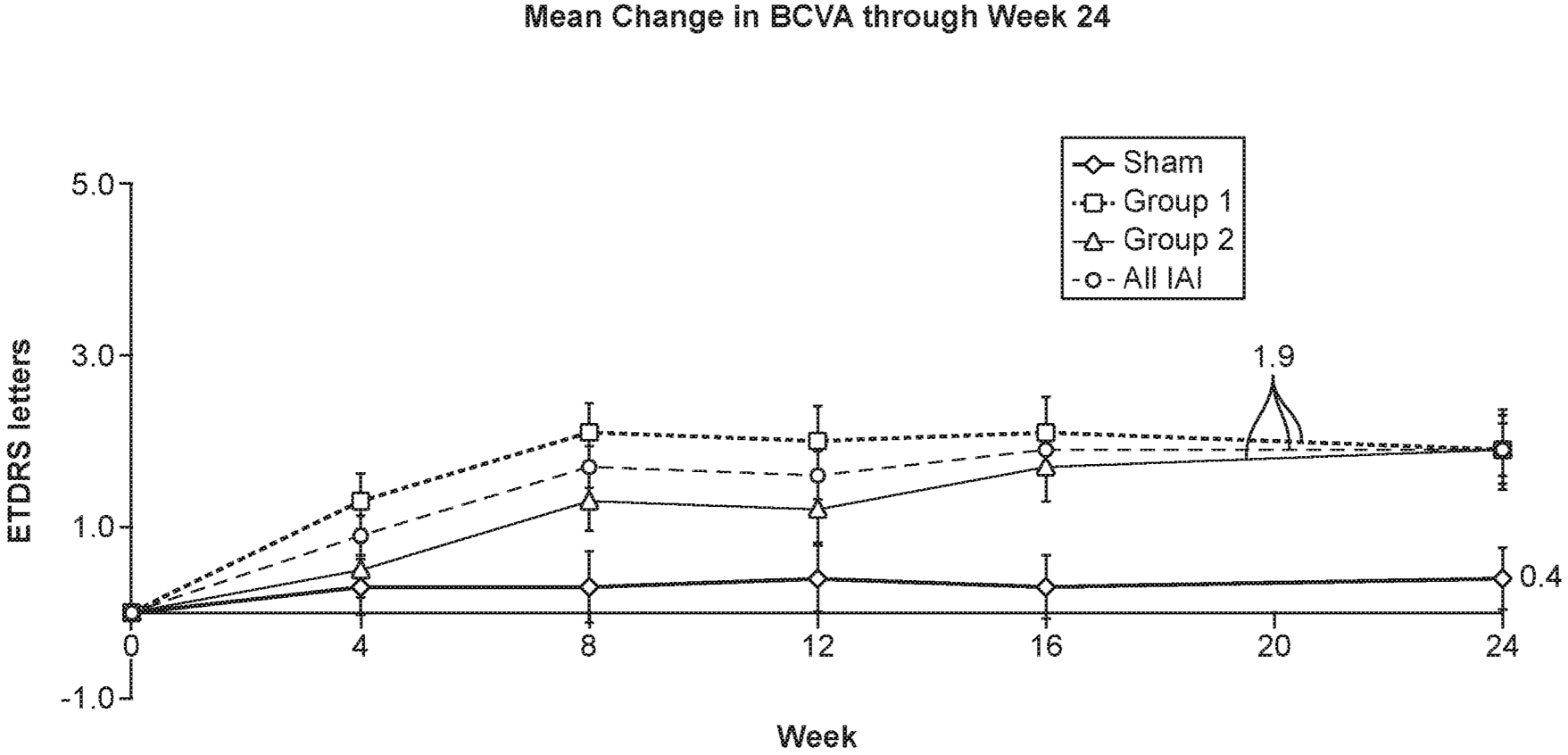
Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses
Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

FIG. 9



Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses
*VTC = Vision threatening complication, PDR/ASNV
+CI-DME evaluable set excludes patients who at baseline had CRT>300μm and had qualitative evidence of CI-DME as assessed by the reading center.

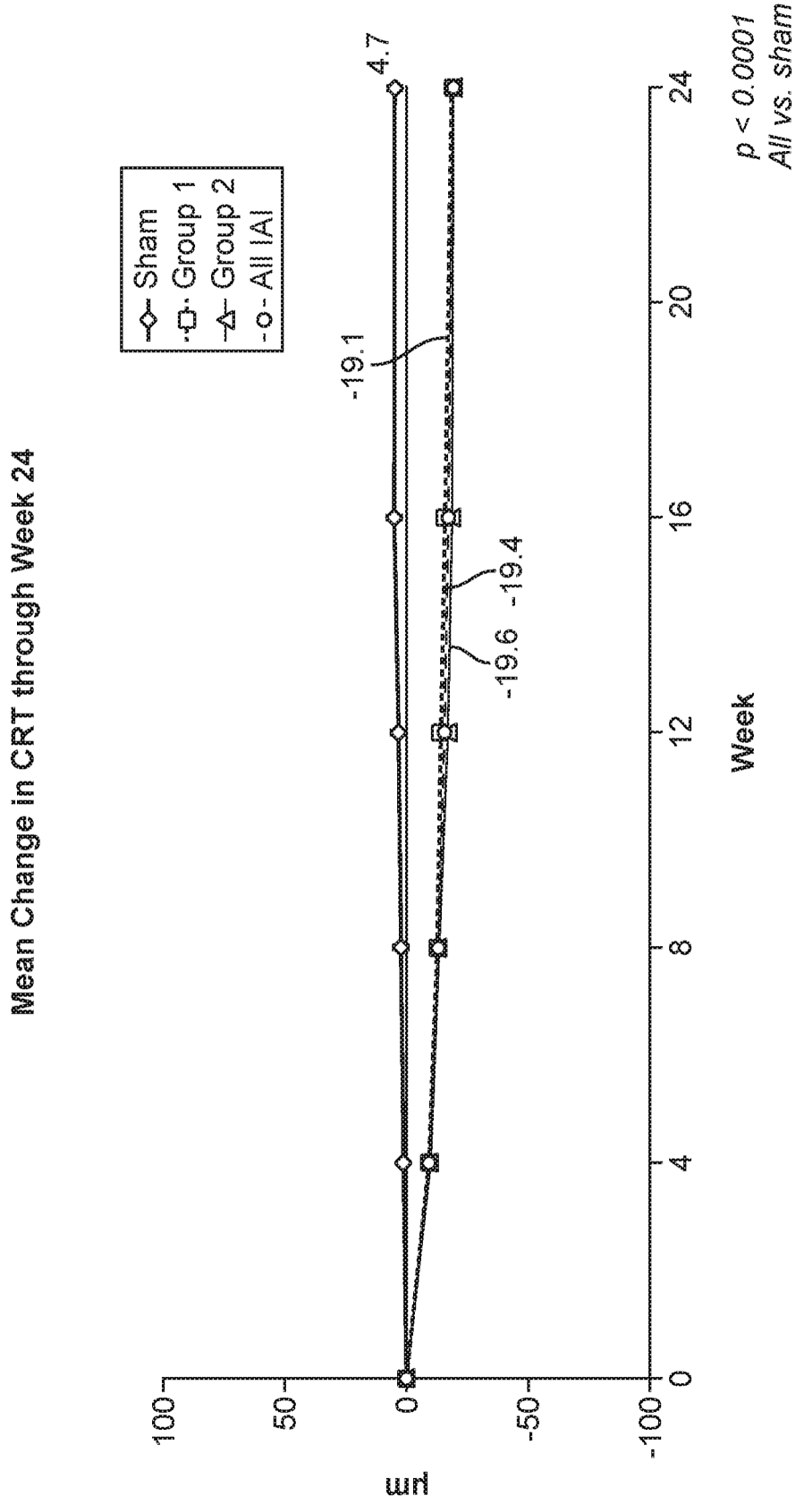
FIG. 10



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

Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses
LOCF.; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

FIG. 11



Group 1: 3 monthly doses followed by 1 q8 intervals, Group 2: 5 monthly doses
LOCF; Sham n= 133, Group 1 n=135, Group 2 n=134, All IAI n=269

FIG. 12

Ocular TEAEs in Study Eye through Week 24
(≥3%)

	— Sham	--- All IAI
N (FAS/SAF)	133	269
Number of Patients ≥ 1 AE, n (%)	44 (33.1%)	77 (28.6%)
Eye disorders	42 (31.6%)	76 (28.3%)
Conjunctival haemorrhage	4 (3.0%)	32 (11.9%)
Vitreous floaters	1 (0.8%)	14 (5.2%)
Diabetic retinal oedema	18 (13.5%)	11 (4.1%)
Eye pain	2 (1.5%)	11 (4.1%)
Diabetic retinopathy	4 (3.0%)	1 (0.4%)

FIG. 13

Ocular Serious TEAEs in Study Eye through Week 24

	— Sham	--- All IAI
N (FAS/SAF)	133	269
Number of Patients with ≥ 1 AE, n (%)	1 (0.8%)	0
Iris neovascularisation	1 (0.8%)	0

FIG. 14

Ocular Inflammation in Study Eye through Week 24

	— Sham	--- All IAI
N (FAS/SAF)	133	269
# of injection	0	1182
Vitreal cells	0	1 (0.4%) (0.08% per injection)

FIG. 15

APTC Events through Week 24

	— Sham	--- All IAI
N (FAS/SAF)	133	269
Number of Patients with ≥ 1 AE, n (%)	2 (1.5%)	1 (0.4%)
Non Fatal Stroke	0	1 (0.4%)
Cerebrovascular accident	0	1 (0.4%)
Vascular Death	2 (1.5%)	0
Cardiac arrest	1 (0.8%)	0
Myocardial infarction	1 (0.8%)	0

FIG. 16

Deaths through Week 24

Treatment Group	Patient Age /Sex /Race	Days from First Treatment to Death	Days from Last Treatment to Death	AE Preferred Term with Fatal Outcome	Rescue/ FE Treatment
Sham	43/F/W	52	23	Acute respiratory failure Pulmonary hypertension	No rescue/ No FE treatment
Sham	65/M/W	73	13	Cardiac arrest	No rescue/ No FE treatment
Sham	73/M/W	86	4	Myocardial infarction	No rescue/ 2 FE treatments

FIG. 17

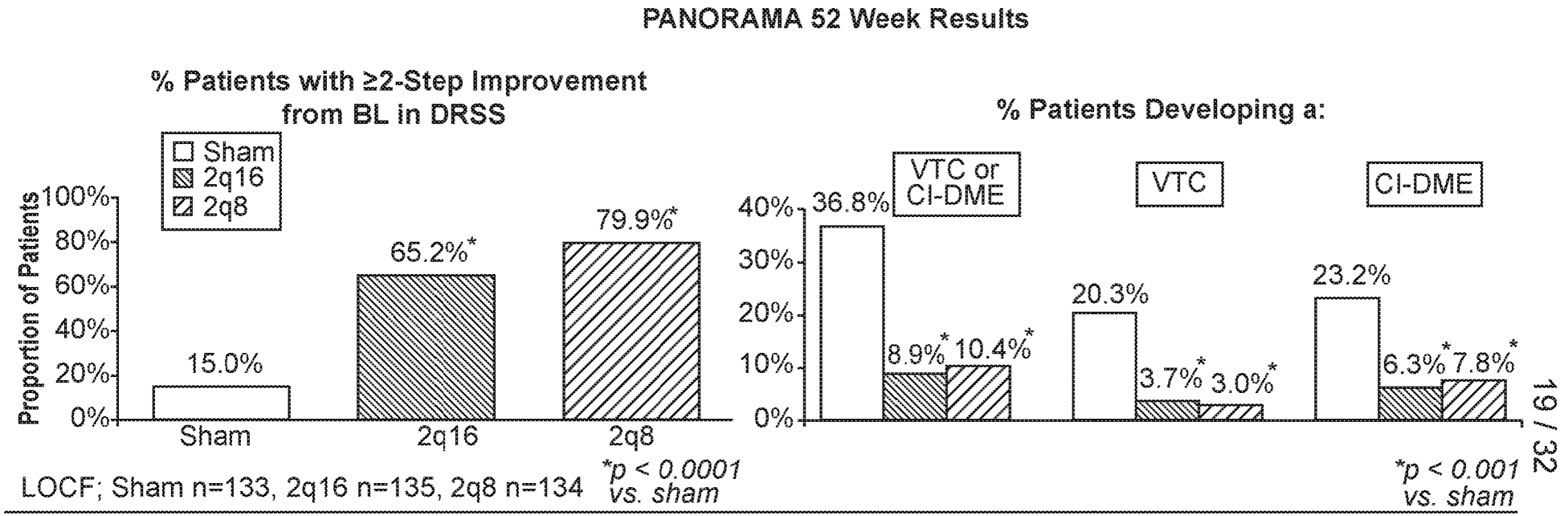
International Clinical Diabetic Retinopathy Disease Severity Scale Detailed Table

LEVEL	SEVERITY
10	DR absent
20	Microaneurysms only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
61	Mild PDR
65	Moderate PDR
71	High Risk PDR
75	High Risk PDR
81	Advanced PDR, fundus partially obscured, center of macula attached
85	Advanced PDR, posterior fundus obscured or center of macula detached
90	Cannot grade, even sufficiently for level 81 or 85

DRSS grading scale was derived from the ETDRS and is used to grade severity of DR and describe the change in severity over time.

ETDRS Group, #12 1991

FIG. 18



- The proportion of patients with ≥ 2-step DRSS improvement was significantly greater with aflibercept vs sham
  - Rate was greater in 2q8 group compared with 2q16
- Vision threatening complications (PDR/ASNV) and CI-DME occurred in a substantially greater proportion of sham patients
  - Rates were similar between the 2q16 and 2q8 treatment groups
- No new safety signals identified

FIG. 19

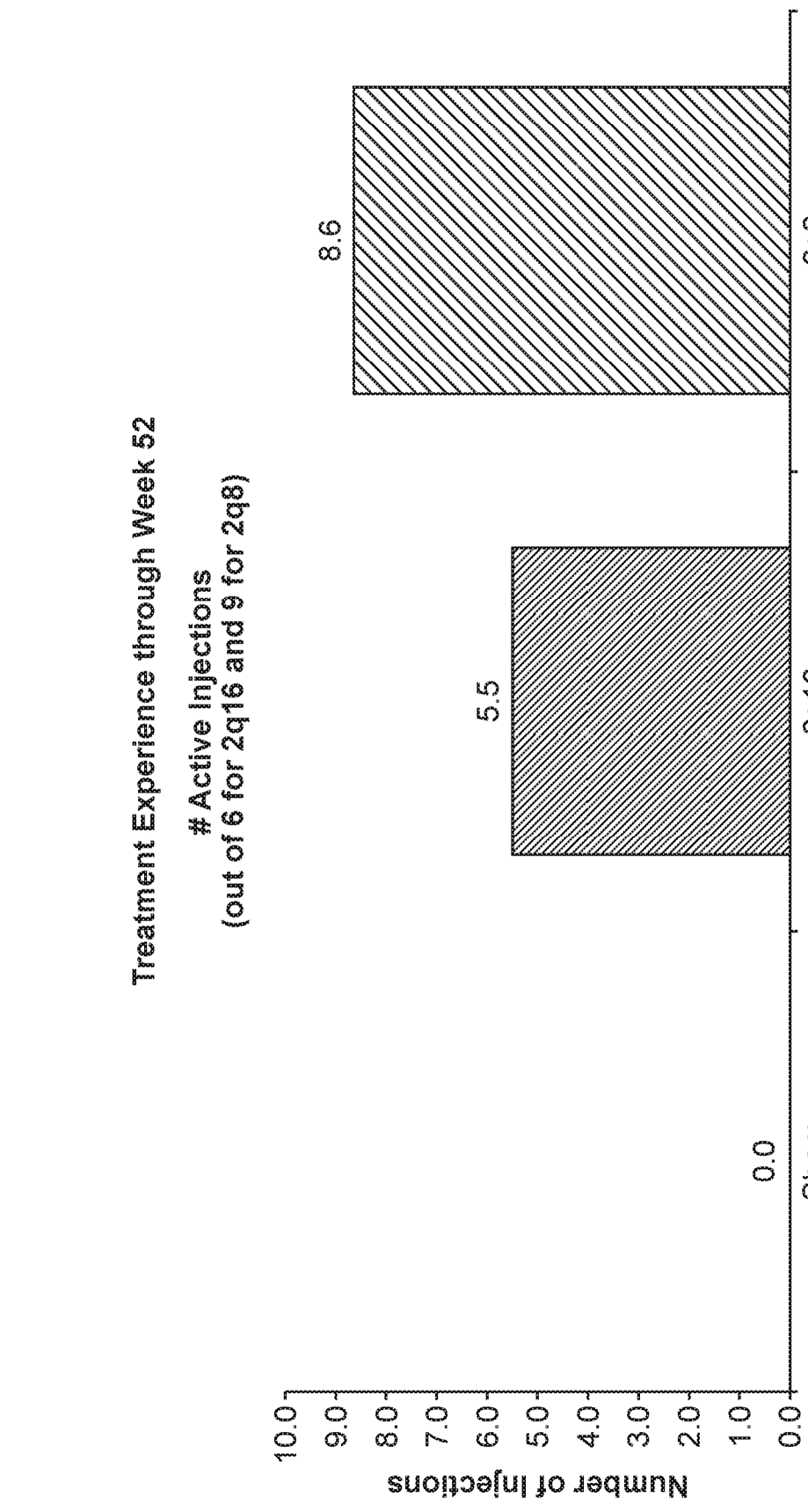

Treatment Experience through Week 52
Active Injections
(out of 6 for 2q16 and 9 for 2q8)
Number of Injections
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.0
5.5
8.6
Sham
2q16
2q8
Sham n=133, 2q16 n=135, 2q8 n=134

FIG. 20

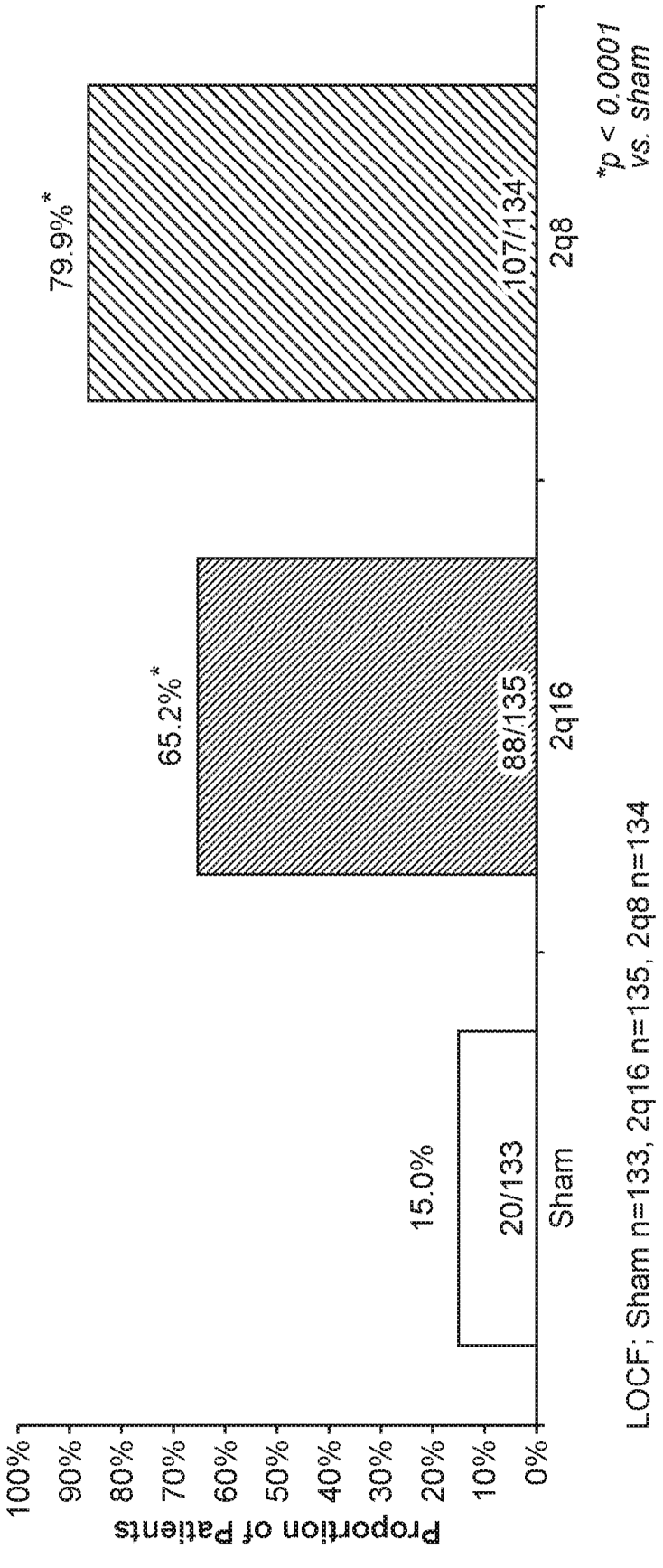

Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS at Week 52
Proportion of Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
15.0%
20/133
Sham
65.2%*
88/135
2q16
79.9%*
107/134
2q8
*p < 0.0001 vs. sham
LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

FIG. 21

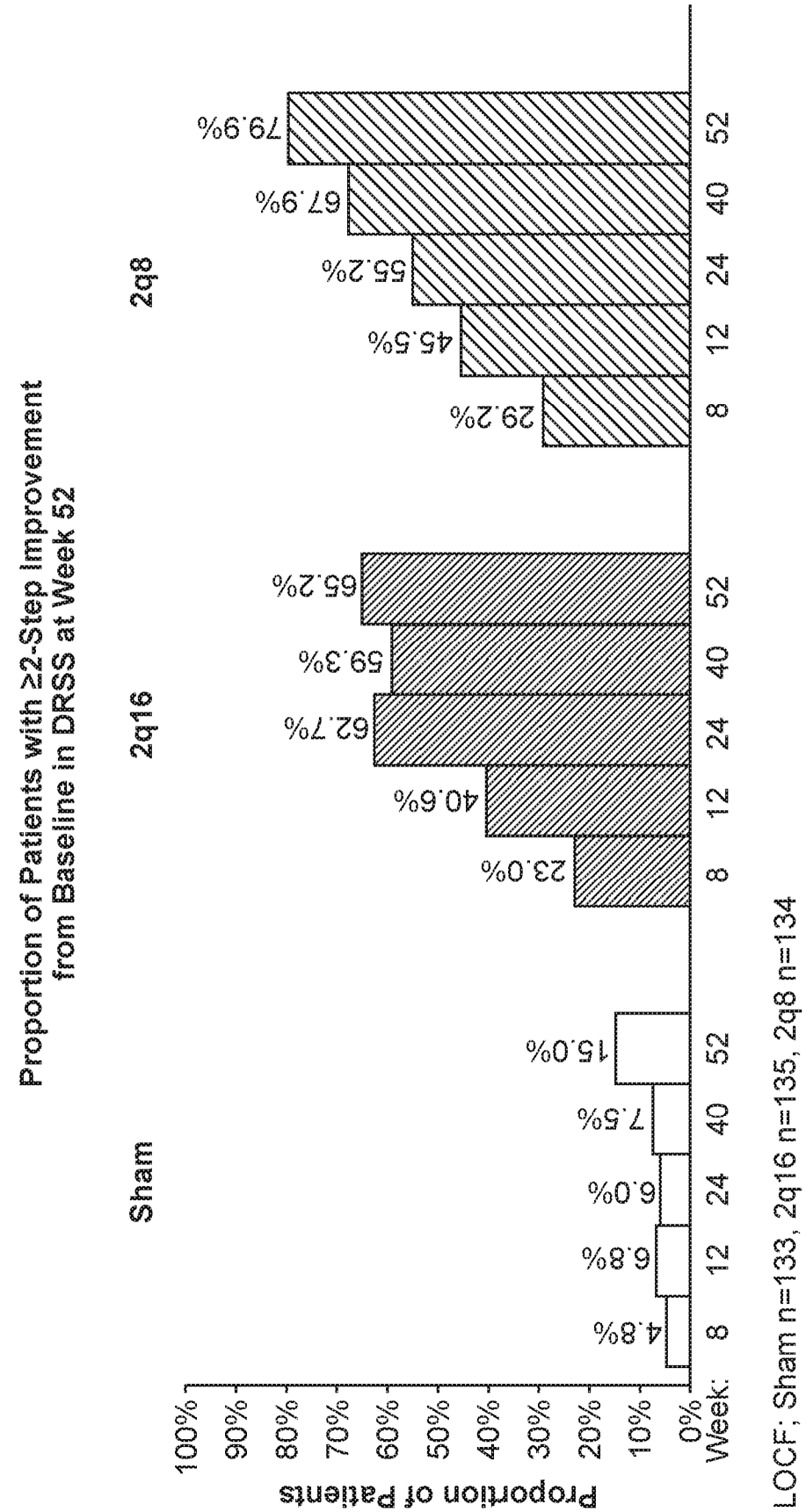

Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS at Week 52
Proportion of Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Week:
8
12
24
40
52
Sham
4.8%
6.8%
6.0%
7.5%
15.0%
2q16
23.0%
40.6%
62.7%
59.3%
65.2%
2q8
29.2%
45.5%
55.2%
67.9%
79.9%
LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

FIG. 22

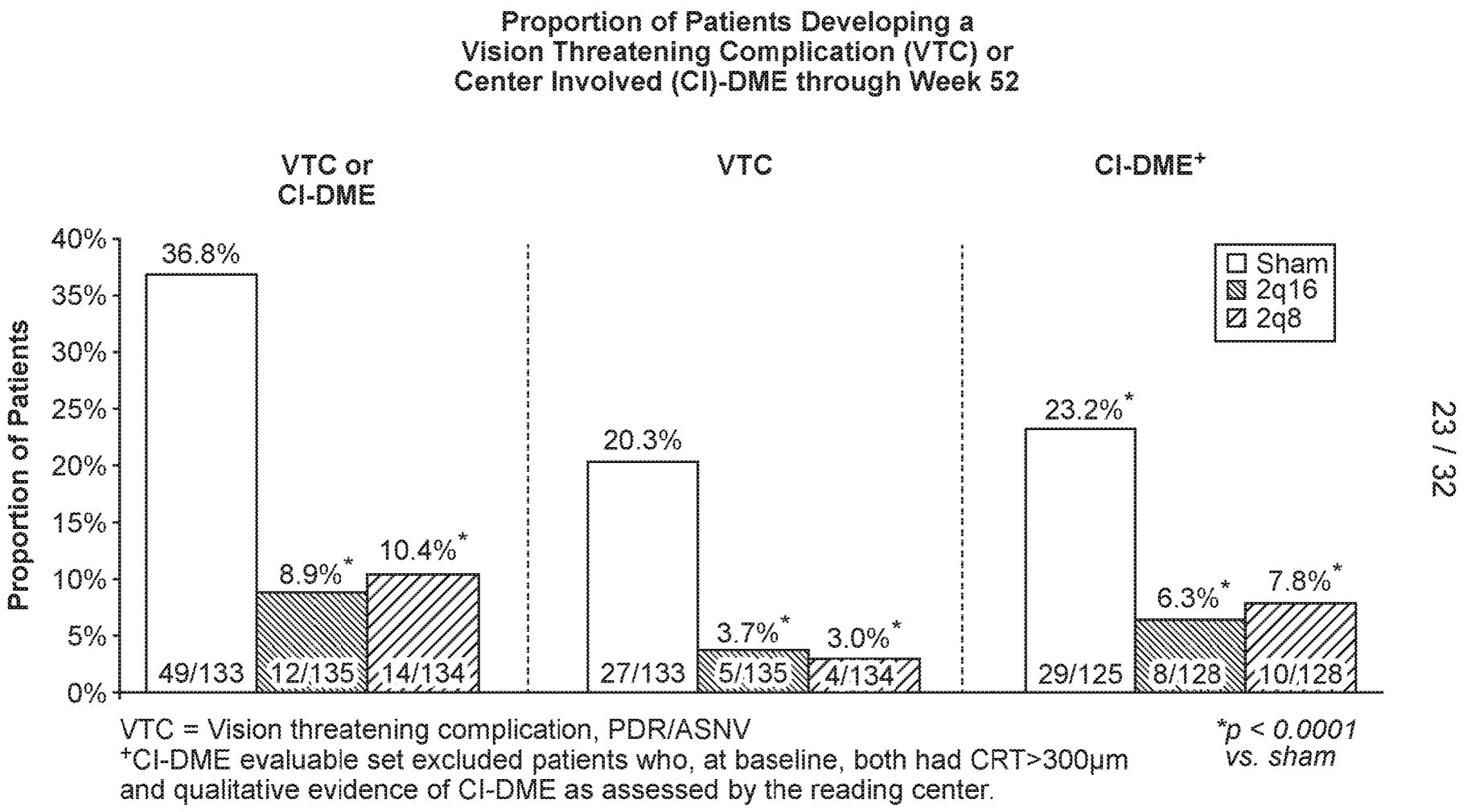
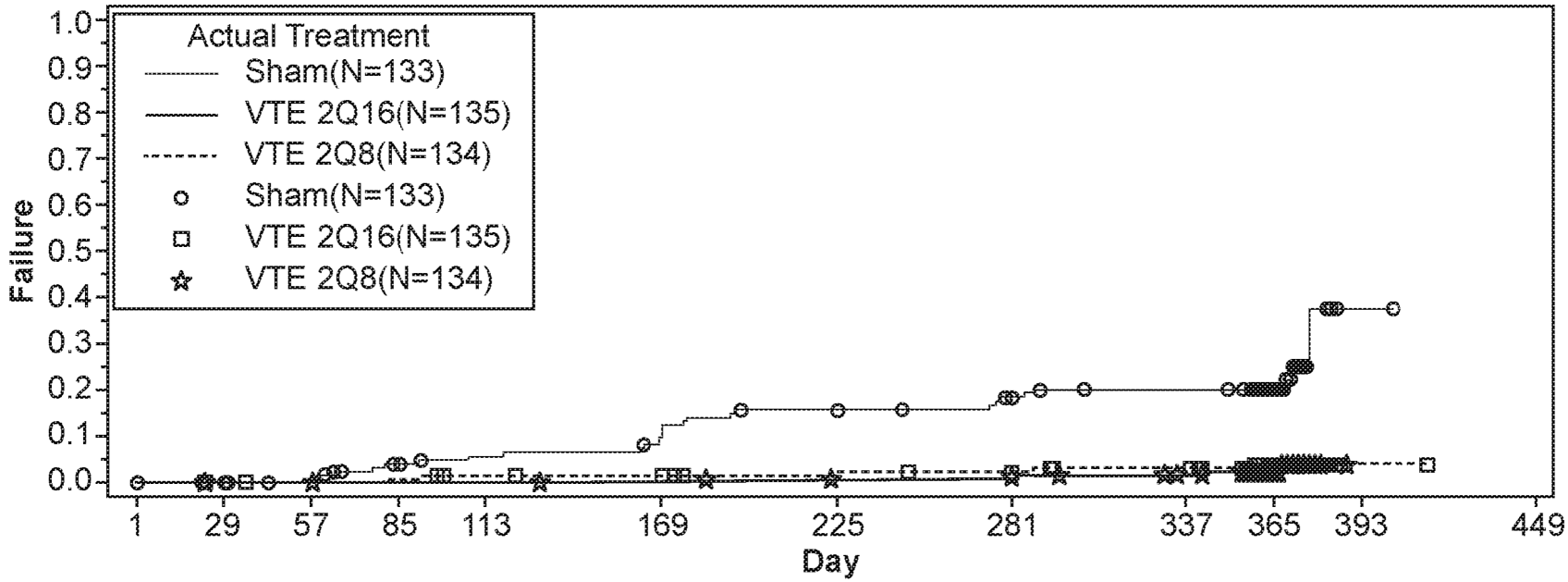

Proportion of Patients Developing a
Vision Threatening Complication (VTC) or
Center Involved (CI)-DME through Week 52
VTC or
CI-DME
VTC
CI-DME+
Proportion of Patients
40%
35%
30%
25%
20%
15%
10%
5%
0%
Sham
2q16
2q8
36.8%
8.9%*
10.4%*
20.3%
3.7%*
3.0%*
23.2%*
6.3%*
7.8%*
49/133
12/135
14/134
27/133
5/135
4/134
29/125
8/128
10/128
VTC = Vision threatening complication, PDR/ASNV
+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.
*p < 0.0001 vs. sham

FIG. 23

Time to Development of a Vision Threatening Complication (VTC)

Figure 14.02.08/2a Time to Development of any Neovascular Vision Threatening Complication (PDR/ASNV) through Week 52 (Full Analysis Set)



Number of Subjects at Risk

Sham(N=133)	133	130	127	118	113	107	99	93	88	64	1
VTE 2Q16(N=135)	135	134	133	132	129	128	125	123	119	86	1
VTE 2Q8(N=134)	134	133	133	132	132	131	128	128	123	89	0

Note: VTE 2Q8: aflibercept 2 mg Q8 to week 48 after 5 initial monthly doses; VTE 2Q16: aflibercept 2 mg Q16 after 3 initial monthly doses and I 8-week interval

Patients who did not have an event were censored at their last visit at or before the Week 52 visit.

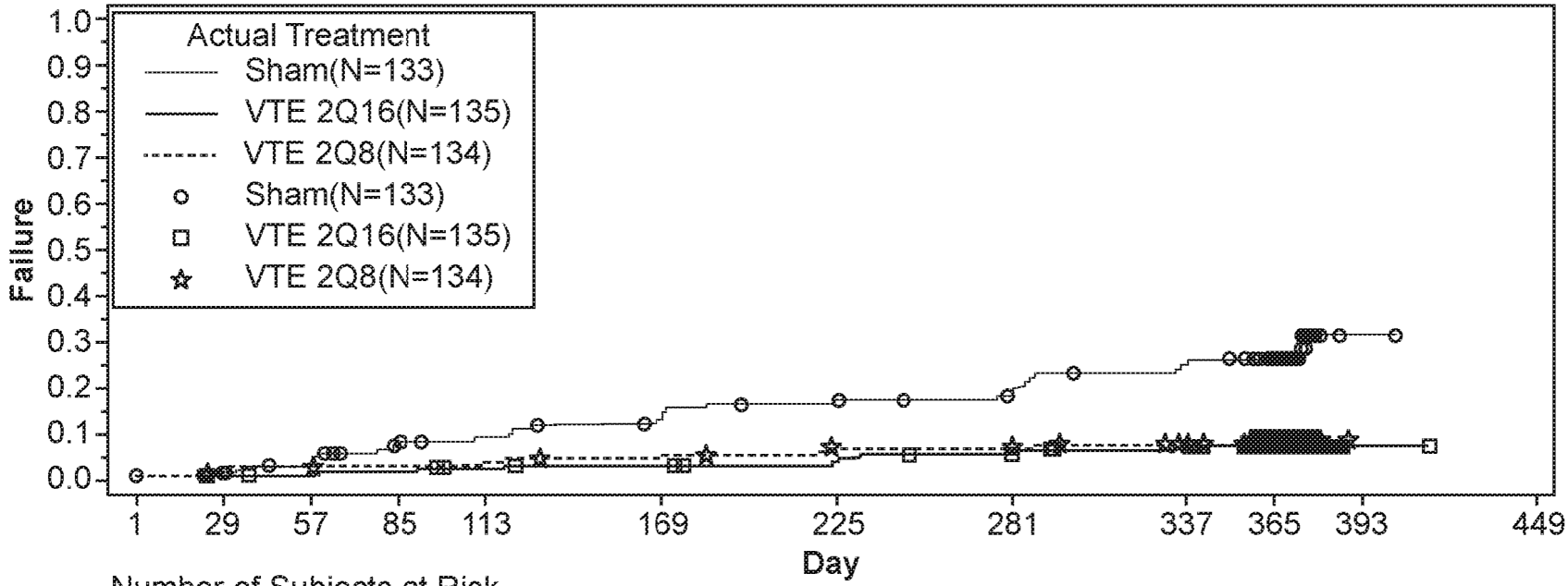
VTC = Vision threatening complication, PDR/ASNV

[+]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.

FIG. 24

Time to Development of CI-DME

Figure 14.02.08/3a Time to Development of CI-DME through Week 52 (Full Analysis Set)



Number of Subjects at Risk

Sham(N=133)	125	121	116	107	102	96	90	86	78	59	1
VTE 2Q16(N=135)	128	127	126	125	122	120	117	114	109	79	1
VTE 2Q8(N=134)	128	126	124	123	122	120	115	115	110	80	0

Note: VTE 2Q8: aflibercept 2 mg Q8 to week 48 after 5 initial monthly doses; VTE 2Q16: aflibercept 2 mg Q16 after 3 initial monthly doses and I 8-week interval

Includes all FAS patients who did not develop CI-DME before first study treatment and satisfied any of the following conditions 1. CRT <= 300nM at baseline; 2.CRT > 300 uM at baseline and intraretinal fluid is not 'definite, center subfield involved' and cystoid spaces is not 'definite, center subfield involved' and subretinal fluid (SSRD) is not 'present' as assessed by reading Center.

Patients who did not have an event were censored at their last visit at or before the Week 52 visit.

VTC = Vision threatening complication, PDR/ASNV

[+]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.

FIG. 25

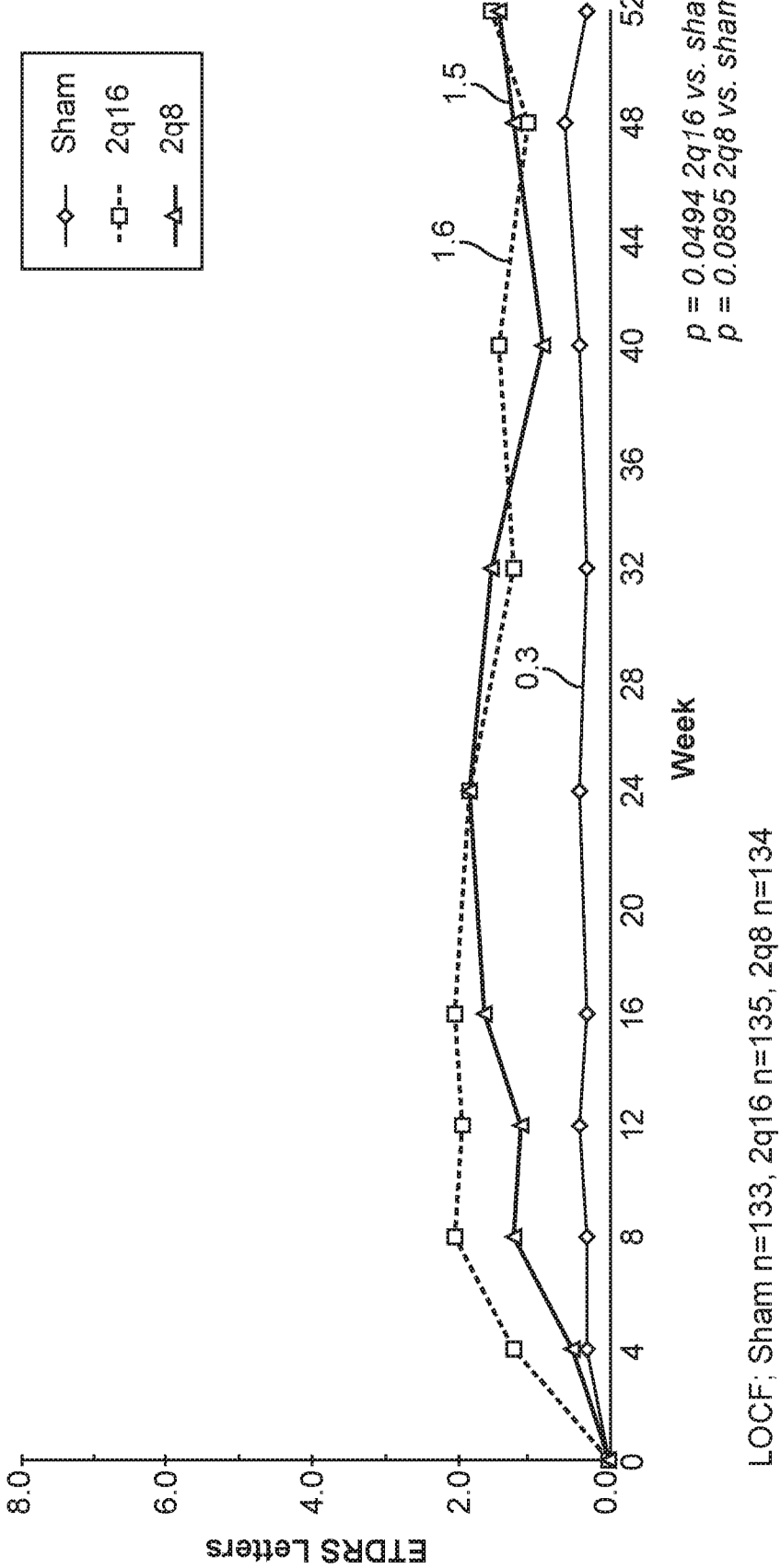

Mean Change in Best Corrected Visual Acuity
ETDRS Letters
8.0
6.0
4.0
2.0
0.0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week
Sham
2q16
2q8
1.6
1.5
0.3
p = 0.0494 2q16 vs. sham
p = 0.0895 2q8 vs. sham
LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

FIG. 26

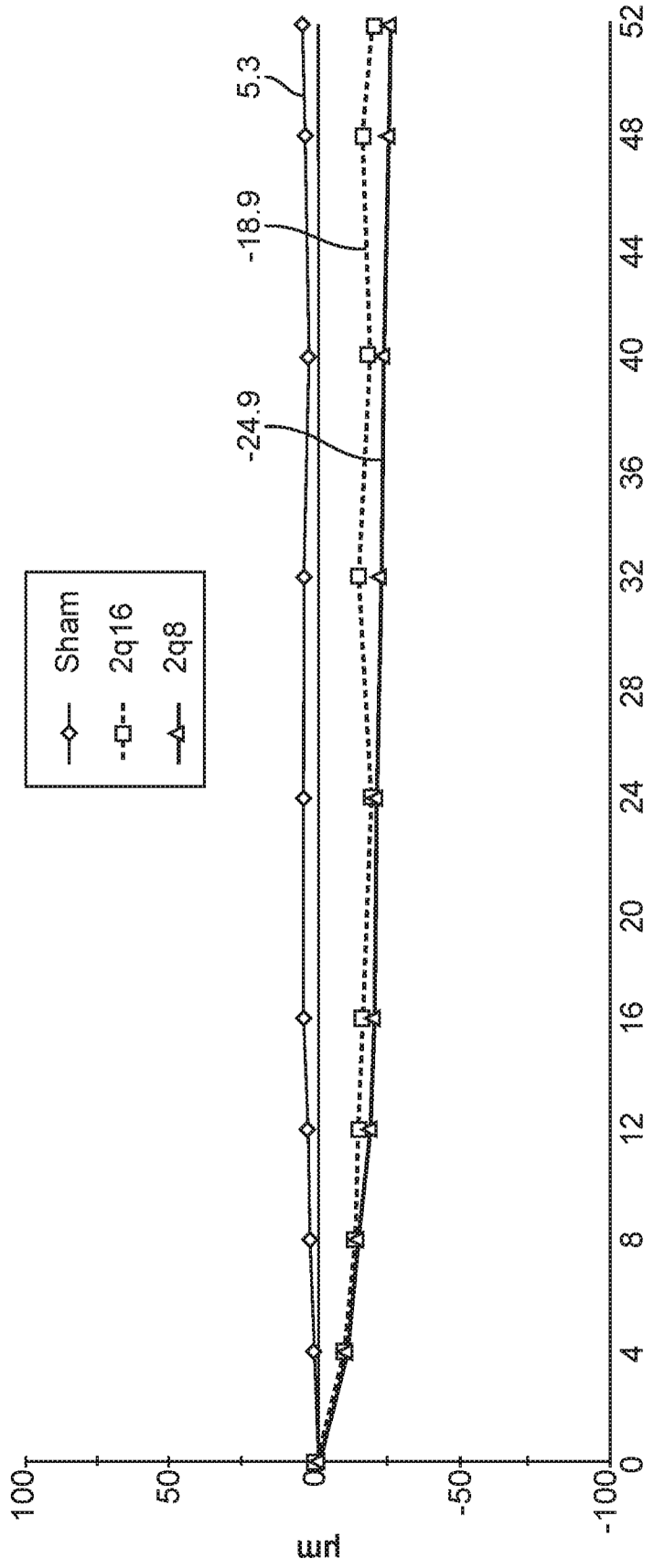

Mean Change in Central Retinal Thickness
Sham
2q16
2q8
-24.9
-18.9
5.3
100
50
0
-50
-100
µm
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week
p < 0.0001
2q16 and 2q8 vs. sham
LOCF; Sham n=133, 2q16 n=135, 2q8 n=134

FIG. 27

Ocular TEAEs in Study Eye through Week 52 (≥3%)

	Sham	2q16	2q8
N (FAS/SAF)	133	135	134
Number of Patients ≥ 1 AE, n (%)	67 (50.4%)	58 (43.0%)	60 (44.8%)
Eye disorders	64 (48.1%)	57 (42.2%)	59 (44.0%)
Conjunctival haemorrhage	7 (5.3%)	16 (11.9%)	23 (17.2%)
Diabetic retinal oedema	32 (24.1%)	8 (5.9%)	12 (9.0%)
Vitreous floaters	3 (2.3%)	6 (4.4%)	12 (9.0%)
Eye pain	4 (3.0%)	10 (7.4%)	5 (3.7%)
Retinal exudates	5 (3.8%)	5 (3.7%)	7 (5.2%)
Blepharitis	1 (0.8%)	2 (1.5%)	6 (4.5%)
Vitreous detachment	1 (0.8%)	4 (3.0%)	4 (3.0%)
Cataract	1 (0.8%)	3 (2.2%)	4 (3.0%)
Dry eye	4 (3.0%)	3 (2.2%)	4 (3.0%)
Diabetic retinopathy	13 (9.8%)	2 (1.5%)	3 (2.2%)
Visual impairment	0	1 (0.7%	4 (3.0%)

FIG. 28

Ocular Serious TEAEs in Study Eye through Week 52

— Sham ---- 2q16 — 2q8

N (FAS/SAF)	133	135	134
# of Patients with ≥ 1 AE, n (%)	1 (0.8%)	0	1 (0.7%)
Visual acuity reduced	0	0	1 (0.7%)
Vitreous haemorrhage	0	0	1 (0.7%)
Iris neovascularisation	1 (0.8%)	0	0

FIG. 29

Ocular Inflammation in Study Eye through Week 52

— Sham	---- 2q16	— 2q8

N (FAS/SAF)	133	135	134
# of injections	0	749	1158
# of Patients with ≥ 1 AE, n (%)	0	1 (0.7%) (0.13% per injection)	1 (0.7%) (0.09% per injection)
Anterior chamber flare	0	0	1 (0.7%)
Iritis	0	1 (0.7%)	0

1 additional event of vitreal cells was included in the IOI table, but it was determined not to be an IOI event

FIG. 30

APTC Events through Week 52

— Sham ---- 2q16 — 2q8

N (FAS/SAF)	133	135	134
Number of Patients with at Least One Such AE, n (%)	5 (3.8%)	4 (3.0%)	2 (1.5%)
Non Fatal Stroke	2 (1.5%)	3 (2.2%)	1 (0.7%)
Non Fatal MI	0	1 (0.7%)	0
Vascular Death	3 (2.3%)	0	1 (0.7%)

FIG. 31

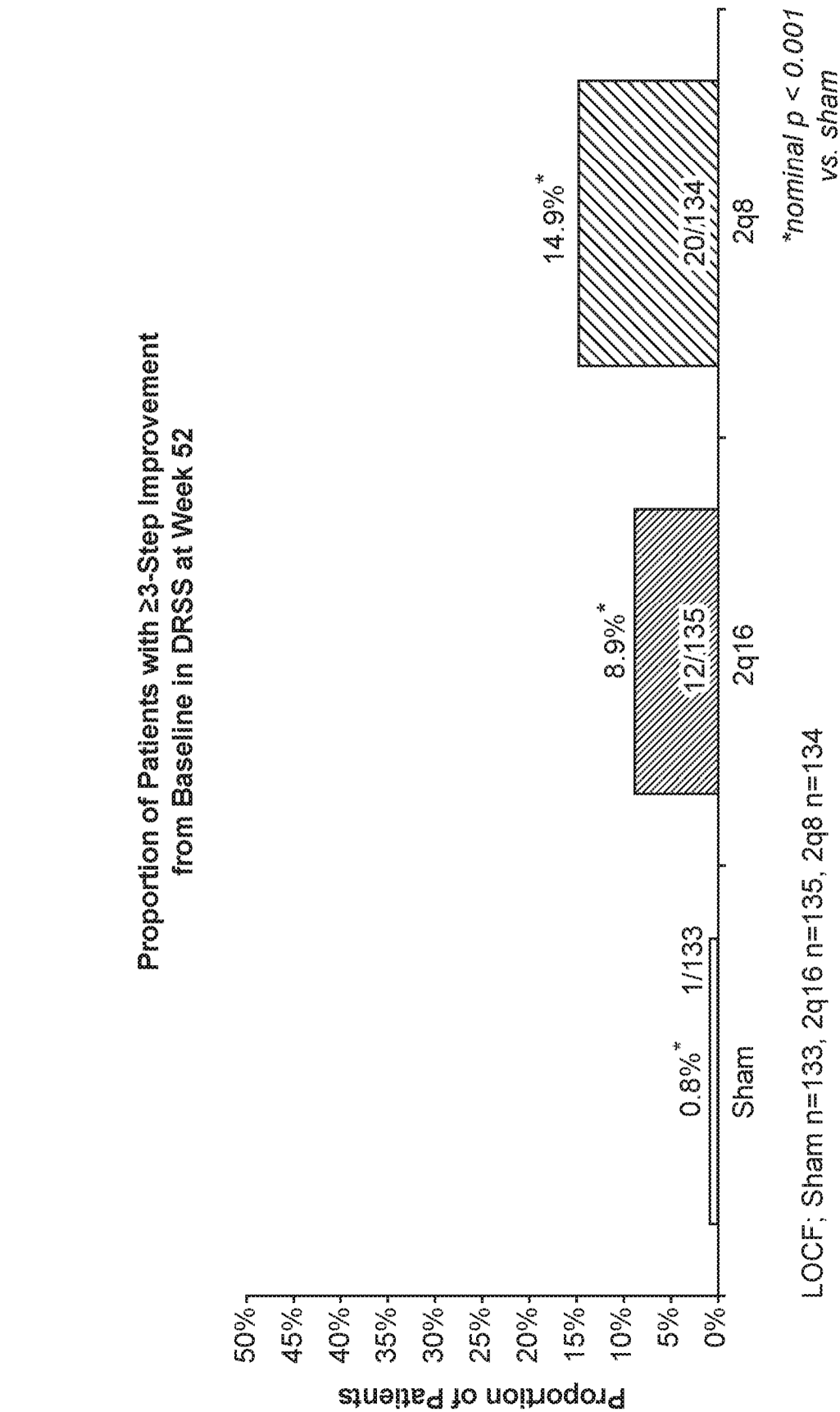

Proportion of Patients with ≥3-Step Improvement from Baseline in DRSS at Week 52
Proportion of Patients
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0.8%*
1/133
8.9%*
12/135
14.9%*
20/134
Sham
2q16
2q8
LOCF; Sham n=133, 2q16 n=135, 2q8 n=134
*nominal p < 0.001 vs. sham

FIG. 32