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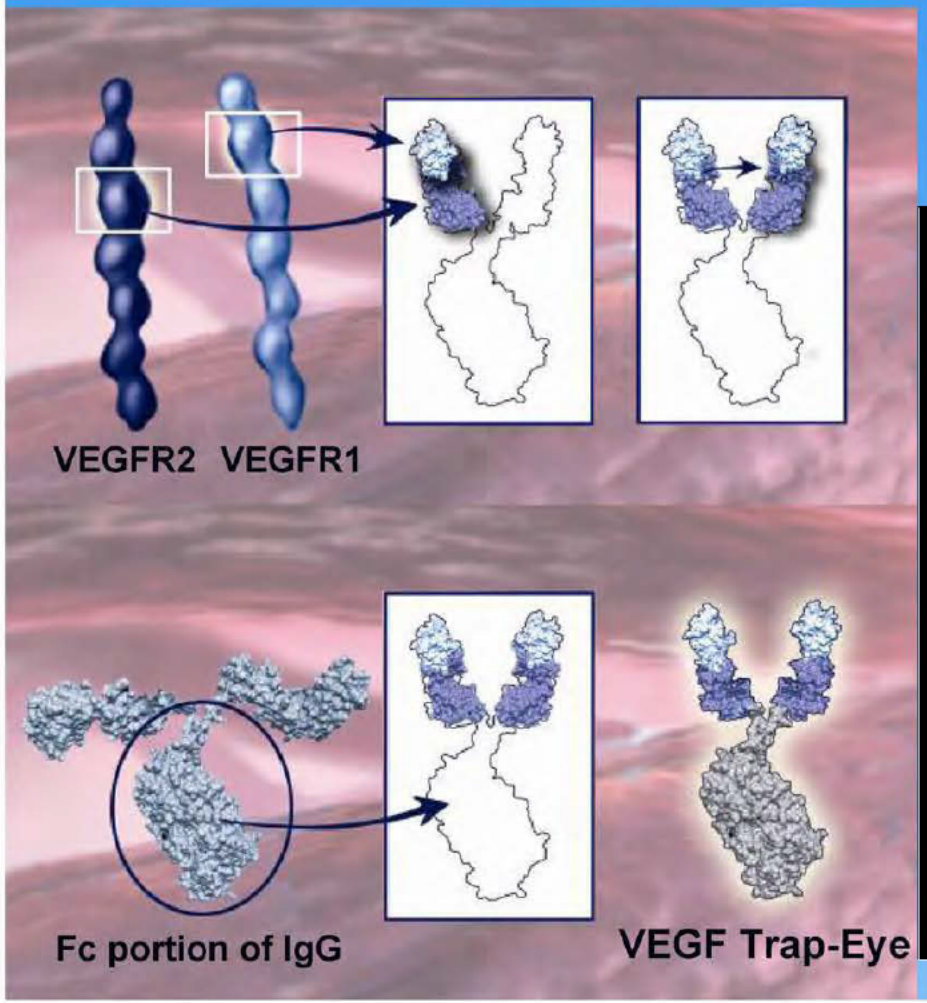
DME And VEGF Trap-Eye: INvestigation of Clinical Impact

One Year Data

VEGF Trap-Eye:

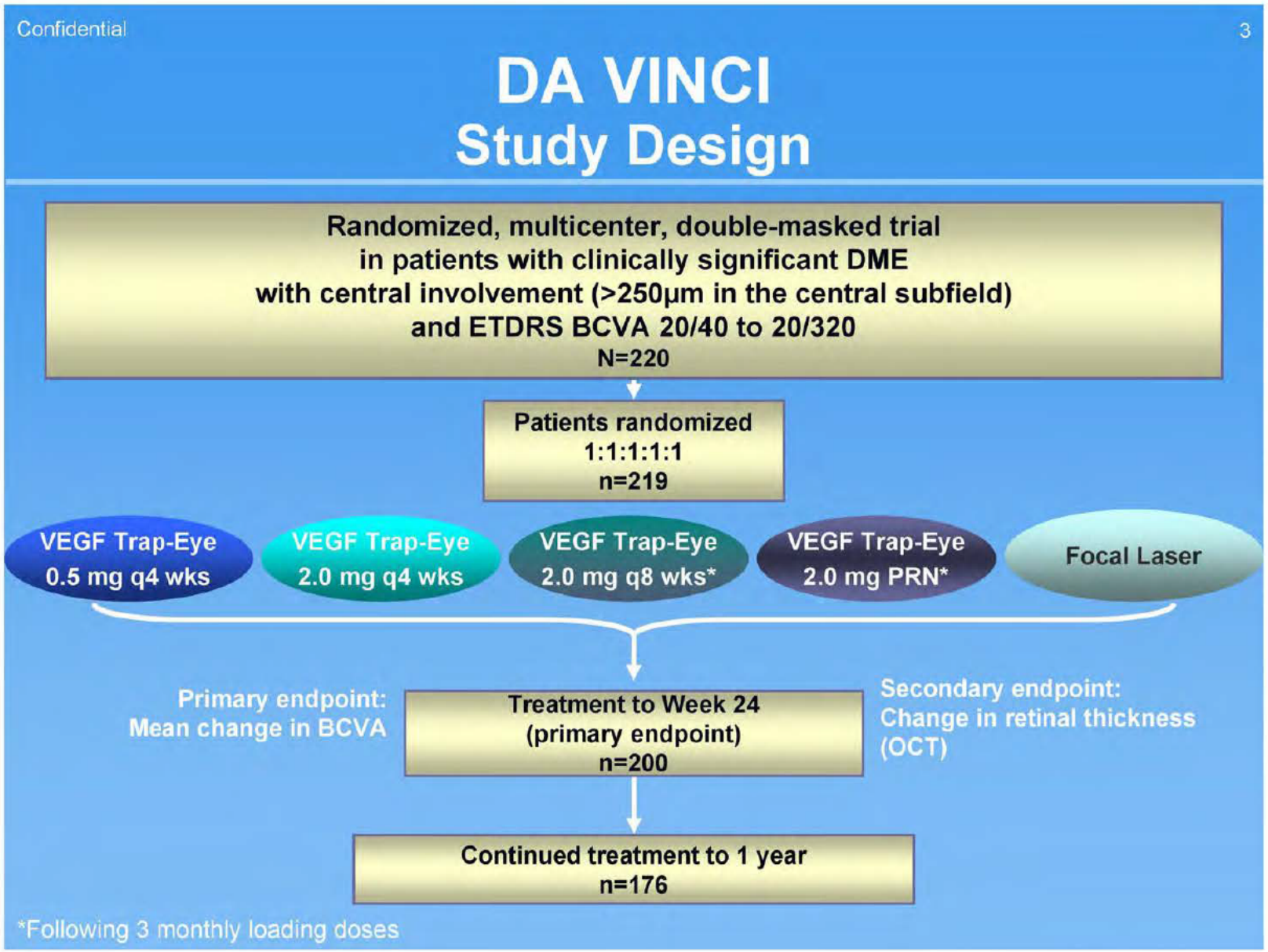
Specifically Designed to Block Members of the VEGF Family



- **Fusion protein** of key domains from human VEGF receptors 1 and 2 with human IgG Fc

[redacted]

IgG=immunoglobulin G; MW=molecular weight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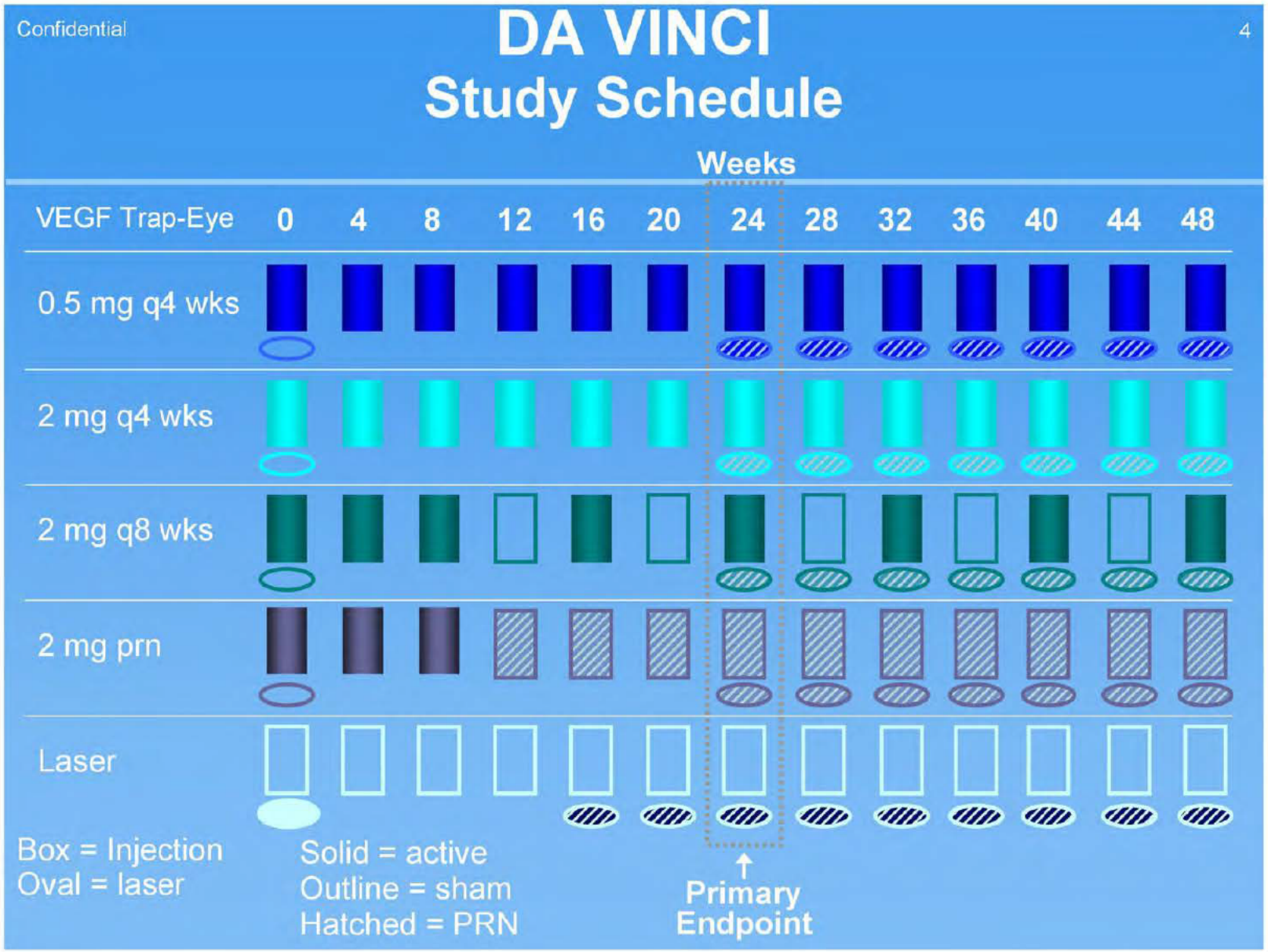
Study Design
Randomized, multicenter, double-masked trial
in patients with clinically significant DME
with central involvement (>250µm in the central subfield)
and ETDRS BCVA 20/40 to 20/320
N=220
Patients randomized
1:1:1:1:1
n=219
VEGF Trap-Eye
0.5 mg q4 wks
VEGF Trap-Eye
2.0 mg q4 wks
VEGF Trap-Eye
2.0 mg q8 wks*
VEGF Trap-Eye
2.0 mg PRN*
Focal Laser
Primary endpoint:
Mean change in BCVA
Treatment to Week 24
(primary endpoint)
n=200
Secondary endpoint:
Change in retinal thickness
(OCT)
Continued treatment to 1 year
n=176
*Following 3 monthly loading doses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Study Schedule
4
Weeks
VEGF Trap-Eye
0
4
8
12
16
20
24
28
32
36
40
44
48
0.5 mg q4 wks
2 mg q4 wks
2 mg q8 wks
2 mg prn
Laser
Box = Injection
Oval = laser
Solid = active
Outline = sham
Hatched = PRN
Primary
Endpoint

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Key Exclusion Criteria

- History of vitreoretinal surgery in study eye
- Panretinal laser photocoagulation or macular laser photocoagulation in study eye within 3 months of screening
- Previous use of intraocular or periocular corticosteroids in study eye within 3 months of screening
- Previous treatment with anti-angiogenic drugs in either eye within 3 months of screening

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Laser Retreatment/Rescue

- Laser Arm patients could receive laser retreatment beginning at at week 16*
- Patients in VTE arms were able to receive laser rescue beginning at week 24*
- Criteria used to determine laser retreatment/rescue (based on ETDRS criteria):
  - Thickening of the retina at or within 500 microns of the center of the macula
  - Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina
  - A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula

*Subsequent laser retreatment may not occur more often than once every 16 weeks

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Retreatment Criteria
for Patients Randomized to VEGF Trap-Eye 2 mg PRN

Following the 3 monthly loading doses, retreatment based on:

- OCT central retinal thickness >=250 µm
- Increase >50µm in OCT central retinal thickness compared to lowest previous measurement
- Increase of >=5 letters in BCVA between current and most recent visit
- Loss of >=5 letters from the previous BCVA measurement w/ any increase in OCT central retinal thickness

*If a patient does not meet criteria, sham injection is given

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Patient Disposition

	Laser n=44	0.5q4 n=44	2q4 n=44	2q8 n=44	2PRN n=45	Total N=221
Randomized	44 (100%)	44 (100%)	44 (100%)	44 (100%)	45 (100%)	221* (100%)
Treated	44 (100%)	44 (100%)	44 (100%)	42 (95.5%)	45 (100%)	219 (99.1%)
Completed Week 24	40 (90.9%)	41 (93.2%)	40 (90.9%)	38 (86.3%)	41 (91.1%)	200 (90.5%)
Completed Week 52	33 (75.0%)	38 (86.4%)	33 (75.0%)	34 (77.3%)	38 (84.4%)	176 (79.6%)
Discontinuation Before Week 52	11 (25.0%)	6 (13.6%)	11 (25.0%)	8 (18.2%)	7 (15.6%)	43 (19.5%)
Withdrawal Consent	2 (4.5%)	1 (2.3%)^	3 (6.8%)^	2 (4.5%)	3 (6.7%)^	11 (5.0%)
Protocol Deviation	1 (2.3%)	0	0	1 (2.3%)	0	2 (0.9%)
Adverse Event	3 (6.8%)	3 (6.8%)	1 (2.3%)#	0	0	7 (3.2%)
Death	1 (2.3%)	1 (2.3%)	2 (4.5%)	2 (4.5%)	0	6 (2.7%)
Lost To Follow-Up	0^	1 (2.3%)	4 (9.1%)	2 (4.5%)	4 (8.9%)^	11 (5.0%)
Treatment Failure	2 (4.5%)	0	0	0	0	2 (0.9%)
Other	2 (4.5%)	0	1 (2.3%)	1 (2.3%)	0	4 (1.8%)

*One patient was randomized to 2q8, discontinued before treatment, and was re-randomized to 2q4.
^An additional patient in each category discontinued after Week 52
#Adverse event (CVA) was fatal

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Baseline Characteristics

	Laser n=44	0.5q4 n=44	2q4 n=44	2q8 n=42	2PRN n=45
Age (years) Mean (SD)	64.0 (8.12)	62.3 (10.70)	62.1 (10.50)	62.5 (11.49)	60.7 (8.66)
Gender (Women)	38.6%	45.5%	38.6%	47.6%	35.6%
Race #(%)					
White (non Hispanic)	30 (68.2%)	28 (63.6%)	26 (59.1%)	33 (78.6%)	28 (62.2%)
White Hispanic	8 (18.2%)	13 (29.5%)	15 (34.1%)	3 (7.1%)	13 (28.9%)
Black	4 (9.1%)	3 (6.8%)	1 (2.3%)	2 (4.8%)	1 (2.2%)
Asian	1 (2.3%)	0	0	1 (2.4%)	2 (4.4%)
Other	1 (2.3%)	0	2 (4.5%)	1 (2.4%)	1 (2.2%)
Diabetes #(%)					
Type 1	5 (11.4%)	1 (2.3%)	3 (6.8%)	4 (9.5%)	2 (4.4%)
Type 2	39 (88.6%)	43 (97.7%)	41 (93.2%)	38 (90.5%)	43 (95.6%)
HbA1c (%) mean (SD)	7.9 (1.8)	8.1 (1.9)	8.1 (1.9)	7.9 (1.7)	8.0 (1.7)
Baseline Cardiac History	8 (18.2%)	21 (47.7%)	15 (34.1%)	18 (42.9%)	15 (33.3%)

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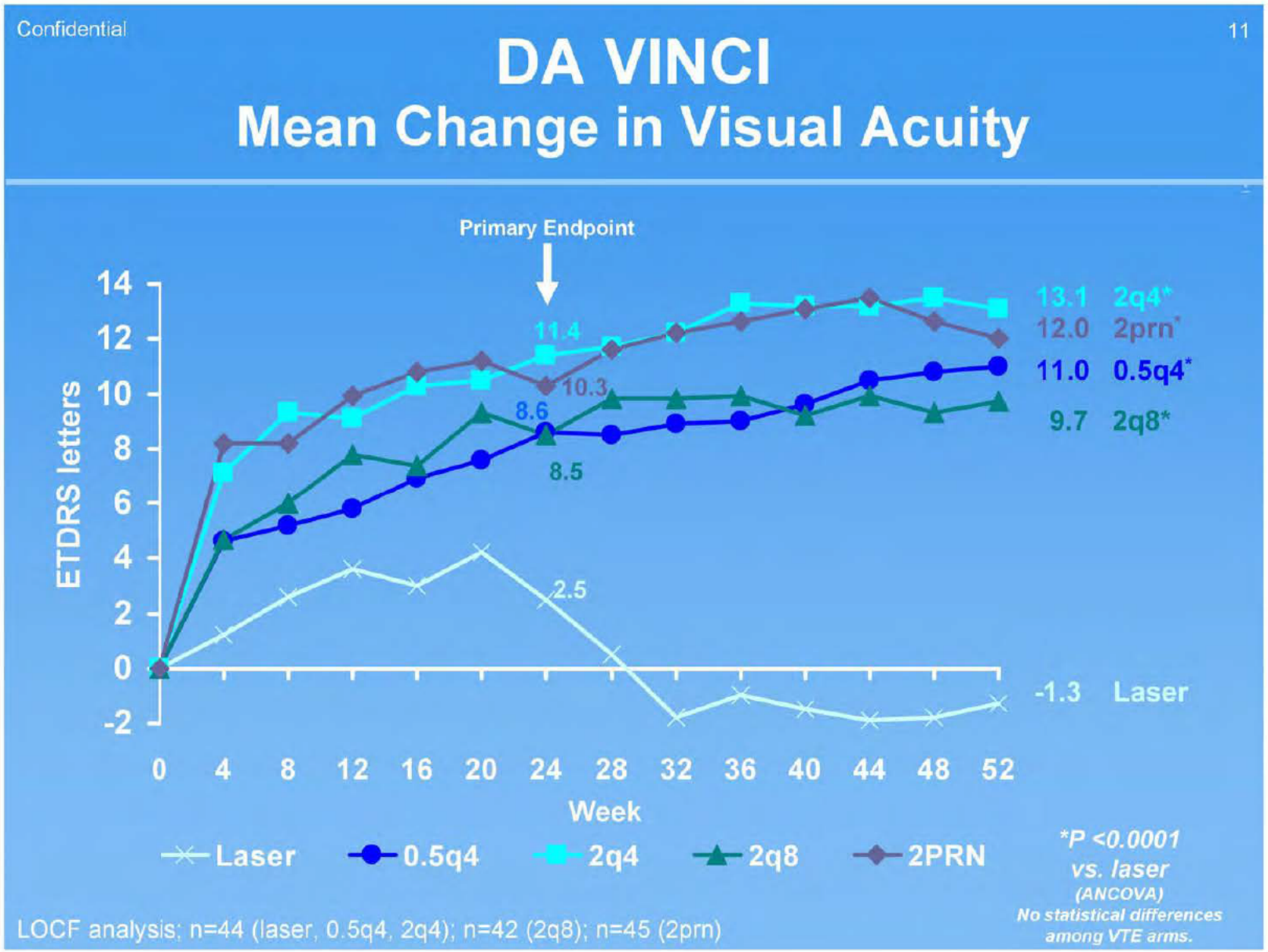
DA VINCI
Baseline Clinical Characteristics

	Laser n=44	0.5q4 n=44	2q4 n=44	2q8 n=42	2PRN n=45
ETDRS BCVA Mean letters (SD) Snellen equivalent	57.6 (12.5) 20/70	59.3 (11.2) 20/64	59.9 (10.1) 20/64	58.8 (12.2) 20/64	59.6 (11.1) 20/64
Central Retinal Thickness (um) Mean (SD)	440.6 (145.4)	426.1 (128.3)	456.6 (135.0)	434.8 (111.8)	426.6 (152.4)
Diabetic retinopathy Severity Score Mean (SD)	3.3 (0.7)	3.5 (0.7)	3.1 (0.9)	3.5 (0.9)	3.2 (0.7)
None (1)	1 (2.3%)	0	3 (6.8%)	0	0
Mild (2)	1 (2.3%)	2 (4.5%)	4 (9.1%)	3 (7.1%)	5 (11.1%)
Moderate (3)	29 (65.9%)	20 (45.5%)	25 (56.8%)	21 (50.0%)	25 (55.6%)
Severe (4)	12 (27.3%)	20 (45.5%)	11 (25.0%)	11 (26.2%)	14 (31.1%)
Proliferative (5)	1 (2.3%)	2 (4.5%)	1 (2.3%)	7 (16.7%)	1 (2.2%)
Previous Treatment					
Laser (focal or grid)	22 (50.0%)	21 (47.7%)	23 (52.3%)	28 (66.7%)	26 (57.8%)
Anti-VEGF(RBZ,BEV,PEG)	10 (22.7%)	5 (11.4%)	10 (22.7%)	6 (14.3%)	6 (13.3%)
Steroids (Tri, Dex)	12 (27.3%)	8 (18.2%)	7 (15.9%)	10 (23.8%)	9 (20.0%)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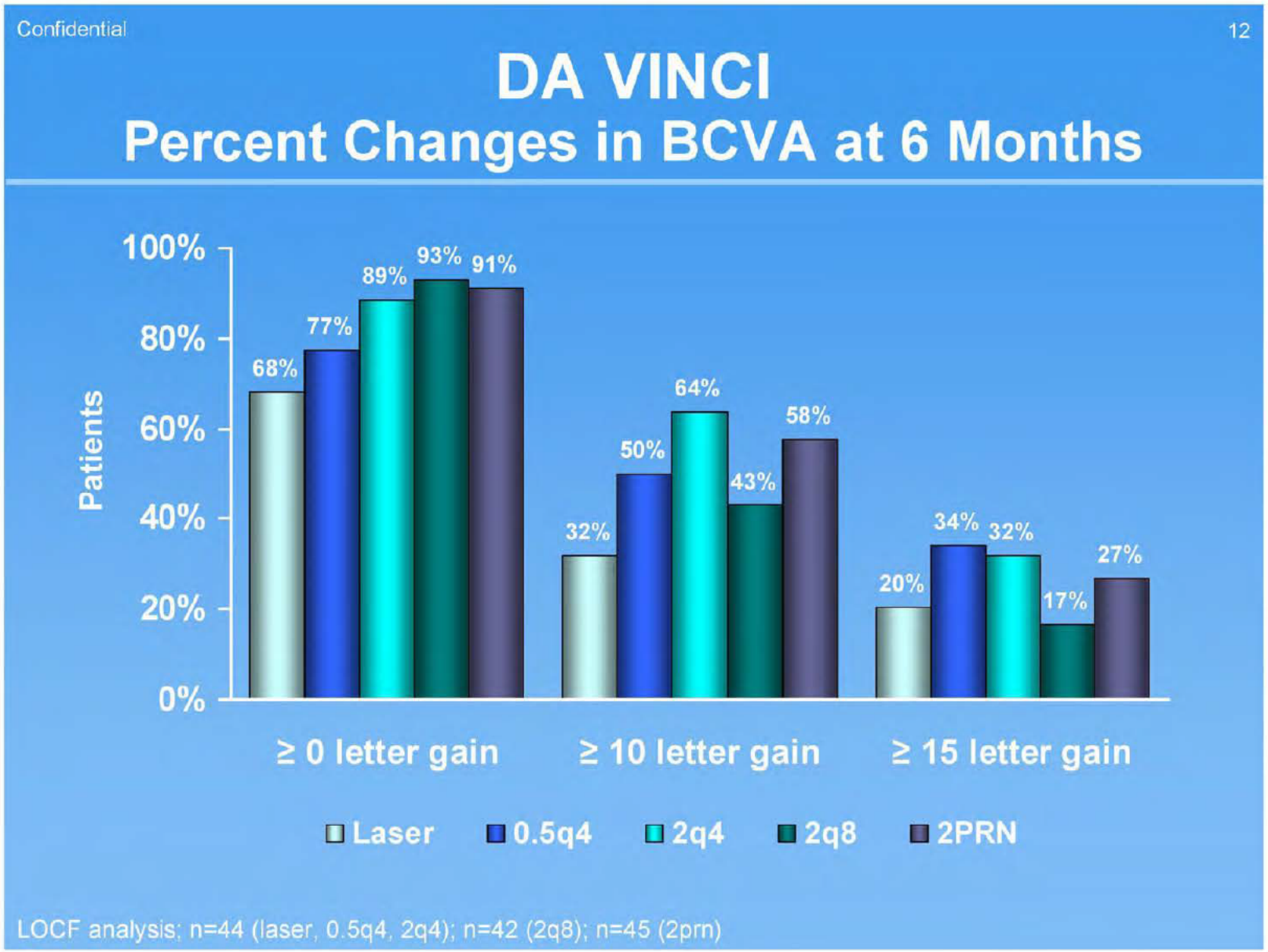
DA VINCI
Mean Change in Visual Acuity
Primary Endpoint
ETDRS letters
14
12
10
8
6
4
2
0
-2
11.4
10.3
8.6
8.5
2.5
13.1 2q4*
12.0 2prn*
11.0 0.5q4*
9.7 2q8*
-1.3 Laser
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Week
Laser
0.5q4
2q4
2q8
2PRN
*P <0.0001 vs. laser (ANCOVA)
No statistical differences among VTE arms.
LOCF analysis; n=44 (laser, 0.5q4, 2q4); n=42 (2q8); n=45 (2prn)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Percent Changes in BCVA at 6 Months
Patients
100%
80%
60%
40%
20%
0%
68%
77%
89%
93%
91%
32%
50%
64%
43%
58%
20%
34%
32%
17%
27%
≥ 0 letter gain
≥ 10 letter gain
≥ 15 letter gain
Laser
0.5q4
2q4
2q8
2PRN
LOCF analysis; n=44 (laser, 0.5q4, 2q4); n=42 (2q8); n=45 (2prn)

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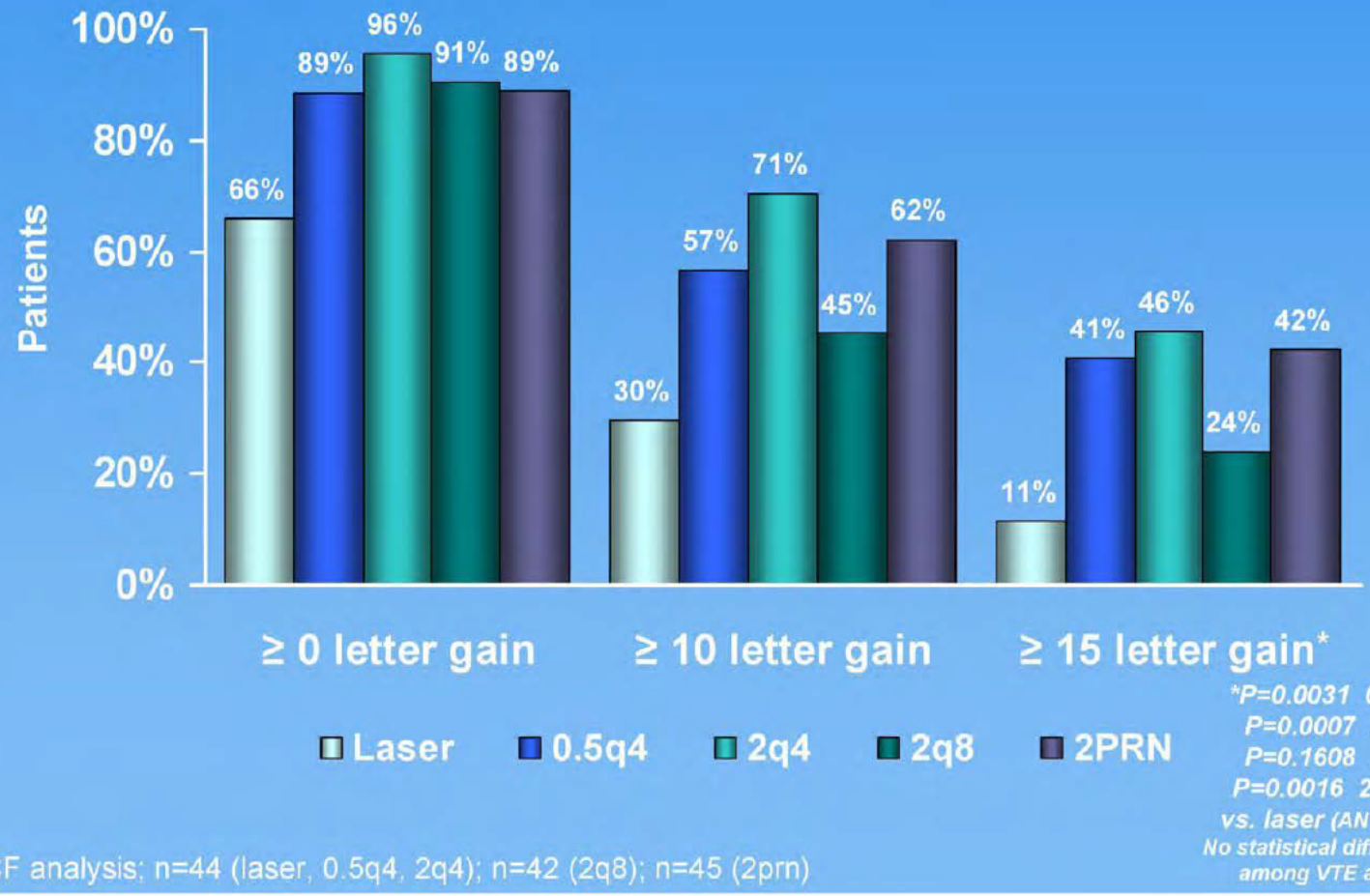
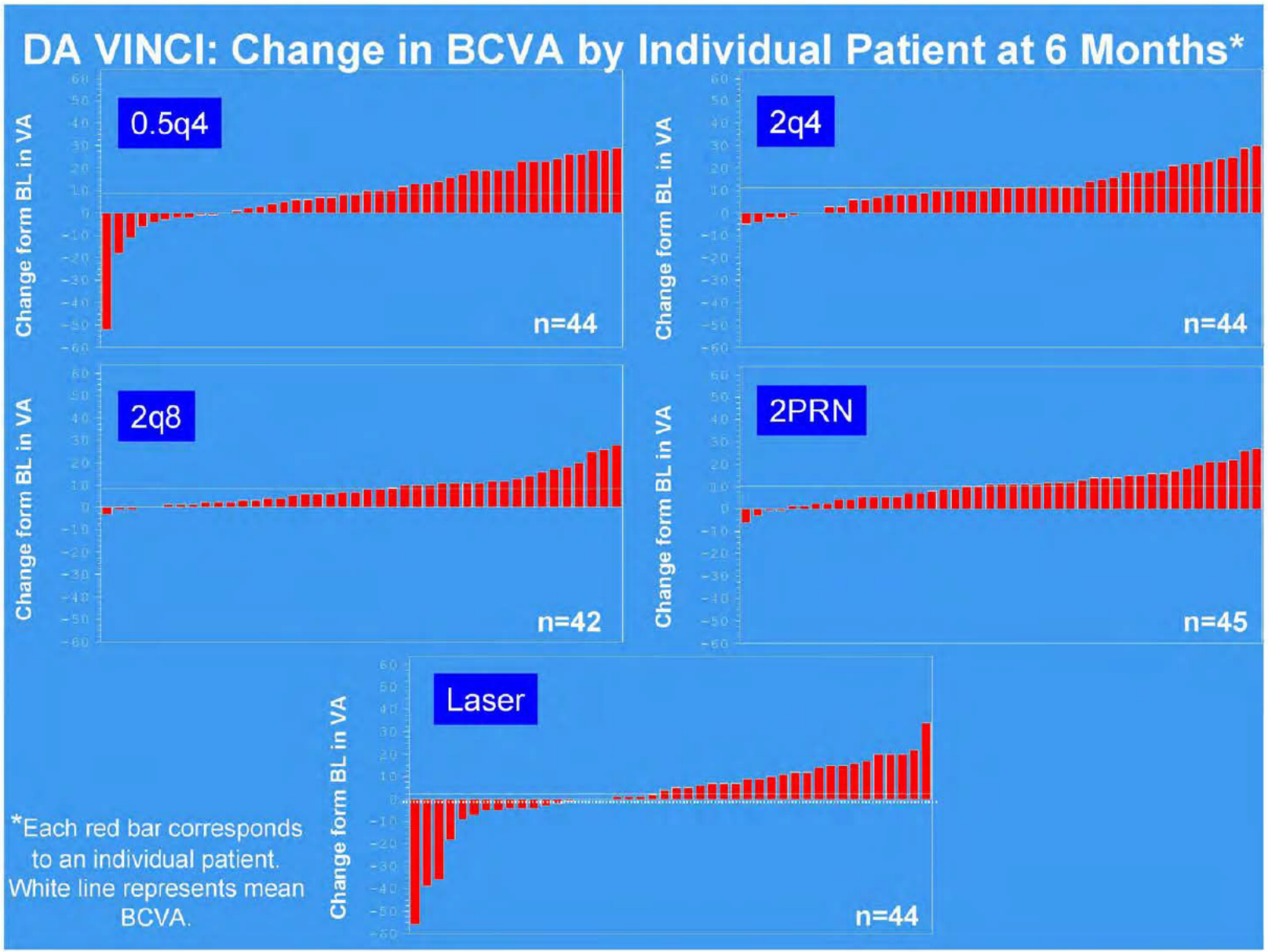
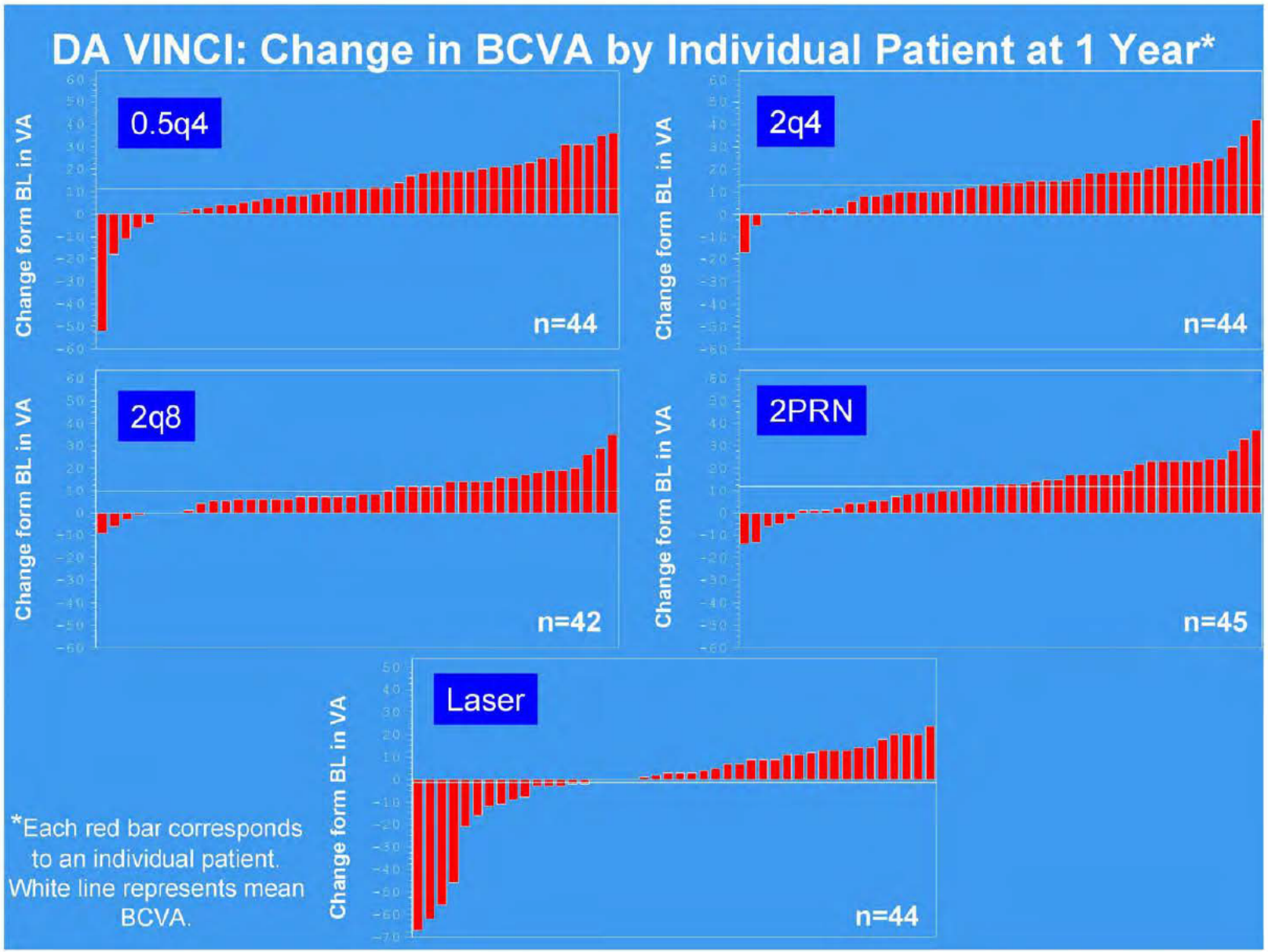
DA VINCI
Percent Changes in BCVA at 12 Months

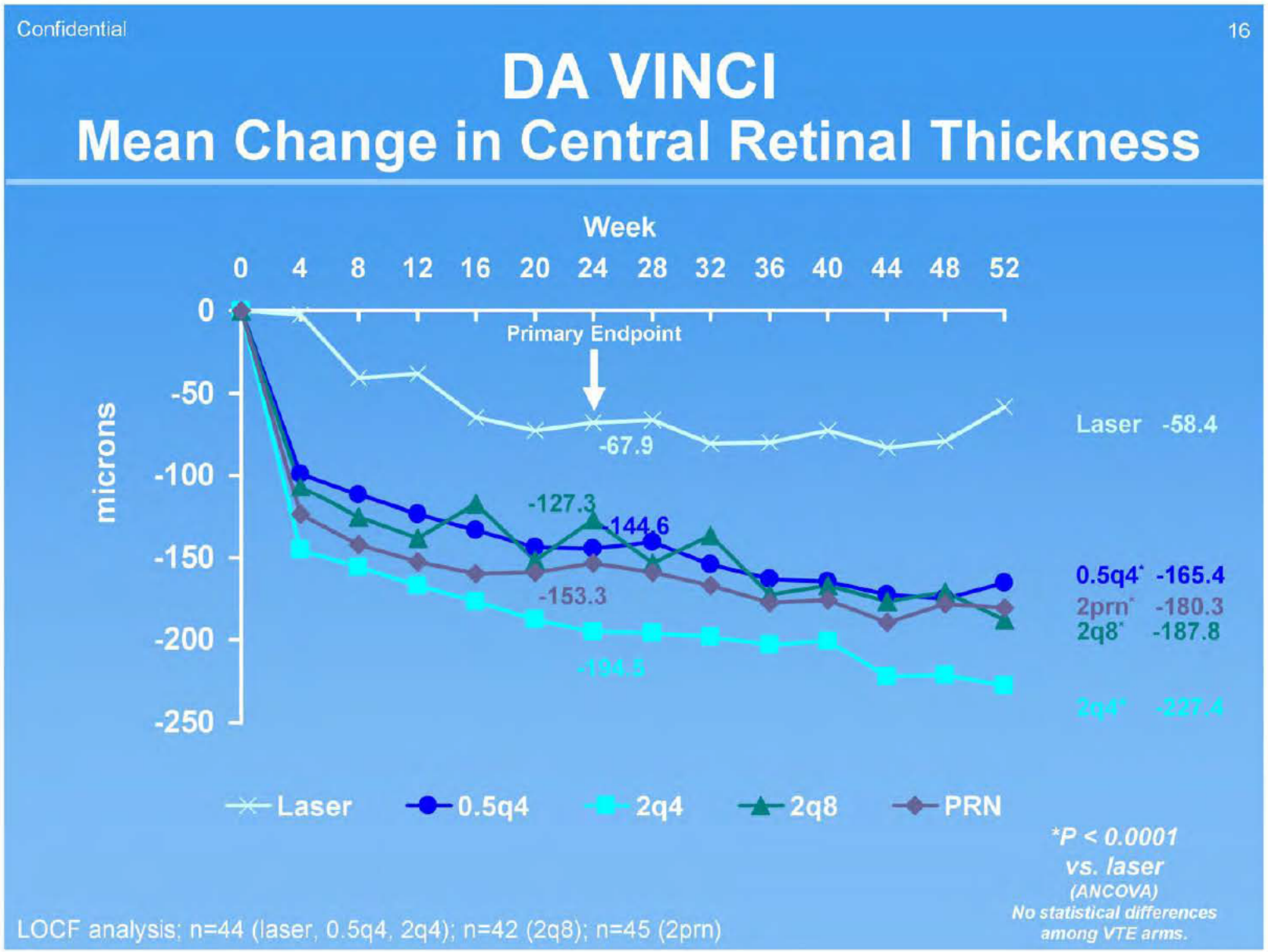


*P=0.0031 0.5q4
P=0.0007 2q4
P=0.1608 2q8
P=0.0016 2PRN
vs. laser (ANCOVA)
No statistical differences among VTE arms.

LOCF analysis; n=44 (laser, 0.5q4, 2q4); n=42 (2q8); n=45 (2prn)


DA VINCI: Change in BCVA by Individual Patient at 6 Months*
0.5q4
n=44
2q4
n=44
2q8
n=42
2PRN
n=45
Laser
n=44
Change form BL in VA
*Each red bar corresponds to an individual patient. White line represents mean BCVA.


DA VINCI: Change in BCVA by Individual Patient at 1 Year*
0.5q4
n=44
2q4
n=44
2q8
n=42
2PRN
n=45
Laser
n=44
Change form BL in VA
*Each red bar corresponds to an individual patient. White line represents mean BCVA.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Mean Change in Central Retinal Thickness
Week
0 4 8 12 16 20 24 28 32 36 40 44 48 52
0
-50
-100
-150
-200
-250
microns
Primary Endpoint
-67.9
-127.3
-144.6
-153.3
-194.5
Laser -58.4
0.5q4* -165.4
2prn* -180.3
2q8* -187.8
2q4* -227.4
Laser
0.5q4
2q4
2q8
PRN
*P < 0.0001
vs. laser
(ANCOVA)
No statistical differences
among VTE arms.
LOCF analysis; n=44 (laser, 0.5q4, 2q4); n=42 (2q8); n=45 (2prn)

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Treatment/Exposure Summary at 6 Months

Total actual VEGF Trap-Eye exposure ove

VEGF Trap-Eye	Required Injections	Mean
0.5q4 (n = 44)	6	5.6
2q4 (n = 44)	6	5.5
2q8 (n = 42)	4	3.8
2PRN (n = 45)	3	4.4

Injections in PRN arm over 3 mont

VEGF Trap-Eye	Total Injections Possible	Mean
2PRN (n = 45)	3	1.5

Laser treatments in laser arm over 6 n

Laser	Total Laser Treatments Possible	Mean
n=44	2	1.7

[redacted]

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DA VINCI
Treatment/Exposure Summary at 12 Months

Total actual VEGF Trap-Eye exposure over 12 months

VTE	Required Injections	Mean (SD)
0.5q4 (n = 44)	13	11.7 (2.49)
2q4 (n = 44)	13	10.8 (2.87)
2q8 (n = 42)	8	7.2 (1.74)
2PRN (n=45)	3	7.4 (3.19)

Injections in PRN arm over 9

VTE	Total Injections Possible	Mean (SD)
2PRN (n = 45)	10	4.6 (3.04)

Laser treatments over 12 m

Study Arm	Total Lasers Possible	Mean (SD)
Laser (n = 44)	4	2.5 (0.9)
0.5q4 (n = 44)	2	0.8 (0.8)
2q4 (n = 44)	2	0.5 (0.7)
2q8 (n = 42)	2	0.8 (0.9)
2PRN (n = 45)	2	0.8 (0.8)

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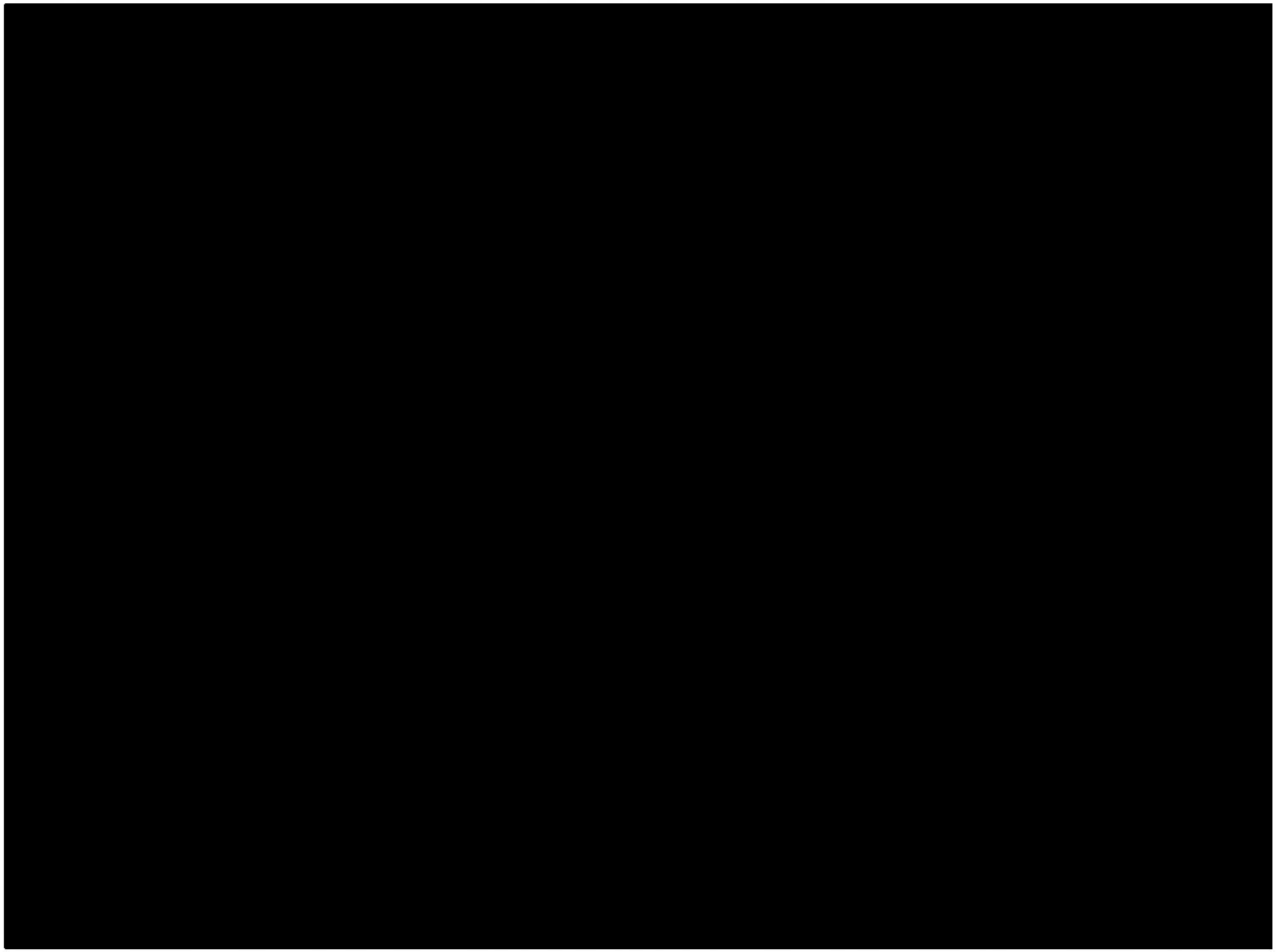

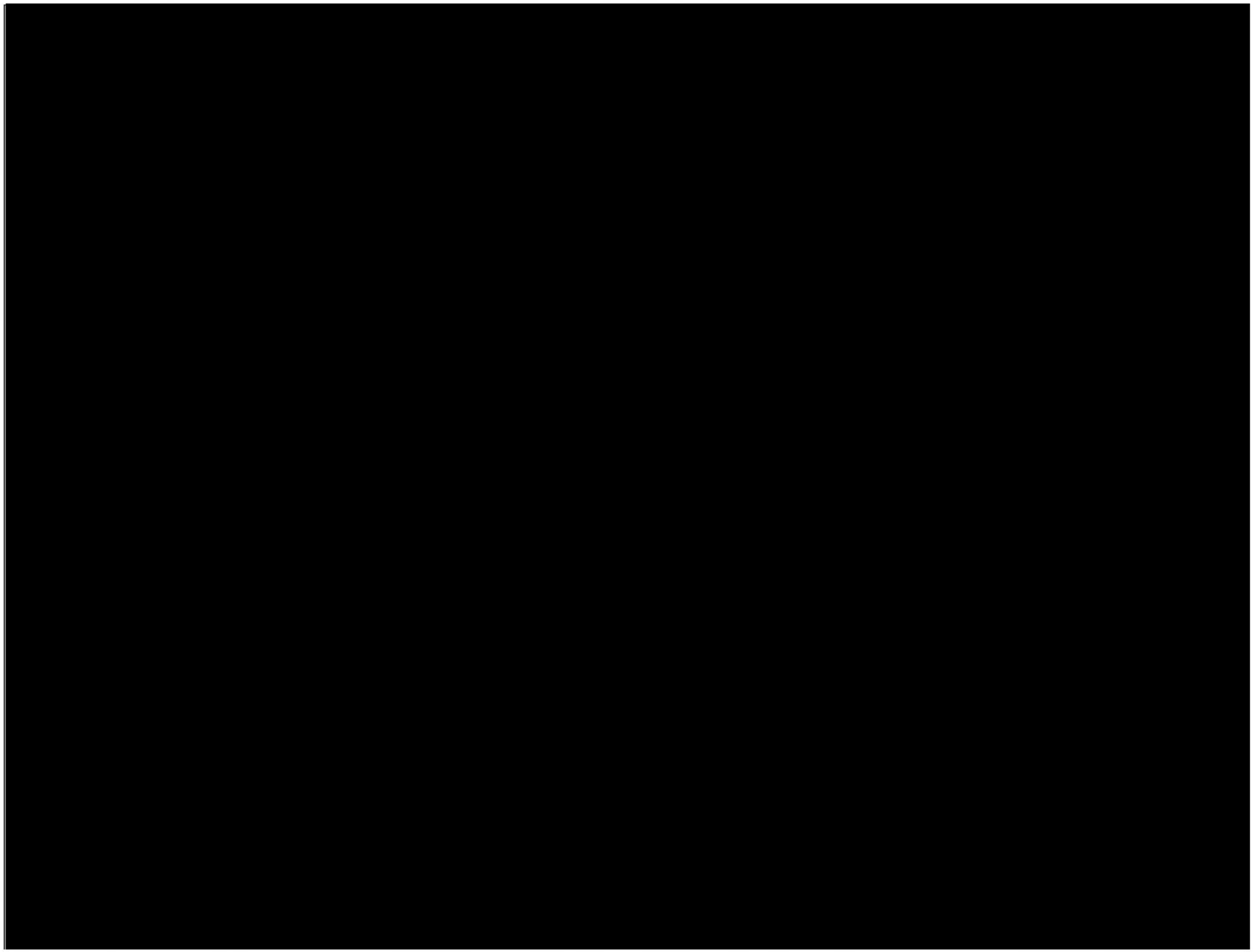

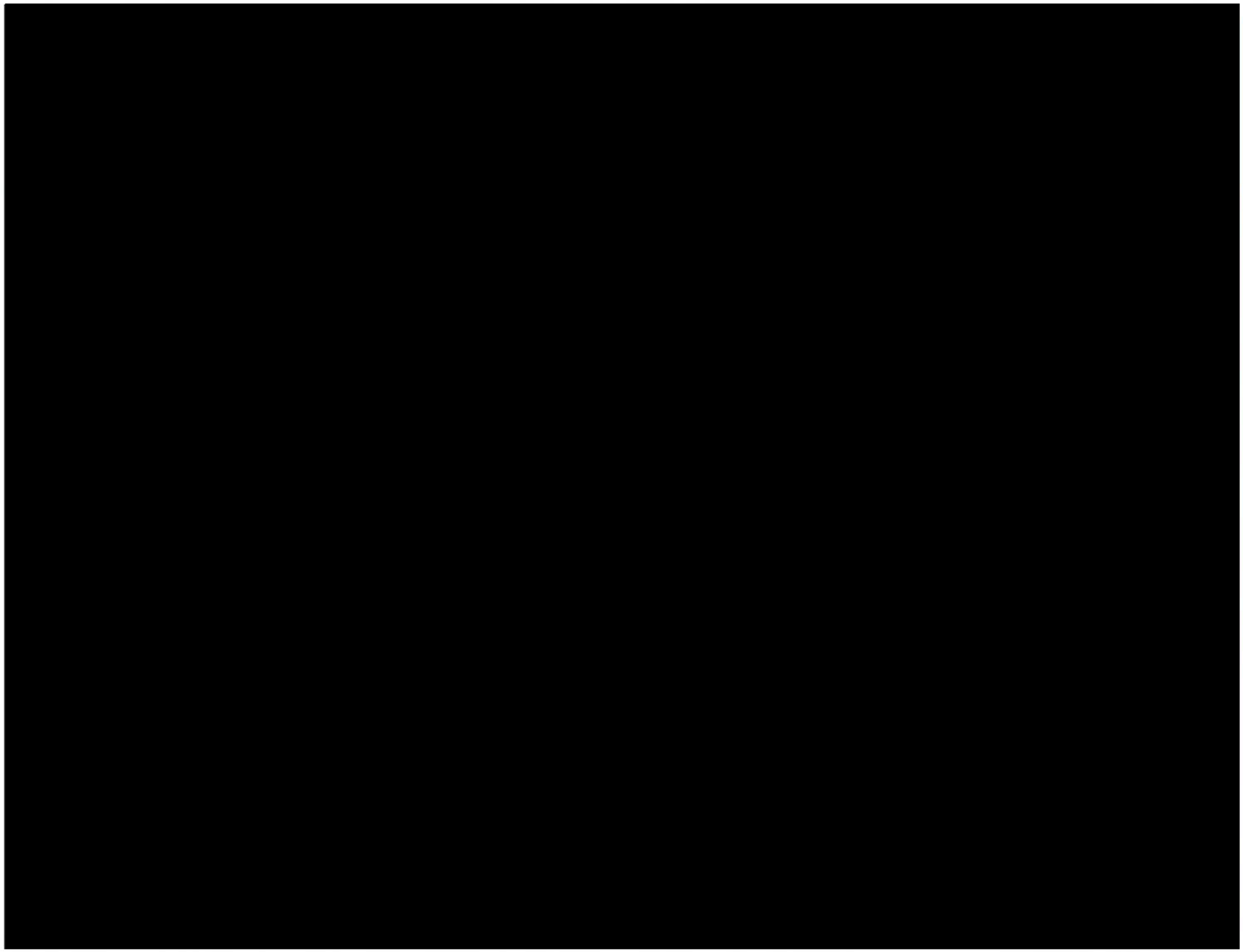

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Ocular Adverse Events in Study Eye (≥ 5%)

	Laser	0.5q4	2q4	2q8	2PRN	All VTE
n (safety analysis set)	44	44	44	42	45	175
# of subjects with at least 1 AE	27 (61.4%)	30 (68.2%)	26 (59.1%)	28 (66.7%)	29 (64.4%)	113 (64.6%)
Conjunctiva hemorrhage	8 (18.2%)	12 (27.3%)	7 (15.9%)	15 (35.7%)	13 (28.9%)	47 (26.9%)
Eye pain	2 (4.5%)	6 (13.6%)	5 (11.4%)	6 (14.3%)	7 (15.6%)	24 (13.7%)
IOP increased	1 (2.3%)	6 (13.6%)	6 (13.6%)	5 (11.9%)	2 (4.4%)	19 (10.9%)
Ocular hyperemia	2 (4.5%)	5 (11.4%)	2 (4.5%)	3 (7.1%)	3 (6.7%)	13 (7.4%)
Cataract	2 (4.5%)	2 (4.5%)	3 (6.8%)	2 (4.8%)	5 (11.1%)	12 (6.9%)
Vitreous floaters	2 (4.5%)	5 (11.4%)	3 (6.8%)	2 (4.8%)	2 (4.4%)	12 (6.9%)
Maculopathy	2 (4.5%)	2 (4.5%)	1 (2.3%)	4 (9.5%)	3 (6.7%)	10 (5.7%)
Retinal exudates	1 (2.3%)	4 (9.1%)	1 (2.3%)	2 (4.8%)	3 (6.7%)	10 (5.7%)
Vitreous detachment	5 (11.4%)	3 (6.8%)	3 (6.8%)	3 (7.1%)	0	9 (5.1%)
Corneal abrasion	0	0	2 (4.5%)	3 (7.1%)	3 (6.7%)	8 (4.6%)
Diabetic retinal edema	1 (2.3%)	1 (2.3%)	3 (6.8%)	1 (2.4%)	3 (6.7%)	8 (4.6%)
Retinal hemorrhage	2 (4.5%)	0	3 (6.8%)	1 (2.4%)	4 (8.9%)	8 (4.6%)
Retinal aneurysm	1 (2.3%)	3 (6.8%)	0	2 (4.8%)	2 (4.4%)	7 (4.0%)
Foreign body sensation	0	1 (2.3%)	1 (2.3%)	1 (2.4%)	3 (6.7%)	6 (3.4%)
Vision blurred	1 (2.3%)	4 (9.1%)	0	0	2 (4.4%)	6 (3.4%)
Blepharitis	0	0	4 (9.1%)	0	1 (2.2%)	5 (2.9%)
Punctate keratitis	1 (2.3%)	1 (2.3%)	0	3 (7.1%)	0	4 (2.3%)
Vitreous hemorrhage	6 (13.6%)	0	2 (4.5%)	1 (2.4%)	1 (2.2%)	4 (2.3%)

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Serious Ocular Adverse Events in Study Eye

	Laser	0.5q4	2q4	2q8	2PRN	All VTE
n (safety analysis set)	44	44	44	42	45	175
# of subjects with at least 1 SAE	5(11.4%)	1(2.3%)	2(4.5%)	1(2.4%)	1(2.2%)	5(2.9%)
Endophthalmitis	0	0	1(2.3%)	0	1(2.2%)	2(1.1%)
Uveitis	0	1(2.3%)	0	0	0	1(0.6%)
Angle closure glaucoma	0	0	1(2.3%)	0	0	1(0.6%)
Diabetic retinal edema	1(2.3%)	0	0	0	0	0
Visual acuity reduced	1(2.3%)	0	0	0	0	0
Vitreous hemorrhage	3(6.8%)	0	0	0	0	0
Corneal abrasion	0	0	0	1(2.4%)	0	1(0.6%)

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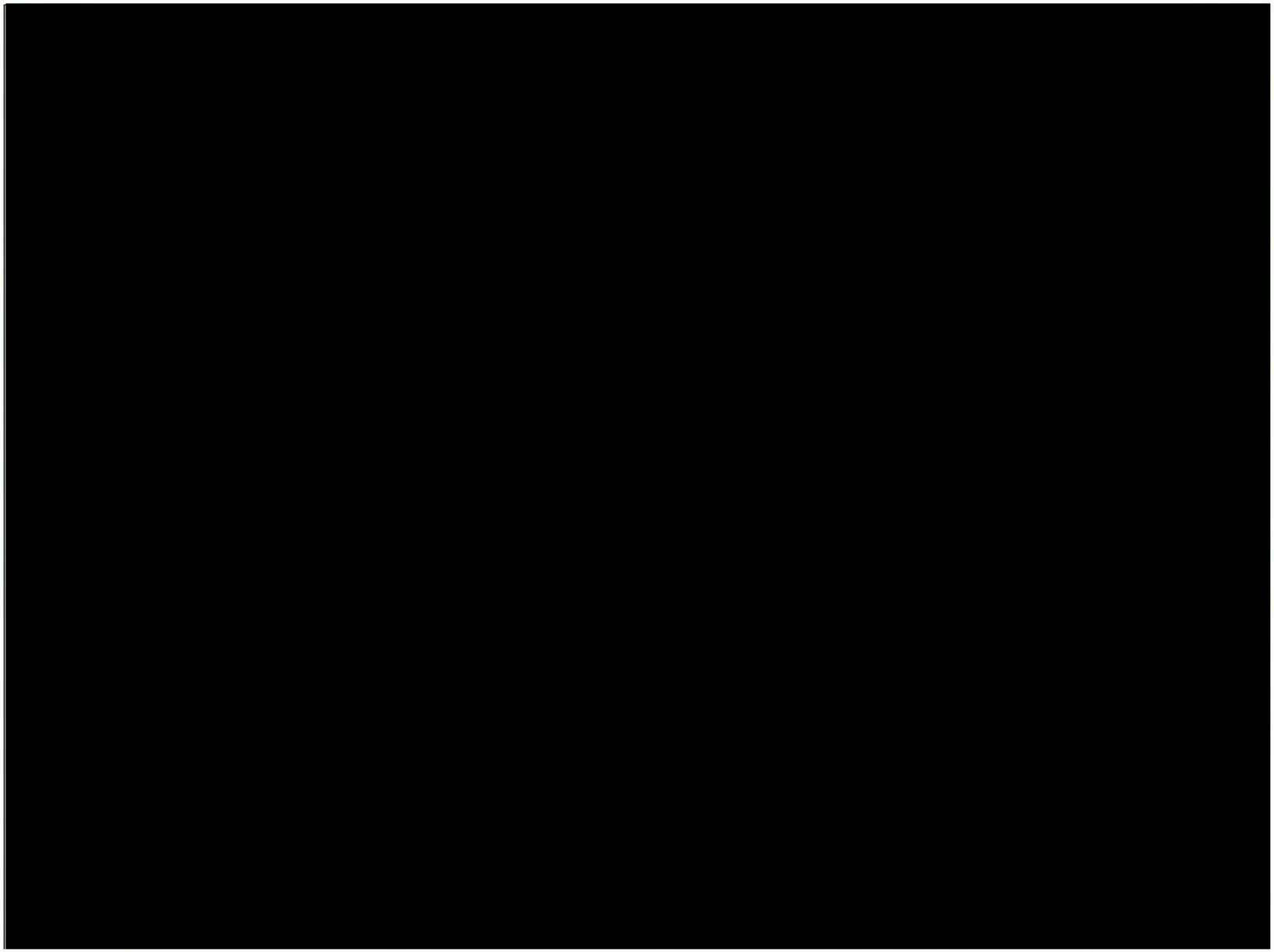
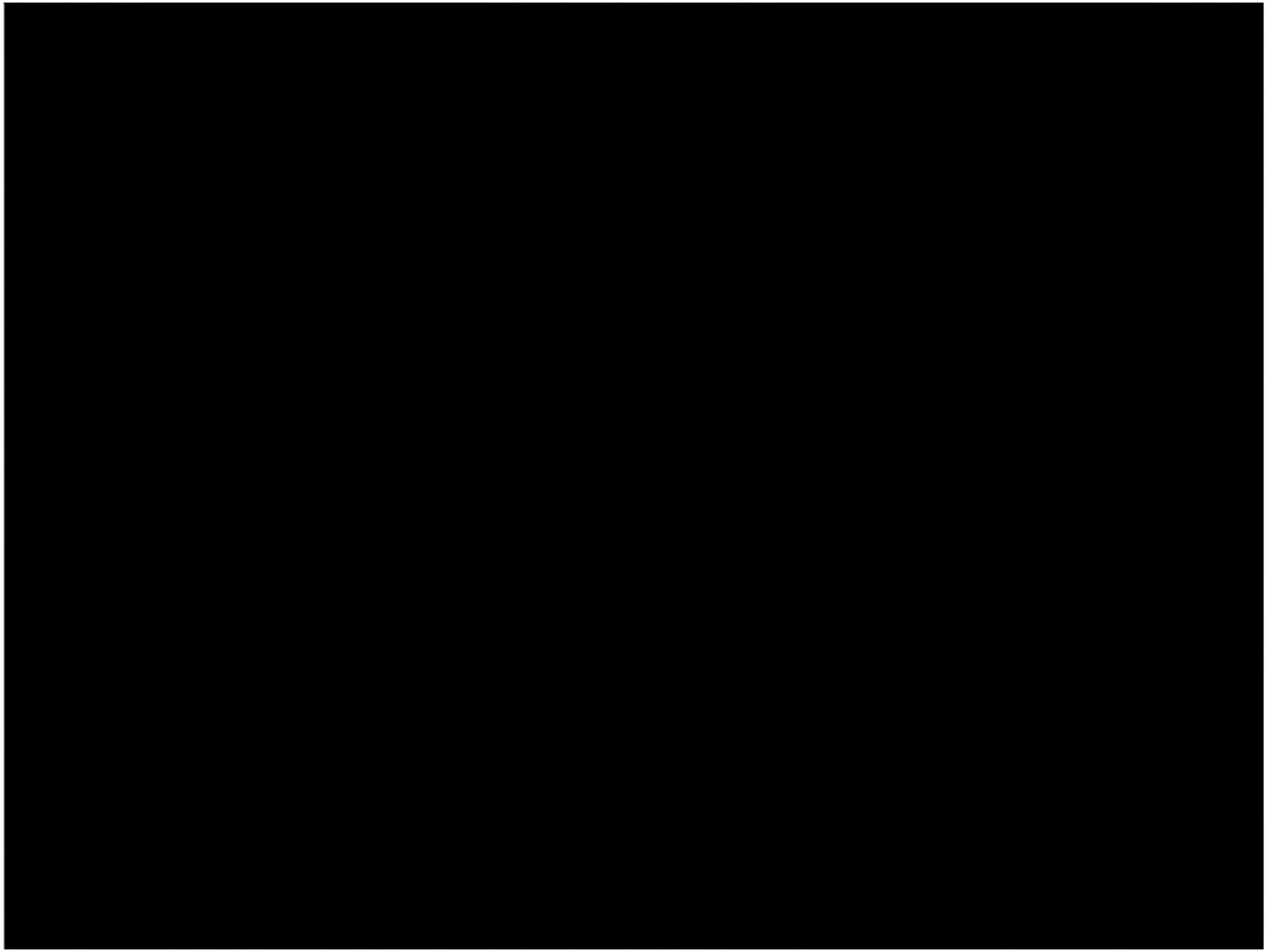
Non-ocular Serious Adverse Events (≥ 4%)

	Laser	0.5q4	2q4	2q8	2PRN	All VTE
n (safety analysis set)	44	44	44	42	45	175
# of subjects with at least 1 AE	10 (22.7%)	14 (31.8%)	13 (29.5%)	12 (28.6%)	6 (13.3%)	45 (25.7%)
Cardiac failure congestive	0	0	3 (6.8%)	1 (2.4%)	2 (4.4%)	6 (3.4%)
Cellulitis	0	3 (6.8%)	2 (4.5%)	0	1 (2.2%)	6 (3.4%)
Chest pain	0	0	2 (4.5%)	0	3 (6.7%)	5 (2.9%)
Cerebrovascular accident	1 (2.3%)	1 (2.3%)	2 (4.5%)	0	0	3 (1.7%)
Hypertension	0	0	2 (4.5%)	1 (2.4%)	0	3 (1.7%)
Anemia	0	1 (2.3%)	2 (4.5%)	0	0	3 (1.7%)
Dehydration	0	0	0	2 (4.8%)	0	2 (1.1%)
Hyperglycemia	0	0	2 (4.5%)	0	0	2 (1.1%)
Myocardial infarction	0	2 (4.5%)	0	0	0	2 (1.1%)





DA VINCI
Summary of 12-Month Results

Efficacy

- Treatment with VEGF Trap-Eye produced statistically significant improvements in BCVA vs. laser at both 6 and 12 months
  - Proportion of patients who gained >=15 letters was statistically better than laser in all VTE groups except 2q8
- Treatment with VEGF Trap-Eye produced statistically significant reductions in CRT compared to laser

Safety

- VEGF Trap-Eye was generally well tolerated
- Most common ocular adverse events were typical of those associated with intravitreal injections