DA VINCI

DME And VEGF Trap-Eye: INvestigation of Clinical Impact

6-Month Phase 2 Primary Analysis

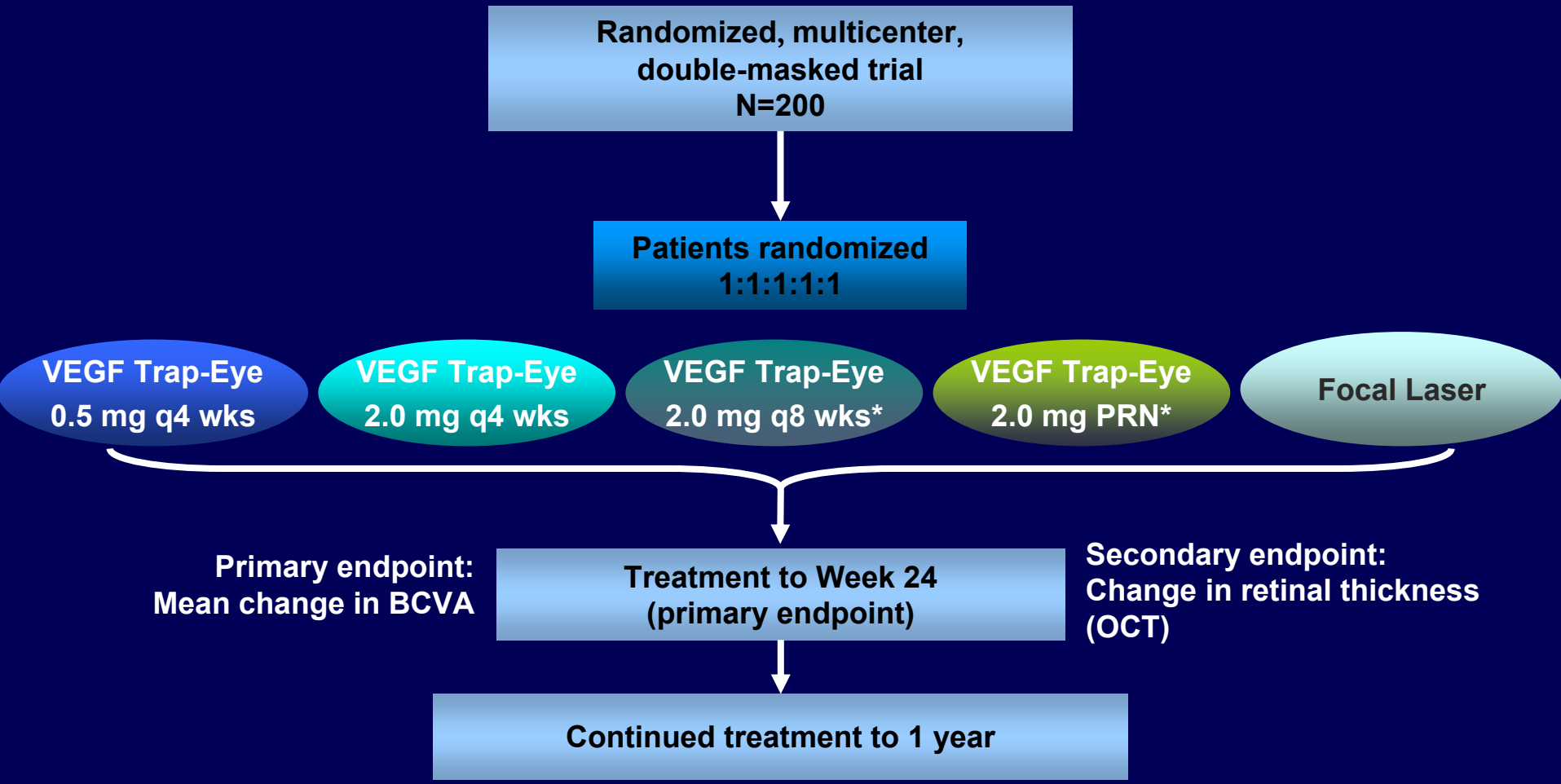
Purpose

This document summarizes the primary analysis of a Phase 2 study of investigational VEGF Trap-Eye in Diabetic Macular Edema (The DA VINCI study). The study results were presented by Diana Do, MD, Assistant Professor of Ophthalmology, Johns Hopkins University School of Medicine, at the Angiogenesis 2010: Clinical Trials meeting in Miami, Florida on Saturday, February 20, 2010.

The Phase 2 DA VINCI study was sponsored by Regeneron Pharmaceuticals, Inc and Bayer HealthCare, who are world wide partners in the development of VEGF Trap-Eye. Dr. Do is the principal investigator for this study and her employer, Johns Hopkins University, has received research funding from Regeneron.

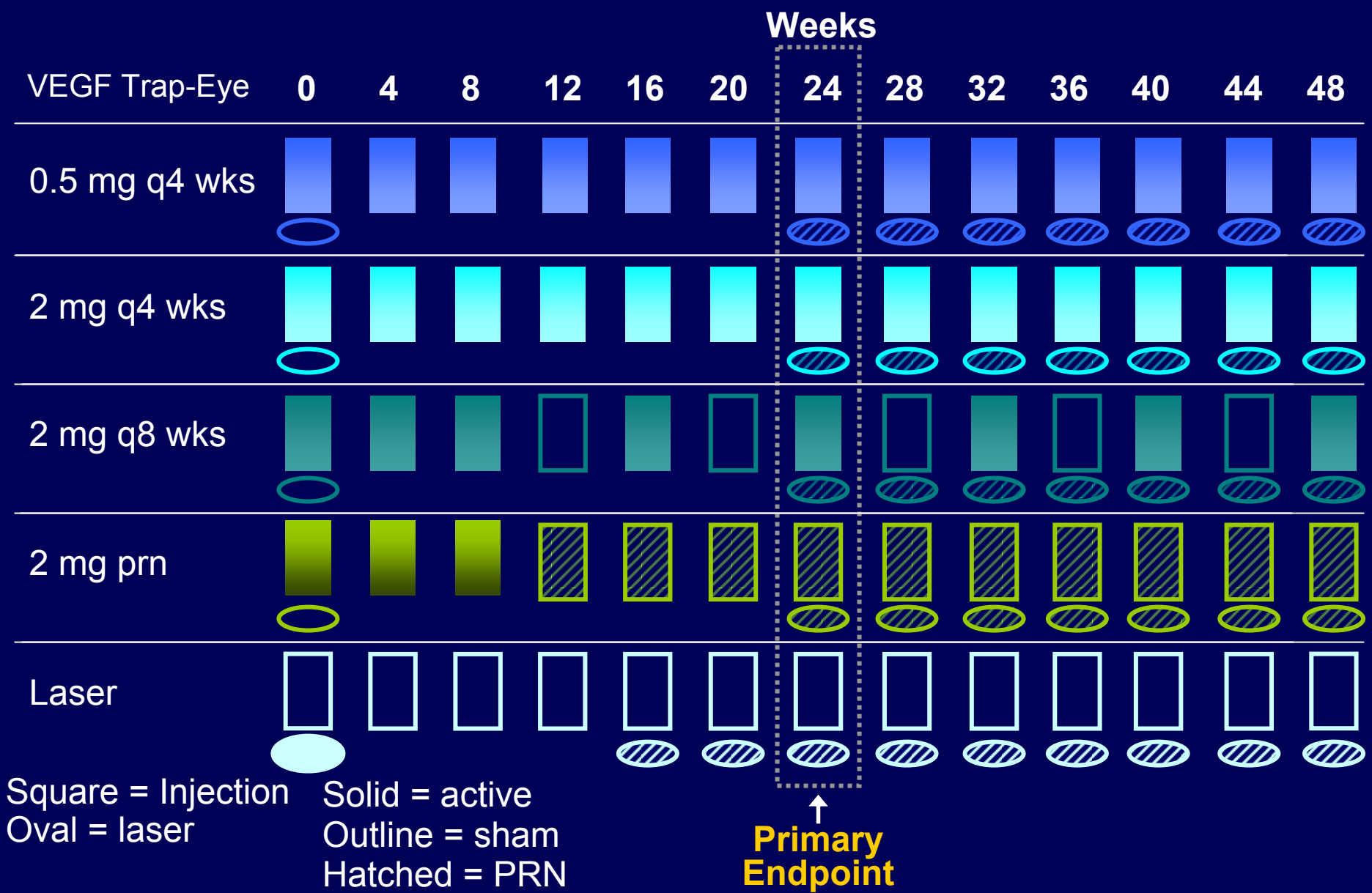
Please note that VEGF Trap-Eye is an investigational agent and that the safety and effectiveness of VEGF Trap-Eye has not been evaluated by regulatory authorities.

DA VINCI Study Design



*Following 3 monthly loading doses

DA VINCI
Study Schedule



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Study Summary

- Enrollment completed June 2009
- 221 patients randomized, 219 treated
- Study sites in US, Canada, Austria
- Primary Objective
  - Explore the effect of various doses and dose intervals of VEGF Trap-Eye versus focal laser on the best-corrected EDTRS visual acuity (BCVA) in patients with DME
- Primary Endpoint
  - Mean change in BCVA from Baseline to Week 24

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Key Inclusion Criteria

- Patients with clinically significant DME with central involvement (≥ 250μm in the central subfield)
- Adults ≥ 18 years with type 1 or 2 diabetes mellitus with diabetic macular edema
- ETDRS BCVA: 20/40 to 20/320 (letter score of 73 to 24) in the study eye

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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 Arm Retreatment

- Laser Arm patients (at week 16)* receive retreatment 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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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	6 (13.6%)	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)**	7.93 (1.84)	8.10 (1.91)	8.08 (1.94)	7.85 (1.72)	7.97 (1.71)
Baseline Cardiac History	8 (18.2%)	21 (47.7%)	15 (34.1%)	18 (42.9%)	15 (33.3%)

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)	57.6 (12.47) 20/70	59.3 (11.16) 20/64	59.9 (10.07) 20/64	58.8 (12.23) 20/64	59.6 (11.06) 20/64
Central Retinal Thickness (µm) Mean (SD)	440.6 (145.41)	426.1 (128.29)	456.6 (134.95)	434.8 (111.83)	426.6 (152.37)
Diabetic retinopathy Severity Score Mean (SD)	3.3 (0.65)	3.5 (0.66)	3.1 (0.85)	3.5 (0.86)	3.2 (0.68)
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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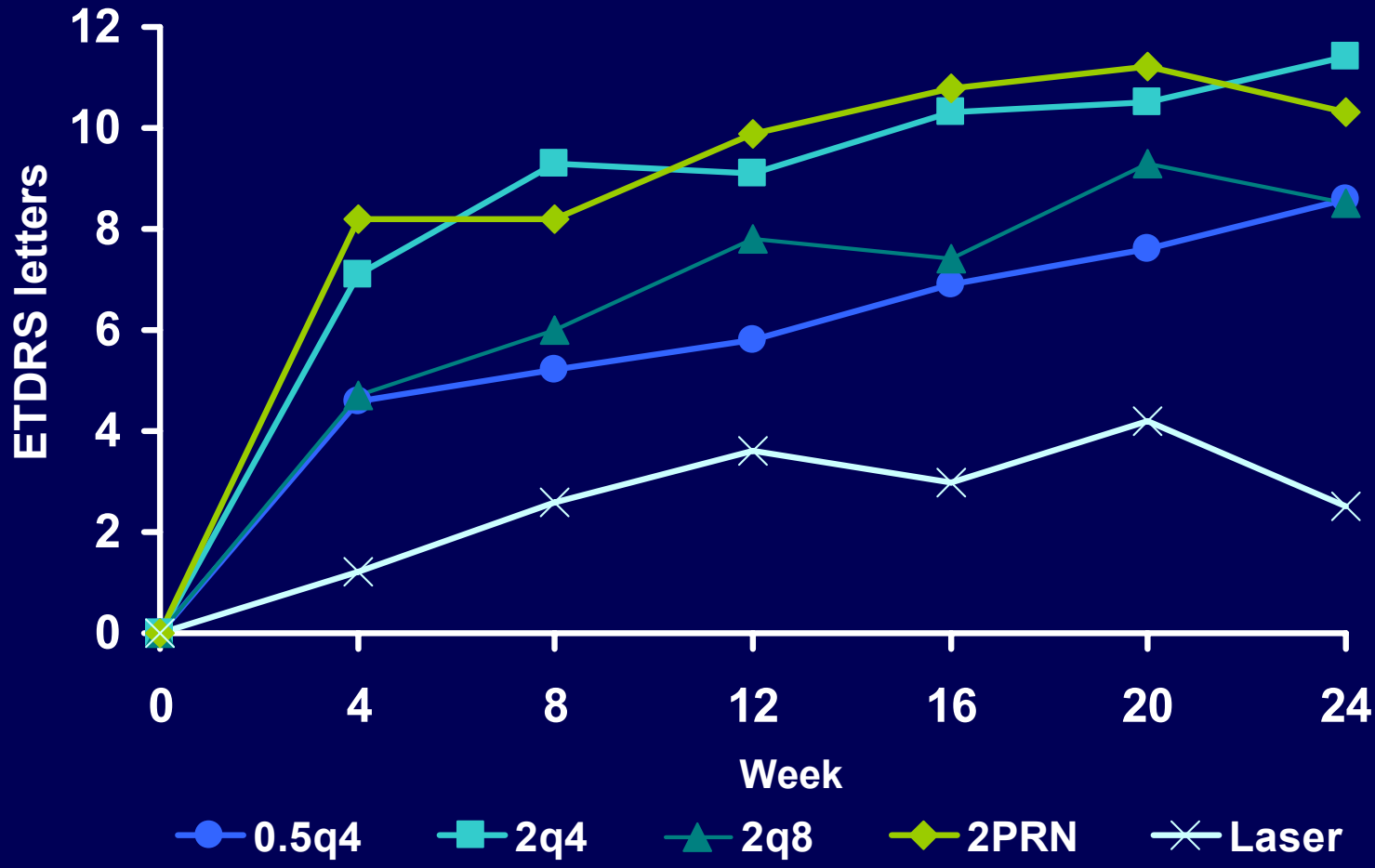
Patient Disposition

	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%)
Premature Discontinuation Within Week 24	4 (9.1%)	3 (6.8%)	4 (9.1%)	5 (11.4%)	4 (8.9%)	20 (9.0%)
Withdrawal Of Consent	2 (4.5%)	0	2 (4.5%)	0	2 (4.4%)	6 (2.7%)
Protocol Deviation	0	0	0	1 (2.3%)	0	1 (0.5%)
Adverse Event*	0	1 (2.3%)	0	0	0	1 (0.5%)
Death†	0	1 (2.3%)	1 (2.3%)	1 (2.3%)	0	3 (1.4%)
Patient Lost To Follow-Up	0	1 (2.3%)	1 (2.3%)	2 (4.5%)	2 (4.4%)	6 (2.7%)
Treatment Failure	2 (4.5%)	0	0	0	0	2 (0.9%)

*Uveitis †multi-organ failure, sudden death, convulsions

DA VINCI
Mean Change in Visual Acuity



2q4* 11.4
2prn+ 10.3
2q8^ 8.5
0.5q4† 8.6
Laser 2.5

*P < 0.0001
^P = 0.0085
+P = 0.0004
†P = 0.0054
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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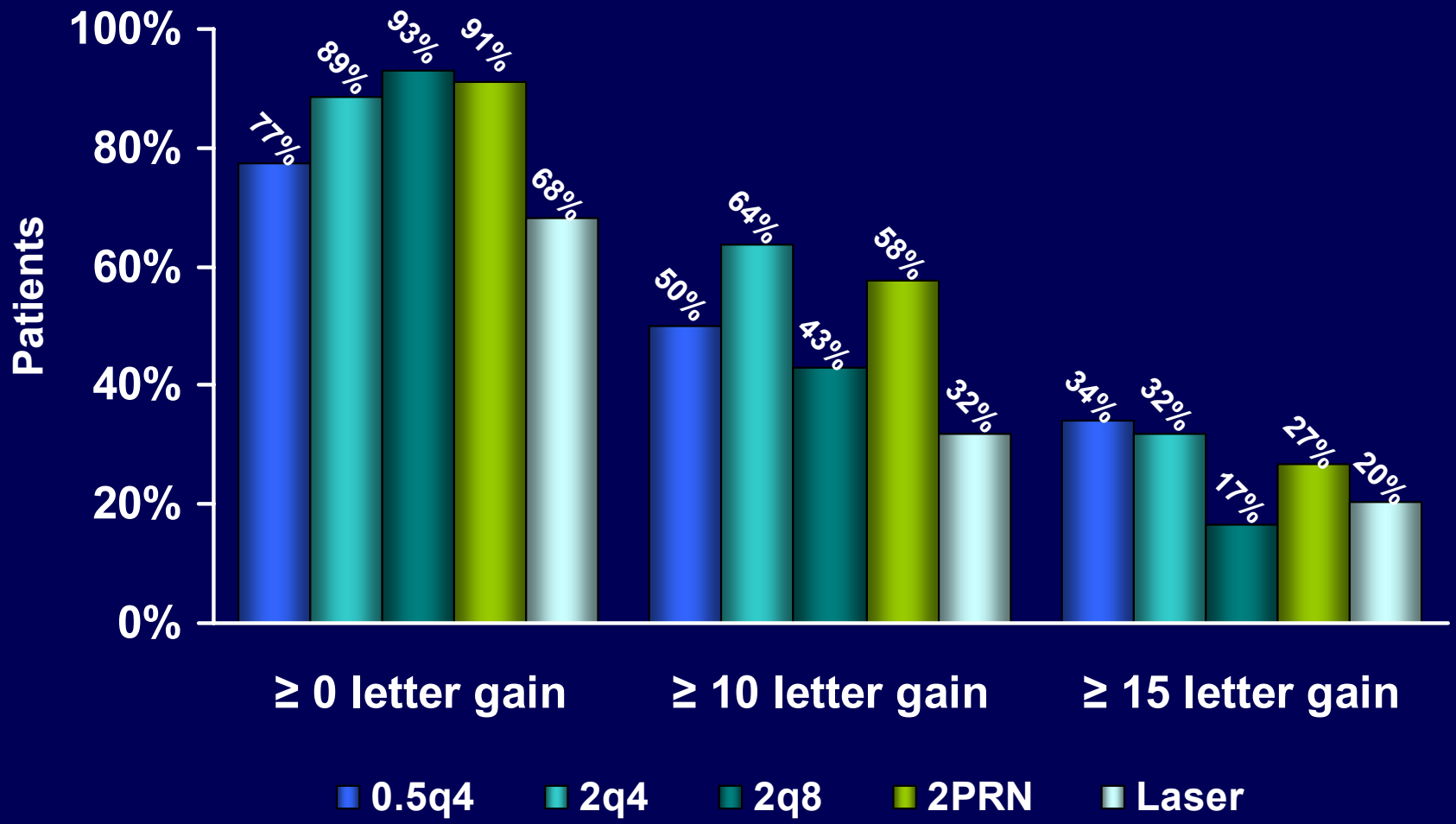
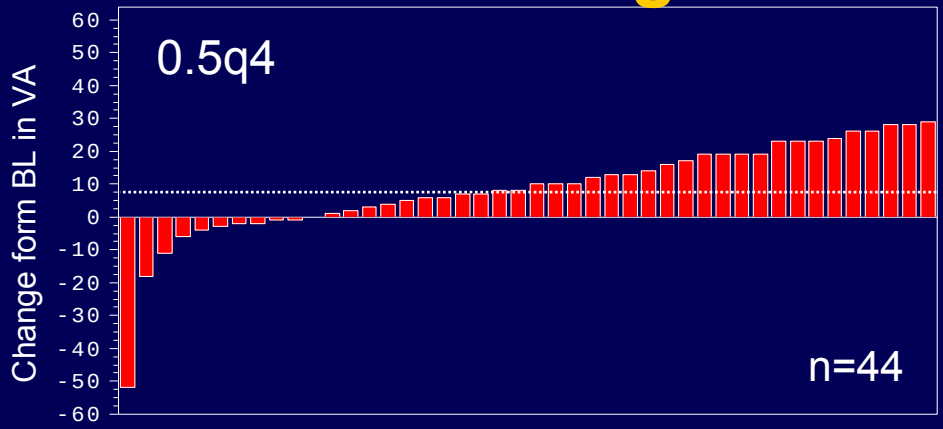
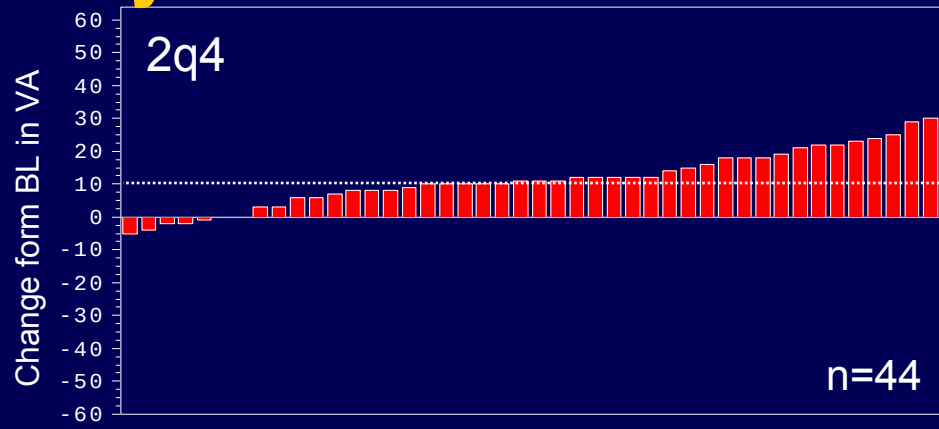
Percent Changes in BCVA at 6 Months

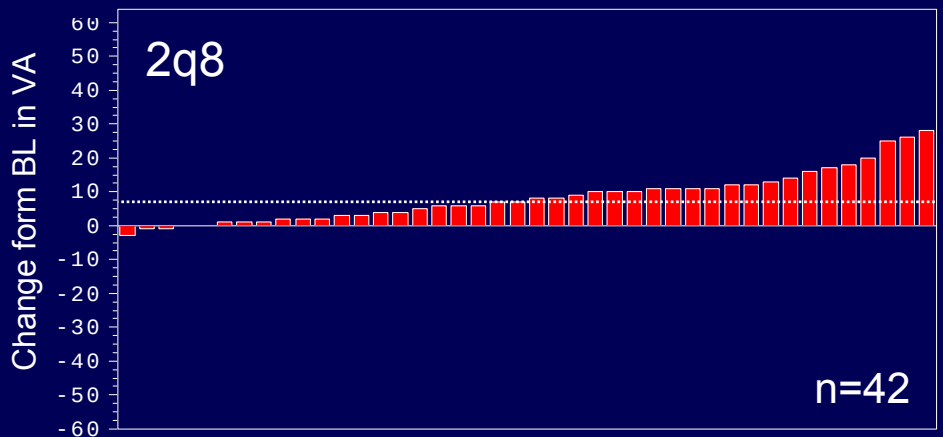


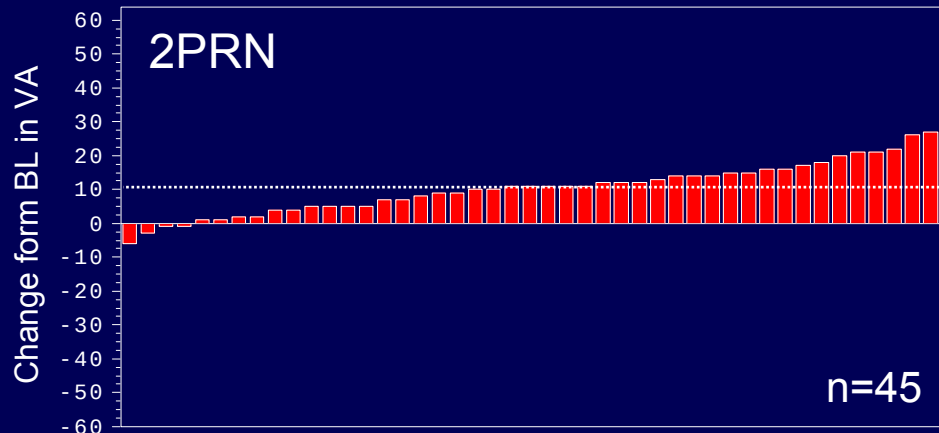
LOCF analysis; n=44 (laser, 0.5q4, 2q4); n=42 (2q8); n=45 (2prn)

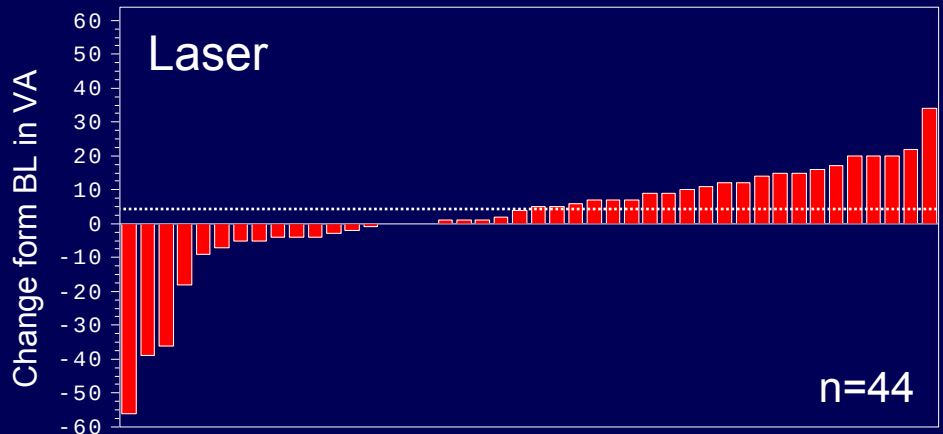
DA VINCI Change in BCVA by Individual Patient*











*Each red bar corresponds to an individual patient. Dotted line represents median BCVA.

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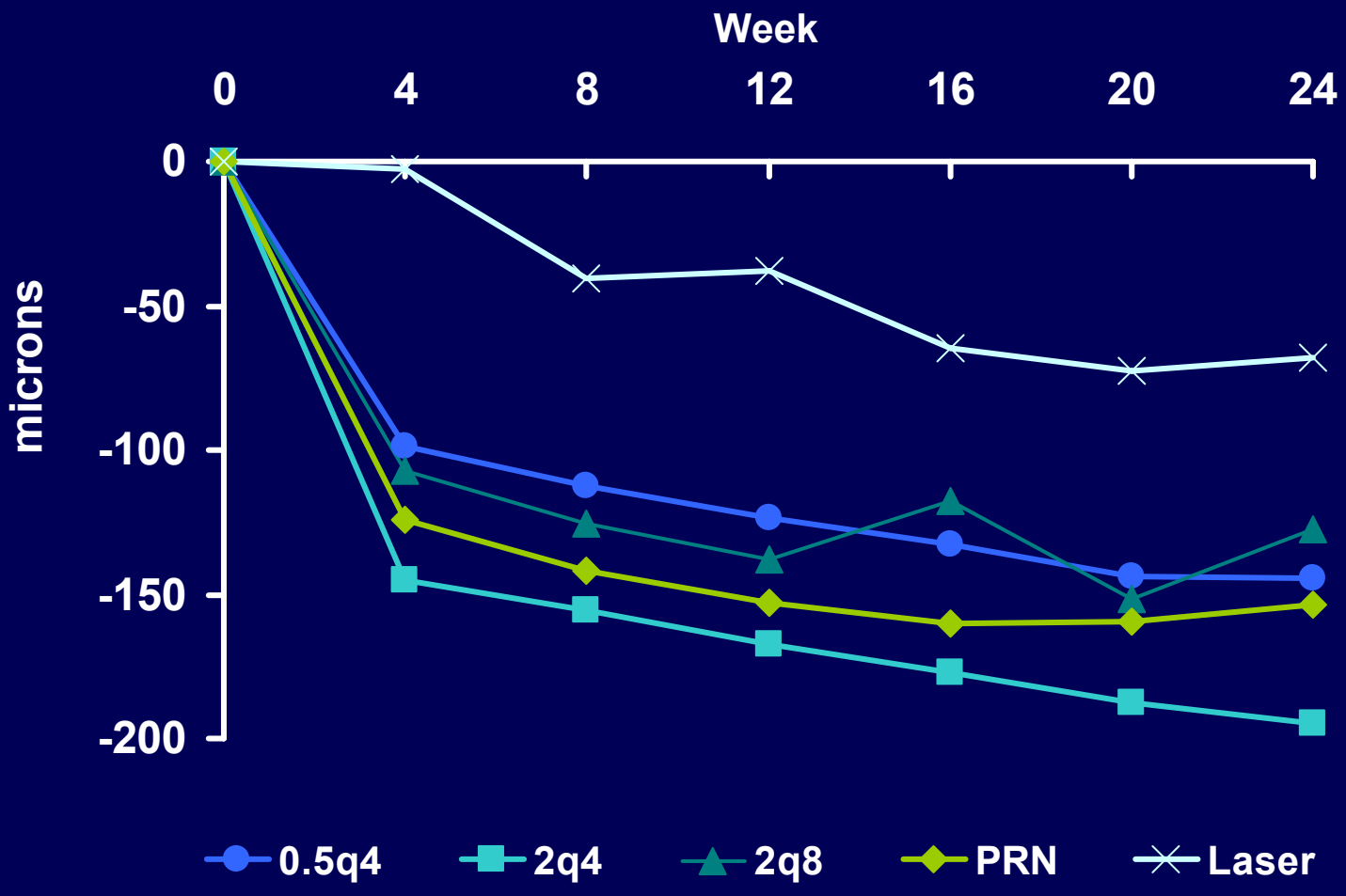
Mean Change in Central Retinal Thickness



Laser -67.9

2q8⁺ -127.3

0.5q4^ -144.6

2prn† -153.3

2q4* -194.5

**P < 0.0001*
^P = 0.0002
⁺P = 0.0066
†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

Total actual VEGF Trap-Eye exposure over 6 months

VEGF Trap-Eye	Required Injections	Mean	Median
0.5q4 (n=44)	6	5.6	6.0
2q4 (n=44)	6	5.5	6.0
2q8 (n=42)	4	3.8	4.0
2PRN (n=45)	3	4.4	4.0

Injections in PRN arm over 3 months

VEGF Trap-Eye	Total Injections Possible	Mean	Median
2PRN (n=45)	3	1.5	1.0

Laser treatments in laser arm over 6 months

Laser	Total Laser Treatments Possible	Mean	Median
n=44	2	1.7	2

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Ocular Adverse Events in Study Eye At 6 Months (≥ 5%)

Preferred Term	Laser n=44	0.5q4 n=44	2.0q4 n=44	2.0q8 n=42	2.0PRN n=45	All VTE n=175
Number (proportion) of pts who had ocular AEs	21(47.7%)	26 (59.1%)	20 (45.5%)	23 (54.8%)	19 (42.2%)	88 (50.3%)
Conjunctival hemorrhage	8 (18.2%)	8 (18.2%)	5 (11.4%)	11 (26.2%)	9 (20.0%)	33 (18.9%)
IOP increased	1 (2.3%)	5 (11.4%)	6 (13.6%)	4 (9.5%)	2 (4.4%)	17 (9.7%)
Eye pain	2 (4.5%)	3 (6.8%)	4 (9.1%)	3 (7.1%)	5 (11.1%)	15 (8.6%)
Ocular hyperemia	2 (4.5%)	4 (9.1%)	1 (2.3%)	3 (7.1%)	3 (6.7%)	11 (6.3%)
Vitreous Floaters	2 (4.5%)	4 (9.1%)	2 (4.5%)	2 (4.8%)	1 (2.2%)	9 (5.1%)

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Serious Ocular Adverse Events in Study Eye At 6 Months

Preferred Term	Laser n=44	0.5q4 n=44	2.0q4 n=44	2.0q8 n=42	2.0PRN n=45	All VTE n=175
Number (proportion) of pts who reported such events	3 (6.8%)	1 (2.3%)	1 (2.3%)	1 (2.4%)	1 (2.2%)	4 (2.3%)
Endophthalmitis			1 (2.3%)		1 (2.2%)	2 (1.1%)
Uveitis		1 (2.3%)				1 (0.6%)
Diabetic retinal edema	1 (2.3%)					
Visual acuity reduced	1 (2.3%)					
Vitreous hemorrhage	1 (2.3%)					
Corneal abrasion				1 (2.4%)		1 (0.6%)

DA VINCI Summary of Adverse Events of Special Interest

Preferred Term	Laser (N=44)	0.5q4 (N=44)	2.0q4 (N=44)	2.0q8 (N=42)	2.0PRN (N=45)	All VGFT (N=175)
Number (proportion) of pts who reported such events	3 (6.8%)	6 (13.6%)	7 (15.9%)	2 (4.8%)	4 (8.9%)	19(10.9%)
Hypertension	3 (6.8%)	4 (9.1%)	7(15.9%)*	2 (4.8%)	4 (8.9%)	17 (9.7%)
Myocardial infarction	0	1 (2.3%)†	1 (2.3%)*	0	0	2 (1.1%)
Cerebrovascular accident	0	1 (2.3%)	1 (2.3%)*	0	0	2 (1.1%)

- 3/175 VEGF Trap-Eye patients and 0/44 laser patients experienced arterial thromboembolic events (p=1.0; not significant)
- 3/175 VEGF Trap-Eye patients and 0/44 laser patients died (p=1.0; not significant)
  - Multi-organ failure (0.5q4, in patient who had cardiac history)†
  - Sudden death (2q4, in patient with previous cardiac history)
  - Convulsions (2q8, in patient with history of convulsions)

*Single patient had 3 events †MI patient subsequently died

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Summary of 6-Month Results

Efficacy

- Treatment with VEGF Trap-Eye produced statistically significant improvements in the mean change from baseline in BCVA as compared to laser
- Treatment with VEGF Trap-Eye produced statistically significant reductions from baseline in central retinal thickness as compared to laser

Safety

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

Based on these encouraging results, further investigation with VEGF Trap-Eye for the treatment of DME is warranted.